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SCIENTIFIC INVESTIGATIONS

Insulin Resistance and Hypertension in Obese Youth With Sleep-Disordered Breathing Treated With Positive Airway Pressure: A Prospective Multicenter Study

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Study Objectives: There is evidence that cardiometabolic disease associated with obesity and sleep-disordered breathing (SDB) in adults is present in youth. SDB is often treated with positive airway pressure (PAP) in youth with obesity. Our aims were to determine: (1) the prevalence of cardiometabolic disease and (2) whether PAP improves markers of cardiometabolic disease, in youth with obesity and newly diagnosed moderate-severe SDB.

Methods: A prospective multicenter cohort study was conducted in youth (8 to 16 years old) with obesity, prescribed PAP therapy for newly diagnosed moderate-severe SDB. Assessments occurred at baseline and at 6 and 12 months. Outcomes included markers of insulin resistance (change in homeostasis model assessment of insulin resistance (HOMA-IR) at 6 months = primary outcome), hypertension (24-hour ambulatory/blood pressure) and inflammation (high-sensitivity C-reactive protein: hs-CRP).

Results: Twenty-seven participants were enrolled. Of those with baseline testing available, 10/25 (40%) had HOMA-IR above the 97th percentile, 10/23 (44%) were hypertensive, 16/23 (70%) had loss of nocturnal blood pressure dip and hs-CRP was elevated in 16/27 (64%). There were no significant changes over time in markers of metabolic dysfunction or blood pressure, nor between PAP-adherent and non-adherent subgroups.

Conclusions: In youth with obesity and SDB, metabolic dysfunction and hypertension were highly prevalent. There were no statistically significant improvements in cardiometabolic markers 1 year after the prescription of PAP therapy, although clinically relevant improvements were seen in insulin resistance and systolic blood pressure load, important predictors of future risk of cardiovascular disease. Larger, longer-term studies are needed to determine whether PAP improves cardiometabolic outcomes in obese youth.

Commentary: A commentary on this article appears in this issue on page 1025.

Keywords: adolescent, biphasic continuous positive airway pressure, child, continuous positive airway pressure, hypertension, inflammation, insulin resistance, sleep apnea syndromes

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INTRODUCTION

The fivefold increase in prevalence of childhood obesity in North America over the past 20 years has led to an increasing number of pediatric cases of obesity-related sleep-disordered breathing (SDB), which includes both obstructive sleep apnea (OSA) and nocturnal hypoventilation.[1] The prevalence of SDB, particularly OSA, is significantly higher among obese children (13% to 66%) compared with the general population (1% to 3%).[2] Routine treatment for SDB with adenotonsillectomy is not curative in 70% to 80% of children with obesity.[3] Thus, positive airway pressure (PAP) treatment is usually prescribed.[2]

Additional obesity-related complications are also increasingly recognized in children, including metabolic disturbances with insulin resistance (IR) and hypertension.[4,5] This is concerning, as IR is an identified surrogate measure of future obesity-related sequelae, including diabetes, dyslipidemia, cardiovascular disease (such as hypertension and heart rate disturbances), inflammation, and impaired

BRIEF SUMMARY

Current Knowledge/Study Rationale: In adults with obesity and sleep-disordered breathing (SDB), treatment with positive airway pressure (PAP) improves metabolic dysfunction, hypertension, and systemic inflammation. It is not known whether these conditions are already present at SDB diagnosis in youth or whether long-term PAP therapy improves markers of cardiometabolic disease in this population.

Study Impact: This study demonstrated that cardiometabolic disease (insulin resistance [HOMA-IR], hypertension, and systemic inflammation) is highly prevalent at the time of SDB diagnosis in youth with obesity. We were unable to detect statistically significant improvements in cardiometabolic markers 1 year after prescription of PAP therapy. There were, however, clinically relevant improvements in insulin resistance and systolic blood pressure load, important predictors of future risk of cardiovascular disease.

quality of life. Of particular interest, the IR related to obesity can be exacerbated by SDB and the severity of IR correlates with SDB severity.[6–8] Repetitive intermittent hypoxia, which occurs as a result of SDB, stimulates sympathetic nervous system activity, which leads to gluconeogenesis and peripheral IR.[9]

In adults with obesity and OSA, the homeostasis model assessment of insulin resistance (HOMA-IR) is a well-accepted surrogate marker of insulin sensitivity[10] that has been shown to improve following PAP therapy.[9,11] The association between OSA and insulin resistance is inconsistent across pediatric studies, possibly due to heterogenous populations of different ages and pubertal stages. Four small pediatric studies have not shown significant improvements in IR with adenotonsillectomy in young children with OSA, some of whom were obese.[4,12–15] Similarly, glucose and insulin levels did not change significantly in a large randomized controlled study of non-obese or obese young children 7 months after randomized treatment of adenotonsillectomy or watchful waiting.[16] In contrast, one study of children undergoing adenotonsillectomy showed improvement in HOMA-IR 8 months later, despite the prevalence of residual OSA and increase in body mass index (BMI).[17] Only one study has evaluated the effect of PAP therapy for OSA in children with obesity and preexisting severe metabolic disturbances, including IR.[15] Improvements in mean fasting glucose and insulin levels as well as insulin sensitivity were demonstrated with 3 months of PAP therapy, without changes in BMI, but the results failed to reach statistical significance (likely due to the small sample). This trend is encouraging and suggests that PAP therapy alone may improve IR in children.

Hypertension is also a recognized complication of both obesity and OSA in adults and children.[5,18] Sympathetic nervous system activation is the proposed pathophysiology, with loss of nocturnal blood pressure (BP) dip initially, progressing to diurnal hypertension.[19,20] Loss of the nocturnal BP dip has been shown in children with OSA to be the first repercussion of OSA on the circulatory system.[19] Treatment of OSA with PAP in adults with obesity improves hypertension and decreases incidence of cardiovascular events including myocardial infarction and stroke.[21] Three pediatric studies have examined the effect of adenotonsillectomy on BP; two of these studies used office BP measurements and did not demonstrate significant improvements in BP,[13,22] whereas one study used 24-hour ambulatory BP measurements (ABPM) and did show improvement.[23] The effect of PAP treatment on 24-hour BP in children with SDB has not been evaluated.

Given the mounting evidence that the cardiometabolic disease associated with obesity and SDB in adults is also present in children and youth,[24] we hypothesized that PAP treatment for children with obesity and moderate-severe SDB would improve markers of obesity-related disease. To our knowledge, no study exists that specifically evaluates outcomes in children with obesity identified to have SDB and treated with PAP for at least 6 months. The aim of this study was therefore to evaluate the change in HOMA-IR and 24-hour BP after 6 months and 1 year of PAP treatment for children and youth with obesity and newly diagnosed SDB.

METHODS

Study Design

We conducted a prospective multicenter cohort study of children and youth with obesity, aged 8 to 16 years, with moderate-severe SDB newly diagnosed on polysomnography, who were prescribed PAP therapy for treatment. Participants were recruited from four tertiary care pediatric centers across Canada between June 2011 and July 2014. Ethics approval was obtained from the hospital Research Ethics Board at each of the participating study sites (Children's Hospital of Eastern Ontario, Ottawa, Ontario; Montreal Children's Hospital, Montreal, Quebec; Stollery Children's Hospital/University of Alberta, Edmonton, Alberta; Alberta Children's Hospital/University of Calgary, Calgary, Alberta). Informed consent/assent was obtained from participants and their parents/guardians. Participants were followed for 1 year following recruitment, with study evaluations performed at baseline (at the time of recruitment and within 3 months of PAP initiation), 6 months, and 12 months.

Study Population

The study population included children and youth 8 to 16 years old with obesity (defined as BMI greater than or equal to the 95th percentile for sex and age based on the 2000 Centers for Disease Control and Prevention Growth Charts for the United States)[25]; with moderate-severe SDB (OSA and/or obesity hypoventilation) which was newly diagnosed on polysomnography; and for which either continuous PAP (CPAP) or bilevel PAP (bilevel) therapy was prescribed by their treating physician. Eligible individuals were also required to be fluent in English or French. Children and youth with the following conditions were excluded: craniofacial anomalies other than tonsillar and adenoid enlargement; central nervous system lesions; neuromuscular, neurological, or genetic syndromes; congenital heart disease and/or diagnosed ventricular dysfunction; chronic respiratory disease with the exception of asthma; use of oral or intravenous corticosteroids within the past 3 months; regular compliant use of PAP therapy; use of pharmacological sleep aids; and/or known type 1 or 2 diabetes treated with medication.

The presence of SDB was confirmed prior to study enrollment, using overnight laboratory diagnostic polysomnograms conducted and scored by sleep technologists, according to the American Academy of Sleep Medicine recommendations, and classified as moderate or severe.[26,27] Moderate to severe OSA was defined as an obstructive apnea-hypopnea index of greater than or equal to 5 obstructive apneas or hypopneas per hour (moderate: 5–9.9 events/h; severe: greater than or equal 10 events/h). Although no strict guidelines for defining severity of OSA in children exist, the definition for this study was derived by a consensus of pan-Canadian pediatric sleep medicine experts, who agreed that this degree of SDB warranted PAP therapy. Obesity hypoventilation was defined as $CO_2 > 50$ mmHg for > 25% of total sleep time.[27] An additional inclusion criterion was fluency of parents/guardians and the children/youth in English or French (due to the need for comprehension and completion of study questionnaires).

Children were excluded from the study if they had the following comorbid conditions that may have contributed to development of SDB: craniofacial anomalies other than tonsillar and adenoid enlargement; central nervous system disorders including structural lesions; neuromuscular, neurological, or genetic syndromes; congenital heart disease and/or diagnosed ventricular dysfunction; or chronic respiratory disease with the exception of asthma. Children were excluded if they had conditions associated with impairment of IR, including known type 1 or 2 diabetes or the use of oral or intravenous corticosteroids within the 3 months prior to initiation of PAP therapy. Children were also excluded if they were already receiving and were adherent with PAP therapy or were using pharmacological sleep aids.

Measurements

Demographic variables including age, sex, height, and weight were determined at baseline. Height and weight measurements were repeated at the 6- and 12-month visits. BMI was calculated as weight in kilograms divided by the square of the height (in meters), following which sex- and age-specific BMI *Z*-scores and corresponding percentiles were calculated.[25] Tanner stage was assessed by a pediatrician at baseline.[28]

Fasting bloodwork was obtained at baseline, 6 months, and 12 months, in order to calculate HOMA-IR (the primary outcome of this study) and to measure C-reactive protein (CRP) using a high sensitivity (hs-CRP) assay. HOMA-IR is calculated from simultaneous fasting blood glucose and insulin levels[10]:

$$\frac{[\text{fasting insulin (pmol/L)} \times 0.1394] \times \text{fasting plasma glucose (mmol/L)}}{22.5}$$

Lower HOMA-IR values indicate higher insulin sensitivity. In order to account for changes in HOMA-IR values that occur with age and sex, HOMA-IR values were converted to *Z*-scores, derived from HOMA-IR percentiles from an overweight/obese population sample.[29] Because reference values were only available up to the 97th percentile, in cases where the HOMA-IR exceeded the 97th percentile, we simply assigned the *Z*-score corresponding to the 97th percentile (ie, 1.88).

A 2-hour oral glucose tolerance test (OGTT) was also performed at baseline and 1 year. This consisted of blood sampling for glucose, measured fasting, and 2 hours after an oral glucose load of 1.75 g/kg weight (maximum of 75 g). This test is used in clinical practice to assess for impaired glucose tolerance,[24] as most children and adolescents with impaired glucose tolerance have normal fasting blood sugar levels.[30] Although the HOMA-IR is a more sensitive measure of changes in insulin sensitivity, the OGTT is uniquely able to evaluate postprandial glucose metabolism and glucose-stimulated insulin secretion.[31] The 2-hour OGTT was considered abnormal if the fasting glucose level was greater than or equal to 6.1 mmol/L and/or the 2-hour postload glucose level was greater than or equal to 7.8 mmol/L.[32]

Blood samples were also obtained at baseline, 6 months, and 12 months for analysis of hs-CRP, which is released during the chronic inflammation underlying atherosclerosis and is predictive of vascular events.[4]

Twenty-four-hour BP measurements were recorded on a portable electronic device (Spacelabs monitor Model # 90207-IQ, Spacelabs Healthcare, Issaquah, Washington, United States) worn by participants at baseline and 1 year later. BP measurements were obtained from the right arm, using an appropriate-sized BP cuff, every 15 minutes until midnight, every 30 minutes from midnight until 6:00 AM and then every 15 minutes thereafter, over a 24-hour sampling period. Outcomes of interest included the total systolic, diastolic, and mean arterial BP percentiles (24-hour, nocturnal, and daytime), BP loads and percent of nocturnal BP dip. Those children/youth with average systolic, diastolic or mean arterial BP (day, night or 24-hour) greater than the 95th percentile for sex and height were considered to be hypertensive.[33] A BP load (defined as the proportion of readings greater than the 95th percentile) greater than 25% was considered abnormal as per pediatric guidelines, representing significant exposure to elevated BP throughout the time period.[34] The percentage of nocturnal BP dip was calculated as:

$$\frac{\text{day systolic average BP percentile} - \text{night systolic average BP percentile}}{\text{day systolic average BP percentile}}$$

A dip < 10% was considered abnormal.[34]

Adherence to PAP therapy was assessed by participants' PAP usage diaries, self-report at clinic visits, and corroborated with downloaded information from PAP machines' internal data-loggers. PAP adherence was defined as use of PAP therapy for an average of ≥ 4 h/night and > 50% of nights. A summary judgment of whether these PAP adherence criteria were met was provided by the treating physician and was used where downloaded PAP information was not available.

Statistical Analysis

Descriptive statistics were generated for demographic variables at baseline. Categorical variables were summarized using percentages. Continuous variables were summarized using median, interquartile range (IQR), and range. Due to small sample sizes and non-normal distributions, all statistical tests were nonparametric.

Spearman correlations were used to assess associations at baseline between sleep parameters and BMI *Z*-score, markers of metabolic dysfunction and hypertension. When a value of $P < .05$ for an association of a sleep parameter with a given marker of metabolic dysfunction or hypertension was obtained, adjustment for the multiple testing of associations with that marker was performed using the Holm method.

To investigate whether there was substantial change over time in the mean BMI among study participants, a linear mixed-effects model was applied to BMI *Z*-score at baseline, 6 months, and 12 months. For the whole group, changes from baseline in markers of metabolic dysfunction were examined at 6 months and 12 months and change from baseline in hypertension was examined at 12 months using the Wilcoxon signed-rank test. Comparisons of changes in these markers were also made between participants who were adherent at 6 months and those who were not, using the Mann-Whitney *U* test. We chose PAP adherence data at the 6-month mark because it was the

Table 1—Characteristics of the cohort at baseline (n = 27).

	Total Group (n = 27)
Age, years, median (IQR) [range]	14.5 (12.6 to 16.5) [8.1 to 17.2]
Male, n (%)	22 (81.5)
Tanner stage†, n (%)	
1	2 (7.7)
2	7 (26.9)
3	3 (11.5)
4	9 (34.6)
5	5 (19.2)
BMI *Z*-score, median (IQR)	2.6 (2.3 to 2.8)
Total AHI*, events/h, median (IQR) [range]	15.5 (7.4 to 25.2) [5.4 to 157.9]
OAHI*, events/h, median (IQR) [range]	16.8 (7.1 to 23.9) [0 to 157.9]
Lowest oxygen saturation*, %, median (IQR) [range]	84 (77 to 90) [50 to 95]
Highest CO_2*, mmHg, median (IQR) [range]	50 (46 to 53) [40 to 70]
Sleep duration, hours, median (IQR) [range]	8.5 (8.2 to 9.8) [7.3 to 10.8]

† = one missing, * = two cases excluded because of split-night studies where diagnostic portion was too short for analysis. AHI = apnea-hypopnea index, BMI = body mass index, IQR = interquartile range, OAHI = obstructive apnea-hypopnea index.

most complete data available for our participants and it has been shown in previous studies that early adherence to PAP predicts longer-term adherence.[35] To examine factors associated with change in HOMA-IR status (above or below the 97th percentile for sex and age) at 6 months, a logistic regression model was constructed incorporating the following predictors: HOMA-IR status at baseline and change in BMI *Z*-score at 6 months. A value of $P < .05$ was considered statistically significant for all tests.

RESULTS

Forty-seven children were screened and 27 were enrolled in the study. Metabolic follow-up was completed by 22 participants at 6 months, and 19 participants at 12 months. Complete HOMA-IR data at baseline and 6 months was available for 20 participants. Blood pressure measurements at 12 months were completed by 16 participants, of whom 15 had complete BP data at baseline and 12 months. Regarding racial/ethnic background, 70% of our sample was Caucasian. There were two Black children, and one each of other backgrounds. Additional demographic information is provided in **Table 1**.

Twenty-five of 27 (93%) had OSA, and 2 had evidence of obesity hypoventilation. At baseline, of the 25 participants with OSA, 7 (26%) had moderate OSA and 18 (67%) had severe OSA. The apnea-hypopnea index (AHI) improved for all 20 participants with follow-up polysomnograms performed on PAP therapy (median improvement 14.3, IQR 7.7 to 22.3, $P = .001$). In all cases but one, AHI improved to less than 5 events/h when the final PAP settings were reached. In the one case where AHI was greater than 5 events/h after PAP titration, the AHI decreased from 157.9 events/h (in the 12 minutes prior to PAP initiation) to 25.5 events/h with PAP therapy, a reduction of 84%.

Fourteen participants (52%) were treated with CPAP and 13 (48%) with bilevel. The range of inspiratory PAPs was 10–20 cmH_2O. Expiratory PAP/CPAP pressures ranged from 6 to 12 cmH_2O. Of the 22 participants completing 6-month follow-up with metabolic outcomes, 14 (64%) were adherent to PAP therapy according to the treating physician's judgment. In all but one case, PAP use exceeded an average of 6 h/night. Data downloaded from PAP machines were available for 17 participants and agreement with physician's judgment was high (kappa = 0.64). There were no significant differences in adherence rates for individuals on CPAP or bilevel (11/13 (85%) versus 6/13 (46%), $P = .10$). The BMI *Z*-score at baseline was not significantly different between adherent and non-adherent subgroups (2.65 ± 0.36 versus 2.49 ± 0.33, $P = .56$).

Baseline

At baseline, HOMA-IR values were available for 25 of 27 participants. Ten of them (40%) had HOMA-IR above the 97th percentile for age and sex compared to a reference population of overweight/obese youth. Tanner stage (Spearman correlation = −.04, $P = .84$) and sleep duration (Spearman correlation = .12, $P = .58$) were not significantly associated with HOMA-IR status. OGTT was performed on 23 of 27 participants, of whom 2 (9%) had abnormalities at baseline. hs-CRP was available for 25 of 27 participants and was above 3 mg/L, a threshold associated with elevated cardiovascular risk, in 16 participants (64%). Only hs-CRP was significantly associated with BMI *Z*-score (**Table 2**). Metabolic and inflammatory parameters were not significantly associated with any sleep parameters (**Table 2**).

Blood pressure measurement data were obtained in 23 participants at baseline. Using a hypertension definition of any of the day, night, or 24-hour systolic, diastolic, or mean arterial pressure values greater than the 95th percentile, 10 of 23 participants (44%) were hypertensive. Nocturnal hypertension was present in 10 (44%) whereas 2 participants (9%) had both nocturnal hypertension and daytime hypertension. Half of those who had nocturnal hypertension had systolic but not diastolic BP elevation, whereas none had isolated diastolic BP elevation.

Table 2—Associations at baseline between cardiometabolic markers with body mass index and sleep parameters.

		Sleep Parameters				
	BMI Z-score	Total AHI (events/h)	OAHI (events/h)	Lowest O_2 Sat (%)	Highest CO_2 (mmHg)	RAI (events/h)
Markers of Metabolic Dysfunction (n = 25)						
HOMA-IR	.37 (*P* = .07)	−.09 (*P* = .69)	.00 (*P* = 1.00)	.29 (*P* = .17)	−.07 (*P* = .74)	−.18 (*P* = .40)
HOMA-IR Z-score (censored)	.38 (*P* = .06)	−.03 (*P* = .89)	−.01 (*P* = .97)	.35 (*P* = .09)	−.06 (*P* = .80)	.13 (*P* = .54)
Fasting glucose (mmol/L)	.18 (*P* = .38)	.17 (*P* = .40)	.20 (*P* = .38)	.20 (*P* = .33)	.14 (*P* = .51)	.01 (*P* = .96)
Fasting insulin (pmol/L)	.33 (*P* = .11)	−.10 (*P* = .62)	−.01 (*P* = .99)	.27 (*P* = .19)	−.08 (*P* = .70)	.01 (*P* = .97)
hs-CRP (mg/L)	.57 (*P* = .003)*	.04 (*P* = .85)	−.08 (*P* = .74)	−.13 (*P* = .55)	−.22 (*P* = .31)	−.06 (*P* = .78)
Measures of Hypertension (n = 23)						
24-h SBP Z-score	.15 (*P* = .50)	−.16 (*P* = .47)	−.33 (*P* = .17)	−.25 (*P* = .26)	−.02 (*P* = .92)	−.01 (*P* = .98)
Nocturnal SBP Z-score	.15 (*P* = .50)	−.05 (*P* = .81)	−.27 (*P* = .27)	−.06 (*P* = .80)	.05 (*P* = .84)	.07 (*P* = .77)
24-h DBP Z-score	−.02 (*P* = .93)	−.02 (*P* = .92)	−.23 (*P* = .35)	−.26 (*P* = .23)	.23 (*P* = .33)	−.07 (*P* = .76)
Nocturnal DBP Z-score	.04 (*P* = .87)	.07 (*P* = .74)	−.09 (*P* = .73)	−.08 (*P* = .71)	.35 (*P* = .12)	.03 (*P* = .89)
24-h MAP Z-score	.06 (*P* = .80)	−.06 (*P* = .77)	−.25 (*P* = .31)	−.43 (*P* = .04)^	−.02 (*P* = .92)	.04 (*P* = .88)
Nocturnal MAP Z-score	.04 (*P* = .86)	−.05 (*P* = .83)	−.24 (*P* = .33)	−.15 (*P* = .50)	.14 (*P* = .56)	.01 (*P* = .98)
SBP load (%)	.25 (*P* = .25)	−.08 (*P* = .73)	−.18 (*P* = .46)	−.29 (*P* = .19)	.02 (*P* = .95)	−.01 (*P* = .96)
DBP load (%)	.12 (*P* = .58)	−.09 (*P* = .68)	−.12 (*P* = .64)	−.10 (*P* = .64)	.14 (*P* = .54)	−.12 (*P* = .60)
Nocturnal SBP dip (%)	−.13 (*P* = .56)	−.02 (*P* = .93)	.14 (*P* = .56)	−.30 (*P* = .17)	−.09 (*P* = .71)	.04 (*P* = .87)
Nocturnal DBP dip (%)	−.06 (*P* = .78)	.08 (*P* = .71)	.15 (*P* = .55)	−.16 (*P* = .46)	−.26 (*P* = .26)	.11 (*P* = .63)
Nocturnal MAP dip (%)	−.07 (*P* = .74)	.12 (*P* = .60)	.22 (*P* = .37)	−.23 (*P* = .30)	−.12 (*P* = .61)	.12 (*P* = .57)

Values are presented as Spearman correlation (*P* value). * = after adjustment for the 5 tests of association involving this marker of metabolic dysfunction, the *P* value was .015. ^ = after adjustment for the 5 tests of association involving this measure of hypertension, the *P* value was .20. AHI = apnea-hypopnea index, BMI = body mass index, DBP = diastolic blood pressure, HOMA-IR = homeostasis model assessment of insulin resistance, hs-CRP = high sensitivity C-reactive protein, MAP = mean arterial pressure, OAHI = obstructive apnea-hypopnea index, RAI = respiratory arousal index, SBP = systolic blood pressure.

At baseline, 16 of 23 participants (70%) did not have a nocturnal dip > 10% in systolic BP, whereas for diastolic BP, the number was 10 of 23 participants (44%). Measures of BP were not significantly associated with any sleep respiratory parameters (**Table 2**). Median sleep duration in participants without hypertension was 8.5 (IQR 8.1 to 10.0) compared to 9.0 (IQR 8.4 to 9.6) for participants with hypertension (*P* = .83). The same results were found when considering only nocturnal hypertension (8.5, IQR 8.1 to 10.0, compared to 9.0, IQR 8.4 to 9.6, *P* = .83).

Change Over Time

Mean BMI *Z*-scores did not change significantly over time (*P* = .57). The estimated mean increase in BMI *Z*-scores from baseline to 6 months was 0.03 whereas the estimated mean increase in BMI *Z*-scores from baseline to 12 months was also 0.03. Similar results were found in the adherent subgroup.

There were no significant changes over time in markers of metabolic dysfunction. Further, changes over time in markers of metabolic dysfunction did not differ significantly between participants judged to be adherent to PAP therapy and those judged non-adherent (**Table 3A**). In the subgroup of adherent participants for whom HOMA values were available at baseline and 6 months (n = 13), 7 had HOMA-IR values above the 97th percentile at baseline. At 6 months, 3 of the 7 had HOMA-IR values below this threshold. One participant in each of the adherent and non-adherent subgroups had a worsening of HOMA-IR from below the 97th percentile to above this threshold. In a logistic regression model, HOMA-IR status (above or below the 97th percentile) at 6 months was associated with elevated HOMA-IR at baseline (*P* = .03, odds ratio = 23.2, 95% confidence interval 1.3 to 405.0) and with increase in BMI *Z*-score from baseline to 6 months (*P* = .03, odds ratio for a 0.1-unit increase = 5.7, 95% confidence interval 1.2 to 26.8).

Measures of BP did not change significantly over time (**Table 3B**). Changes in BP over time did not differ significantly between adherent and non-adherent participants (**Table 3B**).

DISCUSSION

Our study is the first long-term multicenter prospective cohort study to simultaneously evaluate metabolic and cardiovascular markers in a modest sample of youth with obesity newly prescribed PAP therapy for moderate-severe SDB. We found a high prevalence of cardiometabolic dysfunction in youth newly diagnosed with SDB. More than 40% had evidence of insulin resistance (HOMA-IR > 97th percentile) and hypertension. Most (70%) also had loss of the nocturnal BP dip. As some others have found, we observed a significant association between a marker of inflammation (hs-CRP) and obesity (BMI *Z*-score) at baseline, but other metabolic and BP markers were not significantly associated with indices of SDB.[4] Although there were no statistically significant improvements in

Table 3—Baseline values and change in outcome measures for participants who were adherent or non-adherent to PAP at 6 months and 12 months.

A

Markers of Metabolic Dysfunction	Baseline	Change at 6 Months			Change at 12 Months		
	Whole Group (n = 25)	Whole Group (n = 20)	Adherent (n = 13)	Non-Adherent (n = 7)	Whole Group (n = 16)	Adherent (n = 11)	Non-Adherent (n = 5)
HOMA-IR	4.3 (2.9 to 7.3)	0.7 (−1.2 to 4.4)	0.0 (−1.2 to 3.4)	4.3 (−1.6 to 5.8)	0.0 (−1.3 to 3.1)	0.0 (−1.2 to 2.3)	0.0 (−1.7 to 8.9)
HOMA-IR Z-score (censored)	1.2 (0.1 to 2.2)	0.0 (0.0 to 1.06)	0.0 (−0.4 to 0.5)	0.5 (−0.3 to 1.7)	−0.2 (−0.9 to 0.0)	0.0 (−0.4 to 0.0)	−0.6 (−1.9 to 0.8)
Fasting glucose (mmol/L)	4.8 (4.5 to 5.2)	0.3 (−0.3 to 0.5)	0.3 (−0.2 to 0.5)	0.3 (−0.5 to 0.8)	0.0 (−0.3 to 0.3)	0.0 (−0.3 to 0.2)	0.1 (−0.7 to 0.5)
Fasting insulin (pmol/L)	147 (95 to 247)	26 (−29 to 123)	−4 (−34 to 89)	127 (−19 to 168)	0 (−33 to 77)	0 (−18 to 61)	−1 (−42 to 201)
hs-CRP (mg/L)	4.6 (2.0 to 8.5)	0.0 (−1.8 to 1.8)	0.7 (−1.2 to 1.8)	0.0 (−3.7 to 2.2)	−0.1 (−1.5 to 2.1)	0.0 (−1.6 to 1.4)	−0.1 (−1.4 to 4.3)

B

Measures of Blood Pressure	Baseline	Change at 12 Months		
	Whole Group (n = 23)	Whole Group (n = 15)	Adherent (n = 11)	Non-Adherent (n = 4)
SBP percentile 24-h	71.5 (34.4 to 88.5)	−9.9 (−14.8 to 10.7)	0.1 (−17.8 to 21.2)	−10.5 (−13.9 to −0.9)
SBP percentile nocturnal	89.0 (68.0 to 97.8)	9.3 (−8.3 to 26.2)	0.9 (−13.2 to 26.2)	1.1 (−0.6 to 44.1)
DBP percentile 24-h	27.4 (8.8 to 47.1)	−2.2 (−11.9 to 14.7)	−3.7 (−13.4 to 16.0)	−0.5 (−5.2 to 4.3)
DBP percentile nocturnal	75.2 (33.7 to 91.8)	1.8 (−22.4 to 18.7)	4.7 (−37.0 to 18.7)	−4.2 (−19.3 to 47.3)
MAP percentile 24-h	48.8 (30.4 to 76.0)	1.2 (−19.2 to 5.5)	2.7 (−25.8 to 14.7)	0.9 (−12.3 to 1.5)
MAP percentile nocturnal	87.8 (64.9 to 98.3)	5.4 (−3.9 to 29.8)	5.4 (−41.9 to 29.8)	7.6 (−2.9 to 46.2)
SBP load (%)	23.0 (11.0 to 40.0)	−4.0 (−10.0 to 1.0)	−4.0 (−23.0 to 6.0)	−4.5 (−9.0 to 0.0)
DBP load (%)	13.0 (7.0 to 20.0)	−2.0 (−7.0 to 6.0)	0.0 (−7.0 to 6.0)	−3.5 (−8.5 to 3.8)
Nocturnal SBP dip (%)	5.2 (0.7 to 11.5)	−1.3 (−4.8 to 3.4)	−1.3 (−4.8 to 4.3)	−2.8 (−17.3 to 1.8)
Nocturnal DBP dip (%)	13.4 (5.2 to 15.9)	−0.7 (−9.6 to 7.4)	−0.7 (−9.6 to 10.0)	−1.3 (−18.6 to 5.1)
Nocturnal MAP dip (%)	9.5 (4.1 to 12.5)	−2.7 (−6.7 to 2.5)	−2.4 (−6.7 to 2.7)	−4.8 (−14.9 to 1.1)

Values are presented as median (interquartile range). All *P* values were non-significant, *P* > .05 including those for whole-group change and for comparison of change in the adherent and non-adherent groups. DBP = diastolic blood pressure, HOMA-IR = homeostasis model assessment of insulin resistance, hs-CRP = high-sensitivity C-reactive protein, MAP = mean arterial pressure, SBP = systolic blood pressure.

cardiometabolic markers 1 year after the prescription of PAP therapy, clinically relevant improvements were seen in insulin resistance and systolic BP load, important predictors of future risk of cardiovascular disease.[36]

Metabolic Markers

Our study results differ from others in the literature, in which HOMA-IR has been positively associated with AHI[20] and oxygen desaturation index in children and adolescents with obesity, albeit in groups with a wider range of SDB severity that included some individuals without SDB.[22] Studies in adults with OSA have demonstrated improvements in metabolic markers with PAP treatment.[9,11,37] One previous study of a small group of children treated short term with PAP therapy did not show improvements in insulin sensitivity based on OGTT.[15] Our study population is, however, different from those previously studied in that our cohort all had moderate-severe SDB. On detailed testing, only 2 had abnormal OGTT at baseline; however, 40% of participants in our study had elevated HOMA-IR values compared to a reference population of children with obesity, representing a study population with sub-clinical disease. This highlights that children with obesity and SDB have a high prevalence of metabolic dysfunction, which may be at preclinical stages if SDB is identified early. A strength of our study is evaluation from the time of SDB diagnosis and intervention with PAP therapy. Further, we have used HOMA-IR percentiles, which are standardized by age and sex,[29] which partially account for pubertal status in the evaluation of metabolic status.

CRP has been shown to decrease after treatment of OSA in children undergoing adenotonsillectomy in some studies,[22,38] but not others.[4,13] Further, reductions in CRP were most evident in children without obesity.[4] To our knowledge, the effect of PAP therapy treatment for SDB on CRP has not been previously evaluated in children, although the effect of obesity, a proinflammatory state, may confound any potential benefits attributable to PAP. Finally, although hs-CRP is a commonly measured marker of inflammation that is associated with atherosclerotic disease risk,[21] it may not be the most specific or precise marker to measure changes with treatment when confounders such as obesity are present. Markers of endothelial dysfunction or other inflammatory markers, including interleukins, may ultimately prove to be more appropriate measures in this population.[22]

Measures of Hypertension

At the time of SDB diagnosis, hypertension and loss of nocturnal BP dip were highly prevalent in our sample. There is a known association between OSA and BP: 24-hour systolic and diastolic ABPM has been shown to be higher in children with obesity and OSA compared to those without obesity.[39] A longitudinal study of ABPM, however, showed changes in BP were associated with OSA severity in children without obesity but not in those with obesity, suggesting that the effect of obesity on BP may overshadow the effect of OSA on BP.[40] This confounding factor may therefore explain the lack of association of BP with SDB severity in our population at baseline.

Although there were no statistically significant improvements in cardiometabolic markers 1 year after the prescription of PAP therapy, statistically nonsignificant and potentially clinical relevant improvements were seen in insulin resistance and systolic BP load, important predictors of future risk of cardiovascular disease.[36] Our study found statistically nonsignificant improvement in systolic BP load 1 year after prescription of PAP therapy. This is not inconsistent with adult studies, which include a meta-analysis of CPAP therapy for OSA in hypertensive individuals.[18] In children, BP after OSA treatment with adenotonsillectomy has not shown convincing improvement, other than one study demonstrating sustained improvement in diastolic BP.[3,22] Our study has not been able to resolve this question. Future research is needed, with larger sample sizes and even longer follow-up. This is particularly the case because improvements in BP have been associated with changes in obstructive AHI at 4-year follow-up in children, implying that OSA remains an important factor in BP regulation in children, but that changes may occur over longer periods of time.[41]

Limitations

This study has some limitations. First, our sample was small and attrition was high, as seen in other intervention studies in obese youth.[42] This likely limited our power to detect associations between metabolic and hypertension markers and indices of SDB, as well as changes in measures over time. Additionally, our power may have been reduced due to the use of nonparametric statistical techniques, which were selected in order to protect against the influence of the markedly non-normal distributions of several outcomes. All of the study participants had moderate to severe SDB and while the homogeneity of our study population is a strength, a lack of variability in SDB severity may have made it difficult to detect differences in outcomes according to SDB severity. Lower statistical power also likely affected our ability to detect differences between the subgroups of participants who were adherent to PAP therapy and those who were not. This was compounded by incomplete objective downloaded data on PAP adherence. The small sample size is reflective of the fact that the obese children and youth represent a subset of the pediatric population with SDB. Further, this is the first study to evaluate changes associated with PAP therapy introduced at the time of SDB diagnosis in this group.

Second, although a strength of our study was the use of empirically derived thresholds for elevated HOMA-IR that overcome important confounders including age and sex, their application to the minority of non-Caucasian individuals in our sample may not be ideal, as normal HOMA-IR values may vary with ethnic/racial background. Additionally, the dichotomization of HOMA-IR percentiles resulted in lower statistical power to detect clinically meaningful change. Third, data on adherence to PAP were incomplete from gold-standard machine downloads, although the summary judgment of adherence by clinicians was highly correlated with downloaded data. Moreover, we decided to use the PAP adherence data at the 6-month mark, because we did not have complete data at 12 months and it has been shown in previous studies that adherence in the first months post PAP initiation is sustained long term.[35]

Finally, our intention in this study was to examine whether introducing intervention close to the diagnosis of SDB would be associated with improvements in markers of disease known to be associated with SDB in adults. In some cases, however, lack of recognition of symptoms and lengthy wait times for polysomnography may have resulted in delayed diagnosis. The exact duration of OSA in this cohort prior to the time of treatment onset is unknown. Further, the inability to identify changes in metabolic and cardiovascular outcomes of interest after 1 year in the whole cohort (irrespective of adherence) may be due to disease evolution in this population that may occur over a longer time scale. It is also possible that PAP therapy slows or halts the progression of cardiometabolic disease, rather than reversing it, or that irreversible changes are already present at the time of diagnosis. These hypotheses may explain why differences between adherent and non-adherent subgroups in the outcomes of interest could not be detected.

CONCLUSIONS

In our cohort of children and youth with obesity and SDB there was a high prevalence of metabolic dysfunction and hypertension at baseline. Forty percent of our population had elevated HOMA-IR, relative to a reference population at baseline and 40% were hypertensive, with 70% of the sample having a loss of nocturnal BP dip. Increased inflammatory markers were also present in 63% at the time of SDB diagnosis, independent of SDB severity. This highlights the need to evaluate markers of early cardiovascular disease in this high-risk population of obese children with SDB, many of whom will already have subclinical disease at the time of SDB diagnosis.

We were unable to detect statistically significant change in cardiometabolic markers after 1 year of prescribed PAP therapy. A larger study with greater statistical power is needed to detect changes in these outcomes over time. Prevention of disease progression may require follow-up for several years after initiation of PAP treatment.

ABBREVIATIONS

ABPM, ambulatory blood pressure measurements
AHI, apnea-hypopnea index

bilevel PAP, bilevel positive airway pressure
BMI, body mass index
BP, blood pressure
CO_2, carbon dioxide
CPAP, continuous positive airway pressure
CRP, C-reactive protein
HOMA-IR, homeostasis model assessment of insulin resistance
hs-CRP, high sensitivity C-reactive protein
IQR, interquartile range
IR, insulin resistance
MAP, mean arterial pressure
mmHg, millimeters of mercury
mmol/L, millimoles per litre
OAHI, obstructive apnea-hypopnea index
OGTT, oral glucose tolerance test
OSA, obstructive sleep apnea
PAP, positive airway pressure
pmol/L, picomoles per litre
SDB, sleep-disordered breathing

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DISCLOSURE STATEMENT

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