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Difficult and severe asthma in children, volume II

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Difficult and severe asthma in children, volume II

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Editorial: Difficult and severe asthma in children, volume II

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Editorial on the Research Topic
Difficult and severe asthma in children, volume II

This Topic covers many different aspects of childhood asthma, focusing mainly in those children suffering from severe asthma, following on from our previous book (1). As with the first volume, there is a breadth of topics, emphasizing the complexity and diversity of the manifestations of asthma. The overviews include asthma prevention during pregnancy, an exploration of the multiple comorbidities of asthma, and finally focusing on the right approach to personalizing medicine by choosing the correct drug, including the new biologic treatments, in severe asthma.

It is well known that asthma is the most prevalent chronic respiratory disease of childhood and its burden by age group is reviewed in a systematic analysis by Zhang and Zheng. Data were obtained from the Global Burden of Disease (GBD) study, which was conducted from 1990 to 2019 in 204 countries. The authors focused especially on the incidence, mortality and disability-adjusted life years (DALYs) of childhood asthma. They also update the different risk factors according to age group and region/country, emphasizing that there is geographical diversity, and asthma varies between and within countries. The obvious implication is that treatment and prevention strategies cannot be a "one size fits all".

Folic acid supplementation during pregnancy and risk of asthma

Asthma, defined as variable expiratory airflow restriction and recurrent respiratory symptoms, such as wheezing, shortness of breath, chest tightness, and cough, is frequently diagnosed in young children. The origins lie in complex interactions between multiple genes and environmental exposures occurring at critical periods throughout life (2). Ideally, the aim should be primary prevention of childhood asthma, or if that fail, secondary preventive strategies. Therefore, identifying risk factors and thus a high-risk population is important if early intervention is to be feasible (3). Early-life factors were

associated with asthma onset throughout childhood (4) pregnancy adverse exposures are particularly important. Prenatal factors for increased risk of asthma include maternal diet and the maternal microbiome (5). Yang et al. performed a systematic review and dose-response meta-analysis to explore the relationship between maternal folic acid supplementation during pregnancy and risk of childhood asthma. They suggested that the risk of asthma in children significantly increased when maternal folic acid intake reached 581 mcg/day. However, this finding has to be set against the beneficial effects of folic acid preventing neural tube defects (6).

Vitamin D to treat children with asthma: yes or no?

Accumulating evidence suggests that high-dose maternal vitamin D supplementation during pregnancy might reduce the risk of early life asthma/wheeze in the offspring (7) and an increasing number of studies also have suggested that vitamin D can be used to treat childhood asthma but its clinical effects are still unclear. Hao et al. performed a meta-analysis on eight randomized controlled trials and showed that vitamin D supplementation significantly increased patients' serum vitamin D levels, but it had no benefit for asthma control.

Severe asthma and comorbidities

Although in the majority of children with asthma good outcomes are easily achieved with low-moderate dose inhaled corticosteroids if they are inhaled regularly and correctly. However, a small group with severe disease remains uncontrolled despite optimal adherence to prescribed therapy and treatment of contributory factors, including coexisting comorbidities (8, 9). In order to reduce the risk of severe exacerbations and progressive loss of lung function with the likely consequence of chronic obstructive pulmonary disease, all possible comorbidities should be assessed (10). Ronco et al. tackle this topic and nicely review all the major comorbidities that need to be taken into consideration in pediatric severe asthma.

Severe asthma and adolescence

Adolescence is a challenging time of transition and significant differences can exist in the manifestation, exacerbating factors and management strategies for asthma (11). Hence, the adolescent patient cohort is a unique group and are the focus of the review article by Warraich and Sonnappa. The authors especially explored the main factors that may pose a challenge to the management of severe adolescent asthma whilst offering suggestions for changes in clinical practice.

Possible treatments in severe asthma

Before escalating treatment it is important to be confident that the diagnosis is asthma and to check for social and environmental factors which are preventing a good treatment outcome. The medical evaluation should firstly include: possible associated diagnosis, assess adherence, exclude exposure to tobacco, e-cigarettes and allergens and finally, assess psychosocial factors (12).

This section on treatment is introduced by Bush with a detailed overview on how to choose the right medications for school age and preschool children with severe asthma. The main treatment approaches are presented, including also the most recently introduced medications.. In another review article Santamaria et al. summarized the pharmacological effects of the long acting muscarinic antagonist (LAMA) tiotropium bromide based on the current asthma studies at different ages, and delineating future research needs. Finally, the indications for currently available biological treatments, namely omalizumab, mepolizumab and dupilumab are presented in detail by Fenu et al. Ullmann et al. and Ferrante et al. respectively. For each biological the mechanism of action, and the major literature in relation to efficacy and safety data in children are presented.

Summary and conclusions

This Topic offers a perspective on severe asthma in children with useful practical articles. We are grateful to all the authors have made such valuable contributions. The Editors have certainly enjoyed working on this Topic, and we hope it will be of great interest for all readers.

Author contributions

NU wrote the initial draft. All authors contributed to the article and approved the submitted version.

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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The Burden of Childhood Asthma by Age Group, 1990–2019: A Systematic Analysis of Global Burden of Disease 2019 Data

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Background: Asthma is a common respiratory disease in children. We aimed to update information about the incidence and mortality and disability-adjusted life years (DALYs) of childhood asthma and provide evidence-based recommendations for childhood asthma prevention.

Methods: Data were obtained from the Global Burden of Disease (GBD) study, which was conducted from 1990 to 2019 in 204 countries. First, we estimated incidence, mortality and DALY rates of childhood asthma using a Bayesian meta-regression model. Second, we analyzed the relationship between the sociodemographic index (SDI) and DALYs in different age groups. Third, we studied changes in trends of the age-standardized DALY rate between 1990 and 2019 based on age group, SDI, and risk factors.

Results: Globally, the number of deaths due to childhood asthma and the incidence and DALY rates were 12.9 thousand (95% UI 10.6 to 15.7), 22 million (95% UI 15 to 31), and 5.1 million (95% UI 3.4 to 7.5) in 2019, decreasing by 65.1% (95% UI 47.6 to 72.4), 5.3% (95% UI 2.6 to 8.8) and 30% (95% UI 18 to 41) from those in 1990, respectively. With the exception of high-SDI regions, the age-standardized DALY rate in all age groups in all SDI regions declined. In 2019, the age-standardized DALY rate in 1- to 4-year-old individuals was highest in low-SDI regions and that of 5- to 19-year-old individuals was highest in high-SDI regions. In contrast to low-SDI regions, individuals in high-SDI regions had a higher risk of DALYs due to asthma, except in those aged 1 to 4 years. A high body mass index (BMI) was a stronger risk factor than occupational asthmagens for childhood asthma.

Conclusion: Our findings provide insight into asthma prevention and treatment through the identification of key factors related to childhood asthma. Based on the data available, different risk factors according to age group and region/country suggest different prevention strategies, which is key for preventing childhood asthma.

Keywords: disability-adjusted life years (DALYs), sociodemographic index (SDI), childhood asthma, body-mass index, risk factors

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INTRODUCTION

Childhood asthma is a major common chronic respiratory illness characterized by wheezing, coughing, shortness of breath and airflow limitation, which affects daily life (1, 2). The pathogenesis of childhood asthma includes complex interactions involving physics, chemistry, pharmacology, and immunology, resulting in excessive mucus secretion, bronchial edema and spasm, and scar remodeling (3). Although inhaled corticosteroids can control the symptoms of asthma, some children with persistent asthma still experience severe complications and lung dysfunction (4). Due to a lack of understanding of health care for childhood asthma, reduced treatment efficacy and incomplete control of lung damage may occur (5). Childhood asthma imposes the highest disability burden, causing almost 13.8 million days of absence from school in the United States in 2013. Furthermore, children with asthma need to receive psychological support because asthma can lead to a lower education level and early dropout from school (6, 7). In this study, we estimated the disability burden of childhood asthma based on disability-adjusted life years (DALYs) from 1990 to 2019 by region and country as well as by age.

Globally, comorbidities of childhood asthma include allergic rhinitis, loss of lung function and mental illness (8, 9), and the burden of childhood asthma is substantial in high-income countries. Overall, medical expenditures and DALYs due to severe asthma are high. Establishing a model of health care management that will reduce the number of DALYs and costs of childhood asthma is recommended (10, 11). Children with asthma need formal monitoring and disease management to reduce the number of DALYs and to control symptoms. The lack of comprehensive health care policies is likely one of the main reasons for the increasing incidence of DALYs due to childhood asthma. Research on environmental factors, lifestyle behaviors, dietary habits, and other health-related risk factors will guide effective prevention of the occurrence of childhood asthma. Nevertheless, improving the level of medical care requires substantial knowledge about how to prevent diseases and associated risk factors that are harmful and lead to disability. The Global Burden of Disease (GBD) study dataset is useful for risk factor quantification, as it contains reliable data on childhood asthma for 1990–2019; the findings of data analyses can help to inform regional and national health policies (12).

In this study, we estimated the incidence, mortality and DALY rates of childhood asthma using GBD data from 1990 to 2019; the data were stratified by age, sex, sociodemographic index (SDI), region and country. We also discuss detailed information about risk factors for DALYs due to childhood asthma and present the relationship between age group and sociodemographic index (SDI) at DALYs. The results offer evidence for informing healthcare management of childhood asthma.

Abbreviations: DALYs, disability-adjusted life years; GBD, Global Burden of Disease; SDI, sociodemographic index; ICD-10, International Classification of Diseases 10th edition; UI, uncertainty interval; CI, confidence interval; BMI, body mass index.

METHODS

Data Sources

Childhood asthma is a chronic lung disease caused by allergic or hypersensitivity reactions and characterized by bronchospasms and dyspnea (13). Childhood asthma in the GBD study was defined as a diagnosis by a doctor and the presence of International Classification of Diseases, 10th edition (ICD-10), codes J45 and J46. The methods of the GBD study have been widely reported, including data for incidence, death and DALY rates for 1990 to 2019, as based on systematic papers, unpublished reports and surveys, and health service data from the USA. Detailed information on childhood asthma can be found at http://ghdx.healthdata.org/gbd-results-tool.

The SDI is a summary measure that reflects sociodemographic development, including local income, average educational attainment, and total fertility rates (14). SDI values range from 0 (lowest income, lowest educational attainment, and highest fertility rate) to 1 (highest income, highest educational attainment, and lowest fertility rate) (15–17). The 204 countries and territories in the GBD study were classified into high-, high-middle-, middle-, low-middle-, and low-SDI regions. The cutoff values used to determine quintiles for analysis were computed using country-level estimates of the SDI for 2019, excluding countries with populations <1 million.

Statistical Analysis

The standardized methods of GBD 2019 have been published by the GBD team and extensively reported elsewhere. Incidence, mortality, and DALY rates for childhood asthma for 204 countries and territories from 1990 to 2019 were estimated based on age and sex using a Bayesian meta-regression model in DisMod-MR 2.1. During data processing, the mean of 1000 draws was generated for all reported data, and the 2.5th and 97.5th centiles of the ordered draw represent 95% uncertainty intervals (UIs).

A linear regression model was constructed to analyze the association between year and the age-standardized incidence, mortality, and DALY rates for childhood asthma separately. Using a regression model, we scaled the numbers and age-standardized rates to make them comparable, without regard to the measurement units used in the process. Then, a generalized linear model was fitted by a Gaussian function, and the year coefficient was extracted to measure the strength and direction of the time trend. The corresponding 95% confidence interval (CI) of the year coefficient was acquired from this linear regression model. Associations of age-standardized incidence, mortality, and DALY rates with the SDI for 204 countries and territories and 21 GBD regions were evaluated by smoothing spline models (18). We applied R software V.4.0.2 to estimate incidence, mortality, and DALY rates and numbers from the GBD dataset.

TABLE 1 | The burden of childhood asthma by age group, sex and SDI in 1990 and 2019.

	Deaths (95% UI)		Incidence (95% UI)		DALYs (95% UI)	
	1990 cases (thousands)	2019 cases (thousands)	1990 cases (millions)	2019 cases (millions)	1990 cases (millions)	2019 cases (millions)
Age(years)						
1∼4	20.44 (11.75 to 26.60)	6.10 (4.62 to 7.98)	10.16 (6.46 to 15.38)	10.00 (6.28 to 15.28)	2.67 (1.76 to 3.57)	1.40 (0.95 to 2.10)
5∼9	4.10 (3.19 to 4.85)	1.70 (1.40 to 2.05)	5.56 (2.81 to 9.36)	6.42 (3.27 to 10.83)	1.60 (1.03 to 2.51)	1.49 (0.88 to 2.48)
10∼14	3.41 (2.90 to 3.82)	2.11 (1.79 to 2.51)	3.13 (1.42 to 5.00)	3.77 (1.73 to 6.00)	1.16 (0.77 to 1.70)	1.22 (0.76 to 1.86)
15∼19	4.56 (3.76 to 5.21)	2.97 (2.54 to 3.43)	2.17 (1.27 to 3.32)	2.40 (1.41 to 3.66)	0.99 (0.69 to 1.41)	0.95 (0.63 to 1.44)
Sex						
Male	16.48 (12.06 to 20.65)	6.54 (5.45 to 7.94)	11.33 (7.79 to 15.79)	12.30 (8.35 to 17.21)	3.40 (2.49 to 4.72)	2.77 (1.85 to 4.15)
Female	16.02 (8.91 to 21.00)	6.34 (4.97 to 8.40)	9.69 (6.80 to 13.35)	10.30 (7.12 to 14.01)	3.02 (2.04 to 4.16)	2.30 (1.55 to 3.36)
Sociodemographic factor						
Global	32.51 (22.79 to 39.65)	12.88 (10.59 to 15.68)	21.03 (14.58 to 29.22)	22.59 (15.47 to 31.27)	6.42 (4.62 to 8.86)	5.07 (3.42 to 7.51)
High SDI	0.86 (0.79 to 0.91)	0.31 (0.28 to 0.34)	3.55 (2.47 to 4.92)	3.63 (2.57 to 4.78)	0.77 (0.49 to 1.19)	0.75 (0.47 to 1.15)
High-middle SDI	1.71 (1.30 to 2.03)	0.29 (0.25 to 0.36)	3.56 (2.42 to 5.06)	12.62 (8.64 to 17.91)	0.76 (0.50 to 1.15)	0.53 (0.32 to 0.86)
Middle SDI	10.14 (7.29 to 12.11)	2.87 (2.40 to 3.34)	7.02 (4.79 to 9.82)	6.37 (4.31 to 8.89)	2.06 (1.48 to 2.87)	1.39 (0.90 to 2.12)
Low-middle SDI	10.76 (7.42 to 13.43)	3.28 (2.69 to 3.98)	3.92 (2.78 to 5.38)	4.01 (2.72 to 5.58)	1.57 (1.14 to 2.05)	0.99 (0.68 to 1.45)
Low SDI	8.98 (5.40 to 11.98)	6.10 (4.58 to 8.18)	2.95 (2.14 to 4.01)	5.03 (3.50 to 6.87)	1.25 (0.87 to 1.63)	1.41 (1.00 to 1.97)

UI, uncertainty interval; SDI, sociodemographic index.

RESULTS

Global Burden

In 2019, 12.9 thousand (95% UI 10.6 to 15.7 thousand) children died from asthma. From 1990 to 2019, the age-standardized mortality rate decreased significantly by 65.1% (95% UI 47.6 to 72.4) to 0.5 per 100 000 (95% UI 0.4 to 0.6). The greatest decrease in the age-standardized mortality rate was in the high-middle-SDI group, and the number of incident childhood asthma cases was estimated to be nearly 22 million (95% UI 15 to 31 million). From 1990 to 2019, the global age-standardized incidence rate of childhood asthma decreased by 5.3% (95% UI 2.6 to 8.8%) to 876.0 per 100 000 (95% UI 599.7 to 1212.3). Rapid increases in age-standardized incidence rates were observed in the high-SDI and high-middle-SDI groups (**Tables 1**, **2**). DALYs due to childhood asthma in 2019 were estimated to be 5.1 million (95% UI 3.4 to 7.5 million). Between 1990 and 2019, age-standardized DALY rates decreased substantially by 30% (95% UI 18 to 41%) to 196.62 (132.71 to 291.02). A rapid increase in the age-standardized incidence was observed in only the high-SDI group (**Tables 1**, **2**).

In 2019, 6.5 thousand (95% UI 5.4 to 7.9 thousand) males and 6.3 thousand (95% UI 5.0 to 8.4 thousand) females died from childhood asthma. From 1990 to 2019, the age-standardized mortality rates were similar between males, at 0.5 per 100 000 (95% UI 0.4 to 0.6), and females, at 0.5 per 100 000 (95% UI 0.4 to 0.7). Childhood asthma affected almost 12 million (95% UI 8 to 17 million) males and almost 10 million (95% UI 7 to 14 million) females in 2019. From 1990 to 2019, the age-standardized incidence rate was higher in males, with a decrease of 4.9% (95% UI 2.0 to 8.5%) to 925.1 per 100 000 (95% UI 628.4 to 1355.7), than in females, with a decrease of 5.8% (95% UI 2.9 to 9.1) to 874.14 per 100 000 (95% UI 569.4 to 1203.6). DALYs due to childhood asthma were higher in males, at 2.8 million (95% UI 1.8 to 4.2 million), than in females, at 2.3 million (95% UI 1.6 to 3.4 million). Similarly, from 1990 to 2019, age-standardized DALYs were higher in males, with a decrease of 28.5% (95% UI 17.3 to 39.2%) to 208.64 per 100 000 (95% UI 138.84 to 312.52), than in females, with a decrease of 32.5% (95% UI 12.2 to 45.4%) to 183.8 per 100 000 (95% UI 124.03 to 268.95) (**Tables 1**, **2**).

Globally, age-standardized DALYs were estimated to be higher than 500 per 100 000 children in some countries, such as Haiti, the United States of America, Puerto Rico and Madagascar, and lower than 100 per 100 000 children in others, such as Nepal, Bangladesh, Bhutan, Pakistan, Kazakhstan, India and Tajikistan (**Figure 1**). Regarding region, age-standardized DALYs due to asthma in 2019 were highest in the Caribbean

TABLE 2 | Percent change in age-standardized rates of childhood asthma by age group, sex and SDI, 1990–2019.

	Deaths (95% UI)		Incidence (95% UI)		DALYs (95 %UI)	
	2019 Age-Standardized rates (per 1,00,000)	Percent change in age-standardized rates, 1990–2019	2019 Age-Standardized rates (per 1,00,000)	Percent change in age-standardized rates, 1990–2019	2019 Age-Standardized rates (per 1,00,000)	Percent change in age-standardized rates, 1990–2019
Age (years)						
1∼4	1.2 (0.9 to 1.5)	−71.8 (−79.6 to −49.5)	1884.6 (1183.7 to 2879.0)	−7.2 (−11.4 to −4)	264.6 (179.1 to 394.6)	−50.5 (−63.2 to −29)
5∼9	0.3 (0.2 to 0.3)	−63.0 (−69.6 to −48.8)	980.3 (500.0 to 1654.7)	3.1 (7.1 to −14.1)	228.2 (134.9 to 379.3)	−16.6 (−24.9 to −9.9)
10∼14	0.3 (0.3 to 0.4)	−48.3 (−55.1 to −37.5)	587.0 (268.8 to 934.6)	0.5 (4.1 to −1.8)	189.6 (118.6 to 290.2)	−12.1 (−18.4 to −7.1)
15∼19	0.5 (0.4 to 0.6)	−45.3 (−52.0 to −35.4)	387.9 (227.9 to 590.7)	−7.1 (−3.5 to −10.8)	154.1 (102.3 to 231.7)	−18.8 (−25.9 to −13.2)
Sex						
Male	0.5 (0.4 to 0.6)	−65.2 (−72.0 to −49.2)	925.1 (628.4 to 1355.7)	−4.9 (−8.5 to −2.0)	208.64 (138.84 to 312.52)	−28.5 (−39.2 to −17.3)
Female	0.5 (0.4 to 0.7)	−64.9 (−75.0 to −26.7)	874.14 (569.38 to 1203.57)	−5.8 (−9.1 to −2.9)	183.84 (124.03 to 268.95)	−32.5 (−45.4 to −12.2)
Sociodemographic factor						
Global	0.5 (0.4 to 0.6)	−65.1 (−72.4 to −47.6)	876.01 (599.68 to 1212.28)	−5.3 (−8.8 to −2.6)	196.62 (132.71 to 291.02)	−30 (−41 to −18)
High SDI	0.1 4 (0.12 to 0.15)	−62.5 (−65.3 to −57.2)	1642.81 (1165.5 to 2163.38)	8 (1 to 16)	338.46 (212.04 to 520.44)	3 (−3 to 9)
High-Middle SDI	0.09 (0.08 to 0.11)	−79.0 (−83.3 to −70.5)	873.41 (583 to 1230.22)	1 (−4 to 5)	162.21 (97.71 to 261.99)	−13 (−23 to −6)
Middle SDI	0.39 (0.45 to 0.33)	−70.5 (−76.5 to −58.8)	864.82 (584.92 to 1206.9)	−6 (−9 to −3)	188.38 (122.36 to 287.65)	−30 (−42 to −18)
Low-Middle SDI	0.47 (0.39 to 0.57)	−75.0 (−80.8 to −61.6)	577.19 (391.49 to 803.14)	−16 (−22 to −11)	142.23 (97.48 to 208.99)	−48 (−59 to −34)
Low SDI	1.02 (0.77 to 1.37)	−66.4 (−76.1 to −66.4)	842.9 (585.72 to 1150.93)	−16 (−21 to −11)	236.12 (167.92 to 329.67)	−44 (−56 to −34)

UI, uncertainty interval; SDI, sociodemographic index.

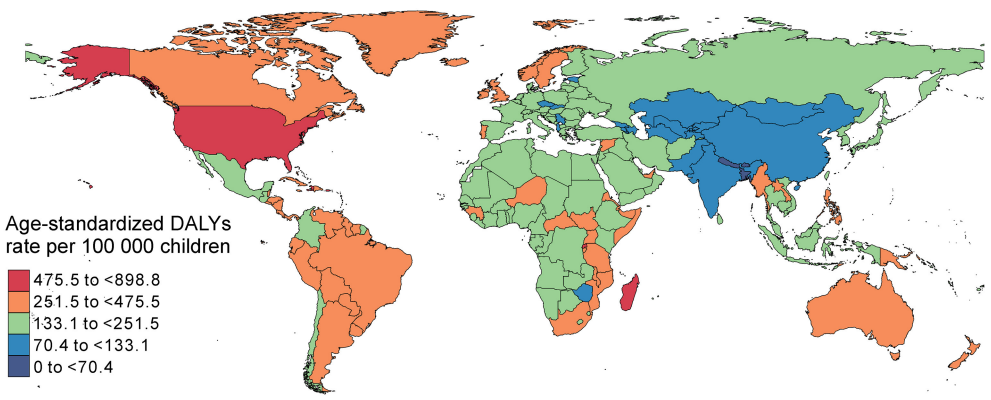

FIGURE 1 | Age-standardized DALYs due to childhood asthma per 100 000 children by country, both sexes, 2019. DALYs, disability adjusted life years.

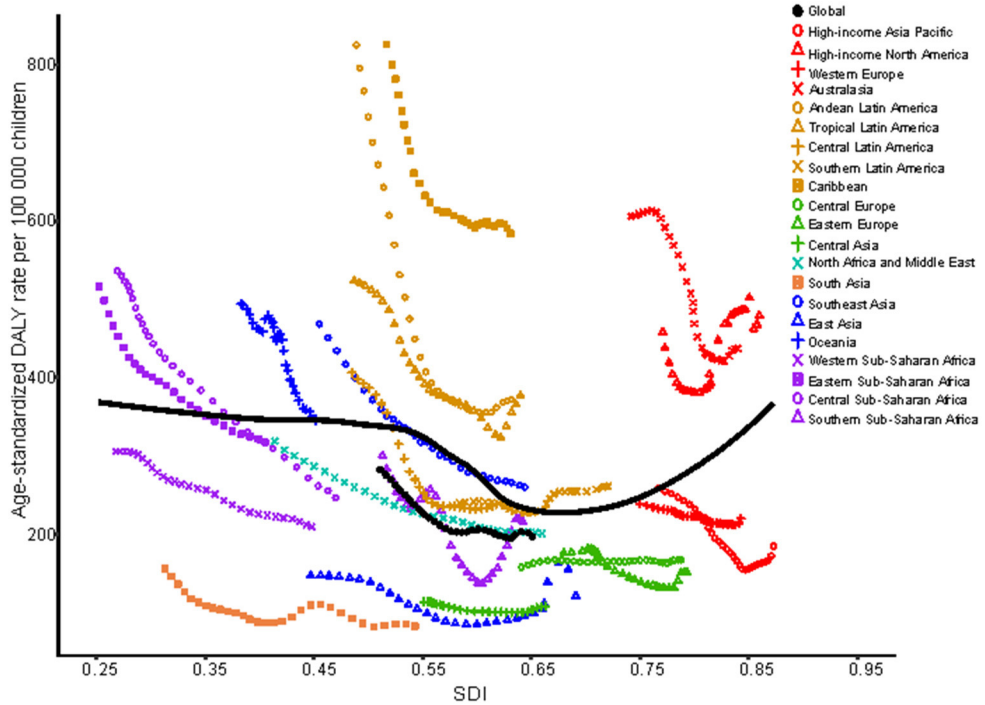

FIGURE 2 | Age-standardized DALYs due to childhood asthma by 21 GBD regions and expected values by SDI, 1990–2019. DALYs, disability adjusted life years; SDI, sociodemographic index.

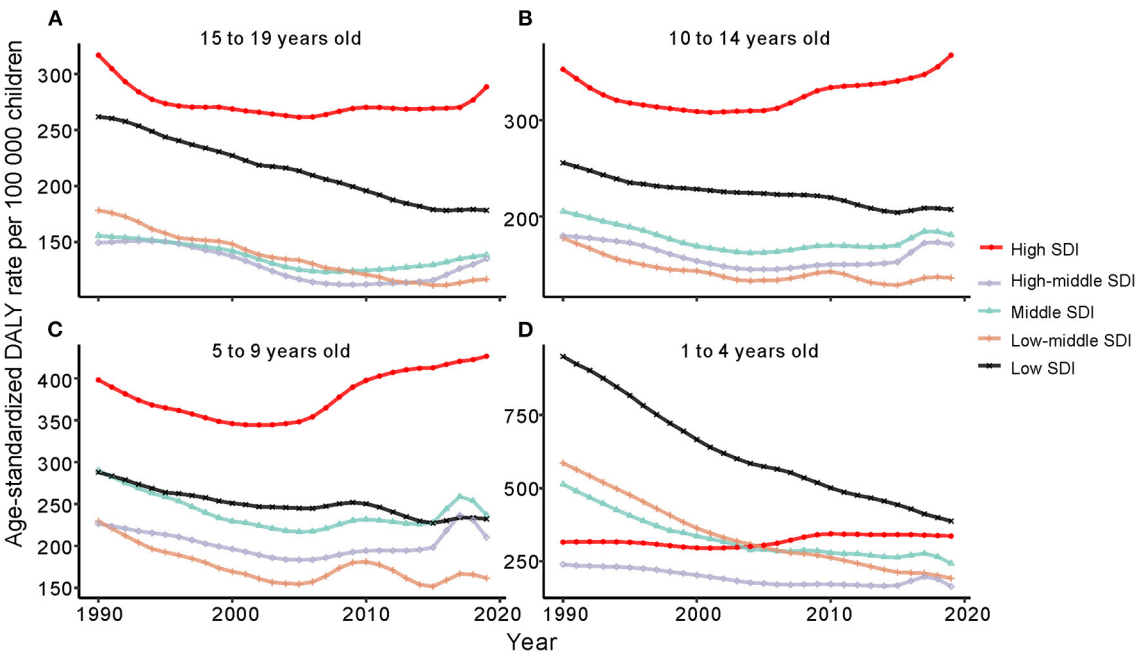

FIGURE 3 | Change trends of age-standardized DALYs due to childhood asthma by age group from 1990 to 2019. **(A)** Change trends of age-standardized DALYs in 15 to 19 year olds. **(B)** Change trends of age-standardized DALYs in 10 to 14 year olds. **(C)** Change trends of age-standardized DALYs in 5 to 9 year olds. **(D)** Change trends of age-standardized DALYs in 1 to 4 year olds. DALYs, disability adjusted life years.

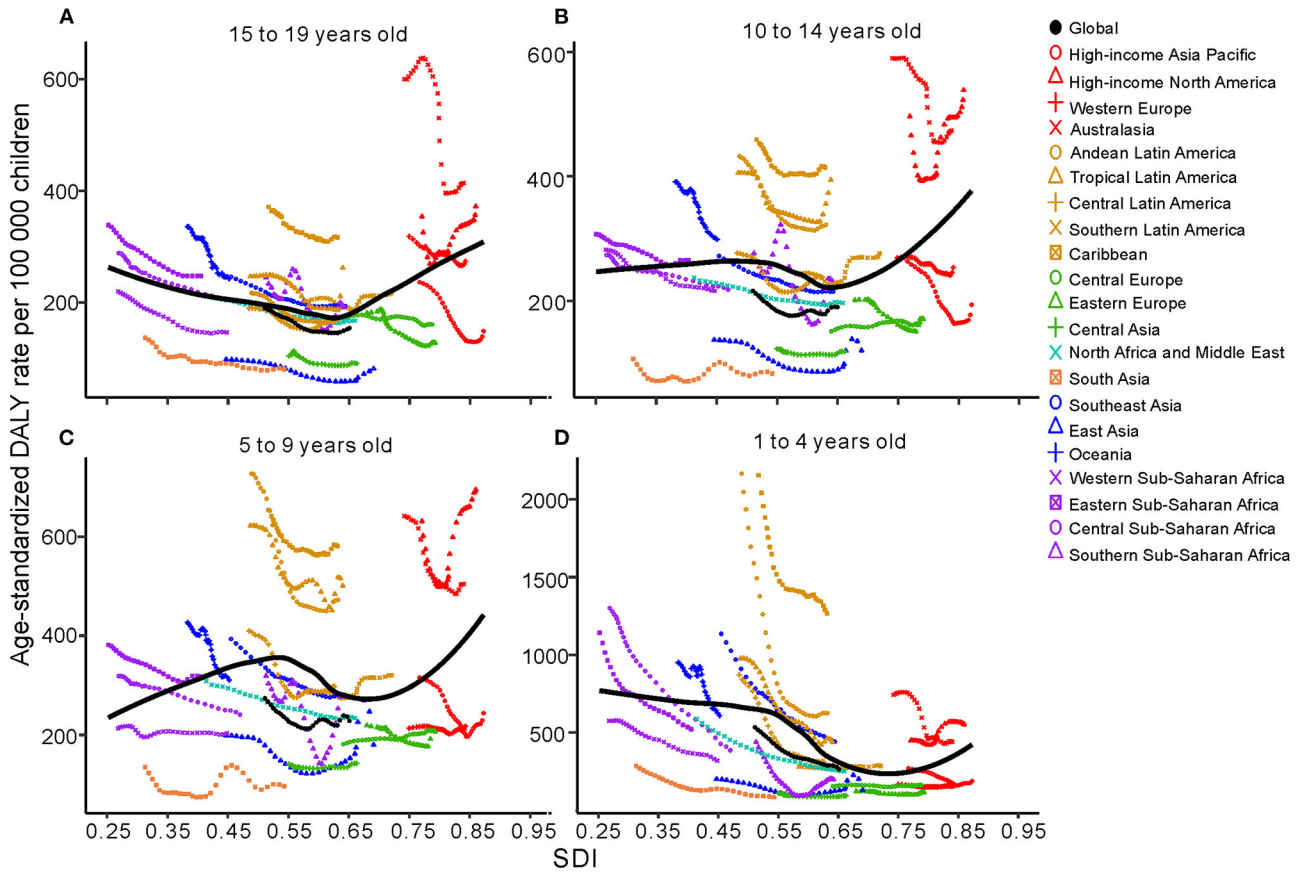

FIGURE 4 | Age-standardized DALYs due to childhood asthma by 21 GBD regions and different age groups, 1990–2019; the black line represents expected values by SDI. **(A)** Change trends of age-standardized DALYs for regions by SDI in 15 to 19 years olds. **(B)** Change trends of age-standardized DALYs for regions by SDI in 10 to 14 years olds. **(C)** Change trends of age-standardized DALYs for regions by SDI in 5 to 9 year olds. **(D)** Change trends of age-standardized DALYs for regions by SDI in 1 to 4 year olds. DALYs, disability adjusted life years; SDI, sociodemographic index.

[584.2 (95% UI 387.7 to 824.9) per 100 000] and high-income regions of North America [510.3 (95% UI 320.8 to 765.9) per 100 000]. Conversely, age-standardized DALYs were lowest in South Asia [82.1 (95% UI 55.4 to 120.7) per 100 000] (**Figure 2**). Details of the data by country, region and the percentage change in the age-standardized incidence and DALY rates between 1990 and 2019 are shown in **Supplementary Table 1**.

The Burden in the 1- 4-Year-Old Age Group

The number of deaths from childhood asthma in 2019 was highest in the 1- to 4-year-old group (6.1 thousand (95% UI 4.6 to 8.0 thousand), 47.4%). The percent change in the age-standardized mortality rate (from 1990 to 2019) in the 1- to 4-year-old group declined sharply by 71.8% (95% UI 49.5 to 79.6). Moreover, 10.0 million (95% UI 6.2 to 15.3 million) children aged 1 to 4 years appeared to have asthma, and almost 44.2% of the total number of children had asthma. The percent change in the standardized incidence rate in the 1- to 4-year-old group (1990 to 2019) decreased by 7.2% (95% UI 4.0 to 11.4). The DALY rate in patients aged 1 to 4 years old was ∼1.4 million (95% UI 1.0 to 2.1). The percent change in the age-standardized DALY rate (from 1990 to 2019) was notably reduced by 50.5% (95% UI 29.0 to 63.2) (**Tables 1**, **2**).

From 1990 to 2019, age-standardized DALYs in the 1- to 4-year-old group in low-SDI, middle-SDI and low-middle-SDI regions dropped sharply, whereas that in the high-SDI region increased gradually; moreover, there was no obvious decrease in the high-middle-SDI region as a whole. The highest age-standardized DALY rate in 2019 was in the low-SDI region; the lowest DALY rate was in the high-middle SDI region (**Figure 3A**). At the regional level, there was an association between the age-standardized DALY rate and SDI. First, the age-standardized DALY rate was highest at an SDI of ∼0.25, and it steadily declined until an SDI of 0.55. Second, age-standardized DALY rates dropped sharply from an SDI of 0.55 to an SDI of 0.75. Last, age-standardized DALY rates increased with SDIs higher than 0.75 (**Figure 4A**). At the national level, age-standardized DALY rates declined gradually with increasing SDI **(Figure 5A)**.

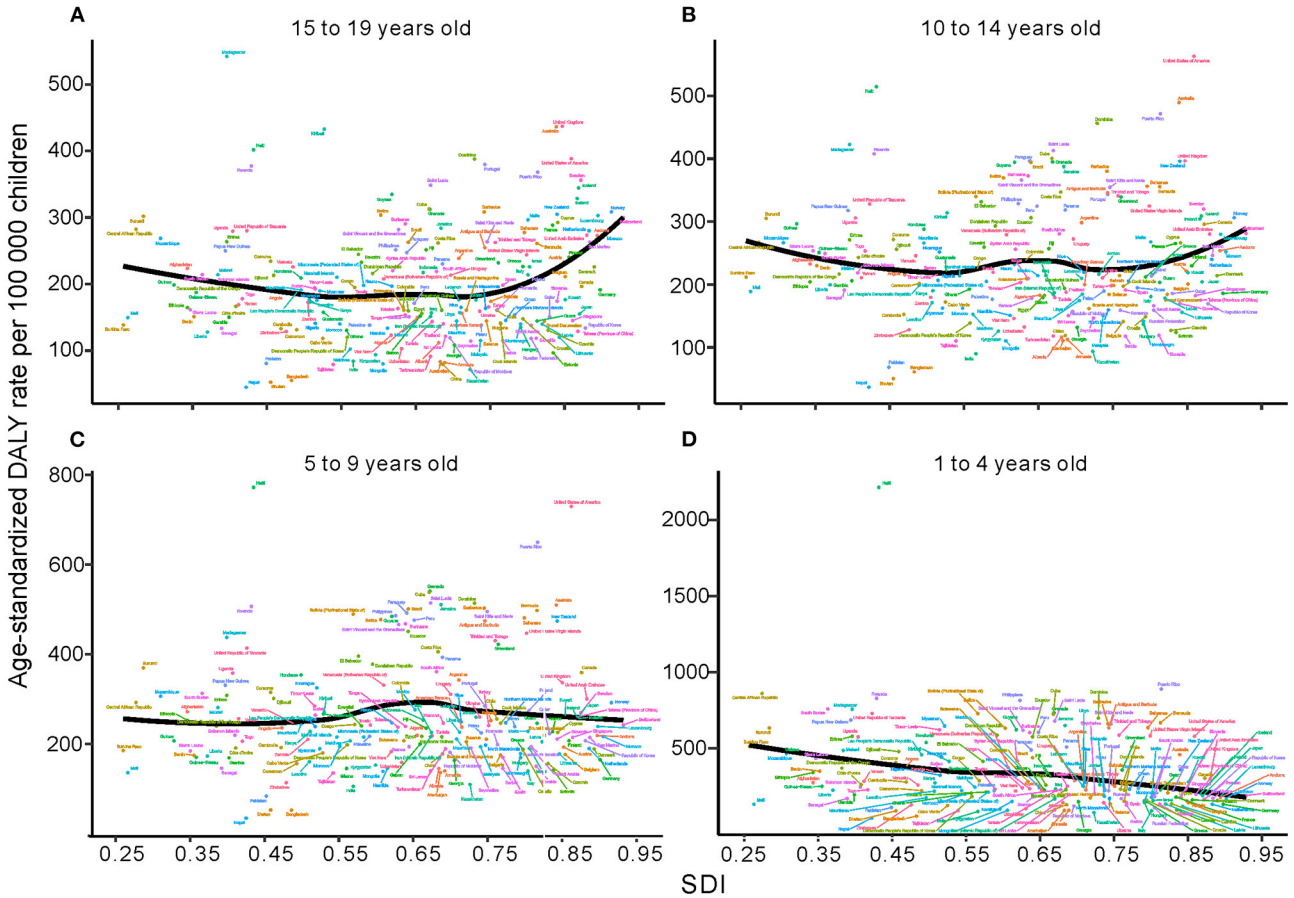

FIGURE 5 | Age-standardized DALYs due to childhood asthma by country and SDI, 2019; the black line represents expected values. **(A)** Change trends of age-standardized DALYs by country and SDI in 15 to 19 year olds. **(B)** Change trends of age-standardized DALYs by country and SDI in 10 to 14 year olds. **(C)** Change trends of age-standardized DALYs by country and SDI in 5 to 9 year olds. **(D)** Change trends of age-standardized DALYs by country and SDI in 1 to 4 year olds. DALYs = disability adjusted life years, SDI, sociodemographic index.

The Burden in the 5- to 9-Year-Old Age Group

The number of deaths due to childhood asthma in the 5- to 9-year-old group in 2019 was nearly 13.2% (1.7 thousand) overall. The percent change in the age-standardized mortality rate (from 1990 to 2019) decreased by 63.0% (95% UI 48.8 to 69.6%), and nearly 28.4% (6.4 million) of all children had asthma. The percent change in the standardized incidence rate increased by 3.1% from 1990 to 2019. The number of DALYs was 1.5 million (95% UI 0.9 to 2.5 million). The percent change in the age-standardized DALY rate decreased from 1990 to 2019 (**Tables 1**, **2**).

In the 5- to 9-year-old group, the trend of the age-standardized DALY rate showed a gradual decline in low-SDI, middle-SDI, high-middle-SDI and low-middle-SDI regions between 1990 and 2019; only high-SDI regions experienced a substantial increase. Nevertheless, the percent change in the age-standardized DALY rate in each SDI region was highest in the high-SDI group and lowest in the low-SDI group (**Figure 3B**). At the regional level, the age-standardized DALY rate showed intermittent increases and decreases as the SDI increased. The two peaks were at SDIs of 0.55 and 0.65 (**Figure 4B**). At the national level, age-standardized DALY rates did not change obviously with increasing SDIs, though the age-standardized DALY rate showed a slight decrease from an SDI of 0.55 to 0.65 **(Figure 5B)**.

The Burden in the 10- to 14-Year-Old Age Group

Nearly 16.4% (2.1 thousand) of children aged 10∼14 years old with asthma died due to asthma in 2019. The incidence was ∼16.7% (3.7 million), and the percent change in the standardized incidence rate increased by 0.5% (95% UI −1.8 to 4.1%) from 1990 to 2019. The number of DALYs was 1.2 million (95% UI 0.8 to 1.9 million, 24.0%). The percent change in the age-standardized DALY rate decreased from 1990 to 2019 (**Tables 1**, **2**).

In children aged 10∼14 years, the change trend of the age-standardized DALY rate with the SDI region was similar to that in those aged 5∼9 years, but the age-standardized DALY rate in the low-SDI region was higher than that

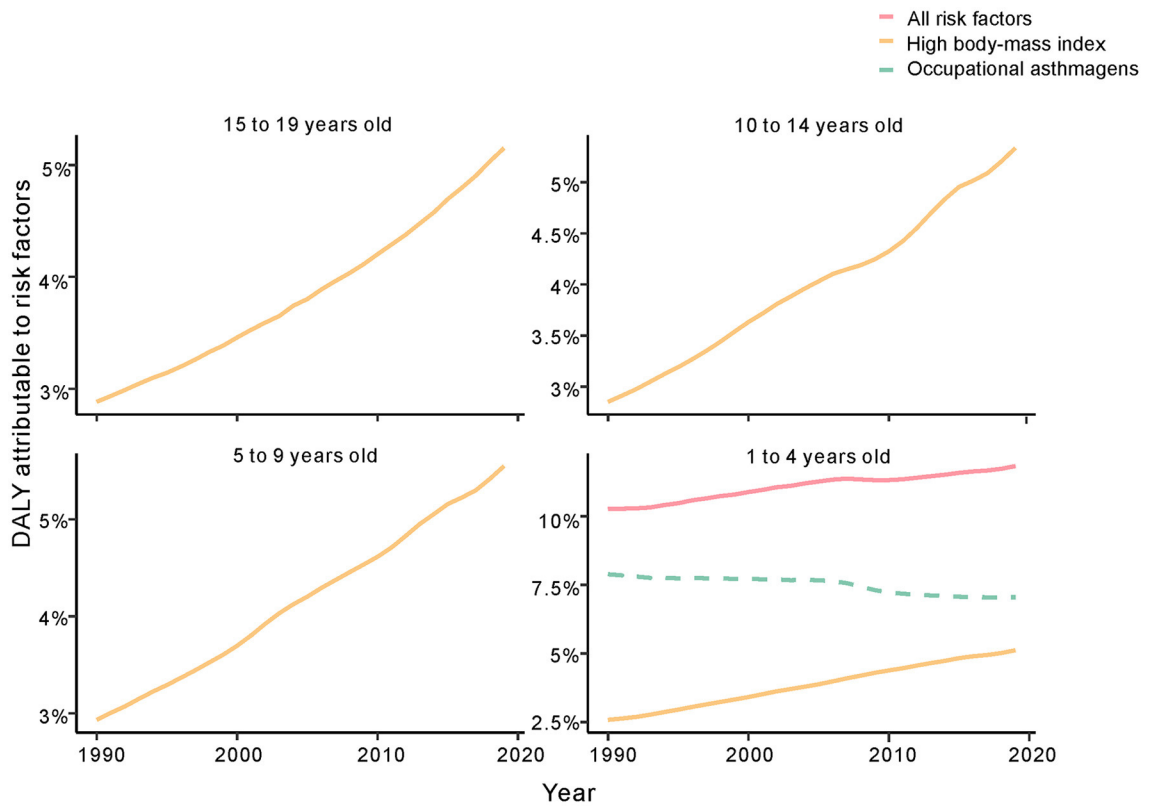

FIGURE 6 | Fraction of age-standardized DALYs attributable to high BMI and occupational asthmagens in childhood asthma by SDI region, 1990–2019. DALYs, disability adjusted life years; SDI, sociodemographic index; BMI, high body mass index.

in the middle-SDI region (**Figure 3C**). The age-standardized DALY rate at the regional level exhibited an upward trend from an SDI of 0.25 to 0.52 followed by a downward trend from 0.52 to 0.65 (**Figure 4C**). At the national level, age-standardized DALY rates increased as SDI increased overall, but they decreased gradually from a low SDI to an SDI of 0.55 (**Figure 5C**).

The Burden in the 15- to 19-Year-Old Age Group

In 2019, the number of deaths due to asthma among those aged 15 to 19 years was the second largest; the number of incident asthma cases in individuals aged 15 to 19 years was also second largest, at close to 2.4 million. The number of DALYs in those aged 15 to 19 years was smallest (**Tables 1**, **2**). Among those aged 15∼19 years, there was no major decreasing trend in the low-SDI region, and the age-standardized DALY rate in the high-SDI region did not change obviously from 1990 to 2019 (**Figure 3D**). At the regional level, the age-standardized DALY rate decreased sharply between SDIs of 0.25 and 0.62, but it increased rapidly with increasing SDIs above 0.62 (**Figure 4D**). At the national level, when the SDI was above 0.75, the age-standardized DALY rate increased significantly, but the change was gradual when the SDI was <0.75 (**Figure 5D**).

DALYs Attributable to Risk by Age Group and SDI

According to GBD data, high body mass index (BMI) was an important risk factor for childhood asthma, followed by occupational asthmagens. High BMI was also an independent risk factor for asthma associated with DALYs in the age groups younger than 14 years. The group aged 15 to 19 years had two risk factors, high BMI and occupational asthmagens, with the latter being the most important (**Figure 6**). In the high-SDI region, the contribution of risk factors to DALYs was largest for high BMI; a similar result was observed in the high-middle-SDI, middle-SDI, low-middle-SDI and low-SDI regions (**Figure 7**). Additional data can be downloaded from the GBD website.

DISCUSSION

Asthma is a common respiratory disease in children (19), with an age-standardized incidence rate of 1884.6 per 100 000 in those aged 1 to 4 years in 2019; this was the highest rate among age groups younger than 19 years. The lowest incidence rate was in the 15- to 19-year-old age group, at nearly five times lower than that in the 1- to 4-year-old age group, namely, 387.9 per 100 000 people, in 2019.The mechanism involves exposure to ambient air pollutants, especially in matter of aerodynamic diameters ≤2.5 μm (PM2.5) and ≤10 μm (PM10),

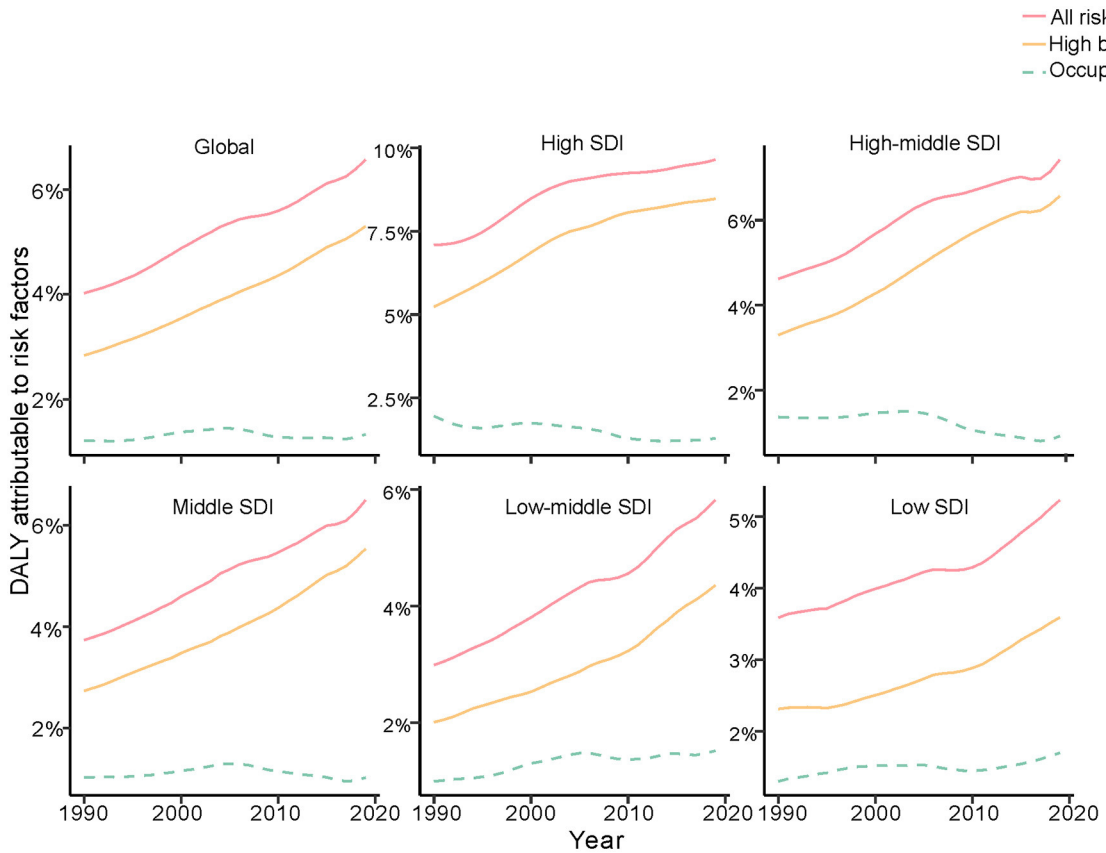

FIGURE 7 | Fraction of age-standardized DALYs attributable to high BMI and occupational asthmagens in childhood asthma by age group, 1990–2019. DALYs, disability adjusted life years; BMI, high body mass index.

SO_2 and NO_2 (20, 21). With the reduction in air pollutants, the risk of asthma decreased in those older than 15 years of age. Moreover, the age-standardized mortality rates of childhood asthma decreased sharply, especially in those aged 1 to 4 years. This situation greatly affected the age-standardized DALY rate, with the highest rates in individuals aged 1 to 4 years (264.6 per 100 000) and 5 to 9 years (228.2 per 100 000). Due to the substantial economic and social burdens imposed by pediatric disability along with the significant declines in incidence and mortality rates, our research mainly focused on the age-standardized DALY rate. The general understanding of asthma treatment and management and interpretation of clinical data proves that regular inhaled corticosteroids and other drugs can reduce the incidence and mortality of asthma in children (22).

In addition, age group analysis showed that the age-standardized DALY rate in individuals aged 1 to 4 years decreased in all SDI regions, with the largest decrease in the low-SDI region. However, the age-standardized DALY rate exhibited different trends in other age groups; the age-standardized DALY rate was highest in the high-SDI region and increased from 1990 to 2019 in individuals aged 5 to 9 years, 10 to 14 years and 15 to 19 years. Based on the results, the largest number of DALYs in children with asthma, excluding those aged 1 to 4 years, occurred in the high-SDI region, and the number of DALYs decreased from 1990 to 2019 in the low-SDI region. The level of medical care in the high-SDI region allows for the availability of more health services and for formal drug treatment and prevention recommendations for childhood asthma (23–25). This may explain the decreasing DALY rate in each SDI region and the lowest rate in the high-SDI region in 2019, indicating an inverse relationship between SDI and DALYs. Despite improvements in medical care, the age-standardized DALY rate was still high in the high-SDI region among children older than 5 years. Furthermore, GBD data analysis showed risk factors for asthma to be high BMI and occupational asthmagens, and the most important risk factor was the latter. BMI is calculated by dividing weight (kg) by the square of height (m) (26); it is related to food intake and is an indicator of overweight and obesity. In the high-SDI region, the increase in the age-standardized DALY rate was mainly caused by high BMI in individuals aged over 5 years. Together, children aged over 5 years in the USA spend much time in school away from their parents. Additionally, they encounter new triggers and stressors, such as struggling with asthma in class because of incomplete management. Schools are not tasked with reminding children to take their asthma medication, and self-sufficiency

should be emphasized (27). As we age, social influence become less important, and children might forget to take medicine or misunderstand instructions. To avoid embarrassment, children may not take their medication regularly, but severe asthma due to lack of control has a heavy medical burden.

The economic burden of childhood asthma is related to medical care, "medication and loss of productivity among families and societies (28). Furthermore, we should raise awareness about the increasing number of DALYs due to childhood asthma (29), reduce the risk of childhood asthma and adopt formal treatment and management recommendations. In 2019, the number of DALYs due to childhood asthma was highest in the low-SDI region, but the age-standardized DALY rate of childhood asthma was highest in the high-SDI region, with an increase of 3% from 1990 to 2019. This difference stems from slow population growth and the change in the population age structure. Therefore, reducing high BMI is vital in high-SDI regions.

Analyses of the regional associations between SDI and the age-standardized DALY rate indicated that the age-standardized DALY rate in children in high-income North America sharply increased compared with the expected rate from 1990 to 2019. The countries in that region should be given more attention to prevent an increase in DALYs due to childhood asthma. Detailed information for each country revealed that different countries had different age-standardized DALY rates for the target age groups; preventive measures should be taken to reduce the age-standardized DALY rate in specific age groups. For example, Madagascar showed a high age-standardized DALY rate in individuals aged 10 to 19 years; therefore, prevention and treatment recommendations need to be more extensive for individuals in this age group. Cockroaches and their excreta are also related to childhood asthma. Air pollution, socioeconomic status and weather have major impacts on the increasing number of childhood asthma cases (30, 31).

Another risk factor for childhood asthma was occupational asthmagens; regrettably, information about occupational asthmagens was missing for children under 15 years of age. According to the data available, the contribution of occupational asthmagens to the age-standardized DALY rate decreased but remained high; simultaneously, the proportion of children with high BMI increased rapidly from 1990 to 2019, indicating that the effect of high BMI may be greater than that of occupational asthmagens. These results show the importance of high BMI for DALYs among children. The highest age-standardized DALY rate was in the high-SDI region, and we estimated the incidence rates of risk factors for childhood asthma from GBD data. Research indicates that BMI is related to the incidence of childhood asthma via DNA methylation (32). Epidemiological studies (2, 7, 33, 34) have proposed various causes of childhood asthma, including environmental exposures, gene interactions, sensitivity to multiple foods and inhalation of allergens. People with the same ethnic background who live in diverse environments with different environmental conditions have very different incidences. However, whether incidence is related to DALYs has not been reported. Our analysis of childhood asthma data in the GBD database by age group revealed a relationship between DALYs and high BMI. In the high-SDI region, weight control and healthy diets are the main methods to reduce DALYs due to childhood asthma.

The estimates of age-standardized DALY rates in each SDI region in all age groups suggest a slow increase in those aged 1 to 4 years but a sharp increase in those aged 5 to 19 years in the high-SDI region. Although the incidence of high BMI increased sharply in children aged 1 to 4 years from 1990 to 2019, the DALY rate may be influenced by low BMI for the first 4 years of life (32, 35). The age-standardized mortality rate in the low-SDI region declined by 66.4% but was still higher than that in other regions from 1990 to 2019. The age-standardized DALY rate declined significantly in all age groups, and the estimated incidence of risk factors was 18.6 per 100 000 for high BMI and 16.7 per 100 000 for occupational asthmagens. Formal treatment and management, effective drug use and improved clinical care are essential ways to reduce DALYs due to childhood asthma in low-SDI regions (36, 37), but information about risk factors for childhood asthma is limited.

High BMI related to eating habits, lifestyle and food intake can lead to obesity in children (38). Current research shows that children's diets and lifestyle behaviors are associated with high BMI (38–40). In general, childhood obesity is an increasing public health problem worldwide.

CONCLUSIONS

Childhood asthma of the age-standardized DALY rates was increasing in high SDI, especially among those aged 5 to 19 years. However, the change in age-standardized DALY rates gradually decreased in those 1–4 years old. Risk factors included BMI, with a greater risk this risk with a high SDI. Childhood asthma is a widespread chronic disease, and the associated medical and economic burdens remain high. We need to establish recommendations for prevention and treatment, as childhood asthma has received less attention than other chronic diseases, such as childhood leukemia or other childhood cancers and cardiovascular disease. Critical and correct intervention policies require information about childhood asthma cases. Based on the current information, children in high-SDI regions, such as the United States and Canada, should change their diet and lifestyle habits and exercise regularly. Data on additional childhood chronic diseases need to be collected to formulate improved health prevention recommendations, especially regarding risk factors.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

DZ wrote the manuscript and analyzed the data. JZ designed the research, downloaded, and explained the generation of related data and graphics. The final manuscript was read and approved by both authors.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2022.823399/full#supplementary-material

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REVIEW
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How to Choose the Correct Drug in Severe Pediatric Asthma

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When a child with severe asthma (asthma defined clinically for the purposes of this review as wheeze, breathlessness, and chest tightness sometimes with cough) does not respond to treatment, it is important to be sure that an alternative or additional diagnosis is not being missed. In school age children, the next step is a detailed protocolized assessment to determine the nature of the problem, whether within the airway or related to co-morbidities or social/environmental factors, in order to personalize the treatment. For example, those with refractory difficult asthma due to persistent non-adherence may benefit from using budesonide and formoterol combined in a single inhaler [single maintenance and reliever treatment (SMART)] as both a reliever and preventer. For those with steroid-resistant Type 2 airway inflammation, the use of biologicals such as omalizumab and mepolizumab should be considered, but for mepolizumab at least, there is a paucity of pediatric data. Protocols are less well developed in preschool asthma, where steroid insensitive disease is much more common, but the use of two simple measurements, aeroallergen sensitization, and peripheral blood eosinophil count, allows the targeted use of inhaled corticosteroids (ICSs). There is also increasing evidence that chronic airway infection may be important in preschool wheeze, increasing the possibility that targeted antibiotics may be beneficial. Asthma in the first year of life is not driven by Type 2 inflammation, so beyond avoiding prescribing ICSs, no evidence based recommendations can be made. In the future, we urgently need to develop objective biomarkers, especially of risk, so that treatment can be targeted effectively; we need to address the scandal of the lack of data in children compared with adults, precluding making evidence-based therapeutic decisions and move from guiding treatment by phenotypes, which will change as the environment changes, to endotype based therapy.

Keywords: asthma, atopy, eosinophil, immunoglobulin E, Type 2 inflammation, SMART regime, inhaled corticosteroids

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INTRODUCTION

For the purposes of this review, it will be assumed that the patient has undergone a full diagnostic workup, eliminating as far as possible non-asthma diagnoses, and seeking positive evidence for the diagnosis of asthma (**Table 1**), acknowledging that there is no one "asthma test" that can definitively diagnose the disease. The protocolized approach to evaluating patients with school age asthma apparently not responding to treatment has been discussed in detail elsewhere (1–4) and will not

be described here; the focus is pharmacotherapy, but the importance of social and environmental factors cannot be overstated. Unfortunately, no such protocols have been evaluated in preschool children, although the general principles [check there is no alternative or associated diagnosis, assess adherence objectively (5–7), look for exposure to tobacco and e-cigarettes and allergens, and assess psychosocial factors] will apply.

KEY DEFINITIONS

Key to personalizing medication in asthma is a clear understanding of what the term means. The *Lancet* commission (8) defines asthma as a clinical syndrome of wheeze, chest tightness, and dyspnea, sometimes with increased cough, and this is the definition used here. This umbrella definition means that, on an individual basis, the underlying cause of the symptoms must be determined, by deconstructing the airway (**Table 2**) with a particular focus on defining what is treatable ("Treatable traits") and what treatment success will look like. This is especially important in the preschool asthmas (below).

The next definition is, what constitutes severe asthma? Traditionally, this has been defined by the levels of prescribed medication (9, 10) (e.g., **Table 3**); although confusingly, many different definitions exist (11). However, definition solely by dose and numbers of medications prescribed is not adequate for clinical practice; around half the asthma deaths reviewed in the United Kingdom were not prescribed medications at a "severe" level (12). Risk needs to be incorporated (13, 14), preferably guided by objective biomarkers (15). Risk is multifaceted, and includes risks of side effects of medication and risk of failure of normal airway growth, but particularly, risk of a severe attack. Markers of risk of an attack include a previous severe attack, under-use of inhaled corticosteroid (ICS), over use of short-acting β-2 agonists (SABAs), failure to attend routine asthma checks, and multiple emergency visits for asthma (14). These factors must be considered when choosing treatment. Unfortunately, there are no internationally accepted definitions for preschool children. Empirically, I here define severe preschool asthma as chronic symptoms (most days a week), especially acute attacks of wheeze despite trials of prescribed ICS at doses of 400 μg/day of beclomethasone equivalent and the leukotriene receptor antagonist (LTRA) montelukast.

Importantly, there are different categories of school age severe asthma mandating different approaches (16, 17). Worldwide, the most common is severe asthma due to the unavailability or lack of access to basic medications, either in low- and middle-income settings or in poverty pockets in high-income countries (HICs) (18). This requires political solutions, and is not discussed here. The other categories are difficult asthma (which will be cease to be difficult if basic management is got right); asthma plus co-morbidities; and true severe, therapy-resistant asthma. With energetic multidisciplinary team (MDT) management, difficult asthma and asthma plus may not require additional therapy, but failure to respond puts the patient in the categories refractory difficult asthma or refractory asthma plus, mandating further consideration of pharmacotherapy.

Finally, before embarking on matching patients to prescription, it is worth reflecting on this quotation from Oscar Wilde "To do nothing at all is the most difficult thing in the world, the most difficult and the most intellectual" – and doing nothing (at least in terms of prescribing more medication) may be the most intellectual course. Two studies demonstrate the truth of this maxim in this context. A well-designed study addresses the question as to whether azithromycin or montelukast was the better add-on therapy in symptomatic patients despite ICS and long-acting β-2 agonist (LABA) being prescribed (19). The study ended in futility because most either did not have asthma or were not taking their treatment. Another study of inner city children which aimed to see if the addition of the measurement of fractional exhaled nitric oxide (FeNO) improved asthma outcomes was also futile (20), because during the 2-week run-in period, with detailed attention to the basics of management, asthma control improved out of all recognition and there was virtually no scope for extra benefits during the study. Prescribing nothing extra, but getting the basics right.

SCHOOL AGE ASTHMA: DECONSTRUCTING THE AIRWAY IN PEDIATRIC SEVERE ASTHMA

The basic components of this process are presented in **Table 2**. A logical sequence of questions should be asked in order to personalize therapy. For example, it surely makes no sense to give ever more potent anti-eosinophil medications if there is no evidence of airway eosinophilia.

1. Is there fixed airflow obstruction? This is not a treatable trait, but should be identified to prevent over-treatment, trying to reverse the irreversible. There is no agreed protocol to exclude persistent airflow limitation. Spirometry is performed after some form of systemic steroid trial and SABA administration. We use a single intramuscular injection of triamcinolone (40 mg if child <40 kg in weight, otherwise 80 mg) so adherence is assured.
2. Is there specifically SABA responsive variable airflow obstruction? This cannot be determined by acute SABA administration if the child does not have airflow obstruction at the time of examination. However, it can be determined using a challenge test (e.g., exercise or methacholine) or in home using preferably spirometry to ascertain whether there is spontaneous fluctuation in airflow obstruction.
3. Is there evidence of ongoing inflammation, and if so, what is its nature? This is a complex issue in severe asthma.
    - First, whether the (at least potentially) treatable trait of airway eosinophilia is present should be determined. The most direct route is fibreoptic bronchoscopy (FOB) with bronchoalveolar lavage (BAL) and endobronchial biopsy, but this is invasive, and induced sputum is a viable alternative (not in preschool children, below).

TABLE 1 | Diagnostic clues suggestive of another diagnosis, and positive indications that asthma is in fact the diagnosis.

Features suggestive that asthma is not the diagnosis	Positive indicators of an asthma diagnosis
History • Respiratory sounds other than true wheeze • Prominent upper airway disease • Symptoms from first day of life • Sudden onset of symptoms • Chronic wet cough for >4–8 weeks • Continuous, unremitting symptoms • Easy vomiting, heartburn, difficult to feed • Evidence of systemic illness or immunodeficiency	Variable airflow obstruction • Acute response to SABA if reduced FEV_1 • Positive exercise or other challenge test • Variable spirometry at home with time or after SABA treatment
Physical examination • Clubbing, weight loss, failure to thrive • Upper airway disease tonsillar enlargement, severe rhinitis, nasal polyps • Unusually severe chest deformity • Abnormal, non-wheeze auscultatory signs, e.g., *fixed* monophonic wheeze, stridor, asymmetrical signs • Signs of cardiac or systemic disease	Atopic sensitization • Positive skin prick tests • Positive sIgE
Initial screening tests • CXR: focal changes, excessive airway thickening, and dilatation • FV curve: should be normal or have reduced flows at low lung volumes	Airway inflammation • Elevated FeNO • Raised peripheral blood eosinophil count • Induced sputum eosinophilia

Obviously, there is no definitive diagnostic test for asthma.
CXR, chest radiograph; FeNO, fractional exhaled nitric oxide; FEV_1, first second forced expired volume; FV, flow volume; SABA, short-acting β-2 agonist; sIgE, specific immunoglobulin E.

Peripheral blood eosinophil count certainly correlates with airway eosinophilia (21), but agreement is far from perfect (below) even in the absence of confounders like parasitic disease and non-asthma airway disease.

– If the phenotype airway eosinophilia is present, what is the endotype? There is usually evidence of Type 2 inflammation with signature cytokines interleukin (IL)-4, -5, and -13, but this is not invariable (below).
– Is there evidence of activation of other inflammatory pathways, such as IL-17? If there is airway neutrophilia, is this beneficial (response to infection) or adverse (release of neutrophil granule contents leading to tissue damage)? Whereas in adults neutrophilic asthma is refractory to therapy (22, 23), in children at least intraepithelial neutrophils are associated with better asthma outcomes (24).

4. Is there evidence of airway infection? This may be particularly relevant in preschool children (below). If this is the case, targeted antibiotics may be indicated. If the child is prescribed high-dose ICS and there is no evidence of airway eosinophilia, consideration should be given to a dose reduction, given the evidence that ICS may cause clinically significant mucosal immunosuppression (25–28).

CHOOSING THE RIGHT MEDICATIONS FOR SCHOOL AGE REFRACTORY DIFFICULT ASTHMA

The usual context is the child who is not given or will not take standard medications even despite the MDT intervention. The differential diagnosis is true therapy-resistant asthma, the medications therefore not being given because they are not effective. To resolve this, the next step is to see if there is a response when medication administration is directly supervised, either by an admission to hospital or in the community. If, as is usual, asthma symptoms disappear, FeNO normalizes, and spirometry improves, severe therapy-resistant asthma is excluded and the young person is diagnosed with steroid-sensitive, eosinophilic asthma (5). Ideally directly observed, effective therapy is continued, but often this is not practical. In that event, I would switch the young person to a single maintenance and reliever treatment (SMART) regime, using a combined ICS and LABA (budesonide and formoterol, respectively) inhaler (29, 30). I would ensure that the young person did not have any possibility of accessing SABAs. Of note, GINA recommends this approach at all levels of asthma severity (31), on the basis of ample evidence (32). I would adjust the aspects of the regime (how much regular therapy and the inhaler strength) on an individual basis (**Table 4**). An additional strategy, not licensed or evidence based, would be to use once daily ICS/LABA preparations such as Relvar (Fluticasone furoate and the LABA vilanterol) with budesonide/formoterol as reliever therapy. Finally, although United Kingdom guidelines insist on ensuring adherence before biologicals can be funded, I take the view that every measure to keep the child from dying from an asthma attack is fully justified (33). A young person must not be penalized because the parents/carers will not ensure ICS is taken regularly and correctly. The hope is that these measures will buy time for increasing age and maturity to bring a new attitude to asthma medications. In any case, good adherence is virtually impossible to confirm in routine clinical practice, although of course

TABLE 2 | Deconstructing the airway to plan treatment.

Airway component	Underlying cause	Potential treatment?
Fixed airflow obstruction	1. Developmentally acquired, e.g., maternal smoking in pregnancy 2. Airway remodeling	Avoid worsening obstruction by tobacco, pollution Do not over-treat, trying to reverse the irreversible
Variable airflow obstruction	1. ASM constriction 2. Airway instability/malacia 3. Intraluminal mucus or inflammatory debris	1. SABA, LABA 2. Might need CPAP 1. Airway clearance, mucolytics
Airway inflammation	1. Present or not? 2. Eosinophilic? 3. Neutrophilic? 4. Mixed picture? 5. Beneficial or not?	2. Eosinophilic: ICS, omalizumab, mepolizumab 3. Neutrophilic: consider azithromycin, but look for other diagnoses such as GERD, CF
Airway infection	Bacterial, viral, fungal	Consider targeted antibiotics for any bacterial infection
Augmented cough sensitivity?	Unknown	None licensed in children

ASM, airway smooth muscle; CF, cystic fibrosis; CPAP, continuous positive airway pressure; GERD, gastro-esophageal reflux disease; ICS, inhaled corticosteroid; LABA, long-acting β-2 agonist; SABA, short-acting β -2 agonist.

non-adherence (e.g., failure to collect prescriptions) is often readily apparent.

CHOOSING THE RIGHT MEDICATIONS FOR SCHOOL AGE REFRACTORY ASTHMA PLUS COMORBIDITIES

Obesity Asthma With Failure of Weight Reduction

This is a situation that requires very careful evaluation. The definition of severe asthma includes chronic symptoms, but it is essential to be sure that these are actually due to asthma. Exercise intolerance due to obesity and deconditioning will not respond to intensifying asthma therapy. This is a general problem – in one big epidemiological study, around half of young people complaining of shortness of breath on exercise had neither exercise-induced bronchoconstriction nor exercise-induced laryngeal obstruction, despite which many had been treated with inhaled therapy for asthma (34). It is, therefore, of primary importance to determine whether symptoms are truly due to asthma before prescribing.

- Fixed airflow obstruction: common but not exclusive to obese young people is dysanaptic airway growth, defined as a normal first second forced expired volume (FEV_1), a greater than normal forced vital capacity (FVC), and therefore a reduced FEV_1/FVC ratio (35). The exact determinants are unclear, but murine studies implicate antenatal nicotine exposure (36), and in humans, excessive weight gain in the first 2 years of life, irrespective of birth weight (37). Dysanaptic growth is associated with worse asthma outcomes, but is not amenable to current therapies.
- Variable airflow obstruction: Related to the need to determine the exact cause of symptoms is the need to be sure that variable airflow obstruction is SABA-responsive, and not due to variable atelectasis related to reduced chest wall compliance. Objective documentation, preferably with spirometry, is essential.
- Airway inflammation: Obesity does not protect against atopic allergic inflammation (38), and obese patients may need escalation of therapies addressing this issue. However, the presence of Type 2 inflammation must first be documented, not only because excessive steroid therapy may worsen obesity, but also because alternative inflammatory pathways may play a role in obesity. Obesity is well known to be a systemic, pro-inflammatory state, and there is evidence that some obese asthma is driven by systemically released IL-6 targeting the airways independent of immunoglobulin E (IgE) or blood eosinophil levels. The advent of the coronavirus disease 2019 (COVID-19) pandemic has led to two licensed approaches to treatment targeting IL-6 in this context. Siltuximab is a monoclonal antibody that binds to IL-6 (39), and sarilumab (40) and tocilizumab (41) are monoclonal antibodies that bind to the IL-6 receptor. Some of these approaches have been used in other contexts, for example, tocilizumab in interstitial lung disease (42), but as yet not in asthma according to the best of my knowledge. However, this might be a therapy for systemic IL-6-driven asthma in the future.

In summary, the breathless obese young person poses particular challenges, and it is essential to measure pathology and personalize therapy rather than blindly prescribing ever more therapies.

Severe Rhinosinusitis

The relationship between upper and lower airway disease has long been debated, but there is compelling evidence that treatment of severe rhinosinusitis can improve asthma control, and treating the upper airway with nasal steroids and anti-histamines may be helpful before escalating asthma therapy (43). It should be noted that nasal steroids may, however, significantly contribute to adrenal suppression (44).

TABLE 3 | Definition of severe asthma by levels of medication, modified from Bel et al. (9).

High dose ICS (>500 mcg FP/day age 6–12 and >1,000 age over 12 years, plus LABA, LTRA, and oral theophylline, or failed trials of these add-ons unless clinically contra-indicated, or systemic CS >50% of the previous year required to control asthma, or uncontrolled asthma despite these medications
Uncontrolled asthma (or better, unacceptable asthma outcomes, defined as: • Chronic symptoms (ACT < 20) • >2 asthma attacks/year treated with systemic CS • One serious attack defined as hospitalization, PICU admission, or need for IPPV • Persistent airflow limitation: FEV_1 < 1.96 *Z*-scores despite a course of systemic corticosteroids and acute SABA administration
Controlled asthma that worsens on tapering high doses of ICS or systemic CS, or additional biologics

ACT, asthma control test; CS, corticosteroid; FEV_1, first second forced expired volume; FP, fluticasone propionate; ICSs, inhaled corticosteroids; IPPV, intermittent positive pressure ventilation; LABA, long-acting β-2 agonist; LTRA, leukotriene receptor antagonist; PICU, pediatric intensive care unit; SABA, short-acting β-2 agonist; Z-score, standard deviation score.

TABLE 4 | Choosing the right medications for school age refractory difficult asthma (when appropriate).

Refractory character	Action
Poor adherence despite every effort to improve	• Check responds to DOTS • Try SMART, Relvar • Confirm eosinophilic airway disease and prescribe biologicals
Ongoing allergen exposure to which child is sensitized, with family unable or unwilling to remedy this	• May be worth trying higher dose ICS, but beware side-effects • Confirm eosinophilic airway disease and prescribe biologicals
Ongoing passive (or active) exposure to cigarettes or vapes despite referral to a smoking cessation clinic	• Phenotype airway to ensure no untreated TH2 inflammation • Consider azithromycin as some adult evidence that smokers asthma may be neutrophilic
Ongoing psychosocial issues	• Ensure symptoms are really due to asthma • Treat any adherence issues (above) • Phenotype airway to ensure all standard treatment is optimal

DOTS, directly observed therapy; SMART, single maintenance and reliever treatment.

TABLE 5 | Choosing the right medications for school age refractory asthma plus comorbidities (when appropriate).

Co-morbidity	Action
Obesity with failed weight loss	Confirm symptoms are due to asthma not deconditioning Consider bariatric surgery Determine whether Type 2 inflammation is present and treat accordingly (Future option?) anti-IL-6 strategies if systemic inflammation is the issue
EILO	Reduce medications until signs of Type 2 inflammation (re)appear Involve skilled physiotherapist, speech therapist, and sports psychologist Consider ENT referral if remains refractory
Allergic rhinosinusitis	Identify and avoid the relevant antigens where possible Topical corticosteroids ENT referral for consideration of surgery if refractory symptoms persist despite medical treatment
Food allergy	A non-causative association of worse outcomes, so a marker of risk, make sure airway Type 2 inflammation is well controlled
Gastro-esophageal reflux	Even if symptomatic, treatment makes no difference to asthma outcomes, so only take action if there are disabling symptoms meriting therapy

ENT, ear, nose, and throat; EILO, exercise-induced laryngeal obstruction.

Breathing Pattern Disorders

There is a spectrum of these including hyperventilation syndromes and exercise-induced laryngeal obstruction (45). Their importance is related to the fact that they are frequently mis-diagnosed as uncontrolled asthma and treatment escalated. Detailed evaluations by specialist respiratory physiotherapists, speech and language therapists, and clinical psychologists, combined with cardiopulmonary exercise testing while laryngoscopy is performed, may help with the diagnosis and guide therapy. Again, escalation of asthma medications is not helpful.

The various options are summarized in **Table 5**.

CHOOSING THE RIGHT MEDICATIONS FOR SCHOOL AGE SEVERE, THERAPY-RESISTANT ASTHMA

The days of prolonged daily or alternate day corticosteroids have fortunately gone. Although an increasing range of monoclonals is becoming available to adult chest physicians, the only current

pediatric options are the monoclonals omalizumab, which binds to IgE, and mepolizumab, which binds to IL-5. Dupilumab blocks the receptors for IL-4 and IL-13. The recent Voyager study, which demonstrated the efficacy of dupilumab in 6–11 year olds (below), raises hopes that this too will become available to pediatricians (46). The biologicals have to be given *via* injection every 2–4 weeks. We now have a program whereby this can be done at home by direct videolink (47).

Omalizumab

This monoclonal complexes with IgE preventing it from binding to the high-affinity IgE receptor (FceRI) on mast cells and basophils which would lead to mediator release. There is, by far, the most pediatric experience with this monoclonal. Dosage depends on the body weight and IgE level. If total IgE is >1,300 kIU/L (or <75), the medication cannot be used in the United Kingdom, which is important because many severe asthmatics have levels well above the therapeutic range. However, there are international variations in the levels of IgE for which omalizumab may be used, and national guidelines need to be checked. Although in many countries aeroallergen sensitization is a requirement for funding, this is illogical because in adults who are not sensitized but have a high IgE the results of treatment are not inferior. The Cochrane review (48) demonstrated a reduction in asthma attacks: [odds ratio (OR) 0.55, 95% confidence interval (CI) 0.42–0.60 in 10 studies recruiting 3,261 patients] with an absolute reduction of 26–16%; reduced hospitalizations (OR 0.16, 95% CI 0.06–0.42; 4 studies that recruited 1,824 patients) with an absolute reduction 3–0.5%; reduced SABA usage (OR 0.16, 95% CI 0.06–0.42; 4 studies that contained 1,824 participants); absolute small but significant reduction in SABA (mean difference −0.39 puffs per day, 95% CI −0.55 to −0.24; 9 studies, 3,524 patients). A systematic review of real-life efficacy in adults and children summarized 86 manuscripts. Treatment effectiveness was excellent or good in 77% patients at 16 weeks (95% CI 0.70–0.84) and in 82% at a year (0.82, 0.73–0.91). The improvements in FEV_1 and Asthma Control Questionnaire (ACQ) were small. The greatest benefits were in the reduction of severe attacks [risk ratio (RR): 0.41, 95% CI: 0.30–0.56], patients receiving oral corticosteroids (RR: 0.59, 95% CI: 0.47–0.75), and number of unscheduled physician visits (mean difference: −2.34, 95% CI: −3.54 to −1.13) in the first year of treatment (49). A French study (50) reported data in 101 children, of whom 92 were still receiving treatment after a year (6 discontinued due to severe adverse effects). Severe asthma attack rate and hospital admissions dropped dramatically (72%, from 4.4 per patient during the preceding year to 1.25 during the treatment year, and 88.5%, 44% during the preceding year to 6.7% during the treatment year, respectively). There was also an improvement in asthma control (0% at baseline to 67% well-controlled at 1 year); a 30% decrease in ICS dose (baseline 703–488 μg fluticasone equivalent/day at a year) but unsurprisingly only a small increase in FEV_1 (88–92.1% predicted). At 2 years (51), 73 (79.3%) were still receiving the treatment. Treatment had been discontinued in further 15 patients due to the lack of improvement (n = 4), adverse events (n = 8), lost to follow-up (n = 4), and personal reasons (n = 3). Severe attacks decreased to a mean (95% CI) of 0.22 (0.03–0.41) per year. No patient needed to be hospitalized. Level of control, spirometry, and daily ICS dose did not change significantly. Taken together, these data show a sustained benefit for omalizumab, in particular, in the reduction of severe attacks. An updated systematic review in children is awaited (52).

To select suitable children for omalizumab therapy remains unclear. Levels of total (53, 54) or specific IgE (sIgE) (55) are not reliable predictors. A study was performed in 850 patients of age 12 and over related the reduction in asthma attacks over a 48 week period to levels of FeNO (n = 394), blood eosinophils (n = 797), and serum periostin (n = 534) (56). Attack reduction was greater in the high subgroups for FeNO and blood eosinophils vs. placebo, respectively, 53% [95% CI, 37–70 vs. 16% (95% CI, 34)] to 46) and 32% (95% CI, 11–48 vs. 9% (95% CI, −24 to 34). Periostin levels showed no statistically significant effect (and in any event, since periostin is released from growing bone, it is not a useful pediatric biomarker). These data suggest that (a) T-helper (TH)2 high adults with multiple asthma attacks will have the best response; and (b) by analogy, these will be predictive biomarkers in children. However, this needs to be tested, and there are also problems with using adult blood eosinophil cutoffs in children (below).

Mepolizumab

There is convincing evidence for the efficacy and safety of mepolizumab in young people of age 12 years and over and in adults (57). A blood eosinophil count of >300 cells/μl is a good biomarker of efficacy (58). However, less than 100 patients aged less than 16 have been included in these studies. There are some limited pediatric data that show safety and a reduction in blood eosinophil count with mepolizumab (59, 60), but there are no large-scale efficacy data, despite which mepolizumab has been licensed for use in children.

Dupilumab

There is extensive evidence for efficacy and safety of dupilumab in the treatment of children and adults with eczema (61) and in children 12 years and over and in adults with asthma (62), but until recently, no evidence of efficacy has been observed in school age asthma. The Voyager study (46) recruited 408 children of age 6–11 years with uncontrolled moderate-to-severe asthma. At baseline, children were required to have either a TH2 inflammatory asthma phenotype (≥150 blood eosinophils per cubic millimeter or FeNO of ≥20 ppb) or a blood eosinophil count >300 cells/μl. In the TH2 inflammation group, severe asthma attacks were reduced by dupilumab [0.31 (95% CI 0.22–0.42) vs. placebo 0.75 (95% CI, 0.54–1.03) (relative risk reduction by dupilumab, 59.3%; 95% CI, 39.5–72.6; $P < 0.001$)]. There was a small but significant improvement in FEV_1 of 10.5 ± 1.0% with dupilumab compared with placebo (5.3 ± 1.4, $P < 0.001$) and better asthma control ($P < 0.001$). The results were similar in those with a baseline eosinophil count >300 cells. The medication was safe and well tolerated.

Specific Issues With Selecting TH2 Inflammation Strategies in Children

These are (a) the biology of severe asthma in children; (b) the use of eosinophils as a biomarker; and (c) the developmental role of

the eosinophil in children, which last may lead to safety questions specific to the pediatric age group.

In the pediatric literature, by no means all severe asthma appears to be driven by TH2 inflammation. We phenotyped a large group of children with severe asthma who had been through our protocol for the assessment of severe asthma. Many, but not all, were eosinophilic on induced sputum, BAL, and endobronchial biopsy, but evidence of TH2 inflammation was scant in all three compartments (63). The mechanisms of eosinophilia in this group have not been determined, but non-TH2 eosinophilia has been described in other contexts (64). The US Severe Asthma Research Program (SARP) network (65) reported 53 children with asthma of whom 31 were severe, and 30 adult controls. They found that the best discriminants between asthma and controls were BAL IL-6 and IL-13. Severe asthma was differentiated from moderate disease by CXCLI, growth related oncogene (GRO), regulated on activation, normal T expressed and secreted (RANTES, CCL5), IL-12, interferon (IFN)-γ and IL-10. When alveolar macrophage lysate was studied, IL-6 was the best discriminant. They concluded that severe asthma in children was not characterized by either a TH1 or TH2 signature. A further study (66) utilizing n = 68 BAL from 52 children with severe, therapy-resistant asthma showed that viruses and bacteria were commonly detected. Although CCR5 positive TH1 cells were enriched in BAL, there were also pro-inflammatory, TH1, TH17, and TH2 profiles detected; of note, there was no control group. Further findings were that TH2 skewing correlated with total serum IgE. Those who were multi-sensitized showed increased IL-5, IL-33, and IL-28A/IFN-λ2. Not all sIgEs had equivalent effects; changes correlated with sIgE to house dust mite, ryegrass, and fungi but not with sIgE to cats, ragweed, and food allergens, which is another important confirmation that atopy is not an "all-or-none" state (67, 68). Only BAL IL-5 increased with age and correlated with BAL and blood eosinophils. Of course, in all these cross-sectional studies, causation cannot be inferred from correlation. Also, when considering treatment the question should be "does it work?" rather than "should it work?," but it is clear that severe asthma has multiple endotypes and this needs to be factored into decisions about trials of treatments. The recommendation would be therefore to clearly define that the disease is truly TH2-driven in a given individual, including if necessary proceeding to bronchoscopy.

A global perspective is also important. Most of the invasive studies come from HICs, and it should not be assumed that severe asthma is the same in low- and middle-income countries (LMICs). It would be a mistake uncritically to follow HIC protocols in LMIC settings.

Blood eosinophil count is a hallowed marker for airway eosinophilia in adult asthma (57) and chronic obstructive pulmonary disease (69), but there is a problem. In children, the normal blood eosinophil count is much higher than in adults, dropping to adult levels throughout childhood (70). Even in adult life, asthmatics with a normal blood eosinophil count may respond to Type 2 biologics (58). This suggests that adult blood eosinophil levels may not be appropriate in guiding decisions in children, but perhaps also, there may be patients (adults and children) with low blood eosinophils who may yet have airway eosinophilia, and additional markers of this are needed. Furthermore, in LMICs in particular, where there is a high parasite burden, "normal" blood eosinophil count may be even higher. The ideal would be to use at least induced sputum to confirm directly that airway eosinophilia is present before instituting Type 2 biologics.

Finally, the assumption that the eosinophil has no beneficial effects needs to be challenged. Even in adults, it would seem that too aggressive an obliteration of circulating eosinophils may be adverse. Benralizumab leads to a much more dramatic reduction in circulating eosinophils then mepolizumab and reslizumab, but is associated with more respiratory infections and more infection-driven asthma attacks (71). A number of studies have attributed important homeostatic functions to the eosinophil, at least in animal models. These include Beige fat thermogenesis and glucose homeostasis; adjuvant-induced B-cell priming and maintenance of memory plasma cells; antigen presentation in the intestine (72–75). Additionally, eosinophils have antiviral properties (76). In an observational study, asthmatic adults infected with COVID-19 were less likely to be admitted, and less likely to die, if they had a high blood eosinophil count (77). This is not to decry the value of anti-eosinophil strategies, merely to highlight that the risk benefit equation may be different in children.

CHOOSING THE RIGHT MEDICATIONS FOR SEVERE PRESCHOOL ASTHMA

Asthma in preschool children is also defined clinically as above; the question?; "at what age can asthma be diagnosed?" is without meaning (78); in the preschool years, attempts should be made to deconstruct the airway prior to escalating treatment exactly as in school age, although this may be more difficult to achieve. Historically, all preschool wheezers were lumped together and treated identically. In 2008, an ERS, 2008 guideline formalized the distinction between episodic viral wheeze (EVW, wheeze solely with a usually clinically diagnosed viral respiratory tract infection), and multiple trigger wheeze (MTW), in which there are symptoms with typical asthma triggers such as exercise even in between viral infections (79). Given that early administration of ICS does not prevent school age asthma developing (80–82), the recommendation was that EVW should be treated intermittently, with ICS or LTRAs montelukast), and MTW with regular ICS. It was recognized that these symptom-based phenotypes could change over time. In a subsequent iteration (83), it was suggested that really severe EVW merited a trial of regular ICS. However, it became clear that the agreement between underlying pathological phenotypes and symptom patterns was very poor, and furthermore, parental perception of the presence or absence of interval symptoms was frequently unreliable.

Traditionally, the interval between babyhood (when lung function can be performed under sedation) and school age (where active cooperation can be obtained) has been a black hole wherein measurements of pulmonary function cannot be made. However, it is clear that quite young children can be shown how to perform good quality spirometry (84), and

bronchodilator responsiveness measured. Another potentially useful technique is forced oscillation. There is no generally accepted definition of persistent airflow limitation, or fixed airflow obstruction, in preschoolers. Current practice (which is not evidence-based) is not to perform a trial of oral corticosteroids, unlike in school age children, but relies on the value obtained after SABA and perhaps inhaled anti-cholinergic administration.

The first real attempt to personalize medicine in preschool wheeze was the INFANT study (85). Preschool wheezing children were given in random order as follows: regular ICS, regulart LTRA, and intermittent ICS. Prespecified subgroups were atopic sensitization, gender, and acute attacks of wheeze, and *post hoc*; blood eosinophil count was added in to the data analyses. In summary, the combination of aeroallergen sensitization and a blood eosinophil count >300 cells/μl predicted a group which was responsive to ICS; in the other patients, it did not matter what treatment was given (there was no placebo group). Of the original 300 patients, 60 improved spontaneously but only 64 were ICS responders, leaving a big unmet need.

A subsequent study has highlighted a potential role of bacterial infection in non-atopic preschool wheeze. A total of 35 children with severe preschool wheeze (n = 21 MTW, n = 14 EVW, classified clinically with a wheeze video questionnaire) underwent venepuncture for blood eosinophils and total and sIgE, and a clinically indicated FOB, BAL, and endobronchial biopsy with the viral polymerase chain reaction (PCR), bacterial culture, and 16S of amplicon sequencing at a time of clinical

TABLE 6 | Clusters of preschool wheeze, and possible implications for treatment (85).

Cluster number	Clinical features	Potential treatment
Cluster 1	100% sensitized, highest blood eosinophils (mean = 5.54%, SD = 2.86%), high ICS use (91.7%), and moderate rate of bacterial (69.5%, especially *Moraxella*) and viral detection (56.5%)	Highly atopic and eosinophilic ICS or even consider Type 2 biologics (unlicensed in most countries)
Cluster 2	Low BAL neutrophils (mean = 9.44%, SD = 13.89%), low rate of positive bacteriology (17.1%), and viral detection (15.0%). All has been prescribed ICS	Low BAL neutrophils and low infection burden Consider LAMA
Cluster 3	Highest rate of bacterial (*HI*, *SA*, *streptococcal*) and viral infection (96.8 and 86.7%, respectively), and the highest BAL neutrophils (mean = 31.7%, SD = 25.11%); 67.7% had been prescribed ICS	No atopy, high infection burden Targeted antibiotics
Cluster 4	Mostly non-atopic with cough the main symptom, but note that 20% of severe wheezers were in this cluster	No sensitization, infection, or inflammation Consider LAMA

BAL, bronchoalveolar lavage; HI, Haemophilus influenzae; ICSs, inhaled corticosteroids; LAMAs, long acting muscarinic agents; SA, Staphylococcus aureus; SD, standard deviation.

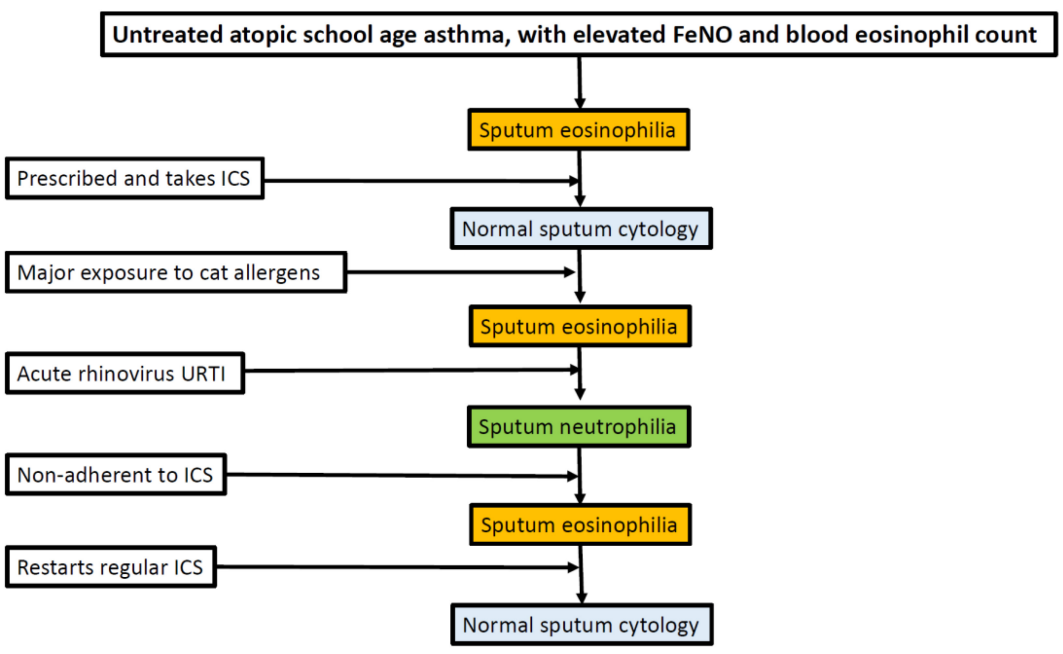

FIGURE 1 | Potential variability of sputum phenotype in an individual who is cat allergic and has asthma. ICSs, inhaled corticosteroids; FeNO, fractional exhaled nitric oxide; URTI, upper respiratory tract infection.

stability (86). Notably, 60% had either a positive bacterial culture or viral detection, and 26% had both. The most common bacteria were *Streptococcus pneumoniae*, *Moraxella catarrhalis*, *Staphylococcus aureus*, and *Haemophilus influenzae*, and the most common viruses were rhinovirus, bocavirus, and adenovirus. Unsupervised analysis revealed two bacterial profiles, i.e., a mixed group (*Streptococcus*, *Prevotella*, *Neisseria*, and *Porphyromonas*) and a *Moraxella* group. The latter had increased BAL but not blood neutrophil counts. There was no difference in clinical wheeze phenotype (EVW, MTW) or atopic status between the two groups. There was evidence to suggest bacterial dysbiosis in the *Moraxella* cluster. Subsequently, the same group attempted a cluster analysis of a large group of severe preschool wheezers (87). A total of 136 children aged 1–5 years (105 with recurrent severe wheeze and 31 non-wheezing respiratory disorders) were studied. Treatment was recorded and the following investigations performed: peripheral blood: leukocyte counts, and sIgE to common inhalant and food allergens, allergic sensitization being defined as sIgE $\geq$0.35 kUA/L to at least one allergen tested; bronchoscopy, BAL, and endobronchial biopsy with bacterial culture and a multiplex PCR to 20 viruses and *Mycoplasma pneumoniae*. Analysis was performed using the partition around medoid (PAM) algorithm coupled with Gower's distance for mixed data and eight variables were used to determine the clusters. These were blood and BAL neutrophil and eosinophil counts, atopic status, a positive viral PCR and bacterial culture, and prescription of ICS. Interestingly, BAL eosinophils and peripheral blood neutrophils did not distinguish between the clusters. Of the severe wheezers, 30/105 were classified as EVW and 44/105 as MTW; in 28, or more than a quarter, it was unclear in which category they belonged, further calling into question the utility of history taking to guide therapy. There were four clusters determined, which bore no relation to clinical wheeze phenotypes. In cluster 1 (24/134, 17.9%), all were sensitized, and there were the highest blood eosinophil counts [mean = 5.54%, standard deviation (SD) = 2.86%], highest ICS doses use (91.7%), and a moderate rate of bacterial (69.5%, especially *Moraxella*) and viral detection (56.5%). In cluster 2 (42/134, 31.3%) there were low BAL neutrophils (mean = 9.44%, SD = 13.89%), and a low rate of positive bacteriology (17.1%) and viral detection (15.0%). All had been prescribed ICS. In cluster 3 (N = 31/134, 23.1%) there was the highest rate of bacterial (*H. influenzae*, *S. aureus*, and *Streptococci*) and viral infection (96.8 and 86.7%, respectively), associated with the highest BAL neutrophil counts (mean = 31.7%, SD = 25.11%); 67.7% had been prescribed ICS. Finally, in cluster 4 (N = 37/134, 27.6%): no patient was prescribed ICS, most were non-atopic, and the most prominent symptom was persistent cough but not wheeze. Possible treatment implications are given in **Table 6**.

In summary, there is now an evidence base for a subgroup of preschool wheezers (atopic, eosinophilic) to guide treatment, but ideally this needs to be confirmed in a second cohort prospectively. In terms of the infected group, further study is needed. In a small proof of concept trial (88), 60 children aged 1–5 years with $\geq$2 wheeze attacks in the previous year were categorized as EVW or MTW. The intervention group was prescribed ICS if blood eosinophils $\geq$3%, or targeted antibiotics if there was a positive culture on induced sputum or cough swab. The control group received standard care. Again, there was no relationship between symptom-based phenotypes and blood eosinophils, atopic status, or infection. Rates of ICS prescription were the same (67%), around half had an unscheduled health care visit, and time to unscheduled visit was the same. Each group were prescribed ICS. There were no differences in any parameter between those who did and did not have an UHCV. Blood eosinophil-driven ICS treatment did not impact outcomes, but ICS adherence was poor. Clearly, until adherence is addressed and there is buy-in to the concept of stopping ICS in the non-allergy, low eosinophil group, it will be difficult to progress these concepts.

CHOOSING THE RIGHT MEDICATIONS FOR SEVERE ASTHMA IN THE FIRST YEAR OF LIFE

First year wheeze is common, but poorly understood (79). We know that even wheeze severe enough to be investigated in a tertiary hospital, even those with atopic sensitization and acute reversibility of airflow obstruction to SABA, is characterized by the absence of Type 2 inflammation (89), so ICS are highly unlikely to be useful. Understanding first year wheeze is a major research priority for the future. At the moment, all we can offer is trial and error of bronchodilators and possibly LTRA.

THE FUTURE: WHERE ARE WE, AND WHERE DO WE NEED TO GO?

Six important areas of unmet need are as follows:

1. *Measurement in clinical practice: For too long, we have been contented with asking questions and chest auscultation without making objective measurements. This is plain wrong in the 21st century. We need a measurement culture in the respiratory clinic. The fact the tools may be difficult to use is not an excuse to discard them when planning treatment. Physiological measurements can be made, and skin prick tests easily performed, and blood eosinophils are now a point-of-care test. We must not let inertia lead to discrimination against young children or be contented with a lower standard of care in this group compared with adults and school age children.*
2. *Research in children: It is an absolute disgrace that there are huge evidence gaps in children. Obvious examples are the use of ICS/LABA as reliever instead of SABA in children under age 12, and, with the honorable exception of VOYAGER, the pitiful lack of efficacy data for most biologicals in children. Clinical trial data in preschool children are even more scant. Legislation is urgently needed to achieve this. The example of cystic fibrosis (CF), in which disease novel small molecule therapy is rapidly accelerated down the age ranges from over 12 years to young babies puts the asthma community to shame.*

3. *Comparison studies: Even with the limited biologics available in school age asthma (omalizumab and mepolizumab), we have no studies comparing the two and are left making haphazard, N-of-1 treatment trials. Hopefully, the TREAT trial will address this (90).*
4. *Phenotype stability: We currently try to use phenotype-based therapy (e.g., treatment of airway eosinophilia) but such limited data that are extant show that, for example, cellular phenotypes in sputum are not stable over time, either in severe or moderate asthma (91). This is unsurprising; a phenotype results from the interactions of an organism with its environment, and if the environment changes then so may the phenotype (**Figure 1**). We are lacking in data on the stability of preschool phenotypes, and validation in a second cohort. As with "asthma genes" a single cohort study cannot be definitive.*
5. *The need to move to determining endotypes: What is really needed, and a destination which is a long way away, is determining the underlying molecular and cellular pathways, which will be robust by definition. This will become more pressing as more biologicals become available. We will need to select medications on the basis of endotypes rather than randomly.*
6. *Biomarkers are desperately needed: If we are to be objective in therapeutic decisions, we need objective biomarkers. This includes biomarkers for risk, in particular risk of a severe asthma attack, so that management efforts including treatment can be focused on those that need it. We also need biomarkers of efficacy, particularly for biologicals. This would enable us to target the right biomarker to the right child and also to do efficacy studies in younger children who may struggle with convantional end-points. Again, the example of CF should be borne in mind. Reduction in sweat chloride by the new molecular therapies is accepted as evidence of efficacy in young children (92), who are so well that demonstrating efficacy by conventional testing would take huge numbers for many years. The other example is the use of in vitro testing of novel therapies using cells harvested by nasal brushing or the generation of rectal organoids has been shown to correlate with in vivo treatment response (93, 94).*

In summary, we have made considerable progress in objectively choosing therapies for children who are struggling with bad asthma, but we have a long way to go. It is essential that we are not complacent, but ensure that we recognize the length of the journey ahead, and are determined to reach the end, whereby children of all ages are treated on the basis of objectively determined need and response. The last century history and physical examination are simply not adequate or acceptable in the 21st century.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

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SYSTEMATIC REVIEW
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The Effect of Vitamin D Supplementation in Children With Asthma: A Meta-Analysis

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Background: An increasing number of studies have suggested that vitamin D can be used to treat childhood asthma, but its clinical effects are still unclear. We conducted this meta-analysis to examine the latest estimates of the effectiveness and safety of using vitamin D to treat childhood asthma.

Methods: The PubMed, The Cochrane Library, ScienceDirect, Embase, Scopus, Ovid MEDLINE, Web of Science, and Google Scholar databases were searched for randomized controlled trials (RCTs) describing vitamin D supplementation interventions for asthmatic children. Asthma exacerbation, vitamin D levels, the predicted percentage of forced expiratory volume in the first second (FEV1%) and adverse effects (AEs) were analyzed as the main outcome measures.

Results: After screening, eight RCTs with 738 children were included. Compared with placebos, vitamin D supplementation had a stronger effect on serum vitamin D levels [mean difference (MD) = 13.51 (4.24, 22.79), $p = 0.004$]. The pooled results indicated that no significant changes were found between the groups in asthma control, as measured by adopting the following indicators: asthma exacerbation [risk ratio (RR) = 0.92 (0.68, 1.25), $p = 0.60$]; Childhood Asthma Control Test (CACT) scores [MD = 0.15 (−0.43, 0.74), $p = 0.61$]; hospitalizations for asthma exacerbation [RR = 1.20 (0.48, 2.96), $p = 0.70$]; acute care visits [RR = 1.13 (0.77, 1.65), $p = 0.63$]; steroid use [RR = 1.03 (0.41, 2.57), $p = 0.95$]; and fractional exhaled nitric oxide (FeNO) [MD =-3.95 (−22.87, 14.97), $p = 0.68$]. However, vitamin D supplementation might reduce the FEV1% [MD = −4.77 (−9.35, −0.19), $p = 0.04$] and the percentage of predicted forced vital capacity (FVC%) [MD =-5.01 (−9.99, −0.02), $p = 0.05$] in patients. Subgroup analysis revealed no difference in AEs between the two groups.

Conclusions: Vitamin D supplementation significantly increased patients' serum vitamin D levels, but it had no benefit for asthma control. However, vitamin D supplementation might reduce patients' lung function. It is essential to systemically search for more large-scale, rigorous, and well-designed RCTs to fully confirm these conclusions.

Systematic Review Registration: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021288838, PROSPERO CRD42021288838.

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INTRODUCTION

Asthma is a chronic inflammation of the airway involving a variety of inflammatory cells. Children account for a large proportion of asthma patients, and it is considered a significant global health burden (1–3). The treatment strategy follows the recommendation of the Global Asthma Initiative (GINA) for childhood asthma, and the key is to control airway inflammation (4).

Vitamin D has potential prospects in the treatment of childhood asthma. Vitamin D is considered to be a complex immunomodulatory molecule, and its role in anti-inflammatory effects and regulating the immune response has attracted increasing attention (5, 6).

The conclusions regarding the efficacy of vitamin D for treating childhood asthma have been inconsistent. The traditional prevention or management methods include long-acting β2 receptor agonists, oral steroids and inhaled corticosteroids (ICS) (7). Although the regular use of ICS and other treatments can reduce mortality, the prevalence and incidence of the disease are still increasing (8). Recent studies have shown that there is a close link between a high asthmatic incidence and vitamin D deficiency (9–11). Increasing evidence has shown that vitamin D is a safe, effective and cost-effective therapy for asthma (12). Some trials have demonstrated that vitamin D can help improve lung function, enhance asthma control and reduce disease severity in the field of asthma therapy (13–15). However, not all studies that have examined vitamin D have reported favorable effects, and there are still disagreements about its effects. Some researchers have also found that vitamin D does not improve asthma control and may even have a negative effect on lung function (16, 17).

To resolve this inconsistency and explore the safety of vitamin D for asthmatic children, we conducted this study by analyzing the relevant literature.

MATERIALS AND METHODS

Our study was conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement, and more details can be found in **Supplementary Table S1**. (Registration information: PROSPERO CRD42021288838).

Search Strategy

We comprehensively searched the PubMed, The Cochrane Library, ScienceDirect, Embase, Scopus, Ovid MEDLINE, Google Scholar and Web of Science databases for eligible RCTs from inception to 24 October 2021. "Asthma," "vitamin D," and "children" were used as keywords. We also manually searched the references lists of the included RCTs for additional eligible studies (**Supplementary Table S2**).

Selection Criteria

Two researchers independently screened relevant articles using Endnote. The inclusion criteria were as follows: (1) population: children (up to 18 years of age) with asthma (doctor's diagnosis and/or objective criteria); (2) intervention and control: vitamin D vs. a placebo; (3) outcomes: CACT scores (18), asthma exacerbation, hospitalizations for asthma exacerbation, steroid use, FeNO, acute care visits, FEV1%, FVC%, FEV1: FVC ratio, serious adverse events, and vitamin D levels; and (4) study design: RCT.

Data Extraction

Two investigators independently screened the information and compiled it into a table. The third researcher had no disagreements in this process. The following data were extracted: name of the first author, year of publication, study country, participants' basic characteristics (age, intervention, number, baseline data), asthma control parameters (CACT scores, asthma exacerbation, hospitalizations for asthma exacerbation, acute care visits, steroid use and FeNO), lung function parameters (FEV1%, FVC%, the FEV1: FVC ratio), safety (AEs), and vitamin D levels.

Quality Assessment

The 5-point Jadad scale (19) was applied to evaluate the quality of the RCTs. The scale includes three questions about randomization, masking and the accountability of the trial. Each question was scored, and if the sum of the final score was more than three points, the article was considered high-quality.

Statistical Analysis

The final statistical analysis of the data was performed using Review Manager 5.4 software and STATA 15.0 software. The MD and 95% confidence intervals (CIs) were used to assess FEV1%, FEV1%, the FEV1: FVC ratio, CACT scores, vitamin D levels (if the MD was > 0, the factor was considered beneficial to the vitamin D group, while an MD < 0 indicated that the factor indicated that the factor was beneficial to the placebo group), and FeNO (if the MD was < 0, the factor was considered beneficial to the vitamin D group, while an MD > 0 indicated that the factor indicated that the factor was beneficial to the placebo group). RRs with 95% CIs were used to analyze asthma exacerbation, hospitalizations for asthma exacerbation, adverse events, acute care visits, and steroid use (if the RR was < 1, the factor was considered beneficial to the vitamin D group, while an RR > 1 indicated that the factor was beneficial to the placebo group). If $I^2 > 50\%$, the results were considered to have heterogeneity, and the random effects model was employed; when I^2 was $<50\%$, the results were considered to have no low heterogeneity, and a fixed effects model was employed. We also employed Egger's test

Abbreviations: AEs, adverse effects; CACT, childhood asthma control test; CI, confidence interval; FeNO, fractional exhaled nitric oxide; FEV1%, predicted percentage of forced expiratory volume in first second; FVC%, percentage of predicted forced vital capacity; GINA, the Global Initiative for Asthma; GRADE, The Grading of Recommendations Assessment, Development, and Evaluation; ICS, include inhaled corticosteroids; MD, Mean Difference; PRISMA, Preferred Reporting Items for Systematic Review and Meta-Analysis; RCT, randomized controlled trial; RR, Risk Ratio.

and Begg's test to quantify the funnel chart and obtain a *p* value to determine whether publication bias was present. When the *P* value was lower than 0.05, it was considered statistically significant.

RESULTS

Search Results and Study Quality Assessment

The initial searched yielded 4,577 articles. A total of 1,078 duplicate studies were deleted. After title and abstract screening, 34 potentially relevant studies remained. After reading the full texts of these studies, eight RCTs involving 738 children (376 children took vitamin D and 362 took placebos) were included in our meta-analysis (**Figure 1**) (16, 17, 20–25). Among the 8 RCTs, seven studies were considered to be high-quality [six had scores of 5 points (17, 21–25) and one had a score of 4 points (20) on the Jadad scale], and one study (16) was considered to be medium-quality (3 points on the Jadad scale) (**Supplementary Table S3**). The geographical distribution of studies was relatively wide, with four studies in Asia (17, 20, 21, 25) and four in North America (16, 22–24). More details on the included RCTs, including baseline characteristics and main outcome indicators, are shown in **Table 1**.

Two reviewers assessed the quality of the 8 studies based on the Cochrane Handbook (26). The handbook clarified that the risk of bias in RCTs needs to be assessed by examining following criteria: random sequence generation, allocation concealment, blinding of the participants and personnel, blinding of the outcome assessment, incomplete outcome data, selective reporting, and other bias (**Supplementary Figure S1**). Six studies (17, 21–25) described random sequence generation and were regarded as having a low risk of bias, but two studies (16, 20) had an unclear risk of bias because of a lack of description. Seven studies (17, 20–25) described the allocation concealment

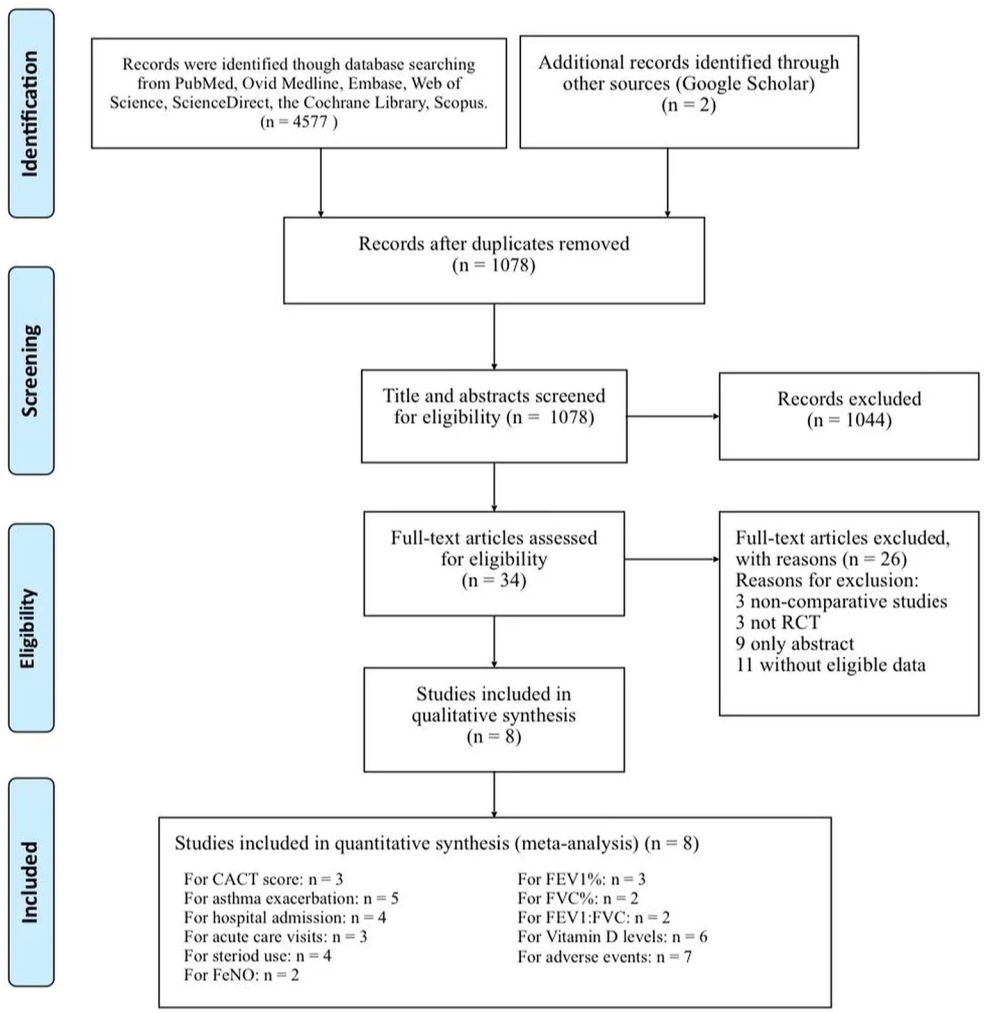

FIGURE 1 | Flow chart of study selection.

TABLE 1 | Summary of the baseline characteristics of the included studies.

Study		Country	Period (year)	Groups	Patients	Sex (M/F)	Age (Mean, year)	Duration	Oral dose	Baseline characteristics					Quality (score)	Follow up
										Vitamin D levels	CACT (score)	Lung fuction (%)				
											FEV1%	FVC%	FEV1:FVC			
2021	Thakur (25)	India	2018.07–2019.11	Vitamin D	30	16/14	9.0	12 weeks	2,000 IU/day	15.8 ±8.2	18.0 ± 2.9	75.3 ± 26.5	NA	NA	5	3 months
				Placebo	30	18/12	8.7			16.5 ± 9.9	15.5 ± 2.7	75.6 ± 15.7				
2021	Jat (17)	India	2017.05–2019.08	Vitamin D	125	89/36	8.2	9 months	1,000 IU/day	11.6 ± 4.6	21.7 ± 4.2	92.5 ± 21.7	92.7 ± 21.7	98.5 ± 10.9	5	9 months
				Placebo	125	91/34	7.8			10.8 ± 4.4	21.9 ± 3.6	97.0 ± 17.5	94.6 ± 17	99.3 ± 10.1		
2020	Forno (24)	USA	2016.02–2019.03	Vitamin D	96	52/44	9.9	48 weeks	4,000 IU/day	22.5 ± 4.6	22.0 ± 3.2	93.9 ± 15.8	NA	91.5 ± 9.3	5	48 weeks
				Placebo	96	63/33	9.7			22.8 ± 4.6	21.3 ± 3.6	90.6 ± 17.3		89.6 ± 10.1		
2019	Ducharme (23)	Canada	2014.09–2015.11	Vitamin D	23	16/7	2.9	0, 3.5 months	100,000 IU at baseline and 3.5 months	28.5 ± 5.8	NA	NA	NA	NA	5	7 months
				Placebo	24	14/10	2.9			29.4 ± 11.1						
2016	Tachimoto (21)	Japan	2010.10–2013.04	Vitamin D	54	28/26	10.0	2 months	800 IU/day	28.1 ± 7.6	25.0 ± 3.0	87.2 ± 6.1	98.1 ± 11.4	87.6 ± 5.3	5	6 months
				Placebo	35	22/13	9.8			29.7 ± 7.7	26.0 ± 1.5	87.1 ± 5.4	96.6 ± 11.6	86.4 ± 7.0		
2016	Kerley (16)	Ireland	2013.11–2014.04	Vitamin D	17	11/6	10	15 weeks	2,000 IU/day	20.45 ± 7.43	19.0 ± 3.2	105.0 ± 16.3	94.1 ± 11.3	94.2 ± 8.9	3	15 weeks
				Placebo	22	13/9	7			20.45 ± 8.92	16.7 ± 3.7	96.0 ± 10.37	91.6 ± 9.5	93.3 ± 6.3		
2016	Jenson (22)	Canada	2013.11–2014.08	Vitamin D	11	4/7	2.2	6 months	100 000 IU bolus then 400 IU/day	24.8 ± 2.5	NA	NA	NA	NA	5	6 months
				Placebo	11	3/8	3.1		400 IU vitamin D / day	27.2 ± 2.5						
2015	Bar (20)	Israel	unclear	Vitamin D	20	12/8	13.5	6 weeks	14,000 IU/week	20.8 ± 6.5	NA	NA	NA	NA	4	6 weeks
				Placebo	18	13/6	12.4			20.0 ± 7.1						

CACT, childhood asthma control test; Data are mean (±SD); FEV1%, predicted percentage of forced expiratory volume in first second; FVC%, percentage of predicted forced vital capacity; IU, international unit; M/F, male/female; NA, not available.

process and were regarded as having a low risk of bias, and only one study (16) was considered to have an unclear risk of bias. In the domain of blinding of participants and personnel and outcome assessment, all studies described blinding assignments, researchers, and patients. Thus, all the studies were regarded as having a low risk of bias. For incomplete outcome data, two (21, 23) had an unclear risk of bias because of the lack of outcome data. For the domain of selective reporting and other biases, all the studies were regarding as having a low risk of bias. Disagreements between the two reviewers were resolved *via* discussion or by consulting a third researcher.

In addition, to evaluate the quality of evidence for each terminal, we adopted the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system (27). This system divided the quality of evidence into four levels by evaluating the risk of bias, inconsistency, indirectness, imprecision, and publication bias. **Supplementary Table S4** summarizes the statistical results and the quality of evidence. We assessed the quality of all outcome measures, and the associated qualities of evidence were rated as very low or low. Consequently, the results should be interpreted cautiously.

Vitamin D Levels

Six studies reported vitamin D levels (heterogeneity: $p < 0.00001$, $I^2 = 98\%$). The vitamin D levels of both groups improved compared with the baseline, and the vitamin D group had a stronger effect [MD = 13.51 (4.24, 22.79), $p = 0.004$; **Figure 2**].

Asthma Control

We evaluated asthma control between the two groups by examining CACT scores (18), FeNO, asthma exacerbation, hospitalizations for asthma exacerbation, acute care visits and steroid use.

The included studies did not provide a clear definition of asthma exacerbation. Therefore, variable definitions reported in major publications were utilized in our meta-analysis. It is defined as increased symptoms of shortness of breath, cough, wheezing or chest tightness, and a progressive decline in lung function or the need for a change in treatment.

Three studies reported CACT scores ($p = 0.85$, $I^2 = 0\%$). The CACT scores improved in both groups compared to the baseline data, but no significant difference was found between the groups [MD = 0.15 (−0.43, 0.74), $p = 0.61$; **Figure 3A**].

Two studies reported FeNO ($p = 0.08$, $I^2 = 68\%$). FeNO was reduced in both groups compared to the baseline data, but no significant difference was found between the groups [MD = −3.95 (−22.87, 14.97), $p = 0.68$; **Figure 3B**].

Four studies reported asthma exacerbation ($p = 0.39$, $I^2 = 1\%$). The pooled results indicated that the results between the two groups were similar, which suggests that vitamin D is not capable of improving asthma exacerbation [RR = 0.92 (0.68, 1.25), $p = 0.60$; **Figure 3C**].

Four studies reported hospitalizations for asthma exacerbation ($p = 0.67$, $I^2 = 0\%$). The pooled results indicated that vitamin D did not improve the rate of hospitalizations for asthma exacerbation [RR = 1.20 (0.48, 2.96), $p = 0.70$; **Figure 3D**].

Three studies reported acute care visits ($p = 0.30$, $I^2 = 7\%$). The pooled results indicated that vitamin D did not improve the rate of acute care visits [RR = 1.13 (0.77, 1.65), $p = 0.53$; **Figure 3E**].

Four studies reported steroid use ($p = 0.13$, $I^2 = 56\%$). The pooled results indicated that vitamin D did not improve the rate of steroid use [RR = 1.03 (0.41, 2.57), $p = 0.95$; **Figure 3F**].

Lung Function

We evaluated lung function by examining FEV1%, FVC%, and the FEV1: FVC ratio between the two groups.

FEV1%, FVC% and the FEV1: FVC ratio are all indicators of ventilation function, which decreases when asthma attacks occur. FEV1% < 80% and FEV1: FVC% < 70% are extremely important indicators of airflow restriction. These coincident indicators may gradually recover during remission.

Three studies reported FEV1% (heterogeneity: $p = 0.60$, $I^2 = 0\%$). The pooled results showed that the influence of placebos on FEV1% was stronger than that of vitamin D [MD = −4.77 (−9.35, −0.19), $p = 0.04$; **Figure 4A**].

Two studies reported FVC% ($p = 0.58$, $I^2 = 0\%$). The pooled results showed that the influence of placebos on FVC% was stronger than that of vitamin D [MD = −5.01 (−9.99, −0.02), $p = 0.05$; **Figure 4B**].

Two studies reported the FEV1: FVC ratio ($p = 0.74$, $I^2 = 0\%$). The pooled results indicated no relevance between vitamin D supplementation and the FEV1: FVC ratio [MD = −0.86 (−3.52, 1.79), $p = 0.52$; **Figure 4C**].

Safety

We evaluated safety in the form of serious adverse events between the two groups.

Four studies reported serious adverse events ($p = 0.55$, $I^2 = 0\%$). The analysis results of the two groups were similar [RR = −0.86 (−3.52, 1.79), $p = 0.99$; **Supplementary Figure S2**].

We conducted a subgroup analysis of AEs and compiled them into a table (**Table 2**). The summary results indicated that no significant difference was found in AEs.

Subgroup Analysis

To determine whether the duration of vitamin D supplementation affected the results, we performed a subgroup analysis of CACT scores (**Supplementary Figure S3A**), asthma exacerbation (**Supplementary Figure S3B**) and FEV1% (**Supplementary Figure S3C**) by dividing the duration into <6 months and >6 months. Subgroup analysis revealed no significant differences in CACT scores, FEV1% or asthma exacerbation between the vitamin D and placebo groups.

Sensitivity Analysis

The pooled results showed that vitamin D levels had high heterogeneity ($I^2 > 50\%$). Therefore, we conducted a sensitivity analysis of vitamin D levels and FEV1%, which is the lung function index. To explore the stability and sensitivity of the outcomes, we assessed the influence of each study on the aggregated results, which indicated that the results regarding

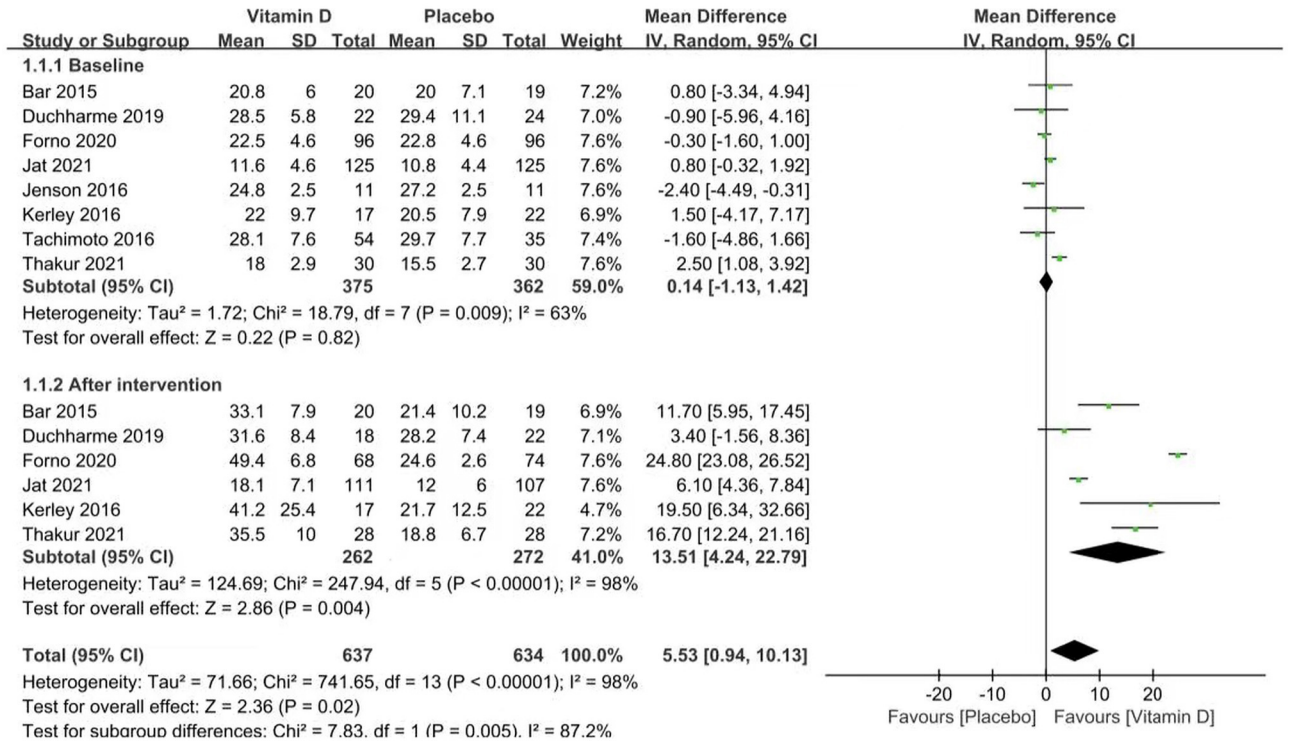

FIGURE 2 | Forest plots of MD of vitamin D levels associated with vitamin D vs. placebo.

vitamin D levels (**Supplementary Figure S4A**) and FEV1% (**Supplementary Figure S4B**) were stable and reliable.

Publication Bias

Latent publication bias was not found in vitamin D levels (Egger's test: $p = 0.408$; Begg's test: $p = 0.260$) and FEV1% (Egger's test: $p = 0.576$; Begg's test: $p = 0.296$). The specific analysis is shown in **Supplementary Figures S5A,S5B**.

DISCUSSION

In recent years, the global prevalence of asthma in children has been increasing, and this fact has increasingly attracted the attention of researchers. (1, 2, 28). Whether vitamin D can be employed clinically to control childhood asthma remains to be verified due to inconsistent findings (12–17). Through the analysis of 8 high-quality RCTs (16, 17, 20–25), we directly compared the influences of vitamin D and placebos on the treatment for childhood asthma, and this is the first meta-analysis based on RCTs exploring the effects and safety of vitamin D supplementation on childhood asthma. Our meta-analysis provides the latest clinical evidence that vitamin D supplementation can significantly enhance serum vitamin D levels, which fails to improve asthma control for pediatric patients. However, vitamin D supplementation may reduce patients' lung function. Regarding vitamin D toxicity, the pooled outcomes showed similar results between the two groups in the form of AEs.

Compared with the placebos, vitamin D affected serum vitamin D levels in a stronger way. However, almost all the included outcome measures did not show favorable changes in asthma control. Four studies proposed definitions of asthma exacerbation (23, 24, 26, 27). The CACT is a validated scale (18) that includes seven questions, and scores on the scale range from 0 to 27. A score > 19 indicates good symptom control, and higher scores indicate better symptom control. Elevated FeNO levels are found in atopic and allergic patients and are associated with airway hyper reactivity and sputum eosinophils (29). This suggests that if vitamin D supplementation does reduce inflammation, FeNO levels in the vitamin D group would be expected to decrease. However, it was observed that there were no changes between the groups in the aspect of CACT scores and FeNO levels. Among the included studies, only one showed favorable results on asthma control after the intervention (23). In contrast, a study in India (30) also found that vitamin D intervention could shorten the severity of asthma attacks for children. The curative effect of vitamin D in improving lung function as well as controlling asthma remains highly controversial. The disagreement may be due to the limited effectiveness of the intervention for children with sufficient vitamin D levels. In many current studies, clinical heterogeneity, small sample sizes or other inaccurate factors still exist, which can all lead to inaccurate analysis results.

Our meta-analysis results indicated that vitamin D intervention has a certain adverse effect on lung function,

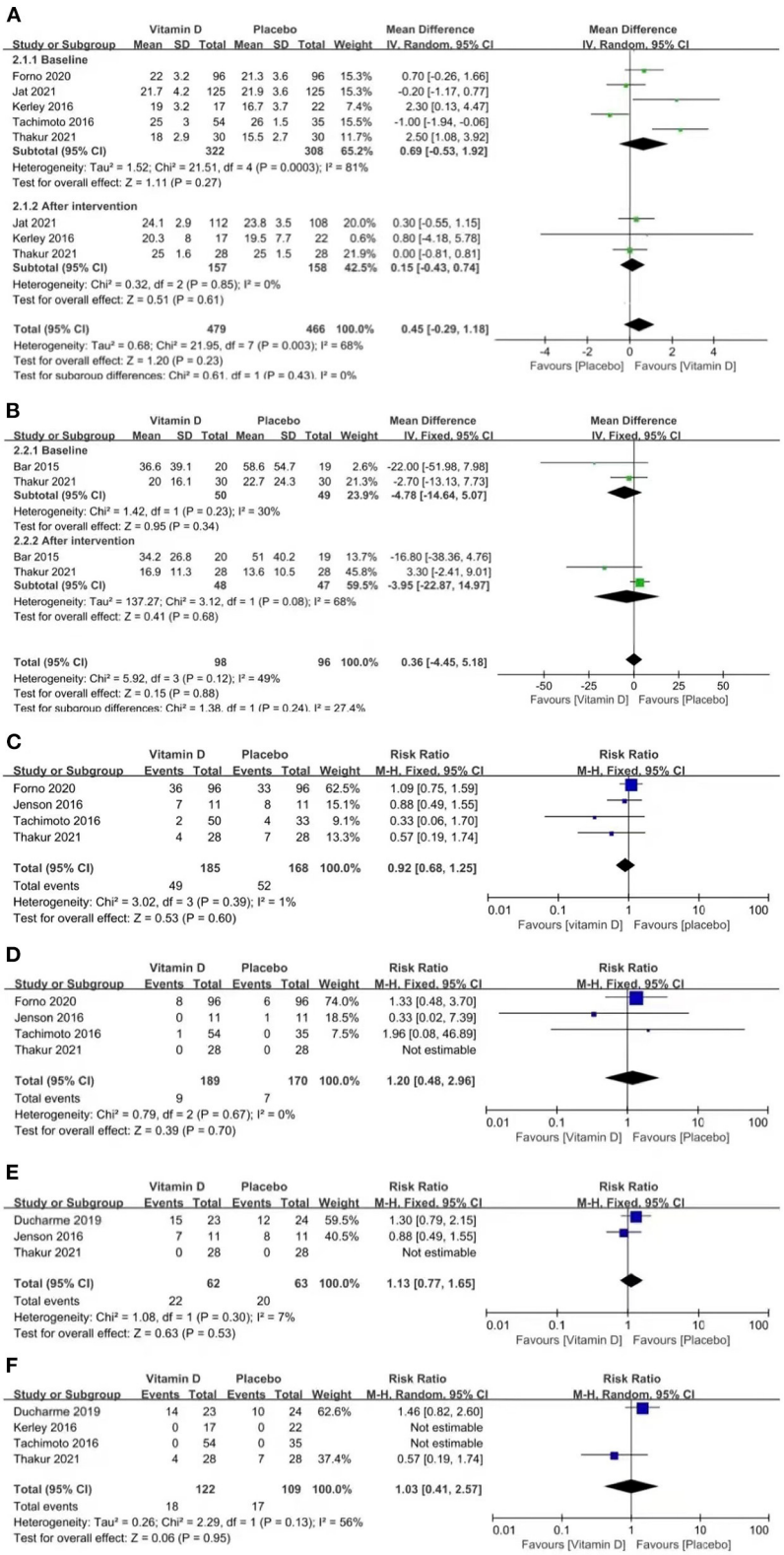

FIGURE 3 | Forest plots of MD of CACT scores **(A)** and FeNO **(B)**, and RR of asthma exacerbation **(C)**, hospitalizations for asthma exacerbation **(D)**, acute care visits **(E),** and steroid use **(F)** associated with vitamin D vs. placebo.

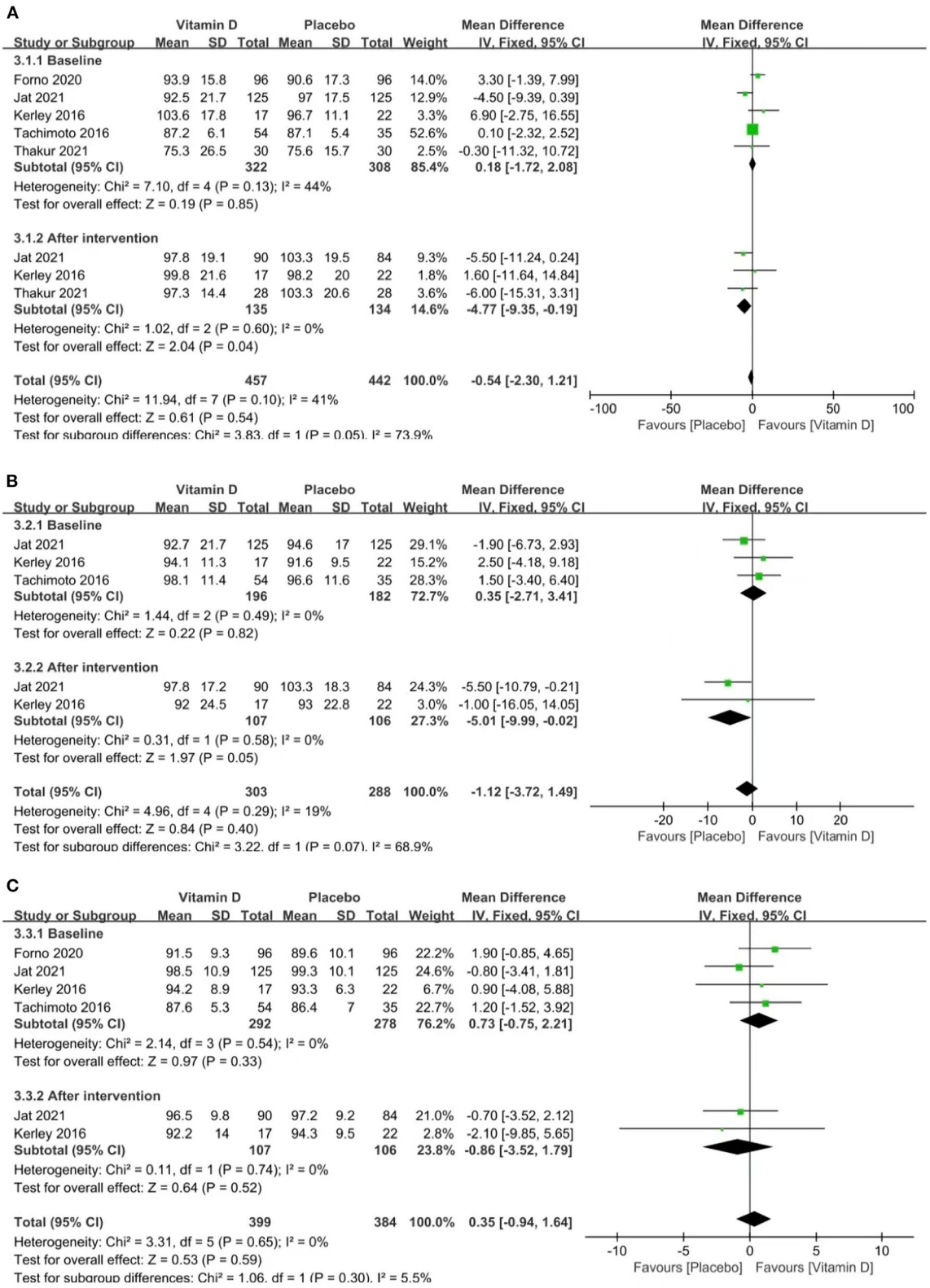

FIGURE 4 | Forest plots MD of FEV1% **(A)**, FVC% **(B)**, and FEV1: FVC **(C)** associated with vitamin D vs. placebo.

TABLE 2 | Adverse effects (all grade) associated with vitamin D vs. placebo.

Adverse effects	Vitamin D group (event/total)	Placebo group (event/total)	RR (95% CI)	*P* value	Heterogeneity	
					I^2 (%)	*P* value
Hypercalciuria	5/62	9/63	0.58 [0.22, 1.53]	0.27	0	0.65
Blood and lymphatic system disorders	5/119	1/120	3.76 [0.64, 22.11]	0.14	0	0.80
Infection	19/23	17/24	1.17 [0.85, 1.60]	0.34	Not applicable	
General disorders	13/23	17/24	0.80 [0.51, 1.24]	0.32	Not applicable	
Investigations	7/23	9/24	0.81 [0.36, 1.82]	0.61	Not applicable	
Nausea	7/249	8/249	0.82 [0.53, 1.27]	0.38	Not applicable	
Constipation	11/249	12/249	0.92 [0.42, 2.00]	0.83	Not applicable	
Vomiting	28/249	34/249	0.82 [0.53, 1.27]	0.38	Not applicable	
Pain abdomen	41/249	40/249	1.02 [0.72, 1.47]	0.89	Not applicable	
Headache	25/153	25/153	1.00 [0.61, 1.64]	1.00	Not applicable	
Ear and labyrinth disorders	0/23	2/24	0.21 [0.01, 4.12]	0.30	Not applicable	
Eye disorders	0/23	1/24	0.35 [0.01, 8.11]	0.51	Not applicable	
Gastrointestinal disorders	3/23	8/24	0.39 [0.12, 1.30]	0.12	Not applicable	
Immune system disorders	2/23	5/24	0.42 [0.09, 1.94]	0.27	Not applicable	
Musculoskeletal disorders	0/23	1/24	0.35 [0.01, 8.11]	0.51	Not applicable	
Nervous system disorders	1/23	1/24	1.04 [0.07, 15.72]	0.98	Not applicable	
Altered sensorium	1/125	0/125	3.00 [0.12, 72.94]	0.50	Not applicable	
Seizures	0/125	1/125	0.33 [0.01, 8.10]	0.50	Not applicable	
Reproductive system and breast disorders	1/23	0/24	3.13 [0.13, 73.01]	0.48	Not applicable	
Respiratory, thoracic and mediastinal disorders	4/23	7/24	0.60 [0.20, 1.77]	0.35	Not applicable	
Skin and subcutaneous tissue disorders	7/23	4/24	1.83 [0.62, 5.42]	0.28	Not applicable	
Surgical and medical procedure	1/23	1/24	1.04 [0.07, 15.72]	0.98	Not applicable	

CI, confidence interval; RR, Risk Ratio.

although many observational studies have described the beneficial aspects of vitamin D interventions on lung function (13–15). Contrary to our conclusion, both groups showed improvement in FEV1 and FVC% after vitamin D supplementation, but the influence on the placebo group was more stronger than that on the vitamin D group. We further analyzed the baseline data of FEV1 and FVC% from both groups, and there was no significant change between them. This may be due to high vitamin D levels having a negative impact on lung function. Some studies have also found that vitamin D interventions had no other advantageous changes (16, 31). One possible explanation for the adverse effect of vitamin D on asthmatic children is their high baseline levels, which may leave little room for improvements in lung function. As the latent adverse effects of vitamin D on children's lung function remain to be further explored, physicians must be cautious in the use of vitamin D for asthmatic children.

Vitamin D toxicity remains a problem and is characterized by severe hypercalcemia (32). In our analysis, we found that the rates of AEs between the two groups of children taking vitamin D and placebos were not significantly different. The data from the pooled results verified the safety of vitamin D at therapeutic doses for asthmatic children. This conclusion was consistent with the results reported by other studies (17, 27).

We recognize that there were still many limitations to this analysis. First, we only included eight RCTS, and the limited sample size of pediatric patients included in the analysis may affect the quality of the outcomes. Second, although the outcomes of the analysis showed the number and severity of asthma exacerbations were similar between the two groups, there were discrepancies in the definition of asthma exacerbation in the included trials, which also made the results less reliable. Third, the doses and durations of intervention in the studies were not the same. The optimal duration and dose of vitamin D needed to effectively control asthma symptoms are still unclear. Fourth, the phenotypes of asthma included in the study varied, which also might lead to study heterogeneity and weaken the quality of the results. It must be pointed out that the influence of vitamin D on asthma control may also be affected by genetic differences in vitamin D metabolic pathways (33). However, the influence of genetic factors was not evaluated in our meta-analysis. Because of the above deficiencies, additional larger, rigorously designed RCTs are still needed to further explore the possible benefits of vitamin D for childhood asthma therapy.

In conclusion, vitamin D supplementation affected the serum vitamin D levels of asthmatic children significantly, but failed to improve their asthma control. Vitamin D supplementation might even reduce patients' lung function. The rate of AEs was similar between the children taking vitamin D and those taking placebos,

so it was generally believed that taking vitamin D was safe. Due to the limitations of the study, it is essential to perform more large-scale, rigorous and well-designed RCTs to fully confirm this conclusion.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

Full access to all of the data in the manuscript, takes responsibility for the integrity of the data, and the accuracy of the data analysis: MH and WZ. Drafting of the manuscript: MH, RX, NL, and ML. Critical revision of the manuscript for important intellectual content: MH and WZ. Statistical analysis and supervision: MH, JX, and WZ. Concept and design, acquisition, analysis, or interpretation of data: All authors. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2022.840617/full#supplementary-material

Supplementary Figure S1 | Risk of bias graph for included studies.

Supplementary Figure S2 | Forest plots RR of serious adverse events associated with vitamin D versus placebo.

Supplementary Figure S3 | Subgroup analysis of CACT scores, asthma exacerbation and FEV1%.

Supplementary Figure S4 | Meta-based influence analyses for vitamin D levels **(A)** and FEV1% **(B)**.

Supplementary Figure S5 | Egger's and Begg's tests for comparisons of vitamin D levels **(A)** and FEV1% **(B)**.

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REVIEW
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Severe Pediatric Asthma Therapy: Mepolizumab

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There is a growing need for advanced treatment in children with persistent and severe asthma symptoms. As a matter of fact, between 2 and 5% of asthmatic children experience repeated hospitalizations and poor quality of life despite optimized treatment with inhaled glucocorticoid plus a second controller. In this scenario, mepolizumab, a humanized monoclonal antibody, has proven to be effective in controlling eosinophil proliferation by targeting interleukin-5 (IL-5), a key mediator of eosinophil activation pathways. Mepolizumab is approved since 2015 for adults at a monthly dose of 100 mg subcutaneously and it has been approved for patients ≥ 6 years of age in 2019. Especially in children aged 6 to 11 years, mepolizumab showed a greater bioavailability, with comparable pharmacodynamics parameters as in the adult population. The recommended dose of 40 mg every 4 weeks for children aged 6 through 11 years, and 100 mg for patients ≥ 12 years provides appropriate concentration and proved similar therapeutic effects as in the adult study group. A marked reduction in eosinophil counts clinically reflects a significant improvement in asthma control as demonstrated by validated questionnaires, reduction of exacerbation rates, and the number of hospitalizations. Finally, mepolizumab provides a safety and tolerability profile similar to that observed in adults with adverse events mostly of mild or moderate severity. The most common adverse events were headache and injection-site reaction. In conclusion, mepolizumab can be considered a safe and targeted step-up therapy for severe asthma with an eosinophilic phenotype in children and adolescents.

Keywords: asthma, biologics, treatment, children, adolescents, mepolizumab, anti-interleukin-5, antibodies

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INTRODUCTION

Severe asthma is a highly heterogeneous disease due to the interaction between genetic predisposition, immune response, and environmental risk factors. This complex interaction influences the onset of symptoms, the clinical evolution, and the severity of illness (1, 2). Severe asthma affects about 0.5% of the general pediatric population and 4.5% of children with asthma (3), with a wide discrepancy between countries. Although the prevalence of severe asthma in childhood is low, it is associated with high morbidity, occasionally mortality, and significant healthcare burden (4). In addition, children with severe asthma report a poor quality of life due to persistent respiratory symptoms, recurrent life-threatening attacks, anxiety and emotional distress, missed school days, and side effects of oral corticosteroids (OCS) (5, 6).

A multidisciplinary assessment is required to exclude comorbidities and modifiable factors, confirm the diagnosis, and initiate the most appropriate treatment for these patients (7). The identification of different phenotypes and endotypes, based on cellular and molecular mechanisms and related biomarkers, may guide physicians in their therapeutic choice (8).

Recently, several innovative monoclonal antibody agents have been approved to target specific inflammatory type 2 mediators and improve uncontrolled severe asthma when added to basal treatment (9). However, it is necessary that pediatric pulmonologists are aware of the benefits and risks of these medications, as well as the practical implications of providing these options for their patients (10).

In this review, especially focused on mepolizumab, we present all current evidence on the indications, use, safety, and efficacy of this fully-humanized anti-interleukin-5 (IL-5) antibody for children with severe asthma.

SEARCH METHODS

This review is based on the most significant results from an extensive PubMed search, conducted independently by three different researchers, using the search terms: "treatment in severe pediatric asthma," "severe asthma," "mepolizumab," "anti-IL-5 therapy," "anti–IL-5 antibody," "children," "adolescents," and all different synonyms or word combinations. More relevance was given to clinical trials especially focused on mepolizumab treatment.

MANAGEMENT OF SEVERE ASTHMA IN PEDIATRICS

Definition of Severe Asthma

There is no uniformly accepted definition of severe asthma (11). Different options can be found in the scientific literature (12–15). However, international societies agree on assessing asthma severity based on the treatment level required to achieve and maintain adequate control.

According to the Global Initiative for Asthma (GINA) guidelines 2022, severe asthma isindicated by needing a high dose of ICS-LABA to maintain symptom control or uncontrolled asthma despite steps 4 and 5 of the care and management of contributory factors (12).

The European Respiratory Society and the American Thoracic Society (ERS/ATS) definitions of severe asthma require that patients have needed therapy with a high dose of ICS and a second controller, such as LABA, leukotriene modifier, or theophylline, for the previous year or have needed OCS for 50% or more of the year to prevent asthma from becoming uncontrolled or that cannot be controlled despite this therapy (13).

Step-by-Step Diagnosis

Patients that need to be moved to GINA steps 4 and 5 care have to be referred to a tertiary center for a specialist evaluation first to confirm the diagnosis and subsequently to identify the best personalized treatment (7). In the beginning, it is very important to distinguish between "difficult to treat asthma," due to modifiable factors, and true "therapy-resistant asthma," which is unresponsive to standard medications (16, 17). Although a concomitance between these two conditions cannot always be excluded, uncontrolled asthma is frequently caused by treatment-related issues such as poor adherence to medication, inadequate or inappropriate inhalation technique (18, 19), and persistent exposure to adverse environmental factors (smoke, irritants, allergens, etc.) (20)or emotional factors.

Moreover, the presence of comorbidities, including allergic conditions (rhinitis, eczema, atopic dermatitis, food or drug allergy, etc), sinus disease, gastroesophageal reflux, obesity, obstructive sleep apnea, anxiety, and depression, may reduce the response to therapy (21–23).

Finally, the exclusion of asthma-mimicking conditions (24), such as tracheobronchomalacia, bronchopulmonary dysplasia, cystic fibrosis, primary ciliary dyskinesia, immunodeficiencies, obliterative bronchiolitis, pertussis, tuberculosis, vascular rings, and foreign body in toddlers (25) and vocal cord dysfunction, exercise-induced hyperventilation, and habitual cough in children and adolescents (26), is necessary.

Once all the following steps are carried out, that is, revising treatment issues, excluduing or treating comorbidities or other differential diagnoses, and confirming that it is severe asthma, it is possible to consider add-on medications, including biologics.

Phenotype and Endotype-Guided Therapy

The introduction of biologics has revolutionized the care of severe asthma in adult and pediatric populations (27–29). Recent studies have suggested that physicians should characterize patients with severe asthma not only by their phenotype but also by their endotype before starting a biological treatment (30). This approach is in line with personalized medicine, which aims to achieve a better characterization of patients with the purpose to prescribe the most suitable treatment at an individual level (31).

The phenotype is the summation of clinical features while the endotype is determined by biomolecular mechanisms leading to the pathogenesis of the disease (32). To date, two endotypes of severe asthma have been described, based on the pathogenetic processes linked to airway inflammation: T2-low endotype and T2-high endotype (33).

The T2-low endotype is more frequent in adults and is characterized by the following: neutrophilic or paucigranulocytic inflammation, T-helper lymphocytes type 17, innate lymphoid type 3 cells, and IL-1, IL-8, IL-17, and IL-23 are the respective implied molecules (34, 35).

The T2-high endotype typically affects children and it is characterized by two specific characteristics: allergic sensitization and eosinophilia (1). Allergic asthma is the most common in childhood; it often presents an early onset, and it is associated with a family or personal history of allergic disease, a positive skin prick test, an elevated serum total IgE level, and increased fractional exhaled nitric oxide (FeNO) (36). Patients with eosinophilia and diffuse airway inflammation often are well responsive to corticosteroids (37, 38). However, a subgroup of T2-high asthma has poor control of symptoms despite corticosteroids, probably due to very high levels of type

2 inflammation. T2-high asthma constitutes 50% of mild to moderate asthma and probably a larger proportion of patients with more severe asthma (37).

In the T2-high endotype, T-helper lymphocytes type 2 signal the production of IL-4, IL-5, and IL-13, while innate lymphoid cells type 3 are activated by the epithelial alarmins TSLP, IL-33, and IL-25. Specifically, IL-4 and IL-13 promote B lymphocyte activation, inducing plasma cell formation, isotype switching to IgE, and their production. On the other hand, IL-5 induces chemoattraction, proliferation, and activation of eosinophils and also decreases their apoptosis (32).

Current research has suggested that these molecular pathways of severe asthma should guide the choice of the most adequate biologic treatment (39). The identification of biomarkers such as total IgE, peripheral eosinophil count, and FeNO, as a surrogate of mechanism generating and maintaining type 2 inflammation, helps design a personalized therapy for patients (30). In this scenario which is constantly and progressively oriented toward tailored treatments, mepolizumab might be the more indicated add-on target therapy for severe eosinophilic asthma.

MEPOLIZUMAB AS TARGET THERAPY FOR SEVERE EOSINOPHILIC ASTHMA

License and Mechanism of Action

Mepolizumab (Nucala, GlaxoSmithKline) has been approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) in patients aged 12 years and older since November 2015 and was licensed in September 2019 in patients aged 6 years and older as an add-on maintenance therapy for severe eosinophilic asthma (40, 41). Mepolizumab is a murine humanized monoclonal antibody belonging to the IgG1 kappa subclass. It binds circulating IL-5 and prevents its interaction with IL-5 receptor alfa. Mepolizumab target (i.e., IL-5) is a 134-amino acid dimeric glycoprotein with a four-helix bundle motif, which consists of a 52-kDa homodimer. Mepolizumab specifically binds to the α-chain of IL-5 with an IC_{50} of <1 nM, a dissociation constant of 4.2 pM, and stoichiometry of 2.2, so that two IL-5 dimers are cross-linked by two molecules of mepolizumab. Therefore, through this mechanism of action, mepolizumab effectively inhibits IL-5 ligation to IL-5Rα (42). As mentioned above, IL-5 is fundamental for the recruitment, activation, and survival of eosinophils.

Eligibility Criteria and Dosage

The eligibility criteria of treatment with mepolizumab for severe eosinophilic asthma in children and adolescents include blood eosinophilia $> 0.15 \times 10^9$/l in the absence of OCS treatment and $> 0.3 \times 10^9$/l in the previous year plus two or more asthma exacerbations requiring hospitalization or OCS treatment. In contrast to adults, among children with severe asthma, a smaller proportion of patients appear to have clear features of type 2 mucosal inflammation, including greater eosinophilia (43).

The recommended dosage of mepolizumab differs according to age: it is administered subcutaneously at a dose of 40 mg every 4 weeks in children aged 6–11 years and at a dose of 100 mg in children aged ≥ 12 years (40).

Safety, Adverse Effects, and Contraindications

Safety evaluations of mepolizumab have raised no significant concerns so far (44–46). The most common adverse effects (incidence ≥ 5%) of mepolizumab included headache, injection site reaction (e.g., pain, erythema, swelling, itching, and burning sensation), back pain, and fatigue (40, 41, 47).

Mepolizumab is not to be used in patients with helminth infection, and whenever found, it needs to be treated before the biological drug can be prescribed. Mepolizumab is also contraindicated in the event of a hypersensitivity reaction (40, 41).

Efficacy Data

Data about the efficacy of mepolizumab were collected from several promising clinical trials conducted on adults and children aged 12 years and older including Dose-Ranging Efficacy And Safety With Mepolizumab In Severe Asthma (DREAM) (44); Mepolizumab As Adjunctive Therapy In Patients With Severe Asthma (MENSA) (45); Steroid Reduction With Mepolizumab Study (SIRIUS) (46); and Mepolizumab Adjunctive Therapy In Subjects With Severe Eosinophilic Asthma (MUSCA) (48). Most recently, a multinational, non-randomized, open-label study was conducted on children aged 6 to 11 years by Gupta et al. (NCT02377427) (49, 50).

Asthma Control

The impact on health-related quality of life has been objectified through several validated questionnaires. The Asthma Control Questionnaires (ACQ-5 and ACQ-7) have been used in most studies (44–46, 49, 50)with a minimally clinically important difference (MCID) in total score (i.e., ≥ 0.5-point reduction from baseline) detected in half of the children in the first weeks (49) and up to 1 year of treatment (50). These results resemble those of adolescents and adults with MCID from baseline achieved from 42 to 59% of population studies (see **Table 1**). Best results were recorded around week 56, suggesting that treatment should not be discontinued before 1 year.

Another tool, the St. George's Respiratory Questionnaire (SGRQ), offers a wider perspective on treatment effectiveness and shows confirmed clinical improvement in all the domains (i.e., symptoms, activity, and impact) after 6 months of therapy compared to the placebo group (48). It is noteworthy that, despite a reduction in exacerbations risk in all the cited studies (see next paragraph), a clear subjective improvement has not always been reported as well (44).

Exacerbation Rate

Although the clinical experience with mepolizumab in pediatric asthma is often heterogeneous and with high rates of treatment discontinuation (51), this drug seems most effective in reducing exacerbations. A total of 10 children (28%) reported an exacerbation and more specifically only three patients had two exacerbations during the first 12 weeks of treatment (49).

TABLE 1 | Minimally clinically important difference (MCID) in children and adults/adolescents at end of treatment.

MCID at end of treatment				
Study population	**Study size *(N)***	**Study duration *(Wks)***	**Placebo *N (%)***	**Treatment group *N (%)***
Children				
Gupta et al. (50)	30	52	–	17/29 (59)
Adults/adolescents				
Pavord et al. (44) (DREAM)	616	52	77/153 (50)	222/452 (49)
Ortega et al. (45) (MENSA)	576	32	85/186 (46)	202/373 (54)
Bel et al. (46) (SIRIUS)	135	24	19/66 (29)	29/69 (42)
Chupp et al. (48) (MUSCA)	551	24	116/276 (42)	161/274 (59)

N, absolute numbers; Wks, weeks.

Another recently published case report showed improvement in asthma exacerbations in two children with eosinophilic nonallergic asthma treated with mepolizumab for 2 years (52). When compared to adolescents and adults, pediatric exacerbation rates were similar (53). As previously stated, a dissociation between clinical efficacy and symptoms has been noted since the first studies. We assume that the main effect of mepolizumab (i.e., reduction in blood eosinophils with modulation of eosinophilic airway inflammation) has more impact on exacerbations than asthma control perception. Thus, exacerbation risk and daily symptoms could be distinct features in patients with severe asthma.

Lung Function

Most studies detected a moderate effect on pulmonary function tests and only a few studies showed a significant improvement in forced expiratory volume during the first second (FEV_1) compared to the placebo group (45, 48). As a matter of fact, a clear pattern of FEV_1 changes from baseline has not been detected in children (49, 50). However, pediatric data are lacking and no studies including a placebo group are available. Baseline blood eosinophils diminish in 97% of patients treated with mepolizumab, but higher levels of blood eosinophils have not been defined as predictive factors for treatment response (54). The best response in terms of FEV_1 improvement has been highlighted in patients with higher baseline sputum eosinophils (55). It can be hypothesized that patients with diffused airway eosinophilic inflammation present with worse baseline lung function. In this scenario, mepolizumab has a double rationale, targeting both local and systemic eosinophils.

Data are summarized in **Table 2**.

Recommendation on Discontinuation and Predictor Response Criteria

There is no validated recommendation on mepolizumab discontinuation, and GINA guidelines 2022 suggest an initial trial of at least 4 months (12). The National Institute for Health and Care Excellence (NICE) guidelines suggest reevaluating patients after 12 months and continuing the treatment if exacerbations have been reduced by $\geq$ 50% (56). However, several studies have reported that patients who discontinued mepolizumab showed an increase in Asthma Control Questionnaire-5 (ACQ-5) score, asthmatic attacks rate, and peripheral eosinophilia (57).

Currently, there are no standardized response criteria for mepolizumab. Blood eosinophil count and the increase in lung function are considered the main parameters of therapy response. Moreover, the improvement of quality of life and physical fitness and the reduction of exacerbations have also been reported as clinical predictor tools to evaluate treatment benefit (54, 58).

The most recent GINA guidelines published in 2022 suggested the following potential predictors of good response to anti-IL5 treatment: (1) higher blood eosinophils, (2) higher number of severe exacerbations in the previous year, (3) adult-onset asthma, (4) adult-onset asthma, (5) nasal polyposis, (6) maintenance oral corticosteroids, and (7) low lung function.

Other Indications in Children or Adolescents

To date, mepolizumab is also approved for the treatment of pediatric patients aged $\geq$12 years with hypereosinophilic syndrome (HES) at a dose of 300 mg every 4 weeks. The recommended patient population includes those with $\geq$ 6 month duration of HES without an identifiable non-hematologic secondary cause (40, 41).

CONCLUSIONS

From a clinical point of view, the main purpose of asthma treatment is to reduce symptoms and the recurrence of exacerbations. Mepolizumab proves its efficacy in the specific phenotype of asthmatic patients with intense eosinophilic airway inflammation and recurrent exacerbations. As often stated in children, we believe that FEV_1 is not the most appropriate marker to detect mepolizumab's beneficial effects. Due to its capacity to target specific inflammatory type 2 mediators, mepolizumab represents a milestone in the application of personalized medicine. The prescription of mepolizumab for the treatment of severe asthma has expanded rapidly and this drug, currently used in adults, has also been registered for children, despite most of the scientific evidence in literature coming from adults. More data on efficacy in pediatric patients would be

TABLE 2 | Available studies on mepolizumab in adults, adolescents and children with summarized the main outcomes and results.

Study characteristics			Outcomes			
Reference	**Population (severe asthmatics)**	**Intervention**	**Asthma control**	**Exacerbation rate**	**Lung function (FEV_1)**	**Main outcome**
Pavord et al. (44) (DREAM)	616 adults and adolescents, 12–74 years	Mepo IV every 4-week x 52 weeks at 75, 250, or 750 mg vs placebo.	AQLQ and ACQ scores *did not differ* significantly between groups.	Mepo *significantly reduced the rate of exacerbations* vs placebo: 75 mg reduced the number of severe exacerbations/patient/year by 48%, 250 mg by 39% and 750 mg by 52%.	FEV_1 *did not differ* significantly from placebo.	A tenfold lower dose of Mepo was equally effective in reducing asthma exacerbations.
Ortega et al. (45) (MENSA)	576 adults and adolescents, 12–82 years	Mepo IV or SC every 4-weeks x 32 week at 75 or 100 mg vs placebo	ACQ score *showed a significant improvement* in the treatment groups.	Mepo *significantly reduced the rate of exacerbations* vs placebo: exacerbations necessitating an emergency department visit or hospitalization were reduced by 32% in the group receiving IV M. and by 61% in the group receiving SC M.	FEV_1 *presented a significant increase* from baseline before/post bronchodilation in IV Mepo (+100/146 ml) and in the SC Mepo (+98/138 ml) vs placebo.	Mepo administered either IV or SC reduced asthma exacerbations.
Bel et al. (46) (SIRIUS)	135 adults and adolescents, 16–74 years	Mepo 100 mg SC every 4-weeks x 20-week vs placebo.	ACQ score *showed a significant improvement* of 0.52 points in the treatment group.	Mepo *significantly reduced the rate of exacerbations* of 32% vs placebo.	FEV_1 *presented a non-significant trend* from baseline before and after bronchodilation in the Mepo group than in the placebo group.	Mepo had a significant glucocorticoid-sparing effect, with a median % reduction in the glucocorticoid dose of 50% in the Mepo group, with no reduction observed in the placebo group.
Chupp et al. (48) (MUSCA)	551 adults and adolescents, >12 years	Mepo 100 mg SC every 4-weeks x 24-week vs placebo.	SGRQ score *showed a significant improvement* from baseline.	Mepo *significantly reduced the rate of exacerbations* and emergency-room visits of 58% vs placebo. The annual rate of exacerbations requiring admission did not differ between groups.	Pre-bronchodilator FEV_1 values *presented a significant improvement* vs placebo.	Mepo was associated with significant improvement in health-related quality of life in the treatment group vs placebo.
Gupta et al. (49)	36 children, 6–11 years	Mepo 40 mg (<40 kg) or 100 mg (≥40 kg) SC every 4-weeks for 12 weeks compared to severe asthmatics adults.	ACQ score *showed a trend* toward improved asthma control.	Ten (28%) children reported ≥1 on-treatment exacerbation with a total of 13 events. Four children (all in the 40 mg dose group) required an on-treatment hospitalization or ER visit.	There was *no clear pattern* of change in FEV_1 from baseline.	Mepo SC 40 or 100 mg showed a positive clinical profile in children 6–11 years providing bodyweight-adjusted drug exposure within twofold of target adult exposure.

AQLQ, Asthma Quality of Life Questionnaire; ACQ, Asthma Control Questionnaire; FEV_1, forced expiratory volume during the first second; Mepo, Mepolizumab; SC, subcutaneous; SGRQ, St. George's Respiratory Questionnaire; IV, intravenous.

necessary to confirm its promising effects. Further clinical trials in the pediatric population are also important to prove long-term safety and the impact of this medication on the natural history of the disease. Finally, the identification of new biomarkers could be useful to predict real benefits from therapy with mepolizumab and to establish its optimal duration.

AUTHOR CONTRIBUTIONS

RC and NU discussed the writing project. RC, NU, FPe, and OF wrote the manuscript with significant support from FPo, EP, and AO. NU and RC supervised the final manuscript. All authors contributed to the article and approved the submitted version.

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Frontiers Review: Severe Asthma in Adolescents

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Asthma remains the most prevalent chronic respiratory disease of childhood. Severe asthma accounts for a minority group of patients but with substantial morbidity burden. It may reflect disease which is resistant to treatment or that which is difficult to treat, or a combination of both. The adolescent patient cohort denote a unique group and are the focus of this review. This group of patients embody transitioning priorities and evolving health beliefs, all of which may influence the management and burden of disease. Factors of importance include the influence of physiological parameters such as sex and race, which have confer implications for medical management and non-physiological factors, such as adherence, risk-taking behavior, and vaping. The holistic approach to management of severe asthma within this group of patients must acknowledge the evolving patient independence and desire for autonomy and strive for a collaborative, patient tailored approach. This review will focus on the factors that may pose a challenge to the management of severe adolescent asthma whilst offering suggestions for changes in practice that might harness patient priorities and shared clinical decision-making.

Keywords: severe childhood asthma, severe adolescent asthma, holistic management, transition, collaborative working

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INTRODUCTION

Asthma is the most prevalent chronic lung disease of childhood (1). Most children with asthma achieve good symptom control with low-moderate dose inhaled corticosteroids (ICS). However, a small group with severe disease and poor control despite maximal treatment need further escalation in support and intervention.

The European Respiratory Society (ERS) /American Thoracic Society (ATS) defines *severe asthma* in those over 6 years of age, as that which obligates treatment with high dose ICS and another maintenance agent, or use of systemic steroids, for more than half of the previous year to achieve control (2).

Along with high treatment burden, severe asthma confers significant morbidity and mortality. Within pediatrics, the National Review of Asthma deaths in the UK revealed that mortality in this population remains alarmingly high (3). Asthma control may be rendered difficult due to a variety of factors that demand recognition (4, 5), particularly within the adolescent group (6).

THE ADOLESCENT WITH SEVERE ASTHMA

The World Health Organization (WHO) defines *adolescence* to be within the ages of 10 and 19 years (7) whilst others propose a more extended length of 10–24 years a more accurate representation (8).

Certainly, adolescence embodies young adulthood and a challenging time of transition, marked by the pursuit for independence (9) and autonomy with transformations in social, emotional, and physical domains (10). Ownership of health and self-care sharpens into focus, becoming a greater priority.

Marked differences can exist in the manifestation, exacerbating factors, and management strategies for asthma at different age groups (11). Furthermore, challenges in management lay bare the influence of disparities in socio-economic status, education, exposure to pollution and healthcare access, categories recognized by the Global Initiative for Asthma as obstacles to decreasing the disease burden (12). Ethnic differences in asthma outcomes have also been postulated, with implications for biologics and therapeutic possibilities (13). A study in pediatric minority populations revealed that higher IgE levels were significantly associated with severe asthma, poor control, and exacerbations in the Puerto Rican group whilst none of these outcomes were observed in Mexican Americans. Furthermore, eosinophilic asthma had links with greater asthma severity and exacerbations in the Puerto Rican group, inferring that eosinophil-targeting therapies may confer an advantage in this group (13). Additionally, influence of sex differences are documented, with notable reference to symptomology within the adolescent period (6). A shift in higher prevalence from males to females during the pubertal period is recognized, with greater occurrence of wheeze and more severe asthma in females (6). In an European Community Respiratory Health Survey study of adult female population, lower lung function and higher likelihood of asthma were observed in those with early menarche, implicating hormonal factors (14). Furthermore, asthma in pregnancy has been linked with obstetric complications (15), which may have significant implications for our female cohort of patients. Therefore, as our patients transition to young adults, the growing relevance of such findings should be considered.

This review will explore the multifaceted parameters that bear significance to the management of severe asthma in the adolescent group.

CONFIRMING THE DIAGNOSIS

The Diagnostic Label

The WHO categorizes severe asthma into three groups; (1) inadequately treated (2) that which is difficult-to-treat and (3) severe treatment-resistant asthma (STRA), the last of which represents asthma for which the highest level of management is necessitated to achieve control, or which does not despite this (16).

A crucial initial step is in ensuring the diagnostic labeling is accurate and should begin with addressing the basics. A multidisciplinary approach is paramount (5) in diagnosing, initiating, and maintaining treatment.

STRA may warrant the use of biologics and in the UK currently omalizumab and mepolizumab are licensed for use in children aged above 6 years and dupilumab for children aged above 12 years, with the caveat that the patient has not shown an adequate response or is not eligible for mepolizumab (17). The US Food and Drug Administration (FDA) and European Medicines Agency (EMA) have licensed all three biologics for children above age 6 years. In addition, Benralizumab is licensed by the FDA and EMA for children aged 12 years and above with severe eosinophilic asthma. Difficult-to-treat asthma, however, necessitates a broader approach, one that embraces extra-pulmonary influences such as obesity, adherence, family values, and symptom perception (18). Moreover, several conditions might present an asthma-like façade and should addressed (5).

Investigations

A thorough history and appropriate investigations facilitate diagnostic clarity. Investigations include blood tests for full blood count, total IgE and specific IgE to aeroallergens, as severe childhood asthma has associations with atopy and increased blood eosinophilia (19). Spirometry with bronchodilator reversibility is useful for diagnosis, although it is important to note that some children with asthma may have non-obstructive spirometry when not acutely unwell. Fractional exhaled nitric oxide (FeNO) is a surrogate measure of eosinophilic airway inflammation and a good predictor of corticosteroid response. Additional investigations such as inhaled methacholine challenge, eucapnic voluntary hyperventilation and cardiopulmonary exercise tests can provide further clarity. Flexible bronchoscopy may be indicated, to assess for anatomical variations including airway malacia and vascular rings (20). Analysis of the bronchoalveolar lavage (BAL) for cytology and culture growth is beneficial and children with STRA are noted to have a higher eosinophil count in the BAL compared to control subjects (21). Further exclusionary investigations including sweat chloride testing, immunoglobulin levels, testing for reflux, and video fluoroscopy for swallow assessment may be useful (20).

FACTORS OF INFLUENCE IN ADOLESCENT SEVERE ASTHMA AND MANAGEMENT

Breathing Pattern Disorders

Several comorbidities may confound the presentation and diagnosis of asthma and should be considered. Of note are breathing pattern disorders. These are best described as chronic or recurrent changes in breathing pattern that cause respiratory symptoms such as breathlessness and non-respiratory symptoms such as anxiety, light-headedness, and fatigue. The prevalence of some breathing pattern disorders in adolescents with asthma may be as high as 25% (22). Disruption of an optimal breathing pattern can contribute to multiple distressing and debilitating symptoms that impact significantly on the quality of life. The symptoms can masquerade as asthma or worsen asthma symptoms particularly in those with exercise induced dyspnoea and during an acute asthma attack. Breathing pattern retraining can therefore be useful in the management of severe asthma.

Obesity

Obesity, a global health concern, is a significant risk factor for severe asthma and is associated with poor asthma control and increased health care utilization (23). Systemic

corticosteroid responsiveness is also impaired in obese children with asthma and is accompanied by heightened patterns of systemic inflammation and metabolites of oxidative stress (24). Additionally, obesity may be associated with other co-morbidities which may impact the holistic quality of life and influence management.

Adherence

The aim of any asthma management strategy should be to achieve symptom control, with minimal therapeutic intervention. The WHO suggests adherence to be "the extent to which a person's behavior—taking medication, following a diet, and/ or executing lifestyle changes, corresponds with agreed recommendations from a health care provider" (25). Contrary to any paternalistic approach, a collaborative effort between the patient and professional, one which embraces the patient priorities, will likely underpin successful adherence. This is particularly relevant since this modifiable factor is recognized as a challenge among adolescents (26), contributing to uncontrolled disease. The National Review of Asthma Deaths in the UK highlighted that over half of asthma deaths were preventable through addressing avoidable factors, including non-adherence and missed appointments (3).

A compendium of factors sway adherence in adolescents (26) and in turn influence the management of severe asthma especially as they transition. Examples of such influences include the determination for greater independence and resistance to parental monitoring (26) paradoxically accompanied by forgetfulness and struggles with organization of time (26). This may also be augmented by social stigma and risk-taking behaviors.

Conflicting and changing priorities and attitudes to health play a key role in this age group (9, 26) and therefore, exploring and accommodating for factors that matter to adolescents may be critical in mitigating the burden of severe disease.

Adherence Monitoring

Adherence to treatment may be viewed in stages; *initiation* (taking the first dose), *implementation* (the actual dosing by the patient in comparison to what is prescribed) and *persistence* (time from starting to eventually stopping treatment) (27). In the context of severe adolescent asthma, which may be subject to variable triggers and alterations to treatment regimens, these stages may be in a dynamic state, especially if compounded by non-adherence. Adherence is considered good if over 80% of the prescribed doses are taken with an appreciation that higher treatment observance is associated with reduced exacerbations (28). Adherence is acknowledged as lower in adolescents (26) and a study of 15–18 year olds with moderate to severe asthma, showed a median adherence of 43% detected through electronic monitoring (29). It is important to recognize that whilst non-adherence may be intentional, it may also be non-intentional (30), creating scope for a change in practice.

Furthermore, monitoring adherence may itself pose a challenge. A combination of history and investigations, including trends in spirometry and FeNO measurements, and prescription uptakes offer some indication. Subjective tools to ascertain treatment observance include self-reporting questionnaires, such as the Medicine's Adherence Report Scale (31). However, over reporting may be observed. Objective monitoring tools include data on prescriptions issued, weighing canisters and directly observed therapy (DOT) (31). Aside from DOT, the former measures do not, in fact, reveal the actual dosing of the treatment. Novel electronic monitoring devices (EMD) may enable clinicians to circumvent this challenge (32).

Mental Health and Risk-Taking Behavior

Symptoms of depression and anxiety are documented in adolescents with asthma (33, 34) and are associated with lower quality of life (35). *Post-hoc* analysis of the IDEAL study noted that 81% of the patients with severe asthma had uncontrolled disease, which was associated with reduced lung function and worsened health related quality of life (35). Furthermore, greater acute healthcare utilization is also observed in adolescents suffering from depression (36, 37).

Worryingly, a higher percentage of risk taking behavior has been described in adolescents with severe asthma (26, 33) including smoking and substance misuse (33). A multi-state survey by the Centers for Disease Control and Prevention revealed that cigarette smoking, cocaine use and low mood were more prevalent in youths with asthma than without (38). Moreover, factors were recognized to co-influence, and where suicidal ideation was reported in those with asthma, there was an association with binge drinking and more than 60% of smoking marijuana (38).

These represent important potential confronts in managing adolescent severe asthma and an integrative approach, which interlocks different tiers of support including school and psychology, is imperative in providing holistic management.

Symptom Perception

Finally, it is important to consider that whilst symptom severity has been described above, poor symptom perception and tolerance to high levels of symptoms is another challenge and may contribute to poor control (26). Poorer symptom control in adolescents has been observed, with the International Study of Asthma and Allergies in Childhood (ISAAC) noting a higher year-long prevalence for symptoms of exercise induced wheeze, severe wheeze limiting speech and night-time cough in adolescents, compared to younger children with asthma (39).

A Growing Threat: E-Cigarettes and Electronic Nicotine Delivery Systems

The Unbiased Biomarkers for the Prediction of Respiratory Disease Outcomes (U-BIOPRED) study reiterate the deleterious impact of smoking on symptomology, noting the association of exhaled smoke with severe wheeze (40). However, vaping is another growing threat and E-cigarettes and Electronic Nicotine Delivery Systems (ENDS) are described as up to two-three times more popular amongst adolescents and young adults in comparison to older adults, despite the original ambition to support smoking cessation in adults (41). A study of young adults in school and colleges (42) revealed that the top promotive factors for e-cigarette experimentation included inquisitiveness,

enticing flavors, and peer influences. Interestingly, the perception that these were a healthier alternative to traditional smoking promoted their use, whilst having health concerns was a deterrent (42). This highlights the unassailable influence of education on adolescent health behaviors, to facilitate a more informed transition into adult health care.

Whilst extensive research is lacking, the present understanding on vaping effects on the lungs highlights the associations with increased severe asthma attacks, airway inflammation, increased risk of acute lung injury and reduction in lung function (41). Two case descriptions of adolescents with severe asthma exacerbations resulting in veno-venous extracorporeal membrane oxygenation (VV-ECMO) with earlier ENDS exposure have been described (43), reinforcing the urgency in understanding the adverse effects.

Furthermore, E-cigarette use has been shown to be a *risk* factor for future smoking, not simply a *marker* for future smoking (44). Data on e-cigarettes from the Children's Health Study (45) reported that 40% of e-cigarette users commenced cigarette smoking, noting a 6 times higher odds of starting cigarettes smoking if they were e-cigarette users, compared to having never-used. More alarmingly, the relationship was stronger for those who had not planned to commence smoking prior to the e-cigarette use. Therefore, E-cigarettes and Electronic Nicotine Delivery Systems are a growing health threat for adolescents and holistic management should include this understanding.

DISCUSSION: SEVERE ADOLESCENT ASTHMA MANAGEMENT—A COLLABORATIVE APPROACH

Family Dynamic and Peers: Support Networks

Family dynamics and influence of peers is consistently recognized as an important factor. Stress at the family level is associated with adverse asthma outcomes (46) and parents of adolescents with severe asthma are recognized as more anxious than those without (47). The pursuit for a new equilibrium, in establishing new responsibility for medication adherence, may be subject to confusion in roles where the adolescent may reject the parental support but also rely on it (26). Parents can support the practicalities of management e.g., prescriptions (28) and are in a position to explain rationale and reasoning to the transitioning young adult (28), which would be beneficial.

Furthermore, peer interactions are a significant factor of influence and clinical management should seek to harness this stimulus positively. Emotions of embarrassment are recognized to influence adherence (28). More than half of non-adherent episodes were amongst friends in one study (48) and hesitation in participating in social activities has also been noted (28). Moreover, social media influences are a very relevant entity for the current adolescent cohort and the influence should be explored in clinical consultations.

Motivational Interviewing and Co-design: Greater Ownership of Care

Approach to severe adolescent asthma should embrace clinical necessity with adolescent priority, to cultivate relevant and sustainable interventions. Acknowledging that management does not rely simply on medical interventions but embraces the multifaceted influences discussed thus far in this review, offers key insight. Creating greater ownership of care should be a priority and listening to and engaging the adolescent patient should underpin all clinical consultations. Shared decision-making with patients has shown to enhance adherence amongst adults with poorly controlled asthma, as it accounts for their priorities (49). This is very relevant for our adolescent cohort, as they embrace greater autonomy in health care decisions. **Figure 1** summarizes the proposed interplay between factors of influence and collaborative working with the adolescent patient.

The Health Belief Model (50) proposes that the actions of individuals balance their beliefs about the perceived health risk with the benefits of the behavioral changes required to address the threat. The susceptibility to the disease and the challenges to overcome in achieving the intended behavior change are important considerations and have been described in the context of asthma in adolescents (29). This study reviewed the perceptions around inhaled steroids and their impact on health, challenges to taking medications (e.g., taste, fear of addiction) and suggested prompts for progress (e.g., audio and visual reminders and incentives) (29).

Understanding adolescent health beliefs is therefore a crucial pedagogical step. Motivational interviewing (MI) may be employed, exploring individual priorities and promoting positive health behavior (30). It has been used with success in different settings amongst the adolescent cohort, including diabetes (51). Furthermore, when paired with social media, online support and other supportive adjuncts such as family contributions, MI outcomes are more effective (30).

Creating a bridge between patient held beliefs and accurate knowledge of disease and treatment is an important next step. Experiencing episodes of severe asthma exacerbations and decline in asthma control, has shown to emphasize the importance of maintenance therapy and motivate greater adherence in adolescents (28). This offers an example of health consequence and subsequent modification of behavior. In one study, despite regular attendances at medical appointments, some youths did not appreciate the rationale for medication use and whilst feeling involved, many did not take the ownership of their healthcare visit (52). This highlights an opportunity for timely engagement in self-care, mitigating learning through negative clinical experiences.

A further example where collaborative working may yield a more effective outcome may be seen in school attendance and symptom perception. School and educational establishments are likely to play an integral role in adolescent lives and educational accomplishments are recognized as a priority for adolescents (6). However, poor awareness of symptoms has a considerable impact on adolescent school attendance, with up to nine times

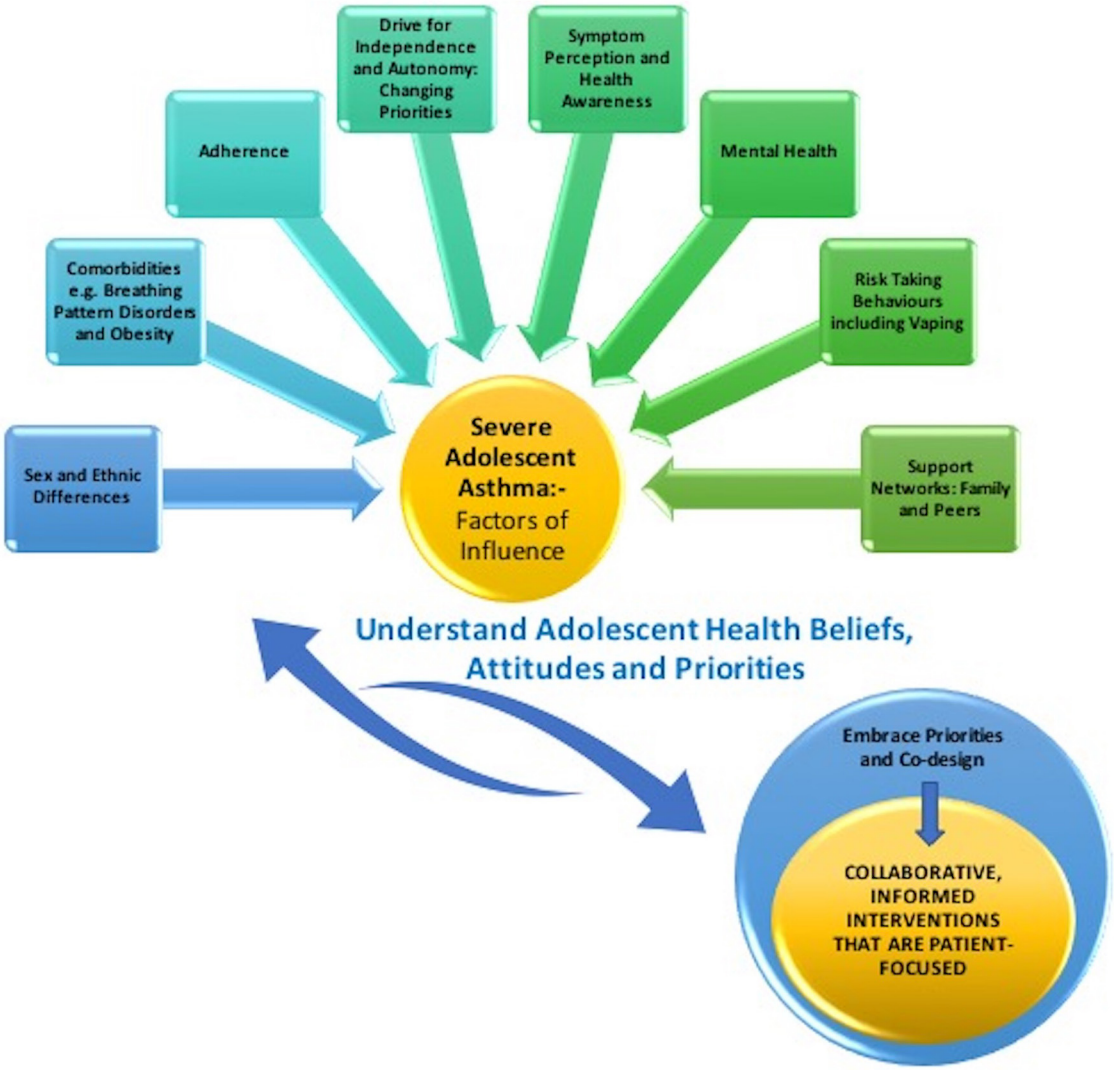

FIGURE 1 | Illustration of the interplay between factors of influence for the adolescent patient with severe asthma and collaborative working.

greater chance of hospital admissions and four times greater likelihood of school absenteeism, in one study (53). Therefore, greater knowledge around symptom presentation and benefits of better control for the priorities that matter to adolescents, will enable shared clinical goals. This may also be harnessed within the practical components, such as inhaler technique, with poor technique shown to contribute to poor adherence and control (54).

Therefore, collaborative working with the adolescent patient and their families, one which endeavors to codesign clinically appropriate but patient-focused management regimens, may offer a bridge to more effective management of severe, difficult to manage asthma.

TABLE 1 | Summary of key learning points.

Key learning points: severe adolescent asthma
• Ensure that the diagnosis of asthma is correct, with a multi-disciplinary approach to diagnosis and management.
• Adolescence marks a transition toward greater independence and autonomy in decision making.
• Factors of influence include family dynamics, peer influences, health beliefs and impact of comorbidities including breathing pattern disorders.
• A collaborative approach, which combines adolescent priorities with stronger health education and treatment rationale, is integral to promoting successful ownership of care and adherence.
• Holistic management must acknowledge the evolving trends of relevance for our adolescent cohort, including social media and vaping.

Transition

Transition from pediatric to adult services is an important phase in the management of severe adolescent asthma and should endeavor to acknowledge the influence of the various aspects discussed in this review. The transition process should involve a named asthma nurse and consultant from the pediatric

and adult services for better outcomes. Whilst a consensus on a set age for transition is lacking, it usually between the ages of 16 and 18. However, the conversations around transition should start early (11, 55), aiming for a gradual process rather than an abrupt event and offering time for readiness. Transition to adult services may be a worrying time for parents and carers, especially when their child's asthma has been difficult to control and they need to be supported in letting their adolescent have control over their asthma before transitioning to adult services. The emphasis should be on self-management by the adolescent with caregiver engagement, whilst acknowledging vulnerabilities (11). Co-production of relevant and informed transition services with young people and their carers is strongly advocated (55) and exploring patients' beliefs and goals is recognized as vital in enabling smooth transition (56). These interactions offer opportunities to identify and address potential challenges and barriers. Therefore, transition should embrace the priorities of the adolescent and family and aim to work in collaboration with all groups, including adult services, to achieve successful transfer of priorities, goals, and care.

Future Directions and Challenges

Despite greater understanding, asthma mortality remains high and there are associations that need further exploration. The authors recognize that one such area is the contribution of ethnic differences in asthma subtypes and outcomes, with recent findings suggesting the influence of race and ethnic differences in asthma outcomes and severity (13). These findings expose the need for further research into the role of racial and ethnic differences in severe asthma disease management.

Summary

Severe asthma in the adolescent requires a broader perspective and demands recognition of the components that are relevant to this unique age group. **Table 1** summarizes the key learning points. Adolescence marks a period of transition and is subject to a variety of influences. Escalation in support may be medical such as the use of biologic therapy but may also warrant a wider approach, which nurtures collaborative decision making with the adolescent cohort and strives for more patient-relevant management regimens.

AUTHOR CONTRIBUTIONS

SW wrote the first draft. Both authors reviewed, revised, made contributions to all subsequent drafts, and contributed to the work of this manuscript.

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REVIEW
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Update on Long-Acting Anticholinergics in Children and Adolescents With Difficult and Severe Asthma

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Tiotropium bromide is the only long-acting muscarinic antagonist (LAMA) approved for treatment of patients aged ≥6 years old who have symptoms of uncontrolled asthma. Results from several clinical trials have found that once-daily inhaled tiotropium bromide is safe and efficacious in 6- to 17-year-olds with symptomatic asthma despite treatment with inhaled corticosteroids, with or without other medications. There are still few available studies investigating the impact of tiotropium bromide treatment in preschool children with suboptimal control. In this narrative review, we summarize the pharmacological effects of the LAMA tiotropium bromide, provide an overview about current asthma studies at different pediatric ages, and describe future research needs.

Keywords: asthma, children, adolescents, preschool children, long-acting anticholinergics, tiotropium bromide

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INTRODUCTION

Asthma is a multifactorial inflammatory disorder of the airways that in 2019 affected approximately 262 million people and caused 461,000 deaths (1), with estimates that 400 million people will be affected by 2025 (2). Currently, asthma is also the most common chronic non-communicable pediatric disease worldwide (3). Exacerbations due to allergen or respiratory pathogens exposure, or exercise-induced are the main causes of hospitalization among children or adolescents with asthma, and this in turn results in schoolchildren and work-parents' absenteeism and high direct and indirect health care costs (4).

In recent years, it has been emphasized that for improving health status the overall goal of asthma management is to achieve symptom control rather than assessing patients based on symptom severity (5). Lack of control in asthma includes persistence of clinical symptoms, high number of exacerbations requiring rescue medications, and progressive lung function deterioration. The importance of symptom control in children is underscored by the results of a national survey that found that asthma control fell short on nearly every goal, indicating a lack of effective asthma symptom control in affected children (6). Moreover, a great proportion of patients with even mild symptoms are inadequately controlled and may face severe exacerbations (7).

Reasons for suboptimal control in children and adolescents include incorrect diagnosis of asthma, especially when spirometry cannot be accurately obtained by uncooperating patients or young children; persistent exposure to environmental triggers such as tobacco smoke or allergens; low or non-adherence to treatment and/or poor inhaler techniques, which are frequently described when long-term anti-inflammatory medications are prescribed; personal concerns about potential

adverse effects; evidence of comorbidities, for instance gastroesophageal reflux, obesity, rhinitis, and/or recurrent airway infections (8). Therefore, based on all the above observations, physicians dealing with asthma feel the strong need to have alternative therapeutic interventions available for patients with uncontrolled asthma.

Patients with asthma are now recommended to take inhaled corticosteroids (ICS) whenever given short-acting β2-agonists (SABA) as rescue therapy (9). This is supported by the evidence that ICS enhance the expression of β2-adrenergic receptors in the airways, prevent severe exacerbations and maintain symptoms control (10). Indeed, according to the Global Initiative for Asthma (GINA) and National Asthma Education and Prevention Program (NAEPP), low-dose ICS is recommended as the best initial treatment when asthma symptoms are under suboptimal control (9, 11). At GINA Steps 3–4 and at NAEPP Steps 4–5, the ICS/Long-Acting beta-agonists (LABA) combination is recommended and in case of further lack of response add-on alternative options are suggested (9, 11). Finally, patients at any age who have persistent symptoms or experience exacerbations despite good adherence to Step 4 treatment and in whom other controllers have been previously considered, should be referred to a center specialized in the management of severe asthma for treatment optimization, i.e., re-evaluation of diagnosis, modification of ongoing therapy or addition of other medications (9, 11, 12).

According to the most recent definitions from adult and pediatric literature, difficult-to-treat asthma is characterized by symptoms that persist despite ICS–LABA treatment even at high-dose ICS, while severe asthma is asthma that is uncontrolled despite good adherence with high-dose ICS– LABA and management of comorbidities, or that worsens when high-dose treatment is decreased (9, 11).

It is indeed important to identify any modifiable factors to differentiate children with difficult asthma from those with true severe therapy-resistant asthma. Acting early on modifiable factors in children with difficult asthma allows better control of symptoms without further investigations. In the absence of these factors, addressing a correct diagnosis of true therapy-resistant severe asthma avoids diagnostic and therapeutic delays, allowing patients to benefit from the use of new therapies (13).

In the last decades, the use of long-acting muscarinic antagonists (LAMA) including tiotropium bromide, glycopyrronium, and umeclidinium as bronchodilators in the long-term treatment of asthma has progressively increased (14). The LAMA tiotropium bromide has recently been incorporated into the GINA document at Steps 4 and 5 in patients with a history of exacerbations (9). However, GINA experts recommend that, in patients experiencing exacerbations despite low-dose ICS/LABA, the ICS dose should be increased to at least medium dose, or treatment converted to Maintenance and Reliever Therapy (MART) with ICS/formoterol before considering the addition of a LAMA (9). In individuals aged 12 years and older with persistent asthma that is not controlled by ICS therapy alone, the NAEPP Expert Panel recommends adding a LABA rather than a LAMA to an ICS (11). However, if the individual is not using or cannot use LABA therapy, adding a LAMA to an ICS is indicated as an acceptable alternative.

New treatment options for asthma are indeed strongly needed in children or adolescents with asthma, especially those with moderate or severe symptoms (15). In the last decade, several pediatric studies have evaluated the use of tiotropium bromide as an add-on to ICS maintenance therapy, with or without leukotriene receptor antagonist (LTRA) or LABA. This narrative review will summarize the pharmacological effects of the LAMA tiotropium bromide, provide an overview about current asthma studies at different pediatric ages, and describe future research needs.

PHARMACOLOGIC CHARACTERISTICS OF TIOTROPIUM BROMIDE AND ITS ADMINISTRATION

Acetylcholine is a neurotransmitter which is released from the neurons of the parasympathetic nervous system in several tissues, including the lung. Acetylcholine stimulates smooth muscle contraction and mucus secretion through M1 to M5 muscarinic receptors (16).

Beyond bronchoconstriction, acetylcholine also regulates airway inflammation and remodeling (17).

Anticholinergic agents are antiasthma medications. Initially, most of the literature was focused on the use of the short-acting anticholinergic ipratropium bromide, a medication predominantly used in combination with SABA to treat bronchoconstriction during asthma exacerbations (18). In 1989, the tiotropium bromide (bromide salt) was patented and then approved for medical use in the form of inhalation powder in 2002 as LAMA bronchodilator drug (19).

Tiotropium bromide is a quaternary ammonium derivative, structurally related to ipratropium bromide (**Figure 1**), but with a significantly higher affinity for muscarinic receptors within the airways. Tiotropium bromide reversibly binds to the M1,

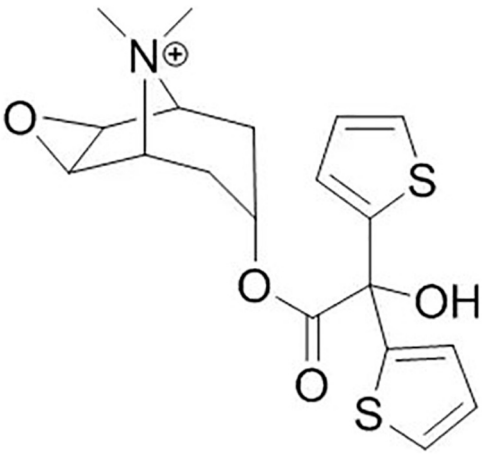

FIGURE 1 | Moulecular structure of tiotropium.

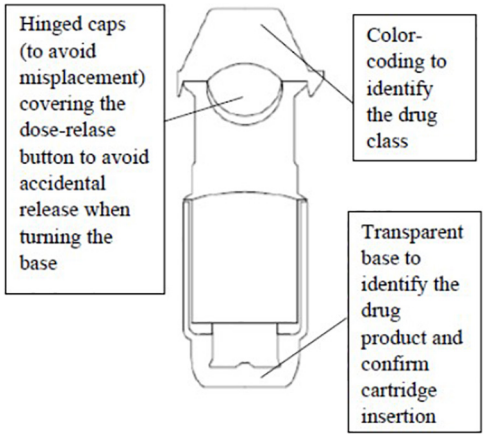

FIGURE 2 | Externarl structure of Respimat© inhaler.

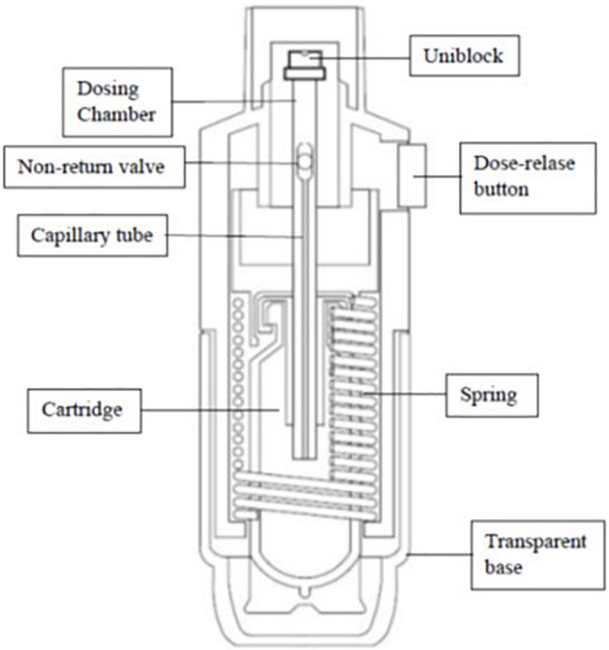

FIGURE 3 | Internal structure of Respimat© inhaler.

M2, and M3 receptors of the airway smooth muscles, and blocks the effects of the acetylcholine released by parasympathetic nerve endings through a competitive and reversible inhibition, with faster dissociation rates from M2 than from M1 or M3 receptors (20). Tiotropium bromide has a maximum effect occurring at 30–60 min, and since the cholinergic transmission is blocked approximately for 35 h, its principal anti-asthmatic property is the long-acting bronchodilation, which allows a once-daily administration.

A pharmacokinetic study in children aged 6–11 years old demonstrated that tiotropium bromide is rapidly absorbed following inhalation and then excreted into urine (21), confirming that systemic exposure of children to the medication is within the range observed in adults (22).

Tiotropium bromide is administered through the Respimat© inhaler (19) (**Figures 2**, **3**). Most children aged ≥6 years can use a Respimat© inhaler without a valved spacer device (23) but younger children should use the Respimat in combination with a valved spacer (24, 25).

EVIDENCE OF TIOTROPIUM BROMIDE USE IN THE PEDIATRIC POPULATION

Unlike inhaled short acting anticholinergic ipratropium bromide that has been extensively investigated in children or adolescents with acute asthma (26), LAMA has been less studied and pediatric studies regarding the use in chronic asthma only date back to the last 2 decades (**Table 1**).

Evidence of Tiotropium Bromide Use in Adolescents With Asthma

The effects of tiotropium bromide inhalation in the pediatric population with chronic uncontrolled asthma were first evaluated in adolescents, and results opened the road for assessing tiotropium in younger children. Most of the published studies are randomized controlled trials (RCT) and focus on type and severity of subjective clinical symptoms [evaluated by the asthma standardized questionnaires such as the Asthma Control Questionnaire (ACQ) or Asthma Control Test (ACT)], and lung function (namely, spirometry) as primary outcomes. The lung function end points included the peak expiratory flow (PEF) or the forced expiratory flow at 1 s (FEV1) either reported as peak FEV1 (within 3 h after administration of the study drug) or trough FEV1, i.e., the predose FEV1 measured at the end of the dosing interval, 10 minutes before the next dose of trial medication at week 24 or week 12 (27), or, less frequently, as forced expiratory flow at 25–75% of the lung volume (FEF25–75%). In 2014, Vogelberg conducted an incomplete crossover RCT of 105 adolescents with moderate symptomatic asthma, who were administered once-daily tiotropium (5, 2.5, and 1.25 μg) as an add-on therapy to medium-dose ICS with or without LTRA. Results showed that peak FEV_1, trough FEV_1 and FEV_1 Area Under the Curve (AUC) (0–3 h) significantly improved (28). The term "incomplete" refers to the study design that requires that treatments are grouped into sets or "blocks," not all of which include every treatment, and each block is administered to a different group of participants to avoid administering too many treatment conditions to the same group of participants.

Results from two additional phase III RCT of once- daily tiotropium administered for 12 or 48 weeks confirmed lung function beneficial effects in adolescents treated with long-term ICS with or without other controller therapies (29, 30). However, only the 5-μg dose significantly improved trough FEV1 at week 24, while in the 48-week RCT asthma control improved using both 5 and 2.5 μg doses of tiotropium, with the 2.5 μg dose also significantly reducing rescue medications use (29). The incidence of adverse effects including asthma worsening or exacerbations, decreased PEF rate, nasopharyngitis, and viral

TABLE 1 | Overview of published studies of tiotropium bromide in pediatric patients with asthma.

Author	Study design	Age group (years)	Asthma severity	Daily dose and treatment duration	Primary outcome	Main findings
Vogelberg et al. (28)	Phase 2, double-blind, placebo-controlled, dose- ranging, incomplete crossover study	Adolescents (12–17)	Moderate persistent asthma	5 μg 2.5 μg 1.25 μg 12 weeks	Peak FEV1 (0–3 h): 5 μg: 113 mL $p = 0.004$ 2.5 μg: 57 mL $p = 0.148$ 1.25 μg: 67 mL $p = 0.066$	Improvement of lung function vs. placebo. Safe and well tolerated
Vogelberg et al. (33)	Phase 2, double-blind, placebo-controlled, incomplete-crossover, dose-ranging study	School-age children (6–11)	Symptomatic asthma	5 μg 2.5 μg 1.25 μg 12 weeks	Peak FEV1 (0–3 h): 5 μg: 87 mL $p < 0.0002$ 2.5 μg: 104 mL $p < 0.0001$ 1.25 μg: 75 mL $p = 0.001$	Improvement of lung function vs. placebo. Safe and well tolerated
Hamelmann et al. (29)	Phase 3, double-blind, placebo-controlled, parallel-group trial	Adolescents (12–17)	Moderate symptomatic asthma	5 μg 2.5 μg 48 weeks	Peak FEV1 (0–3 h): 5 μg: 174 mL (95% CI, 76–272 mL) $p < 0.001$ 2.5 μg: 134 mL (95% CI, 34–234 mL) $p < 0.01$	Improvement of lung function vs. placebo. Safe and well tolerated
Huang et al. (36)	Phase 3, double-blind, placebo-controlled study	School-age children and adolescents (6–14)	Moderate symptomatic asthma	1.25 μg 12 weeks	FEV1% at week 12 and FVC at week 8 $p < 0.05$. Other indicators $p < 0.01$	Improvement of lung function vs. placebo. Decreased need for SABA Night symptoms improvement
Hamelmann et al. (30)	Phase 3, double-blind, placebo-controlled, parallel-group study	Adolescents (12–17)	Severe symptomatic asthma	5 μg 2.5 μg 12 weeks	Peak FEV1 (0–3 h): 5 μg: 90 mL (95% CI, −19 –198 mL) $p = 0.104$ 2.5 μg:111 mL (95% CI, 2–220 mL) $p = 0.046$	Improvement of lung function only at 2.5 μg vs. placebo.
Szefler et al. (34)	Phase 3, double-blind, placebo-controlled, parallel-group study	School-age children (6–11)	Severe symptomatic asthma	5 μg 2.5 μg 12 weeks	Peak FEV1 (0–3 h): 5 μg: 139 mL (95% CI, 75–203 mL) $p < 0.001$ 2.5 μg: 35 mL (95% CI, –28 to 99 mL) $p = 0.27$	Improvement of lung function only at 2.5 μg vs. placebo. Well tolerated
Vogelberg et al. (35)	Phase 3, double-blind, placebo-controlled, parallel-group study	School-age children (6–11)	Moderate symptomatic asthma	5 μg 2.5 μg 48 weeks	Peak FEV1 (0–3 h) (week 24) 5 μg: 164 mL (95% CI, 103–225 mL) $p < 0.001$ 2.5 μg: 170 mL (95% CI, 108–231 mL) $p < 0.001$	Improvement of lung function vs. placebo.
Vrijlandt et al. (41)	Phase 2/3, double-blind, placebo-controlled, parallel-group study	Pre-school children (1–5)	Persistent asthma symptoms (wheezing, cough, shortness of breath)	5 μg 2.5 μg 12 weeks	Combined daytime asthma symptom score: 5 μg: –0.048 (95% CI, –0.29 to 0.19) 2.5 μg: –0.080 (95% CI, –0.31 to 0.15)	Asthma scores not significantly different between the two active groups vs. placebo. Potential to reduce asthma exacerbations vs. placebo Tolerability as placebo

CI, confidence interval; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; FEV1 (0–3 h), forced expiratory volume in 1 second within 3 hours after dosing; ICS, inhaled corticosteroid; SABA, short-acting β2 agonists; LABA, long-acting β 2-agonist.

respiratory tract infection was comparable across the treatment groups and did not lead to discontinuation of treatment, as previously reported (31).

In conclusion, tiotropium appears to improve lung function and reduce the need for rescue treatments in adolescents with severe asthma and is well tolerated.

Evidence of Tiotropium Bromide Use in School-Aged Children With Asthma

Once demonstrated that tiotropium was to be well tolerated and efficacious in adolescents with uncontrolled asthma, it became urgent to assessing its use for treatment of younger children. There are fewer therapeutic options for school-age children than adolescents and adults, however, this age group shows more unmet medical needs than others. A systematic review on the efficacy and safety of tiotropium as an add-on in children with moderate to severe asthma lasting from >3 to >6 months, uncontrolled despite use of an ICS with or without additional controller medications (32), has included the analysis of 3 RCT of 905 children aged 6–11 years (33–35). Duration of treatment ranged from 12- to 48-weeks. Once-daily tiotropium (5, 2.5, or 1.25 μg) improved lung function parameters, including peak and trough FEV1 or morning and evening PEF (only 5 μg dose) vs. placebo, however there were no statistically significant differences in asthma control and quality of life (33). Huang and coworkers conducted a 12 week-study of eighty children aged 6–14 years, with newly diagnosed moderate persistent asthma who were randomly administered fluticasone propionate aerosol or fluticasone propionate aerosol plus tiotropium *via* the dry powder HandiHaler® device (36). They showed that lung function significantly improved in both groups at 4, 8, and 12 weeks compared with baseline, in particular in the tiotropium group compared to the control group. Of all clinical variables, no significant difference in the incidence of severe asthma between the two groups (36.3 and 26.8%, respectively) was found, however the proportion of days and frequency of SABA use and awakenings during the night was significantly reduced in children given tiotropium, with no severe adverse effects (36).

In conclusion, in school-aged children, the use of tiotropium appears to improve lung function and, albeit on limited data, reduces the risk of exacerbations and the need for corticosteroid therapy even though a significant difference in the incidence of severe asthma was not documented.

Evidence of Tiotropium Bromide Use in Pre-school-Aged Children With Asthma

In early life, asthma presentation and clinical course are very different from those described in school-aged children and adolescents due to variable phenotypic heterogeneity and different responses to asthma medications (37). Yet asthma treatment of preschool children is challenging since a high proportion of patients who require frequent health care use because of asthma exacerbations belong to that age group, and this makes prevention of such events a crucial goal for reducing future morbidity (38). However, in young children the response to ICS is sometimes unpredictable because of different airway inflammatory findings (39). Yet not all young children have evidence of eosinophilic airway inflammation, even those with recurrent severe multi-trigger wheeze, and this can justify the poor response to ICS at least in selected cases (40). All the above issues explain why alternative therapeutic options to ICS are warranted in the preschool age group.

In a small exploratory RCT of limited duration (only 12 weeks), tiotropium bromide was administered at 5 and 2.5 μg to 102 children aged 1–5 years with persistent asthma compared to a placebo group (41). The study showed no benefit in the primary outcome measures, i.e., safety, assessed by comparing adverse events between the active and placebo groups, and efficacy, measured as the change in weekly mean combined daytime asthma symptom score from baseline to week 12. Adverse events were less frequent with tiotropium treatment than with placebo, however, no formal statistical comparison between groups was performed by the authors, and more importantly, no significant differences in symptom scores vs. the placebo group were found (41).

A very recent study conducted by Zielen and coworkers in children aged <6 years with uncontrolled severe asthma has showed that adding tiotropium bromide to LABA/ICS significantly improved the systemic corticosteroid prescriptions, the physician's visits and the antibiotics need recorded 6 months before and after treatment (42). However, the study design, that included the analysis of electronic records, has indeed many limitations, primarily its retrospective nature and the extremely low number of patients enrolled. An ongoing open-label trial of infants and toddlers with recurrent episodes of wheeze and/or shortness of breath is evaluating the effects on episode-free days of a novel strategy of LAMA administration, i.e., as needed intermittent inhaled tiotropium bromide (5 μg once a day, beginning at the onset of an upper respiratory tract infection and continuing for 7–14 days) and as needed SABA vs. intermittent fluticasone propionate and SABA as needed, or solely SABA as needed (NCT03199976). The rationale of the study is that in young children viral-induced wheezing episodes are associated with increased parasympathetic nerve activity, therefore acetylcholine production can be blocked by the inhaled anticholinergic agent tiotropium (43). In conclusion, based on the findings of the scant literature on tiotropium bromide at preschool age, at present there is insufficient evidence to support efficacy of tiotropium use in infants and toddlers with persistent asthmatic symptoms.

ELIGIBILITY CRITERIA AND DOSES

Based on the evidence from literature data on asthma (44), indications for administration of tiotropium bromide inhalation spray include the long-term, once-daily, maintenance treatment of moderate-to-severe asthma that is not adequately controlled on ICS. The drug was approved by the US Food and Drug Administration in 2015 in patients with asthma aged ≥12 years, and more recently in February 2017 in pediatric patients aged ≥6 years (18). The approved doses are 2.5 μg in the United States and 5 μg in the European Union (45).

FUTURE NEEDS

The goal of asthma management is to achieve symptom control and prevent exacerbations by prescribing a therapeutic plan which ensures the greatest clinical benefits and the smallest risk of adverse effects to the patients. Current treatment options for children and adolescents with asthma are progressively growing, and overall, most bronchodilators and anti-inflammatory medications are effective on relevant clinical and lung function outcomes.

Ideally, as low adherence to multiple daily treatments is a big issue in school-aged children and adolescents, providing antiasthma medications once-daily *via* an easy-to-use inhaler has a beneficial added value.

A major issue that should not be underestimated when antiasthma treatment is prescribed to young children is lack of cooperation in inhaling medications (46). In young children the preferred delivery system of inhaled medications is the pressurized metered-dose inhaler with a valved spacer (with or without a face mask, according to the patient's age) (9). Future research also including the development of devices designed for different pediatric patients ages and sizes will hopefully improve the standard of care to infants and children with severe wheezing disorders (46).

FEV_1 is good indicator to assess the severity of asthma or the efficacy of asthma medications in adult population studies about tiotropium. However, FEV_1 may not be the best measure of outcome of pediatric asthma because children spirometry does not always correlate well with symptom severity, especially during asthma exacerbations (47). Thus, since a *post-hoc* analysis found that improvements in FEF25–75% response with tiotropium vs. placebo were largely more pronounced than improvements in FEV_1 (47), measurement of low to medium lung volume flows may be a more sensitive than FEV_1 for evaluating peripheral airway response to tiotropium in children and adolescents.

Although studies of tiotropium in children and adolescents overall show improvement of spirometry, the small sample sizes, and short study duration of the trials indicate that the impact of tiotropium should be investigated in longer-term trial cohorts of sufficient size to estimate the maximum clinical effect and the long-term safety (48). Lung function should not be the single endpoint of future studies. Indeed, most of the RCTs demonstrate that spirometry significantly improved, but subjective clinical symptoms evaluated by the asthma questionnaires, or the proportion of exacerbations modestly or not significantly improved (29, 30, 33, 41). Finally, also quality of life should be included as a substantial outcomes measure. In conclusion, pediatric research on tiotropium needs to be indeed directed toward several primary objectives possibly including the identification of predictor response. Future studies should focus on the identification of subgroups of children or adolescents with severe asthma preferentially responsive to LAMA who do not show beneficial effects from treatment with ICS/LABA or high ICS dose. Interestingly, patients with fixed or baseline airflow obstruction might preferentially respond to LAMA, as indicated by two trials in children and adolescents that enrolled asthma patients with FEV1 60–90% predicted (30, 34). In addition to this, other clinical outcome measures, for instance a high proportion of exacerbations or worse asthma control test scores at baseline should be considered in the study design to identify which patients respond better than others to treatment. In the phase III RCT of a large group of children and adolescents, Szefler and coworkers concluded that the effects of tiotropium bromide as an add-on treatment were not influenced by Th 2 phenotype, indicating that the decision of adding tiotropium does not require the evaluation of Th 2 and that tiotropium is effective regardless of allergic status (49). Based on these findings, tiotropium bromide was proposed as alternate option to biologic agents which are recommended to patients aged $\geq$6 years with severe asthma allergic phenotype (50). Yet biologics are very expensive, therefore, pending further comparative studies of biologics vs. LAMA, tiotropium bromide may also be considered as an appropriate option to biologics in children or adolescents with uncontrolled severe asthma and a confirmed Th 2 phenotype.

Cost-utility of tiotropium bromide in children and adolescents has been rarely discussed. A unique study of children has shown that add-on tiotropium bromide achieves better outcomes at lower cost compared to ICS/LABA therapy (51).

Recently, the glycopyrronium and umeclidinium LAMA combined with LABA and ICS have been studied as add-on triple therapy in adults with asthma that is uncontrolled despite treatment with an ICS/LABA association (13). The single-inhaler ICS/LABA/LAMA regimen is now recommended by GINA before any biologic or systemic steroid treatment is initiated in individuals aged 18 years or older at GINA step 5 (9). There are no published pediatric studies of ICS/LABA/LAMA triple therapy and, given the beneficial effects on pulmonary function in adults (13), whether the regimen is efficacious also in children older than 6 years with uncontrolled asthma should be explored.

An additional point that deserves to be pointed out is the possible effects of tiotropium bromide on airways inflammation and remodeling. As several cells involved in the inflammatory cascade of the asthma process express muscarinic receptors, it has been hypothesized that tiotropium can modulate the function of these cells and attenuate airway inflammation and smooth muscle mass thickening (52). In an animal model of chronic asthma, Kistemaker et al. showed that eosinophilic inflammation in response to allergen exposure and remodeling were reduced by combined administration of tiotropium and ciclesonide (53), suggesting that inhibition of airway inflammation and remodeling may contribute to the long-term beneficial effects of tiotropium (54). An additional mechanism through which anticholinergic drugs may impact on airway diseases is by modulating the asthma-associated mucus overproduction. In a study of mice and mucin production *in vitro*, Arai et al. showed that tiotropium inhibits neutrophil elastase-induced goblet cell metaplasia, probably by suppressing inflammation and through a direct action on epithelial cells (55). These effects of tiotropium bromide have been poorly investigated in humans and might be the issue of future pediatric studies, also including the comparison vs. the cornerstone anti-inflammatory treatment of asthma with ICS.

CONCLUSION

Tiotropium bromide is the only LAMA licensed for asthma long-term treatment of patients aged ≥6 years who continue to have symptoms despite controller medication administration. Since the greatest effects of tiotropium bromide on lung function was evaluated in the short-term, whether treatment could affect also the long-term evolution of lung function is unknown. Most relevant changes are reported in spirometry when patients are administered 5 μg rather than other doses. Clinical effects are less significant, probably because most pediatric protocols include a short treatment period and therefore could not appraise the maximum clinical effect of an add-on therapy. An important limitation is also the difference in treatment duration (12 or 48 weeks), which hampers establishment of the long-term effectiveness of the medication.

Treatment with tiotropium bromide as an add-on medication appears to be well tolerated by children and adolescents with suboptimal control of moderate-to-severe asthma, is safe and no fatal events have been reported so far. However, long-term safety should be evaluated in future studies including longer periods of treatment. Since the goal of asthma treatment is to minimize symptom burden and risk of exacerbations, achieving adequate control of asthma symptoms is also imperative for reducing the risk of development of severe asthma. Although the results from the studies of children and adolescents with moderate-to-severe asthma are promising, additional well powered trials are needed to further assess the safety and efficacy of tiotropium bromide added-on to long-term treatment in larger pediatric populations also including preschool children, a population with special needs in whom the novel as needed intermittent administration might be an ideal treatment strategy.

AUTHOR CONTRIBUTIONS

FS and MB made substantial contributions to conception and design, involved in drafting the manuscript, and gave final approval of the version to be published. CZ conceived the idea, involved in drafting the manuscript, and gave final approval of the version to be published. PL made substantial contributions to conception and design, involved in drafting the manuscript and revised it critically for important intellectual content, and gave final approval of the version to be published. CB as graduate in Pharmacy supported all co-authors in the final revision of the manuscript, focusing on the critical aspects of tiotropium use in children and adolescents, and gave approval of the version to be published. All authors contributed to the article and approved the submitted version.

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Do not forget asthma comorbidities in pediatric severe asthma!

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Asthma is the most common chronic respiratory disease in childhood. The long-term goals in managing asthma aim to control symptoms and prevent exacerbations, as well as to reduce side effects of therapy and mortality disease-related. Most of patients have mild to moderate asthma and respond well to standard therapies. However, a minor proportion of children with asthma has severe disease that remains uncontrolled despite optimal adherence to prescribed therapy and treatment of contributory factors, including trigger exposures and comorbidities, which can mimic or worsen asthma and contribute to exacerbations and poor quality of life. Evaluation of comorbidities is fundamental to optimize the management of the disease in a subgroup of patients with poor responder asthma. The overall aim of this article is to describe characteristics of main pediatric severe asthma comorbidities reported in literature, giving clinicians tools to recognize and manage properly these conditions.

KEYWORDS

asthma, severe asthma, children, comorbidities, difficult to treat asthma

Introduction

Asthma is a heterogeneous disease characterized by chronic inflammation of the airways. Clinical presentation can be various in time and intensity with asthma attacks characterized by wheezing, shortness of breath, chest tightness and cough together with a variable and reversible limitation to the expiratory flow. Most of patients have mild to moderate asthma and respond well to standard therapies (1). However, a minor proportion of children with asthma has severe disease that remains uncontrolled with continuous symptoms, frequent exacerbations and increased risk of hospitalization (2). Severe asthma is a coexistence of clinical, molecular, and cellular inflammatory characteristics and it assessed retrospectively on the level of therapy required to control symptoms and exacerbations, once the disease has been stabilized (3). Its prevalence among children with asthma is estimated up to 5% (4), with a significant socio-economic impact, requiring the consumption of 30–50% of the health resources destined for asthma in general (5). In most cases, severe asthma is related to bad adherence to therapy, incorrect use of inhalers, environmental and psychological factors and co-existing and

inadequately treated comorbidities as show in Figure 1 (6). Comorbidities are diseases, disorders or medical conditions that are simultaneously present with another or others in a patient and may not have etiological association with asthma. Moreover, specific clusters of comorbidities may develop at the same time, interacting with each other and playing an aggregate effect on the individual's asthma outcomes (7). Co-occurring of different conditions in asthma is associated with more complex clinical management and worse health outcomes (8). Phenotypic differences and underlying comorbidities will impact treatment choices, therefore these conditions should be carefully assessed and properly managed to avoid inappropriate therapy and improve asthma management (9). In this review we will discuss main comorbidities associated to asthma in children, describing their possible role in severe asthma (Table 1).

Obesity

Obesity is known to be an aggravating factor of many pulmonary conditions, through effects on lung mechanical function (10) and altered immunological and inflammatory state (11, 12). The interactions between asthma and obesity are varied and complex and can have causes and/or predisposing factors in common, including environmental, genetic and microbiological factors (13). Obesity is known to be significantly associated with a greater asthma severity (14) and a poorer asthma control and quality of life (15), with chronic systemic inflammation and steroid resistance as the main explanations for this correlation. Moreover dysanapsis, defined as the incongruence between the growth of the lung parenchyma and the airways caliber among overweight or obese children, has been demonstrated to worse disease severity and reduce response to treatment, as airflow obstruction is anatomical and/or developmental and thus at least partly not related to bronchospasm or airway inflammation (9). In a retrospective cohort study by Lang et al. obesity increases asthma incidence in preschoolers, school-age children and adolescent population, with the highest risk observed in the youngest subgroup, moreover depending on sex, ethnicity and allergic status (16). On the other hand, asthma itself drives an increase in the onset of obesity among schoolchildren, as the same anti-asthma drugs, in particular steroids, and poor tolerance to physical exertion can favor overweight (17). Moreover, other comorbidities like gastro esophageal reflux disease (GERD) and obstructive sleep apnea syndrome (OSAS) co-exist in obese patients, contributing to asthma poor control (18). Obesity is an easily identifiable condition, but it often leads to an incorrect diagnosis of asthma, rather than coexist as a separated comorbidity. Obese subjects in fact can be misdiagnosed as asthmatic patients, as their symptoms during exercise or bronchial challenge are equal to or higher than those experienced by asthmatic patients, without evidence of airflow obstruction or bronchial hyper responsiveness (19). This is due to high excessive ventilator response for metabolic demands and chronic mild inflammation caused by augmented proinflammatory cytokines such as leptin and reduced anti-inflammatory ones (adipokine) from the adipose tissue (12). Obesity is a modifiable risk factor for asthma and weight loss has been shown to improve control of asthma symptoms (20), so that diet, exercise and behavioral therapy should be always encouraged in obese asthmatic and non-asthmatic children and the possibility of practicing physical activity free from respiratory symptoms must always be part of the therapeutic goals (21). As suggested by Fainardi and colleagues, in a child with obese-asthma phenotype, a step-wise approach including the evaluation and management of obesity-associated comorbidities, mainly OSAS and GERD, is fundamental (22).

Gastro esophageal reflux disease

GERD worsen asthma control, increasing odds of suffering asthma exacerbations (23) and is associated with severe asthma in a bidirectional relationship, as demonstrated by longitudinal follow-up studies (24). Its prevalence among children with asthma is estimated to be 43–87% (18). GERD is thought to enhance bronchoconstriction through vagal nerve stimulation and micro aspiration of small amount of gastric and duodenal contents that irritate and damage the airways leading to release of inflammatory cells and mediators. On the other hand, asthma pulmonary hyperinflation and increased negative pleural pressure due to bronchoconstriction increase the pressure gradient between the thorax and the abdomen, favoring reflux. Moreover, asthma therapies may worsen GERD symptoms increasing gastric acid production or lowering esophageal sphincter tone (25). Diagnosis is based on typical symptoms of regurgitation and heartburn but in some cases extra-esophageal symptoms like cough or wheezing may represent the only clinical manifestations. Lifestyle changes including postural therapies and weight loss should always be encouraged. In clinical practice, symptomatic GERD is treated with proton pump inhibitors (PPI), although data to suggest that this therapy reducing asthma severity are limited (26). A recent review investigated the pharmacological intervention to manage GERD in asthma patients, both adults and children, concluding that medical treatment of GERD has an uncertain effect on reducing exacerbations, using of rescue medications and improving respiratory function (27). PPI use has been associated with an increased risk of asthma in children and the hypothesized underlying mechanism is supposed to be the change of the microbiome in the lung and the gut, leading to a dysregulation of immunity. Therefore, these drugs should be prescribed only when clearly indicated, weighing the potential benefit against potential harm (28). Additionally, surgical treatment for GERD

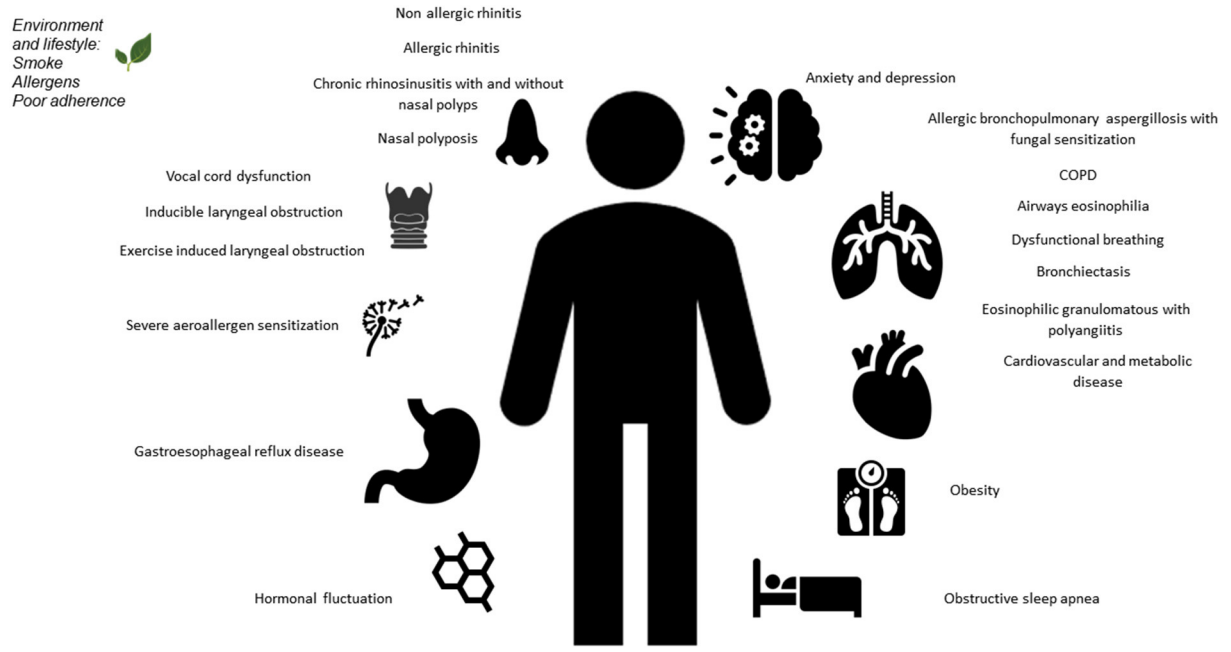

FIGURE 1
Overview of pulmonary and extrapulmonary comorbidities in severe asthma, in adults and children.

in people with asthma are currently under-studied and evidence is lacking, especially among children

Obstructive sleep apnea syndrome

Episodes of complete or partial upper airway closure in OSAS are associated with blood-gas changes and altered normal sleep architecture with long-term sequelae (29). In patients with co-existing asthma, OSAS is widely known to be associated with poor asthma control and more frequent severe exacerbations (30, 31). Their co-existence is explained by common risk factors (mainly obesity and GERD) in a bidirectional relationship where an underlying pathogenetic pathway promote both upper and lower airway inflammation (31) and a neutrophilic inflammation is predominant in patients with OSAS and severe asthma (32). Moreover, repeated episodes of upper airways collapse in OSAS trigger cyclical hypoxemia and vagally-induced bronchospasm (33). The prevalence of OSAS in children with asthma is reported about 35% (34), rising up to 66% when diagnosed with polysomnography (35) and, among those with severe asthma, 63% have concomitant OSAS (36). A retrospective cohort among children hospitalized for acute asthma found that those with coexisting OSAS had higher risk of noninvasive positive pressure ventilation use and longer length of stay compared with those without OSAS (37). At the same time, the presence of asthma is associated with more severe OSAS and need for continuous positive airway pressure, but it has not been established if controlling asthma decreases severity of OSAS (38). Conversely, a retrospective case-control analysis showed that asthma might reduce the risk of OSAS, explaining this result with the point that the avoidance of airway collapsibility and reduction of systemic inflammation actually might prevent progression to OSAS (39). Being adeno tonsillectomy the first-line treatment for OSAS in children, a systematic review by Sanchez et al. summarized that surgical intervention was associated with clinically significant reductions in markers of asthma severity (40). According to this, a more recent prospective controlled study demonstrated that adeno tonsillectomy improves asthma outcomes as measured by the Childhood Asthma Control Test C-ACT, but with only minimal improvements in the asthma clinical outcomes (41). Asthmatic children with non-fully controlled asthma or frequent nocturnal symptoms or those who have risk factors for OSAS (obesity and other comorbidities) should be evaluated to rule out an underlying sleep disorder (31).

Allergic bronchopulmonary aspergillosis and fungal sensitization

Fungal sensitization is common in asthmatic children and is associated with a worsening in asthmatic feature

such as lung function, airway inflammation and bronchial reactivity (42). Airway damage in severe asthma may lead the environment be more easily colonized by fungi and fungi directly contribute to the development of severe asthma by augmenting the immunological response (43). Moreover, the alteration of mucosal immunity related to treatment with systemic corticosteroids in severe asthma patients predispose to an increased fungal load, augmenting the type 2 inflammatory response in sensitized patients (44). Allergic bronchopulmonary aspergillosis (ABPA) is caused by repeated inhalation of *Aspergillus fumigatus* spores which remain trapped in the thick sputum of patients causing a hypersensitivity reaction (45). Main clinical manifestations include frequent exacerbations, productive cough with mucus plugs, hemoptysis and constitutional symptoms as fever, weight loss and fatigue (46). Specific laboratoristic and radiological criteria are needed to diagnose ABPA among asthmatic patients and asthma is considered itself a predisposing condition to develop ABPA, besides cystic fibrosis or tuberculous disease (47, 48). Epidemiological studies to evaluate the prevalence of ABPA in children are mainly from India whereas in developed countries ABPA is considered a rare condition. The reason for this regional difference may be due to environmental factor or genetic predisposition. Kumari observed prevalence of ABPA as 11.3% in Indian children with poorly controlled asthma, without identifying any specific risk factor for ABPA (45). The goals in the treatment of ABPA aimed to reduce exacerbations, prevent deterioration of lung function and evolution to end-stage fibrotic disease (49). Systemic steroids are the most effective treatment to reduce inflammatory response, whereas efficacy of antifungal drugs to eradicate A. fumigatus is uncertain and is not currently recommended as first-line treatment with steroids in children with ABPA. Omalizumab and mepolizumab are monoclonal antibody recently proposed as an alternative treatment in ABPA and asthma (50).

Allergic rhinitis

Allergic rhinitis (AR) is considered a major risk factor for asthma onset and uncontrolled or moderate-to-severe AR can significantly affect asthma control, being associated with more frequent wheeze attacks (51). Chronic disease with inflammation of the nasal mucosa and nasal airway hyper reactivity in AR is caused by exposure to inhaled allergens in a sensitized patient (52). Interactions between the upper and lower respiratory tracts are well known as they share anatomical, functional, pathogenic and immunological patterns (53), so that allergic airway disease represents a continuum of a single inflammatory process (54). Moreover, the impaired function of the upper airways in AR leads to reduction of filtering, warming and humidifying air before it reaches the lower airways, causing inhalation of cold dry air and greater delivery of allergens (55). AR prevalence estimated is between 10 and 30% of children and adults (56), whereas ∼60–80% of children with asthma have AR (4), considering asthma itself as a major risk factor for the onset of AR (54, 57) and, on the other hand, severity of AR has shown to be associated with poor degree of asthma control (58). The diagnosis of AR is based on clinical presentation with itching, nasal discharge, sneezing and nasal airway obstruction. Skin prick test, with serum specific Immunoglobulin E and allergen provocation tests are used as a second-line tests when other investigations are inconclusive (59). Current treatment for children with asthma and AR include allergen avoidance whenever possible and standard pharmacotherapy to manage and reduce symptoms, mainly using oral and intranasal H1-antihistamines, intranasal corticosteroids and leukotriene receptor antagonists (60). Allergen-specific immunotherapy, either in the subcutaneous or sublingual form, has a immune modulator effects by augmenting the production of IgG in the serum and IgA in nasal secretions and lowering specific IgE (61). Despite having been shown to be safe in children as young as 3 years of age, in clinical practice it remains secondary to symptomatic therapies probably due to its elevated costs and lack of awareness of its clinical efficacy in children with asthma, which remains controversial (62).

Chronic rhinosinusitis

Chronic rhinosinusitis (CRS) is an inflammatory condition in the nose and paranasal sinuses (63). It has been demonstrated to be associated with impaired asthma control and increased exacerbation frequency (64), in a common ground due to a systemic cyclic inflammatory response (65), which is not only by contiguity between upper and lower airways, but it is the result of a complex interplay among several immunological mechanisms both inside and outside the respiratory system (66). Moreover, chronic inflammatory process leads to a remodeling process of sinonasal tissues, with epithelial edema, basal membrane thickening and polyps formation, similarly to lower airways remodeling occurring in asthmatic patients (67). Diagnosis is made clinically, recurring to nasal endoscopy to identify purulent drainage and the presence of polyps protruding in the nasal cavities, distinguishing in that way CRS with (CRSwNP) or without (CRSsNP) nasal polyps (63). Epidemiological association between CRS and asthma is quite clear. In a study of Marseglia et al. asthmatic children were investigated by nasal endoscopy and occult sinus involvement was demonstrated in 7.5% of them, who resulted to have poorly controlled asthma, suggesting that it is reasonable that children and adolescents affected by poorly controlled asthma should be investigated for occult or manifest CRS (68). More recently researchers followed

TABLE 1 Main articles reporting comorbidities in pediatric severe asthma.

Comorbidities	Airways eosinophilia	Allergic bronchopulmonary aspergillosis with fungal sensitization	Allergic rhinitis	Anxiety and depression	Bronchiectasis	Cardiovascular and metabolic disease	Chronic rhinosinusitis with and without nasal polyps	COPD	Dysfunctional breathing	Exercise induced laryngeal obstruction	Eosinophilic granulomatous with polyangiitis	Gastroesophageal reflux disease	Hormonal fluctuation	Inducible laryngeal obstruction	Nasal polyposis	Non allergic rhinitis	Obesity	Obstructive sleep apnea	Severe aeroallergen sensitization	Vocal cord dysfunction
Authors																				
Jonathan M. Gaffin et al.		x	x				x		x			x	x	x			x	x		
Andrew Bush										x							x			
Paola Rogliani et al.	x	x	x		x	x	x	x	x			x				x		x		x
Celeste Porsbjerg, Andrew Menzies-Gow		x	x	x	x		x		x			x			x		x	x		x
Elizabeth Scotney, Sejal Saglani											x								x	
T. R. Tay, M. Hew				x			x		x			x				x	x	x		x
Samriti Gupta et al.												x						x		

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adults and pediatric patients for 5 years after the diagnosis of CRS and found that they were at increased risk to develop respiratory diseases, including asthma (69). Treatment is aimed at reducing airway inflammation with saline washes and sprays, intranasal and systemic corticosteroids, antibiotics and antileukotriene agents (70). In patients in whom these medical interventions do not result in sufficient improvement in symptoms, surgical treatment (endoscopic sinus surgery or polypectomy) could take place. Biologic agent as dupilumab are not validated to treat CRS in pediatric population, being approved in adults and adolescents with moderate-to-severe asthma with an eosinophilic phenotype or with oral corticosteroid-dependent asthma, and in adults only for severe CRSwNP (71).

Dysfunctional breathing

Dysfunctional breathing (DB) is as an alteration in the normal biomechanical pattern of breathing that result in intermittent dyspnea, wheezing, cough and upper chest pain and other non-respiratory symptoms (4). DB is associated with asthma morbidity through a number of potential mechanisms and a complex interrelationship including anxiety, psychological disorders and emotional distress (72). As symptoms of DB may mimic or be mistaken for those of asthma, identifying DB as a comorbidity complicating asthma attack or severe asthma can be challenging as there is considerable overlap in these conditions. In addition, when hyperventilation is documented, there might be symptoms that overlap also with anxiety, for example dizziness, palpitation, paresthesia, lack of concentration and fatigue (8, 73). An association of DB and poor asthma control was strong and well documented in a study population of 760 Italian adolescents, where DB were ten times more common in subjects with asthma (25%) than in those without asthma (2,5%) (74). Hepworth et al. reported a higher prevalence of DB symptoms (35%) in a cohort of children, probably due to the baseline suspicion of DB and the consequent referral to physiotherapist intervention (75). Directly observing breathing pattern by a specialist respiratory physiotherapist is useful to detect DB, as it provides a semi-objective tool to characterize DB in treatment-refractory asthma (76). Other objective assessments have been tested and validated, including the cardiopulmonary exercise testing and hyperventilation provocation test (77). An early referral to an experienced respiratory physiotherapist, a specialist in speech and language therapy or a psychologist might help to manage DB and to improve asthma symptom in children (73). A review of randomized controlled trials evaluated the effects of breathing exercises in children with asthma but did not draw reliable conclusions, due to the unclear risk of bias and the low quality of the evidence (78), despite breathing exercise intervention improved significantly asthma symptoms (75).

Vocal cord dysfunction

Vocal cord dysfunction (VCD) is an involuntary adduction of vocal cords during inspiration that can be misdiagnosed as asthma or can amplify symptoms of asthma, with poor or no response to asthma medicaments and unavoidable persistent poor asthma control (79). Symptoms can be very similar to those of asthma and vary from mild dyspnea to acute breathlessness, whereas inspiratory stridor (often mistaken for wheezing) is the hallmark presentation of VCD (80, 81). The cause of VCD is unknown, but functional component due to psychological stresses is thought to be the most involved. Also exercise, upper respiratory tract infections and local irritation (e.g., smoke, chemical irritant, reflux) that lead to increased laryngeal sensitivity can be responsible for VCD (81). Among pediatric patients, VCD prevalence is not well established as it can mimic asthma (82), or it can coexist with asthma (83) masquerading as a difficult to treat asthma. It is largely known to be more frequent in female patients and in elite or intense young athletes (79, 81, 84). The gold standard for diagnosing VCD is fiberoptic laryngoscopy, which ideally should be performed while the patient is symptomatic or under circumstances that elicit VCD symptoms (81), as exercise, methacholine or irritant substances. In patients with exertional dyspnea, continuous laryngoscopy exercise-test (CLE) during physical exercise reveals VCD occurring and peaking during exercise, whereas in case of asthma, it usually peaks 5–20 min after the end of exercise (79). As laryngeal dysfunction responds to speech pathology intervention, psychotherapy coupled with breathing techniques are considered the milestone treatment of VCD (9). Pharmacological therapies are used to treat co-existing or triggering comorbidities of VCD, as rhinitis or GERD. Ipratropium or injection with Clostridium botulinum toxin (off-label in the pediatric population) into laryngeal muscles can also be considered (81).

Conclusions

Severe asthma in children remains a clinical challenge. Comorbid conditions may complicate asthma management or can lead to misdiagnosis of asthma, with consequent undertreatment or overtreatment. Identifying asthma comorbidities is essential to better asthma and severe asthma management and to improve symptom control and patients' quality of life. Multiple comorbidities can coexist in the same patient, as GERD and obesity, moreover some comorbid conditions may not have a clear etiological

association with asthma, being a coincidental finding, as ABPA or VCD. All possible risk factors for comorbidities need to be investigated to ensure the maximal effort to get symptoms control. An appropriate multidisciplinary assessment and a stratified diagnostic approach are mandatory for the best management and treatment of comorbidities.

Author contributions

LR and AF: critical revision of the article. BC, MG, and IE: drafting the article. EB: conception or design of the work. All authors contributed to the article and approved the submitted version.

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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Relationship between maternal folic acid supplementation during pregnancy and risk of childhood asthma: Systematic review and dose-response meta-analysis

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Growing evidence suggests that maternal folic acid supplementation during pregnancy may be associated with the risk of childhood asthma, but these findings remain controversial. Therefore, the purpose of this systematic review and meta-analysis was to assess the association between maternal folic acid supplementation during pregnancy and the risk of childhood asthma, and to determine the safe dose of folic acid supplementation during pregnancy based on a dose-response analysis to lower the risk of childhood asthma. The PubMed, Embase, Cochrane Library, and Web of Science databases were searched for relevant studies published before April 2022. The Newcastle-Ottawa Scale (NOS) was used to evaluate the quality of eligible studies, and a fixed-effect model was employed to calculate the odds ratio (OR) of asthma with 95% confidence intervals (CI). In addition, the generalized least-squares trend (GLST) was used to explore a nonlinear dose-response relationship. Stata 15.0 was used for the statistical analysis mentioned above. This systematic review included 18 studies (13 cohort studies, 5 case-control studies) with a total of 252,770 participants, 50,248 of whom were children with asthma. The meta-analysis showed that maternal folic acid supplementation during pregnancy was significantly associated with the risk of childhood asthma (OR = 1.07; 95% CI = 1.04–1.11). The subgroup analysis revealed a significant correlation between the risk of childhood asthma and the folic acid supplementation in the first Trimester (OR = 1.09; 95% CI = 1.05–1.12), the third Trimester (OR = 1.15; 95% CI = 1.04–1.26) and the whole pregnancy (OR = 1.13; 95% CI = 1.10–1.16). At the same time, the dose-response analysis showed a nonlinear relationship between maternal folic acid intake during pregnancy and the risk of childhood asthma. The risk of asthma in children significantly increased when maternal folic acid intake reached 581 μg/day. This meta-analysis showed that maternal folic acid supplementation during pregnancy increased the risk of asthma in children. Based on the results of the dose-response analysis, less than 580 μg folic acid per day is advised in order to effectively prevent birth defects without increasing the risk of childhood asthma.

Systematic Review Registration: https://www.crd.york.ac.uk/prospero/display_record.php?, identifier: CRD42022332140.

KEYWORDS

folic acid, asthma, children, pregnancy, risks, dose-response meta-analysis

Introduction

Asthma is the most prevalent chronic respiratory disease in children and adults, affecting approximately 334 million people worldwide. It is characterized by variable expiratory airflow restriction and recurrent symptoms, such as wheezing, shortness of breath, chest tightness, and cough (1, 2). Furthermore, asthma in children may represent 20% of the population (3). Asthma prevalence is steady or falling in many developed countries, but rising rapidly in developing countries where lifestyles are getting westernized (4, 5). Despite the widespread use of inhaled corticosteroids and the standardization of guidelines for asthma treatment, most children's asthma control remains suboptimal (6, 7). Although global asthma-related mortality continues to decrease (8), the high incidence of asthma in children leads to stunting (9), absenteeism (10), and increasing personal (11) and socioeconomic burdens (12). Therefore, identifying the risk factors for childhood asthma is important for primary prevention and early intervention of asthma (13, 14).

Asthma is caused by a complex gene-environment interaction. The occurrence of asthma is closely correlated with nutritional supplementation (15). Folic acid, an essential B vitamin, plays a key role in protein synthesis and cell division and growth, because it acts as a single-carbon donor in the synthesis of methionine, nucleotides, and pantothenic acid (16, 17). In addition, folic acid features in epigenetics by providing methyl groups for DNA methylation reactions (18). As a result, folic acid plays an irreplaceable role in people's health, especially in the early stages of life's growth and development (19). Several studies have reported that insufficient maternal folate levels during pregnancy may cause multiple birth defects in the fetus, such as neural tube defects (20), heart defects (21), and craniofacial malformations (22). Therefore, the World Health Organization recommends that all pregnant women should supplement and fortify folic acid in their diet to prevent birth defects (23). Some countries have even made folic acid fortification mandatory in recent years (24). However, supplementation combined with mandatory fortification has resulted in higher levels of folic acid and related metabolites in women of childbearing age (25). Recent studies have shown that excessive folic acid intake may harm the health of an offspring, such as impaired embryonic brain development (26), metabolic dysfunction (27), and allergic diseases (28).

In recent years, researchers have increasingly focused on the association between folic acid supplementation during pregnancy and the risk of childhood asthma, but their findings are inconsistent. Therefore, we conducted a comprehensive systematic review and meta-analysis based on available evidence to investigate (1) whether maternal folic acid supplementation during pregnancy is associated with the risk of childhood asthma; (2) whether there is a relationship between the occurrence of asthma in children and the daily intake of folic acid in mothers; (3) the relationship between folic acid supplementation and childhood asthma development at different stages (before conception, first trimester, second trimester, third trimester, whole trimester, and others); and (4) whether the association between maternal folic acid supplementation and the risk of childhood asthma varies with economic development levels of different countries.

Methods

This meta-analysis was reported according to the PRISMA 2020 (The Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020) guideline and MOOSE (Meta-analysis of Observational Studies in Epidemiology) recommendations (29, 30). PROSPERO Registration ID: CRD42022332140.

Search strategy

The PubMed, Embase, Cochrane Library, and Web of Science databases were retrieved for relevant studies published before April 12th, 2022. Both subject words (MeSH) and free words were searched. The search terms included "Folic Acid" [Mesh] and "Asthma" [Mesh]; the keywords were: "Folic Acid" OR "Vitamin M" OR "Vitamin B9" OR "B9, Vitamin" OR "Pteroylglutamic Acid" OR "Folvite" OR "Folacin" OR "Folate" in combination with "Asthma" OR "Asthmas". The search strategy is shown in **Supplementary Annex 1**. In addition, the references of review articles were searched for potentially eligible studies.

Selection criteria

This systematic review complied with the following inclusion and exclusion criteria to select eligible studies.

Inclusion criteria: original studies on the association between folic acid supplementation during pregnancy and the

risk of childhood asthma; (2) cohort studies or case-control studies; (3) studies that provided risk evaluation of the association between childhood asthma and maternal daily folic acid intake or serum folate concentrations in women during their pregnancy; (4) studies published in English.

Studies with the following characteristics were excluded: (1) the sample size was too small (sample size <50); (2) there was no direct or indirect access to the odds ratio (OR) or relative risk (RR); (3) there were serious defects in the research data, and the literature was published in gray journals.

Literature screening and data extraction

The retrieved studies were imported into EndNote X9. After removing duplicates, irrelevant studies were also deleted based on the titles and abstracts. Then the full texts of the remaining articles were downloaded and read to determine whether they could be finally included. The following data were extracted from all included studies: first author, date of publication, country and region, study design, source of participants, time of sampling, sample size, age, the period of folic acid supplementation, folic acid intake, statistical analysis, covariate adjustment, outcome measures, and other relevant characteristics. If several included studies reported ORs adjusted for different covariates, the ORs with the most adjusted covariates were extracted.

Literature screening and data extraction were independently carried out by two researchers (Y. F. S. and W. Z. T.) and cross-checked after completion. If there were any dissent, a third researcher (S. L. P.) was consulted to assist in the determination. If there was a lack of data, the researchers tried to contact the author to obtain it. If the information was inadequate, the researchers contacted the corresponding authors for more detailed data or other relevant information.

Quality assessment

The Newcastle-Ottawa Scale (NOS) (31) was used to evaluate the quality of the included studies. The NOS scale comprises three domains with a total of eight items: four items for study subject selection, one for comparability between groups, and three for outcome measures. The total score ranges from 0 to 9 points. A score of 0–3, 4–6, and 7–9 is considered low quality, medium quality, and high quality, respectively.

Statistical analysis

The meta-analysis was performed using Stata 15.0 (StataCorp, College Station, TX, United States), and the effect size was evaluated by OR with 95% confidence intervals (CI). The heterogeneity among the included studies was calculated by the Q test, and the heterogeneity index I^2 was used to quantify the size of the heterogeneity. If $I^2 < 50\%$, a fixed-effects model was used for meta-analysis; if $I^2 > 50\%$, a random-effects model was employed. Subgroup analyses and sensitivity analyses were conducted to explore potential sources of heterogeneity. A dose-response meta-analysis was also performed to explore the association between folic acid intake and the risk of childhood asthma. Restricted cubic spline models at four knots (10th, 35th, 65th, and 95th centiles) were established using the generalized least-squares trend (GLST). Furthermore, the cubic splines were used to model the nonlinear association between the daily dose of folic acid supplementation and childhood asthma. Accordingly, a dose-response nonlinear curve was plotted. A funnel plot was used to evaluate the publication bias, and Egger's and Begg's tests were also used to diagnose the publication bias. A $p < 0.05$ indicates the existence of publication bias. Under this circumstance, the impact of publication bias on the meta-analysis was evaluated using the trim-and-fill method. In this study, a $p < 0.05$ indicated that the difference was statistically significant.

Results

Literature search

Initially, 999 studies were retrieved from PubMed ($n = 111$), Embase ($n = 537$), Cochrane Library ($n = 87$) and Web of Science ($n = 264$). After the duplicates and irrelevant studies were removed based on the titles and abstracts, the full texts of the remaining 28 articles were downloaded and read to exclude ineligible studies according to the inclusion and exclusion criteria. Finally, 18 studies were included in this meta-analysis. The literature selection process is presented in **Figure 1**.

Characteristics of the included studies and quality evaluation

Table 1 shows the characteristics of the included studies. A total of 18 (32–49) studies were eligible for our meta-analysis, including 13 cohort studies and five case-control studies. These studies were published between 2006 and 2022, involving 252,770 participants, including 50,248 children with asthma. Seven studies were conducted in Europe (37, 39, 42, 43, 45, 46, 48), five in North America (35, 36, 38, 40, 49), four in Asia (32–34, 44) and two in Australia (41, 47). The included studies adjusted for potential confounders, such as maternal age, race, parity, education level, smoking history, asthma history, infant sex, birth weight, mode of delivery, and feeding method. The NOS

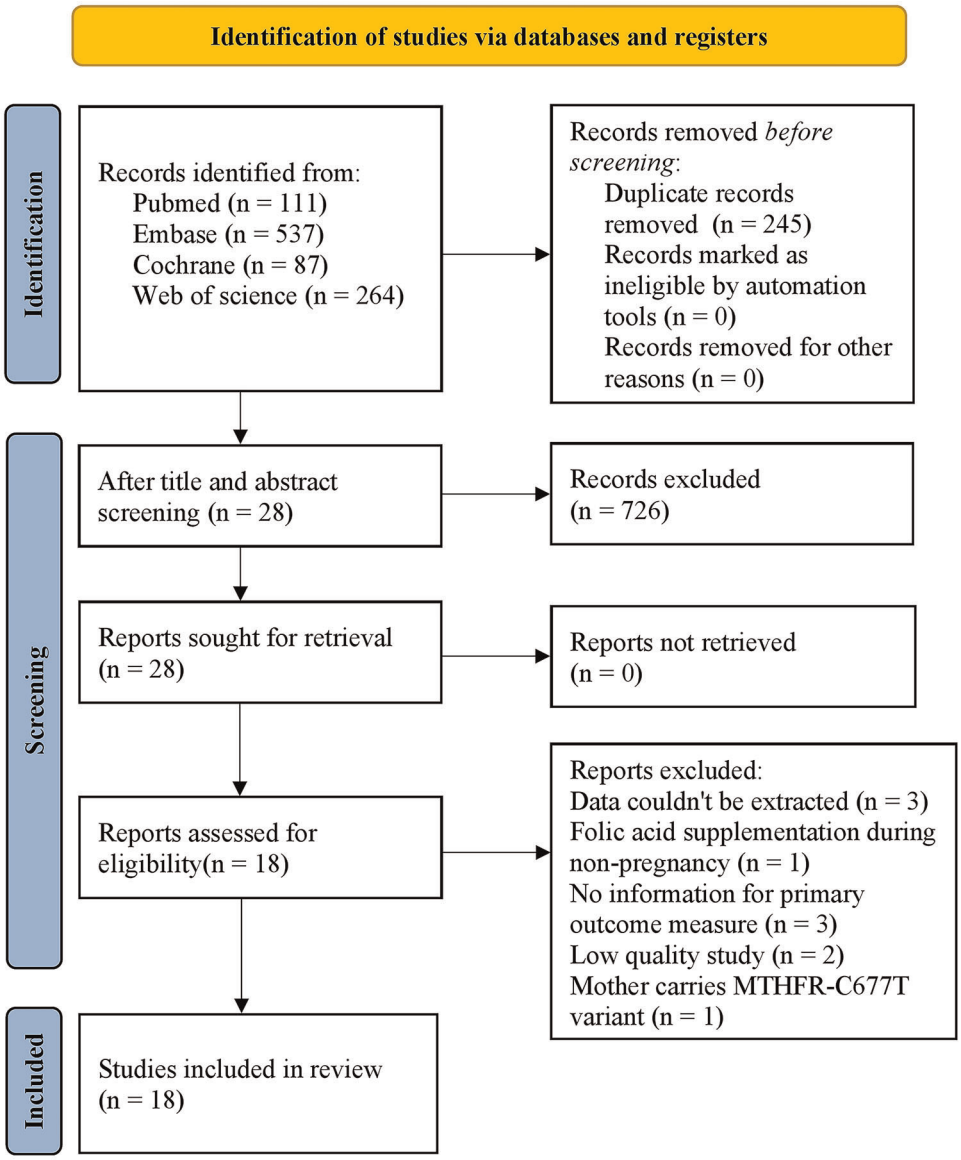

FIGURE 1
Flow diagram of literature selection.

evaluation results are shown in **Table 1**. Overall, the scores for study quality ranged from 5 to 8. Twelve original studies (32, 33, 36–38, 40–42, 44–46, 49) were assessed as high quality, and six (34, 35, 39, 43, 47, 48) assessed as medium quality.

Relationship between folic acid supplementation during pregnancy and the risk of childhood asthma

Of the 18 included studies, 13 studies (32–35, 37, 39, 41–46, 49) reported an association between maternal folic acid supplementation during pregnancy and the risk of asthma in children. A fixed-effect model ($I^2 = 21.8\%$) was used to pool effect sizes. The OR of maternal folic acid supplementation was 1.07 (95% CI = 1.04–1.11; $P = 0.128$), indicating that maternal folic acid supplementation during pregnancy was significantly associated with the risk of childhood asthma. Sensitivity analyses showed that deleting any single study had no significant effect on the overall OR.

Eight studies (32, 36, 38, 40, 43, 45, 47, 48) found a link between maternal folic acid supplementation at different times and the risk of childhood asthma. A subgroup analysis was performed based on the folic acid supplementation at different stages of pregnancy. The subgroup analysis found a significant association between the risk

TABLE 1 Basic information for the included studies.

The first author (y)	Country	Study design	Sources of participants	Sampling time	No. of participants/cases	Age (years)	Folic acid intake	Statistical analysis	Adjustment for covariates	Outcome measure	Study quality
Chu S, 2022	China	Case-control study	Shanghai, China	2015.06–2016.01	1364/548	4–12	400–800 μg/D	Unconditional logistic regression models.	Maternal education levels, paternal education levels, family history of allergic diseases in any of his family members, child age, gender, birthweight, gestational age, delivered by caesarean section, newborn resuscitation, and feeding in the first 6 months.	Period of folic acid exposure supplementation	7
Miyashita C, 2021	Japan	Cohort study	Hokkaido, Japan	2008–2015.09	6651/732 (1 years of age); 6651/1087 (2 years of age); 6651/838 (4 years of age); 6651/466 (7 years of age)	1, 2, 4, and 7	—	Logistic regression analysis.	Maternal age, parity, delivery year, alcohol consumption during pregnancy, log10-transformed maternal cotinine level, maternal allergic history, paternal allergic history, annual household income, and sex of the child.	Folic acid exposure	8
Liu J, 2020	China	Case-control study	China	2000.12–2001.09	9090/109	4–6	400 μg/D	Logistic regression analysis.	Maternal age at child birth, education, occupation, and parity.	Folic acid exposure	6
Alfonso VH, 2018	United States	Case-control study	Los Angeles, United States	2006–2007	1176/465	3	—	Poisson regression models with robust error variance and a log link function.	Mother's race/ethnicity and nativity, mother's age at pregnancy, mother's education at the time of pregnancy, use of preconception vitamins, initiation of prenatal care, alcohol use during pregnancy, home environmental tobacco smoke during pregnancy, pre-pregnancy BMI, marital status, primary source of payment for prenatal care, parity, and birth outcome. Maternal history of atopy, duration of exclusive breastfeeding, child attendance to daycare or preschool, infection during pregnancy, and housing characteristics.	Folic acid exposure	6
Roy A, 2018	United States	Cohort study	Memphis, Tennessee, United States	2006–2011	849/174	3	10 ng/ml (Maternal plasma folate level)	Logistic regression analysis.	Maternal age at enrollment, self-reported race, education, prenatal smoking, asthma, pre-pregnancy body mass index, 2nd trimester vitamin D levels, parity, delivery route, and child sex and birth weight, breastfeeding.	Supplementary period	8

(*continued*)

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TABLE 1 Continued

The first author (y)	Country	Study design	Sources of participants	Sampling time	No. of participants/cases	Age (years)	Folic acid intake	Statistical analysis	Adjustment for covariates	Outcome measure	Study quality
Parr CL, 2017	Norway	Cohort study	Norwegian birth registry and Norwegian Prescription Database	2014.04.01	39,846/1901	7	400 μg/D	Log binomial regression or multinomial logistic regressio.	Maternal age at delivery, parity, maternal education, prepregnancy body mass index, maternal smoking in pregnancy, and use of cod liver oil, other dietary supplements, and maternal energy intake in pregnancy.	Folic acid exposure supplement dosage	8
Veeranki SP, 2015	United States	Cohort study	Tennessee, United States	1996–2005	104,428/15,776	4.5–6	1000 μg/D	Multivariable logistic regression analysis.	Maternal characteristics included race, age at delivery, education, smoking during pregnancy, marital status, year of pregnancy, history of asthma, region of residence, and adequacy of prenatal care. Child characteristics included gender, birth weight, estimated gestational age and number of siblings.	Supplementary period	7
Zetstra-van der Woude PA, 2014	Netherlands	Case-control study	The pregnancy database IADB.nl, Netherlands	1994–2011	35,604/11,780	—	5000 μg/D	Logistic regression analysis.	Age of the mother, single or multiple pregnancy, maternal asthma medication, and paternal asthma medication. Dispension of iron supplements, antifolate medication, antidepressants, antihypertensives, antidiabetics, and benzodiazepines during pregnancy.	Folic acid exposure	6
Martinussen MP, 2012	United States	Cohort study	Massachusetts and Connecticut, United States	2003.09–2007.01	1499/223	6	Q1, 0 μg/D; Q2, <400 μg/D; Q3, 400–800 μg/D; Q4, >800 μg/D.	Logistic regression analysis. Variance (ANOVA) with Bonferroni and Scheffes Post Hoc tests.	Maternal parity, ethnicity and marital status, household income, maternal asthma, smoking during pregnancy, use of other vitamins (C, D and E), iron use, and calcium use in first trimester.	Supplementary period	8
Dunstan JA, 2012	Australia	Cohort study	Western Australia	—	628/59	1	Q1, <200 μg/D; Q2, 200–499 μg/D; Q3, >500 μg/D.	Associations between normally and lognormally distributed variables were evaluated in linear models. Logistic regression analysis.	Maternal age, maternal allergic disease, previous pregnancies, socioeconomic status, and education level. Infants' daycare attendance, infection history, postnatal dietary intervention, pet keeping, breast-feeding, and infant dietary patterns.	Folic acid exposure supplement dosage	8

(*continued*)

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TABLE 1 Continued

The first author (y)	Country	Study design	Sources of participants	Sampling time	No. of participants/cases	Age (years)	Folic acid intake	Statistical analysis	Adjustment for covariates	Outcome measure	Study quality
Bekkers MB, 2012	Netherlands	Cohort study	Netherlands	2004–2005	3604/822, 3 years of age; 3484/653, 4 years of age; 3418/605, 5 years of age; 3389/496, 6 years of age; 3299/406, 7 years of age; 3237/419, 8 years of age.	1–8	—	Log binomial regression analyses.	Sex, birth weight, gestational age, number of older siblings, maternal education, maternal allergy, maternal body mass index before pregnancy, maternal smoking during pregnancy, maternal use of other vitamin supplements (A, C, D or E) than folic acid-only, prenatal and multivitamin or vitamin B complex supplements, maternal age at child birth, breast feeding duration, smoking in the home by anyone at 1 yr of age, type of day care at 1 yr of age and region.	Folic acid exposure	8
Kiefte-de Jong JC, 2012	Netherlands	Cohort study	Netherlands	2002.04–2006.1	8742/3409, 1 years of age; 8742/1923, 2 years of age; 8742/1311, 3, 4 years of age.	0–4	400–500 μg/D	Logistic GEE analyses.	Maternal age at pregnancy; maternal BMI at inclusion; maternal educational level; maternal ethnicity; infant's sex; infant's birth weight and gestational age at birth; any maternal smoking during pregnancy; any maternal alcohol consumption during pregnancy; duration of breastfeeding; any attendance of day care of the child in the first 24 mo of the infant's life; parental atopic constitution.	Period of folic acid exposure supplementation	6
Miyake Y, 2011	Japan	Cohort study	Neyagawa City, Japan	2001.11–2003.03	763/169	16–24 months	Q1, 206.8 μg/D; Q2, 255.1 μg/D; Q3, 291.2 μg/D; Q4, 370.6 μg/D.	Logistic regression analysis; Multiple logistic regression analysis.	Adjustment for maternal age, gestation at baseline, residential municipality at baseline, family income, maternal and paternal education, maternal and paternal history of asthma, atopic eczema, and allergic rhinitis, changes in maternal diet in the previous 1 month, season when data at baseline were collected, maternal	Folic acid exposure supplement dosage	7

(*continued*)

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TABLE 1 Continued

The first author (y)	Country	Study design	Sources of participants	Sampling time	No. of participants/cases	Age (years)	Folic acid intake	Statistical analysis	Adjustment for covariates	Outcome measure	Study quality
									smoking during pregnancy, baby's older siblings, baby's sex, baby's birth weight, household smoking in same room as infant, breastfeeding duration, age at which solid foods were introduced, age of infant at the third survey, and maternal intake of docosahexaenoic acid, n-6 polyunsaturated fatty acids, vitamin D, calcium, vitamin E, and β-carotene during pregnancy.		
Magdelijns FJ, 2011	Netherlands	Cohort study	the KOALA study, Netherlands	2002.01	2640/130	6–7	—	Univariable and multivariable logisticregression analysis.	Recruitment group, maternal antibiotic, smoking and alcohol use during pregnancy, mode and place of delivery, birth weight, gender, treatment with antibiotics during the first 6 months of life, exposure to environmental tobacco smoke and domestic animals, breastfeeding, maternal education level, family history of atopy, siblings, day care attendance, and multivitamin or other supplement use during pregnancy.	Period of folic acid exposure supplementation	8
Håberg SE, 2011	Norway	Case-control study	the MoBa study, Norway	2002.07–2004.06	1962/507	3	Q1, <5.54 nmol/l; Q2, 5.54–7.68 nmol/l; Q3, 7.68–10.6 nmol/l; Q4, 10.6–17.84 nmol/l; Q5, >17.84 nmol/l. (Maternal plasma folate level)	Univariate and multivariate logistic regression analysis.	Maternal atopy, maternal educational level, parity, maternal prepregnancy body mass index (BMI) calculated from height and prepregnancy weight, maternal smoking in pregnancy, maternal smoking when the child was three years, and the child's use of vitamin supplements or cod liver oil at three years of age.	Folic acid exposure	8
Whitrow MJ, 2009	Australia	Cohort study	Adelaide, Australia	1998–2005	557/57, 3.5 years of age; 557/50, 5.5 years of age.	3.5, 5.5	400 μg/D	Poisson regression model.	—	Supplementary period	5

(*continued*)

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TABLE 1 Continued

The first author (y)	Country	Study design	Sources of participants	Sampling time	No. of participants/cases	Age (years)	Folic acid intake	Statistical analysis	Adjustment for covariates	Outcome measure	Study quality
Håberg SE, 2009	Norway	Cohort study	the MoBa study, Norway	2000.01–2005.06	32,077/12,656	6–18 months	400 μg/D	Generalized linear model.	Other supplements in pregnancy, sex, birth weight, month of birth, and maternal atopy, maternal educational level, parity, maternal smoking in pregnancy, type of day care, parental smoking in first 3 months after birth, breast feeding at 6 months, and exposure to vitamin supplements or cod liver oil at 6 months of age.	Supplementary period	6
Litonjua AA, 2006	United States	Cohort study	Boston, United States	1999.04–2002.07	1290/376	2	400 μg/D	Bivariate logistic regression models.	Birth weight, neonate sex, maternal age, maternal prepregnancy body mass index, breastfeeding duration, the number of children <12 y old in the home, postnatal passive smoke exposure, family income, and maternal and paternal asthma.	Folic acid exposure	8

of childhood asthma and the folic acid supplementation in the first trimester (OR = 1.09; 95% CI = 1.05–1.12), the third trimester (OR = 1.15; 95% CI = 1.04–1.26), and the whole pregnancy (OR = 1.13; 95% CI = 1.10–1.16). Since few studies focus on prefecundation and the second trimester, we failed to explore the association between folic acid supplementation and childhood asthma risk during the two periods based on available evidence. The subgroup analysis based on folic acid supplementation in different periods of pregnancy is shown in **Figure 2**.

Another subgroup analysis was conducted according to the economic development level of different countries. Eleven studies (33, 35, 37, 39, 41–46, 49) were included in the analysis of high-income economies (OR = 1.05; 95% CI = 1.01–1.09), and two studies (32, 34) were included in the analysis of middle-income economies (OR = 1.26; 95% CI = 1.13–1.41). However, no literature was available for the analysis of low-income economies. According to this subgroup analysis, folic acid supplementation during pregnancy increased the risk of asthma in children regardless of the economic development levels.

Dose-response analysis

Studies with relevant data were selected for a dose-response analysis (37, 41, 44). The results of the dose-response analysis showed a nonlinear relationship between maternal folate intake during pregnancy and childhood asthma risk. Maternal folate intake of less than 581 μg/day had no association with childhood asthma risk, whereas the intake of 581 μg/day or more significantly increased the risk of childhood asthma. The dose-response nonlinear curve is shown in **Figure 3**.

Publication bias

A funnel plot was plotted to test the publication bias. The results showed that the left and right distributions were symmetrical, as shown in **Figure 4**. Neither Egger's test (P = 0.982) nor Begg's test funnel plot revealed publication bias. The results of Egger's test are shown in **Figure 5**.

Discussion

The results of the meta-analysis suggested that maternal folic acid supplementation during pregnancy was associated with the risk of childhood asthma. According to subgroup analyses, the effects of folic acid supplementation were found to be significant in the first trimester, the third trimester, and the whole pregnancy. In addition, folic acid supplementation during pregnancy increased the risk of childhood asthma regardless of the economic development levels of different

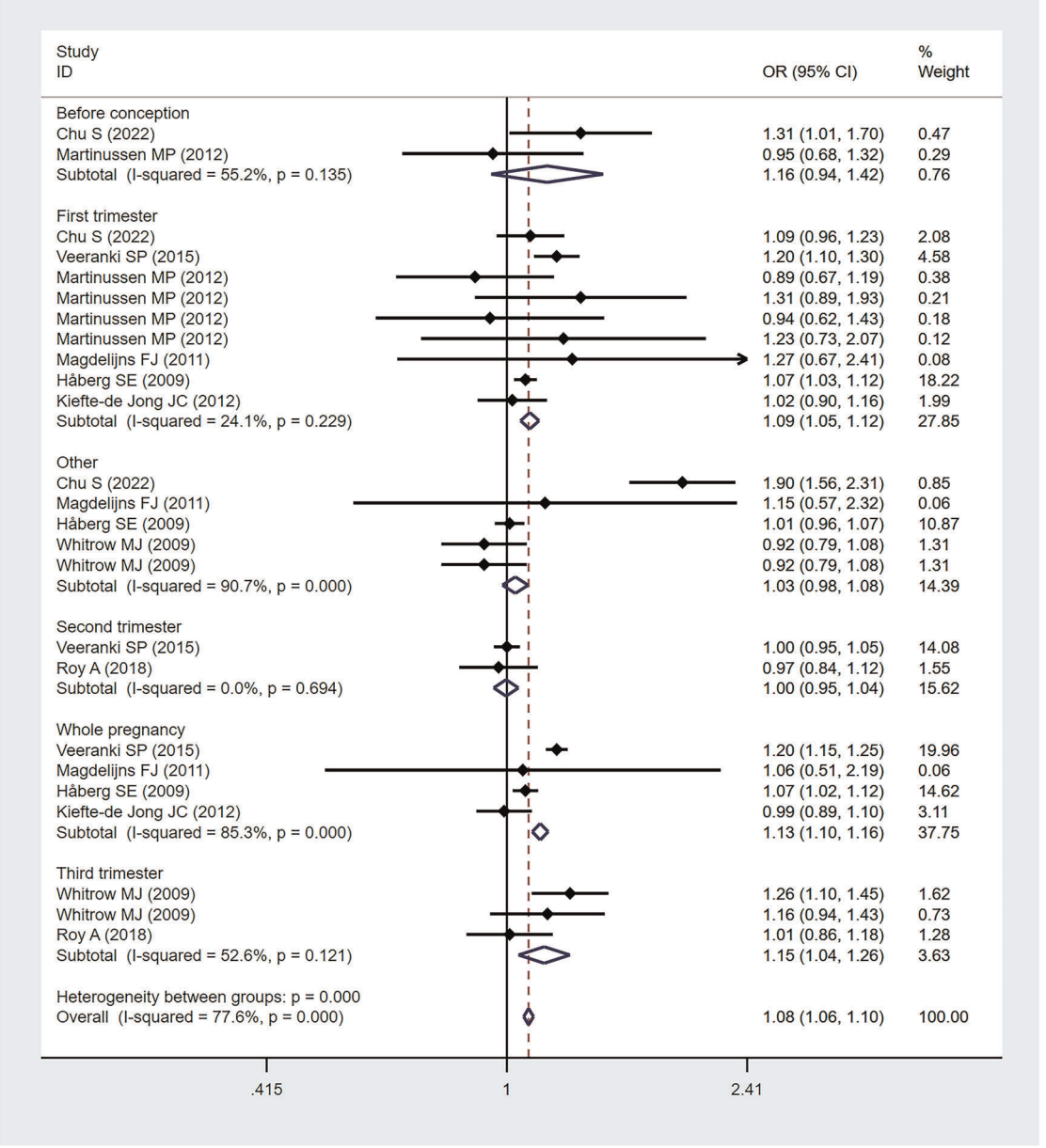

FIGURE 2
Subgroup analysis based on folic acid supplementation in different periods of pregnancy.

countries. The dose-response analysis showed a nonlinear relationship between maternal folic acid intake during pregnancy and the risk of childhood asthma. The maternal folic acid intake of less than 581 μg per day is not correlated with the risk of childhood asthma. However, the risk of childhood asthma significantly increases when the intake reaches 581 μg or more per day.

Litonjua AA. et al. (49) were the first to study the association between maternal folic acid supplementation during pregnancy and childhood asthma. Since then, researchers have been increasingly interested in this topic, but their findings are inconsistent and conflicting. This association was summarized in four previous meta-analyses. Krista et al. (50) conducted a meta-analysis of 5 studies, which showed that folic acid supplementation had no association with an increased risk of childhood asthma between preconception and the first trimester (RR = 1.01, 95% CI = 0.78–1.30); in addition, a meta-analysis of 5 studies by Yang L et al. (51) reported the same results (OR = 1.06, 95% CI = 0.99–1.14). However, a meta-analysis by Wang T et al. (52) suggested

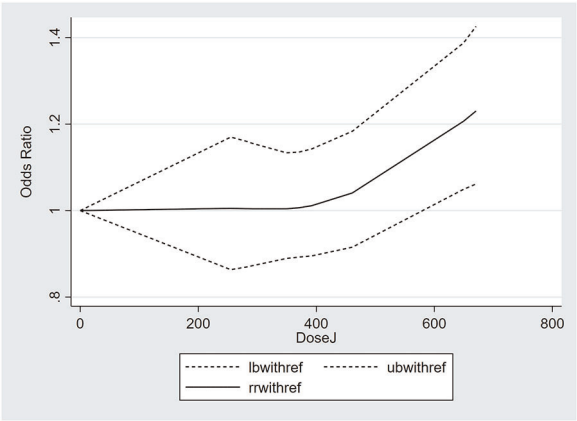

FIGURE 3
Dose-response analysis of daily maternal folic acid intake and risk of childhood asthma.

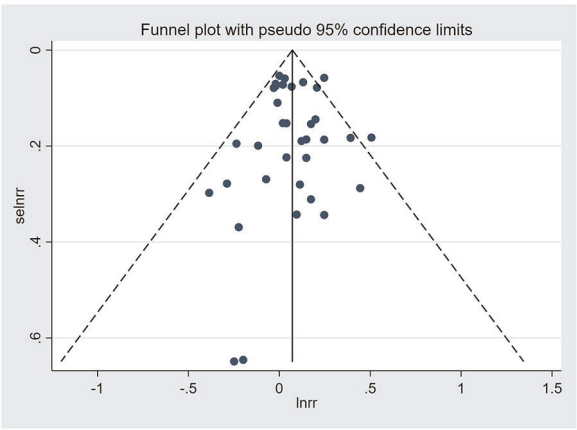

FIGURE 4
Funnel diagram.

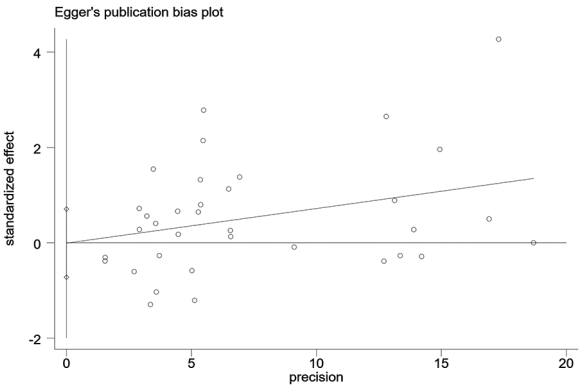

FIGURE 5
Egger's test.

that maternal folic acid supplementation in early pregnancy may increase the risk of asthma in young children (RR = 1.06, 95% CI = 1.02–1.09); Li W et al. (53) also reported that maternal folic acid exposure during pregnancy was significantly associated with infant asthma risk (RR = 1.11; 95% CI = 1.06–1.17). Since the last meta-analysis was published, six more related studies with inconsistent results have emerged, allowing for more robust estimation and quantification. Given the controversy over the association between maternal folic acid supplementation during pregnancy and the risk of childhood asthma, we included new and updated studies for further meta-analysis to thoroughly investigate this relationship and clarify the dose-response association between maternal folic acid intake and childhood asthma.

The relationship between folic acid supplementation during pregnancy and childhood asthma is under exploration. Current evidence suggests that DNA methylation plays a key role in this process (54). DNA methylation is catalyzed by the enzymes that transfer methyl groups (methyl-transferases) from the methyl agent S-adenosylmethionine to cytosine. It is an epigenetic modification that is essential for normal genome regulation and development (55). Folate is a key source of the one-carbon group used to methylate DNA. Hollingsworth JW et al. (56) found that high-methyl donor diets may increase the risk of allergic airway disease in children through DNA methylation and transcription of abnormal genes. Studies also found that Runx3 mRNA (Runt-related transcription factor 3, a gene known to negatively regulate allergic airway disease) and protein levels were suppressed in offspring exposed to a hypermethylated (overmethylated) diet *in utero*. İscan B et al. (57) found that maternal folic acid supplementation during pregnancy affected offspring's airway remodeling and increased allergic reactions caused by offspring's ovalbumin excitation; additionally, the intensity of the response increased with the duration of supplementation and the accumulative dose. Despite an increasing number of related studies, we recognize that the mechanisms of folic acid inducing asthma in children remain unknown.

WHO and most countries recommend that pregnant women should maintain a healthy diet and take folic acid supplementation of 400 micrograms/day to prevent birth defects (58). According to this dose-response analysis, the risk of asthma in children significantly increased when the maternal folate intake reached 581 μg/day. A study with similar results suggested that maternal folic acid supplementation at a high dose during pregnancy was associated with an increased risk of asthma in infants, while a relatively low dose reduced the risk of asthma in infants (51). This reveals that although folic acid can effectively prevent birth defects, the adverse effects of high-dose supplementation on the health of children cannot be ignored. Therefore, how to safely supplement folic acid during pregnancy needs to be explored and verified by relevant

research. In the subgroup analysis, we found that folic acid supplementation was significantly associated with the risk of asthma in children in the first trimester, the third trimester, and the whole pregnancy. Recommendations vary from country to country, but most advise folic acid supplementation from the first trimester (4 to 12 weeks) to the end of the second trimester (8 to 12 weeks) (58). Given that the neural tube closes around the 28th day of the embryo, the critical period for folic acid supplementation is in the first and second trimesters (59). The need for folic acid supplementation at other stages of pregnancy and its impact on the risk of childhood asthma requires further studies to confirm.

There are several advantages to our study. First, our analysis included 18 relevant studies, including those published in 2022. It is more statistically convincing than previous studies due to newer and larger sample sizes. Second, a subgroup analysis was conducted according to the different folic acid supplementation periods to explore the effect of folic acid supplementation at different periods on the risk of childhood asthma. Third, we made full use of the dose data of the included studies to conduct a dose-response analysis, which quantitatively revealed the relationship between folic acid intake during pregnancy and the risk of childhood asthma based on a qualitative summary. A dose-response curve was drawn, which may help develop strategies for safe folic acid supplementation during pregnancy. Finally, there is no publication bias in our analysis. However, some limitations of the present study should also be taken into account. First, all included studies adjusted for multiple confounding factors, but these factors were inconsistent and the effects of other confounding factors could not be excluded. Second, it is difficult to accurately calculate the dose of folic acid that pregnant women consume from both natural food and synthetics (vitamin supplements or prenatal fortification supplements). Third, the age of study participants varied widely from less than one year old to twelve years old, which might lead to a bias in the study results. Finally, only three studies were included in the dose-response analysis; therefore further dose-response studies are required for further validation.

Conclusion

Maternal folic acid supplementation during pregnancy increases the risk of childhood asthma. At the same time, dose-response analysis testified a nonlinear relationship between folic acid intake during pregnancy and the risk of childhood asthma. When the maternal folate intake is ≥581 μg/day, the risk of asthma in children significantly increases. Although folic acid supplementation during pregnancy can prevent birth defects, its adverse effects on the health of offspring cannot be ignored. Therefore, we recommend that the daily dose of folic acid supplementation for pregnant women should be less than 580 μg, which can effectively prevent birth defects without increasing the risk of asthma in children.

Data availability statement

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

Author contributions

Concept and design: FSY, JPZ, ZTW, LW, THT, LPS. Acquisition of data: FSY, JPZ, LPS. Statistical analysis: FSY, ZTW, LPS. Interpretation of data: FSY, LW, THT, LPS. Writing original draft: FSY, LPS. Writing review and editing: all authors. All authors contributed to the article and approved the submitted version.

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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.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2022.1000532/full#supplementary-material.

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Severe pediatric asthma therapy: Dupilumab

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Severe asthma is a rare disease affecting <5% of children with asthma. This group of patients account for about 50% of the costs of healthcare for children with asthma. Nowadays, several biological agents are available for pediatric severe asthma. One of these is dupilumab, a monoclonal antibody against the Interleukin (IL)-4 receptor α-subunit that acts as an antagonist against both IL-4 and IL-13. Dupilumab binds the subunit of the IL-4 receptor, at the level of the subunit shared by the IL-13 receptor, blocking the inflammatory cascade of these two cytokines and the progression of the Th2-inflammatory pathway. The efficacy and safety of dupilumab have been investigated in recently published randomized controlled trials including pediatric patients with asthma. Currently, its use in asthma is approved in adults, adolescents, and children with severe asthma with type 2 inflammation, that are not controlled in spite of high-dose inhaled corticosteroids plus another maintenance drug. Studies are warranted for the evaluation of long-term treatment with dupilumab, including steroid sparing effect and discontinuation of treatment. Further research should also be planned in order to investigate dupilumab potential ability to interfere with the natural history of atopy since early childhood.

KEYWORDS

asthma, children, monoclonal antibody, IL-4, IL-13, asthma therapy, dupilumab

Introduction

Asthma is a chronic disease characterized by reversible airflow obstruction, hyper-responsiveness, remodeling and progressive deterioration of lung function.

Severe asthma is defined as deficient control of asthma symptoms despite a therapy with high doses of inhaled corticosteroids (ICS) and long-acting β2-agonists (LABA) or need of recurrent oral corticosteroids (OCS) (level 4–5 GINA guidelines) (1) or by loss of asthma control when reducing the high-intensity treatment (2).

In the pediatric field, severe asthma is a rare pathology affecting <5% of children with asthma (3). Despite the low number of children with severe asthma, this group of patients account for about 50% of the costs of healthcare for children with asthma. Therefore, these patients are a challenge related to ample diagnostic evaluation and high consumption of healthcare sources.

It is firstly mandatory to confirm the diagnosis and evaluate the patient for at least three months to define severe asthma and the specific endotype of the patient.

According to the international guidelines (4), the evaluation of pediatric patient with severe asthma is based on the optimization of the standard therapy. Furthermore, the use

of biological drugs must be considered when symptoms are not controlled, despite all the measures suggested (control of the environment factors and rigorous adhesion to drug therapy). Then, it is important to correctly select suitable patients for a specific biologic therapy, both for medical reasons and the high cost of these drugs.

Pediatric asthma is mainly characterized by a T helper type (Th)-2-inflammation in which the release of interleukin (IL)-4, IL-13, IL-5, and the immunoglobulin E (IgE) production increase eosinophilic survival.

In the last decades, many advances have been made in knowledge of pediatric asthma diseases and the role of the Th2-mediated inflammatory response.

Nowadays, several biological agents are now available for pediatric severe asthma. The approved biological drugs for the treatment of uncontrolled severe asthma target specific points of the Th2-inflammatory cascade and different agents target different endotypes of disease.

Their mechanism of action acts on peculiar cytokines of the Th2-inflammation cascade, such as IL-4, IL-5, and IL-13, and IgE, inhibiting definite targets in patients that do not respond to traditional therapy modifying the natural course of allergic inflammatory response (5).

One of these biological agents is dupilumab, a monoclonal antibody directed against the IL-4 receptor α-subunit (IL-4Ra) that acts as an antagonist against both IL-4 and IL-13 and is approved for pediatric severe type 2 asthma.

Mechanisms of dupilumab

"Th2-mediated diseases" such as allergic asthma, atopic dermatitis (AD), allergic rhinitis (AR), chronic rhinosinusitis with nasal polyps (CRSwNP), and eosinophilic esophagitis (EoE) are characterized by type 2 inflammation associated to different pro-inflammatory cytokines released by epithelial cells (6–8).

These groups of inflammatory disorders that involved different tissues share the same mechanisms of action driven by CD4+ Th2 lymphocytes and type 2 innate lymphoid cells (ILC2). Inside that inflammatory pathway, IL-4 and IL-13 are produced by eosinophils, basophils, mast cells, CD8+ cells, and natural killer (NK) cells and have a key role in the allergic inflammatory response. Airways inflammation and remodeling are the typical asthma features related to these mediators.

IL-4 and IL-13 are involved in the pathophysiology as evidenced by the high level of these cytokines in peripheral blood, bronchoalveolar lavage (BAL), induced sputum, and bronchial mucosa of asthmatic subjects.

The polymorphisms found in the RAD50-IL-13 region of chromosome 5q31.1 of IL-13 is involved in determining the individual predisposition to asthma (9).

IL-4 and IL-13 play separate pathophysiologic functions in asthma. IL-4 acts in the initial polarization of naïve CD4+ Th cells to a Th2 phenotype, while IL-13 is essential in the bronchial hyperresponsiveness and in promoting airway inflammation and remodeling.

The heterodimeric IL-4 complex is composed by a common subunit called IL-4Rα, which pairs with subunits that mediate the action of IL-4 and IL-13 in different tissues (10).

The "subtype I" is expressed in hematopoietic cells and binds only—IL-4 to form IL-4R type 1. The first step starts when IL-4 binds the subunit IL-4Rα with high affinity. The complex IL-4/IL-4Rα is identified by the γ-chain and the IL-4 signaling is activated 10.

The "subtype II" is expressed in hematopoietic cells and non-hematopoietic cells and can be derived from the union of IL-4Rα with the IL-13 (IL-13Rα1) receptor to form a heterodimer between IL-13 and IL-4.

The connection between IL-4 and IL-13 to their receptor triggers the transduction of the signal by transphosphorylation and activation of the receptor subunit associated with Janus family protein kinase (JAK). In particular, receptor type I interacts with Janus kinases 1 (JAK1), 2 (JAK2), and 3 (JAK3), which are combined to the IL-4Rα, IL-13Rα1, and γc chains, respectively. JAK cascade induces the release of transcription factors and specific tyrosine residues located in the cytoplasmatic domain of the IL-4Rα (11, 12).

JAK1 and JAK3 phosphorylate specific tyrosine, which can then act as reduction sites for signal transducer for both activation of transcription (STAT)-6 and for insulin receptor substrate-2 (IRS-2) proteins.

After JAK1/JAK3-dependent tyrosine phosphorylation, STAT-6 dimerizes and move to the nucleus, where it upregulates the transcription factor GATA3. Then the binding to the promoter regions of the IL-5 and IL-13 genes improves their expression. IRS-2 proteins cooperate with the p85 subunit of phosphoinositide-3 kinase (PI3K) and with the adaptor protein growth factor receptor-bound protein 2 (Grb2), which are related to the PI3K/AKT pathway characterized by the proliferation of Th2 cells and differentiation of M2 macrophages. The heterodimeric IL-4Rα/IL-13Rα1 type II receptor complex is functionally correlated to JAK1/2, tyrosine kinase 2 (Tyk2), and STAT-6, but not to JAK3 and IRS-2 (13, 14).

IL-13 also binds with high affinity to the α2 chain of the IL-13 receptor (IL-13Rα2) implementing an endogenous self-regulating negative circuit that limits IL-13 activities (15, 16).

Furthermore, other pathways involved in the regulation of allergic responses (insulin receptor substrate IRS1/2)/phosphoinositide 3-kinases (PI3K)/mTOR Complex 2 (mTORC2)/AKR mouse thymoma kinase (AKT), SHC/MAPK, and Src homology 2 domain-containing protein tyrosine phosphatase-1 (Shp-1)) are activated by the IL-4 receptor.

Receptor type II interacts with JAK1, JAK2, and the tyrosine kinase 2 (TYK2), which can turn on STAT6 but not IRS2.

IL-4Rs play a key role in the differentiation of Th2 cells and IgE switch in B cells through this complicated mechanism causing specific disease phenotypes and endotypes.

This pathway of action of the IL-4R axis makes it a crucial target for precision medicine therapies with the aim to limit allergic inflammation and intervene in disease chronicity. In children, this aspect is particularly important, in consideration that an early intervention could limit the evolution of the atopy march and the onset of chronic inflammation and tissue remodeling (17).

In the field of monoclonal antibodies, dupilumab is an IgG monoclonal antibody that acts in this inflammatory pathway against the alpha subunit of the IL-4 receptor IL-4Rα (**Figure 1**), blocking the signal transduction pathways activated by both IL-4 and IL-13 in the IgE-mediated allergic inflammatory asthma.

The main ability of this monoclonal antibody is to bind the subunit of the IL-4 receptor, at the level of the subunit shared by the IL-13 receptor, blocking the inflammatory cascade of these two cytokines and the progression of the Th2-inflammatory pathway.

The interaction of dupilumab with the respective receptor complexes are still evaluated. Potential mechanisms of action of this drug include the inhibition of IL-4 binding to IL-4Rα, the inhibition of the recruitment of γc to IL-4Rα chain (for type I IL-4R), and the inhibition of the recruitment of the IL-4Rα to IL-13Rα1 (for type II IL-4R) (6).

At the present dupilumab is approved for treating adults, adolescents and children from the age of 6 years. In EU, EMA has also recently extended the use of dupilumab in TH2 severe asthma for treating adults, adolescents and children (age 6 years) characterized by high blood eosinophils and/or elevated fractional exhaled nitric oxide (FeNO) and symptoms not controlled by high-dose ICS plus another drug for

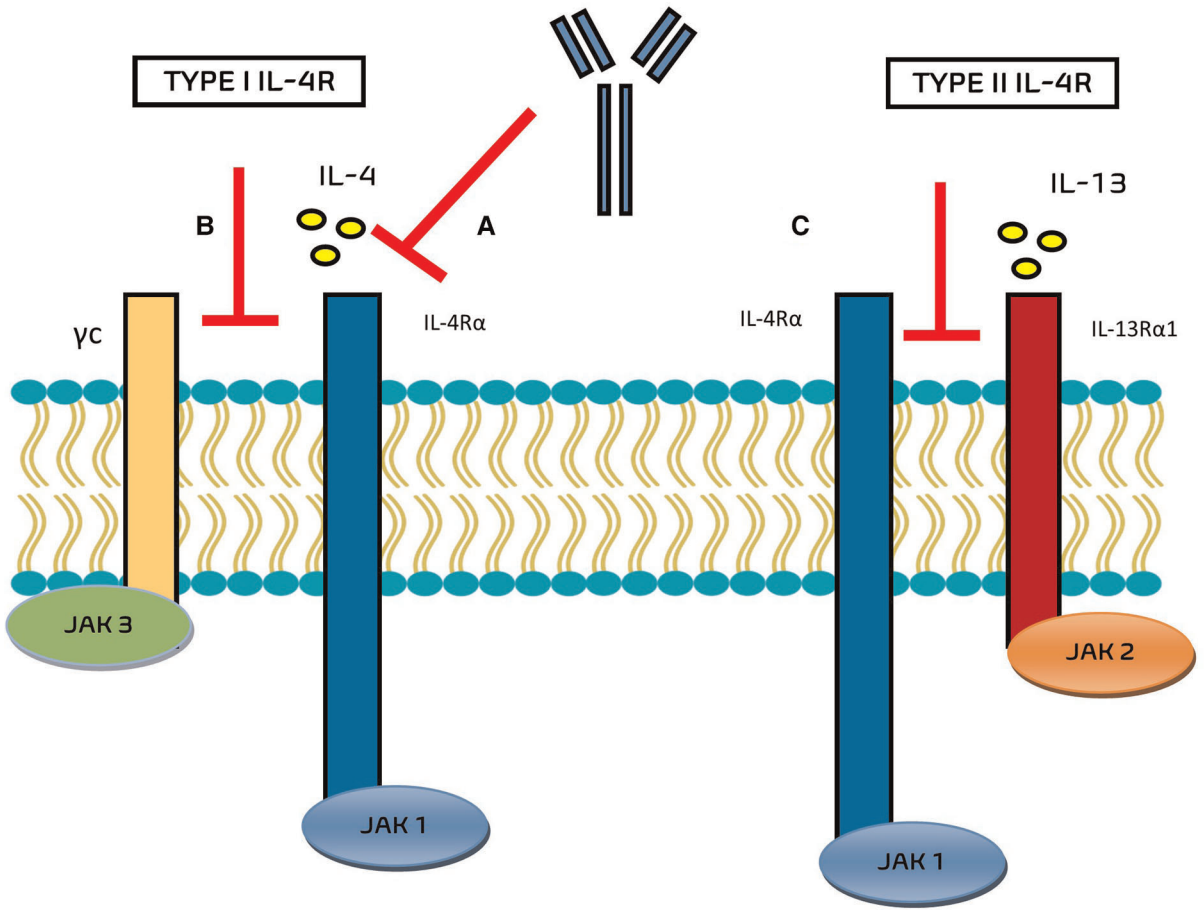

FIGURE 1
Mechanisms of action of Dupilumab. (A) Dupilumab inhibits IL-4 binding to IL-4Rα and/or (B) inhibits the recruitment of γc to IL-4Rα chain. (C) Dupilumab inhibits the recruitment of the IL-4Rα to IL-143Rα1.

maintenance treatment. GINA recommends dupilumab as an add-on treatment for patients (>12 years of age) with severe eosinophilic or type 2 asthma with blood eosinophilia (>300 cells/μl), high FeNO values (>20 ppb), uncontrolled respiratory symptoms, despite high-dose ICS plus long-acting ß2-agonist (LABA) or OCS.

The drug is available as a subcutaneous injection in prefilled syringes and is administered 400 mg once, then 200 mg every 2 weeks.

In patients with OCS dependent-asthma or for patients with severe asthma and comorbidity (moderate to severe atopic dermatitis or severe chronic rhinosinusitis with nasal polyposis) a subcutaneous starting dose of 600 mg (two 300 mg for injections), followed by 300 mg given every other week are recommended.

Efficacy and safety of dupilumab in pediatric severe asthma

The efficacy and safety of dupilumab have been investigated in recently published randomized controlled trials (RCTs) including pediatric patients with asthma (**Table 1**).

In the phase 3 trial LIBERTY ASTHMA VENTURE, 210 patients aged >12 years with severe OCS-dependent asthma were randomized to placebo or to add-on dupilumab 300 mg every 2 weeks for 24 weeks. The dupilumab group showed a percentage change in the OCS dose of −70.1%, in comparison with −41.9% in the group assigned to placebo ($p < 0.001$). Moreover, patients treated with dupilumab showed a severe exacerbation rate 59% [95% confidence interval (CI), 37–74] lower and a forced expiratory volume in 1 s (FEV_1) 0.22 L (95% CI, 0.09–0.34) higher than that in those assigned to placebo. Reactions at the injection site were more commonly observed in patients assigned to dupilumab than placebo (9% vs. 4%), as well as transitory blood eosinophilia (14% vs. 1%). However, it should be pointed out that adolescent data were not extrapolated from the overall results (18). In the phase 3 trial LIBERTY ASTHMA QUEST, 1,902 patients aged >12 years with not controlled asthma were randomly assigned (2:2:1:1) to receive add-on dupilumab (200 or 300 mg every 2 weeks) or placebo for 52 weeks. The rate of severe asthma exacerbations was 0.46 (95% CI, 0.39–0.53) in patients assigned to dupilumab 200 mg and 0.87 (95% CI, 0.72–1.05) in those assigned to placebo, therefore 47.7% lower ($p <$ 0.001). Notably, in participants with blood eosinophil

TABLE 1 Summary of Dupilumab RCTs including pediatric patients with asthma.

Author	Study population	Intervention	Summary of main results
Rabe et al. (17) (LIBERTY ASTHMA VENTURE)	210 patients older than 12 years with severe OCS-dependent asthma	Add-on dupilumab (at a dose of 300 mg) every 2 weeks for 24 weeks or placebo for 24 weeks	↓ OCS use ↓ annualized severe exacerbation rate ↑ FEV_1
Castro et al. (18) (LIBERTY ASTHMA QUEST)	1,902 patients aged 12 years or older with uncontrolled asthma	Add-on dupilumab (at a dose of 200 or 300 mg every 2 weeks) or placebo for 52 weeks	↓ annualized severe exacerbation rate (greater efficacy in participants with blood eosinophil concentrations >300 cells/μl) ↑ FEV_1
Corren et al. (19) (LIBERTY ASTHMA QUEST)	1,083 patients aged 12 years or older with and 819 without uncontrolled allergic asthma	Add-on dupilumab (at a dose of 200 or 300 mg every 2 weeks) or placebo for 52 weeks	↓ annualized severe exacerbation rate ↑ FEV_1 ↑ asthma control ↓ type 2 inflammatory biomarkers
Busse et al. (20) (LIBERTY ASTHMA QUEST)	814 patients aged 12 years or older with uncontrolled, moderate-to-severe asthma and comorbid perennial allergic rhinitis	Add-on dupilumab (at a dose of 200 or 300 mg every 2 weeks) or placebo for 52 weeks	↓ annualized severe exacerbation rate ↑ FEV_1 (greater efficacy in patients with baseline blood eosinophil counts ≥300 cells/μl and FeNO >25 ppb) ↑ asthma control ↑ rhinoconjunctivitis health-related quality of life
Maspero et al. (21) (LIBERTY ASTHMA QUEST)	107 patients aged 12–17 years treated with medium-to-high-dose ICS plus one or two controllers	Add-on dupilumab (at a dose of 200 or 300 mg every 2 weeks) or placebo for 52 weeks	↑ FEV_1 (greater efficacy in patients with baseline elevated baseline type 2 biomarker levels treated with dupilumab 200 mg) ↓ annualized severe exacerbation rate in patients treated with dupilumab 200 mg ↓ type 2 inflammatory biomarkers
Bacharier et al. (22) (LIBERTY ASTHMA VOYAGE)	408 children aged 6-11 years with uncontrolled moderate-to-severe asthma (two primary efficacy populations: patients with baseline blood eosinophil counts ≥150 cells/μl and FeNO ≥20 ppb and patients with baseline blood eosinophil counts ≥300 cells/μl)	Add-on dupilumab (at a dose of 100 or 200 mg every 2 weeks) or placebo every 2 weeks for 52 weeks	↓ annualized severe exacerbation rate ↑ FEV_1 ↑ asthma control

FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 s; ICS, inhaled corticosteroid; OCS, oral corticosteroid.

concentrations >300 cells/μl, the rate of exacerbation was 65.8% lower than in the group assigned to placebo. With regard to pulmonary function, FEV_1 increased by 0.32 L in patients receiving dupilumab 200 mg and by 0.14 L in those receiving placebo ($p < 0.001$), at week 12. Overall, similar findings were observed in patients assigned to a dupilumab dose of 300 mg every 2 weeks. Hypereosinophilia was more commonly observed in the dupilumab study groups (4.1%) than in patients receiving placebo (0.6%), whereas conjunctivitis was observed in 2.3% of the patients receiving dupilumab and 3.3% of those receiving placebo (19). Of interest, Corren et al. assessed dupilumab's effect in QUEST patients with ($n =$ 1,083) and without ($n = 819$) atopic asthma (total serum IgE ≥30 IU/ml and ≥1 perennial aeroallergen-specific IgE ≥0.35 kU/L at baseline), demonstrating its ability to reduce severe exacerbation rates, improve FEV_1 and asthma control, and suppress type 2 biomarkers of inflammation in both the subgroups. Therefore, these results highlight the beneficial role of dupilumab in treating both allergic and nonallergic asthma patients (20). Furthermore, Busse et al. published a *post hoc* analysis of the phase 3 LIBERTY ASTHMA QUEST study evaluating the efficacy of dupilumab in patients with not controlled, moderate-to-severe asthma and perennial allergic rhinitis (PAR). Out of the 1,902 patients, 814 (42.8%) had PAR, i.e., an allergic rhinitis history and ≥1 perennial aeroallergen specific IgE level ≥0.35 kU/L at baseline. Dupilumab, 200 and 300 mg every 2 weeks, vs. placebo significantly decreased severe exacerbations rates by 32.2% and 34.6% ($p < 0.05$ for both) and increased FEV_1 at week 12 by 0.14 L and 0.18 L ($p < 0.01$ for both). Even higher efficacy was reported in patients with high blood eosinophil counts (≥300 cells/μl) and FeNO (25 ppb) levels. Patients in the dupilumab group also showed improvement in asthma control and rhinoconjunctivitis-specific health-related quality of life. Finally, dupilumab suppressed type 2 biomarkers of inflammation during the 52-week study period. Therefore, the study demonstrated that dupilumab, acting on type 2 inflammation occurring in both conditions, may contribute to increase the control of asthma and comorbid PAR (21). Again, adolescent data were not reported separately in these studies. However, in a subgroup analysis on 107 patients aged 12–17 years treated with medium-to-high-dose ICS plus one or two controllers, a change from baseline in FEV_1 at week 12 vs. placebo ($p < 0.05$) was reported for both 200 mg (0.37 L; 95% CI, 0.13–0.61; $p = 0.003$) and 300 mg (0.27 L; 95% CI, 0.02–0.52; $p = 0.037$). Interestingly, in the majority of adolescents with high levels of type 2 inflammatory biomarkers assigned to dupilumab 200 mg, such improvement was even greater (0.43 L; 95% CI, 0.17–0.69; $p = 0.002$) than in the matched intention-to-treat adolescent subgroup. Furthermore, a 46% reduction in adjusted severe exacerbation rate (95% CI, 0.24–1.21) was reported in the dupilumab 200 mg subgroup vs. placebo. Nonetheless, the adjusted severe exacerbation rate in the dupilumab 300 mg subgroup was 13% higher than in the placebo subgroup. This may be ascribed to the imbalanced number of severe exacerbations reported in the past 12 months between the dupilumab 300 mg and the placebo subgroups (mean 1.53 and 2.22, respectively) that likely affected the adjusted rate of exacerbations. Indeed, the unadjusted severe exacerbation rate was numerically lower in both dupilumab subgroups vs. placebo in the overall population, as well as in adolescents with high levels of type 2 biomarkers. Finally, dupilumab reduced levels of type 2 biomarkers such as FeNO and serum total IgE and was overall well tolerated, supporting its use in the adolescent population (22).

More recently, in the LIBERTY ASTHMA VOYAGE, a 52-week phase 3 study, 408 children aged 6–11 years with not controlled moderate-to-severe asthma were randomized to receive add-on dupilumab (100 mg if weight ≤30 kg and 200 mg if weight >30 kg) or placebo every 2 weeks. In patients with the type 2 inflammatory phenotype (≥150 blood eosinophils/μl or FeNO levels ≥20 ppb at baseline), the annualized severe asthma exacerbations rate was 0.31 (95% CI, 0.22–0.42) in the dupilumab group and 0.75 (95% CI, 0.54–1.03) in the placebo group (relative risk reduction in the dupilumab group, 59.3%; 95% CI, 39.5–72.6; $p < 0.001$). The mean change from baseline in the predicted prebronchodilator FEV_1 was 10.5 ± 1.0 percentage points with dupilumab and 5.3 ± 1.4 percentage points with placebo (mean difference, 5.2 percentage points; 95% CI, 2.1–8.3; $p < 0.001$). Additionally, dupilumab significantly improved asthma control with respect to placebo ($p < 0.001$). Similar findings were reported in the subgroup of patients with an eosinophil count ≥300 cells/μl at baseline. In both the two subgroups dupilumab generally showed an adequate safety profile in children, similarly to those reported in adults and adolescents. In particular, the most common adverse event in the dupilumab group was viral upper respiratory tract infection (12.2% vs. 9.7% in the placebo group). Eosinophilia was observed in 5.9% and 0.7% of the patients assigned to dupilumab and to placebo, respectively. However, most episodes were transitory laboratory findings with no associated symptoms. Mild parasitic infections were reported in 2.6% of the patients in the dupilumab group. Hospitalization due to asthma exacerbations were reported only in the dupilumab group (1.5%). The incidence of conjunctivitis was low in both groups and one case of keratitis was observed in each group (23). Additionally, within the LIBERTY ASTHMA VOYAGE study dupilumab was found to quality of life in children with type 2 asthma (24) and their caregivers (25); allergic rhinitis (AR)- health-related quality of life also improved in patients with comorbid AR (26).

With regard to the efficacy of biological treatment options in uncontrolled persistent asthma, very recently an indirect treatment comparison of dupilumab vs. each of the anti-IL-5

(benralizumab, mepolizumab, and reslizumab) and anti-IgE (omalizumab) therapies was conducted. The analysis included fourteen RCTs in patients aged 12 years and older. In the matched dupilumab subgroups annualized severe exacerbation rates were significantly reduced in comparison with benralizumab, mepolizumab, and reslizumab (54%, 28%, and 38%, respectively). Moreover, dupilumab was associated with significantly greater increase in FEV_1 in comparison with benralizumab and reslizumab (at week 24) and omalizumab (at week 52). Hence, in this study dupilumab significantly reduced asthma exacerbation rates and was associated with greater improvements in pulmonary function than anti-IL-5s and omalizumab (27). These findings are in agreement with those of a previously published Cochrane intervention review assessing the efficacy and safety of anti-IL-13 or anti-IL-4 agents, in comparison with placebo, anti-IgE or anti-IL-5 agents, for the treatment of patients with asthma. Four studies evaluating dupilumab were included. In comparison with placebo, anti-IL-13/-4 agents were associated with a decrease in exacerbations that needed hospitalization or emergency department visit, in spite of increased adverse events, whereas no significant improvements in health-related quality of life and asthma control were observed. However, only four studies recruited children and adolescents, so participants in this age group accounted for less than 5% and therefore this review's results should be interpreted with caution for the pediatric population (28).

Safety of biological therapies is a major concern for clinicians dealing with the pediatric population. Due to the short-to-medium-term duration of studies on children and adolescents, evidence on the safety of dupilumab in the treatment of pediatric asthma is still limited. In particular, data for long-term use are required to estimate the risk of long-term adverse events/side effects. At present, there is no information about clinical significance and consequences of increases in peripheral blood eosinophils. When IL-13 is blocked by dupilumab, eosinophils migration is blocked. Therefore, increased eosinophilia can be considered consequent to IL-4/IL-13R blockade. Wechsler et al. recently conducted extensive *post hoc* analyses of 6,642 adults and adolescents who participated in dupilumab randomized, double-blind placebo-controlled trials, reporting transient increases in mean eosinophil counts in dupilumab-treated patients with asthma that were rarely associated with clinical symptoms (29). Nonetheless, concern has arisen about this potential adverse event and eosinophil-associated inflammation in other organs. Besides eosinophilic asthma, eosinophils may drive the inflammatory cascade underlying immunological hypereosinophilic conditions characterized by multiple-organ involvement, e.g., eosinophilic granulomatosis polyarthritis and hypereosinophilic syndrome. Although rare in children, these diseases should be considered in managing patients eligible for dupilumab with baseline elevated eosinophils. For this reason, it is advisable that a basal complete blood count must be included in the initial evaluation of patients affected by asthma and eligible for dupilumab, as well as rule out common parasitosis in case of basal elevated eosinophil count. With regard to conjunctivitis, a recent study evaluated the incidence and severity of conjunctivitis in dupilumab clinical trials involving adolescents with moderate-to-severe atopic dermatitis or uncontrolled asthma reporting no significant differences between the dupilumab and placebo groups, in contrast to the findings in patients with atopic dermatitis (30).

Conclusion

Dupilumab is a biological drug with proven efficacy and reassuring safety profile in patients with type 2 inflammatory diseases, such as asthma. Currently, its use in asthma is approved by FDA and EMA in adults, adolescents, and children affected by severe asthma with type 2 inflammation characterized by high levels of eosinophils and/or FeNO, which is ineffectively controlled with high-dose ICS plus another maintenance drug. Additional studies are warranted for the evaluation of long-term treatment with dupilumab, including steroid sparing effect and discontinuation of treatment. Further research should also be planned in order to investigate the effect of dupilumab in children with asthma and comorbid conditions, as well as its potential ability to interfere with the natural history of atopy since early childhood. Moreover, data for long-term use are required to estimate the risk of long-term adverse events/side effects.

Author contributions

GP: conceptualization. GF and LT: writing original draft. MP: review and editing. All authors contributed to the article and approved the submitted version.

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.

Publisher's note

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Severe pediatric asthma therapy: Omalizumab—A systematic review and meta-analysis of efficacy and safety profile

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Background: Omalizumab is the first biological therapy used to treat moderate-to-severe asthma and certainly the one with the highest number of publications.
Methods: A systematic review and meta-analysis were performed to examine two critical outcomes of omalizumab therapy, asthma exacerbation rate, the reduction of the use of inhaled corticosteroids (ICS), and the improvement of the lung function as a secondary outcome using the following keywords in the MEDLINE database: "anti-IgE, severe asthma, children, and randomized controlled trial." We specifically selected papers that included moderate-to-severe asthma patients and collected data on children and adolescents.
Results: Four RCT studies (total number of patients = 1,239) were included in the analysis. The reported data on exacerbations showed an overall improvement in the exacerbation rate with a decreased use of inhaled steroids and some other minimal clinically important difference (MCID).
Conclusions: Our systematic review confirms the known findings that omalizumab therapy decreases asthma exacerbation rate and reduces background therapy inhaled steroid dose. Therefore, add-on therapy with omalizumab shows a good efficacy and safety profile, thus proving to be a useful additional therapeutic option.
Systematic Review Registration: https://www.crd.york.ac.uk/prospero/, identifier: CRD42023396785.

KEYWORDS
anti-IgE, severe asthma, children, randomized controlled trial, systematic review

1. Introduction

Omalizumab, an anti-IgE antibody, has been used to treat adults and adolescents with severe asthma since 2003 and in children aged 6–11 years since 2009.

Asthma is a chronic inflammation that can be differentiated into type 2 (Th2) and non-type 2 (non-Th2) inflammation (1).

Type 2 asthma is characterized by eosinophilic airway inflammation and sensitization, such as IgE-mediated, T helper 2 (Th2)-dependent cytokines, including interleukin (IL)-4, IL-5, and IL-13 (2).

The non-type 2 (non-Th2) asthma is rare in children and adolescents and is characterized by either a neutrophilic or paucigranulocytic pattern promoted by IL-8, IL-17, IL-22, and epithelial cell-derived cytokines (3–6).

Omalizumab is a humanized monoclonal antibody that specifically binds to IgE, preventing it from binding to antigen-presenting cells, mast cells, and basophils. This can help to prevent inflammatory responses or the long-term consequences of allergen exposure, including tissue remodeling, inflammatory cell recruitment, and Th2 inflammation (7).

IgE-type immunoglobulins play a decisive role in the pathogenesis of allergic diseases. After exposure to triggers such as allergens, infectious (especially viral) pollutants trigger a series of IgE-dependent mechanisms.

Therefore, omalizumab by binding to free IgE prevents its binding with its receptor and leads to the formation of inert, nonfunctioning immune complexes (8).

Omalizumab is indicated for treating severe persistent uncontrolled allergic asthma in children aged 6 years and older who are inadequately controlled by high-dose inhaled corticosteroids plus long-acting beta-agonists and who have a positive skin test or in vitro reactivity to a perennial aeroallergen (9).

In adolescents aged >12 years, a reduced forced expiratory volume in 1 s (FEV1) is also required to be less than 80% of the predicted value (9).

From 2009 to 2019, omalizumab was the only biological drug licensed as add-on therapy in children aged ≥6 years with severe allergic asthma not controlled by treatment with high-dose inhaled corticosteroids (ICS) plus long-acting inhaled beta2-agonist (LABA).

The first European Respiratory Society (ERS)/American Thoracic Society (ATS) guidelines on severe asthma in adults and school-age children were published in 2014 (10).

At that time, severe asthma was defined as "asthma that requires treatment with high dose ICS […] plus a second controller (and/or systemic corticosteroids) to prevent it from becoming 'uncontrolled' or which remains 'uncontrolled' despite this therapy" (10).

Nowadays, there is not a universally accepted definition of severe asthma, and several definitions have been published in different guideline documents (10, 11, 12).

The meeting point in all definitions of severe asthma is poor symptom control despite high-dose ICS treatment (usually budesonide or equivalent ≥400 μg for children younger than 12 years and ≥1,000 μg for older children) (13).

2. Methods

We performed systematic research from the database of MEDLINE among papers written in English using the following keywords: "anti-IgE, severe asthma, children, and randomized controlled trial," including articles from the earliest records up to October 2022. We included all RCTs conducted in pediatric patients with asthma that compared the efficacy or safety of omalizumab with a placebo or common therapy. This search was further refined using the following inclusion criteria (**Figure 1**):

1. studies in pediatric patients;
2. studies with a comparison between omalizumab and placebo looking at efficacy and/or safety of omalizumab;
3. studies with the use of omalizumab for asthma; and
4. studies with at least one of the following outcomes: asthma exacerbations, decrease in inhaled corticosteroid dose, and/or drug-related adverse events.

The PRISMA 2020 27-item checklist addressing the introduction, methods, results, and discussion sections was compiled, providing a quality check of the systematic review report (14).

We performed a statistical analysis using Medcalc and Microsoft Excel. We calculated the odds ratio (OR) and 95% confidence interval (CI) for categorical variables. Weighted mean difference and standard deviation (SD) between groups were used for continuous outcomes; the effect on the number of exacerbations was measured by OR analysis and visually represented by a forest plot. The effect on dose-sparing of inhaled steroids was available in two studies and was measured by comparing mean differences; Student *t*-test on unpaired variables was executed to verify the results; results were also represented by a forest plot. Graphs were made with Medcalc.

The safety profile was compiled by summarizing in a table all the adverse events found in three RCTs (15–17) and then categorizing

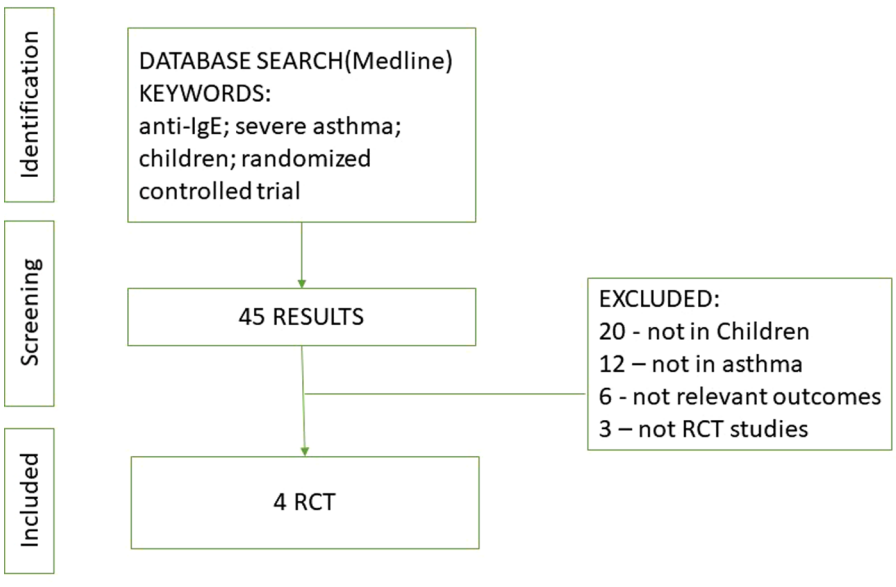


FIGURE 1
Process identifying studies eligible for the systematic review.

them by systems. Teach et al. (17) used a different categorization by symptoms; to compile the table, we collected them in various systems.

3. Results

Four RCTs (including 1,239 pediatric patients) were included (15–18). The characteristics of the included RCTs studies are summarized in **Table 1**.

3.1. Efficacy

The four RCT studies (15–18) that compared omalizumab with. placebo demonstrated a clinical benefit of omalizumab in reducing asthma exacerbations in children with moderate-to-severe persistent asthma (**Figure 2**).

3.1.1. Exacerbation rate

In the Lanier study that included adolescents with moderate-to-severe allergic asthma, exacerbations were defined as a worsening of symptoms that required doubling of baseline ICS dose and/or rescue treatment with OCS for 3 or more days (15). The risk of exacerbations was reduced by 31% after 24 weeks of treatment with omalizumab when used in conjunction with stable treatment of ICS (15).

When considering the subgroup of patients with severe asthma, as assessed by Kulus et al., the RR was 0.66 (0.44;0.99); this value was considered statistically significant and surpassed the minimal clinically important difference (MCID) of 25% (19).

A study by Busse et al. on 419 children and adolescents who experienced at least one exacerbation found that the rate of exacerbations was 30.3% in the group receiving omalizumab and 48.8% in the placebo group (16).

In a study by Teach et al. on 478 children and adolescents with asthma, those who were treated with omalizumab had a 37% lower risk of exacerbations (defined as a worsening of asthma control requiring oral corticosteroids or hospitalization) over a period of 90 days than those who received a placebo (17).

Finally, in the fourth RTC considered, in the treatment of asthma by omalizumab vs. placebo, it was found that 7% of those in the omalizumab group and 46% of those in the placebo group had experienced a severe exacerbation after 5 months. At the 2-year follow-up, no differences were observed between the two groups. No difference was found in the frequency of moderate exacerbations between the two groups (18).

The rate of asthma exacerbations was an outcome investigated in all four RCTs (15–18).

Of the 620 patients in the placebo group, 54.6% (339 patients) had asthma exacerbations, while in the group receiving omalizumab (1,195 patients), 35.5% of patients had asthma exacerbations. Omalizumab therapy was effective in decreasing the rate of asthma exacerbations compared to placebo [OR 0.44; 95% CI(0.35, 0.56), $P < 0.001$] (**Figure 2**).

3.1.2. Reduction in ICS use

In the Lanier study, no significant difference was observed in the omalizumab group vs. placebo in the subgroup with severe asthma. The reduction in fluticasone dose from baseline to 52 weeks including both the stable and the steroid adjustment phase was 2.5% in the omalizumab group compared to 2.0% in the placebo group (15).

The Busse study demonstrated a statistically significant difference at the end of the study period, between those receiving omalizumab and placebo, with 663 (SE 23.3) and 771 (23.5) μg budesonide equivalent/day, respectively. This corresponds to a difference of −109 μg/day (95% CI 172; −45), $p = 0.0012$. There was no significant difference between the omalizumab group and the placebo group in terms of moderate dose at the study end (16).

The other two studies considered did not designate corticosteroid reduction as an outcome (17, 18); therefore, in our study, we collected data from two studies (15, 16) that reported mean and SD values for the dosage of inhaled corticosteroids. Patients receiving omalizumab had a statistically significant reduction in the required dosage of inhaled corticosteroids compared to the placebo group (mean difference, −108 μg/day, 95% CI −151.19 to −64.81 μg/day, $p < 0.01$) (**Figure 3**).

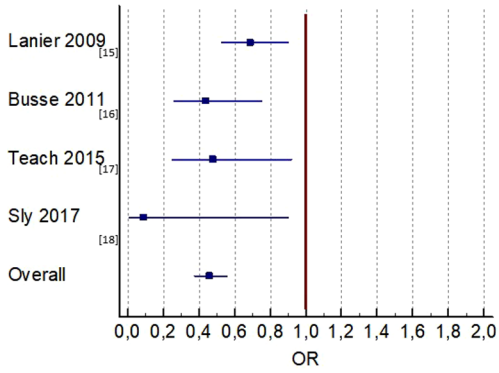
3.2. Safety

Three (15–17) out of the four studies considered evaluated the safety profile of omalizumab and listed the adverse events of the two groups of omalizumab and placebo; in particular, in Teach et al., the organs involved rather than the individual symptoms are reported (17).

Severe adverse events were counted, and in two (15, 17) of them, no difference was found between omalizumab and placebo groups; in

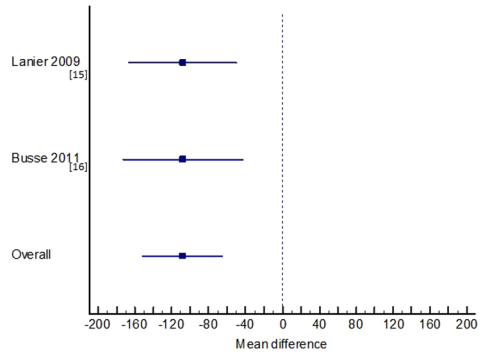
TABLE 1 Demographic and clinical characteristics of the selected studies.

Study	Study design	Mean age	Study duration	Asthma severity	Number of patients (omalizumab/ placebo group)
Lanier 2009 (15)	Omalizumab add-on/placebo add-on	8,6 (6–12 years)	24 weeks, 52 weeks	Moderate-to-severe	421/206
Busse 2011 (16)	Omalizumab add-on/placebo add-on	8.4 (6–11 years)	24 weeks	Moderate-to-severe	117/120
Teach 2015 (17)	Omalizumab add-on/placebo add-on (third arm with ICS boost)	10,1 (6–12 years)	17–39 weeks	Moderate-to-severe	259/89
Sly 2017 (18)	Omalizumab add-on/placebo add-on	11,5 (6–15 years)	104 weeks	Moderate-to-severe	14/13



OR	95% IC Low	95% IC High
0,69	0,53	0,9
0,441298	0,258824	0,752417
0,48	0,25	0,92
0,089744	0,008927	0,902174
0,457514	0,375495	0,55745

FIGURE 2
Effect of omalizumab vs. placebo on the number of exacerbations.



Mean Difference	IC-H	IC-L
-108,00	-165,99	-50,01
-108,00	-172,73	-43,27
-108,00	-151,19	-64,81

FIGURE 3
Effect of omalizumab vs. placebo on reduction in ICS use.

the study by Busse et al., the placebo group had more severe adverse events (30 events) than omalizumab (10 events).

A summary of all adverse events is presented in **Table 2**.

3.3. Lung function

From the studies considered in our review, only three studies have looked at the relation between omalizumab and lung function (16–18).

In the study by Busse et al., the difference in predicted FEV_1% values was 0.92 (95% CI, 0.81;2.64) in the omalizumab group, but it did not reach statistical significance (16).

In the Teach et al. study, the estimated lung function, measured with the predicted FEV_1% value, was not statistically significant (17).

In an Australian study by Sly et al., lung function was not considered a primary outcome, but the authors concluded that no statistically significant or clinically relevant difference was observed between the two groups when looking at predicted FEV_1 values (18).

4. Discussion

A recent systematic review by the European Academy of Allergy and Clinical Immunology (EAACI) showed that patients with severe asthma reported a reduction to approximately half of the exacerbations and an improvement in other outcomes such as quality of life (QoL) scores and a reduced need for inhaled glucocorticoids to maintain this improved level of asthma control and FEV_1 (20).

The study by Busse et al. (16) found in 419 participants a reduction in the number of days with asthma symptoms (per 2-week interval: 1.96–1.48 days, with a difference of 24.5%, $P < 0.001$). Another endpoint confirmed a reduction in exacerbations comparing omalizumab with the placebo group (30% vs. 48%); in particular, the percentage of hospitalized patients was 6.3% vs. 1.5%. This study also showed significantly lower doses of inhaled glucocorticoids ($P < 0.001$) and LABA ($P = 0.003$) needed to achieve asthma control.

Omalizumab in patients who were sensitized to cockroach allergen (Bla g1 in house dust ≥2 U per gram) has been

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TABLE 2 Adverse events reported in the included studies.

	Lanier 2009 (15)		Busse 2011 (16)		Teach 2015 (17)		Total	
	Placebo	Omalizumab	Placebo	Omalizumab	Placebo	Omalizumab	Placebo	Omalizumab
Severe adverse events	17	17	30	10	3	3	**50**	**30**
Blood and lymphatic system disorders	–	–	16	1	1	1	**17**	**2**
Eye, ear, and labyrinth disorders	39 (l)	70	7	2	1	6	**47**	**78**
Gastrointestinal disorders	24 (i)	34	2	11	10	19	**36**	**64**
General disorders and administration-site conditions	–	–	8	10	10	63	**18**	**73**
Immune system disorders	–	–	6	1	2	5	**8**	**6**
Infections and infestations	56 (a), 46 (b), 20 (c), 28 (d), 29 (e), 26 (f)	117, 69, 59, 51, 37, 34	26	18	22	63	**253**	**448**
Musculoskeletal and connective tissue disorders	–	–	3	3	1	8	**4**	**11**
Nervous system disorders	33 (g)	58	10	3	9	21	**52**	**82**
Psychiatric disorders	–	–	3	0	2	7	**5**	**7**
Respiratory, thoracic, and mediastinal disorders	25 (h)	44	95	57	11	29	**131**	**130**
Skin and subcutaneous tissue disorders	–	–	24	22	18	41	**42**	**63**
Other	–	–	22	31	4	37	**26**	**68**
Any adverse events	**343**	**590**	**222**	**159**	**97**	**300**	**662**	**1,049**

a, nasopharyngitis; b, URTI; c, pyrexia; d, influenza; e, bronchitis; f, viral URTI; g, headache; h, cough;, i, vomiting; l, sinusitis.

demonstrated to be more effective, showing a reduction of 1.1 days with symptoms per 2-week interval (vs. 1.48 of the entire omalizumab group). Also, a greater reduction in the dose of inhaled glucocorticoids and asthma exacerbations was found in those treated with omalizumab compared to the placebo group (16).

Three of the four RCT studies focused on viral infection-induced asthma exacerbations. In both children and adults, asthma exacerbations are indeed often caused by a viral infection (80% of cases) (21–23). Patients with severe asthma are more likely to experience asthma exacerbations caused by respiratory viruses, especially when they have high levels of IgE. The most common virus involved is human rhinovirus (HRV), which is the most commonly detected causative agent in the 5 days prior to exacerbation onset, followed by respiratory syncytial virus (RSV), influenza viruses, parainfluenza viruses, metapneumovirus, bocavirus, adenovirus, and coronavirus (24).

A 2018 Cochrane Review assessing the effects of pharmacotherapy and behavioral interventions to decrease asthma exacerbations in children during the school return in the fall concluded that seasonal omalizumab treatment reduces inflammation but is more effective when combined with other methods (25).

This strategy results in being more expensive with a good safety profile except for injection site pain. This study did not find any data to suggest that this or other seasonal interventions affect asthma control, quality of life, or asthma-related death (25).

A possible explanation for the antiviral role of omalizumab is that it may act by forming IgE/anti-IgE immune complexes. This connection may prevent the interaction of IgE with membrane receptors of plasmacytoid dendritic cells (PD cells) that bind viruses, and this results in the release of interferon-α and activation of the innate immune response (26).

Since asthma has a seasonal pattern of disease activity, with peaks in the spring and fall, a possible change in the efficacy of omalizumab throughout the year has also been studied. The rate of asthma exacerbations doubled during fall and spring in the placebo group while remaining steady in the omalizumab group (4.3% in fall and 4.2% in spring vs. 3.3% in summer).

As for safety, omalizumab is a generally well-tolerated drug. Surveillance on long-term safety reported that the most common adverse events were upper respiratory tract infection and headache (47.1 and 42.7%, respectively), while urticaria occurred in 11 of 225 patients (4.9%) (26).

However, a meta-analysis published in 2021 analyzing more than 1,000 patients included in three RCTs observed the following safety profile: there was no significant difference between placebo and omalizumab groups regarding nasopharyngitis, gastrointestinal disorders, upper respiratory tract infection, skin problem, sinusitis, pyrexia, headache, cough, and influenza (27).

There was also evidence that patients treated with omalizumab experienced less serious adverse events than those who received a placebo. It is worth mentioning that the most serious adverse events were asthma exacerbations requiring hospitalization (27).

5. Conclusions

Omalizumab is the first biological therapy that has been used in moderate-to-severe asthma, and it is certainly the one with better evidence of safety and efficacy.

Our systematic review and meta-analysis provide further confirmation that omalizumab reduces the rate of exacerbations and inhaled steroid use in children with moderate-to-severe asthma with a great safety profile.

Its antiviral role is emerging more and more and finds application in pathology such as asthma, where the main actors are viruses, especially in children.

Data availability statement

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

Author contributions

GF: first author, conceived and designed the study, wrote most of the manuscript, revised and corrected the manuscript, and helped create the table and the figures. AT wrote sections of the manuscript, performed statistical analysis, and edited the graphic part of figures and tables. CC reviewed the article and edited the language. EL supervised the studio. All authors contributed to the article and approved the submitted version.

Conflict of interest

GF, in the last 3 years, declares to have financial or non-financial support from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, and Sanofi. EL, in the last 3 years, declares to have financial or non-financial support from Abbvie, Angelini, Boehringer Ingelheim, Chiesi, Cosmed, GlaxoSmithKline, Lusofarmaco, Novartis, Omron, Restech, Sanofi, Vertex, and Vifor.

The remaining 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.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2022.1033511/full#supplementary-material.

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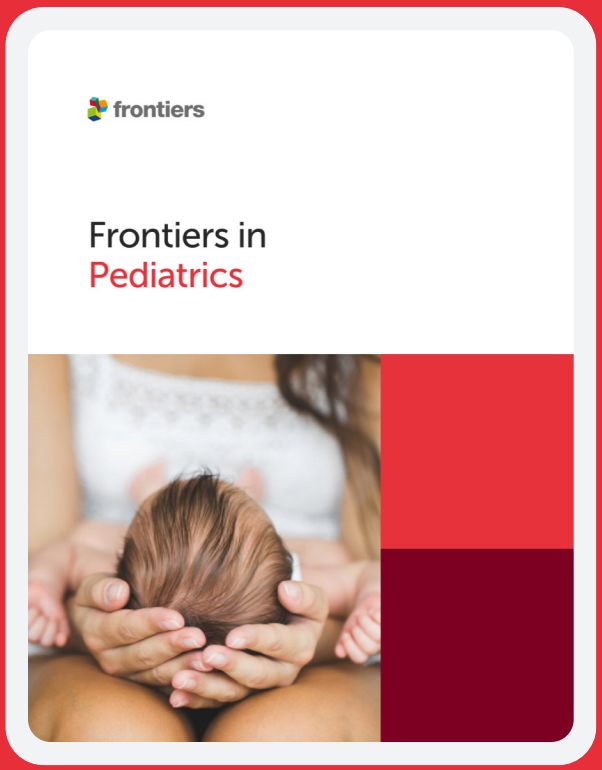

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