Sleep breathing disorders in adolescents with asthma

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Summary

Background. Childhood asthma, a chronic inflammatory disease, is linked to sleep-breathing disorders (SBD). The vulnerability of asthmatic children to SBDs is well-established, yet limited research focuses on adolescents. This study addresses the research gap, exploring the frequency and risk factors of SBD in adolescents with asthma. **Methods.** A cross-sectional study was conducted among 98 adolescents (12-17 years) with asthma at a Lisbon healthcare facility. Comprehensive assessments, including sociodemographic data, medical history, lung function variables, and validated questionnaires for SBD risk (Pediatric Sleep Questionnaire), rhinitis control, and asthma control (Control of Allergic Rhinitis and Asthma Test and Asthma Control Test), were employed. **Results.** The study revealed a substantial frequency of SBD symptoms, with 25.5% of adolescents classified as high-risk based on the Pediatric Sleep Questionnaire. Significant associations were identified between high SBD risk and elevated body mass index (BMI), uncontrolled rhinitis, and uncontrolled asthma. Logistic regression analysis confirmed elevated BMI as a robust predictor of SBD risk, indicating a 5.9-fold increase compared to normal-weight counterparts. **Conclusions.** This study contributes valuable insights into the interplay between asthma and SBD in adolescents. The high prevalence of SBD symptoms, particularly among those with excess weight and uncontrolled respiratory symptoms, underscores the need for targeted preventive strategies. The identified risk factors, notably elevated BMI, provide clinicians with actionable information for intervention, emphasizing the importance of addressing modifiable factors associated with asthma and SBD in this specific population.

Keywords

Asthma, Sleep-breathing disorders, Adolescents, Body mass index

Impact Statement

Adolescents with asthma have a high prevalence of SBD symptoms, particularly those with excess weight and uncontrolled respiratory symptoms, which underscores the importance of targeted preventive strategies.

Introduction

Asthma, characterized as a chronic inflammatory disease of the lungs and airways, is particularly important during childhood (1,2). It has been declared as one of the major non-communicable diseases worldwide, and its prevalence is increasing (3). Pediatric asthma imposes a substantial burden on healthcare systems, and the goal of treatment is to achieve good symptoms' control and to prevent exacerbations. However, many comorbid conditions negatively influence asthma management (1).

Among these comorbidities, sleep-breathing disorders (SBD) are highly common in children, with a reported prevalence ranging from 1-6% (1,4). Predominant among SBDs is obstructive sleep apnea (OSA), resulting from an intermittent upper airway obstruction that disrupts physiological ventilation during sleep and normal sleep patterns (1,5). The susceptibility of children with asthma to the development of SBDs is well-established (4), and OSA has been linked to worse asthma control and increased frequency of exacerbations (6). Additionally, other comorbidities, such as elevated body mass index (BMI), seem to contribute to both poor asthma management and higher risk of SBD (1), revealing a complex interplay between these conditions.

While the association between asthma and SBD has been acknowledged (5,7), there is a paucity of research focusing on the adolescent population, particularly in the context of a well-defined asthma cohort. This age-specific focus is critical, given the unique physiological and behavioral characteristics of adolescents, including the dynamic changes during puberty. Existing literature has highlighted the bidirectional relationship between asthma and SBD (1,7,8), but the nuances of this interplay in adolescents remain insufficiently explored.

Our study aims to address a research gap concerning the frequency and risk factors of SBD in adolescents diagnosed with asthma, employing a comprehensive assessment approach, and shedding light on modifiable risk factors. The goal of this study is to examine the frequency of SBD within adolescents diagnosed with asthma, and to identify specific patient characteristics that correlate with an augmented susceptibility to the development of SBD. Through such analyses, we aspire to provide valuable insights into the interplay between asthma and SBD, promoting more targeted preventive strategies and enhancing clinical understanding in this specific population.

Material and Methods

Study design, setting and participants

This was an exploratory study with a cross-sectional design conducted within the Allergy and Clinical Immunology Department at Hospital Dona Estefânia, ULS São José, a tertiary pediatric healthcare facility located in Lisbon, Portugal.

Adolescents who were scheduled for an examination in the lung function test laboratory of our centre between May 2022 and October 2023 were invited to participate.

Participation eligibility conditions were to be between 12 and 17 years old, present a medical diagnosis of asthma and be able to perform a spirometry. Exclusion criteria were the parent's inability to understand the consent form or the questionnaires.

Ethical approval for this study was obtained from the Ethics Committee of the ULS São José. Participants and their parents were informed about the study, and signed consent was obtained.

Data Collection

Data were collected using a patient reported standardised questionnaire, completed by the parents, covering sociodemographic information, medical history, SBD risk (Pediatric Sleep Questionnaire - PSQ), rhinitis symptoms and control (Control of Allergic Rhinitis and Asthma Test, upper airway subscore - CARAT-UAS), and asthma control (CARAT, lower airway subscore - CARAT-LAS - and Asthma Control Test - ACT). Lung function test, encompassing spirometry or plethysmography and fractional exhaled nitric oxide (FeNO), were recorded on the day of questionnaire completion. Additional data, including daily prescribed asthma medications, rhinitis diagnosis, and sensitization to airborne allergens, were obtained from electronic medical records.

The CARAT is a validated questionnaire to evaluate rhinitis and asthma control: CARAT-UAS encompasses the first four questions and CARAT-LAS the last six questions of CARAT, all answered on a 4-point Likert scale that address, respectively, upper and lower airway symptoms over a four-week period (9,10). The ACT Questionnaire is a validated tool to assess asthma control, it contains five questions about the frequency of asthma symptoms and required rescue medication use during the previous four weeks (11). These parameters were included as categorical variables.

Asthma severity was classified as an ordinal variable, in accordance with the Global Initiative for Asthma (GINA) 2023 classification (steps 1-5) (12). The GINA stages were dichotomized into two categories: GINA 1-2, representing patients with mild disease severity, and GINA 3-5, representing patients with moderate to severe disease severity, allowing a clearer comparison between low and high disease severity group.

The Pediatric Sleep Questionnaire is a validated screening toll for identifying patients at high risk for sleep breathing disorders (4). Positive PSQ scoring was defined as greater than or equal to 0.33, being indicative of risk for sleep-breathing disorders (4).

Body weight and height were measured at the time of the lung function test, BMI was calculated and converted to a normalized z-score based on the 2000 Centers for Disease Control and Prevention (CDC) growth charts (13), and defined as overweight (BMI between 85^{th}-95^{th} percentile) or obese (BMI greater than 95^{th} percentile) (13). For the purpose of modeling, this variable was dichotomized into normal BMI (lower than 85th percentile) versus elevated BMI (equal to or higher than 95th percentile).

Lung function tests results were evaluated following ERS/ATS recommendations (14). GLI reference equations were used to standardize lung function measurements and the proportion of participants below the lower limit of normal (LLN) were calculated. A change >10% of the predictive value of forced expiratory volume in the 1^{st} second (FEV_1) was considered positive response to bronchodilator. FeNO was used to assess the presence of airways inflammation.

Variables

The outcome variable was the presence of SBD defined according to the PSQ.

Parent academic graduation, school grade retention, exposure to tobacco smoke, previous otolaryngology (ENT) surgery, high BMI (>85^{th} percentile), allergic rhinitis, allergen sensitization, CARAT and ACT scores, asthma severity, spirometry changes (FEV_1/Forced vital capacity (FVC) < LLN and positive bronchodilation test) and airways inflammation were considered as potential risk factors. Gender and age were considered as potential confounders.

Statistical analysis

Categorical data were presented as frequencies, while continuous variables were expressed as median and interquartile range (IQR). Chi-square and Fisher tests were employed to evaluate the associations between categorical variables, while Mann-Whitney U tests were used to evaluate associations between categorical and a continuous variable with a non-normal distribution.

Logistic regression models were used to analyse the association between SBD risk (outcome) and the above-mentioned risk and confounding factors. First, crude regression coefficients and corresponding odds ratios (OR) with 95% confidence intervals (95% CI) were calculated. Covariates with a p-value of less than 0.250 were selected as candidates for multivariable analysis. For asthma control, the variable with a stronger statistical association with SBD risk was selected. A stepwise backward elimination variable selection method was performed to obtain the final model. Statistical significance was set at a p-value < 0.05, although p-values greater than 0.05 and lower than 0.1 were reported for multivariable analysis. Data analysis was performed using IBM SPSS (Statistical Package for the Social Sciences) version 28 (Chicago, USA).

Results

A total of 98 patients were enrolled in this study (table Ia). There was a male predominance (n=61, 62.2%) with a median (IQR) age of 14 (3) years. While all patients underwent spirometry, FeNO measurement was performed on 47 (48.0%).

Patient clinical characteristics

SBD risk was present on 25.5% (n=25) of participants (table Ib). Every participant had asthma and allergic rhinitis.

Overweight and obese children accounted for 27.5% of the children. Concerning tobacco exposure, 40.8% reported it. Most participants presented sensitization to airborne allergens, mostly to house dust mites.

Asthma control was higher according to ACT (82.7%) than with CARAT (60.2%). The Spearman correlation analysis revealed a significant positive correlation between ACT and CARAT ($r = 0.717$, $p < 0.001$). The majority presented uncontrolled rhinitis according to CARAT (71.4%). About 20% of the adolescents had airways obstruction ($FEV_1/FVC <$ LLN) and positive bronchodilation test.

SBD risk factors

Patients were stratified into two groups according to the risk of SBD (Table II).

A higher proportion of patients with high risk of SBD presented with elevated BMI (56.0% versus 17.8%, *p<.001*), more frequently uncontrolled rhinitis according to CARAT UAS (88.0% versus 65.8%, *p=0.034*), and uncontrolled asthma according to ACT (32.0% versus 12.3%, *p=0.034*) in comparison with lower-risk patients. In the multivariable analysis (table III), sex, elevated BMI, rhinitis control according to UAS, and asthma control according to ACT were included. Following a backward elimination process, the variables elevated BMI, rhinitis control according to UAS, and asthma control according to ACT persisted in the final model, with elevated BMI exhibiting the highest odds ratio for SBD risk (OR 5.91, CI 2.08-16-80), followed by uncontrolled rhinitis (OR 3.35, CI 0.83-13.59) and uncontrolled asthma (OR 2.91, CI 0.87-9.68). Other variables included in univariate analysis, including socio-demographic data, other comorbidities, and lung function, were considered non-significant.

Discussion

Population characterization

Our study focuses on a homogeneous sample of adolescents diagnosed with asthma, exhibiting a slight male predominance. During the initial years of life, asthma incidence is notably higher in young males, attributed to smaller airway dimensions compared to young females, however, this trend tends to reverse during puberty (1,7,15). Our findings may be influenced by the transitional phase our studied cohort is experiencing, where a male predominance over females persists.

A quarter of our patients were identified as having high-risk of SBD, based on the PSQ results. This frequency surpasses the estimated prevalence of SBD in general pediatric population, which is approximately 5% (1,16). However, our results are in line with current literature, which finds that children with asthma are more likely to suffer from SBD (2,6). Additionally, the utilization of PSQ, a self-reported symptom-based tool, rather than polysomnography, the gold standard for the diagnosis of SBD (4,5), may have contributed to the observed variance. Despite this limitation, PSQ remains a practical and validated tool, demonstrating good sensitivity for identifying children at risk of SBD (4).

All enrolled patients had allergic rhinitis, predominantly sensitized to house dust mites. A significant proportion exhibited uncontrolled rhinitis at the time of the evaluation. Asthma patients are at higher risk of suffering from nasal symptoms and uncontrolled rhinitis is a risk factor for uncontrolled asthma and has also been implicated in the development of SBD (1,8,17).

A noteworthy concern arises from the observation of a high rate of patients exposed to secondhand tobacco smoke. This exposure, a well-established risk factor for asthma and SBD development, adversely impacts asthma control (1,18). Although our cohort did not reveal any differences between groups – potentially due to the reliance on self-reported exposure – it is essential to address this exposure, given its preventable nature, to mitigate serious consequences.

An elevated BMI was evident in almost one-third of patients, with 6% categorized as obese. These metabolic abnormalities are intricately linked with asthma prevalence and may serve as predictors of pulmonary function deficits (19). Elevated BMI, an independent risk factor for both asthma and SBD (1), underscores the importance of addressing this modifiable risk factor in clinical practice. Regarding asthma control, discrepancies were noted between the ACT and the CARAT-LAS, with ACT classifying more patients as controlled. However, the significant positive correlation found between ACT and CARAT suggests a strong relationship where higher scores on ACT are associated with higher scores on CARAT. Both instruments, relying on patient-reported outcomes, offer valuable insights. While ACT represents one of the most extensively validated prognostic tools for asthma assessment (20,21), CARAT holds the advantage of assessing both asthma and AR control (9). Previous studies, similar to ours, have found a good correlation between the CARAT score and the ACT, although with substantial heterogeneity (22).

FEV_1/FVC is one of the most employed spirometry measurements to identify the presence of obstruction (14). We found that a significant proportion of patients exhibited decreased

FEV_1/FVC, and a positive bronchodilation response, which is indicative of poor asthma control and correlates with worse clinical outcomes (23).

An intriguing observation was the elevated FeNO in the tested patients. FeNO serves as a biomarker reflecting type 2 airway inflammation and is frequently elevated in patients with uncontrolled asthma (24). However, interpretation should consider potential confounding factors, such as high allergic sensitization rate or dietary influences (24).

SBD Risk Comparison

Comparing SBD risk groups, factors such as overweight status, rhinitis control, and asthma control according to ACT were associated with higher risk of developing SBD.

Consistent with prior studies, more than half of the high-risk SBD patients were overweight. Increased fat accumulation in the thoracic and abdominal cavities may contribute to airway and lung restrictions, exacerbating asthma and SBD pathogenesis (1), emphasizing the association between higher BMI and these respiratory conditions (2,25).

Uncontrolled rhinitis and asthma were more frequent in the high-risk SBD group. Nasal obstruction results in intranasal resistance, increasing negative pressures in the upper airway during inspiration and contributing to the pathogenesis of SBDs (8,26). Asthma is a recognized risk factor for SBDs, and the overlap between these conditions is associated with increased airway inflammation, disease severity, frequent asthma exacerbations and decreased quality of life (6,8,25,26).

A potential tendency toward female predominance was noted in our cohort. This unexpected finding may be linked to the focus on adolescents undergoing puberty, where females experience an increase in asthma prevalence and may be more predisposed to SBD due to anatomic changes and hormonal effects (1,17).

This study exhibits several strengths that enhance the robustness of its findings. Firstly, it focuses on a homogeneous population of adolescents with asthma, providing a well-defined and specific cohort for analysis. The comprehensive collection of data, encompassing various parameters, adds depth to the understanding of factors influencing asthma and SBDs. The study also utilized well-validated assessment tools, including the PSQ, ACT and CARAT, thereby enhancing the reliability of the results.

While this study provides valuable contributions, it is essential to acknowledge its limitations. The cross-sectional design restricts the ability to establish causation, highlighting the need for future longitudinal investigations. Reliance on self-reported data for SBD risk assessment using the PSQ introduces the potential for recall bias, and the absence of polysomnography may impact the precision of risk estimation. Being a single-center study, with a limited sample size, it is not possible to generalize the findings to broader populations, emphasizing the importance of

multicenter approaches. As with any clinical study, the potential for selection bias arising from the recruitment of patients from a clinical setting should be considered when interpreting the findings.

In conclusion, our study revealed a substantial frequency of sleep-breathing symptoms in adolescents with asthma. Notably, a significant proportion of patients are exposed to tobacco smoke and exhibit elevated BMI, both carrying potential deleterious implications. We found overweight status, uncontrolled rhinitis and uncontrolled asthma to be potent predictors of higher risk of developing SBDs, which underscores the importance of screening patients with uncontrolled respiratory symptoms and excess weight. These findings emphasize the need for heightened clinical awareness and intervention to address modifiable risk factors associated with asthma and SBD.

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Author Contributions

PSC - Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Writing - original draft.

GMS - Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Writing - original draft.

MM - Data curation, Investigation, Writing - original draft.

FC - Data curation, Investigation, Writing - original draft.

MC - Data curation, Investigation, Writing - original draft.

SS - Data curation, Resources, Writing - original draft.

SS - Data curation, Resources, Writing - original draft.

AB - Data curation, Resources, Writing - original draft.

PCM - Conceptualization, Formal Analysis, Methodology, Project administration, Supervision, Validation, Writing – review & editing

PLP - Conceptualization, Formal Analysis, Methodology, Project administration, Supervision, Validation, Writing – review & editing

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Table Ia: Participants' characteristics (n=98).

Demographics	n
- Median age, years (IQR)	14.0 (3.0)
- Female	37 (37.8%)
- Exposure to tobacco smoke	40 (40.8%)
- Previous ENT surgery	22 (22.4%)
- School Grade Retention	12 (13.3%)
- Parent graduation	
- Primary School	2 (2.0%)
- Middle School	26 (26.5%)
- High School	38 (38.8%)
- Academic Degree	32 (32.7%)
Anthropometry	
- BMI Category, z-score (IQR)	0.22 (1.31)
- Underweight < 5^{th} percentile	1 (1.0%)
- Normal weight 5^{th} – 84^{th} percentile	70 (71.4%)
- Overweight 85^{th} – 95^{th} percentile	21 (21.4%)
- Obesity > 95^{th} percentile	6 (6.1%)
Allergic Sensitization	89 (90.8%)

IQR: interquartile range; ENT: ear, nose, and throat; BMI: body mass index.

Table Ib: Participants' characteristics (n=98).

Asthma	n
- CARAT - Controlled Asthma (LAS ≥ 16)	59 (60.2%)
- ACT - Controlled Asthma (ACT ≥ 20)	81 (82.7%)
- Severity	
- GINA STEP 1	3 (3.0%)
- GINA STEP 2	31 (31.6%)
- GINA STEP 3	58 (59.2%)
- GINA STEP 4	4 (4.1%)
- GINA STEP 5	2 (2.0%)
Allergic Rhinitis	
- CARAT - Controlled AR (UAS > 8)	28 (28.6%)
Sleep-breathing disorder	
- PSQ score, median (IQR)	0.20 (0.20)
- PSQ score > 0.33	25 (25.5%)
Lung Function Tests	
- Spirometry with bronchodilation	
- FEV_1 < LLN	6 (6.1%)
- FEV_1 / FVC < LLN	20 (20.4%)
- Positive bronchodilation	20 (20.4%)
- Fraction of Exhaled Nitric Oxide (*)	
- FeNO ≥ 20 ppb	31 (66.0%)

IQR: interquartile range; CARAT: Control of Allergic Rhinitis and Asthma Test; UAS: upper airway subscore; LAS: lower airway subscore; ACT: Asthma Control Test; GINA: Global Initiative for Asthma; FEV_1: forced expiratory volume in the first second; FVC: Forced vital capacity; LLN: lower limit of normal; FeNO: Fractional exhaled nitric oxide; ppb: parts per billion.
* FeNO was evaluated in 47 patients.

Table II: Comparison between patients with high-risk vs low risk of SBD.

	High-risk SBD (n=25)	Low risk SBD (n=73)	*p-value*
Female	13 (52.0%)	24 (32.9%)	.089
Age, median (IQR)	14 (4)	14 (3)	.791
Parent academic graduation	6 (24.0%)	26 (35.6%)	.285
School grade retention	5 (20%)	8 (11.0%)	.307
Exposure to tobacco smoke	11 (44%)	29 (39.7%)	.707
Previous ENT surgery	5 (20%)	17 (23.3%)	.734
Elevated BMI (>85th percentile)	14 (56.0%)	13 (17.8%)	**<.001**
Rhinitis	25 (100%)	73 (100%)	1.000
Allergic sensitization	24 (96.0%)	65 (89.0%)	.441
CARAT-UAS <9 points	22 (88.0%)	48 (65.8%)	**.034**
CARAT-LAS <16 points	13 (52%)	26 (35.6%)	.149
ACT <20 points	8 (32.0%)	9 (12.3%)	**.034**
GINA Step 1-2	9 (36.0%)	25 (34.2%)	.874
FEV_1/FVC < LLN	4 (16.0%)	16 (21.9%)	.526
Positive bronchodilation	4 (16.0%)	16 (21.9%)	.526
FeNO ≥ 20ppb*	10 (76.9%)	21 (61.8%)	.494

IQR: interquartile range; ENT: ear, nose, and throat; BMI: body mass index; CARAT: Control of Allergic Rhinitis and Asthma Test; UAS: upper airway subscore; LAS: lower airway subscore; ACT: Asthma Control Test; GINA: Global Initiative for Asthma; FEV_1: forced expiratory volume in the first second; FVC: Forced vital capacity; LLN: lower limit of normal; FeNO: Fractional exhaled nitric oxide; ppb: parts per billion. * FeNO was evaluated in 13 patients in the high-risk group and in 34 patients in the low-risk group.

Table III: Analysis of the association between patients' characteristics and the risk of SBD

	Unadjusted Odds Ratio	95% Confidence interval	*p-value*	*Adjusted Odds Ratio*	95% Confidence interval	*p-value*
Female	1.21	0.35-4.15	.089	-	-	-
Age	1.11	0.79-1.58	.791	-	-	-
Parent academic graduation	0.90	0.24-3.291	.285	-	-	-
School grade retention	4.05	0.79-20.75	.307	-	-	-
Exposure to tobacco smoke	1.19	0.37-3.80	.707	-	-	-
Previous ENT surgery	0.62	0.14-2.74	.734	-	-	-
Elevated BMI (>85th percentile)	6.52	2.04-20.83	**<.001**	5.91	2.08-16-80	**<.001**
Allergic sensitization	3.43	0.27-43.37	.441	-	-	-
CARAT-UAS <9 points	4.20	0.86-20.63	**.034**	3.35	0.83-13.59	.090
CARAT-LAS <16 points	1.34	0.31-5.90	.149	-	-	**-**
ACT <20 points	4.35	0.85-22.29	**.034**	2.91	0.87-9.68	.082
GINA Step 1-2	1.12	0.33-3.84	.874	-	-	-
FEV_1/FVC < LLN	0.77	0.13-4.68	.526	-	-	-
Positive bronchodilation	0.93	0.15-5.69	.526	-	-	-

IQR: interquartile range; ENT: ear, nose, and throat; BMI: body mass index; CARAT: Control of Allergic Rhinitis and Asthma Test; UAS: upper airway subscore; LAS: lower airway subscore; ACT: Asthma Control Test; GINA: Global Initiative for Asthma; FEV_1: forced expiratory volume in the first second; FVC: Forced vital capacity; LLN: lower limit of normal; - p-value> 0.100 in the multivariable analysis.