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SCIENTIFIC INVESTIGATIONS

# Evaluation of obesity and asthma as risk factors for moderate to severe obstructive sleep apnea in children

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**Study Objectives:** Asthma and obesity are risk factors for obstructive sleep apnea (OSA) in children but their link to OSA severity is uncertain. We aimed at determining whether asthma or obesity was associated with an increased risk of moderate/severe OSA.

**Methods:** Children undergoing a one-night polysomnography for suspicion of OSA were retrospectively included. Univariate and multivariate analyses were conducted to assess the clinical and demographic characteristics linked to moderate/severe OSA (obstructive apnea-hypopnea index ≥ 5 events/h of sleep) with odds ratio and 95% confidence interval reported.

**Results:** Four hundred ninety children (311 [64%] boys) were included with a median [25th; 75th percentile] age of 8.7 [5.4; 12.9] years, 164 (33%) nonasthmatics nonobese, 122 (25%) obese nonasthmatics, 125 (26%) asthmatics nonobese, 79 (16%) asthmatics and obese. Moderate/severe OSA was present in 157 (32%) children (75/157 [48%] obese and 52/157 [33%] asthmatics). Independent factors associated with increased or decreased risk of moderate/severe OSA were obesity and male sex (odds ratio 1.82 [1.16; 2.87], $P = .01$, and 1.55 [1.02; 2.36], $P = .04$, respectively), and current asthma, age > 6 years, or behavioral disorders (odds ratio 0.45 [0.29; 0.70], $P < .001$; 0.44 [0.27; 0.73], $P < .001$; and 0.55 [0.33; 0.92], $P = .02$, respectively). Abnormal resistance of the respiratory system (measured in 241 children), but not abnormal spirometry (measured in 213 children), increased the risk of moderate/severe OSA (odds ratio 2.95 [1.46–5.96], $P = .003$).

**Conclusions:** In our cohort enriched in obese and asthmatic children, obesity was associated with higher risk of moderate/severe OSA whereas current asthma was not.

**Keywords:** polysomnography, apnea index, children, asthma, obesity

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**BRIEF SUMMARY**

**Current Knowledge/Study Rationale:** Asthma and obesity are 2 disorders for which the relationships with obstructive sleep apnea are not totally elucidated.

**Study Impact:** In our large cohort enriched in obese and asthmatic school-aged children, obesity and male sex increased the risk to have moderate or severe obstructive sleep apnea compared to no or mild obstructive sleep apnea. Current asthma, child's age > 6 years, and behavioral problems were likely to be associated with less severe obstructive sleep apnea. Obesity and asthma have opposite effects in our school-aged children with suspicion of obstructive sleep apnea.

## INTRODUCTION

Obstructive sleep apnea (OSA) is characterized by repeated episodes of upper airway obstruction leading to a decrease (hypopnea) or an arrest (apnea) of the airflow.[1] OSA prevalence in children is about 2 to 5%, being most common between 2 and 6 years of age.[1,2] Hypertrophy of adenoids and tonsils narrow the airway lumen and represent the primary cause of OSA, especially in children with no chronic condition.[3] OSA syndrome is characterized by nighttime symptoms (snoring, disrupted sleep, awakenings, or respiratory efforts) associated with daytime symptoms (sleepiness, irritability, or hyperactivity). Polysomnography (PSG) in a sleep lab is the gold standard to confirm OSA diagnosis and to assess its severity.[1]

In children, untreated OSA may lead to neurocognitive complications (attention deficit interfering with learning abilities), behavioral disorders (hyperactivity and irritability) and, in the long term, impaired growth, cardiovascular diseases with systemic and pulmonary hypertension, and metabolic syndrome.[4] Adenotonsillectomy usually resolves OSA symptoms. Nevertheless, severe OSA might be associated with persistent symptoms postadenotonsillectomy for which several risk factors have been involved such as obesity, asthma, male sex, craniofacial abnormalities, and prematurity.[1] Asthma and obesity are frequent and treatable conditions

for which the relationships with OSA are not totally elucidated. There is a bidirectional link between OSA and obesity, both conditions being characterized by the presence of a systemic inflammation. The metabolic syndrome can be a complication of OSA,[5,6] while obesity or rapid increase in body mass index (BMI) are established risk factors for OSA.[7–9] The relationship between asthma and OSA is debatable because chronic upper airway inflammation is present in both diseases. In some studies asthma was found to be a protective factor for OSA,[10] while in others it was a risk factor for OSA.[11] Finally, obesity and asthma may also be related as increasing weight is associated with more frequent or more severe asthma exacerbations and with more difficult-to-control symptoms.[12] This latter finding may result from the multiple effects of obesity on pulmonary function.[13]

In this study, we aimed to clarify the interaction between asthma, obesity, and OSA severity. Our hypothesis was that OSA severity in children could depend on the presence of obesity and/or of asthma, these 2 comorbidities being likely to have a synergistic effect. The main objective was to evaluate whether obesity and asthma could predict the risk of moderate to severe OSA in children, taking into account other demographic and clinical characteristics. In order to reach conclusions, we needed to study a population including a large number of children having 1 or both of these comorbidities and likely to have OSA on clinical assessment.

The secondary hypothesis was that obesity and asthma could influence OSA severity through their consequences on pulmonary function, ie, the former decreases resting volume (rapid onset of desaturations and increased upper airway collapsibility[14]) and the latter induces bronchial obstruction (increased lower airway resistance and decreased dynamical compliance[15,16]). To answer this question, we studied whether different pulmonary function patterns constituted risk factors of more severe OSA in asthmatic and obese children.

## METHODS

This is a retrospective cohort study including children aged 0 to 18 years who underwent a PSG in the sleep unit of Armand Trousseau University Hospital in Paris, France, between March 2014 and January 2019. Only one file per child (the first one if repeated recordings) including PSGs performed for suspicion of OSA was selected. The exclusion criteria were PSG recorded in children with chronic comorbidities other than asthma or obesity (such as genetic disorders, craniofacial anomalies, neuromuscular disorders, cerebral palsy, or prematurity with gestational age of < 35 weeks), PSG with less than 4 hours of recording time, and children treated with continuous positive airway pressure, noninvasive ventilation, or oxygen therapy. Children and their parents were informed of the possible retrospective use of their data and gave oral consent.

### PSG

Nocturnal PSG was performed using the PSG device CID102-108D (CIDELEC, Sainte Gemmes sur Loire, France). Electroencephalogram with 3 derivations (F2-A1, C4-A1, and O2-A1), 2 electrooculograms, and 2 chin electromyogram recordings were used to define sleep stages and arousals. We scored respiratory events according to the American Academy of Sleep Medicine recommendations for children, using a nasal cannula to record respiratory flow, thoraco-abdominal belts and suprasternal pressure transducer to monitor respiratory efforts, a microphone to detect snoring, pulse oximetry to count oxygen desaturations, electrocardiogram to record cardiac frequency, and actimetry to assess body positioning.[17] The following indices were retained for analysis: total sleep time, sleep efficiency computed as the total sleep time reported to the period from the first falling asleep until the last awakening, obstructive apnea-hypopnea index (OAHI) as the sum of obstructive apneas and of hypopneas associated with a ≥ 3% desaturation and/or microarousal or arousal per hour of sleep, oxygen desaturation index as the number of ≥ 3% desaturation episodes per hour of sleep, snoring index as the number of snoring episodes per hour of sleep, and microarousal index as the number of microarousals per hour of sleep. Transcutaneous partial pressure of $CO_2$ ($TcPCO_2$) was used to detect nocturnal alveolar hypoventilation defined as $TcPCO_2 > 50$ mm Hg for > 25% of total sleep time.

### Clinical characteristics

Children's clinical data were extracted from the standardized questionnaire filled out during the medical appointment on the day of PSG recording or a few days before. We retrieved demographic characteristics, ie, age, sex, weight, height, BMI, ethnicity, medical history of prematurity, atopy, passive smoking, previous tonsillectomy, current asthma, rhinitis, primary or secondary enuresis, behavioral disorder or teachers' complaint, and family history of tonsillectomy or sleep disorders. Endobuccal examination was performed to assess tonsils volume (hypertrophy when Friedman score ≥ 2),[18] buccal aperture (reduced when Mallampati score ≥ 3),[19] and malocclusion of the teeth.

### Pulmonary function testing

Children older than 3 years of age underwent pulmonary function testing (PFT) on the day of the PSG if they were obese or had asthma or atopy or a history of asthma or of recurrent atypical respiratory symptoms. PFT data were collected from the unique database of the department. Short-acting bronchodilator (BD) therapy was withheld for 8 h before PFT. Spirometry, lung volumes, and resistance by interrupter technique (Rint) measurements were performed according to pediatric recommendations using a plethysmograph BodyBox (Medisoft, Sorinnes, Belgium) and a Whistler device (MediSpirit, Nuenen, The Netherlands), respectively.[20–22] Spirometry and Rint measurements were repeated after inhalation of a BD (salbutamol 400 µg). Pulmonary function indices included in the analysis were total lung capacity and functional residual capacity (FRC) expressed as absolute values and as percentages of the predicted values (total lung capacity % and FRC%, respectively)[23]; baseline and post-BD forced vital capacity (FVC), forced expiratory volume in 1 second ($FEV_1$), and $FEV_1$/FVC ratio, expressed as absolute values and as z-scores (zFVC, $zFEV_1$, and $zFEV_1$/FVC for baseline, respectively)[24]; $FEV_1$ response to BD ($\Delta FEV_1$, expressed as percentage of predicted value); Rint measurement at baseline and after BD (Rint-postBD) expressed as absolute values and as percentage of predicted values

(Rint% and Rint-postBD%); and Rint response to BD (ΔRint, expressed as percentage of predicted value).[25,26]

### Statistical analysis

Statistical analysis was performed using SAS 9.4 (SAS Institute, Cary, North Carolina) and R 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria) software. Quantitative variables were expressed as median [25th; 75th percentile] and qualitative variables as number (percentage). Overweight and obesity were defined using the World Health Organization Child Growth Standards and definitions (https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight). Overweight and obesity corresponded to BMI z-scores 2 to 3, or > 3 in children less than 5 years of age, respectively, and to BMI z-scores 1 to 2, or > 2 from the age of 5, respectively.

OSA was defined as OAHI ≥ 1.5 events/h of sleep and it was classified as mild, moderate, or severe (OAHI ≥ 1.5 events/h and ≤ 5 events/h, > 5 events/h and ≤ 10 events/h, > 10 events/h, respectively).[1] Children were divided into 4 groups according to the presence or absence of asthma and obesity as follows: No-Asthma/No-Obesity group (NAs/NOb), No-Asthma/Obesity group (NAs/Ob), Asthma/No-Obesity group (As/NOb), and Asthma/Obesity group (As/Ob). Comparisons between these groups were performed using an analysis of variance test and Tukey-Kramer procedure or chi-square test as needed.

A logistic regression model was created with nonproportional cumulative odds to study the factors associated with the severity of OSA considered as an ordinal categorical variable. The results were presented as odds ratio (OR) of the probability of being greater than each threshold and their 95% confidence interval (the threshold shown in results is "no OSA/mild OSA versus moderate/severe OSA"). The model was cumulative because the probability of being above a threshold was estimated, and the assumption of proportional odds was not respected (the odds of each threshold were not equal to each other). The log-linearity assumption was tested for all quantitative covariates and the covariate was categorized if the assumption was not checked. A multivariate model was constructed including clinical variables associated with OSA severity selected from the variables with $P < .20$ in the univariate analysis that included all demographic characteristics and clinical history detailed in **Table 1** (except for height, weight, and BMI), while ethnicity, obesity, and current asthma were forced into the model because of their possible influence. $TcPCO_2$ and PFT results were not included in this multivariate analysis due to too many missing data, but PFT results were tested in a univariate model. A stepwise descendant selection based on the Akaike information criterion to discriminate models was used to optimize the choice of variables in the final multivariate model. Statistical tests used were 2-sided and a $P$ value ≤ 0.05 was considered significant.

## RESULTS

### Children's characteristics

Four hundred ninety children with a median [25th; 75th percentile] age of 8.7 [5.4; 12.9] years undergoing a PSG for suspicion of OSA were selected; 311 (64%) were boys. Their demographic and clinical characteristics are presented in **Table 1**. According to the presence of obesity and asthma there were 164 (33%) children in the NAs/NOb group, 122 (25%) children in the NAs/Ob group, 125 (26%) children in the As/NOb group, and 79 (16%) children in the As/Ob group (**Table 2**). Demographic and clinical characteristics of these 4 groups and their comparisons are shown in **Table 2**. The proportion of children

**Table 1**—Anthropometrics and clinical characteristics of the 490 study children.

| | |
|---|---|
| Number of children | 490 |
| Male | 311 (64) |
| Age, y | 8.7 [5.4; 12.9] |
| Height, cm / (z-score) | 136 [115; 158] / 0.90 [0.05; 1.82] |
| Weight, kg / (z-score) | 35.5 [20.0; 73.0] / 2.04 [0.24; 6.40] |
| BMI, $kg \cdot m^{-2}$ / (z-score) | 19.0 [15.7; 30.5] / 1.47 [−0.15; 4.29] |
| Overweight / obese | 48 (10) / 201 (41) |
| Ethnicity | |
| Caucasian | 345 (70) |
| African-Caribbean | 104 (21) |
| Metis | 30 (6) |
| Asian | 11 (2) |
| History | |
| Prematurity | 36/489 (7) |
| Passive smoking | 157/487 (32) |
| Atopy | 142/484 (29) |
| Adenoidectomy / adenotonsillectomy | 149/486 (31) / 69/486 (14) |
| Family history of tonsillectomy | 124/484 (26) |
| Family history of sleep-disordered breathing | 228/486 (47) |
| Clinical examination | |
| Behavioral disorders | 112/486 (23) |
| Poor concentration span | 89/109 (82) |
| Hyperactivity | 49/109 (45) |
| Aggressive behavior with peers | 7/109 (6) |
| Disobedience, defiant with adults | 12/109 (11) |
| Emotional lability | 8/109 (7) |
| Learning disability | 6/109 (6) |
| Current chronic rhinitis | 146/482 (30) |
| Primary / secondary enuresis | 32/471 (7) / 67/471 (14) |
| Hypertrophy of palatine tonsils* | 288/474 (61) |
| Crowded oropharynx† | 89/453 (20) |
| Malocclusion of teeth | 179/480 (37) |

Data are expressed as median [25th; 75th percentile] or as number (percent). *Hypertrophy of palatine tonsils defined as Friedman score ≥ 2. †Crowded oropharynx defined as Mallampati score ≥ 3. BMI = body mass index.

**Table 2**—Description and comparisons of clinical characteristics according to presence or absence of asthma and obesity in the 490 study children.

| | NAs/NOb Group | NAs/Ob Group | As/NOb Group | As/Ob Group |
|---|---|---|---|---|
| Total number n (%) | 164 (33) | 122 (25) | 125 (26) | 79 (16) |
| Age, y | 7.4 [4.5;10.6] | 12.6 [9.9; 15.4] | 5.7 [4.8; 8.2] | 11.1 [8.1; 15.1] |
| Boys | 101 (62) | 64 (53) | 89 (71) | 57 (72) |
| BMI, $kg{\cdot}m^{-2}$ | 16.1 [14.5; 17.7] | 33.7 [29.0; 40.8] | 16.1 [15.0; 18.0] | 30.7 [24.8; 37.7] |
| BMI (z-score) | −0.07 [−1.02; 0.84] | 4.75 [3.94; 5.46] | 0.29 [−0.52; 1.16] | 4.44 [3.87; 5.00] |
| Ethnicity origin | | | | |
| Caucasian | 126 (77) | 81 (66) | 93 (74) | 45 (57) |
| African-Caribbean | 23 (14) | 34 (28) | 23 (18) | 24 (30) |
| Mixed | 11 (7) | 6 (5) | 7 (6) | 6 (8) |
| Asian | 4 (2) | 1 (1) | 2 (2) | 4 (5) |
| History | | | | |
| Prematurity | 8 (5) | 2 (2) | 17/124 (14) | 9 (11) |
| Passive smoking | 41 (25) | 49 (40) | 35/122 (29) | 32 (41) |
| Atopy | 31/162 (19) | 15/120 (13) | 55/123 (45) | 41 (52) |
| Adenotonsillectomy | 19 (12) | 13/120 (11) | 22/123 (18) | 15 (19) |
| Family history of tonsillectomy | 41/163 (25) | 31 (25) | 35/121 (29) | 17/78 (22) |
| Family history of sleep disorder | 69 (42) | 63/120 (53) | 55/124 (44) | 41/78 (53) |
| Clinical examination | | | | |
| Behavioral disorders | 50/163 (31) | 20/121 (17) | 30/123 (24) | 12 (15) |
| Current chronic rhinitis | 43/161 (27) | 26/121 (22) | 48/123 (39) | 29/78 (37)† |
| Primary enuresis | 21/157 (13) | 2/121 (2) | 7/115 (6) | 2/78 (3) |
| Secondary enuresis | 21/157 (13) | 18/121 (15) | 14/115 (12) | 14/78 (18) |
| Hypertrophy of palatine tonsils* | 109/161 (68) | 69/116 (60) | 70/120 (58) | 40/77 (52)‖ |
| Crowded oropharynx$ | 38/152 (25) | 24/116 (21) | 17/113 (15) | 10/72 (14)‡ |
| Malocclusion of teeth n (%) | 74/161 (46) | 38/120 (32) | 42/122 (34) | 25 (33) |

Data are expressed as median [25th; 75th percentile] or as number (percent). Percentages are related to the total number of children in the group or in case of missing data the denominator is specified. *Hypertrophy of palatine tonsils defined as Friedman score ≥ 2. $Crowded oropharynx defined as Mallampati score ≥ 3. †Significant differences between groups ($P$ = .008), with more frequent rhinitis in asthmatic children. ‖No between-group difference for the frequency of hypertrophy of palatine tonsils; $P$ = .11. ‡No between-group difference for the frequency of crowded oropharynx; $P$ = .12. As/NOb = Asthma/No-Obesity group, As/Ob = Asthma/Obesity group, BMI = body mass index, NAs/NOb = No-Asthma/No-Obesity group, NAs/Ob = No-Asthma/Obesity group.

with chronic rhinitis was higher in the 2 groups including asthmatic children (As/NOb and As/Ob) compared to groups without asthmatics (NAs/Ob and NAs/NOb) ($P$ = .008), but hypertrophy of palatine tonsils or crowded oropharynx was similarly present across the 4 groups ($P$ = .11 and $P$ = .12, respectively).

## Polysomnographic data

In the whole study population, PSG data indicated a median [25th; 75th percentile] total sleep time of 508 [454; 550] minutes with sleep efficiency at 85 [78; 91]% and OAHI of 3.0 [1.4; 5.8] events/h. OSA, which was detected in 374 (76%) of the study children, was mild in 217 (44%) cases, moderate in 84 (17%) cases, and severe in 73 (15%) cases. The between-group comparisons of sleep results according to the presence of asthma and obesity are presented in **Table 3**. OAHI was significantly different in As/Ob children ($P$ = .002) but only was OAHI of lean asthmatic children (As/NOb) significantly lower than that of obese asthmatic children (As/Ob) ($P$ = .001). There was no other between-group difference for sleep results. Among the 332 children with $TcPCO_2$ recorded without technical problems, only 20 (6%) had alveolar hypoventilation, of which 13 had moderate or severe OSA. In the remaining 7 children, maximum $TcPCO_2$ ranged from 51 to 56 mm Hg, in favor of mild alveolar hypoventilation.

## PFT results

Pulmonary function indices were available in 316 (65%) children. Lung volumes, Rint, and spirometry measurements were available in 172 (35%) children, 241 (49%) children, and 213 (43%) children, respectively (**Table 4**). Obese asthmatic children (As/Ob) had significantly lower FRC% ($P$ < .001), especially when compared to lean children with or without asthma ($P$ < .001 vs As/NOb, and $P$ = .031 vs NAs/NOb). But also, nonasthmatic obese

**Table 3**—Description and comparisons of sleep studies across the 4 groups of children according to presence or absence of asthma and obesity.

| | NAs/NOb Group | NAs/Ob Group | As/NOb Group | As/Ob Group |
|---|---|---|---|---|
| Number of children | 164 | 122 | 125 | 79 |
| TST, min | n = 161 527 [481; 568] | n = 122 484 [435; 525] | n = 124 526 [472; 558] | n = 79 491 [434; 532] |
| Sleep efficiency, % | n = 161 87 [78; 92] | n = 122 84 [77; 90] | n = 124 85 [81; 89] | n = 78 85 [76; 92] |
| OAHI (events/h) | n = 164 3.3 [1.6; 5.8] | n = 122 3.2 [1.5; 7.8] | n = 125 2.5 [1.3; 4.3] | n = 79 3.3 [1.5; 10.1]* |
| Oxygen desaturation index (/h) | n = 163 1.4 [0.3; 3.3] | n = 121 2.0 [0.9; 7.6] | n = 122 0.8 [0.4; 2.4] | n = 79 2.2 [0.9; 10.1] |
| Nadir oxygen saturation, % | n = 163 92 [90; 93] | n = 122 91 [87; 93] | n = 122 92 [89; 93] | n = 79 91 [86; 92] |
| $TcPCO_2$, mm Hg | n = 88 43 [41; 45] | n = 94 43 [41; 46] | n = 85 42 [40; 44] | n = 65 44 [41.5; 46] |
| $TcPCO_2$ > 50 mm Hg for > 25% TST | 3 (3) | 8 (8) | 4 (5) | 5 (8) |
| Microarousal index (/h) | n = 158 7.3 [5.3; 9.9] | n = 119 6.5 [4.4; 11.5] | n = 124 6.2 [4.2; 10.0] | n = 79 6.9 [4.9; 13.8] |
| Snoring index (/h) median | n = 155 126 [24; 294] | n = 120 203 [54; 451] | n = 123 93 [9; 276] | n = 79 236 [51; 421] |
| No-OSA (OAHI < 1.5 events/h) | 35 (21) | 29 (24) | 34 (27) | 18 (23) |
| Mild OSA (OAHI ≥ 1.5 events/h and ≤ 5 events/h) | 71 (43) | 46 (38) | 67 (54) | 33 (42) |
| Moderate OSA (OAHI > 5 events/h and ≤ 10 events/h) | 36 (22) | 24 (20) | 19 (15) | 5 (6) |
| Severe OSA (OAHI > 10 events/h) | 22 (13) | 23 (19) | 5 (4) | 23 (29) |

Number of children is the top cell of each column or specified in the cell in case of missing data. Data are expressed as median [25th; 75th percentile] or as number (percent). *$P$ = .002 (analysis of variance), with significant difference between the As/NOb vs As/Ob groups. As/NOb = Asthma/No-Obesity group, As/Ob = Asthma/Obesity group, NAs/NOb = No-Asthma/No-Obesity group, NAs/Ob = No-Asthma/Obesity group, OAHI = obstructive apnea-hypopnea index, OSA = obstructive sleep apnea, $TcPCO_2$ = transcutaneous partial pressure of CO2, TST = total sleep time.

children (NAs/Ob) had a significantly or nearly significantly lower FRC% compared to lean children with or without asthma ($P$ < .001 vs As/NOb, and $P$ = .062 vs NAs/NOb). Similarly, baseline Rint% ($P$ < .001), Rint post-BD% ($P$ < .001), and ΔRint after BD ($P$ = .005) were significantly different across the 4 groups with Rint% and Rint post-BD% being significantly higher in obese children compared to lean children (**Table 4**). The $zFEV_1$/FVC was significantly lower only in As/Ob children compared to NAs/NOb children ($P$ = .047 for between-group Tukey test and 0.02 in analysis of variance).

## Univariate analysis

The risk factors associated with OSA severity in the univariate analysis are presented in **Figure 1**. As we observed an inflection point at 6 years in the curve representing the relationship between the log(odds ratio) and age, we studied the effect of age using this cut-off in order to not violate the proportional odds assumption. Obesity (OR 1.50 [1.02–2.21], $P$ = .04), Mallampati score ≥ 3 (OR 1.63 [1.01–2.64], $P$ = .045) and increased baseline Rint% (OR 2.95 [1.46–5.96], $P$ = .003) were found to increase the risk of moderate/severe OSA in comparison to no/mild OSA. Conversely, current asthma (OR 0.59 [0.40–0.88], $P$ = .01) and behavioral problems (OR 0.53 [0.33–0.87], $P$ = .01) were likely to be associated with less risk of moderate/severe OSA. Atopy or chronic rhinitis were not found to increase the risk of moderate/severe OSA (OR 0.74 [0.48–1.14], $P$ = .17 and 0.90 [0.59–1.37], $P$ = .62, respectively). Regarding pulmonary function indices, there was an increased risk of moderate/severe OSA in case of abnormal high Rint% (n = 241, OR 2.95 [1.46–5.96]; $P$ = .003), while no such risk existed with other pulmonary function indices including $zFEV_1$/FVC (n = 213, OR 0.89 [0.66–1.19], $P$ = .42).

## Multivariate analysis

**Figure 2** represents the clinical risk factors associated with OSA severity in the multivariate analysis performed without pulmonary function indices included. Male sex and obesity were independently associated with an increased risk of moderate/severe OSA (OR 1.55 [1.02; 2.36], $P$ = .04 and 1.82 [1.16; 2.87], $P$ = .01, respectively). Conversely, age > 6 years, behavioral disorders, and current asthma were likely to be associated with less risk of moderate/severe OSA (OR 0.44 [0.27; 0.73], $P$ = .001; 0.55 [0.33; 0.92], $P$ = .02; and 0.45 [0.29; 0.70], $P$ < .001, respectively).

# DISCUSSION

Our study conducted in a large cohort of school-aged children undergoing a PSG for suspicion of OSA found that obesity and male sex increased the severity of OSA, whereas child's age > 6 years, behavioral problems, and current asthma were likely to be associated with less risk of moderate/severe OSA. In a subgroup of patients with PFT, the risk of moderate/severe OSA was 3 times increased in the presence of an abnormal resistance of the respiratory system, Rint, whereas other

**Table 4**—Description and comparisons of pulmonary function tests across the 4 groups of children according to presence or absence of asthma and obesity.

| | NAs/NOb Group | NAs/Ob Group | As/NOb Group | As/Ob Group |
|---|---|---|---|---|
| Pulmonary function testing, n = 316° | n = 27 | n = 107 | n = 105 | n = 77 |
| Plethysmography | | | | |
| TLC measurement, n = 172 | n = 14 | n = 81 | n = 24 | n = 53 |
| TLC, L | 3.3 [2.7; 4.1] | 4.7 [3.9; 5.4] | 3.5 [2.9; 4.1] | 4.4 [3.3; 5.2] |
| TLC, % predicted | 94 [82; 99] | 100 [94; 107] | 96 [90; 100] | 99 [89; 108]* |
| FRC measurement, n = 163 | n = 17 | n = 70 | n = 26 | n = 50 |
| FRC, L | 1.6 [1.1; 2.0] | 1.9 [1.5; 2.1] | 1.5 [1.3; 1.8] | 1.6 [1.3; 2.1] |
| FRC, % predicted | 87 [77; 93] | 79 [67; 86] | 85 [78; 100] | 77 [69; 83]† |
| Spirometry, n = 213 | n = 18 | n = 90 | n = 42 | n = 63 |
| FVC, L | 2.3 [1.9; 2.9] | 3.5 [3.0; 4.2] | 2.3 [1.8; 2.8] | 3.2 [2.4; 4.1] |
| FVC z-score | −0.01 [−0.84; 0.60] | 0.56 [0.00; 1.21] | 0.30 [−0.30; 0.88] | 0.66 [−0.22; 1.23] |
| $FEV_1$, L | 2.0 [1.7; 2.6] | 3.0 [2.5; 3.6] | 2.0 [1.5; 2.4] | 2.7 [2.0; 3.4] |
| $FEV_1$ z-score | 0.12 [−0.83; 0.44] | 0.30 [−0.44; 0.94] | 0.15 [−0.50; 0.81] | 0.14 [−0.88; 0.89] |
| $FEV_1$/FVC | 0.86 [0.83; 0.91] | 0.85 [0.81; 0.88] | 0.86 [0.83; 0.91] | 0.83 [0.78; 0.87] |
| $FEV_1$/FVC z-score | −0.27 [−0.61; 0.30] | −0.28 [−1.08; 0.04] | −0.26 [−0.97; 0.32] | −0.80 [−1.47; −0.19]‡ |
| $\Delta FEV_1$, % predicted | 4.7 [2.2; 6.4] | 3.4 [0.0; 6.1] | 4.0 [0.4; 8.6] | 3.9 [0.9; 7.1] |
| Rint measurement, n = 241 | n = 16 | n = 81 | n = 85 | n = 59 |
| Rint, $kPa \cdot s^{-1} \cdot L^{-1}$ | 0.80 [0.67; 0.98] | 0.62 [0.48; 0.75] | 0.96 [0.83; 1.06] | 0.72 [0.55; 0.92] |
| Rint, % predicted | 125 [119; 139] | 170 [147; 224] | 135 [120; 151] | 183 [151; 215]# |
| Rint-post BD, $kPa \cdot s^{-1} \cdot L^{-1}$ | 0.67 [0.57; 0.74] | 0.51 [0.43; 0.62] | 0.77 [0.65; 0.91] | 0.60 [0.46; 0.75] |
| Rint-post BD, % predicted | 106 [97; 118] | 148 [126; 177] | 113 [96; 123] | 152 [119; 176]¶ |
| ΔRint, % predicted | −23 [−31; −15] | −33 [−48; −16] | −19 [−34; −9] | −29 [−48; −16]‖ |

°Number of children with at least one result using the pulmonary function technique. Data are expressed as median [25th; 75th percentile]. *$P$ = .045 (ANOVA) with no between group difference found with Tukey-Kramer test. †$P$ < .001 (ANOVA) with significant differences between As/Ob vs NAs/NOb ($P$ = .031) and As/NOb ($P$ < .001), and between As/NOb vs NAs/Ob ($P$ < .001). ‡$P$ = .02 (ANOVA) with significant differences between As/Ob vs NAs/NOb ($P$ = .047). #$P$ < .001 (ANOVA) with significant differences between NAs/Ob and NAs/NOb ($P$ < .0001) or As/NOb ($P$ < .0001), and between As/Ob and NAs/NOb ($P$ = .0001) or As/NOb ($P$ < .0001). ¶$P$ < .001 (ANOVA) with significant differences between NAs/Ob and NAs/NOb ($P$ < .0001) or As/NOb ($P$ < .0001), and between As/Ob and NAs/NOb ($P$ = .0002) or As/NOb ($P$ < .0001). ‖$P$ = .005 (ANOVA) with significant differences between As/NOb and NAs/Ob ($P$ = .015) or As/Ob ($P$ = .023). ANOVA = analysis of variance, As/NOb = Asthma/No-Obesity group, As/Ob = Asthma/Obesity group, BD = short-acting bronchodilator, $FEV_1$ = forced expiratory volume in 1 s, $\Delta FEV_1$ = $FEV_1$ response to bronchodilator, NAs/NOb = No-Asthma/No-Obesity group, NAs/Ob = No-Asthma/Obesity group, TLC = total lung capacity, FRC = functional residual capacity, FVC = forced vital capacity, Rint = resistance measured by interrupter technique, Rint-postBD = Rint value after bronchodilator administration, ΔRint = Rint response to BD.



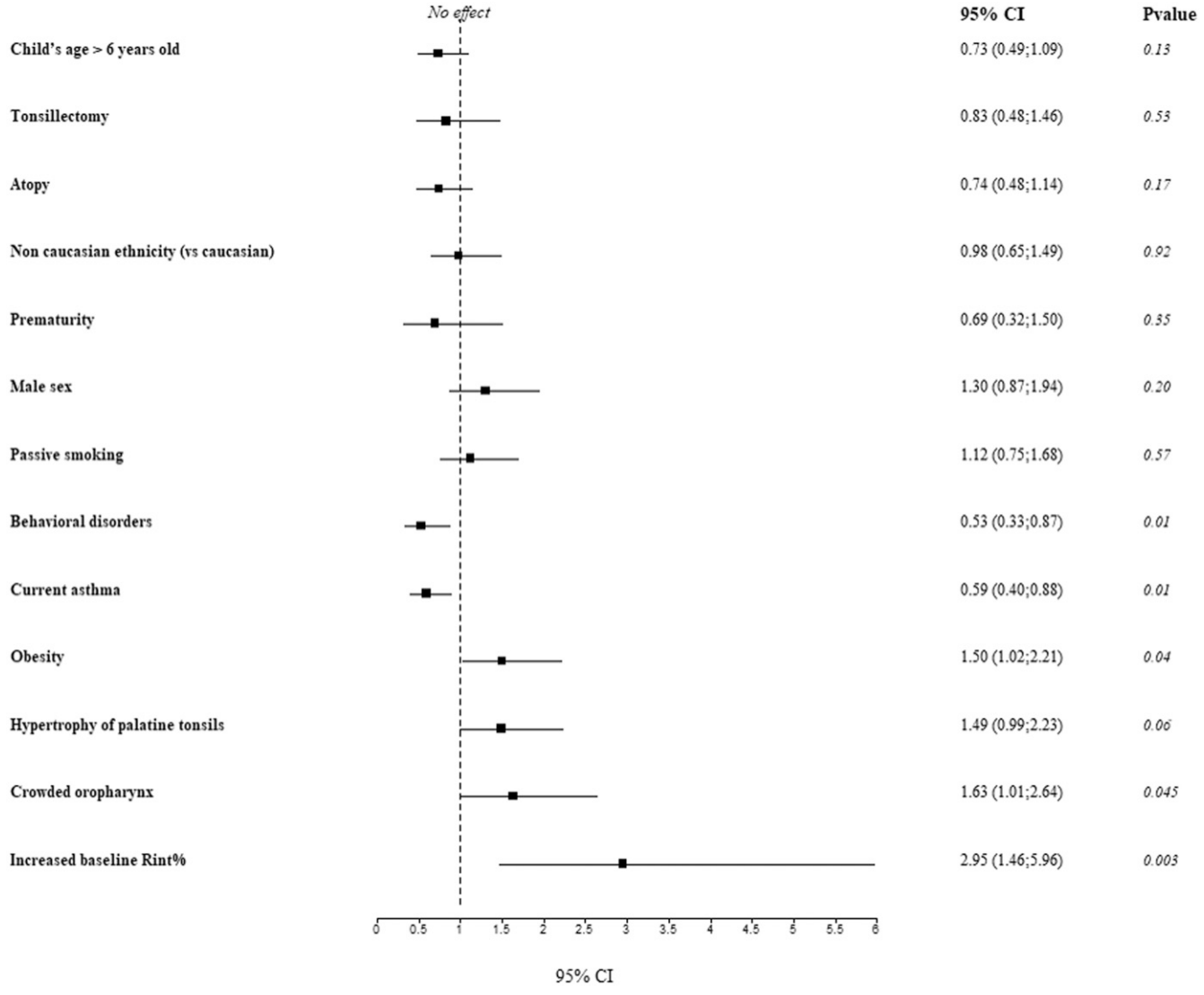
indices, especially spirometry indices, did not demonstrate any relationship to OSA severity.

The evaluation of OSA severity by PSG is essential to guide the clinicians in OSA management. Several factors such as obesity or asthma have been described to play a role in the pathophysiology of severe OSA and in the persistence of OSA after surgical tonsils removal.[27,28] In the present study, the proportion of children with hypertrophy of palatine tonsils was not different according to the presence of obesity or asthma (**Table 2**). Conversely, in a previous study conducted in 1- to 14-year-old children (mean [standard deviation] age 6.5 [0.2] years) with OSA of different level of severity, the magnitude of adeno-tonsillar hypertrophy was significantly smaller among obese children compared to lean children.[29] In that study, the Mallampati score was higher in obese children compared to lean children, suggesting that they had a decreased upper airway diameter secondary to other mechanisms than mild adenoids and tonsils hypertrophy (fat deposition in soft tissues, posterior displacement of the tongue).[29] Our results concur with this study by not showing larger tonsils in obese children (we did not evaluate the adenoid size) and odds of moderate/severe OSA 1.63 times higher for Mallampati scores ≥ 3 in the univariate analysis. Other studies demonstrated a significant correlation between OSA severity and high Mallampati score, the odds ratio of having OSA increasing by more than 6-fold for every additional point in Mallampati score.[30,31] However, we did not find that Mallampati score had an independent effect on OSA severity. This might reflect the subjectivity of this score that requires child's full cooperation and remains at the discretion of the physician.

## Relationship between obesity and OSA

In our study, the presence of obesity increased 1.82 times the odds of moderate/severe OSA (**Figure 2**). The prevalence of

**Figure 1**—Forest plot including the risk factors associated with obstructive sleep apnea (OSA) severity in the univariate analysis (presented odds ratio were moderate/severe OSA over no/mild OSA.

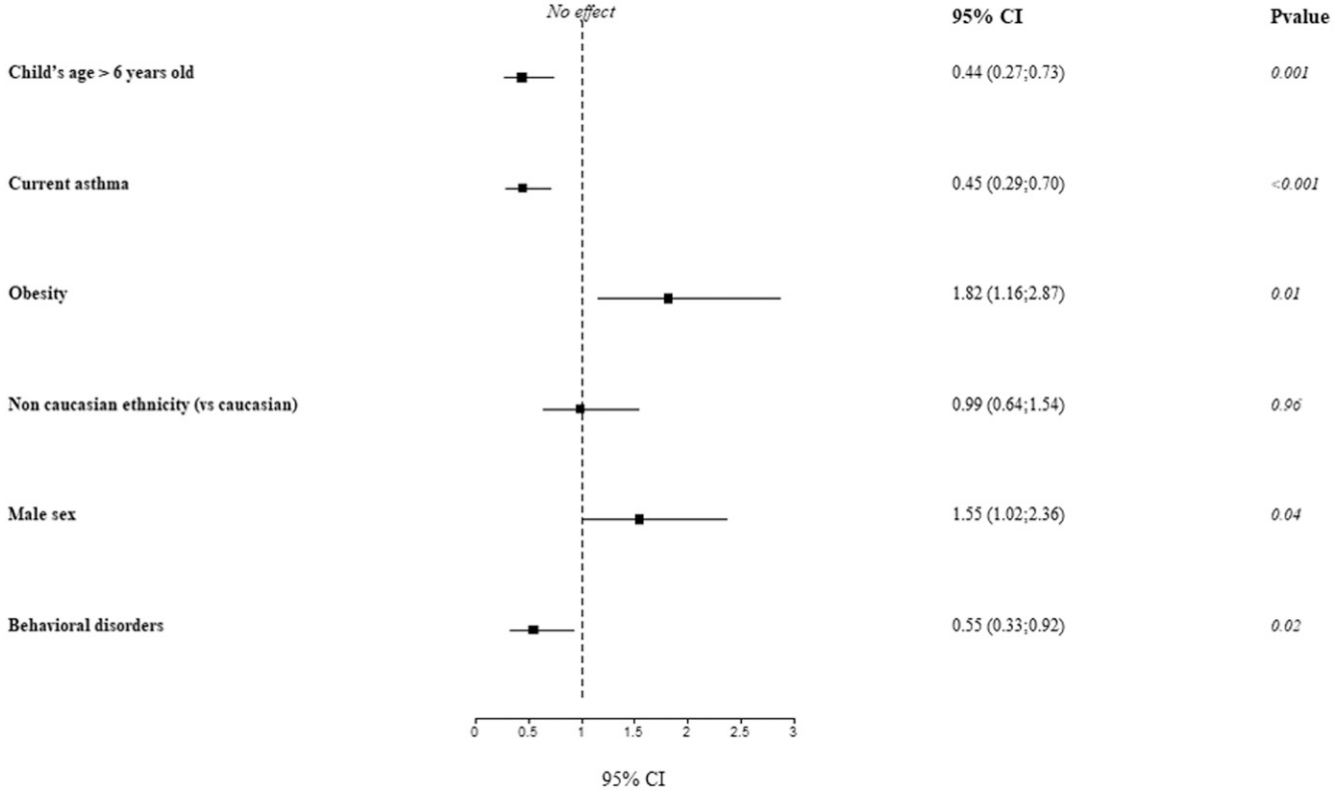



OSA in overweight/obese children and adolescents has been reported between 24 and 61%[9,32,33] with significant correlation between BMI and AHI.[34] Anatomical factors, such as deposition of fat in the pharyngeal region,[35] low lung resting volumes as an effect of obesity on the respiratory system, and a greater collapsibility of upper airways, have been suggested as mechanisms involved in OSA associated to obesity.[36] In addition, disturbed central drive during sleep in obese adolescents resulting in a blunted hypercapnic ventilatory response may hamper compensatory mechanisms during OSA-induced hypoventilation in these patients.[37] Age > 6 years was found to be independently associated with less risk of moderate/severe OSA (**Figure 2**) despite the presence of obesity in older children. This could reveal a recruitment bias as we offer an easy access to our sleep center for obese adolescents followed by physicians of the pediatric obese clinic. As a result, the obese adolescents referred may have only mild symptoms such as snoring or diurnal sleepiness. Conversely, younger children with severe OSA but no comorbidity might need to exhibit severe and multiple symptoms before alerting on their sleep-disturbed breath and being referred to a sleep physician.

## Relationship between asthma and OSA

Current asthma at the time of PSG recording was linked to a lower risk of moderate/severe OSA (**Figure 2**). This is in keeping with results of a similar study including adolescents (mean [standard deviation] age of 14 [1.7] years) in whom asthma reduced the risk of severe OSA by half, regardless of the degree of obesity.[34] The 2 conditions, asthma and OSA, share common pathophysiological mechanisms such as persistent airway inflammation, decrease in β receptors density, and alteration of circadian variations in cytokines and hormonal secretions leading to sleep fragmentation and

**Figure 2**—Forest plot including the risk factors associated with obstructive sleep apnea (OSA) severity in the multivariate analysis (presented odds ratio were moderate/severe OSA over no/mild OSA.




upper airway closure.[11] With this respect, early treatment of asthma symptoms could prevent OSA from evolving.[34] Although atopy and chronic rhinitis are risk factors for both asthma and OSA, they did not increase the likelihood of moderate/severe OSA in our children. Furthermore, when a parent reported a history of asthma in a child suspected of OSA, the risk of severe OSA was found decreased by 34%, suggesting that a benchmark bias exits as parents of asthmatic children are more likely to notice and report to physicians their child's nighttime noisy breathing symptoms (early consultation and PSG to rule out OSA).[10] Our hospital hosts large asthma and obesity outpatient clinics from which were referred most of the study asthmatic and obese children. Asthmatic children were likely to have an adapted antiasthma treatment (confirmed by the normal pulmonary function of the As/NOb group in **Table 4**) but their frequent interactions with health care professionals may have resulted in early request for PSG in case of mild symptoms such as primary snoring in these children with significantly more frequent chronic rhinitis (**Table 2**).[10] This observation could be expanded to our findings that behavioral problems were likely to be associated with less risk of moderate/severe OSA (**Figure 1**) as teachers' and/or parents' complaints might have encouraged pediatricians in our asthma and obesity clinics to refer patients with mild clinical suspicion of OSA for a PSG recording. Finally, fewer asthma exacerbations and antiasthma medication requirements have been described after adenotonsillectomy in a vast epidemiological study.[38] While we were not able to compare asthma outcomes before and after adenotonsillectomy in the 37 operated asthmatic children, we did not find any effect of adenotonsillectomy or of asthma severity as assessed by $zFEV_1/FVC$ on OSA severity. Therefore, if adenotonsillectomy would modify OSA severity through asthma improvement we were not able to detect such an effect.

## PFT

Asthmatic and nonasthmatic obese children had significantly lower FRC% and higher Rint% at baseline and a larger Rint response to bronchodilator compared to their nonobese counterparts (**Table 4**). Conversely, there was no difference in spirometry indices attributable to asthma or obesity. Rint, measured at the mouth opening, reflects the overall resistance of upper and lower airways as well as the lung tissue and thoracic wall resistance. Obese children may have abnormalities in all these components, explaining why Rint increased.[13] Moreover, FRC, the volume at which Rint is measured, has been found to be a volume at which esophageal and gastric pressures were significantly higher in obese participants as compared to their healthy counterparts.[39]

The similar OAHI between the 2 groups of obese children as compared to NAs-NOb children (**Table 4**) is not in favor of a specific role of upper airway dysfunction in obese children to explain increased Rint. On the other hand, obese children had higher OAHI than the As-NOb group, suggesting that the impairment of

the respiratory mechanics (lower resting volumes, ie, FRC%) may result in more decrease in bronchial diameter[40] and early closure of small airway[41] than asthma.

Bronchial obstruction assessed by spirometry ($zFEV_1/FVC$) was significantly lower only in the Ob/As group as compared to the NAs/NOb group, but no systematic effect of obesity on spirometry was detected. Data on the effect of obesity on spirometry indices are conflicting, $FEV_1/FVC$ being normal or increased in adults whereas it can be decreased in children due to large FVC in the latter.[42,43] These results are in favor of measuring other indices than just spirometry in obese patients in order to detect pulmonary impairment.

### Limitations and strengths of the study

The limitations of our study are the single-center evaluation and its retrospective nature with missing data such as the degree of asthma severity or the use of antiasthmatic medications. Another limitation is that we were not able to include the PFT results in the multivariate analysis due to missing PFT in NAs/NOb children in this retrospective study. Therefore, we cannot state whether the changes in respiratory mechanics we observed were independently linked to the severity of OSA. We noted a high prevalence of OSA in the study population (76%) compared to that of pediatric sleep clinics (30 to 50%),[44,45] thanks to the screening of patients before the PSG recording. Because of this selection bias our study cannot be interpreted as a population study. However, without such a large amount of data for children with OSA it would have been difficult to study the role of as many clinical factors as we did on OSA severity. The strengths of this study are the use of PSG for OSA diagnosis in all children and the inclusion of large populations of obese and asthmatic children with different levels of clinical OSA symptoms.

## CONCLUSIONS

In conclusion, our study showed that male sex and obesity were associated with a higher risk of moderate/severe OSA whereas current asthma was not. Obese children had impaired respiratory mechanics, irrespective of the presence or absence of asthma, which was linked to more severe OSA. Future prospective studies recording, in addition to the risk factors found in our study, the degree of asthma severity, the step of antiasthmatic therapy, and data on the long-term follow-up of children could lead to significant advances in the management of these diseases.

## ABBREVIATIONS

As/NOb, Asthma/No-Obesity group
As/Ob, Asthma/Obesity group
BD, short-acting bronchodilator
BMI, body mass index
$FEV_1$, forced expiratory volume in 1 second
FRC, functional residual capacity
FVC, forced vital capacity
NAs/NOb, No-Asthma/No-Obesity group
NAs/Ob, No-Asthma/Obesity group
OAHI, obstructive apnea-hypopnea index
OR, odds ratio
OSA, obstructive sleep apnea
PFT, pulmonary function testing
PSG, polysomnography
Rint, resistance measured using interrupter technique
Rint-postBD, Rint value after BD administration
$TcPCO_2$, transcutaneous partial pressure of $CO_2$
TLC, total lung capacity
TST, total sleep time
(PFT index)%, PFT index expressed as percentage of predicted value
z(PFT index), PFT index expressed as z-score
Δ(PFT index), PFT index response to BD

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