Obesity Rather Than Severity of Sleep-Disordered Breathing as the Major Determinant of Insulin Resistance and Altered Lipidemia in Snoring Children

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ABSTRACT. *Objective.* Sleep-disordered breathing (SDB) is associated with insulin resistance and dyslipidemia in adults and in obese children. However, the prevalence of such metabolic abnormalities among snoring children is unknown. This study was done to prospectively assess the relative contribution of SDB and obesity to metabolic disturbances in a large cohort of snoring children.

Methods. Measurements of fasting serum glucose, insulin, and lipids were obtained after polysomnographic evaluation in 116 snoring children and in 19 control subjects. Insulin resistance was assessed using the insulin/glucose ratio (I/G ratio) and homeostasis model assessment (HOMA).

Results. A total of 135 children (79 boys; mean age: 8.9 ± 3.5 years) were studied. Sixty-four children had moderate to severe SDB (AHI = 5 per hour of total sleep time [TST]), 52 had mild SDB (AHI = 1 but <5 per hour of TST), and 19 were control subjects (AHI <1 per hour of TST). Seventy of these children were obese. No significant correlations were found between AHI, lowest arterial oxygen saturation, or arousal index and serum insulin, serum glucose, I/G ratio, HOMA, or serum lipids for either the whole group or the obese children only. However, significant positive correlations were found between I/G ratio and relative BMI (relBMI; $r = 0.58$), HOMA and relBMI ($r = 0.52$), triglycerides and relBMI ($r = 0.30$), and high-density lipoprotein and relBMI ($r = 0.50$). No significant differences were found in relBMI, I/G ratio, and lipid levels between boys and girls.

Conclusions. Among children with suspected SDB, insulin resistance and dyslipidemia seem to be determined primarily by the degree of body adiposity rather than by the severity of SDB. *Pediatrics* 2005;116:e66–e73. URL: www.pediatrics.org/cgi/doi/10.1542/peds.2004-2527; *metabolic syndrome, sleep apnea, pediatrics, obesity, diabetes.*

ABBREVIATIONS. SDB, sleep-disordered breathing; CPAP, continuous positive airway pressure; CRP, C-reactive protein; Spo_2, arterial oxygen saturation; AHI, apnea hypopnea index; TST, total sleep time; relBMI, relative BMI; HOMA, homeostasis model assessment; I/G ratio, insulin/glucose ratio; HDL, high-density lipoprotein; TG, triglyceride.

The incidence of childhood obesity has been increasing steadily in Western countries.[1] Recent reports place the prevalence of obesity and overweight in children at levels ranging from 7% up to 22% in various countries,[2–9] and such elevated figures will undoubtedly impose major health implications, particularly on the development of insulin resistance, type 2 diabetes, and cardiovascular morbidity.[10–12]

The term "metabolic syndrome" is a known risk factor for cardiovascular disease in adults and refers to the clustering of insulin resistance, dyslipidemia, hypertension, and obesity. Elevation of fasting insulin levels and increased BMI during childhood are the strongest predictors of the metabolic syndrome in adulthood,[13,14] possibly through the combination of altered insulin signaling and adrenocortical function, induction of inflammation and endothelial and vascular dysfunction, abnormal cardiac autonomic regulation, and aberrant hormonal output.[15–17] Moreover, insulin resistance in childhood is associated with increased risk for later cardiovascular morbidity and mortality.[18–20] Taken together, these data support the hypothesis that the metabolic disturbances, which are known to be associated with increased risk for cardiovascular disease, start developing in childhood. Thus, early identification of insulin resistance and obesity provide an opportunity for early intervention such as to minimize the risk of adult cardiovascular disease.

Sleep-disordered breathing (SDB) was identified recently as an important risk factor for the metabolic syndrome in adult patients.[21–24] Indeed, adults with SDB have many features in common with the metabolic syndrome, including systemic hypertension, central obesity, and insulin resistance. However, whereas several reports have found SDB to be an independent predictor of insulin resistance even after controlling for BMI,[25,26] this association was not confirmed by other reports.[27,28] Moreover, the effect of continuous positive airway pressure (CPAP) on the metabolic disturbances associated with SDB has yielded conflicting results.[29–32] SDB in children is associated with increased sympathetic activity,[33–35] elevated blood pressure, and left ventricular geometry changes.[36–38] In addition, we recently reported on altered plasma C-reactive protein (CRP) levels, a marker of inflammation and atherogenesis, as a consequence of SDB in children.[39] Although these findings could strongly suggest the presence of an asso-

TABLE 1. Demographic and Sleep Characteristics and Corresponding Serum Lipids and Glucose Regulation in 19 Control Children, 52 Children With Mild SDB, and 64 Children With Moderate to Severe SDB

	Controls ($n = 19$)	Mild SDB ($n = 52$)	Moderate to Severe SDB ($n = 64$)
Gender, male/female	12:7	33:19	34:30
Age, y	9.2 ± 3.0	8.5 ± 3.3	9.1 ± 3.8
relBMI	135.9 ± 40.3	144.3 ± 56.9	161.5 ± 55.7
AHI, per hour of TST	0.55 ± 0.27	2.2 ± 0.98*	20.0 ± 20.7†‡
Spo$_2$ nadir, %	91.1 ± 2.4	89.2 ± 4.5	80.8 ± 12.1†‡
Arousal index	8.0 ± 2.1	10.5 ± 4.7*	21.3 ± 18.6†‡
Cholesterol, mg/dL	160.7 ± 17.0	173.1 ± 33.1	161.4 ± 31.1
TGs, mg/dL	90.6 ± 47.5	105.7 ± 79.3	107.2 ± 57.4
HDL, mg/dL	52.4 ± 14.5	53.0 ± 16.6	47.0 ± 12.3
LDL, mg/dL	82.2 ± 24.8	98.4 ± 28.7	93.4 ± 30.3
Glucose, mg/dL	92.9 ± 10.6	91.1 ± 9.6	90.8 ± 9.0
Insulin, μIU/mL	12.9 ± 12.3	12.8 ± 12.7	13.3 ± 10.8
I/G ratio	0.14 ± 0.13	0.13 ± 0.12	0.14 ± 0.10
HOMA	3.1 ± 2.9	3.0 ± 3.2	3.1 ± 3.0

LDL indicates low-density lipoprotein.
* $P < .001$ mild SDB versus control.
† $P < .001$ moderate to severe SDB versus mild SDB.
‡ $P < .001$ moderate to severe SDB versus control.

TABLE 2. Demographic and Sleep Characteristics and Corresponding Serum Lipids and Glucose Regulation in 70 Obese Children and 65 Nonobese Children

	Obese ($n = 70$)	Nonobese ($n = 65$)
Gender, male/female	41:29	38:27
Age, y	9.8 ± 3.5*	7.9 ± 3.3
relBMI	191.6 ± 48.0*	107.8 ± 10.9
AHI, per h of TST	14.2 ± 21.0*	6.3 ± 9.4
Spo$_2$ nadir, %	83.6 ± 10.2*	87.5 ± 9.1
Arousal index	18.2 ± 17.9*	11.7 ± 7.2

* $P < .02$.

ciation between SDB and the metabolic syndrome in the pediatric population, this issue thus far has been investigated in only 1 study exclusively involving obese children.[40] In this particular study, a correlation between the respiratory disturbance index and fasting insulin levels was identified, even after adjustments for BMI. Thus, it is plausible that such a relationship may be found in a more representative pediatric population of snoring children. We therefore undertook the present study to assess prospectively the contribution of SDB to the metabolic disturbances in a large cohort of snoring children.

METHODS

A total of 116 children who were evaluated consecutively at the Kosair Children's Hospital Sleep Medicine Center for snoring and suspected SDB were studied. In addition, 19 nonsnoring children were recruited from the community as control subjects. The study was approved by the University of Louisville Human Research Committee. Parental informed consent and child assent, in the presence of a parent, were obtained. Children were excluded when they had any chronic medical condition, were receiving medications that are known to affect glucose homeostasis or serum lipids, had any psychiatric diagnoses, or had any genetic or craniofacial syndromes.

Overnight Polysomnography

A standard overnight multichannel polysomnographic evaluation was performed in the sleep laboratory. No drugs were used to induce sleep. The following parameters were measured: chest and abdominal wall movement by inductance plethysmography, heart rate by electrocardiogram, air flow triply monitored with a nasal pressure cannula, a thermistor, and a sidestream end-tidal capnograph that also provided breath-by-breath assessment of end-tidal carbon dioxide levels (BCI SC-300, Menomonee Falls, WI), a nasal pressure cannula and a thermistor. Arterial oxygen saturation (Spo$_2$) was assessed by pulse oximetry (Nellcor N 100; Nellcor Inc, Hayward, CA), with simultaneous recording of the pulse waveform. The bilateral electro-oculogram, 8 channels of electroencephalogram, chin and anterior tibial electromyograms, and analog output from a body position sensor (Braebon Medical Corp, Ogdensburg, NY) were also monitored. All measures were digitized using a commercially available system (Rembrandt, MedCare Diagnostics, Amsterdam, The Netherlands). Tracheal sound was monitored with a microphone sensor (Sleepmate, Midlothian, VA), and a digital time-synchronized video recording was performed. Sleep architecture was assessed by standard techniques, as previously reported.[41,42] Briefly, obstructive apnea was defined as the absence of airflow with continued chest wall and abdominal movement for duration of at least 2 breaths.[43,44] Hypopneas were defined as a decrease in nasal flow of >50% with a corresponding decrease in Spo$_2$ of >4% and/or terminated by a 3-second electroencephalogram arousal.[44] The obstructive apnea/hypopnea index (AHI) was defined as the number of apneas and hypopneas per hour of total sleep time (TST). Children with an AHI = 1 but <5 per hour of TST were considered to have mild SDB, whereas children with AHI = 5 per hour of TST were considered to have moderate to severe SDB. The mean oxygen saturation, as measured by pulse oximetry (Spo$_2$) in the presence of a pulse waveform signal void of motion artifact, and the Spo2 nadir were recorded. Because criteria for arousals have not yet been developed for children, arousals were defined as recommended by the American Sleep Disorders Association Task Force report[45] using the 3-second rule and/or the presence of movement arousal.[46,47]

Height and weight were obtained using standard techniques from each child. BMI then was calculated (body mass/height²) and was expressed as relative BMI (relBMI), using the following formula: (BMI/BMI of the 50th percentile for age and gender) × 100, based on standardized percentile curves.[48] Children with BMI values that exceeded 95% for age and gender were classified as fulfilling the criteria for obesity.

Blood for insulin and glucose levels was drawn on the morning after the sleep study, corresponding to an overnight fast. Plasma insulin level was measured using a commercially available radioimmunoassay kit (Coat-A-Count Insulin; Diagnostic Products Inc). This method has a detection level of 1.2 μIU/mL and exhibits
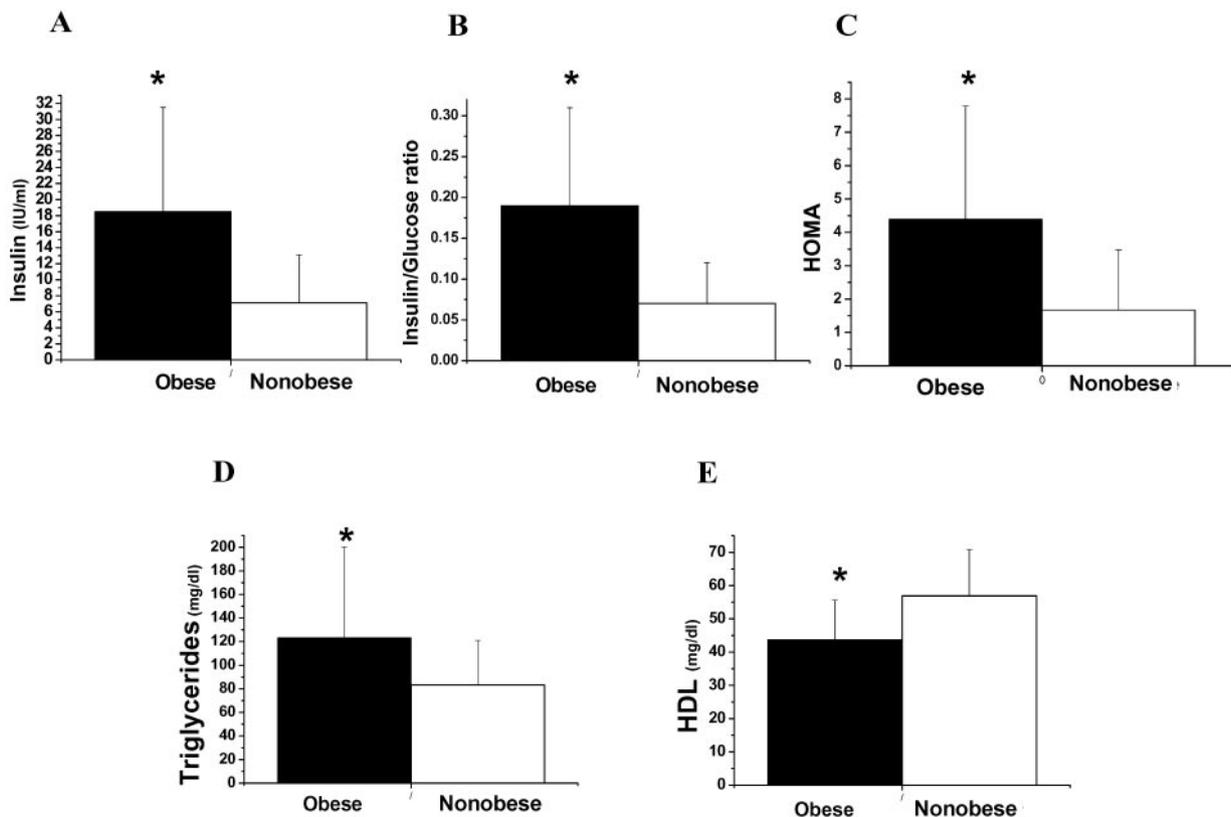
Fig 1. Mean fasting plasma insulin (A), I/G ratio (B), HOMA (C), and TG (D) and HDL (E) levels in 70 obese children and 65 nonobese children. Bars represent ±SD. *$P < .001$.
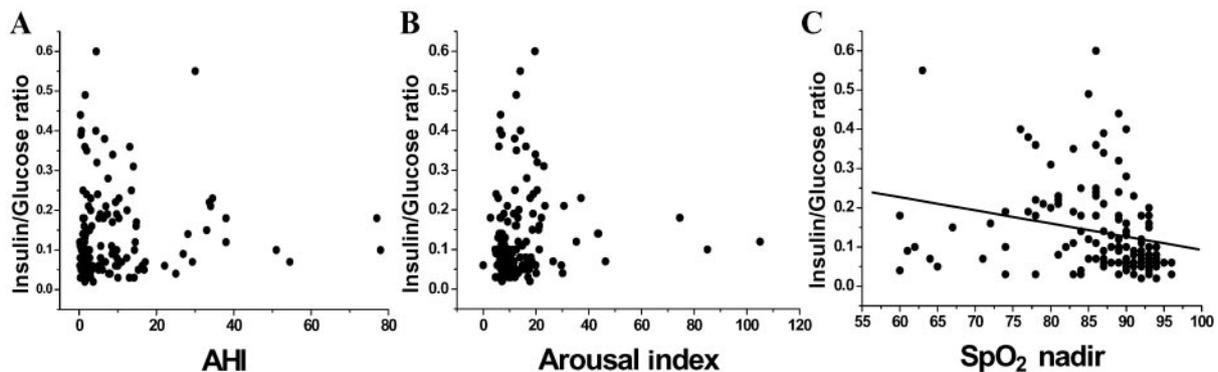

Fig 2. Scatterplot of individual fasting I/G ratio in 135 children plotted against AHI (A), arousal index (B), and Spo₂ nadir (C). No significant correlations were found for A and B. Linear regression line is shown for C; however, the statistical significance of this correlation did not persist after controlling for relBMI using partial correlation.

linear behavior up to 350 μIU/mL, with intra-assay and interassay coefficients of variability of 3.1% and 4.9%, respectively. Plasma glucose level was measured using a commercial kit based on the hexokinase-glucose-6-phosphate dehydrogenase method (Flex Reagent Cartridges; Dade Behring, Newark, DE).

Insulin resistance was assessed using the fasting insulin/fasting glucose ratio (I/G ratio) and the homeostasis model assessment (HOMA) equation (fasting insulin × fasting glucose/22.5).[49] Serum lipids including total cholesterol, high-density lipoprotein (HDL) cholesterol, calculated low-density lipoprotein cholesterol, and triglycerides (TGs) were also assessed using Flex Reagent Cartridges (Dade Behring).

Data Analysis

Data are presented as means ± SD unless otherwise indicated. Comparisons of demographics according to group assignment

were made with independent t tests or analysis of variance followed by post hoc comparisons, with P values adjusted for unequal variances when appropriate (Levene's test for equality of variances), or χ^2 analyses with Fisher exact test (dichotomous outcomes). Correlations were performed using linear regression, followed by calculation of Pearson correlation coefficients. All P values reported are 2-tailed with statistical significance set at <.05.

RESULTS

A total of 135 children (79 boys), with a mean age of 8.9 ± 3.5 years (range: 3–18 years), were studied. Of these, 64 (47%) children fulfilled the polysomnographic characteristics of moderate to severe SDB, 52 (39%) children had mild SDB, and 19 (14%) were
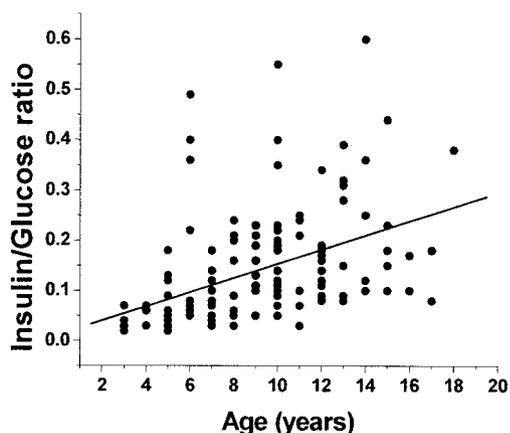
Fig 3. Scatterplot of I/G ratio plotted against corresponding age in 135 children. Linear regression line is shown and was statistically significant ($r = 0.44$, $P < .0001$). The correlation remained significant after controlling for relBMI ($r = 0.30$, $P < .001$).

control subjects (AHI < 1). Of the 135 children, 70 (52%) were obese. Subject characteristics according to the 3 groups are shown in Table 1. There were no significant differences in age, gender, and relBMI among the 3 groups. However, there was a trend toward higher relBMI in the moderate to severe SDB group. No significant differences were found for glucose, insulin, I/G ratio, HOMA levels, or serum lip-

ids among the 3 groups (Table 1). No significant differences were found in relBMI, I/G ratio, and lipid levels between boys and girls. For the entire cohort, insulin resistance (defined as serum insulin >25 μIU/mL or I/G ratio >0.33) was present in 16 or 12 children, respectively, only 1 of whom was not obese.

Because the severity of SDB did not seem to contribute to the occurrence and/or severity of metabolic disturbances, we reexamined these issues by partitioning our cohort into obese and nonobese categories (Table 2). Obese children were significantly older and had more SDB problems. Furthermore, significant differences in insulin levels, I/G ratio, HOMA, TG, and HDL levels ($P < .01$) were found between the obese and the nonobese groups (Fig 1). No significant correlations were found between AHI, Spo$_2$ nadir, arousal index, and I/G ratio or serum lipids either for the whole group when controlled for BMI or for the obese children (Fig 2). However, I/G ratio was positively correlated with age ($r = 0.44$, $P < .0001$; Fig 3), even after controlling for relBMI. Significant positive correlations were also found for I/G ratio and relBMI ($r = 0.58$, $P < .0001$), HOMA and relBMI ($r = 0.52$, $P < .0001$), TG levels and relBMI ($r = 0.30$, $P = .0009$), and HDL levels and relBMI ($r = 0.50$, $P < .0001$; Fig 4). Significant corre-
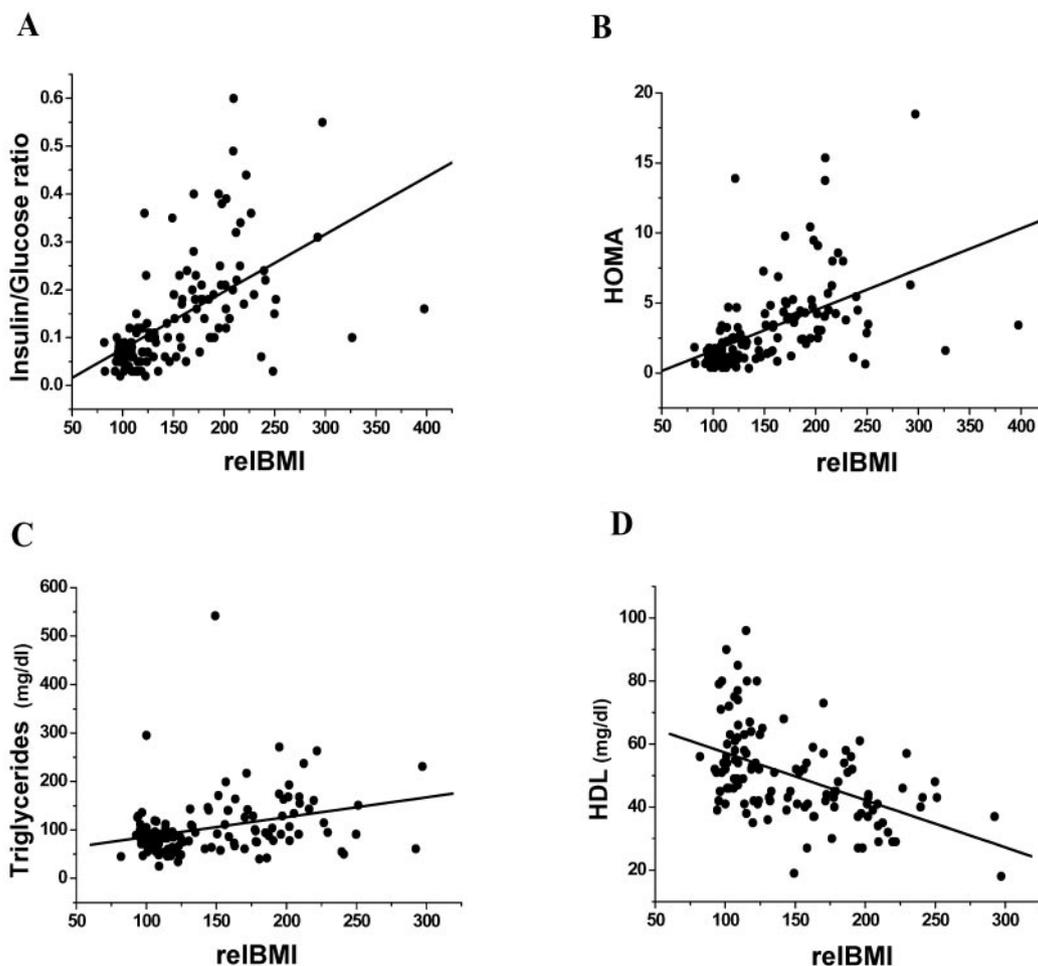

Fig 4. Scatterplot of fasting I/G ratio (A), HOMA (B), plasma TG (C), and HDL levels (D) plotted against relBMI in 135 children. Linear regression lines are shown, and were all statistically significant (see text for details).

TABLE 3. Demographic and Corresponding Serum Glucose Homeostasis Variables in 19 Control Children, 19 Children With Mild SDB, and 19 Children With Moderate to Severe SDB Matched For relBMI

	Controls ($n = 19$)	Mild SDB ($n = 19$)	Moderate to Severe SDB ($n = 19$)
Gender, male/female	12:7	12:7	12:7
Age, y	9.2 ± 3.0	8.1 ± 3.3	9.1 ± 4.0
relBMI	135.9 ± 40.3	132.0 ± 41.3	135.6 ± 40.5
AHI, per h of TST	0.5 ± 0.3	2.2 ± 1.1	21.5 ± 27.0*†
Glucose, mg/dL	92.9 ± 10.6	90.7 ± 8.8	88.7 ± 6.5
Insulin, μIU/mL	12.9 ± 12.3	10.8 ± 10.3	9.6 ± 5.9
I/G ratio	0.14 ± 0.13	0.10 ± 0.07	0.11 ± 0.06
HOMA	3.1 ± 2.9	2.6 ± 2.7	2.1 ± 1.3

* $P < .001$ moderate to severe SDB versus mild SDB.
† $P < .001$ moderate-severe SDB versus control.

lations between I/G ratio, TGs, and HDL and corresponding relBMI persisted even after controlling for age. Significant correlations were found between I/G ratio and both TG and HDL levels ($r = 0.43$, $P < .0001$; and $r = -0.45$, $P < .0001$, respectively).

Stepwise linear regression analysis confirmed relBMI as the major contributing factor for elevated I/G ratio (34% of the variance), with lesser contributions from serum TG levels and age. Thus, relBMI, age, and TG level accounted for 47% of the variance. However, incorporation of AHI and SpO$_2$ nadir failed to improve the strength of the prediction in the linear model (51% of the variance).

Because we were unable to match completely the SDB subjects and the control subjects for relBMI in this cohort, we performed a subanalysis whereby we matched each control child to both a child with mild SDB and a child with moderate to severe SDB on the basis of relBMI to exclude the possibility that SDB may impose a small albeit detectable effect on glucose homeostasis (Table 3). This subanalysis clearly supports the above findings.

DISCUSSION

This study shows that obesity is the major determinant of insulin resistance and lipid dysregulation in snoring children and that SDB plays a minimal if any role in the occurrence of such metabolic abnormalities. Our study cohort consisted of an otherwise typical referral-based pediatric population that required clinical evaluation for suspected SDB, such that the large proportion of children with BMI >95% may have accounted for the higher risk for SDB in the context of obesity.[50–52] Indeed, we have observed progressively an increasing prevalence of obesity during the past decade among snoring children who presented at a large pediatric sleep center (Gozal D, unpublished observations, 2003), such that ~40% to 50% of the patients fulfill the criteria for obesity, as opposed to ~17% obesity prevalence in the metropolitan area of Louisville. This increased representation of obese children among symptomatic snoring children is not surprising considering the effect of excessive fat deposition on upper airway collapsibility[53] and the overall higher prevalence of SDB among obese children.[54,55] Therefore, to account for such disparate overrepresentation of obesity, we included a relatively high number of control subjects who also fulfilled obesity criteria (37%).

The present study strongly concurs with previous publications demonstrating a high prevalence of insulin resistance among obese children[10,56] and also supports changes in insulin sensitivity as a function of age.[18,40,57,58] Moreover, the significant correlations among obesity, increased I/G ratio, and serum lipid profile alterations support the notion that risk factors for cardiovascular disease tend to cluster in childhood and are strongly associated with obesity.[59,60]

In contrast with some of the reports on adult patients with SDB, SDB in children does not seem to impose an added risk for development of insulin resistance. Although the exact reasons of this discrepancy are currently unknown, differences in the overall duration of SDB and in SDB severity could account for at least some of the contributing factors to the added risk for metabolic syndrome among adult patients with SDB. Indeed, adult patients with SDB are much more likely to present after SDB has gone undiagnosed over prolonged periods of time, and higher AHI, deeper falls in SpO$_2$, and more severe sleep fragmentation are usually observed in the average adult patient compared with the pediatric SDB patient.[61] Our findings do not lend support to the conclusions by de la Eva et al[40] in obese children with SDB. These investigators showed that significant correlations were present between AHI and fasting insulin levels independent of BMI. However, this study included only obese children; therefore, separation of the preponderant role of obesity from the putative role of SDB on glucose homeostasis would be difficult, if not altogether impossible. Moreover, all of the patients who were studied by de la Eva et al had abnormal insulin levels, suggesting a potentially skewed population in that study. As shown above, additional analyses using only obese individuals in our cohort ($n = 70$) failed to reveal the presence of any significant association between SDB severity and insulin resistance. In this context, it is noteworthy that even in adult populations, the effect of CPAP on insulin resistance has yielded conflicting results,[25,26,29–32,62,63] thereby raising the possibility that although SDB may induce an adverse effect on

glucose regulatory mechanisms, this effect is small at most. Indeed, the effect of CPAP on insulin sensitivity was found to be smaller in obese patients than in nonobese patients, suggesting that in obese individuals, insulin sensitivity is determined primarily by obesity and to a smaller extent by respiratory disturbances during sleep.[26] However, the experimental evidence linking components of SDB to glucose dysregulation supports the notion that both exposure to hypoxia[62,63] and sleep loss can induce insulin resistance.[64] It therefore is possible that for the average nonobese pediatric population with SDB, much larger sample sizes will be needed to reveal the putative, albeit small, size effects of respiratory and sleep disturbances on the homeostatic control of glycemic levels. Furthermore, such future studies will require incorporation of a treatment arm (tonsillectomy and adenoidectomy) to establish irrevocably the contribution of SDB to insulin resistance in the pediatric population.

The present study supports the previously suggested association between obesity and altered lipid profiles.[14,65,66] Dyslipidemia, characterized by high plasma concentrations of TGs and low concentrations of HDL, is a potent risk factor for coronary heart disease.[67] This "atherogenic" lipid profile is of particular significance in a population such as that of children with SDB, who show plasma elevations of the cardiovascular risk factor marker CRP.[39] However, in contrast with CRP levels, which correlate with SDB severity even after controlling for obesity, dyslipidemia in our cohort was determined primarily by obesity and degree of the insulin resistance. Indeed, stepwise linear regression analysis showed I/G ratio and relBMI as the major contributing factors for high levels of TGs and low levels of HDL.

A technical issue that pertains to this study deserves comment. We consistently sampled all of the study participants in the morning after a sleep study so as to ensure standard fasting collection procedures as well as an identical timing in relation to their sleep period. Thus, we did not examine whether SDB imposes any acute effects on homeostatic glycemic control during sleep. On the basis of the absence of any obvious differences in the morning levels of HOMA among the children when divided according to the degree of SDB, it is unlikely that sleep-to-waking differences might be present.

Exercise training favorably affects insulin sensitivity in both adults and children.[68–70] Thus, lack of physical activity in obese children could account for the higher I/G found in obese children compared with the nonobese children in our cohort. We are unable to examine this potential confounder, however, because information regarding physical activity was not collected in our cohort. Similarly, we did not specifically obtain information on the dietary habits and body fat distribution of our population, and these factors have been shown to modify the propensity for insulin resistance and the occurrence of dyslipidemia.[71–74] The absence of a significant difference between boys and girls in insulin resistance does not exclude the effect of puberty on glucose homeostasis in our cohort. Because Tanner

staging was not performed, this is a limitation of the current study.

Notwithstanding such limitations, our findings do not support a major role for SDB in the emergence of insulin resistance or altered lipid metabolism in children. Thus, in contrast with adults, insulin resistance and dyslipidemia seem to be determined primarily by adiposity in snoring children, suggesting that weight loss should be encouraged aggressively as part of the management of SDB in obese children. Additional larger scale studies of SDB and glucose homeostasis and lipid regulation that include treatment will be required to examine the potential interactions between obesity and SDB in pediatric patients.

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