Review Article

Obstructive sleep apnea in children and adolescents with cystic fibrosis and preserved lung function or mild impairment: a systematic review and meta-analysis of prevalence

Luisa Pedrada de Sousa [a], Fernanda Mayrink Gonçalves Liberato [b], Fernanda Maria Vendrusculo [c], Márcio Vinícius Fagundes Donadio [c], Roberta Ribeiro Batista Barbosa [a, *]

[a] Department of Physiotherapy, Escola Superior de Ciências da Santa Casa de Misericórdia de Vitória, Vitória, Espírito Santo, Brazil
[b] Cystic Fibrosis Reference Center, Hospital Infantil Nossa Senhora da Glória, Vitória, Espírito Santo, Brazil
[c] Laboratory of Pediatric Physical Activity, Centro Infant, Pontifícia Universidade Católica do Rio Grande do Sul (PUCRS), Porto Alegre, Rio Grande do Sul, Brazil

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ABSTRACT

Objective/Background: Sleep disorders in cystic fibrosis may be present before daytime clinical manifestations, regardless of lung function impairment, affecting quality of life and disease progression. This study investigated the prevalence of obstructive sleep apnea in children and adolescents with cystic fibrosis and preserved lung function or mild impairment, and evaluated its association with clinical variables.
Methods: A systematic review with meta-analysis of prevalence was conducted, including observational studies with polysomnographies in patients with cystic fibrosis who presented mean lung function values > 60% predicted. The methodological quality of the studies was analyzed, and a meta-analysis was performed to assess the prevalence of obstructive sleep apnea.
Results: Of the 2318 studies identified, 7 were included in the systematic review and 6 in the meta-analysis of prevalence. The confounding factors and strategies identified were the items with greatest weakness in the methodological quality assessment. Most studies were cross-sectional, and sample size ranged from 9 to 67 individuals. The most frequent criterion for defining obstructive sleep apnea was apnea-hypopnea index (AHI) > 1 per hour. The prevalence found ranged from 32.3 to 100% and the pooled prevalence was 65% ($I^2 = 53.4\%$), considering AHI>1, and 52% ($I^2 = 89.4\%$) for AHI>2 per hour. It was not possible to verify the association between obstructive sleep apnea and clinical variables.
Conclusions: A high prevalence of obstructive sleep apnea in children and adolescents with cystic fibrosis was found, regardless of age and lung function impairment, reinforcing the importance of investigating sleep-disordered breathing during clinical visits even when lung function is not yet compromised.

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1. Introduction

Cystic fibrosis (CF) is a multisystem autosomal recessive hereditary disease resulting in chronic airway inflammation even in childhood, leading to progressive deterioration of lung function and hospitalization and contributing to early mortality [1,2]. Individuals with CF have poorer sleep quality and awaken more, and consequently have reduced sleep efficiency due to frequent coughing, snoring, and sleep-disordered breathing such as hypoxemia and obstructive apnea [3—10]. Studies have shown a prevalence of obstructive sleep apnea syndrome (OSAS) of 1.2—5.7% in healthy children and adolescents [11—13]; this prevalence has been shown to be much higher in individuals with CF in this same age group, affecting more than half of this population, and may vary according to the apnea-hypopnea index (AHI) cutoff point used in each study to define OSAS [1,14].

A recent systematic review with meta-analysis showed that individuals with CF have lower AHI values and minimum

peripheral oxyhemoglobin saturation (SpO_2) during sleep, poorer sleep efficiency, and a lower percentage of total rapid eye movement sleep time compared to healthy peers. The prevalence of OSAS was not explored, however, and the study concluded that the relationship between sleep disorders and disease severity as well as the impact of sleep apnea and its treatment on individuals with CF require further study [15]. There is evidence that the presence of sleep disorders in CF may precede daytime respiratory signs and symptoms [16,17], but in most studies and in clinical practice sleep assessment via polysomnography is only performed during more advanced stages of the disease, when lung function is already compromised. This may indicate late detection of sleep disorders, when potential consequences are already established, impacting quality of life and worsening the prognosis.

The real prevalence of OSAS in children and adolescents with CF remains uncertain, since the methodology varies among studies and most examine individuals with significant lung disease. This study investigated the prevalence of OSAS in children and adolescents with CF and preserved lung function or mild impairment to determine the association between this syndrome and clinical outcomes.

2. Methods

The protocol for this systematic review was registered in the PROSPERO international prospective register of systematic reviews (ID CRD42019119633) and followed the guidelines for meta-analysis of observational studies in epidemiology (MOOSE) [18].

2.1. Eligibility criteria

This analysis included original observational studies using polysomnography with samples of children and adolescents diagnosed with CF and mean spirometry values for forced expiratory volume in the first second (FEV_1) >60% of predicted, constituting a sample with preserved lung function or mild impairment [19]. The exclusion criteria were (i) inclusion of patients diagnosed with diseases other than CF, (ii) no description of the criteria to define OSAS or its prevalence, (iii) inclusion of patients with pulmonary exacerbation, (iv) abstracts of scientific events, and (v) inclusion of individuals >18 years of age in study samples without providing separate data for children and adolescents. There were no restrictions on publication date or language.

2.2. Information sources and search strategy

The last search for articles was carried out in June 2021 in the Pubmed, Web of Science, Scielo, Scopus, and Lilacs databases using the descriptors ("Cystic Fibrosis" OR Mucoviscidosis) AND (Sleep OR Apnea OR Apnea). No filters were used.

2.3. Study selection

The articles were selected by two authors (LPS and FMGL) in four independent steps. In the first stage, the articles were identified by searching each database and then exported to a Microsoft Excel spreadsheet, where they were organized and reviewed to check for duplicates. In the second stage, each article title was analyzed by the two authors and those that indicated any exclusion criteria were discarded. The third stage involved reading the abstracts of these selected articles and discarding any studies that failed to meet the eligibility criteria. In the final stage, the full text of the selected articles was saved and reviewed in detail to identify which articles best met the defined criteria. Agreement for selection was determined after each stage; disagreements between the

authors were resolved by consensus, and the opinion of a third author (RRBB) was requested when necessary.

2.4. Data extraction

A protocol was defined to extract data from the full texts. This extraction was performed by two authors (LPS and RRBB), and disagreements were resolved by consensus. The following data were extracted from the articles: first author, publication year, country of origin, period of data collection, sample size, age of participants, study type, criteria to diagnose OSAS, and OSAS prevalence. In addition, polysomnography data (apnea-hypopnea index [AHI], minimum and maximum oxyhemoglobin saturation [SpO_2], percentage of total sleep time [TTS] with SpO_2 <90%) and clinical variables (nutritional variables, Shwachman-Kulczycki score, and presence of upper airway changes) were collected. When articles did not describe data relevant to the context of this present study, the corresponding author was contacted by e-mail.

2.5. Quality analysis

Methodological quality was analyzed individually and independently by three authors (FMGL, FMV, LPS) using the Joanna Briggs Institute (JBI) quality appraisal tool [20]. Eight criteria were evaluated: (i) inclusion criteria and sample definition, (ii) detailed description of the study population, (iii) exposure measured validation and confidence, (iv) standards and objectives used to measure the condition, (v) identification of confounding factors, (vi) confounding factor strategies, (vii) validity results and reliability, and (viii) appropriate statistical analysis in all selected studies.

One point was awarded for each criterion: studies with scores of 7—8 were considered high quality, 4—6 moderate quality, and 0—3 low quality [20]. The scores were discussed with a fourth author (RRBB), and disagreements were resolved by consensus.

2.6. Data synthesis and statistical analysis

The demographic, clinical, and polysomnographic data of each study included in this systematic review are presented in Table 1. A meta-analysis of prevalence was performed to assess the prevalence of OSAS in children and adolescents with CF, separating the studies according to the cutoff point for the apnea-hypopnea index used (AHI>1 and AHI>2). Estimates of OSAS pooled prevalence and the 95% confidence interval (95% CI) were calculated by the random effects model, assessing heterogeneity with the Q test and quantifying magnitude by I^2; I^2 < 40 was considered low heterogeneity, 40—60 acceptable, and >60 high heterogeneity [21]. All analyses were performed using Comprehensive Meta-Analysis software (Biostat, Englewood, New Jersey). Forest plots, where point size reflected the weight of each study included, were used to visually describe the results.

3. Results

3.1. Study selection

A total of 2318 articles were found (1099 in Pubmed, 490 in Web of Science, 708 in Scopus, 9 in Scielo, and 12 in Lilacs); 483 were duplicates, resulting in 1835 articles for the selection process. Title inspection excluded 1689 articles describing studies that did not include patients with CF. The remaining 146 abstracts were read and 106 did not meet the eligibility criteria. After accessing and reading the full text of 40 articles, 7 met the criteria and were included in this systematic review and 6 in the meta-analysis of prevalence. Fig. 1 illustrates the study flowchart with the reasons for exclusions at each stage.

Table 1
Characteristics of eligible studies included in the systematic review.

Reference	Country	Data collection	Sample (n)	Age (years)	Sex Male (%)	FEV₁ (%)	BMI (kg/m²)	SK Score	Upper airway dysfunction	AHI (n/h)	SpO₂ (%)	Main conclusions
Ramos et al. 2011 [14]	Brazil	2006 – 2008	67	8 (5–10) median (IQR)	56.7	78.5 (67–92.8) median (IQR)	Percentile 34 (11–64) median (IQR)	85.6 ±9.1	n/a	1 (0–1) median (IQR)	SpO_2 mean 94 ± 2 SpO_2 minimum 81 ± 6 %TST<90% 0.3 (0–1) median (IQR)	Clinically stable pediatric patients with CF have a high prevalence of sleep-disordered breathing, with significant changes in sleep architecture and episodes of oxygen desaturation.
Spicuzza et al. 2012 [8]	Spain	n/a	40	6 months to 11 years	57.5	78.6 ± 4.7 (children ≥6 years old)	17.8 ±13.4 (children ≥6 years old)	n/a	Adenotonsillar hypertrophy (26%) Chronic rhinosinusitis (36%) Both conditions (5%)	7.3 ± 1.3	SpO_2 mean 94.7 ± 1.8 SpO_2 minimum 89.4 ± 5.1 %TST <90% n/a	Early occurrence of OSAS in stable children with CF, associated with mild sleep disruption. Early routine nocturnal respiratory monitoring is advised for children with CF.
Veronezi et al. 2015 [23]	Brazil	2010 – 2012	9	8.6 ±1.4	56	109.8 ±20.1	17.2 ± 2	83.4 ± 9.8	Lund–Mackay 13.2 ± 5	5.9 ± 2.9	SpO_2 mean 96.2 ± 0.67 SpO_2 minimum 87.2 ± 3.3 %TST<90% n/a	The main determinants of sleep apnea were nutritional status, SpO_2, and daytime sleepiness. This model explains 51% of the variation in the AHI and provides clinicians with an opportunity to predict cases of significant sleep apnea.
Waters et al. 2017 [26]	Australia	n/a	46	11.1 ± 1.5	34.8	74.6 ± 18.8	17.9 ± 4.1		Mild (63%) Moderate (30.4%) Severe (6.5%)	n/a	1.1 ± 0.9	SpO_2 mean 96.2 ± 1.8 SpO_2 minimum 91.4 ± 3.3 %TST<90% 0.22 ± 0.1	In children with CF and mild to moderate daytime respiratory impairment, respiratory abnormalities were detectable in overnight sleep studies, including higher respiratory rates and evidence of limited CO_2 diffusion in REM.
Isaiah et al. 2019 [1]	USA	2007 – 2014	35	11.6 (9.5–13.1) Mean (95% CI)	57.1	60.7 (53–68.5) Mean (95% CI)	Percentile 42.1 (31.5–2.6) Mean (95% CI)	n/a	Sinus disease (23%) Tonsil enlargement (23%)	1.6 (0.9–2.3) Mean (95% CI)	SpO_2 mean 92.9 (91.7–94.1) Mean (95% CI) SpO_2 minimum	FEV₁ is the best predictor of sleep hypoxemia in children with CF

									Allergic rhinitis (43%)		86.5 (84.7—88.1) Mean (95% CI) %TST <90% 22.6 (11.2—34.1) Mean (95% CI)	and referred for PSG. No demographic or clinical predictors of hypoxemia were identified in this population.
Lumertz & Pinto 2019 [27]	Brazil	2015 — 2016	16	11 ± 5.6	75	87.95 ±26.21	BMI z-score 0.13 ± 0.61	89.51 ± 8.57	n/a	1.4 ±1.8	SpO2 mean 95.7 ± 2.3 SpO2 minimum 89.5 ± 3.9 %TST<90% n/a	Sleep-disordered breathing was frequently observed in children with CF and was associated with progression markers. Sleep studies are an important tool for assessing the respiratory status of these individuals.
Barbosa et al. 2020 [24]	Brazil	2018	31	9.6 (7.9—15.1) median (IQR)	35.48	68.1 ±24.4	16.6 ±2.6	90 (75—95) median (IQR)	Nasal polyps (32.3%)	2.1 (1.3—3.9) median (IQR)	SpO2 mean 95 (94—97) SpO2 minimum 85.5 (83—91) %TST <90% 0.3 (0.1—5.6)	Children and adolescents with nocturnal hypoxemia presented lower lung function, poorer clinical score, and higher morbidity. TST with SpO2 <90% was associated with length of hospitalization.

FEV$_1$: forced expiratory volume in 1 s; BMI: body mass index; CF: cystic fibrosis; OSAS: obstructive sleep apnea syndrome; TST: total sleep time; SpO$_2$: peripheral oxyhemoglobin saturation; AHI: apnea-hypopnea index; PSG: polysomnography; REM: rapid eye movement; SK: Shwachman-Kulczycki score; IQR: interquartile; CI: confidence interval; n/a: not applicable.

3.2. Studies description

The studies included in the systematic review were performed in pediatric hospitals and reference centers for CF in different countries, including four in Brazil, and one each in the USA, Spain, and Australia. All were published between 2011 and 2020. Most of the studies were cross-sectional, and there was only one retrospective study [22]. The sample size ranged from 9 [23] to 67 [14] children and adolescents, mostly males, with mean FEV_1 ranging from 60.7% [1] to 109.8% [23].

Upper airway changes such as nasal polyps were reported in four studies, affecting 5—60% of the individuals [1,8,24]. Mean absolute BMI values were presented in six studies and ranged from 16.6 to 17.8 kg/m^2 [8,23,24,26]. Two other studies reported BMI percentile: 42.1 (31.5—52.6) [1] and 34 (11—64) [14]. The mean Shwachman-Kulczycki score was described in five studies, and ranged from 72.5 to 89.5 [22—24]. As for polysomnography data, mean AHI ranged from 1.1 to 7.3 per sleep hour, mean SpO_2 was 92.9—96.2%, and minimum SpO_2 was 81.2—91.4%. Table 1 shows the main characteristics of the included studies.

3.3. Prevalence of OSAS

The pooled prevalence of OSAS in patients with CF and preserved lung function or mild impairment ranged from 32.3% [24] to 100% [23], and the most frequent methodological criteria to define OSAS was AHI>1 per hour of sleep. The AHI cutoff points used as criteria to diagnose OSAS diverged between studies; most used AHI>1 [1,14,23,24,26,27], and two studies utilized AHI>2 [8,24]. Barbosa et al. (2020) and Spicuzza et al. (2012) reported a prevalence of 32.3% and 70%, respectively, although these studies used an AHI cutoff point of >2 per sleep hour [8,24]. Considering that most studies used AHI>1 per hour to define OSAS, in an attempt to standardize the criteria for inclusion we contacted these two authors to obtain information on the prevalence of OSAS considering AHI>1 per hour. One author reported 77.4% prevalence using this criteria [24], while the other did not respond to our contact [8]. Veronezi et al. (2015) evaluated 34 individuals divided into two groups with different cutoff points for AHI: <12 years (n = 9) and >12 years (n = 25), which only permitted the inclusion of data referring to <12 year old group, in which the prevalence of apnea was 100% [23]. The prevalence of OSAS and the cutoff points used for diagnosis in each study are presented in Table 2.

3.4. Critical assessment of methodological quality

The risk of bias in the studies included is shown in Table 3. The questions regarding details of the studied population, exposure validation and reliability, and article results were 100% positive. Some studies [1,23,26] demonstrated high methodological quality (7—8 points), while the others [8,14,22,24] were classified as moderate (4—6 points).
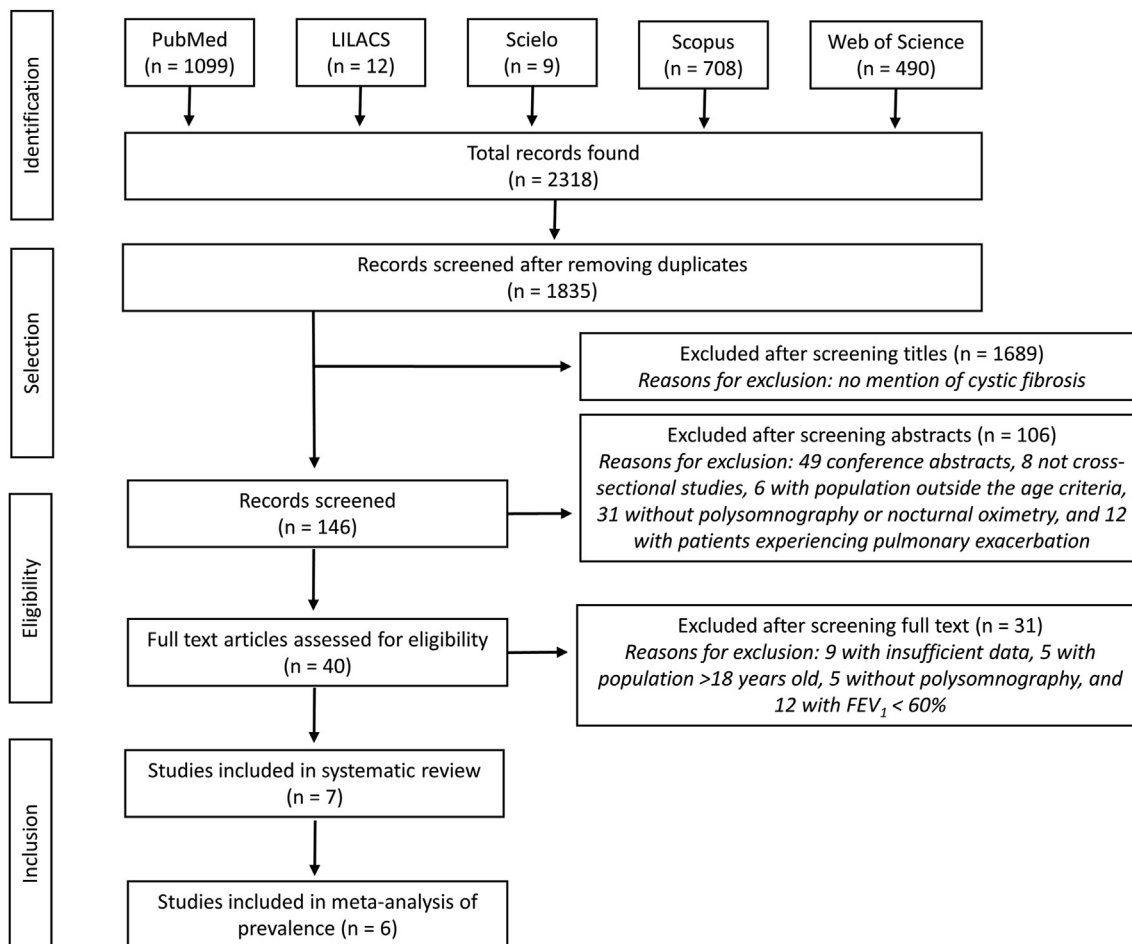

Fig. 1. Flow diagram of the search and selection process.

Table 2
Criteria for defining OSAS and prevalence in each study.

Studies	AHI>2	AHI>1	OSAS Prevalence (%)
Ramos et al., 2011 [14]		X	56.7
Spicuzza et al., 2012 [8]	X		70
Veronezi et al., 2015 [23]		X	100
Waters et al., 2017 [26]		X	73.9
Isaiah et al., 2019 [1]		X	51
Lumertz & Pinto 2019 [22]		X	62.5
Barbosa et al., 2020 [24]		X	77.4
	X		32.3

OSAS: obstructive sleep apnea syndrome; AHI: apnea-hypopnea index.

Table 3
Critical evaluation of methodological quality.

Studies	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Total
Ramos et al., 2011 [14]	Y	Y	Y	Y	U	n/a	Y	Y	6
Spicuzza et al., 2012 [8]	U	Y	Y	Y	N	N	Y	U	4
Veronezi et al., 2015 [23]	Y	Y	Y	Y	Y	S	Y	Y	8
Waters et al., 2017 [26]	U	Y	Y	Y	Y	S	Y	Y	7
Isaiah et al., 2019 [1]	Y	Y	Y	Y	Y	S	Y	Y	8
Lumertz & Pinto 2019 [22]	Y	Y	Y	Y	U	n/a	Y	Y	6
Barbosa et al., 2020 [24]	Y	Y	Y	Y	U	n/a	Y	Y	6

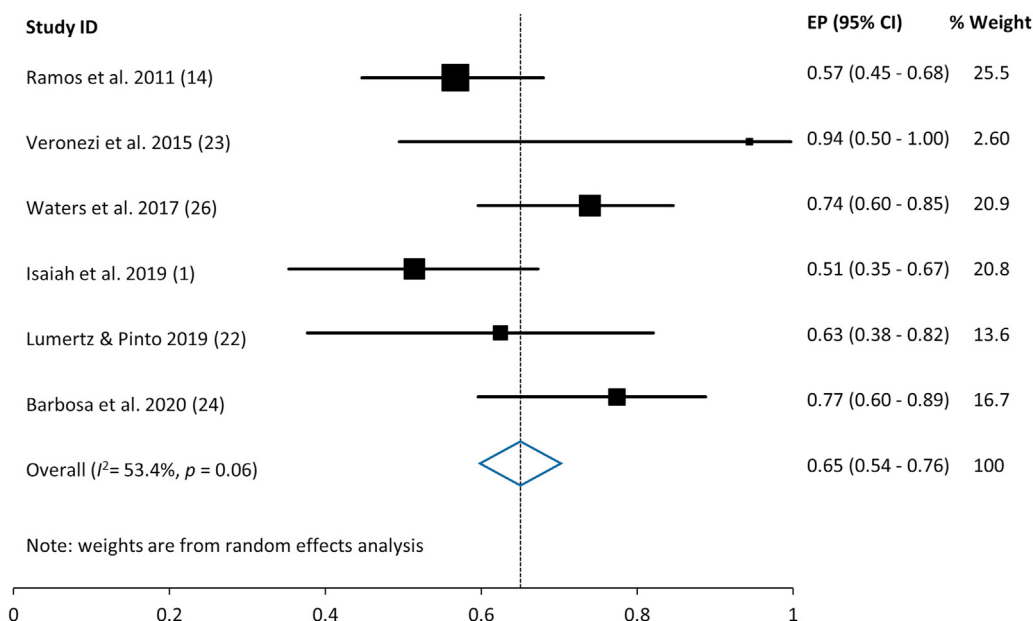Y: yes; N: no; U: unclear; n/a: not applicable.

3.5. Meta-analysis

The pooled prevalence of OSAS in the 6 studies, considering AHI>1 per hour as the diagnostic criteria, was 65% (95%CI: 0.54—0.76) using the random model. The analysis exhibited acceptable heterogeneity, with I^2 = 53.4% (Fig. 2). Considering AHI>2 per hour, 2 studies were included in the analysis and the pooled prevalence of OSAS was 51.5% (95% CI: 0.18 to 0.84) using the random model. The I^2 was 89.4%, showing high heterogeneity; even though this value approached 90%, the confidence intervals in the studies did not overlap, so a forest plot figure was not included.

4. Discussion

The prevalence of OSAS in children and adolescents with CF and preserved lung function or mild impairment in the studies included in this systematic review ranged from 32.3 to 100%. The main hypothesis to explain this significant variability was the different methodological criteria used to diagnose OSAS. When the AHI cutoff point was standardized to >1 per hour, prevalence was high in all studies, exceeding 50% of the studied sample. In contrast, studies have shown that the prevalence of OSAS in healthy children and adolescents is 1.2—5.7% [11—13]. Nevertheless, this prevalence may reach approximately 51% in a pediatric cohort study in which signs or signals of sleep disorders are present [28].

Neither the relationship between sleep disorders and disease severity nor the impact of sleep apnea and treatment for CF patients is clear [15]. There does not seem to be a direct cause/effect phenomenon, and the heterogeneous nature of studies makes it even more difficult to identify the main mechanisms. The definition of OSAS in pediatrics is quite controversial; although the American Academy of Sleep Medicine recommends an obstructive apnea and hypopnea index (IAHO) of ≥1 per hour of sleep [29], relevant pediatric studies use a cutoff point of AHI>2 per hour [30]. Furthermore, some authors apply the adult criteria to studies including subjects under 12 years of age (AHI>5 per hour). Only one author in this meta-analysis considered this criteria, and even using this cutoff point reported a 46% prevalence of OSAS in adolescents and adults with CF [23]. Ramos et al. (2011), who did not utilize hypopnea events and adopted an obstructive apnea index (OAI) of ≥1 per hour, found OSAS in 56.7% of their sample [14]. Two other studies reported low prevalence, although it is noteworthy that the sample size was small (10 participants) in both cases, and they did not describe their criteria for defining OSAS [10,25].

Occurrence of OSAS in healthy children is associated with upper airway changes. A randomized study in children without CF with upper airway changes, using IAHO≥2 per hour as a criteria, showed a prevalence rate of 33% [30], corroborating the 32.3% found by Barbosa et al. (2020), who used the same criteria to define OSAS in children and adolescents with CF [24]. Spicuzza et al. (2012) found a

Study ID		EP (95% CI)	% Weight
Ramos et al. 2011 (14)		0.57 (0.45 - 0.68)	25.5
Veronezi et al. 2015 (23)		0.94 (0.50 - 1.00)	2.60
Waters et al. 2017 (26)		0.74 (0.60 - 0.85)	20.9
Isaiah et al. 2019 (1)		0.51 (0.35 - 0.67)	20.8
Lumertz & Pinto 2019 (22)		0.63 (0.38 - 0.82)	13.6
Barbosa et al. 2020 (24)		0.77 (0.60 - 0.89)	16.7
Overall (I^2= 53.4%, p = 0.06)		0.65 (0.54 - 0.76)	100

Note: weights are from random effects analysis

Fig. 2. Prevalence of OSAS in children and adolescents with cystic fibrosis and preserved lung function or mild impairment, considering an AHI criterion of >1 per hour. EP: estimated prevalence; CI: confidence interval.

significantly higher AHI in the CF group compared to controls without the disease but who exhibited upper airway abnormalities. For this reason, OSAS appears to be present in children with CF regardless of upper airway changes [8].

Further studies are still needed to investigate an association between OSAS and airway changes in children and adolescents with CF. In the present systematic review, upper airway dysfunction was mentioned in 4 of the articles [1,8,23,24]; however, they described different dysfunctions and forms of evaluation, which makes it difficult to establish a potential causal relationship between the occurrence of OSAS and upper airway changes. As a result, the main hypothesis to explain the high prevalence of OSAS in children with CF (namely its association with upper airway obstruction caused by chronic rhinosinusitis and nasal polyps frequently found in this population) remains uncertain.

Some studies have shown another possible explanation for the development of OSAS in healthy children and adolescents: nutritional status [30]. Li et al. (2010) demonstrated that the prevalence of OSAS in healthy children aged 5—14 with mean BMI of 33.3 ± 6.1 kg/m^2 was 7.2% [12]. The results of this systematic review were quite different: prevalence of 70% and 74% in children and adolescents with CF and mean BMI of 17.8 ± 3.4 and 17.9 ± 4.1 kg/m^2, respectively [8,26]. Only one study included in the review correlated AHI with BMI, and found a significant inverse correlation between variables [24]. Although disease evolution and decline in lung function are important contributors to the development of OSAS in CF, none of these factors should be considered in isolation when OSAS is suspected, considering that this present meta-analysis demonstrated a high prevalence of OSAS even in children and adolescents with mean FEV$_1$ >60% before pronounced decline in lung function. We believe that age should also be considered, since the inclusion of older children may illustrate an interaction between sleep-disordered breathing and greater decline in lung function as CF exacerbates.

Taken together, the evidence indicates that CF appears to be a risk factor for OSAS, and potential explanations may stem from the fact that patients with CF experience periods of exacerbation, with frequent coughing, epithelial and upper airway damage, and inflammation with neutrophil infiltration, leading to an increase in the soft tissue in the surrounding oropharynx and decreased airway diameter that contributes to airway obstruction during sleep [16].

The main limitation of this review is that although we only included studies in which the mean FEV$_1$ value was >60% of predicted, this does not completely rule out the possibility that severe patients were included in the sample. Another limitation is the use of different methodological criteria in pediatric OSAS studies, which made it difficult to include more data in the meta-analysis. It is also important to add that most of the articles were from Brazil, which limits extrapolation of the results to other realities and countries, and that the sample in some studies may have been a cohort of patients referred for sleep studies due to the presence of signs and symptoms related to sleep disorders. Furthermore, few studies have investigated the association between OSAS, nasal polyps, nutritional status, and other clinical variables, which makes it impossible to elucidate the high prevalence found in this population.

Future studies are needed to evaluate associations between OSAS and clinical variables such as hospitalization, antibiotic use, nutritional status, and careful upper airway assessment in order to better understand these relationships, along with research utilizing experimental designs that permit the establishment of causal effects.

5. Conclusion

This meta-analysis found a high prevalence of OSAS in children and adolescents with CF and preserved lung function or mild impairment. Results varied according to the criteria for OSAS diagnosis, with a prevalence of 65.6% for AHI>1 and 51.5% for AHI>2 per hour, reinforcing the importance of investigating sleep disorders regardless of age or lung function decline in patients with CF.

Author contributions

All five authors made substantial contributions to this study. RRBB: conceptualization and design, supervision and oversight, formal analysis, and drafting significant parts of the article. LPS: literature search, conceptualization and design, data extraction, formal analysis, drafting the article. FMGL, FMV, MVFD: methodology, formal analysis, critical review.

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Conflict of interest

None.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2021.09.017.

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