Ambulatory clinical parameters and sleep respiratory events in a group of obese children unselected for respiratory problems

Marco Zaffanello, Giorgio Piacentini, Angelo Pietrobelli, Cristiano Fava, Giuseppe Lippi, Claudio Maffeis, Emma Gasperi, Luana Nosetti, Sara Bonafini, Angela Tagetti, Franco Antoniazzi

Verona, Italy

Background: **Obstructive sleep apnea in children is frequently due to tonsil and adenoid hypertrophy. This study aimed to investigate the relationship between ambulatory clinical parameters and sleep respiratory events in obese children.**

Methods: **We carried out a prospective respiratory sleep study between 2013 and 2015. Nails obstruction, tonsils enlargement and palate position were subjectively measured. Italian attention deficit hyperactivity disorder (ADHD) rating scale for parents was also performed. The polygraph study was performed using a portable ambulatory device.**

Results: **Forty-four obese children were consecutively recruited into this study. Mild sleep respiratory disturbance was showed in 31.8 % of patients; 18.2% previously had an adeno (tonsillectomy). In 50% of these obese children, both apnea-hypopnea index and oxygen desaturation index showed polygraph abnormal results. ADHD rating scale for parents scores were positive in 9.1% of patients.**

Conclusions: **We found a high rate of mild sleep respiratory disturbance and ADHD-like symptoms referred by parents. The respiratory disturbance was not totally cured by surgery. Finally, otorhinolaryngology variables were not able to explain mild sleep respiratory disturbance.**

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Author Affiliations: Department of Surgical Sciences, Dentistry, Gynecology and Pediatrics, Pediatric Division (Zaffanello M, Piacentini G, Pietrobelli A, Gasperi E, Antoniazzi F); Pediatric Diabetes and Metabolic Disorders Unit (Maffeis C); Department of Medicine, Section of General Medicine and Hypertension (Fava C, Bonafini S, Tagetti A); Department of Neuroscience, Biomedicine and Movement, Chemistry and Clinical Microscopy Section (Lippi G), University of Verona, Verona, Italy; Department of Pediatrics, University of Insubria, Varese, Italy (Nosetti L)

Corresponding Author: Marco Zaffanello, MD, Department of Surgical Sciences, Dentistry, Gynecology and Pediatrics, Pediatric Division, University of Verona, Piazzale L.A. Scuro 10, 37134 Verona, Italy (Tel: +39 45 8124469; Fax: +39 45 8124790; Email: marco.zaffanello@univr.it)

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Introduction

Obstructive sleep apnea syndrome (OSAS) is characterized by episodes of complete or partial upper airway obstruction during sleep. In childhood, it is more frequently due to tonsil and adenoid hypertrophy. However, obesity, craniofacial malformations or other anatomic alterations of the upper airways may also play an important role.[1] In childhood, OSAS is a relatively common disease with a prevalence ranging from 1% to 5%.[1] The complications of OSAS are neurocognitive[2] and cardiovascular pathologies. In particular, in pediatric OSA patients, sleep fragmentation associated with OSAS is a key determinant of behavioral alterations and episodic hypoxemia causes pulmonary vasoconstriction and ultimately pulmonary artery hypertension.[3,4] Screening and treatment are recommended for children at high-risk of sleep-related breathing disorders.[5]

Childhood obesity has an impact on OSAS. Body mass index (BMI) was found to be an independent risk factor for snoring.[1] Obesity can result in reduced lung volume and decreased upper airway caliber.[1] For these reasons, particular attention must be paid to signs and symptoms of OSAS in these children.

The gold standard for diagnosis of OSAS is overnight polysomnography (PSG) performed in a sleep lab. Recently, a respiratory polygraph in children with a clinical suspicion of OSAS emerged as a potentially

useful and reliable approach for the diagnosis with a very good sensitivity and specificity.[6]

The aim of the present study was to investigate the relationship between ambulatory clinical parameters [anthropometry, nails, tonsil and palate, and Italian attention deficit/hyperactivity disorder (ADHD) rating scale for parents (SDAG)] related to possible OSAS and sleep respiratory events measured with an overnight polygraph study in a group of obese children, who were referred to a tertiary pediatric center.

Methods

Study population

This study was part of a cross-sectional study on nutrition and cardiovascular problems in obese children and approved by the Institutional Ethical Committee of Verona and Rovigo, Italy. Caregivers signed an informed consent document prior to enrollment in the study.

We carried out a prospective overnight cardiorespiratory sleep study between 2013 and 2015 on 44 consecutive Caucasian obese children, as they referred for ambulatory consultation. Subjects who had craniofacial syndromic abnormalities, chromosomal disorders, lung disease, neuromuscular disorders, endocrine disorders and genetic diseases related to obesity were excluded. Restless leg syndrome was excluded by interview at admission.

Anthropometry

All measurements were recorded in the morning after an overnight fast with patients wearing only underwears. Height and weight were measured by trained personnel using standardized techniques. BMI [weight (kg)/height (m^2)], BMI percentiles and BMI *Z* scores were calculated according to age and sex (http://nccd.cdc.gov/dnpabmi/Calculator.aspx).

Tonsil size

The tonsils were subjectively measured in seated position using a grading system. In particular, tonsil size 1 implies tonsils hidden within the pillars; tonsil size 2 implies the tonsil extending to the pillars; size 3 tonsil are beyond the pillars but not to the midline; and tonsil size 4 implies tonsils that extend to the midline.[7]

Palate position

The palate position was subjectively measured using a grading system. The procedure involved asking the patient to open their mouth widely without protruding their tongue. In particular, palate grade I allows the observer to visualize the entire uvula and tonsils or pillars; palate grade II allows visualization of the uvula but not the tonsils; palate grade III allows visualization of the soft palate but not the uvula; and palate grade IV allows visualization of the hard palate only.[8] The procedure is repeated five times so that the observer can assign the most accurate level.

Nasal patency

To assess nasal patency,[9] one nostril was gently blocked at a time with one finger, avoiding the compression of the other nostril. The patient then breathed in through the unoccluded nostril and the maneuver was repeated with the other nostril. Unilateral and bilateral nasal obstructions were quoted equally from 0 (unoccluded) to 3 (completely occluded). The sum of the score from each nostril was considered for each patient.

Italian attention and hyperactivity behavior rating scale for parents

An 18-item ADHD scale for parents was performed (rating 0=never to 3=very often). Positivity was considered if overall scoring was more than 28.[10]

Cardio-respiratory polygraph

An overnight polygraph study was performed using a portable ambulatory device (SOMNOscreenTM PSG, SOMNOmedics GmbH, Randersacker, Germany) with continuous monitoring of nasal airflow by cannula, chest and abdominal respiratory movements (thoracic and abdominal belts), arterial oxygen saturation (SaO_2; digital pulse oxymetry), heart rate and trace with electrocardiogram (ECG), body position (mercury sensor) and tracheal sounds (microphone). The device was applied between 6:00 p.m. and 8:00 a.m. and the recording was on for the entire night. Throughout the study, all the children underwent recordings for ≥6 hours in a quiet, appropriately prepared sleep room in the presence of one of their caretakers.

Analysis of the entire recording session was done automatically (DOMINO software, Somnomedics v.2.6.0) and accurately manually checked. Estimated total sleep time (eTST) was calculated according to published criteria.[11] Briefly, the first 10-minute period with no recorded movement, artifact, or a distorted pulse waveform was defined as sleep onset. Artifacts were defined as a distorted pulse waveform or the loss of nasal pressure or of thorax or abdominal effort for more than 1 minute. Recordings were manually analyzed for artefactual or non-interpretable periods of nasal flow, thoracic effort, abdominal effort or oximetry channel. These periods with artefactual data were subtracted from the eTST. Movement periods were also excluded.[11]

Respiratory events were inspired by the American Academy of Sleep Medicine Guidelines.[12] The

number of obstructive apneas (OA), mixed apneas, central apneas (CA) and hypopneas (H) was divided by the hours of eTST and expressed as obstructive apnea-hypopnea index (AHI). Mild OSAS (AHI: 1-5 episodes/hour) and moderate-to-severe OSAS (AHI: >5 episodes/hour) were the main outcome measures.[13] We scored a respiratory event named CA if associated with absent respiration (absent signaling from chest and abdominal movements) and without thoracoabdominal effort throughout the entire duration of the event;[14] moreover, the event lasted at least the duration of two breaths during baseline breathing. The CA (*n*/hour) was defined as the number of CA per hour of eTST.

Desaturation was considered if there was a drop of ≥3% oxygen.[13] All oxygen desaturations from the baseline, mean SaO_2 and minimum SaO_2 were quantified. The oxygen desaturation index (ODI) was calculated as the total number of desaturations divided by the eTST. Snoring (percent of eTST) and mean phase angle (angle of obstruction) in overall recording were also calculated. As an index of inspiratory effort, phase angle is a vector of rib cage and abdominal respiratory movements recorded during natural nocturnal active and peaceful sleep. A rise in inspiratory resistance, as observed during OA and H, produces an asynchrony between the rib cage and the abdomen.[15]

Pulse transit time (PTT) is the time taken for the arterial pulse to travel from the heart to the pulse oximeter site (finger). PTT analysis is calculated from the electrocardiogram (ECG) signals and the plethysmographic waveforms from the pulse oximeter.[16] When a sleep apnea occurs sympathetic activity increases as a response to the obstructive event in order to reestablish respiration. The increase in sympathetic activity is associated with vasoconstriction. PTT decreases after an apneic event due to a sympathetic activation related to arousal which produces heart rate (HR) increment, higher stroke volume and vasoconstriction, which in turn generate pulse wave acceleration. Documented evidences indicate that PTT has high correlations when it is utilized as a surrogate semi-quantitative monitor of abrupt blood pressure changes.[17,18] We measured PTT decreases index-PTTdec, as the number of PTT decreases per hour of sleep (eTST). Each event is defined as a change of almost 20 ms, minimal duration 3 seconds and maximal duration 30 seconds. We also analyzed PTTdec related to respiratory events or PTTdec_respiratory, and PTT variations related to snoring or PTTdec_snore.

Sympathetic activation related to arousal produces a HR increment. We measured the HR acceleration index-HRacc, as the number of increases in the HR per hour of eTST and the number of cardiac arrhythmias[19] per hour of eTST using ECG included in the machine. In particular, HRacc is defined as the number of increases in the HR (40%) per hour of eTST (minimal duration: 3 seconds, maximal duration: 30 seconds), and arrhythmia is defined as the number of 20% distance variations between two R-waves per hour of eTST.

Statistical analysis

Statistical analysis was done using SPSS 22.0 statistics software for Windows. Descriptive statistics (mean, standard deviation and range) were calculated for the quantitative variables considered in this study. Percentage of children with addressed scoring (nails obstruction, tonsils enlargement and palate position) was also calculated.

Mann-Whitney test was performed between selected sub-groups (non-OSAS *vs*. OSAS obese patients) to explore differences between continuous measures. One-way ANOVA analysis was performed between selected sub-groups (non-OSAS *vs*. OSAS obese patients) to explore differences between categorical measures.

The strength of the association between two quantitative variables (BMI *Z* score and SDAG score) was evaluated by calculating the simple and partial correlation analysis.

Binary logistic regression model was employed to detect predictors of cluster membership between clusters of corresponding OSAS category. As such, two pairs were selected for comparisons: non-OSAS *vs*. OSAS obese children.

Results

Table 1 (panel A) shows the anthropometric characteristics of the obese children along with SDAG scores. There were 41 obese children (BMI >95th percentile) and 3 overweight children (BMI=93rd-94th percentile). SDAG scores were positive in a minority of patients (9.1%). In addition, 18.2% of children had a surgery previously (AHI=1.19±0.90 *n*/hour, range: 0.1-2.5 *n*/hour; ODI=1.19±0.93 *n*/hour, range: 0.1-2.5 *n*/hour). In 50% of these obese children, both AHI and ODI showed abnormal polygraph results. Table 1 (panel B) shows the distribution (percent of patients) of the clinical scoring regarding nails obstruction, tonsil enlargement and palate position.

Table 2 shows the results of the cardio-sleep respiratory parameters measured in the study. 31.8% of the obese patients had OSAS (AHI >1 event/hour), but none had >5.0 events/hour or moderate OSAS. AHI ≤1 event/hour or normal was observed in 68.2%.

Table 3 shows the results of the Mann-Whitney tests between non-OSAS and OSAS obese children category. PTTdec_respiratory (P<0.001) was different between the non-OSAS and OSAS obese children. One-

Table 1. Study population, anthropometric parameters, SDAG scoring (panel A), nails patency, tonsil enlargement and palate position (panel B) at the time of the polygraph study

Panel A

Physical characteristics	Mean	SD	Minimum-maximum
Number (% of males)	44 (54.5)	-	-
Age (y)	12.1	2.7	16.5-17.2
Weight (kg)	71.8	20.6	35.0-128.0
Height (cm)	155.0	13.5	122.0-182.0
BMI (kg/m^2)	29.3	5.0	23.5-46.5
BMI (percentiles)	97.9	1.7	93.0-100.0
BMI (*Z* score)	2.1	0.3	1.46-2.80
SDAG-inattentive (positive >14)	8.0	5.0	1.0-21.0
SDAG-hyperactive (positive >14)	6.4	4.9	0-20.0
SDAG-combined (positive >28)	14.5	9.3	1.0-38.0

BMI: body mass index; SD: standard deviation; SDAG: Italian attention deficit/hyperactivity disorder rating scale for parents. "-": none.

Panel B

Clinical evaluation	Scoring (percentage of patients)
Nails patency (right+left: 0=totally opened; 6=totally obstructed)	0 (45.5); 1 (22.7); 2 (11.4); 3 (18.2); 4 (2.3)
Tonsils hypertrophy (Mallampati)	1 (54.6); 2 (36.4); 3 (9.1)
Palate position (Friedman)	1 (40.9); 2 (43.2); 3 (11.4); 4 (4.5)

Table 2. Summary of the results of the respiratory sleep study of the obese patients

Respiratory parameters	Mean (SD)	Minimum-maximum
eTST (h)	8.2 (0.83)	6.5-10.0
OA (*n*/h)	0.2 (0.37)	0.0-1.3
H (*n*/h)	0.5 (0.7)	0.0-2.9
CA (*n*/h)	0.1 (0.2)	0.0-0.9
AHI (*n*/h)	0.9 (0.9)	0.0-4.1
Mean SpO_2 (%)	97.6 (0.7)	96.0-99.0
Minimum SpO_2 (%)	90.8 (3.5)	79.0-95.0
ODI (*n*/h)	0.9 (1.0)	0.0-3.7
Snoring (% of eTST)	3.1 (7.4)	0.0-39.0
Phase angle (degree)	37.1 (14.6)	15.0-85.0
HRacc (*n*/h)	38.8 (37.8)	4.9-244.1
Cardiac arrhythmia (*n*/h)	21.7 (40.8)	0.0-173.9
PTTdec (*n*/h)	75.8 (20.9)	21.6-109.8
PTTdec_respiratory (*n*/h)	0.4 (0.7)	0.0-2.70
PTTdec_snore (*n*/h)	3.1 (6.6)	0.0-37.9

eTST: estimated total sleep time; OA: obstructive apnea; H: hypopnea; CA: central apnea; AHI: apnea-hypopnea index; SpO_2: peripheral capillary oxygen saturation; ODI: oxygen desaturation index; HRacc: hearth rate acceleration; PTTdec: pulse transit time decreases; SD: standard deviation.

way ANOVA analysis revealed no significant difference in nails obstruction, tonsils enlargement and palate position scoring between obese children with non-OSAS and OSAS. Mann-Whitney test showed no significant difference in PTTdec between children with absent CA (n=24) and present CA (n=20, P=0.750), and between children with absent OA (n=21) and present OA (n=23, P=0.751). Moreover, no significant difference was found between PTTdec and CA (r=-0.164, P=0.288) or OA (r=0.888, P=-0.022). Interestingly, correlation analysis between PTTdec was significant only for ODI in our obese patients (r=0.386, P=0.010).

Table 3. Mann-Whitney test between non-OSAS (n=30) and OSAS (n=14) group category of physical characteristics and sleep respiratory parameters

Variables	Non-OSAS (n=30), mean (SD)	OSAS positive (n=14), mean (SD)	P value
Age (y)	12.2 (2.7)	11.9 (2.5)	0.650
BMI *Z* score	2.2 (0.3)	2.0 (0.4)	0.378
SDAG score	14.5 (9.2)	14.5 (10.0)	0.820
eTST	8.4 (0.8)	7.8 (0.8)	0.047
AHI (*n*/h)	0.4 (0.3)	2.0 (0.8)	<0.001
CA (*n*/h)	0.1 (0.1)	0.2 (0.3)	0.161
ODI (*n*/h)	0.5 (0.4)	1.9 (1.2)	0.001
Mean SpO_2	97.6 (0.7)	97.5 (0.7)	0.501
Minimum SpO_2	90.9 (4.0)	90.8 (2.1)	0.293
HRacc (*n*/h)	38.0 (43.4)	40.8 (22.9)	0.144
Arrhythmia (*n*/h)	20.2 (39.3)	21.7 (45.4)	0.371
Phase angle (degree)	37.4 (14.2)	36.6 (16.0)	0.715
Snoring (% of eTST)	1.8 (5.0)	5.7 (10.6)	0.537
PTTdec (*n*/h)	74.6 (21.7)	78.5 (19.7)	0.520
PTTdec_respiratory (*n*/h)	0.1 (0.2)	1.0 (0.9)	<0.001
PTTdec_snore (*n*/h)	2.2 (4.1)	5.0 (10.0)	0.255

OSAS: obstructive sleep apnea syndrome; BMI: body mass index; SDAG: Italian attention deficit/hyperactivity disorder rating scale for parents; eTST: estimated total sleep time; AHI: apnea-hypopnea index; CA: central apnea; ODI: oxygen desaturation index; SpO_2: peripheral capillary oxygen saturation; HRacc: hearth rate acceleration; PTTdec: pulse transit time decreases; SD: standard deviation.

Correlation and partial correlation analysis (adjusting for nostril obstruction, tonsils enlargement and palate position) revealed that BMI *Z* score correlated positively with phase angle, even adjusting for nostril obstruction, tonsils enlargement and palate position (P=0.033). SDAG score did not correlate with any cardio-respiratory parameters. Binary logistic regression analysis detected no clinical parameter was associated with the presence of OSAS.

Discussion

The main result of this study is the high frequency of sleep respiratory disruption, although mild, in one out of 5-6 obese patients being unselected for this problem. In addition, one of 5-6 patients undertook surgery prior to the polygraph study and, however 50% of them showed a persistent sleep respiratory disturbance persistence. Furthermore, obesity severity was associated with phase angle, a surrogate parameter of obstruction that can be linked to adiposity contributing to turaco-abdominal unbalance during respiration. Respiratory efforts were evidenced by increased amplitude of out-of-phase respiratory movements of the thorax and the abdomen in severely obese patients. Moreover, one out of 11 obese patients scored positive at SDAG. In addition, this study showed a significant difference of PTTdec variation associated with respiratory events between non-

OSAS and OSAS obese children. Therefore, this study failed to demonstrate a difference of snoring, arrhythmia index, overall PTTdec and SDAG score between mild OSAS and non-OSAS obese groups during sleep.

Sleep disorderd breathing (SDB) is a relevant complication in childhood obesity since it has been associated with long term complications, such as increased blood pressure, altered glucose metabolism and quality of life.[20] Cardiovascular consequences of OSAS include abrupt changes in autonomic tone, which can trigger cardiac arrhythmias.[19,21] In our patients with mild respiratory disturbance, it was not found a significant difference of HRacc, arrhythmia and overall PTTdec between OSAS and non-OSAS groups, suggesting an unrevealing cardiac involvement testified only by PTTdec variation in coincidence of respiratory events. In agreement, only those children with moderate-severe OSA had decreased PTT, indicating increased blood pressure compared with children with mild OSA.[22,23] Our children may not have been exposed to severe disease process enough for it to have an overt effect on the cardiovascular system during sleep.

Previously, PTT arousal was reported a sensitive measure of obstructive events in children.[24] Therefore, spontaneous variations of the blood pressure and PTTs can be seen during physiological sleep because variations in sympathetic tone are spontaneously high.[25] We found that PTTdec was slightly higher in obese children with OSAS, although not significant. On the contrary, the PTTdec_respiratory was significantly different, suggesting that respiratory disturbance was able to act on autonomic activity (leading to more PTTdec events) among obese children with underlined OSAS. In particular, recurrence of desaturation events leaded to an increased variation of the autonomic activity during sleep.

In our study group of children aged 12±3 years, mean AHI was lower (0.8±0.9 *n*/hour *vs*. 3.4±8.8 *n*/hour) than previously reported in 117 Spanish obese children with similar mean age (11±3 years) and BMI (29±5 *vs*. 28±5 kg/m^2).[26] In agreement with this study, we found that there was a high percentage of residual OSAS in those who undergone surgery. Children who are obese and have OSA might continue to have breathing difficulties even after having their tonsils and adenoids removed. Other abnormalities related to obesity may affect OSAS and may add to abnormalities of respiration during sleep.[1]

Adenotonsillar hypertrophy has been considered to be the main factor contributing to OSAS in both obese and non-obese children.[27] McKenzie et al[28] reported that in obese children only tonsillar hypertrophy, history of apnea and restless sleep (but not BMI) were significantly related to significant OSA detected by oximetry and audiovisual recordings. In obese children, the clinical staging of tonsil size was a useful measure to predict OSAS.[29] Only enlarged tonsils were predictive of moderate-to-severe OSAS in these children.[30] Kang et al[31] reported that obese children had a significantly higher AHI, OA index and lower minimum SpO_2, with tonsillar hypertrophy remaining as a major determinant. Adenoid size is important in obese children with symptoms of sleep disordered breathing because it is strongly related to the presence of OSAS.[32] In our obese children, nails patency, tonsils enlargement and palate position seems not to be differently related to sleep respiratory symptomatology. Recently, we showed that snoring, objectively measured by polygraph, was associated with palate position and ODI.[33] The present study, did not showed differences regarding clinical grading for nails, tonsils and palate between obese children with and without OSAS, suggesting that other factors can be involved in a subset of these obese patients. Finally, in our obese children, snoring doesn't affect SDAG score.

Concerning the degree of obesity, from a large clinical sample of Australian Caucasian children undergoing overnight PSG for the evaluation of snoring, regression analyses revealed that increased BMI was a weak predictor of OSAS.[34] In other studies, the degree of obesity was considered an aggravating factor for OSAS. In particular, the prevalence of OSAS was significantly higher in obese children, with or without adenotonsillar hypertrophy, than their nonobese counterparts.[35] Kang et al[31] reported that both obesity and tonsillar hypertrophy were predictive of OSAS. Overweight and obesity were considered a significant risk for OSAS among adolescents, when in combination with snoring and adenotonsillar hypertrophy.[36] Therefore, obese children had smaller adenotonsillar size than nonobese ones with similar degrees of OSAS severity.[37] This suggests that a smaller change in magnitude of adenotonsillar size was required among obese children for an equivalent change in severity of upper airway obstruction.[27,37] The level of obesity remains an important aggravating factor for OSAS and reduced pulmonary function.[36] Mitchell et al[38] showed that obesity, ethnicity (African American) and the Pediatric Sleep Questionnaire total score were associated with higher levels of AHI and ODI. Tonsil size and palate position were not associated with those higher levels. These patients were recruited among those who were considered candidates for adenotonsillectomy, including different races and BMI.

ADHD is a common childhood disorder. Most prevalence estimates range between 3% and 7%.[39] Recent reports have highlighted neurocognitive consequences of OSAS including decreased concentration, reduced memory, and behavioral manifestations such as hyperactivity mimicking

ADHD.[39,40] Therefore, our study failed to demonstrate an overall difference in attention and hyperactivity symptoms between obese OSAS and non-OSAS children. The percentage of patients with symptoms was double than that expected from the general population; if ADHD may be associated with increased risk of obesity is questioned in the literature.[41] It is possible that, given the limitation of the number of patients the observation can be due to a pitfall in the sampling.

Limitations of the present study were related to the fact that we did not have a scoring of sleep, and TST was only estimated. However, many cardiorespiratory sleep studies (including our own) were undertake with thorax and abdomen effort bands, airflow measures, ECG, SpO_2 monitoring,[42] snoring by laryngeal microphone and position analysis[43] with good sensitivity and specificity[44,45] also for school-aged children.[1]

This technique did not distinguish between airway obstruction and out-of-phase breathing normally present in active sleep, and it is another limitation. Nevertheless, we found a correlation between phase angle and BMI *Z* score suggesting that adiposity may alter thorax and abdomen expansion relationship. Moreover, we did not evaluate the adenoid size, which requires nasal fibroscopy or radiology, but we tested for a simple made nails obstruction test.

Another potential limitation of the study is that our in-hospital monitoring is carried out in an unnatural environment and conditions in a designed sleep chamber. However, we did not evaluate both sleep efficiency and quality but the respiratory parameters during sleep, which they can be less influenced by environmental conditions.

Also the cross-sectional design of our study is such that the results cannot explain the cause-effect relationship but just associations between variables. Finally, wide age range of children recruited may be inappropriate, but BMI Z score variable takes into account the age and gender of the child.

Strengths of the study are: 1) Obese children referred to our ambulatory were not mentioned for sleep respiratory problems; this supposes that a not-overt problem alerted their physician practitioners; 2) The simplicity of the parameters used and the questionnaire for parents are really affordable in the clinical setting; 3) The time-sparing evaluation of the risk factor for SDB in obese children in ambulatory setting; in particular, just a few minutes are necessary to evaluate the needs for a sleep respiratory study.

In conclusion, in our cohort of obese children, we found a high rate of mild sleep respiratory disturbance and an ADHD-like symptoms referred by parents. Therefore, they are not linked each other. The respiratory disturbance is not totally cured by surgery in half of these patients. Therefore, otorhinolaryngology variables scoring was not able to explain mild sleep respiratory disturbance observed in these patients. Other variables, perhaps an increased pharyngeal collapsibility during sleep in one out of third obese children, must be taken into account making these subjects at risk for long-term persistence.

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