Original Article

Inflammatory Cytokines and Childhood Obstructive Sleep Apnoea

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Abstract

Objective: To evaluate serum cytokine concentrations in children with and without obstructive sleep apnoea (OSA) and to investigate the effects of OSA treatment on cytokines. Materials and Methods: Consecutive children with habitual snoring and symptoms suggestive of OSA were recruited. They completed a sleep apnoea symptom questionnaire, underwent physical examination and overnight polysomnography (PSG). OSA was diagnosed if obstructive apnoea index (OAI) >1. A blood sample was collected for analysis of IL-6, IL-8, and TNF-α after PSG. Results: One hundred forty-two children (97 males) with a median (IQR) age of 11.1 years (9.0-12.8) were recruited. The commonest presenting symptoms were nocturnal mouth breathing, prone sleeping position and poor attention at school. Forty-seven children were found to have OSA and they had higher serum IL-6 [0.1 (0.1-0.4) vs 0.1 (0.1-0.1) pg/mL, *P* = 0.001] and IL-8 [1.7 (1.0-2.3) vs 1.3 (0.9-1.7) pg/mL, *P* = 0.029] concentrations compared to their non-OSA counterparts. Multiple regression analysis indicated that OAI was significantly associated with both IL-6 (r = 0.351, *P* <0.001) and IL-8 (r = 0.266, *P* = 0.002). Sixteen children underwent treatment and there was significant reduction in mean (SD) serum IL-8 after intervention [pre vs post levels of 1.9 (1.0) vs 1.1 (0.6) pg/mL, *P* = 0.001] independent of weight loss. Conclusion: Children with OSA had elevated levels of pro-inflammatory cytokines that normalised following treatment suggesting that the inflammatory response is potentially reversible. Early detection and intervention may be beneficial.

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Key words: Interleukin 6, Interleukin 8, Polysomnography, Tumour necrosis factor

Introduction

Obstructive sleep apnoea (OSA) is characterised by repeated episodes of upper airway occlusion during sleep that are associated with daytime behavioural changes and abnormalities in cardiovascular function.[1-4] In adults, it has been shown that OSA is an independent risk factor for cardiovascular diseases.[5,6] This increase has been attributed to the development of pro-inflammatory processes occurring within the microvasculature leading to sympathetic activation and endothelial dysfunction.[7,8] Circulating pro-inflammatory cytokines, such as interleukin 6 (IL-6), have been shown to be elevated in adult subjects with OSA independent of obesity.[9-13] In these subjects, IL-6 concentrations were increased in those with OSA compared with controls.[10] Furthermore, a significant reduction in IL-6 levels was demonstrated in those with OSA who were treated with continuous positive airway pressure.[10]

There is accumulating evidence to suggest cardiovascular morbidity also exists in childhood OSA,[14,15] and while the precise prevalence of paediatric OSA is not known, estimates as high as 10.3% have been made.[16] It is possible that the mechanisms linking OSA to cardiovascular morbidity in childhood also involve pro-inflammatory processes. However, few studies have investigated the associations between circulating inflammatory cytokine concentrations and paediatric OSA.[17] Although the study by Tam et al[17] did not demonstrate statistically significant differences between cases and controls in terms of IL-6 and 8, a trend towards higher interleukin-8 (IL-8) concentrations was noted in

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OSA subjects, even though these subjects were only mildly affected.

We hypothesised that, as in adults, children with OSA would exhibit higher pro-inflammatory cytokine levels compared with their non-OSA counterparts, and that treatment could significantly decrease their levels. We therefore aimed to evaluate the associations between childhood OSA and circulating concentrations of the pro-inflammatory cytokines IL-6, IL-8 and TNF-α and assess the effects of OSA treatment on their levels.

Materials and Methods

Subjects

Consecutive children with habitual snoring who were being assessed for the presence of OSA were recruited from our Paediatric Respiratory, Sleep Disorder and Obesity Clinics. Patients were excluded from the study if they had an intercurrent upper respiratory tract infection within 4 weeks of recruitment, suffered from neuromuscular disorder such as Duchenne muscular dystrophy, craniofacial anomalies, syndromic disorder for example Down syndrome, or if they had previously undergone upper airway surgery. Each subject and their parent completed a sleep-disordered breathing questionnaire that enquired about nighttime and daytime symptoms of OSA and past personal medical history. The study was approved by the Clinical Research Ethics Committee of the Chinese University of Hong Kong and informed written consent from parents was obtained at the beginning of the assessment.

Anthropometry and Physical Assessment

The weight and standing height of the subjects were measured with a calibrated weighing scale and stadiometer by standard anthropometric methods.[18] Body mass index (BMI) was calculated as weight / height^2 (kg/m^2). Blood pressure of the subjects after 10 minutes rest was also documented. The sizes of the adenoids (percentage occupying post-nasal space) and tonsils (standardised scale: 0, absent to 4, kissing tonsils) were documented.[19]

Sleep Study

An overnight polysomnographic (PSG) study was performed on each subject using Siesta ProFusion II PSG monitor (Compumedics Telemed PTY Ltd, Abbotsford, Australia) as previously described.[20] Obstructive apnoea (OA) was defined as absence of airflow with persistent respiratory effort lasting longer than 2 baseline breaths, irrespective of SaO_2 changes. Obstructive apnoea index (OAI) was defined as the number of OAs per hour of sleep. Central apnoea (CA) was defined as absence of respiratory effort associated with absence of airflow. Those of greater than 20 seconds with or without oxygen desaturation or arousals, and those of any duration but associated with oxygen desaturation of at least 4% and/or arousals are quantified. Hypopnoea was defined as a reduction of 50% or more in the amplitude of the airflow signal. It was only quantified if longer than 2 baseline breaths and associated with oxygen desaturation of at least 4% and/or arousals. Apnoea hypopnoea index (AHI) was defined as the total number of apnoeic and hypopnoeic episodes per hour of sleep. Oxygen saturation nadir and the percentage of total sleep time where oxygen saturation was below 90% were noted. Arousal was defined as an abrupt shift in electroencephalography (EEG) frequency during sleep, which may include theta, alpha and/or frequencies greater than 16 Hz but not spindles, with 3 to 15 seconds in duration. In rapid eye movement (REM) sleep, arousals were scored only when accompanied by concurrent increases in submental electromyography (EMG) amplitude. We defined OSA as OAI ≥1.0 episode per hour of sleep. Subjects who had an OAI value <1.0 episode per hour of sleep were grouped as control.

Laboratory Measurements

All subjects had fasting blood samples taken at 0800h in the morning following overnight PSG. Serum IL-6, IL-8 and TNF-α were measured by enzyme-linked immunosorbent assay (BioSource International Inc, Camarillo, California, USA). The sensitivity and inter-assay coefficients of variation of IL-6, IL-8 and TNF-α were 0.104 pg/mL, 8.7% at 0.8 pg/mL; 0.1 pg/mL, 7.9% at 1.5 pg/mL; and 0.09 pg/mL, 8.9% at 0.6 pg/mL, respectively.

Treatment and Follow-up

Subjects identified to have OSA were offered adenotonsillectomy after assessment by an ENT surgeon. Those who declined surgical intervention and those in whom surgery was not indicated according to pre-determined criteria (small tonsils; tonsils not extending beyond the anterior tonsillar pillar and small adenoids; adenoids which occupy less than 25% of post-nasal space with minimal obstructive sleep apnoea syndrome (OSAS) symptoms or poorly controlled allergic rhinitis with supine nasal obstruction) were offered nocturnal non-invasive positive pressure ventilation (NIPPV) and/or nasal corticosteroid therapy.[21] Subjects were re-assessed 6 to 8 weeks after the operation/start of NIPPV or 3 months after commencing nasal corticosteroids.

Statistical Analysis

The subjects were divided into 2 groups (control: OAI ≤1, OSA: OAI >1), according to their OAI score. The demographic data and laboratory results were expressed as median with interquartile ranges (IQR) as the distribution

of the results were non-parametric. The Mann-Whitney U test for the quantitative variables and chi-square test for the categorical variables were used to explore the associations of the factors between these 2 groups. To assess the correlations between the cytokines (IL-6 and IL-8) and other factors, the Pearson's correlation analysis was used. For the assessments of the relative strength of the association, we used a stepwise multiple regression model with the cytokines as the dependent variable and age, weight, height, BMI z-score, systolic blood pressure, diastolic blood pressure, tonsillar size, OAI, O_2 nadir, %TST <90% and arousal index as independent variables. For the comparison of parameters before and after treatment of OSA, paired *t*-test was used to determine the differences. SPSS for Windows 14 (SPSS, Inc, Chicago, IL, USA) was used in the analysis, and the level of significance was set at 5% for all comparisons.

Table 1. Descriptive Data of the Study Population

	Non-OSA (n = 95)	OSA (n = 47)	*P* value
Age (y)	10.7 (8.2-12.8)	11.1 (8.8-13.2)	0.507
Gender, male/female	64/31	33/14	0.732
Weight (kg)	46.4 (28.0-61.7)	49.5 (29.5-75.5)	0.384
Height (m)	1.44 (1.26-1.54)	1.46 (1.29-1.60)	0.495
BMI z-score	2.1 (-0.3-2.8)	1.9 (0.8-3.0)	0.488
SBP (mmHg)	114 (101-128)	122 (106-133)	0.045
DBP (mmHg)	66 (61-70)	68 (62-78)	0.049
Tonsil (left)	1.0 (1.0-2.0)	2.0 (1.0-3.0)	0.010
Tonsil (right)	1.0 (0.0-2.0)	2.0 (1.0-4.0)	0.010
AR (no/yes)	73/22	36/11	0.302
Asthma (no/yes)	86/9	42/5	0.230
IL-6 (pg/mL)	0.1 (0.1-0.1)	0.1 (0.1-0.4)	0.001
IL-8 (pg/mL)	1.3 (0.9-1.7)	1.7 (1.0-2.3)	0.029
TNF-alpha (pg/mL)	0.5 (0.4-0.6)	0.4 (0.4-0.6)	0.405
OAI	0.0 (0.0-0.2)	4.6 (1.5-13.9)	<0.0001
AHI	0.7 (0.1-2.2)	14.1 (5.6-32.8)	<0.0001
O_2 nadir (%)	88.0 (82.0-92.0)	74.0 (68.0-85.0)	<0.0001
% TST < 90%	0.0 (0.0-0.0)	0.1 (0.0-0.2)	<0.0001
ArI	6.0 (4.0-8.0)	10.0 (6.0-17.0)	<0.0001

Median (IQR)

AR (no/yes) – allergic rhinitis (whether the condition was absent or present)
Asthma (no/yes) – asthma (whether the condition was absent or present)

%TST <90%: percentage total sleep time with oxygen saturation <90%; AHI: apnoea hypopnoea index; ArI: arousal index; AR: allergic rhinitis; DBP: diastolic blood pressure; IL-6: interleukin 6; IL-8: interleukin 8; O_2 nadir: lowest oxygen saturation recorded; OAI: obstructive apnoea index; OSA: obstructive sleep apnoea; TNF-alpha: tumour necrosis factor alpha; Tonsils (L): left side tonsils; Tonsils (R): right side tonsils; SBP: systolic blood pressure

Results

One hundred and forty-two consecutive subjects were invited and they all agreed to participate in this study. There were 97 boys and the median (IQR) age of the subjects was 11.1 years (9.0-12.8). Thirty-three subjects had allergic rhinitis for which they used antihistamine as required, and 10 were using regular corticosteroid nasal spray. Fourteen subjects had asthma and all were only taking inhaled bronchodilator on an as required basis. The condition of all asthmatics had been well controlled prior to and during this study. The demographic characteristics, size of the tonsils, laboratory results and sleep study parameters were similar between boys and girls. The 3 most common presenting OSA-related complaints of the subjects were nocturnal mouth breathing, prone sleeping position and poor attention at school. All subjects had normal physical examination.

Forty-seven subjects satisfied the diagnostic criteria for OSA and 33 of them were boys. The clinical characteristics of the subjects with and without OSA were compared in Table 1. There were no significant differences in age, gender distribution, anthropometric parameters, blood pressure measurements and the presence of atopic diseases between the groups. Subjects with OSA had significantly larger left- and right-sided tonsil than non-OSA subjects. OSA subjects had greater IL-6 [0.1 (0.1-0.4) vs 0.1 (0.1-0.1) pg/mL, $P = 0.001$] and IL-8 [1.7 (1.0-2.3) vs 1.3 (0.9-1.7) pg/mL, $P = 0.029$] levels than non-OSA subjects. On multiple regression analysis, OAI was found to have

Table 2. Stepwise Multiple Regression Analysis of the Relationship Between the Dependent Variables (IL-6 And IL-8) and the Independent Variables

	IL-6		IL-8	
	r	*P* value	r	*P* value
OAI	0.351	<0.001	0.266	0.002
Age	-0.007	0.939	-0.088	0.323
Weight	0.002	0.980	-0.145	0.101
Height	-0.020	0.819	-0.156	0.078
BMI z-score	-0.121	0.169	-0.183	0.052
SBP	-0.011	0.901	-0.075	0.400
DBP	-0.006	0.943	0.102	0.249
Tonsils (L)	0.007	0.936	0.171	0.052
Tonsils (R)	0.013	0.884	0.132	0.137
O_2 nadir (%)	0.074	0.402	-0.026	0.770
%TST <90%	-0.151	0.086	-0.098	0.271
ArI	0.065	0.462	0.159	0.071

r = partial correlation coefficient
For definition of abbreviations, see Table 1.

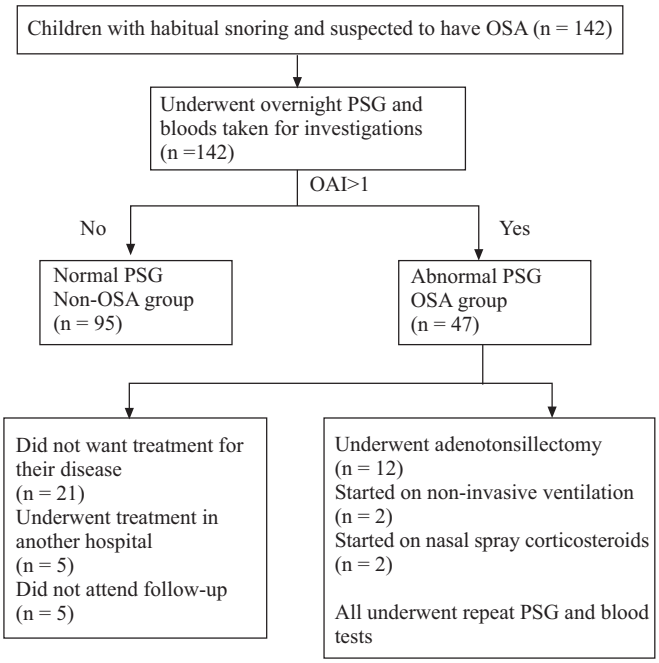

Fig. 1. Flow chart showing different pathways undertaken by the recruited subjects.

significant association with both IL-6 (r = 0.351, P <0.001) and IL-8 (0.266, P = 0.002) (Table 2).

The diagnostic cut-off for childhood OSA has not been firmly established. Witmen et al[22] recently proposed AHI >1.5 as a diagnostic parameter for this condition. We re-analysed our results using different cut-offs of AHI >1, AHI >1.5 and AHI >5 and the results are shown in Table 3. There was no significant difference in TNF-α between non-OSA and OSA groups at different cut-offs. However, greater and more statistically significant differences between the 2 groups in IL-6 and IL-8 levels with more severe OSA were clearly demonstrated. OAI >1 was found to have the best correlation with AHI >5 (r = 0.702, P <0.001). Of the 47 subjects identified to have OSA using OAI >1, 39 (83%) were also captured with the AHI >5 diagnostic cut-off.

Sixteen OSA subjects underwent treatment. Twelve had adenotonsillectomy and 2 obese subjects were started on NIPPV. The average number of hours used per night was 6 for the 2 patients given NIPPV. Two subjects with mild OSA (OAI 1.9 and 4.4) and allergic rhinitis symptoms were given 3 months of nasal spray corticosteroids and the drug compliance was >80%. Thirty-one subjects did not undergo repeat assessment. Of these patients, 21 refused to have treatment for their disease. Five subjects received treatment in hospitals outside our region. Another 5 subjects were lost to follow-up (Fig. 1). There were, however, no significant differences in demographic characteristics, laboratory results and sleep apnoea parameters between those who did receive treatment and had repeat assessment and those who did not (Table 4). For the 16 subjects with pre- and post-intervention data, there was significant reduction in mean (SD) serum IL-8 after treatment [1.9 (1.0) vs 1.1 (0.6) pg/mL, P=0.001] independent of change in body weight (Table 5).

Discussion

To our knowledge, this is the first study to demonstrate the effects of treatment of childhood OSA on serum cytokine profiles. Significantly higher serum IL-6 and IL-8 levels were exhibited by children with OSA compared to those without. Independent associations between OSA and the 2 cytokines were demonstrated, providing evidence of the pro-inflammatory nature of childhood OSA. Furthermore, the IL-8 levels decreased after intervention within 2 to 3 months, suggesting a causal association between OSA and the pro-inflammatory state.

Inflammatory markers such as C-reactive protein (CRP), IL-6 and IL-8 have all been found to increase in adult patients with OSA.[10-13] Similarly, the association between childhood OSA and elevated inflammatory mediators, e.g. CRP[23] and percentage sputum neutrophils,[24] has been demonstrated in recent studies. Our study adds further

Table 3. Serum Cytokine Concentrations Between Non-OSA and OSA Groups at Different OSA Diagnostic Cut-Offs

	OAI >1 Non-OSA (n = 95) vs OSA (n = 47)	AHI >1 Non-OSA (n = 56) vs OSA (n = 86)	AHI >1.5 Non-OSA (n = 62) vs OSA (n = 80)	AHI >5 Non-OSA (n = 96) vs OSA (n = 46)
IL- 6 (pg/mL)	0.1(0.1-0.1) vs 0.1(0.1-0.4) P = 0.001	0.1(0.1-0.1) vs 0.1(0.1-0.22) P = 0.027	0.1(0.1-0.1) vs 0.1(0.1-0.2) P = 0.004	0.1(0.1-0.1) vs 0.15(0.1-0.37) P <0.0001
IL- 8 (pg/mL)	1.3(0.9-1.7) vs 1.6(1.0-2.3) P = 0.029	1.32(0.85-1.69) vs 1.33(0.85-1.82) P = 0.456	1.2(0.8-1.7) vs 1.4(1.0-1.9) P = 0.066	1.27(0.84-1.69) vs 1.56(1.15-2.08) P = 0.01
TNF-α (pg/mL)	0.5(0.4-0.6) vs 0.4(0.4-0.6) P = 0.405	0.48(0.4-0.66) vs 0.43(0.4-0.63) P = 0.693	0.5(0.4-0.6) vs 0.4(0.4-0.6) P = 0.952	0.43(0.4-0.62) vs 0.47(0.4-0.67) P = 0.703

Median(IQR)

Table 4. Descriptive Data of OSA Subjects With and Without Intervention

	No intervention (n=31)	Invention (n=16)	*P* value
Age (y)	11.2 (9.0-13.2)	10.9 (6.2-14.2)	0.849
Gender, male/female	20/11	13/3	0.235
Weight (kg)	48.5 (33.5-75.5)	51.5 (19.5-73.4)	0.445
Height (m)	1.46 (1.4-1.6)	1.48 (1.2-1.6)	0.670
BMI z-score	1.97 (1.0-3.1)	1.46 (0.2-2.7)	0.135
SBP (mmHg)	123 (107-135)	117 (102-127)	0.286
DBP (mmHg)	69 (64-79)	68 (59-73)	0.247
Tonsil (left)	2.0 (1.0-3.0)	3.0 (1.0-4.0)	0.117
Tonsil (right)	1.0 (0.0-4.0)	3.0 (1.0-4.0)	0.112
AR (no/yes)	12/19	5/11	0.614
Asthma (no/yes)	29/2	12/4	0.071
IL-6 (pg/mL)	0.13 (0.10-0.36)	0.14 (0.10-0.44	0.572
IL-8 (pg/mL)	1.56 (0.80-2.08)	1.87 (1.26-2.57)	0.302
TNF-alpha (pg/mL)	0.43 (0.39-0.59)	0.44 (0.39-0.85)	0.670
OAI	3.4 (1.5-13.9)	8.6 (2.1-16.7)	0.281

Median (IQR)
For definition of abbreviations, see Table 1.

Table 5. Laboratory and PSG Parameters of the 16 Subjects Before and After Treatment

	Before treatment	After treatment	*P* value
Weight (kg)	48.6 (26.6)	50.6 (25.8)	0.125
BMI z-score	1.24 (1.54)	1.52 (1.40)	0.117
IL-6 (pg/mL)	0.3 (0.4)	0.2 (0.3)	0.304
IL-8 (pg/mL)	1.9 (1.0)	1.1 (0.6)	0.001
TNF-alpha (pg/mL)	0.7 (0.7)	0.6 (0.2)	0.530
OAI	11.6 (16.5)	0.4 (1.3)	0.020
AHI	28.7 (27.7)	1.4 (2.0)	0.002
O_2 nadir (%)	69.3 (8.5)	85.5 (7.3)	<0.0001
%TST <90%	0.4 (1.3)	0.2 (0.4)	0.598
ArI	14.5 (9.8)	5.3 (2.9)	<0.0001

Mean (SD)
For definition of abbreviations, see Table 1.

support to the theory that there is systemic activation of the inflammatory response in children with OSA, putting them at increased risk of future atherosclerosis and cardiovascular disease. In the only other study evaluating serum cytokines in children with OSA, Tam et al[17] were unable to demonstrate significantly elevated levels of IL-6 and IL-8 in children with OSA after correction for age, sex and BMI, although there was a trend of elevated IL-8 amongst children with OSA ($P = 0.05$). This trend is compatible with our findings of elevated IL-8 concentrations in subjects with OSA. OSA subject age in this study tended to be younger than in ours (mean 7.3 years vs median 11.1 years). Younger subjects tend to have shorter duration of disease and therefore reduction in duration of the theoretical pro-inflammatory period. Furthermore, subjects in our study had more severe disease (median AHI of 13.6 in our study vs mean RDI 5.3). It is therefore possible that the differences in chronicity and severity of OSA could explain the discrepancy seen between Tam et al's and our study.

We were not able to demonstrate any significant differences in serum TNF-α between cases and controls. This is compatible with the study by Tam et al.[17] There is evidence in experimental animals that systemic TNF-α enhances sleep and, conversely, inhibition of this cytokine suppresses sleep.[25] Elevated levels of TNF-α in OSA adults appeared to be associated with daytime sleepiness and fatigue.[26] A recent report documented a marked decrease in sleepiness in adult OSA patients given etanercept, a medication that neutralises TNF-α.[27] Our results suggest that the inflammatory response to OSA in children may be different from adults. The observation that daytime sleepiness is much less common in children with OSA[28] is compatible with our finding, suggesting that TNF-α plays less of a role in childhood OSA. Further, the shorter duration of disease in children compared with adults may also explain the relatively weaker association between paediatric OSA and circulating pro-inflammatory cytokine concentrations. The importance of the severity of disease is also supported by further analysis of our results. There is a dose-dependent effect of OSA on both IL-6 and IL-8 levels (Table 2), with larger and more statistically significant differences between the non-OSA and OSA groups in IL-6 and IL-8 serum concentrations when using higher cut-offs to define OSA (Table 3). However, an appropriate cut-off that would predict long-term cardiovascular morbidity will only be answered by large-scale long-term follow-up studies.

In patients with OSA, cyclical alterations of arterial oxygen saturation develop with decrease in oxygen saturation during apnoea and re-oxygenation during subsequent hyperventilation. This phenomenon has been referred to as hypoxia/reoxygenation and might alter the oxidative balance through the production of excess oxygen free radicals as seen in ischaemia/reperfusion injury. Chronic, cyclical hypoxia upregulates the synthesis of pro-inflammatory cytokines by mononuclear cells.[29]

There are limitations in our study. First, we managed to obtain post-intervention data in only 16 out of 47 OSA subjects. Twenty-one subjects (44.6%) refused treatment for their disease. There were, however, no significant differences in demographic, laboratory and sleep apnoea characteristics between those whose post-intervention

results were available and those who did not have repeat assessment. The 16 subjects who underwent treatment had normalisation of their cytokines parallel with resolution of disease. This temporal association provided support for the statistically significant association between OSA and serum cytokine levels. Second, we did not have a control group of non-snoring children for comparison. We fully acknowledged this to be a significant limitation; however, there were substantial difficulties in recruiting normal healthy children without symptoms of OSA for blood-taking and polysomnography.

In summary, our results demonstrated significantly higher pro-inflammatory cytokine levels in children with OSA than those without. After adjustment for important covariates, severity of OSA remained an important predictor, independent of factors such as BMI z-score, for both blood IL-6 and IL-8 levels. Treatment of the OSA resulted in reduction in serum levels of IL-6 and IL-8 (statistically significant for IL-8) and possibly a degree of reversal of the pro-inflammatory response. Further, longitudinal studies involving a larger cohort of children would be needed to demonstrate the clinical significance of persistently raised serum cytokines and its influence on atherosclerotic diseases in the long term.

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