Catecholamines, Adiponectin, and Insulin Resistance as Measured by HOMA in Children with Obstructive Sleep Apnea

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Precis: Severe OSA is associated with lower adiponectin and higher urinary catecholamines and a tendency toward more insulin resistance in the pediatric population.

Abbreviated title: Adiponectin and Pediatric OSA

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Abstract

Introduction: Obstructive sleep apnea(OSA) has been implicated in the pathophysiology of metabolic syndrome. Its contribution to insulin resistance is complicated by obesity and puberty. We hypothesized that OSA is associated with worse insulin resistance and lower adiponectin after adjustment for obesity and puberty and that catecholamines might mediate these changes.

Methods: Normal controls and children with suspected OSA were recruited and categorized as pubertal or prepubertal. Overnight polysomnography(PSG) was performed. Subjects were categorized as OSA for total apnea hypopnea index(Total-AHI) $\geq$1.5 events/hr. 24-hour urinary catecholamines, fasting blood glucose, insulin, and adiponectin were obtained. Homeostatic model assessment of insulin resistance(HOMA) was calculated. The independent effects of OSA upon HOMA, adiponectin, and urinary catecholamines following adjustment for body mass index(BMI) were determined.

Results (median; min,max): Subjects (n=98, 42F; 11$\pm$4 years, 37 prepubertal) were generally overweight (BMI-Z=2.1; -3, 4.1) and had wide-ranging insulin sensitivities (HOMA=2.7; 0.5, 27) and PSG parameters (Total-AHI=1.6; 0, 185). The risks of elevated insulin (p=0.04) and HOMA (p=0.05) were higher in OSA vs non OSA obese pubertal children. Polysomnographic markers of OSA, including Total-AHI (p=0.001, R^2=0.32), were negatively associated with adiponectin in pubertal children. Total-AHI and oxygen desaturation were associated with higher urinary normetanephrine and norepinephrine.

Conclusions: In obese pubertal children, OSA was associated with worse insulin resistance. Worsening OSA was associated with lower adiponectin and increasing urinary catecholamines. Whether OSA directly lowers adiponectin and aggravates a predisposition to insulin resistance is unknown, but these preliminary findings highlight the importance of further studying pediatric OSA.

Introduction

The metabolic syndrome describes the complex of hyperinsulinemia, abdominal obesity, and dyslipidemia.[1] It has been linked to diabetes, [2] cardiovascular disease and increased mortality,[3] highlighting the alarming nature of estimates that it affects 20-25% of the US population.[4] Obstructive sleep apnea (OSA) has been associated with the metabolic syndrome in adults. Deciphering the relationship between OSA and the metabolic syndrome is complicated since obesity is a risk factor for both disorders, even in children.[5-7] However, after adjusting for obesity, studies in adults found OSA to be an independent risk factor for insulin resistance and hypertension.[8-11]

Increased sympathetic output due to hypoxemia and repetitive arousals during sleep is purported to be causal in insulin resistance and elevated blood pressure.[11] However, the mechanisms linking OSA and the metabolic syndrome remain poorly understood. A possible link may be adiponectin. Adiponectin, an insulin sensitizing hormone secreted by adipose tissue, decreases hepatic glucose output and increases fatty acid oxidation by muscle. Low serum adiponectin concentrations have been associated with obesity, Type 2 diabetes, and hypertension.[12] Both mutations and polymorphisms of the adiponectin gene have been found in Type 2 diabetes and in states of impaired glucose tolerance.[13-16] In vitro, catecholamines suppress adiponectin secretion/production.[17] Thus, the increased sympathetic output associated with OSA may suppress serum adiponectin, potentially contributing to insulin resistance. The data in adults with respect to OSA and adiponectin are conflicting.[18-23]

Until recently, few studies have examined OSA and its contribution to the metabolic syndrome in the pediatric population.[24-26] Preliminary studies in children with OSA have found increased diastolic blood pressure,[25] increased blood pressure variability with loss of the normal circadian rhythm in blood pressure,[27] and increased fasting insulin[24] but not necessarily a direct association between OSA and insulin resistance or adiponectin.[26,28] The disparate results may arise from differences in study

populations and analytical approaches as well as failure to account for puberty,[24,26, 28] a period marked by insulin resistance.[29] The obesity epidemic and parallel debut of Type 2 diabetes in children and adolescents[30-32] demand that factors, including OSA, that may contribute to the development of diabetes in this population be explored. We hypothesized that OSA-related hypoxemia and repeated arousals would lead to excess catecholamine release, thereby suppressing secretion of adiponectin, and increasing insulin resistance.

Materials and Methods

Study Group

Children aged 4-18 years with suspected OSA were recruited from the Sleep Center at Children's Hospital of Philadelphia. OSA was suspected based upon the presenting complaint of habitual snoring associated with symptoms of labored breathing during sleep and/or excessive daytime sleepiness. With the exception of children with mild asthma, children with significant, chronic medical conditions such as genetic syndromes, craniofacial anomalies, neurologic disease, or diabetes were excluded. Children receiving medications that could affect sleep or metabolic functions, such as anticonvulsants, sedatives, or oral glucocorticoids were also excluded. In addition, healthy subjects without symptoms of OSA, age 4-18 years, were recruited 1) from the primary care practices affiliated with Children's Hospital of Philadelphia and 2) through regional newspaper advertisement.

The protocol was approved by the Institutional Review Board at the Children's Hospital of Philadelphia. Informed consent was obtained from young adult participants aged 18 years and from parents/guardians of participants < 18 years of age. Assent was obtained from participants > 7 but < 18 years of age.

Anthropometry and Pubertal Development

Weight was measured to the nearest 0.1 kg using a digital scale (Scaltronix, White Plains, NY, USA). Height was measured to the nearest 0.1 cm using a stadiometer (Holtain, Crymych, UK). Age- and gender-specific standard deviation scores (Z-scores) for body mass index (BMI-Z) were calculated

using current reference data from the Centers for Disease Control and Prevention 2000 growth charts for the United States.[33]

Pubertal status was ascertained using a validated self-assessment questionnaire[34-35] to categorize Tanner stages of pubic hair distribution, and genital development for boys and breast development for girls.[36] Subjects were categorized as prepubertal, defined as Tanner stage 1, or pubertal, defined as Tanner stage 2 or greater.

Polysomnography

Overnight polysomnography commenced between 8 and 9 PM and ended at 6 AM. The following parameters were recorded (Somnostar Alpha, SensorMedics, Yorba Linda, CA or Rembrandt, Embla, Broomfield, CO; data output is the same for these devices): electroencephalogram (C3/A2, C4/A1, O1/A2, O2/A1), electrooculogram (left and right), submental electromyogram (EMG), tibial EMG, modified lead 2 electrocardiogram, chest and abdominal wall motion by respiratory inductance plethysmography (SensorMedics, Yorba Linda, CA), airflow by nasal pressure (Pro-Tech Services, Inc, Mukilteo, WA) and three-pronged thermistor (Pro-Tech Services, Inc, Mukilteo, WA); end-tidal PCO_2 by capnography (Novametrix 7000; Novametrix, Wallingford, CT), arterial oxygen saturation (Novametrix 7000 or Masimo, Irvine, CA), oximeter pulse waveform, and digital video.

Sleep architecture, arousals, and respiratory events were analyzed using standard pediatric criteria as recommended by the American Academy of Sleep Medicine.[37] All data were scored by a single Board-certified sleep physician (LJB) who was unaware of subject details and metabolic results.

The following definitions were used:

- Obstructive apnea was defined as cessation of airflow at the nose and mouth, for two or more respiratory cycles, in the presence of movements of the rib cage and abdomen.
- Central apneas were recorded if there was no airflow for 20 seconds in the absence of movements of the rib cage or abdomen. Shorter events were recorded if they were associated with a $\geq$3% decrease in oxyhemoglobin saturation and/or an arousal.

- Hypopnea was defined as a 50% or greater decrease in the amplitude of the airflow signal, associated with a ≥3% decrease in oxyhemoglobin saturation and/or an arousal.
- The Obstructive Apnea Hypopnea Index (O-AHI) was defined as the number of obstructive apneas plus hypopneas, per hour of sleep.
- The Central Apnea Hypopnea Index (Central-AHI) was defined as the number of central apneas plus hypopneas, per hour of sleep.
- The Total Apnea Hypopnea Index (Total-AHI) was defined as the number of obstructive and central apneas plus hypopneas, per hour of sleep.
-The arousal/awakening index (ArI) was defined as the number of arousals (3-15 seconds) plus awakenings (>15 seconds) per hour of sleep.
- Subjects were divided into two groups based upon Total-AHI:

NonOSA: Total-AHI < 1.5[38-40]

OSA: Total-AHI ≥ 1.5

The following polysomnographic parameters were analyzed in relation to metabolic outcomes: Total-AHI, O-AHI, arousal/awakening index (ArI), arterial oxygen saturation nadir (SaO_2 nadir), % total sleep time with SaO_2< 90% (%time SaO_2< 90%), peak end-tidal CO_2 ($ETCO_2$), and total sleep time. O-AHI has been used in previously published pediatric studies, but because central apnea may follow periods of partial upper airway obstruction and increased respiratory effort,[41] metabolic data were analyzed using both O-AHI and Total-AHI.

Metabolic Studies

The morning following polysomnography, blood was drawn for fasting glucose, insulin, and adiponectin. Samples were batched and hormonal assays were completed in the Children's Hospital of Philadelphia Clinical and Translational Research Center Biochemistry Core Laboratory using the

following kits 1) Insulin: ALPCO diagnostics (Catalogue #:08-10-1113-99, Salem, NH) 2) Adiponectin ELISA (B-Bridge; Mountain View, CA), sensitivity 0.02 ng/mL. Homeostasis Model Assessment (HOMA), a measure of insulin sensitivity, was calculated as [fasting blood glucose (mg/dL)* insulin (μU/mL)]/405,[42] We defined HOMA >4.39 as a conservative threshold for insulin resistance from a number of proposed thresholds based upon adolescents with normal weight and normal fasting blood glucose.[43] A 24-hour urine collection for catecholamines (epinephrine, norepinephrine, metanephrines, and normetanephrines) and creatinine was completed and total urine volume recorded. Total volume and creatinine were reviewed to assure adequacy of collection. Urinary catecholamines were analyzed using HPLC (Associated Regional and University Pathologists, Salt Lake City, UT).

Statistical Analyses

Means and standard deviations were used to summarize continuous variables that were normally distributed. Median, minimum, and maximum are presented for variables that were not normally distributed. Proportions were used to summarize categorical variables. To account for the effect of puberty on metabolic outcomes, prepubertal and pubertal children were analyzed separately except with respect to urinary catecholamines where age is an important determinant.

Unpaired t-tests were then used to compare continuous data between children with and without OSA. Either the Mann-Whitney rank-sum or the Kruskal-Wallis test was used to compare non-normally distributed measures. Binary outcomes were compared using the chi-square test.

Logistic regression was used to compare the risks of impaired fasting glucose and elevated fasting insulin in OSA vs nonOSA groups after adjustment for BMI-Z. We performed these same analyses after limiting the groups to children who were obese (BMI-Z$\geq$1.65).

Simple linear regression was first used to assess the unadjusted impact of various polysomnographic measures on HOMA and adiponectin. Multiple linear regression was then used to assess the impact of various polysomnographic measures upon HOMA and adiponectin after adjustment for BMI-Z. Multiple linear regression was also used to assess the association of urinary catecholamines

with various polysomnographic measures after adjustment for age and BMI. The R^2 and likelihood ratio tests were used to assess model fit.

Type I error rate of 0.05 was imposed for assessing statistical significance. All statistical analyses were performed using Stata statistical software (Stata Corp., College Station, TX, USA).

Results

Study Group

Polysomnography and metabolic studies were performed in 100 children Eighteen of these children were recruited as controls from the community, and the remainder (n=82) was recruited from the Sleep Center. One child was excluded because positive airway pressure was initiated during the overnight polysomnography due to the severity of OSA. A second child was eliminated based upon the finding of central apnea arising from a Chiari malformation. Thus, 98 children completed the study (57% male/ 43% female): 37 prepubertal and 61 pubertal, Table 1. Racial composition was 48% Caucasian, 45% African-American, two Asian, three mixed and one child of unknown race.

Polysomnography: Despite the suspicion of OSA in 80 children, 33 of these had normal polysomnograms (Total-AHI<1.5), findings consistent with those reported in the literature.[44] Seven of the 18 children recruited from the local community had mild OSA (Total-AHI≥1.5 but <5) and one had moderate OSA (Total-AHI=5.5) despite absence of symptoms. Data from asymptomatic and symptomatic children were pooled and characterized according to polysomnographic results.

Metabolic Studies: Three samples were excluded from glucose, insulin, and HOMA data as the subjects did not fast. Five were excluded due to specimen collection issues. These data were missing completely at random and should not introduce bias into the results.

Obstructive Sleep Apnea and Metabolic Studies

In the regression models, HOMA and adiponectin were both positively associated with puberty, BMI-Z, and the various polysomnographic parameters. However, stratification of models by puberty improved fit. Thus, data were analyzed separately for prepubertal and pubertal children.

Prepubertal Children

BMI-Z was similar in prepubertal children with and without OSA, p=0.3 (see Table 1). Only three prepubertal children with OSA had an AHI$\geq$5 (8.5, 15, and 104 events/hour), Table 2.

Mean fasting blood glucose, insulin, HOMA, and adiponectin were similar in prepubertal children with and without OSA Table 3. Two obese prepubertal children had impaired fasting glucose ($\geq$100 mg/dL), but only one had OSA (Total-AHI=1.6). Two obese children had fasting insulin $\geq$ 20 μU/mL (a threshold frequently used to define insulin resistance), but only one had OSA (Total-AHI=104). No associations between the various polysomnographic measures and either HOMA or adiponectin were found after adjustment for BMI-Z.

Pubertal Children

In pubertal children, BMI-Z was higher if OSA was present (p=0.03), Table 1. As expected, polysomnographic parameters were significantly different between pubertal children with and without OSA with the exception of total sleep time (p=0.11), Table 2.

Thirteen obese pubertal subjects had impaired fasting glucose ($\geq$100 mg/dL). Ten of these had OSA. The proportion of subjects with impaired fasting glucose did not differ between OSA and nonOSA groups (p=0.08), and the risk did not differ with inclusion of BMI-Z in the model (p=0.1) or with inclusion of only obese children.

The overall fasting insulin (23$\pm$18 μU/mL) tended to be increased in pubertal children. In fact, fasting insulin was $\geq$20 μU/mL in 10/27 nonOSA and 22/34 OSA pubertal children (p=0.03). The risk of having elevated insulin was not different after adjustment for BMI-Z (0.1), but if only obese pubertal children were included, the relative risk of having an elevated fasting insulin was 1.5 times higher in the

OSA group (0.04), despite similar BMI-Z in the two obese groups (p=0.2). The risk of elevated HOMA was similarly increased in obese pubertal children with OSA (p=0.05).

As expected, BMI-Z was positively associated with HOMA in pubertal children (p<0.001). Similarly, Total-AHI (p=0.03), O-AHI (p=0.02), lowest SaO_2 (p=0.049). and peak $ETCO_2$ (p=0.05) were associated with higher HOMA in pubertal children. However, following adjustment for BMI-Z, none of these polysomnographic measures was associated with worse insulin resistance. Neither sex nor other polysomnographic measures, including total sleep time, was associated with HOMA.

Total-AHI (p=0.01), O-AHI (p=0.01), %time SaO_2<90% (p=0.001), SaO_2 nadir (p=0.04), and peak ETCO2 (p<0.001) were associated with significantly lower adiponectin in pubertal children. In contrast to the findings with HOMA, these associations persisted following adjustment for BMI-Z, although an effect modification was present with BMI-Z (see Table 4).

OSA and Catecholamines

The association between OSA and urinary catecholamines was then examined following adjustment for BMI and age, since urinary catecholamine decrease with age in children (see Table 5).[45] Total-AHI, O-AHI, SaO_2 nadir , %time SaO_2<90% , and arousal index were all associated with increased urine normetanephrine, a metabolite of norepinephrine. Although a weaker relationship was present, Total-AHI, O-AHI, and SaO_2 nadir were also associated with increased urine norepinephrine. No association between urinary catecholamines and adiponectin or HOMA was found.

Discussion

We have shown that in pubertal children a number of markers of OSA severity are negatively associated with adiponectin, even after adjustment for BMI-Z. Moreover, OSA was associated with increased risk of insulin resistance in obese pubertal children. Additionally, worsening OSA parameters were associated with higher urinary catecholamines, particularly normetanephrine, consistent with increased sympathetic tone. These findings suggest OSA aggravates an obese child's predisposition to metabolic syndrome, potentially through multiple mechanisms including effects on adipose and the

sympathetic nervous system. They also highlight the importance of considering separately the effect of puberty on metabolic outcomes.

Several potential mechanisms by which OSA portends insulin resistance and inflammation have been proposed. The finding of lower adiponectin in the setting of severe OSA supports one such potential mechanism. Adiponectin is an adipocyte-secreted protein hormone; its plasma level, unlike most adipokines, negatively correlates with body fat. It has insulin-sensitizing, anti-inflammatory, and anti-atherogenic properties. In a previous study of pediatric OSA, lower adiponectin was not observed in children with an AHI>5 after adjustment for BMI-Z.[28] Whether the disparity arises from lack of accounting for the effect of puberty upon adiponectin[46] or differences in severity or duration of OSA is not clear. It is important to note that while BMI-Z, like many measures of OSA, is negatively associated with adiponectin, it is also an effect modifier. The association between the various polysomnographic parameters and adiponectin was not simply additive; it was attenuated with increasing BMI-Z and AHI.

In addition to an association of OSA with lower adiponectin levels, we also report an association of pediatric OSA with enhanced sympathetic output, as measured by urinary normetanephrine and norepinephrine. Two recent pediatric studies have also identified increased morning urinary norepinephrine[47-48] in the setting of OSA. Even more compelling, alterations in the expression profiles of genes involved in catecholamine production and signaling.[47] In contrast to our study, however, an increase in urinary epinephrine[47] was found; this difference may reflect metabolism of epinephrine to norepinephrine given that a 24-hour collection was completed in our study vs the first morning void, presumably reflecting overnight sympathetic activity. In the Snow study[47], catecholamines were not related to BMI; the difference between the Snow study[47] and the Kaditis[48] and our pediatric study may involve inclusion of age in the model since catecholamines decrease with age in children.[45] Catecholamines are known to be increased in adults with OSA.[49-50] In addition, catecholamines suppress adiponectin secretion in vitro [51] and likely regulate adiponectin in vivo.[52] Based on these data, we originally hypothesized that catecholamines might be the mediator of lower adiponectin. Our inability to demonstrate an association between adiponectin and catecholamines does not exclude a direct effect of

catecholamines upon insulin resistance; for instance, catecholamines increase adipocyte secretion of tumor necrosis factor-α,[53] which acts directly to inhibit insulin action.

The importance of adjusting for puberty in a pediatric study of insulin sensitivity cannot be over-emphasized. Puberty is a well-recognized period of insulin resistance.[29] In our study, even after adjustment for BMI-Z, puberty was associated with a HOMA that was an average of 2.8 points higher than that in prepubertal children. In one of the first studies highlighting the importance of OSA and insulin, OSA was found to be associated with higher insulin concentrations in obese children age 5-16 years after adjustment for age.[24] While age captures some degree of puberty it is not synonymous with puberty. Thus, some of the effect could arise from puberty, particularly if the pubertal children were more likely to have worse OSA as observed in our study. In our study, failure to find an association between OSA and metabolic parameters may have less to do with lack of an association than with the generally milder OSA in our prepubertal group or, perhaps, duration of OSA.

Several limitations of this study are worth mentioning. First, BMI-Z is a surrogate for body fat and adjustment for BMI does not rule out an effect of fat mass on adiponectin. Additionally, BMI-Z does not differentiate between visceral and peripheral adiposity. Specifically, increased visceral adiposity is associated with greater insulin resistance and inflammation. Moreover, inflammation characterizes obese adipose tissue,[54] and this inflammation of obese adipose tissue is one proposed mechanism leading to insulin resistance. Nonetheless, BMI-Z has been found to corrleate well with direct measures of body fat and to be accurate at classifying children who were overfat.[55] Since Gozal et al. found OSA was associated with worse insulin resistance only in overweight/obese children,[56] OSA may be aggravating the inflammatory state of the obese individual, driving insulin resistance through perturbations in obese adipose tissue. In the current study, we had insufficient numbers of normal weight children with moderate or severe OSA to test the specific hypothesis that OSA interacts with obese adipose tissue to aggravate insulin resistance. Further larger scale studies which include more objective measures of fat mass are needed to better delineate these relationships.

Additionally, total adiponectin rather than high molecular weight adiponectin, which is considered the most biologically active form of the hormone,[57] was measured; however, both are associated with increased risk for diabetes.[58] The hyperinsulinemic euglycemic clamp, considered the gold-standard for measuring insulin sensitivity, was not performed for ethical concerns in children.[59-61] Instead, HOMA, a simple method of assessing insulin sensitivity, was used. While HOMA is a surrogate measure with inherent limitations, it has been validated in non-diabetic children.[62] Finally, sleep deprivation has been associated with increased risk of impaired glucose tolerance,[63] diabetes, [64] and insulin resistanc.[65] While data on duration of sleep was not related to the metabolic outcomes in this study, actigraphy was not performed and future studies are necessary to unravel the contribution of chronic sleep deprivation to both OSA severity and metabolic derangements.

Finally, self assessment was used to determine pubertal stage using a validated tool. [34-35] While assessment by trained personnel would have been ideal, use of the self-assessment exam are unlikely to bias results as both children with OSA and nonOSA used the tool. In addition, in a subset of subjects serum gonadotropins, estradiol, and testosterone were obtained in the morning and were consistent with pubertal status (data not shown).

Given current findings of lower adiponectin, enhanced catecholamine output, and increased risk insulin resistance in obese pubertal children with OSA, the long-term burden of OSA may be a substantial threat to cardiovascular health. These findings underscore the need to recognize and address co-morbidities of obesity and they highlight the importance of understanding the pediatric origins of adult disease.

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Table 1 Patient Characteristics by Pubertal and OSA Status

	AHI (events/hr)	n (males)	Age, yrs mean±SD	BMI-Z Median (min, max)
Prepubertal	<1.5	17 (12)	6.9±1.9	0.7 (-1.8, 2.8)
	>1.5	20 (11)	6.7+1.8	1.6 (-3, 4.1)
Pubertal	<1.5	27 (12)	13.4+2.5	2.2 (-2.5, 2.8)*
	>1.5	34 (21)	13+2.8	2.4 (-0.05, 3.2)

*p=0.03 Pubertal OSA vs nonOSA

1 Table 2. Polysomnography Results median (min,max)

OSA category	O-AHI events/hr	Central-AHI events/hr	Total AHI events/hr	Arousal Index events/hr	SaO_2 nadir (%)	% Sleep Time SaO_2 <90%	$ETCO_2$mm Hg	Sleep Time (hrs)
Prepubertal								
nonOSA (n=17)	0.1 (0, 0.7)	0.4 (0, 1.3)	0.3 (0,1.3)	0 (0, 0.7)	93 (89, 97)	0 (0, 2.5)	50 (43, 58)	7.4 (5.7,8.8)
OSA (n=20)	0.95* (0, 104)	1.1 (0, 2.6)	2.6* (1.5, 104)	0.2# (0, 8.2)	92 (62, 95)	0 (0, 33)	52 (46, 60)	7.6 (4.9,8.9) (6.7, 7.7)
Pubertal								
nonOSA	0.3 (0, 1.3)	0.1 (0, 1.3)	0.6 (0, 1.3)	0 (0, 1)	92 (87, 96)	0 (0, 2.8)	48 (40, 55))	6.9 (4.9, 8.2)
OSA	7.4* (0.6, 185)	0.7 (0, 18)	7.5* (1.9, 185)	0.8 (0, 110)	86# (44, 96)	1.1### (0, 56)	54* (45, 85)	6.8 (4.4, 8.3)

2 *p=0.0001 p=0.02 p=0.04 #p=0.002 ###p=0.005

1 Table 3. Metabolic Characteristics, median (min, max)

OSA category	Fasting glucose (mg/dL)	Fasting insulin (μU/mL)	HOMA	Adiponectin (μg/mL)
Prepubertal				
nonOSA	85 (63, 101) n=16	4.7 (3, 36) n=16	1 (0.5, 8.5) n=16	19 (4.7, 51) n=16
OSA	87 (77, 100) n=19	6.7 (3, 29) n=19	1.5 (0.6, 6.7) n=19	15.2 (3.5, 38) n=19
Pubertal				
nonOSA	91 (80, 107) n=25	15 (3, 59) n=25	3.3 (0.6, 16) n=25	14 (3, 25) n=27
OSA	92 (77, 115) n=34	24 (3, 99) n=28	5.4 (0.6, 27) n=28	9.2 (2.5, 28) n=33

1 Table 4. Effects of OSA Adjusted for BMI-Z upon log Adiponectin in Pubertal Children (n=60)

Variable	Partial β-coefficient (95% CI)	p-value	R^2
			0.32
BMI-Z	-0.25 (-0.33 to –0.07)	<0.0001	
Total AHI	-0.04 (-0.07 to –0.2)	0.001	
BMI-Z*Total AHI	0.01 (0.006 to 0.03)	0.002	
			0.34
BMI-Z	-0.24 (-0.36 to –0.12)	<0.0001	
Time SaO_2<90%	-0.1 (-0.18 to –0.03)	0.004	
BMI-Z*Time SaO_2<90%	0.04 (0.01 to 0.06)	0.015	
			0.32
BMI-Z	-0.18 (-0.30 to –0.06)	0.004	
$ETCO_2$	-0.03 (-0.05 to –0.01)	0.005	

2 similar results if O AHI was used

Table 5. Effects of OSA Adjusted for Age and BMI upon Urine Catecholamines (n=81)

Variable	Partical β-coefficient (95% CI)	p-value	R^2	Partial β-coefficient (95% CI)	p-value	R^2
	Log Normetanephrine			Log Norepinephrine		
Total AHI*	0.004 (0.002-0.008)	0.001	0.35	0.0043 (-0.0004 to 0.006)	0.03	0.09
Lowest SaO_2	-0.02 (-0.03 to -0.01)	<0.001	0.37	-0.02 (-0.03 to –0.003)	0.003	0.13
Time SaO_2<90%	0.01 (0.001-0.02)	0.024	0.30	NS		
ArI	0.008 (0.002-0.01)	0.008	0.32	0.008 (-0.0002 to 0.02)	0.054	0.07

*similar results if O-AHI

NS not significant