

Review

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[Marco Zaffanello](#) ^{*}, [Giuliana Ferrante](#), [Michele Piazza](#), [Luana Nosetti](#), [Laura Tenero](#), [Giorgio Piacentini](#)

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Review

Exploring the Relationship Between Inhaled Corticosteroid Usage, Asthma Severity, and Sleep-Disordered Breathing: A Systematic Literature Review

Marco Zaffanello ^{1,*}, Giuliana Ferrante ¹, Michele Piazza ¹, Luana Nosetti ², Laura Tenero ¹ and Giorgio Piacentini ¹

¹ Department of Surgery, Dentistry, Pediatrics and Gynecology, University of Verona, 37100 Verona, Italy; marco.zaffanello@univr.it; giuliana.ferrante@univr.it; michele.piazza@univr.it; laura.tenero@aovr.veneto.it; giorgio.piacentini@univr.it

² Pediatric Sleep Disorders Center, Division of Pediatrics, "F. Del Ponte" Hospital, University of Insubria, 21100 Varese, Italy; luana.nosetti@uninsubria.it

* Correspondence: marco.zaffanello@univr.it

Highlights:

What are the main findings?

- In adult patients with asthma, inhaled corticosteroids, especially at high doses, appears to increase the risk of sleep apnea.
- In children, inhaled corticosteroids seem to be a less relevant risk factor of sleep apnea compared to adults.

What is the implication of the main finding?

- There is a complex relationship between inhaled corticosteroids use, asthma severity, and the onset of sleep apnea.
- Since the high overall risk of bias of these studies was categorized as high, further studies are needed.

Abstract: (1) Background: Sleep-disordered breathing and asthma are often interrelated. Children and adults with asthma are more susceptible to sleep apnea. Inhaled corticosteroids effectively reduce inflammation and prevents structural changes in the airways. Objective: to explore the existing literature to determine whether inhaled corticosteroids play a role in sleep-disordered breathing in patients with asthma; (2) Methods: We systematically searched the Medline PubMed, Scopus, and Web of Science databases for articles published in English until May 12, 2024. We utilized the ROBINS-E tool to assess the risk of bias; (4) Conclusions: 136 articles was discerned upon conducting the literature search. A total of 13 articles underwent exhaustive full-text scrutiny, resulting in 6 being considered non-relevant. The remaining 7 articles, assessed for eligibility, were incorporated into the final analysis. Five studies were identified in adults and two in children. In adult patients, inhaled corticosteroids, especially at high doses, appear to increase the risk of sleep apnea in a dose-dependent manner. Additionally, the characteristics of inhaled corticosteroids (inhaled particle sizes) may influence the risk of sleep apnea. In children, the severity of asthma plays a crucial role in influencing the prevalence of sleep apnea, while using inhaled corticosteroids seems to be a less relevant risk factor compared to adults. The overall risk of bias was categorized as high or with some concerns in 100% of the studies analyzed. Each study identified at least one form of bias that raised significant concerns. Studies showed a complex relationship between inhaled corticosteroids use, asthma severity, and the onset of sleep apnea. Further studies are needed.

Keywords: asthma; fluticasone propionate; inhaled corticosteroid; obstructive sleep apnea; sleep-disordered breathing

1. Introduction



Sleep-disordered breathing (SDB) can lead to significant health issues in both children and adults [1-3]. SDB is linked to a variety of detrimental effects, including intermittent hypoxia, oxidative stress, sleep fragmentation, high blood pressure, and heart disease [4-7].

Children

In children, the incidence of SDB has been on the rise. Parent-reported habitual snoring varies from 1.5% to 6%, while sleep apnea episodes range from 0.2% to 4%. Depending on the combination of symptoms reported by parents on questionnaires, the prevalence of SDB ranges from 4% to 11%. The minimum prevalence rate for pediatric obstructive sleep apnea syndrome (OSAS) is around 1% [8]. Diagnosed OSA, based on various diagnostic study criteria, ranges from 1% to 4% [9].

Adults

The 5-year incidence rate in adults is roughly 7.5% for moderate to severe SDB and 16% (or less) for mild to moderate SDB combined [10]. The prevalence of OSA associated with daytime sleepiness is about 3-7% for adult males and 2-5% for adult females in the general population [9]. SDB affects approximately 17% of men and 9% of women aged 50 to 70 [11].

Treatment

Regarding treatment, medical therapy with intranasal corticosteroids (ICS) is more effective in reducing OSA than a placebo [12]. ICS manage OSA symptoms by reducing inflammation and nasal congestion [13]. In children with mild OSA, ICS such as budesonide and fluticasone have been shown to improve symptoms and reduce adenoid size, but they do not entirely resolve OSA. However, the effectiveness of ICS in managing OSA symptoms is a matter of debate [14].

Recent evidence has been insufficient to support the efficacy of ICS for OSA treatment in children [15]. In a recent randomized, double-blind, placebo-controlled study, it was reported that in children aged 5-12 years with OSAS, ICS treatment did not result in significant changes in polysomnography (PSG) outcomes, neurobehavioral symptoms, or OSA symptoms after 3 and 12 months of treatment [16].

Adenotonsillectomy (A&T), where applicable, remains the first-line treatment for adenotonsillar hypertrophy (ATH), and it is associated with significant improvements in SDB in most children, being effective in 70% to 100% of patients [17].

In adults, continuous positive airway pressure (CPAP) is the gold standard treatment for OSA [18]. Maxillomandibular advancement (MMA) is a highly effective surgical option for patients with OSA who have difficulty tolerating CPAP and whose OSA has been refractory to other surgical modalities [19].

Asthma

Asthma is a chronic inflammatory condition of the airways in the lungs characterized by recurrent episodes of wheezing, coughing, chest tightness, and shortness of breath [20].

The overlapping symptoms of OSA and asthma can complicate the diagnosis of either condition. The nocturnal respiratory symptoms of OSA and asthma are often interrelated, necessitating in-hospital PSG for accurate diagnosis, particularly in pediatric cases [21].

Prevalence

A study has revealed significant disparities in asthma prevalence. Over a two-decade period, the overall prevalence of asthma has fluctuated. It increased from 2003 (8.5%) to 2009 (9.6%) and then decreased in 2019 (7.0%) [22]. Asthma prevalence peaked at 17.8% among children aged 5-9 years and then declined to 6.9% among those aged 45-49 years, only to gradually increase to 8.1% among those aged 65-69 years [23].

SDB in Asthmatic Patients

Children

Children with asthma are more susceptible to OSA. A significant 60.4% of children with asthma were found to have OSA, a rate notably higher than the prevalence of OSA in the general pediatric population [24,25].

Adults

In adults, research has consistently demonstrated that the incidence of OSA is significantly greater in individuals with asthma compared to those without, with rates varying from 38% to 70%. Asthmatic patients with OSA are 3.6 times more likely to experience uncontrolled asthma [26]. A meta-analysis revealed that the prevalence of OSA in adult patients with asthma was 49.5% and that the likelihood of having OSA was 2.6 times higher in patients with asthma compared to healthy controls [27].

Treatment

Regarding treatment, ICS effectively reduce inflammation and prevents structural changes in the airways, thereby preserving lung function over time [28]. ICS is approved by the FDA for the prevention of asthma exacerbations in both children and adults [29].

Aims of the Study

Given the prevalence of OSA in patients with asthma, this review aims to explore the existing literature to determine whether ICSs play a role in SDB/OSA in patients with asthma.

2. Materials and Methods

We systematically searched the Medline PubMed, Scopus, and Web of Science databases for articles published in English from inception until May 12, 2024. We adjusted Medical Subject Heading (MeSH) terms to search each database, including their combinations and truncated synonyms.

PUBMED: (Inhaled Corticosteroids [Title/Abstract] OR Inhaled Glucocorticoids [Title/Abstract] OR Inhaled Steroids [Title/Abstract] OR Inhaled Fluticasone [Title/Abstract] OR inhaled mometasone [Title/Abstract] OR ciclesonide [Title/Abstract] OR inhaled budesonide [Title/Abstract] OR beclomethasone [Title/Abstract]) AND (Obstructive Sleep Apnea [Title/Abstract] OR Obstructive Sleep Apnoea [Title/Abstract] OR OSA [Title/Abstract] OR Sleep Apnea Syndrome [Title/Abstract] OR Sleep Apnoea Syndrome [Title/Abstract] OR Obstructive Sleep Disorder [Title/Abstract] OR sleep apnea [Title/Abstract] OR sleep apnoea [Title/Abstract] OR sleep-disordered breathing [Title/Abstract] OR Obstructive sleep apnea/hypopnea syndrome [Title/Abstract] OR Obstructive sleep apnoea/hypopnea syndrome [Title/Abstract])

SCOPUS: TITLE-ABS-KEY ("Inhaled Corticosteroids" OR "Inhaled Glucocorticoids" OR "Inhaled Steroids" OR "Inhaled Fluticasone" OR "inhaled mometasone" OR "inhaled ciclesonide" OR "inhaled budesonide" OR "inhaled beclomethasone") AND TITLE-ABS-KEY ("Obstructive Sleep Apnea" OR osa OR "Sleep Apnoea Syndrome" OR osa OR "Sleep Apnea Syndrome" OR "Sleep Apnoea Syndrome" OR "Obstructive Sleep Disorder" OR "sleep apnea" OR "sleep apnoea" OR "sleep-disordered breathing" OR "Obstructive sleep apnea/hypopnea syndrome" OR "Obstructive sleep apnoea/hypopnea syndrome")

WEB OF SCIENCE: AB=("Inhaled Corticosteroids" OR "Inhaled Glucocorticoids" OR "Inhaled Steroids" OR "inhaled fluticasone" OR "inhaled mometasone" OR "inhaled ciclesonide" OR "inhaled budesonide" OR "inhaled beclomethasone") AND AB=("Obstructive Sleep Apnea" OR "Obstructive Sleep Apnoea" OR osa OR "Sleep Apnoea Syndrome" OR "Sleep Apnea Syndrome" OR "Obstructive Sleep Disorder" OR "sleep apnea" OR "sleep apnoea" OR "sleep-disordered breathing" OR "Obstructive sleep apnea/hypopnea syndrome" OR "Obstructive sleep apnoea/hypopnea syndrome")

PICOS Criteria

The PICOS criteria [30] were followed to define the research scope and select the included studies. The criteria were defined as follows:

Participants:

Inclusion criteria: patients of all ages with a confirmed diagnosis of both asthma and SDB.

Exclusion criteria: patients with significant comorbidities, genetic disorders, or other asthma-related medical conditions. Studies that do not provide information on the use of ICS.

Intervention:

Inclusion criteria: patients with asthma and OSA/SDB/snoring treated with ICS.

Exclusion criteria: patients not explicitly treated with ICS.

Comparison:

Inclusion criteria:

Longitudinal studies: patients with both OSA and asthma observed before and after treatment.

Cross-sectional comparative studies: patients with OSA and asthma compared to a control group.

Exclusion criteria: asthmatic patients without specified OSA/SDB/snoring status and/or ICS treatment.

Outcome:

Primary outcome: changes in OSA/SDB/snoring severity before and after treatment with ICS.

Exclusion criteria: patients with significant comorbidities that could affect OSA outcomes in asthmatic patients treated with ICS.

Study Design:

Inclusion criteria: observational studies with a control group (including observational and comparative designs), studies with temporal perspectives (prospective, observational, cross-sectional, and longitudinal), and studies with unspecified temporal structures (cross-sectional, comparative, observational, retrospective).

Exclusion criteria:

Language: articles not written in English.

Study type: reviews, case reports, letters, studies without specific outcome measures, and duplicate studies identified through various data sources.

Data Extraction:

To minimize potential errors and interpretive bias, two independent reviewers meticulously examined the data extraction process for each study. In discrepancies between reviewers, a third reviewer was consulted to resolve issues, ensuring the accuracy and consistency of data extraction. The PRISMA flow diagram was employed to document and visualize the selection process of included and excluded studies (<http://www.prismastatement.org/PRISMAStatement/FlowDiagram>).

Evaluation of the Risk of Publication Quality Distortion

We thoroughly examined potential sources of bias that could influence the results of these studies. The sources of bias considered included:

Measurement of exposure bias: this bias may occur if the exposure is not accurately measured, such as through self-reported questionnaires.

Selection bias: this type of bias can arise if participants are not selected in a representative manner from the target population.

Post-exposure intervention bias: may occur if participants receive interventions after exposure to the interest factor.

Missing data bias: this bias can arise if data is missing from the study, such as when participants drop out.

Measurement of outcome bias: this bias may occur if the outcome is not accurately measured, such as when subjective measures are used.

Reporting bias: this type of bias can occur if researchers selectively report results that support their hypothesis.

As a systematic method to assess the risk of bias in observational epidemiological studies, we utilized the ROBINS-E (Risk Of Bias In Non-randomized Studies - of Exposure) tool [31]. The

questions in these tools meticulously assessed the methods and results of the studies, providing ratings of "High", "Some concerns" or "Low"..

3. Results

A corpus of 136 articles was discerned upon conducting the literature search, with 36 identified as duplicates. Consequently, 87 studies were excluded: 33 were utterly irrelevant, 38 were immaterial reviews, 3 were guidelines, 6 were non-pertinent case reports or series, and 7 were in languages other than English (Figure 1). A total of 13 articles underwent exhaustive full-text scrutiny, resulting in 6 being considered non-relevant (as encapsulated in the accompanying table). The remaining 7 articles, assessed for eligibility, were incorporated into the final analysis (as summarized in the table).

PRISMA Flow Diagram.

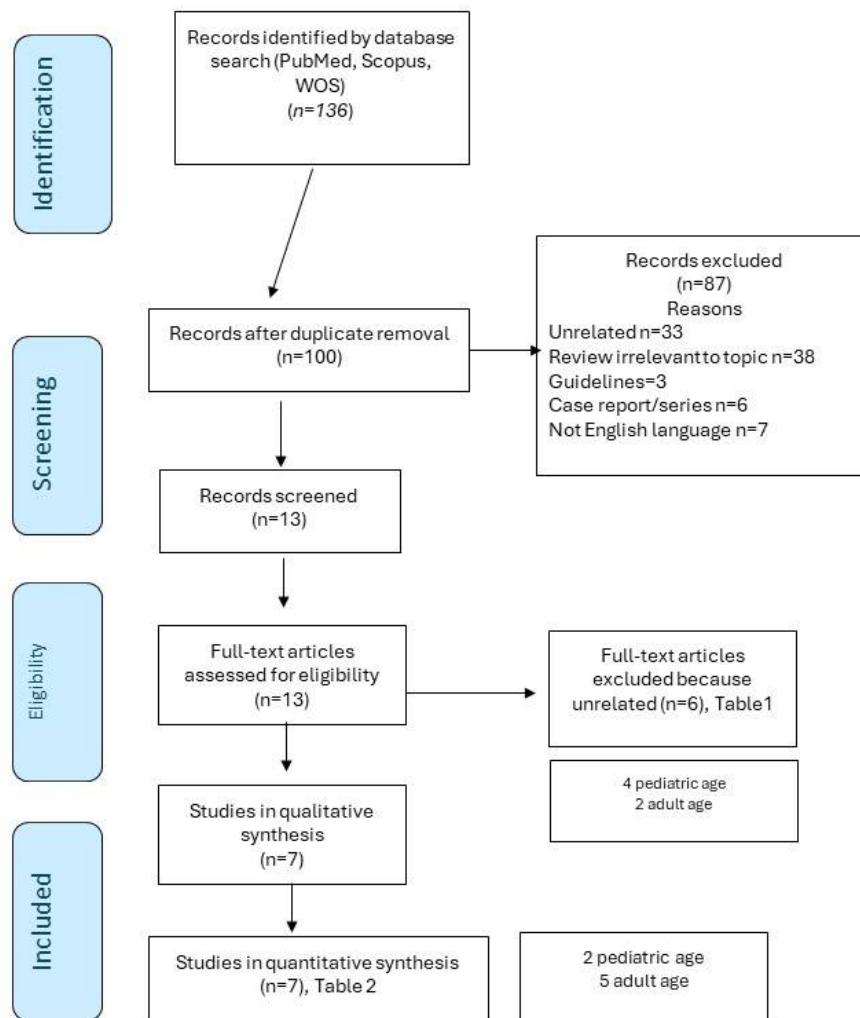


Figure 1. PRISMA Flow Diagram.

Study Data

The research enumerated in Table 1, omitted from the review, encompasses four pediatric and two adult studies. Bhattacharjee et al. investigated 5,942 children who underwent A&T alongside 537 control subjects, aiming to evaluate the impact of A&T on SDB and asthma management. They observed a marked decline in asthma symptoms, ICS usage among children post-A&T, and a simultaneous decrease in SDB [32]. Kheirandish-Gozal et al.'s study involved 92 children with poorly controlled asthma (PCA). Using PSG, the authors assessed the prevalence of OSA in asthmatic children and the effect of A&T on the frequency of asthma exacerbations. They demonstrated a significant improvement in asthma exacerbations and a reduction in the use of rescue β -agonists after

A&T [33]. Alfurayh et al. conducted a study on a cohort of 363 children, examining asthma exacerbations in those visiting the emergency department (ED) by analyzing demographic data and comorbidities. They found that most children using ICS did not present nocturnal symptoms, with a low prevalence of OSA [34]. Heatley et al. evaluated the association between intermittent ICS usage and adverse outcomes in asthma patients. Based on medical records from various age groups, they discovered an increased risk of pneumonia and OSA related to cumulative exposure to orally administered corticosteroids (OCS), with a higher prescription of ICS in patients with frequent OCS use [35].

Ferguson et al. conducted a comprehensive analysis of 812 individuals with asthma to investigate the relationships between lower airway dimensions, OSA, and asthma-related parameters with systemic hypertension (HTN). By examining medical histories, spirometry results, and medication regimens, they identified a significant link between high-dose ICS usage and increased HTN risk and a strong correlation between a history of OSA and HTN [36]. Magnoni et al. used questionnaires to study 174 patients in a separate investigation, focusing on epidemiology, risk factors, and treatment strategies. They concluded that the combination of ICS with long-acting beta-agonists (LABA) was the preferred therapeutic approach, while OSA and obesity emerged as critical comorbidities and risk factors for PCA [37].

Although these studies provide relevant insights into asthma and SDB, they diverged from the primary focus of the main investigation. Specifically, the excluded studies targeted different primary outcomes, such as the effects of A&T, the impact of OCS, or general risk factors like HTN, rather than the direct interplay between ICS and SDB.

Table 1. Excluded studies from the review.

First Author, Year	Aim of the Study	Subjects and methods	Asthma	ICS	OSA or SDB	Conclusion	Reasons of exclusion
CHILDREN							
Kheirandi sh-Gozal L, 2011 [38]	Prevalence of OSA in asthmatic children. Effect of A&T on AAE frequency	92/135 children (age 6.58 ± 1.8 years) with PCA; children. A&T was performed in the case of OSA. AAE frequency ≥5/ora TST	AAE (n. 92), 3.27 ± 2.4/year. AAE: PSG. AAE+ (n. 58) 3.57 ± 2.9 versus 1.37/year. oAHI ≥5/ora TST (n.58) 3.12 ± 1.40/year (p<0.05)	β-rescue agonists (4.1 ± 2.4/week) β-Rescue agonists (No. 35) 4.3 ± 1.8 vs. after T&A OSA+: 4,7 ± 2,9 versus OSA- 3,6 ± 2,1 (p<0,04)	β-Rescue agonists (/week): Before T&A OSA+ (No. 35) 4.3 ± 1.8 vs. after T&A OSA+: 4,7 ± 2,9 versus OSA- 3,6 ± 2,1 (p<0,04) Before PSG OSA- (n.24) 4.2 ± 1.9 against after PSG 3.9 ± 2.2 (p=NS)	The prevalence of OSA is higher in children with PCA vs. after T&A (p<0.001) Before PSG A&T is associated with OSA by treatment of OSA by A&T is associated with improvement (p=NS) AAE (/year): Before T&A OSA+ (No.	Effect of A&T on AAE Frequency Children With PCA and Associate d OSA

					35) 4.1 ± 1.3 vs. after T&A 1.8 ± 1.4 (p<0.001)		
					Prima di PSG OSA- (n.24) $3,5 \pm 1,5$ versus dopo PSG $3,7 \pm 1,7$ (p=NS)		
Bhattacha rjee R, 2014 [32]	A&T+ Comparis on with Controls, SDB, and Asthma Control	ATH n.5,942 (44%) vs Asthma controls n.537 (2%)	AAE decrease A&T 2,243 (30%) pre-A&T to 1,566 (2%) post- A&T in children (p<0.000 1)	Reduction in ICS d from prescription vs -2.0% controls (p<0.001) to 1,566 (2%) ICS/LABA -2.2% A&T vs -20.1% controld (p<0.001)	Reduction of OSA, snoring, and/or sleep disturbances: A&T n.3603 (27%) vs controlli n.1099 (1%)	Children A&T: 30% reduction in AAE 1 year before A&T versus 1 year after	Efficacy of A&T in Improvin g Asthma Symptom s and Reducing SDBs
Alfurayh, MA, 2022 [34]	Exacerbat ion of Bronchial Asthma in the ED in a Paediatr ic Populatio n	Cohort study: Children in ED due to asthma exacerbatio n. Data collection: demograp hics, comorbidit ies, and asthma-	Visits to the ED: yes (33.9%) vs no (66.1%) Of the 123 patients who used steroids, 74% (91) had no	Of the 363 asthma patients (age $4.9 \pm$ 2.5 years; 68.8% male), 33.9%	1.9% with FBO (n.7). Number of patients hospitalized with OSA (p=0.203).	Association Between Steroid Use in Asthmatic Patients, Number of ED Visits, and Nocturnal Symptom s	Steroid Use in Asthmatic Patients, Number of ED Visits, and Nocturnal Symptom s

related variables. nocturna l symptoms (p < 0.001)							
Heatley H, 2023 [35]	Intermitt ent prescribi ng of OCS in asthmatic patients and the associatio n with adverse outcomes	Cohort study. Primary Care Medical Records	Dose-response relations between cumulati ve annual exposur e to OCS and risk years)	ICS prescription s (0, 1–3, 4–6, 7–9, 10–12, and ≥13 administrati on)	Higher risks of adverse outcomes related to OCS, pneumonia, and OSA	Patients with asthma who received intermittent OCS have frequent prescription s: received 1–2 administrati ons of SABA and ≤3 of ICS	Associatio n Between Intermitte nt OCS Prescribin g in Asthmatic Patients and Adverse Outcomes , Such as Pneumoni a and OSA
		Categories: prescription: single, least frequent (≥90 day range), frequent (<90 day interval)		Proportion of patients receiving ≥3 administrati ons of SABA and ≥4 of ICS at baseline increased with more frequent OCS prescription s		associated with higher risk of adverse outcomes	
		Controls: patients not treated with OCS, matched 1:1		Higher number of ICS prescription s in those who had more frequent OCS prescription s			

Ferguson S, 2014 [36]	Associati on Between Lower Airway Caliber, OSA, and Other Asthma- Related Factors With HTN	Multicenter study; use of ICS (ages 46 ± 14) (78%): OSA scale of the SA- SDQ Medical records: HTN, OSA, spirometry and medication s	Subjects with asthma, use of ICS (n.631) (78%): low dose (n.189) (23%), medium dose (n.235) (29%), high dose (n.207) (25%)	Association s of HTN: Low-dose ICS (OR 0.86, CI 0.50-1.45), medium doses (OR 1.1, CI 0.75-1.95), and high-dose (OR 2.18, CI 1.37-3.48)	Association of HTN with history of OSA (OR= 5.18, CI 3.66-7.32; p<0.0001)	Concomita nt OSA has been associated with HTN	Associatio n Between OSA and ICS, with Hyperten sion in Asthmatic Patients
Magnoni M.S., 2017 [37]	How Italian allergists deal with asthma patients	174 questionnaires, 16 questions: epidemiology, risk factors, therapeutic approaches and adherence to therapy	Follow-up visits at 56.5%, worsen ing of symptoms for 41%, percenta ge of visits due to adverse effects of drugs 3%	ICS combined with LABA were considered the treatment of choice	Sleep apnea and obesity were assessed as the most important comorbidities /risk factors of PCA	Recognizin g and managing OSA could be key to improving asthma control in patients	Survey or a questionn aire exploring how Italian allergists manage asthma patients, including their treatment approaches and asthma managem ent

Legend: AAE, esacerbazioni asmatiche acute; ACT, punteggio del Test di Controllo dell'Asta; AO, adverse outcomes; ATH, Hypertrophy of tonsils and adenoids; A&T, adenotonsillectomy; ; ED, emergency department; ESS, Epworth Sleepiness Scale; HTN, systemic hypertension; ICS, corticosteroidi per via inalatoria; LABA, long-acting beta-agonists; oAHI, obstructive apnea hypopnea index; OCS, Oral corticosteroids; OSA, obstructive sleep apnea; PCA, poor controlled asthma; PSA, polysomnography; TST, total sleep time.

The studies in Table 2, included in the analysis, were chosen for their direct relevance to the topic. Five studies were identified in adults and two in children.

Studies in Adulthood

A survey-based investigation examined 284 asthma patients, averaging 46 ± 13 years (range 18-75 years). The authors discovered a linear and dose-dependent relationship between ICS usage (OR

4.05; 95% CI 1.56–10.53) and the risk of OSA, irrespective of asthma severity [39]. Specifically, asthma patients on ICS, especially at higher doses, showed a significantly increased risk of developing OSA. The risk heightened with increased ICS doses (OR 2.29 for low doses, OR 3.67 for medium doses, OR 5.43 for high doses) [39].

A prospective, single-center, single-group study included 18 asthmatic participants with a mean age of 25.9 ± 6.3 years. This research examined the effects of ICS on upper airway collapsibility (UAW) during sleep and wakefulness in asthmatic subjects. Participants were treated with fluticasone propionate (FP) for 16 weeks. Evaluations included passive critical closing pressure (Pcrit) and nuclear magnetic resonance imaging (MRI) to measure the fat fraction and volume around the upper airways [40]. The results indicated variable changes in the AHI, with some patients improving, others worsening, and some showing no significant changes [40].

A retrospective cohort study analyzed factors linked to habitual snoring and the risk of OSA in a large sample of 38,840 asthmatic patients (mean age 52.8 ± 18.1 years) and 155,347 individuals without asthma (mean age 53.3 ± 18.0 years). The follow-up duration was around 7 years for asthmatic patients and approximately 6.5 years for the control group [41]. Findings indicated that asthmatic patients on ICS had a heightened risk of developing OSA compared to those not receiving ICS treatment, with an adjusted hazard ratio (HR) of 1.33 (95% CI = 1.01–1.76). Additionally, the asthmatic cohort overall exhibited a significantly higher risk of OSA compared to non-asthmatic individuals [41].

A prospective, randomized, controlled trial investigated the impact of cPAP on asthma control, airway reactivity, daytime sleepiness, and overall health status in asthmatic patients with nocturnal symptoms and OSA. The study included 122 participants with asthma (mean age 50.5 ± 12.0 years), divided into two groups based on the AHI: ≥ 10 (n = 41) and < 10 (n = 81). Participants were further split into CPAP (n = 17) and control (n = 20) groups [42]. The results showed no significant differences in AHI changes between the groups. However, AHI was associated with BMI and neck circumference, suggesting that OSA in asthmatic patients may be influenced by anthropometric factors and ICS use [42].

A study investigated the influence of ICS on the diagnosis of OSA, with a particular focus on the particle size of ICS. The risk associated with ICS may vary depending on the size of the emitted particles. Inhaler devices produce particles that vary in size, ranging from less than 1 μm to more than 10 μm in diameter. To effectively reach the airways, particles should be smaller than 5 μm . This cohort study included 29,816 asthmatic patients with an average age of 42.8 ± 21.1 years. Evaluations included the asthma control test (ACT) and pulmonary function tests (PFT) [43]. Findings revealed that the use of ICS with standard-size particles was linked to an increased risk of OSA (adjusted odds ratio [aOR] 1.56; 95% confidence interval [CI] 1.45–1.69), whereas ICS with extra-fine particles ($< 2 \mu\text{m}$) did not significantly elevate the risk (aOR 1.11; 95% CI 0.78–1.58). Additionally, asthma control played a crucial role in the risk of OSA, with a higher probability of OSA diagnosis observed in patients with uncontrolled asthma [43].

Studies in Childhood

A prospective observational comparative study examined 108 asthmatic children with an average age of 9.1 ± 3.4 years (range 4 to 18 years). The participants were categorized into groups without SDB (n = 76) and with SDB (n = 32). The study analyzed the associations between SDB, obesity, and asthma severity at follow-up [44]. SDB was more frequently observed in children with severe asthma compared to those with mild or moderate asthma. However, no significant correlation was found between SDB and asthma severity in children using high-dose ICS alone or in combination with other medications [44].

A retrospective study investigated the relationships between sleep, obesity, and asthma in urban minority children. This study involved a review of medical records of 443 asthmatic children (average age 10.2 ± 4.1 years), who underwent PSG. The analysis focused on the associations between spirometry measurements, BMI, and PSG parameters, adjusting for asthma and antiallergic medications [45]. Findings indicated that obese children with asthma had a significant AHI (5.9 ± 12.1

events/h) compared to their normal-weight counterparts (3.1 ± 5.7 events/h; $p=0.009$). ICS usage was prevalent in both groups but did not directly correlate with AHI [45].

Table 2. Included studies from the review.

First Author, Year	Aim of the Study	Subjects and methods	Inhaled corticosteroid	Asthma	OSA o SDB	Conclusion
ADULTS						
Teodorescu M, 2009 [39]	Risk Factors Associated with Habitual Snoring and OSA Risk in Asthmatic Patients	Survey 284 asthmatics (age 46 ± 13, range 18–75 years) Valutazione SDB: Self-Reported OSA Symptom, SA-SDQ	Use of ICS: n.201 (82%): 284 asthmatics (age 46 ± 13, range 18–75 years) No. 65 patients with grade 1 asthma: n.13 (20%) with high doses of ICS n.20 (31%) senza ICS n.77 patients with grade 4 asthma => n.12 (16%) non-use of ICS n.43 (56%) high doses of ICS	Recent spirometry data collected to assess asthma severity step: N.143/284 (50%) had SDB or met the criteria for high OSA risk Asthma severity step: n.13 (20%) with high doses of ICS n.20 (31%) senza ICS n.77 patients with grade 4 asthma => n.12 (16%) non-use of ICS n.43 (56%) high doses of ICS	+129% risk of OSA with low-dose ICS (OR, 2.29; C.I.95% = 0.66-7.96); +267% with Predictors of mid-dose ICS Habitual Snoring in 244 Asthma Patients was Asthma severity step high-dose ICS aOR 1.22 (95% CI 0.94- 1.60), p=0.14 compared to Predictors of no use of ICS High Risk OSA in 244 Dose- dependent Asthma Patients was relationship between Asthma severity step aOR 1.59 (95% CI 1.23- 2.06), p<0.001 snoring and ICS dose (overall p = 0.004)	Increased risk of OSA associated with ICS use. Proportional increase in risk based on the dosage of ICS used. Dose-dependent relationship between high OSA risk and ICS dose (overall p < 0.001)

Teodorescu M, Effects of Orally Inhaled FP on UAW During Sleep and Wakefulness in Asthmatic Subjects 2014 [40]	Prospective, single group and center study	High dose inhaled FP (1,760 mcg/day).	FEV1 % pretreatment (events/h) = 88.8 ± 1.9 , post treatment (0.51 ± 0.48), Dose adherence of FP was 91.2% ± 1.7%. (p=0.001)	AHI baseline (1.2 ± 2.0, improved n.8 (0.51 ± 0.48), unchanged (1.64 ± 0.79), worsened n.2 (2.40 ± 2.40)	High-dose FP led to improvements in lung function (FEV1%). Improved Pcrit in some participants.
	16-week ICS (FP) treatment			SA-SDQ = n. 18 (21.2 ± 3.9),	No significant impact on AHI after FP treatment.
	Asthma duration: 14.4 ± 10.2 years.			Improved No.8 (19.38 ± 0.98)	No reduction in overall AHI.
	Pcrit; MRI (Fat Fraction and Volume Around the Upper Airway)			Worsened No. 2 (25.00 ± 4.00)	High-dose FP appears to be associated with an increase in fat fraction and total fat volume in invariato n.8 surrounding upper airway structures
	Valutazione SDB: Self-Reported OSA Symptom, SA-SDQ			Pcrit: improved n.8 (-8.16 ± 1.36), unchanged n.8 (-8.51 ± 2.18), worsened n.2 (-7.35 ± 0.85)	
				Changes in tongue strength with fluticasone inhaled treatment, in the anterior (p=0.02) and posterior (p=0.002) positions	
Shen T.-C., Factors Associated with Habitual Snoring and OSA Risk in 2015 [41]	Retrospective cohort study.	OSA Risk Ratio Among Asthma Patients Based on Different Treatments	aHR +2.51 (95% CI (1.61, 2.17) of OSA in the asthmatic cohort	OSA in asthma patients:	Overall incidence of OSA is higher in the asthmatic cohort than in the control cohort.

Asthmatic Patients	With asthma: 38,840 (age 52.8 \pm 18.1 years)	ICS 11,214 (15.3 per 1000 persons/year).	compared to control (12.1 vs 4.84 per 1,000 person-years).	Non-steroid aHR 1 (reference)	ICS appears to be associated with an even higher incidence of OSA among asthmatic patients.
	Asthma-free: 155,347 (age 53.3 \pm 18.0 years)	No ICS 13,792 (10.6 per 1000 persons/year).	OSA development during follow-up:	Inhaled steroid aHR 1.33 (95% CI 1.01 - 1.76)	
	Follow-up period: 6.95 \pm 3.33 years		aHR +1.87 (95% CI = 1.61-2.17) for the asthma cohort		
	with asthma control 6.51 \pm 3.44 years		compared to the non-asthma cohort		
	SDB Rating: PSG				
Henao MP, 2020 [43]	Effects of ICS on the diagnosis of OSA, with sub- analysis by particle size of ICS.	Cohort study. 29,816 asthmatics (age 42.8 \pm 21.1 years). ACT, PFT	Higher likelihood of OSA in ICS users with standard particle sizes (aOR +1.56, 95% CI 1.45-1.69) than in non-users	Patients with uncontrolled asthma showed a higher likelihood of receiving a diagnosis of OSA (aOR +1.60, 95% CI 1.32-1.94) among compared to those with OSA	Probability of having a diagnosis of OSA with standard-sized particles, compared to non-users of ICS. (OR 1.55, 95% CI 1.11-2.16) compared to those with OSA
	[A diagnosis of OSA was determined by ICD-9 or ICD-10 codes reported during the study period]	There was no increased risk of OSA in users of ICS with extra-fine particles compared to those with OSA	ACT score (aOR +1.60, 95% CI 1.32-1.94) among having OSA in BMI \geq 25 patients	Increased odds of having OSA in BMI \geq 25 patients	Increased risk of OSA among users of ICS with extra-fine particles.
		asthmatics who did not use ICS	asthma (aOR 1.11, 95% CI 0.78-1.58). controlled asthma	users of particle ICS compared to users of extra-fine particles	Patients with PCA showed a higher likelihood of OSA.
		(aOR 1.11, 95% CI 0.78-1.58). controlled asthma	PFT score (aOR +1.45, 95% CI 1.19-1.77) among 1,229 uncontrolled patients	(aOR 1.70, 95% CI 1.15-2.50).	The association between ICS and OSA might vary based on asthma control and individual patient characteristics, such as BMI
			versus 3288 normal-sized particles		
			controlled asthma	compared to controlled asthma	
			PFT score (aOR +1.45, 95% CI 1.19-1.77) among 1,229 uncontrolled patients	versus 1,199 receiving a controlled diagnosis of asthma.	
				versus 1,199 receiving a controlled diagnosis of asthma.	
				versus 1,199 receiving a controlled diagnosis of asthma.	
				versus 1,199 receiving a controlled diagnosis of asthma.	

<p>Ng S.S.S., 2018 cPAP Effect on: [42]</p> <p>Asthma Control, Airway responsiveness, Daytime Sleepiness, and Health Status in Asthmatic Patients With Nocturnal Symptoms and OSAS</p>	<p>Prospective, randomized controlled trial.</p> <p>122 asthmatic subjects (age 50.5 ± 12.0 years).</p> <p>SDB Rating: PSG</p> <p>Patients with AHI ≥ 10 (n = 41)</p> <p>Patients with AHI < 10 (n = 81)</p> <p>CPAP group (n = 17) and control group (n = 20)</p>	<p>Beclomethasone 500 µg or more per day within the last 3 months.</p> <p>Baseline</p> <p>High-dose inhaled steroids 90.1%</p> <p>Medium-dose inhaled steroids 9.9%</p>	<p>Baseline</p> <p>Baseline</p>	<p>FEV1 (%) predetto</p> <p>79.2 ± 20.5</p>	<p>AHI correlates with BMI (r = 0.255, P = 0.008) and neck circumference (r = 0.247, P = 0.007).</p> <p>No significant difference in the change of the ACT score between n.17 the change of CPAP group the AHI score 15.9 ± 2.6 vs between n.17 n.20 control CPAP group group 21.7 ± 19.1 ± 11.4 vs 10.1 (P = 0.145) n.20 control group 21.7 ± 10.1 (P = 0.474)</p>	<p>BMI ≥ 25 users of normal-sized particle ICS compared to users of extra-fine particles (aOR 2.45, 95% CI 1.22-4.93).</p>
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CHILDREN

Ross K.R., 2012 [44]	Relationships Between Obesity, SDB, and Asthma Severity in Children	Prospective observational study, comparative study Baseline	Severe asthma: children using high dose ICS alone or in combination 108 (82%) asthmatic children (age	Asthma Severity at 12-month follow-up: Mild/Mod (n.79) Severe (n.29) Not severe asthma: low	32 children (29.6%) with SDB Children with prevalent SDB (OR 4.85, 95% CI 1.94 - 12.10) in Asthmatic severe children	Children who are asthmatic, obese, and with SDB: Higher risk of having severe asthma than those without SDB. Asthmatic, normal-weight, and SDB children using
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		9.1 ± 3.4 years).	to moderate dose ICS	with BMI z-score=2 and SDB had a +6.7-fold risk (OR 1.74; 95% C.I: 25.55) of having severe asthma	(55.2%) vs mild/mod asthma (20.3%, p <0.01); Children with SDB had OR 5.02 (95% CI 1.88 - 13.44) to have severe asthma at follow-up	high doses of ICS alone or in combination with other medications: There was no significant association between SDB and asthma severity
	Valutazione SDB: overnight finger pulse oximetry monitoring	No SDB (n.76) età 9.3 ± 3.4 years				
		SDB (n.32) età 8.7 ± 3.3 years				
	Predicted FEV1 %:					
	No SDB 98.7 ± 17.7					
	With SDB 90.9 ± 17.1					
	Associations between SDB, obesity and asthma severity at follow-up.					
Conrad L.A., 2022 [45]	Associations Between Sleep, Obesity and Asthma in Urban Minority Children	Retrospective review of medical records	Inhaled steroids: Obese asthmatics	FEV1: 83.1 ± 16.5, n.214 (74.1%),	289 obese asthmatics versus 154	In obese asthmatic children, both ICS and montelukast are associated with lower AHI.
		448 children with asthma (ages 10.2 ± 4.1 years) who performed PSG.	Normal weight asthmatics	Normal weight asthmatics	3.1 ± 5.7 (p=0.009)	Neither ICS nor montelukast are associated with sleep respiratory parameters in children with asthma of normal weight.
	Association between spirometry variables,	[Montelukast: n.174 (60,2%) versus n.92	FEF25%–75%:			

BMI and PSG parameters, adjusting for asthma and anti-allergy medications. (59,7%), p=0,92] [Steroidi nasali: Asma obesi n.89 (30,8%) versus Asma normopeso n.44 (28,6%); p= 0,63]

Obese asthmatics 74.8 ± 26.5 Normal weight asthmatics 76.8 ± 28.2 (p=0.4)

Legend: AAE, acute asthma exacerbation; ACT, Asthma Control Test Scores; AHI, apnoea-hypopnoea index; aHR, adjusted HR; aOR, adjusted Odds Ratio; AT, adenotonsillectomy; ASA, acute status asthmaticus; ARERs, asthma-related emergency room visits; ARHs, asthma-related hospitalizations; BMI, body mass index; CPAP, continuous positive airway pressure; ER, emergency room; FP, fluticasone propionate; GER, gastroesophageal reflux; GINA, Global Initiative for Asthma 2020; HR, Hazard Ratio; HTN, hypertension sistematica; ICS, corticosteroidi inalati; LABA, long acting beta agonists; MRI, risonanza magnetica nucleare; OCS, corticosteroidi orali; OSAS, obstructive sleep apnoea syndrome; PCA, poor controlled asthma; Pcrit, passive critical closing pressure; PFT, Pulmonary Function Test; PSG, polysomnography; SABA, beta2-agonisti a breve durata d'azione; SA-SDQ, Questionario sui Disturbi del Sonno; SDB, sleep disordered breathing; UAW, colllassabilità delle vie aeree superiori.

Figure 2 illustrates the results regarding three distinct levels of bias, categorized as "Low" risk, "Some concerns," and "High" risk. The assessment of bias resulting from confounding revealed that 5 studies are problematic [39,40,42,44,45]. Bias resulting from exposure measurement was considered problematic or at high risk in 5 studies [39,41,42,44,45]. Bias in participant selection was also identified as problematic in all studies [39–45]. Bias related to post-exposure intervention was found problematic or with increased risk in 4 studies [42–45]. Furthermore, bias due to missing data emerged as a significant concern, with a high risk identified in 5 of the studies [39,40,42–44]. Moreover, outcome measurement bias was considered problematic or high risk in 5 studies [39,40,43–45]. Reporting outcome selection bias was seen as problematic in 100% of the studies [39–45]. In summary, the overall risk of bias was categorized as high or with some concerns in 100% of the studies analyzed. Each study identified at least one form of bias that raised significant concerns.

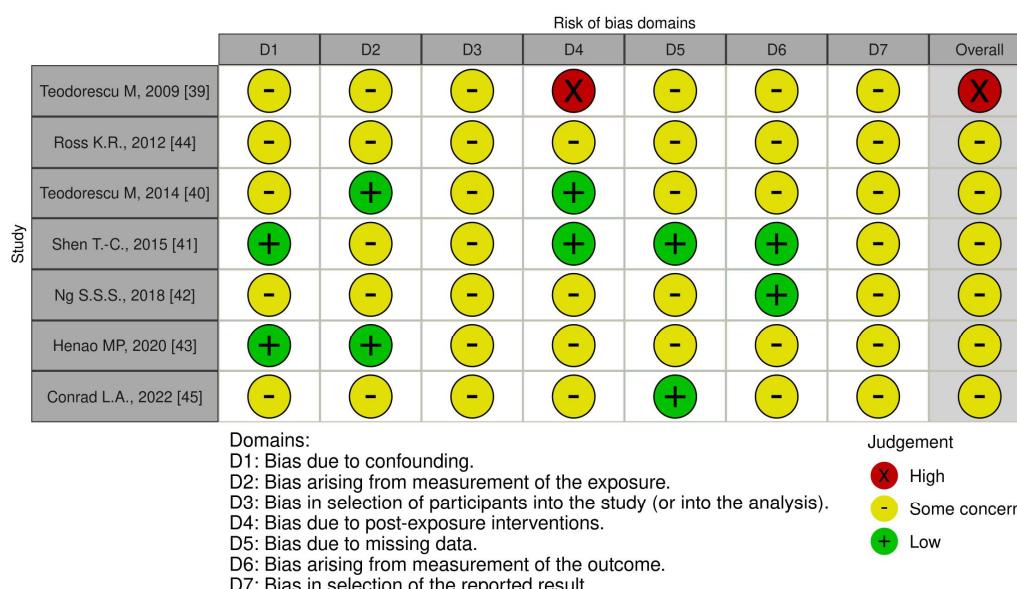


Figure 2. Risk-of-bias plots ROBINS-E.

4. Discussion

Despite the heightened prevalence of OSA among asthmatic patients, the impact of ICS on SDB and OSA remains a controversial issue. The studies herein reviewed offered limited and sometimes conflicting information on the intricate relationship between ICS usage for asthma and the occurrence of SDB, such as OSA.

The potential mechanism underlying the escalation of OSA or SDB in pediatric and adult asthmatic populations may stem from multiple factors. These include nasal obstruction and bronchoconstriction, leading to increased lower airway resistance and the upper airways' collapsibility during sleep [46]. Weight gain and fat accumulation in the upper airway region have also been implicated [47]. The incidence of OSA is generally higher in the asthmatic population compared to non-asthmatics, and this incidence is further elevated in asthmatic patients treated with ICS [41]. Treatment with FP has been observed to induce notable alterations in the structure of tongue muscles, evident by an augmentation in the percentage of laminin-stained areas across various muscle groups [48]. It's noteworthy that ICS usage can elicit localized effects on upper airway dilators, potentially increasing the susceptibility to OSA, akin to the mechanisms underlying the heightened risk of dysphonia in ICS users [49]. In adults, ICS usage has been linked to an increased risk of OSA, with the risk proportionally rising with higher ICS dosages [39]. Moreover, ICS formulations with larger particle sizes may prompt more pronounced pharyngeal adverse effects compared to those with smaller particle sizes [43]. While standard particle size ICS is associated with a greater risk of developing OSA, extra-fine particle ICS does not significantly elevate this risk [43]. The size of particles in ICS emerges as a critical determinant in the context of OSA, with users of extra-fine particle ICS exhibiting no significant increase in OSA risk compared to non-users, unlike those using standard particle sizes [43]. This underscores the potential impact of particle size on adverse outcomes, including OSA development, suggesting the opportunity to consider ICS particle size in asthma treatment to mitigate OSA risk in susceptible individuals [43]. Indeed, extra-fine particle ICS ($<2\text{ }\mu\text{m}$) disperse more uniformly throughout the lower airways in contrast to larger particle sizes ($>5\text{ }\mu\text{m}$), with larger particles tending to deposit more in the upper airways [43].

Prolonged therapy with ICS has been associated with modulations in hormone secretion patterns, particularly affecting growth hormone release, which may lead to metabolic and cardiovascular complications, thereby exacerbating the impact of OSA [50]. Despite some indications, research findings do not unequivocally support the notion that high-dose FP improves lung function without significantly reducing AHI in asthma patients [40]. Furthermore, it is worth pointing out that high-dose FP may not consistently lower AHI below a clinically significant threshold in all adult patients [51]. Notably, using ICS exhibits a dose-dependent relationship with the risk of OSA [39]. The use of FP did not significantly affect the AHI. However, high-dose FP usage appears to be linked to increased fat fraction and total fat volume in the structures surrounding the upper airways [40]. In obese asthmatic children, the use of ICS and montelukast is associated with a reduced AHI, although neither ICS nor montelukast significantly impacts sleep respiratory parameters in children with asthma who have normal weight [45].

Asthmatic patients undergoing ICS treatment face an elevated likelihood of OSA development [41]. This risk is particularly pronounced in cases of PCA. OSA exerts an influence on airway inflammation within asthmatic airways and correlates with inadequate asthma control. Although the precise interplay between these conditions remains elusive, inflammation should be recognized as a significant contributing factor [21]. The inflammatory infiltration of the upper airways in asthma and increased fat accumulation in pharyngeal walls due to ICS usage results in diminished cross-sectional diameter of the upper airways, likely impacting pharyngeal muscle function [21]. Consequently, asthma and its pharmacological treatments can augment the collapsibility of the upper airways, thereby contributing to OSA development and exacerbation [52].

In children, obesity and SDB heighten the risk of severe asthma. Obese asthmatic subjects tend to utilize all classes of asthma medications more frequently and particularly higher doses of ICS compared to their normal-weight counterparts [53]. Moreover, obesity and SDB escalation amplify the risk of severe asthma in children, particularly in conjunction with elevated ICS doses [44]. The correlation between ICS and nocturnal respiratory parameters varies depending on BMI [45].

Clinical studies have evidenced the positive impact of CPAP on asthma outcomes in patients concurrently experiencing OSA [54]. CPAP, advocated as the primary treatment for OSA, can

potentially ameliorate asthma symptoms in adults [55]. As the frontline intervention for OSAS, CPAP therapy might modulate airway smooth muscle function and enhance asthma management in individuals with both conditions, particularly demonstrating efficacy in severe OSA cases or in those with PCA [56]. Consequently, in patients with comorbid asthma and OSA, the effectiveness of ICS therapy in alleviating asthma symptoms might be limited [42]. Notably, asthma control did not show marked improvement with CPAP, even with administering moderate doses of ICS, suggesting that CPAP might not be effective in alleviating asthma symptoms in patients with asthma and OSA [42].

This review's limitations encompass the scarcity of available studies and the heterogeneity of research findings from both pediatric and adult populations, potentially affecting the uniformity and comparability of results. Disparities in OSA definitions, aetiology, and treatments between adults (primarily addressing obesity and CPAP therapy) and paediatrics (concerning adenotonsillar hypertrophy and adenotonsillectomy) further complicate the analysis [42]. Moreover, the overall quality of existing studies is deemed suboptimal.

Since no studies have specifically investigated the interplay between ICS usage and OSA in asthmatic patients, further research to elucidate the factors contributing to the heightened prevalence of OSA among asthma patients, especially those with severe asthma, is needed. Exploring the potential variances in the interaction between ICS and OSA among pediatric and adult patients, likely influenced by distinct OSA etiologies, may shed light on such intricate relationships and guide more effective management strategies for patients affected by asthma and OSA.

5. Conclusions

In adult patients, using ICS, especially at high doses, appears to increase the risk of OSA in a dose-dependent manner. Additionally, the characteristics of ICS (inhaled particle sizes) may influence the risk of OSA. In children, the severity of asthma plays a crucial role in influencing the prevalence of SDB, while using ICS seems to be a less relevant risk factor compared to adults. These studies suggest a complex relationship between ICS use, asthma severity, and the onset of SDB. Further studies are needed.

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