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An overview on allergic and pulmonary diseases: from birth to childhood, volume II

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Editorial: An overview on allergic and pulmonary diseases: from birth to childhood, volume II

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allergy, children, asthma, artificial intelligence, wheezing, airway

Editorial on the Research Topic
An overview on allergic and pulmonary diseases: from birth to childhood, volume II

Allergic and pulmonary disorders in childhood involve a complex interplay of genetic, developmental, environmental, and technological factors. Volume II of our Research Topic builds upon Volume I, presenting nine diverse studies—from large-scale epidemiological surveys and biomarker discoveries to epigenetic insights and AI-driven innovations—that collectively map respiratory health from birth through adolescence.

Yan and Li's epidemiological study in Bayannur City, China, revealed an alarming allergic rhinitis prevalence of 39.8% among elementary school children, more than twice the national average. They identified male sex, minority ethnicity, antibiotic use, and urban residence as key risk factors, highlighting the need for integrated public health interventions, including air-quality management, urban planning, and responsible antibiotic use, to curb pediatric allergic conditions.

Gao et al. reinforced the concept of united airways diseases (UAD) through Mendelian randomization, establishing causal links between pediatric asthma and related conditions such as chronic rhinitis and bronchitis. This evidence underscores the necessity for comprehensive clinical strategies that treat the respiratory tract as a unified system.

In their longitudinal study, Alonso-Lopez et al. found adolescents born moderately to late preterm faced a three-fold higher risk of asthma and persistent lung function deficits at 12–15 years. These findings stress the importance of sustained respiratory monitoring beyond infancy, advocating for routine spirometry, symptom tracking, and early intervention strategies to support affected individuals.

Dastgheib et al. explored the epigenetic foundations of bronchopulmonary dysplasia (BPD), detailing disruptions in DNA methylation, histone modifications, and non-coding RNA interactions that impair alveolar development in premature infants. They identified RUNX3 as a critical gene silenced by epigenetic modifications, opening new avenues for targeted therapies, including DNMT and HDAC inhibitors, and predictive epigenetic assessments to identify infants at risk.

Chen et al. employed advanced machine-learning methods on public transcriptomic datasets, identifying XIST—a long non-coding RNA—as a strong sex-specific biomarker for asthma. Their research illustrates AI's potential in uncovering subtle patterns not detectable through traditional methods. Such AI-driven biomarker discoveries hold promise for patient stratification, personalized treatment, and proactive disease management, though challenges around data privacy and clinical integration remain.

Indolfi et al. addressed the critical transition from pediatric to adult allergy care, showcasing AI's capacity to enhance medication adherence, patient autonomy, and continuity of care. They advocated structured, multidisciplinary approaches augmented by AI-driven solutions to bridge care gaps effectively.

Kapus et al. validated home-based telespirometry as an effective management tool for pediatric asthma, demonstrating its accuracy and feasibility for continuous, remote monitoring. Their findings support integrating telemedicine into routine care, offering timely interventions and improved patient outcomes.

Venditto et al. reviewed AI and machine-learning innovations for respiratory condition detection and asthma prediction, highlighting devices such as digital stethoscopes and smartphone-based cough analyzers with diagnostic accuracies exceeding 90%. While promising, these technologies emphasize ethical considerations, including data privacy, transparency, and equitable access, essential to avoid exacerbating health disparities.

Foti Randazzese et al. explored the outcomes of discontinuing omalizumab in children with severe allergic asthma, revealing sustained lung function improvement and reduced exacerbations up to a year post-therapy in selected patients. Their findings advocate for biomarker-guided therapeutic strategies, optimizing patient management and healthcare resources.

Collectively, these contributions emphasize several overarching themes: the necessity of lifelong surveillance to identify enduring impacts of early respiratory insults; leveraging omics and epigenetics, amplified by AI, to guide personalized interventions; implementing preventive public health measures targeting environmental factors; and adopting telemedicine technologies for continuous patient monitoring and timely interventions. As AI-driven healthcare solutions expand, rigorous validation, equitable accessibility, and robust data governance will be crucial to ensure these innovations translate effectively into enhanced pediatric respiratory health outcomes.

Author contributions

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Conflict of interest

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Causal associations between pediatric asthma and united airways disease: a two-sample Mendelian randomization analysis

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Background: Prior observational research has indicated a potential link between pediatric asthma and united airways disease (UAD). However, these findings could be subject to confounding factors and reverse causation. Therefore, our study utilizes Mendelian randomization (MR) method to further investigate the causal relationship between pediatric asthma and UAD.

Methods: We conducted a comprehensive two-sample Mendelian randomization (MR) analysis to investigate the association between pediatric asthma and seven groups of UAD, including chronic sinusitis, chronic rhinitis, nasopharyngitis and pharyngitis, chronic diseases of tonsils and adenoids, chronic laryngitis and laryngotracheitis, chronic bronchitis, bronchiectasis, chronic obstructive pulmonary disease (COPD). The present study employed a range of methods for two-sample MR analysis, including inverse variance weighted (IVW), MR-Egger regression, Simple mode, weighted median, and weighted models. The conclusion of the MR analysis primarily relies on the IVW results, while other analytical methods are utilized as supplementary evidence to ensure result robustness in this MR analysis. And sensitivity analyses were conducted, including heterogeneity test, horizontal pleiotropy test, MR-PRESSO test, and leave-one-out analysis to validate the results.

Results: The results of the MR analysis indicate significant causal effects of pediatric asthma on chronic rhinitis, nasopharyngitis and pharyngitis (IVW: OR = 1.15, 95%CI: 1.05–1.26, p-value = 0.003), chronic diseases of tonsils and adenoids (IVW: OR = 1.07, 95%CI: 1.00–1.15, p-value = 0.038), chronic bronchitis (IVW: OR = 1.51, 95%CI: 1.42–1.62, p-value <0.001), bronchiectasis (IVW: OR = 1.51, 95%CI: (1.30–1.75), p-value <0.001), and COPD (IVW: OR = 1.43, 95%CI: 1.34–1.51, p-value <0.001). However, no significant causal association was observed between pediatric asthma and chronic sinusitis (IVW: OR = 1.00, 95%CI: 1.00–1.00, p-value = 0.085), chronic laryngitis and laryngotracheitis (IVW: OR = 1.05, 95%CI: 0.90–1.21, p-value = 0.558).

Conclusion: Our findings support a potential causal relationship between pediatric asthma and UAD, suggesting that pediatric asthma may be a potential risk factor for various UAD.

KEYWORDS

Mendelian randomization, pediatric asthma, united airways disease, chronic respiratory diseases, chronic rhinitis, chronic obstructive pulmonary disease

1 Introduction

Asthma, a prevalent chronic condition in childhood that typically manifests early in life, is a serious global health issue affecting approximately 20% of children worldwide, causing significant distress to individual patients, and imposing a substantial burden on both the community and healthcare system (1, 2). Over half of children will experience a wheezing episode by the age of 6 years (3). Fortunately, this condition demonstrates a favorable treatment response, and a substantial proportion of pediatric asthma cases resolve prior to school-age and adolescence (4). However, the clinical remission of symptoms does not necessarily equate to the complete disappearance of the underlying pathological phenomenon. In fact, despite the absence of obvious symptoms, airway hyperresponsiveness and airway inflammation may still exist, and airway remodeling can also be observed in preschool children and school-age children with asthma, and these phenomena may even have a lifelong impact on airway health (4–6).

The concept of united airways disease (UAD) posits that the airway constitutes a comprehensive anatomical and functional entity spanning from the nasal cavity to the bronchus, thereby challenging the conventional division of the respiratory tract into upper and lower regions solely based on vocal cord demarcation (7, 8). The concept of UAD was initially conceived based on the observed coexistence of allergic rhinitis and chronic sinusitis with asthma (9). However, through further research, its scope has expanded beyond these specific diseases to gradually encompass other chronic inflammatory conditions affecting the upper and/or lower respiratory tract, such as adenoid hypertrophy, bronchiectasis, and COPD (7, 10).

The risk factors for pediatric asthma and UAD overlap significantly, encompassing exposure to secondhand smoke, environmental particulate matter, household air pollution, high body mass index, infections, and immune dysfunction (1, 11). For instance, prenatal and postnatal exposure to air pollution and maternal smoking increase the risk of asthma in children (12). Recurrent respiratory infections, smoking, childhood and adolescent asthma, and early-life exposure to air pollution are potential risk factors associated with the development of chronic bronchitis in young individuals (13). Globally, smoking is the most common risk factor for COPD, followed by environmental particulate matter pollution (11). UAD is prevalent in clinical practice, supported by extensive epidemiological evidence. Asthma and sinusitis frequently coexist, particularly among children; 34–50% of sinusitis patients have comorbid asthma, and the prevalence of sinusitis in individuals with asthma can reach up to 84% (14). Allergic asthma-rhinitis phenotype typically manifests during childhood, with 40% of patients diagnosed with allergic rhinitis also presenting symptoms of asthma, and nearly all individuals with asthma exhibiting manifestations of allergic rhinitis (15). A longitudinal cohort study on asthma phenotypes from childhood to middle age demonstrates that early-onset remitting, early-onset adult remitting, early-onset persistent, and late-onset persistent phenotypes are significantly associated with the incidence of COPD by age 53 (16).

Mendelian randomization (MR) is a genetic epidemiological approach that utilizes genetic variants associated with varying exposures to evaluate their causal relationship with outcomes, aiming to mitigate confounding and potential bias arising from reverse causation (17). Genetic variants are randomly distributed during meiosis and remain unaffected by later-life diseases. Consequently, the MR method can effectively mitigate confounding factors and eliminate interference from reverse causality, making it superior to traditional observational studies (18, 19). Given the aforementioned characteristics, MR methods have gained widespread utilization in investigating the causal relationship between traits and diseases, as well as among different diseases. UAD encompasses a diverse range of diseases across various disciplines; however, clinicians often concentrate on diagnosing and treating diseases within their own specialty, overlooking the clinical manifestations and diagnosis of these diseases in other areas. This oversight hampers the improvement of diagnostic accuracy and treatment efficacy (20). We conducted this MR study to elucidate the causal relationship between pediatric asthma and UAD, encompassing chronic sinusitis, chronic rhinitis, nasopharyngitis and pharyngitis, chronic diseases of tonsils and adenoids, chronic laryngitis and laryngotracheitis, chronic bronchitis, bronchiectasis, COPD, through genetic analysis. This study provides novel insights for managing comorbidities associated with pediatric asthma as well as facilitating the diagnosis, prevention, and treatment of UAD.

2 Materials and methods

2.1 Study design

The two-sample MR approach was employed to investigate the causal impact of pediatric asthma on UAD. MR analysis primarily employs the inverse variance weighting (IVW) method to infer causal effects between exposure and outcome. In this study, pediatric asthma was used as the exposure factor, single nucleotide polymorphisms (SNPs) significantly associated with pediatric asthma were used as instrumental variables (IVs), and UAD was considered as the outcome factor. MR analysis employs genetic variants to assess causality of observational data and IVs included in the study must satisfy three key assumptions: firstly, relevance assumption: there is a robust and strong association with the exposure factor; secondly, independence assumption: there is no confounding variable between exposure and outcome; thirdly, exclusivity assumption: it should not have any direct relationship with the outcome, but only affect it through exposure (21, 22). The study design overview is presented in Figure 1.

2.2 Data sources

The genome-wide association studies (GWAS) summary data for pediatric asthma was selected as the exposure factor, while the GWAS summary data for seven common UAD were chosen as outcome factors, including chronic sinusitis, chronic rhinitis, nasopharyngitis and pharyngitis, chronic diseases of tonsils and adenoids, chronic laryngitis and laryngotracheitis, chronic bronchitis, bronchiectasis, and COPD (Table 1 and Supplementary material). The GWAS data utilized in this study were exclusively sourced from the Finn Gen and European Bioinformatics Institute (EBI) databases. The primary goal of the Finn Gen database is to collect and analyze genomic data from 500,000 Finns, integrating it with national health registry data to reveal relationships between genetic variations and diseases, thus advancing genetics in human health (23). The EBI database encompasses an extensive array of genotype and phenotype data, providing a multitude of data analysis and integration tools, thereby advancing applications and developments

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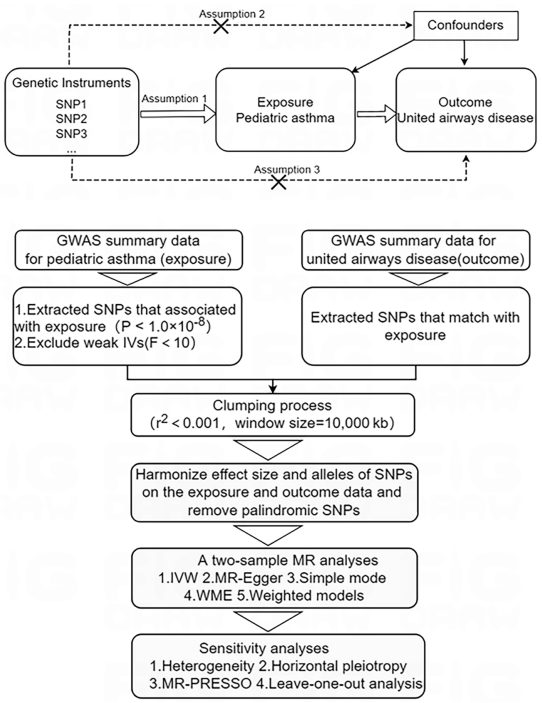

FIGURE 1
Study design overview. IVs, instrumental variables; MR, Mendelian randomization; SNPs, single nucleotide polymorphisms. Mendelian randomization study design and assumptions. Assumption 1: relevance assumption; Assumption 2: independence assumption; Assumption 3: exclusivity assumption.

in genomics, proteomics, transcriptomics, and other related fields (24). The GWAS data on pediatric asthma was obtained from the EBI database, comprising 27,712 cases and 411,131 controls. The GWAS data on chronic sinusitis was obtained from the EBI database, comprising 3,014 cases and 481,584 controls. The GWAS data on chronic rhinitis, nasopharyngitis and pharyngitis was obtained from the Finn Gen database, comprising 5,355 cases and 167,849 controls. The GWAS data on chronic diseases of tonsils and adenoids was obtained from the Finn Gen database, comprising 24,463 cases and 167,849 controls. The GWAS data on chronic laryngitis and laryngotracheitis was obtained from the Finn Gen database, comprising 2,138 cases and 167,849 controls. The GWAS data on chronic bronchitis was obtained from the EBI database, comprising 10,159 cases and 440,263 controls. The GWAS data on bronchiectasis was obtained from the EBI database, comprising 2,888 cases and 440,263 controls. The summary dataset on COPD was obtained from the EBI database, comprising 13,530 cases and 454,945 controls. To mitigate potential bias arising from confounding factors within the population, we specifically limited our study to individuals of European ancestry. The pooled data utilized in this investigation were obtained from publicly available summary data of GWAS, thereby obviating the need for additional ethical approval.

2.3 IV selection

IVs necessitate three fundamental assumptions that are in accordance with the principles of MR. Firstly, SNPs associated

TABLE 1 Overview of study data.

Trait	Data type	Consortium	GWAS ID	Case	Control	SNPs	Ethnicity	Year
Pediatric asthma	Exposure	EBI database	ebi-a-GCST90018895	27,712	411,131	24,166,696	European	2021
Chronic sinusitis	Outcome	EBI database	ebi-a-GCST90038673	3,014	481,584	9,587,836	European	2021
Chronic rhinitis, nasopharyngitis and pharyngitis	Outcome	Finn Gen database	finn-b-J10_CHRONRHINITIS	5,355	167,849	16,380,284	European	2021
Chronic diseases of tonsils and adenoids	Outcome	Finn Gen database	finn-b-J10_CHRONTONSADEN	24,463	167,849	16,380,381	European	2021
Chronic laryngitis and laryngotracheitis	Outcome	Finn Gen database	finn-b-J10_CHRONLARYNGITIS	2,138	167,849	16,380,258	European	2021
Chronic bronchitis	Outcome	EBI database	ebi-a-GCST90018824	10,159	440,263	24,182,745	European	2021
Bronchiectasis	Outcome	EBI database	ebi-a-GCST90018801	2,888	440,263	24,189,609	European	2021
COPD	Outcome	EBI database	ebi-a-GCST90018807	13,530	454,945	24,180,654	European	2021

with pediatric asthma, meeting the locus-wide significance threshold (p-value $<1.0\times10^{-8}$), were identified as potential IVs; secondly, to evaluate the robustness of IVs and minimize potential bias from weak IVs, we calculated the F-statistic for each SNPs, excluding SNPs with an F-value less than 10 (25); thirdly, we performed Linkage disequilibrium-based clumping procedure ($r^2<0.001$ and window size = 10,000 kb) to ensure the independence of each IVs. Linkage disequilibrium estimation was conducted utilizing the 1,000 Genomes European reference panel (26); fourthly, harmonize the exposure and outcome data, ensuring that the effect size for exposure and outcome correspond to the same effect allele, while removing palindrome SNPs with intermediate allele frequencies (27). The study flow overview is depicted in Figure 1.

2.4 Statistical analysis

The MR approach was employed in this study to investigate the causal relationship between pediatric asthma and seven common UAD. Five two-sample MR analysis methods, namely inverse variance weighted (IVW), MR-Egger regression, Simple mode, weighted median (WME), and weighted model, were utilized with a significance level of p-value <0.05 indicating statistical significance. The primary inference drawn from the MR analysis is predominantly based on the IVW outcomes, while other analytical approaches are employed as supplementary evidence to ensure result robustness (28). IVW can integrate the Wald estimates of individual SNPs to derive a comprehensive estimate, thereby facilitating robust and accurate causal assessment (29, 30). The association between pediatric asthma and UAD risk is quantified using odds ratio along with its 95% confidence interval (CI), where a significance level of p-value <0.05 indicates a causal relationship. Additionally, scatter plots and forest plots are employed to visually present the findings of the MR analysis. The statistical analysis in this study was conducted using R (version 4.3.1) and the Two-Sample MR package (version 0.5.7), as well as the MRPRESSO package (version 1.0).

2.5 Sensitivity analysis

Sensitivity analysis mainly includes tests for heterogeneity, tests for horizontal pleiotropy, MR-PRESSO test, and leave-one-out test. Heterogeneity testing will be conducted using IVW and MR-Egger regression methods, while the Cochran Q statistic will be calculated to evaluate the extent of heterogeneity. If the p-value is less than 0.05, it indicates heterogeneity, leading to subsequent analysis employing a random effects model. Conversely, if the p-value is greater than or equal to 0.05, a fixed effects model will be utilized (31). Using MR-Egger regression for testing horizontal pleiotropy, if the p-value is less than 0.05, it suggests the presence of horizontal pleiotropy. The MR-PRESSO method is employed to detect the presence of outliers, and if any are identified, the causal estimates undergo reassessment subsequent to their removal. The leave-one-out analysis is a systematic method employed to ascertain whether the MR result is influenced by an individual SNPs, through the deliberate exclusion of each SNPs in a sequential manner (32).

3 Results

3.1 Results of IV screening

According to the pre-established criteria, SNPs that simultaneously satisfied all three major hypotheses were selected after undergoing a series of rigorous quality control steps. The F-values of the SNPs included in the analysis ranged from 30.43 to 287.58, and no evidence of weak instrumental variable bias was observed (Supplementary Table S1). Detailed information regarding the final number of included SNPs is provided in Figure 2.

3.2 Results of MR analysis

3.2.1 Pediatric asthma and chronic sinusitis

The IVW analysis did not reveal a significant causal relationship between pediatric asthma and chronic sinusitis (OR = 1.00, 95%CI:1.00–1.00, p-value = 0.085), and was replicated via MR-Egger (OR = 1.00, 95%CI: 1.00–1.00, p-value = 0.195), WME (OR = 1.00, 95%CI: 1.00–1.00, p-value = 0.168), Simple mode (OR = 1.00, 95%CI: 1.00–1.00, p-value = 0.263), weighted mode (OR = 1.00, 95%CI: 1.00–1.00, p-value = 0.352).

The heterogeneity test results revealed that both MR-Egger (p-value = 0.009) and IVW (p-value = 0.006) exhibited p-value <0.05, indicating the presence of heterogeneity in the data set, so the random-effect model was employed for analysis. The horizontal pleiotropy test revealed no evidence of horizontal pleiotropy (p-value = 0.214 > 0.05). No outliers were detected by MR-PRESSO test. Leave-one-out analyses did not identify any SNPs exerting a substantial impact on the estimated causal associations (Figures 2, 3).

3.2.2 Pediatric asthma and chronic rhinitis, nasopharyngitis, and pharyngitis

The IVW analysis found a significant causal association between pediatric asthma and chronic rhinitis, nasopharyngitis and pharyngitis (OR = 1.15, 95%CI (1.05–1.26), p-value = 0.003), and was replicated via WME (OR = 1.19, 95%CI (1.05–1.36), p-value = 0.008), but MR-Egger (OR = 1.23, 95%CI: 0.92–1.63, p-value = 0.164), Simple mode (OR = 1.09, 95%CI: 0.84–1.41, p-value = 0.502) and weighted mode (OR = 1.16, 95%CI: 0.97–1.40, p-value = 0.110) did not support the IVW results.

The heterogeneity test results revealed that both MR-Egger (p-value = 0.837) and IVW (p-value = 0.859) exhibited p-value >0.05, indicating the absence of heterogeneity in the data set, so the fixed-effect model was employed for analysis. The horizontal pleiotropy test revealed no evidence of horizontal pleiotropy (p-value = 0.627 > 0.05). No outliers were detected by MR-PRESSO test. Leave-one-out analyses did not identify any SNPs exerting a substantial impact on the estimated causal associations (Figures 2, 3).

3.2.3 Pediatric asthma and chronic diseases of tonsils and adenoids

A significant causal relationship between pediatric asthma and chronic diseases of tonsils and adenoids was observed in IVW analysis (OR = 1.07, 95%CI: 1.00–1.15, p-value = 0.038), which could

Outcome	Method	nSNP	P.value	OR(95%CI)	Heterogeneity.Q_p	Pleiotropy.P
Chronic sinusitis	MR Egger	37	0.195	1.00(1.00 to 1.00)	0.009	0.214
	IVW	37	0.085	1.00(1.00 to 1.00)	0.006	
	WME	37	0.168	1.00(1.00 to 1.00)		
	Simple mode	37	0.263	1.00(1.00 to 1.00)		
	Weighted mode	37	0.352	1.00(1.00 to 1.00)		
Chronic rhinitsi, nasopharyngitis and pharyngitis	MR Egger	35	0.164	1.23(0.92 to 1.63)	0.837	0.627
	IVW	35	0.003	1.15(1.05 to 1.26)	0.859	
	WME	35	0.008	1.19(1.05 to 1.36)		
	Simple mode	35	0.502	1.09(0.84 to 1.41)		
	Weighted mode	35	0.110	1.16(0.97 to 1.40)		
Chronic diseases of tonsils and adenoids	MR Egger	35	0.094	1.21(0.97 to 1.50)	0.001	0.271
	IVW	35	0.038	1.07(1.00 to 1.15)	0.001	
	WME	35	<0.001	1.16(1.07 to 1.26)		
	Simple mode	35	0.054	1.19(1.00 to 1.40)		
	Weighted mode	35	0.002	1.21(1.08 to 1.35)		
Chronic laryngitis and laryngotracheitis	MR Egger	35	0.529	1.17(0.73 to 1.88)	0.253	0.636
	IVW	35	0.558	1.05(0.90 to 1.21)	0.283	
	WME	35	0.529	0.90(0.72 to 1.11)		
	Simple mode	35	0.487	0.86(0.56 to 1.31)		
	Weighted mode	35	0.399	0.86(0.62 to 1.21)		
Chronic bronchitis	MR Egger	37	<0.001	1.66(1.34 to 2.05)	0.349	0.369
	IVW	37	<0.001	1.51(1.42 to 1.62)	0.356	
	WME	37	<0.001	1.52(1.38 to 1.68)		
	Simple mode	37	<0.001	1.49(1.26 to 1.76)		
	Weighted mode	37	<0.001	1.53(1.34 to 1.75)		
Bronchiectasis	MR Egger	37	0.611	1.13(0.71 to 1.81)	0.009	0.214
	IVW	37	<0.001	1.51(1.30 to 1.75)	0.006	
	WME	37	0.001	1.35(1.13 to 1.61)		
	Simple mode	37	0.088	1.34(0.97 to 1.87)		
	Weighted mode	37	0.111	1.34(0.94 to 1.92)		
COPD	MR Egger	37	<0.001	1.53(1.27 to 1.86)	0.111	0.443
	IVW	37	<0.001	1.43(1.34 to 1.51)	0.118	
	WME	37	<0.001	1.43(1.32 to 1.55)		
	Simple mode	37	<0.001	1.35(1.17 to 1.55)		
	Weighted mode	37	<0.001	1.43(1.29 to 1.59)		

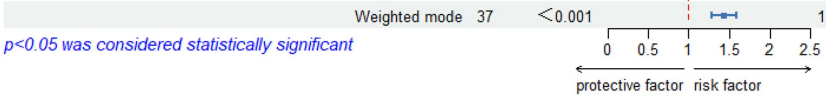

FIGURE 2
Results of Mendelian randomization studies, heterogeneity analysis and pleiotropy between pediatric asthma and UAD. CI, confidence interval; OR, odds ratio; SNP, single nucleotide polymorphism; IVW, inverse variance weighted; WME, weighted median; *Q*, Cochran's *Q* statistic; COPD, chronic obstructive pulmonary disease.

be confirmed by WME (OR = 1.16, 95%CI: 1.07–1.26, *p*-value <0.001), and weighted mode (OR = 1.21, 95%CI: 1.08–1.35, *p*-value = 0.002), but MR-Egger (OR = 1.21, 95%CI: 0.97–1.50, *p*-value = 0.094), and Simple mode (OR = 1.19, 95%CI: 1.00–1.40, *p*-value = 0.054) did not support the IVW results.

The heterogeneity test results revealed that both MR-Egger (*p*-value = 0.001) and IVW (*p*-value = 0.001) exhibited *p*-value <0.05, indicating the presence of heterogeneity in the data set, so the random-effect model was employed for analysis. The horizontal pleiotropy test revealed no evidence of horizontal pleiotropy (*p*-value = 0.271 > 0.05). No outliers were detected by MR-PRESSO test. Leave-one-out analyses did not identify any SNPs exerting a substantial impact on the estimated causal associations (Figures 2, 3).

3.2.4 Pediatric asthma and chronic laryngitis and laryngotracheitis

The IVW analysis did not reveal any significant causal relationship between pediatric asthma and chronic laryngitis and laryngotracheitis (OR = 1.05, 95%CI: 0.90–1.21, *p*-value = 0.558). This finding is consistent with the conclusions drawn from MR-Egger (OR = 1.17, 95%CI: 0.73–1.88, *p*-value = 0.529), WME (OR = 0.09, 95%CI: 0.72–1.11, *p*-value = 0.529), Simple mode (OR = 0.86, 95%CI: 0.56–1.31, *p*-value = 0.487), and weighted mode (OR = 0.86, 95%CI: 0.62–1.21, *p*-value = 0.399).

The heterogeneity test results revealed that both MR-Egger (*p*-value = 0.253) and IVW (*p*-value = 0.283) exhibited *p*-value >0.05, indicating the absence of heterogeneity in the data set, so the random-effect model was employed for analysis. The horizontal pleiotropy test revealed no evidence of horizontal pleiotropy (*p*-value = 0.636 > 0.05). No outliers were detected by MR-PRESSO test. Leave-one-out analyses did not identify any SNPs exerting a substantial impact on the estimated causal associations (Figures 2, 3).

3.2.5 Pediatric asthma and chronic bronchitis

The IVW analysis revealed a significant causal association between pediatric asthma and chronic bronchitis (OR = 1.51, 95% CI: 1.42–1.62, *p*-value <0.001). This finding is corroborated by other

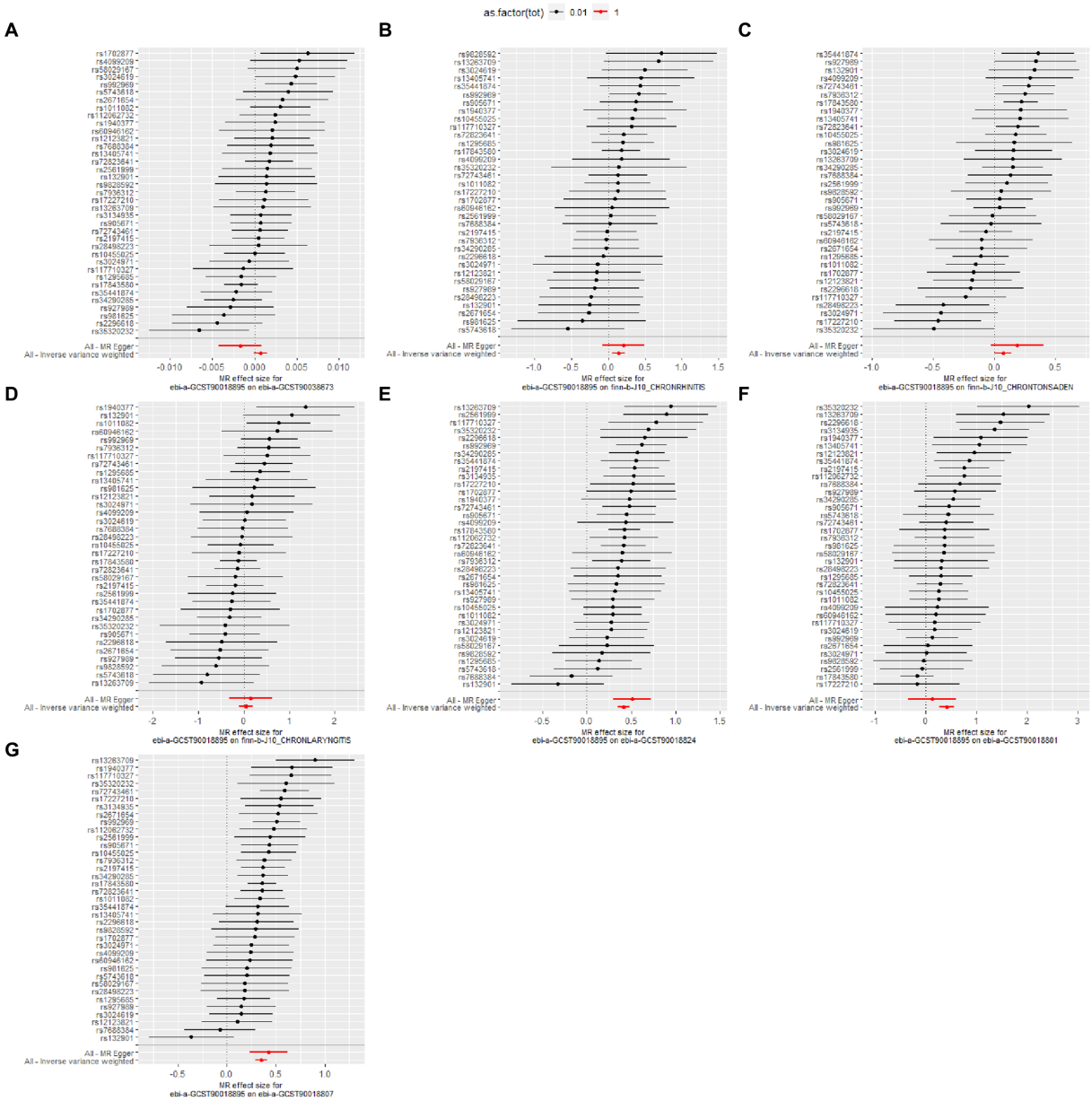

FIGURE 3
Leave-one-out analysis for the causal effect of pediatric asthma on the risk of UAD. **(A)** Chronic sinusitis; **(B)** Chronic rhinitis, nasopharyngitis and pharyngitis; **(C)** Chronic diseases of tonsils and adenoids; **(D)** Chronic laryngitis and laryngotracheitis; **(E)** Chronic bronchitis; **(F)** Bronchiectasis; **(G)** Chronic obstructive pulmonary disease.

methods including MR-Egger (OR = 1.66, 95% CI: 1.34–2.05, $p < 0.001$), WME (OR = 1.52, 95%CI: 1.38–1.68, p-value < 0.001), Simple mode (OR = 1.49, 95%CI: 1.26–1.76, p-value < 0.001), and weighted mode (OR = 1.53, 95 %CI: 1.34–1.75, p-value < 0.00 L).

The heterogeneity test results revealed that both MR-Egger (p-value = 0.349) and IVW (p-value = 0.356) exhibited p-value >0.05, indicating the absence of heterogeneity in the data set, so the fixed-effect model was employed for analysis. The horizontal pleiotropy test revealed no evidence of horizontal pleiotropy (p-value = 0.369 > 0.05). No outliers were detected by MR-PRESSO test. Leave-one-out analyses did not identify any SNPs exerting a substantial impact on the estimated causal associations (Figure 2).

3.2.6 Pediatric asthma and bronchiectasis

A significant causal relationship between pediatric asthma and bronchiectasis was observed in IVW analysis (OR = 1.51, 95%CI: 1.30–1.75, p-value <0.001), which could be confirmed by WME (OR = 1.35, 95%CI: 1.13–1.61, p-value = 0.001). But MR-Egger (OR = 1.13, 95%CI: 0.71–1.81, p-value = 0.611), Simple mode (OR = 1.34, 95%CI: 0.97–1.87, p-value = 0.088), weighted mode (OR = 1.34, 95%CI: 0.94–1.92, p-value = 0.111) did not support the IVW results.

The heterogeneity test results revealed that both MR-Egger (p-value = 0.009) and IVW (p-value = 0.006) exhibited p-value <0.05, indicating the presence of heterogeneity in the data set, so the

random-effect model was employed for analysis. The horizontal pleiotropy test revealed no evidence of horizontal pleiotropy (p-value = 0.214 > 0.05). MR-PRESSO test detected one outlier (rs17843580). Leave-one-out analyses did not identify any SNPs exerting a substantial impact on the estimated causal associations (Figures 2, 3).

When the MR analysis was repeated after the outliers were removed, the significant causal relationship between pediatric asthma and bronchiectasis was still observed in the IVW analysis (OR = 1.63, 95%CI: 1.42–1.88, p-value <0.001), which could be confirmed by the WME (OR = 1.45, 95%CI: 1.21–1.74, p-value <0.001) were replicated, but MR-Egger (OR = 1.69, 95%CI: 1.01–2.83, p-value = 0.052), Simple mode (OR = 1.35, 95%CI: 0.97–1.86, p-value = 0.081), weighted model (OR = 1.35, 95%CI: 1.00–1.81, p-value = 0.056) did not support the IVW results (Supplementary material).

3.2.7 Pediatric asthma and COPD

The IVW analysis reported a significant causal relationship between pediatric asthma and COPD (OR = 1.43, 95%CI: 1.34–1.51, p-value <0.001), and was consistent with the findings of the MR-Egger (OR = 1.53, 95%CI: 1.27–1.86, p-value <0.001), WME (OR = 1.43, 95%CI: 1.32–1.55, p-value <0.001), Simple mode (OR = 1.35, 95%CI: 1.17–1.55, p-value <0.001), and weighted mode (OR = 1.43, 95%CI: 1.29–1.59, p-value <0.001).

The heterogeneity test results revealed that both MR-Egger (p-value = 0.111) and IVW (p-value = 0.118) exhibited p-value >0.05, indicating the absence of heterogeneity in the data set, so the fixed-effect model was employed for analysis. The horizontal pleiotropy test revealed no evidence of horizontal pleiotropy (p-value = 0.443 > 0.05). No outliers were detected by MR-PRESSO test. Leave-one-out analyses did not identify any SNPs exerting a substantial impact on the estimated causal associations (Figures 2, 3).

The details of leave-one-out analysis are shown in Figure 3. The forest plot and scatter plot illustrating the causal relationships between genetically predicted pediatric asthma and the risk of UAD are presented in Figures 4, 5. The detailed estimates of causal effects.

4 Discussion

To the best of our knowledge, this study represents the first investigation in the field of MR research to examine the causal impact of pediatric asthma on UAD. Our findings demonstrated a significant causal relationship between pediatric asthma and the occurrence of chronic rhinitis, nasopharyngitis, pharyngitis, chronic diseases of tonsils and adenoids, chronic bronchitis, bronchiectasis, as well as COPD. However, there was no discernible causal relationship observed between pediatric asthma and the occurrence of chronic sinusitis, chronic laryngitis, or laryngitis.

The concept of UAD was initially proposed in the late 1990s, positing that the respiratory tract constitutes a cohesive entity with numerous shared anatomical and histological characteristics, and the lesions in any region of the airway will exert an impact on the function of the whole airway (33). The concept is grounded in the shared pathophysiological and immunological mechanisms that underlie specific respiratory diseases (34). Persistent and increased inflammation is a common pathological characteristic of UAD, accompanied by significant genetic modifications and stringent gene regulation (35). In the context of allergic inflammation, upper and lower airway diseases exhibit overlapping immunopathological features, including activation of epithelial immune responses, infiltration of eosinophils, production of Ig E antibodies, and activation of mast cells (36). Studies have shown that nasal allergen provocation in allergic rhinitis not only increases nasal eosinophilia but also induces bronchial eosinophilic inflammation, bronchoconstriction, and bronchial hyperresponsiveness, indicating inflammatory crosstalk between the upper and lower airways (37).

The primary pathological mechanisms of pediatric asthma include chronic airway inflammation, airway hyperresponsiveness, and airway remodeling. These pathological processes undoubtedly affect airway function to varying degrees and may be potential contributing factors for the development of UAD in later life. Airway Inflammation: Airway inflammatory responses are endogenous factors in the progression of pediatric asthma and UAD, involving the infiltration of inflammatory cells and the release of inflammatory mediators. These processes are dynamic and can be influenced by treatment, infection, environmental exposure, and disease progression characteristics (8). For instance, eosinophilic airway inflammation associated with TH2 cytokines (IL-4, IL-5, and IL-13) and/or Ig E is an underlying pathological mechanism in both chronic rhinosinusitis with nasal polyps and asthma (38). Inflammation observed in Asthma-COPD Overlap Syndrome (ACOS) is primarily driven by eosinophils and neutrophils, as evidenced by studies demonstrating significantly elevated levels of IL-6 in ACOS patients compared to healthy individuals and those with asthma (39). Airway Remodeling: Prolonged chronic airway inflammation can lead to mucosal swelling and excessive mucus secretion, resulting in structural changes and remodeling of the airways. This phenomenon can be observed in both pediatric asthma and UAD. Airway remodeling phenomena, such as thickening of the airway wall, damage to epithelial cells, hyperplasia of goblet cells, and proliferation of smooth muscle cells, are observed in both asthma and COPD (40, 41). In severe corticosteroid-dependent asthma, there can be an increase in the number and area occupied by bronchial blood vessels—a condition that is also seen in severe COPD and bronchiectasis (40). Airway Hyperresponsiveness: Airway hyperresponsiveness refers to an exaggerated sensitivity of the airways to stimuli, such as allergens or irritants, resulting in bronchospasm and constriction. It is a crucial clinical feature in pulmonary diseases (allergic rhinitis, asthma, COPD) and is closely related to airway inflammation, remodeling, and mucus secretion, playing a significant role in the progression of UAD (42, 43).

Pediatric asthma exhibits a strong correlation with upper respiratory conditions, including chronic rhinitis, chronic diseases of the tonsils and adenoids. Firstly, both of these conditions are frequently observed as comorbidities in asthma, with chronic rhinitis being diagnosed in more than a quarter of children with asthma (44). Secondly, chronic inflammation plays a pivotal role of airway remodeling and irreversible airflow limitation in patients with long-term asthma, and in the upper respiratory tract, it can not only cause chronic rhinitis, but also stimulate adenoids and tonsils, leading to hyperplasia and hypertrophy (45, 46). Furthermore, the occurrence and progression of these diseases are intricately linked to prolonged exposure to nasal allergens (47). Similarly, pediatric asthma exhibits a robust association with lower respiratory conditions, including chronic bronchitis, bronchiectasis, and COPD. Although chronic bronchitis primarily occurs in middle-aged and elderly individuals, it may have its origins in childhood. Research

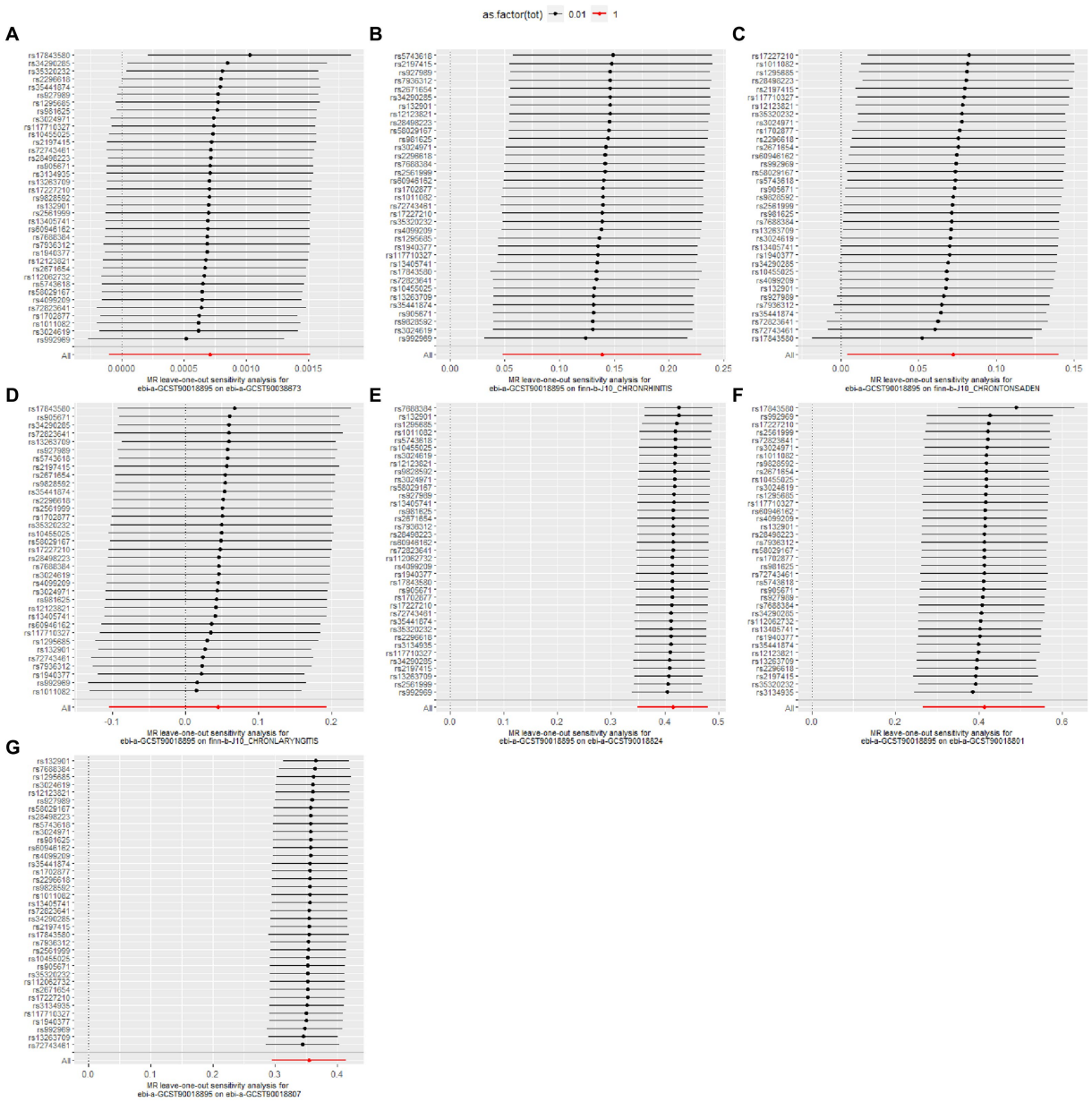

FIGURE 4
Forest plot for the causal effect of pediatric asthma on the risk of UAD. **(A)** Chronic sinusitis; **(B)** Chronic rhinitis, nasopharyngitis and pharyngitis; **(C)** Chronic diseases of tonsils and adenoids; **(D)** Chronic laryngitis and laryngotracheitis; **(E)** Chronic bronchitis; **(F)** Bronchiectasis; **(G)** Chronic obstructive pulmonary disease.

indicates that childhood asthma can serve as a clinical predictive factor for adult chronic bronchitis (48). Moreover, recent data indicates a tenfold increase in the risk of developing chronic bronchitis among current asthma patients compared to two decades ago (49). A mate analysis revealed that the average prevalence of bronchiectasis among patients with asthma was determined to be 36.6% (50). Bronchiectasis is a rare occurrence in the pediatric population and is typically considered as the ultimate result of many years of chronic, poorly controlled asthma. However, findings from a cross-sectional study indicate that approximately one-third of children with severe asthma exhibit bronchiectasis (51). Furthermore, research indicates that eosinophilic airway inflammation plays a crucial role in the formation and development of bronchiectasis in asthmatic patients, characterized by elevated peripheral blood eosinophil count and sputum eosinophil percentage (52). The findings of a 50 year cohort study demonstrate a significant association between pediatric asthma and an increased risk of developing COPD in later life (53); children with a prior history of asthma exhibit a 3.45-fold increased likelihood of developing COPD compared to children without such a medical background (54). Pediatric asthma can impair lung development, hindering the attainment of normal peak lung function during adolescence and diminishing adult lung function, thereby augmenting the susceptibility to developing COPD (55). Nevertheless, early suppression of airway inflammation and prevention of asthma exacerbations in childhood can foster optimal lung development and maturation, culminating in enhanced lung function and a reduced risk of COPD in adulthood (55). In a cross-sectional survey conducted on 851 patients with chronic sinusitis in seven cities across China, the prevalence of Chronic sinusitis

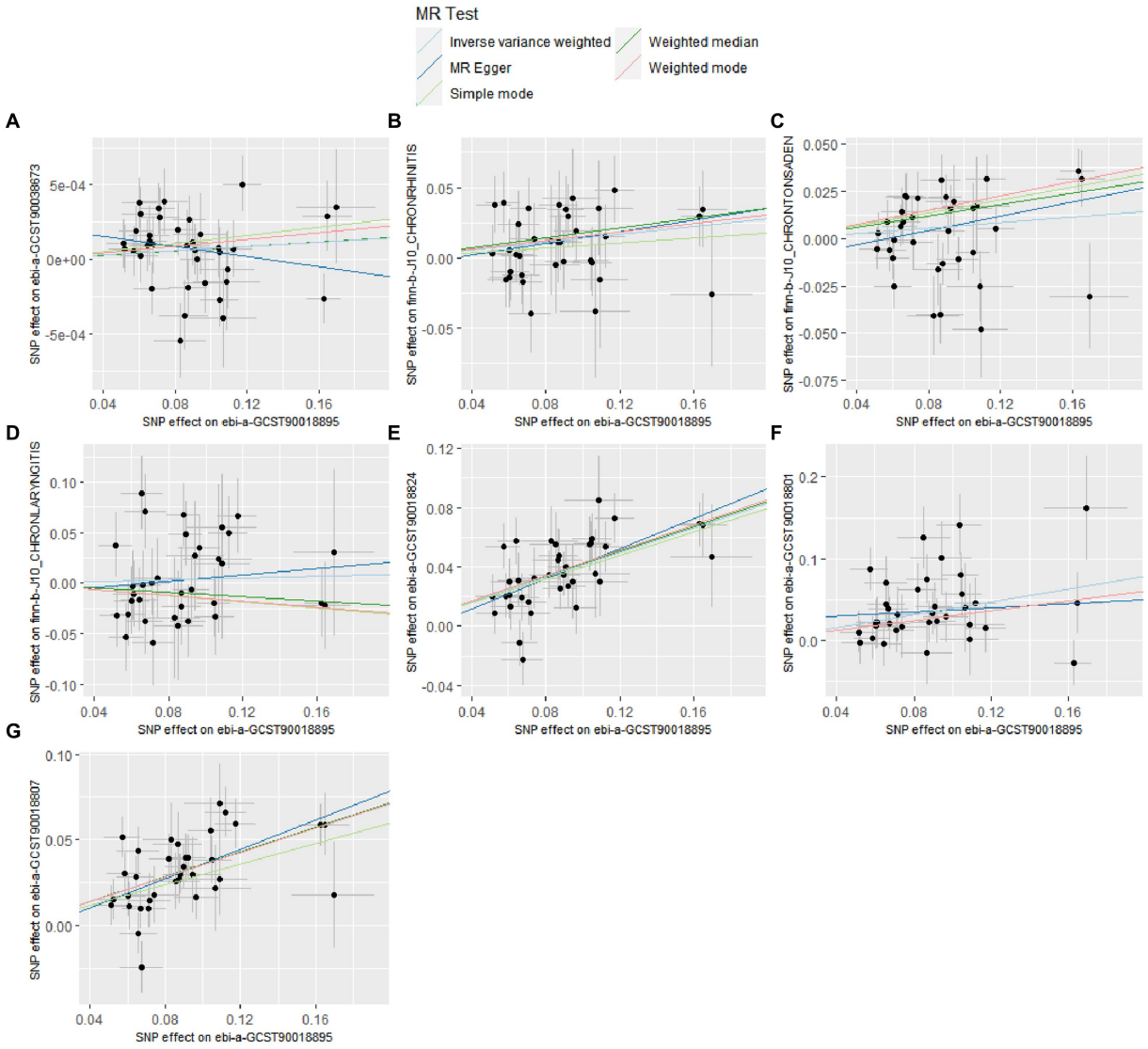

FIGURE 5
Scatter plot for the causal effect of pediatric asthma on the risk of UAD. **(A)** Chronic sinusitis; **(B)** Chronic rhinitis, nasopharyngitis and pharyngitis; **(C)** Chronic diseases of tonsils and adenoids; **(D)** Chronic laryngitis and laryngotracheitis; **(E)** Chronic bronchitis; **(F)** Bronchiectasis; **(G)** Chronic obstructive pulmonary disease.

among individuals with asthma was observed to be 24%, which is significantly higher compared to the 7% prevalence found among non-asthmatic participants (56). However, our research findings do not provide evidence for a causal relationship between childhood asthma and chronic sinusitis. Furthermore, further investigation is warranted to determine whether there exists a reverse causal link between these two conditions (57). Chronic laryngitis and laryngotracheitis, although categorized as respiratory disorders, are commonly linked to factors such as pharyngolaryngeal reflux, prolonged exposure to irritants, excessive vocal cord use, and bacterial or viral infections. There are significant differences in the pathogenesis compared to pediatric asthma. Likewise, our research results do not lend support to the existence of a causal relationship between the two diseases (58).

Pediatric asthma and UAD are closely linked in terms of disease risk factors, epidemiology, and pathological mechanisms. Conventional observational studies encounter challenges in effectively mitigating exposure measurement errors, confounding bias, and reverse causality, necessitating substantial time and social resources. MR analysis is an efficient causal analysis method that effectively mitigates potential individual differences and biases in intervention allocation by randomly assigning study participants to different treatment groups, thereby ensuring the reliability and generalizability of research findings (59). This study contributes to enhance our understanding of UAD and facilitates accurate predictions regarding the developmental trends and long-term outcomes of asthma in children. For instance, our study establishes a causal association between pediatric asthma and COPD. A large cohort study indicates that even clinically remitted childhood asthma may remain a significant risk factor for late-life COPD, consistent with our conclusions (16). The 2023 Global

Initiative for Asthma statement emphasizes the importance of managing and identifying asthma comorbidities. Developing specific treatment strategies based on the UAD concept to manage asthma and its comorbidities could enhance treatment efficacy, reduce medication use, and save medical resources (1). Biologics such as dupilumab, omalizumab, and mepolizumab have been approved for severe asthma and severe chronic rhinosinusitis with nasal polyps. These medications improve asthma symptoms and lung function, reduce disease recurrence, and streamline medication regimens, demonstrating broad potential in the treatment of UAD (34).

Leveraging the unique advantages of the MR method, our study systematically assessed the causal relationship between pediatric asthma and UAD. This approach emulates randomized controlled trials within an observational study framework and incorporates multiple sensitivity analyses, thereby augmenting the scientific validity and robustness of our findings (30). This study partially validated previous observational research, deepening our understanding of the "one airway, one disease" concept. However, there remains a paucity of scientific evidence on the integrated management of pediatric asthma and UAD. Most clinical trials and real-world studies regard asthma or UAD as independent conditions or comorbidities, rather than exploring these diseases based on the concept of UAD. Further experimental and observational studies are needed to elucidate the pathological mechanisms underlying these causal associations, to promote the advancement of preventive and therapeutic systems for asthma and UAD. Furthermore, certain limitations of this MR study should be acknowledged: Firstly, due to the unavailability of raw GWAS data, more specific phenotypes such as gender, age and asthma severity could not be explored, and further subgroup analysis could not be carried out, which may lead to bias of the study results; Secondly, the data utilized in this study exclusively originated from European populations, thus the generalizability of the findings to other populations may be constrained; Thirdly, MR is a robust approach for investigating causal relationships without the need to examine underlying biological mechanisms, and its research findings necessitate further rigorous validation.

5 Conclusion

In conclusion, our findings suggest that pediatric asthma may be a potential risk factor for various UAD, underscoring the significance of the "one airway, one disease" concept in the prevention and management of chronic respiratory diseases. Additionally, elucidating the mechanisms underlying the causal relationship between pediatric asthma and UAD is crucial for the comorbidity management of pediatric asthma and the diagnosis and prevention of UAD.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: relevant tables are included in the manuscript.

Ethics statement

Ethical approval was not required for the study involving humans in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and the institutional requirements.

Author contributions

TG: Software, Writing – original draft, Formal analysis, Methodology. QC: Writing – original draft, Investigation, Methodology. SH: Supervision, Validation, Writing – review & editing. RZ: Writing – original draft, Formal analysis. JW: Writing – original draft, Formal analysis.

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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/fmed.2024.1369695/full#supplementary-material

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Artificial intelligence in the transition of allergy: a valuable tool from childhood to adulthood

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1 Introduction

Artificial intelligence (AI) is having a revolutionary effect in several industries, including healthcare. Nowadays AI plays an increasingly significant role in managing chronic diseases. A study published in *The Lancet Digital Health* highlighted the effectiveness of AI-driven virtual health assistants in improving medication adherence among patients with chronic illnesses (1). The study by Downing et al. (2), demonstrated that Livongo's AI-driven approach significantly improved glycemic control and reduced the incidence of diabetes-related complications. A recent study published in *Nature* demonstrated that AI could predict adverse cardiovascular events by analyzing electronic health records, helping to tailor preventive measures more effectively than traditional approaches (3).

AI has the potential to completely transform our understanding, diagnosis, treatment, and management of allergic diseases including asthma (4–6). AI has already been demonstrated to be useful in allergic diseases in children. In the study by Smith et al., AI was used to analyze electronic health records data to diagnose asthma from 500 pediatric patients who presented with respiratory symptoms. The results were compared with traditional diagnostic methods. The AI tool demonstrated an accuracy of 92%, sensitivity of 89%, and specificity of 94% in diagnosing asthma, outperforming traditional methods which had an accuracy of 85%, sensitivity of 82%, and specificity of 88% (7).

AI, used as machine learning, demonstrated to be superior to traditional diagnostics also in allergic rhinitis, chronic cough, and respiratory infections (8–10).

Conversely, as of now, there are no studies on the effectiveness of AI in managing the transition from pediatric to adult stages in allergic diseases. The transition is one of the biggest obstacles for people with asthma and allergies, as well as their families. The European Academy of Allergy and Clinical Immunology (EAACI) has developed evidence-based guidelines for healthcare professionals to support the transitional care of adolescents and young adults with allergic diseases and/or asthma. These recommendations advocate for early transition initiation (11–13 years), a structured multidisciplinary approach, patient education, medication simplification, psychological support, and involving peers and family in self-management (11).

Patients with allergies face several unique obstacles while moving from pediatric to adult treatment, which can negatively affect their health and quality of life. Adherence to drug therapy is one of the main issues. Due to forgetfulness, a lack of awareness of the significance of adherence, or dealing with unpleasant side effects, adolescents and young adults sometimes find it difficult to maintain regular adherence to prescribed drugs. This inconsistency might worsen symptoms and raise the likelihood of serious allergic responses. Another key problem is self-management. As patients reach maturity, they are expected to take on increasing responsibility for controlling their allergies. This includes recognizing symptoms, avoiding triggers, and understanding how to utilize emergency medications like epinephrine auto-injectors. Many young individuals may be unprepared for this additional responsibility, which can lead to worry and failures in good management. Communication breakdowns between healthcare professionals exacerbate the shift. Effective transition necessitates smooth communication between pediatric and adult healthcare practitioners, which is sometimes hampered by disparate medical record systems and a lack of standardized processes for transferring care. Consequently, critical information about the patient's allergy history and management plan may not be adequately communicated, leading to fragmented care and potential health risks.

Moving from the care of a pediatric specialist who has followed the patient for years, providing regular follow-ups and understanding both clinical and personal details (such as treatment difficulties, friendships and school issues), often makes it difficult to detach from that trusted figure (12). The family and the patient frequently request continued care from the pediatrician even into adulthood because they trust them and are concerned about relying on a new professional unfamiliar with the patient's medical history. Pediatricians who have cared for their patients since childhood possess valuable insights into their medical history, treatment plans, and individual needs. Transitioning to a new healthcare provider can be challenging, as it involves navigating unfamiliar territory and establishing trust with a new professional figure. It is not merely a matter of transferring medical records. It requires establishing a new therapeutic relationship built on trust and comprehensive knowledge of the patient's clinical history, especially if the patient has a complex allergy history. For example, patients with multiple food allergies undergoing years-long desensitization processes or those with asthma or atopic dermatitis receiving biologic therapy who require specialized care and monitoring. The transition can also pose a real problem for patients with co-morbidities. Continuity of care during this period is crucial for maintaining the patient's wellbeing and ensuring their medical needs are adequately addressed.

The purpose of this article is to explore the potential of AI in addressing these specific challenges faced by allergic and asthmatic patients. We will examine how AI can improve adherence to therapy, enhance self-management practices, and bridge communication gaps between pediatric and adult care providers, ultimately aiming to improve the overall transition experience for allergic patients.

2 How AI can aid in the transition of allergic diseases?

AI can be particularly beneficial during the transition in two critical phases: (a) assisting patients in taking responsibility for independently managing their disease and (b) facilitating the transfer of information from the pediatric allergist to the allergy specialist.

2.1 Assisting patients in taking responsibility

Adolescents transitioning to adulthood face the challenge of moving from a parent-guided healthcare regimen to independently managing their health. The use of AI-driven mobile apps can offer reminders for medication adherence, monitor symptoms, and suggest lifestyle adjustments based on real-time data. These apps can educate patients about their condition, treatment plans, and the importance of adhering to prescribed therapies. Interactive features, such as virtual health assistants, can answer questions, provide motivational support, and offer feedback on the patient's self-management practices. AI can also be useful in managing the switching of the device used for inhalation therapy, from the spacer to the diskus for asthma.

Adolescents and adults need to learn to carry and self-administer adrenaline effectively and safely. AI can assist patients in learning and independently managing the administration of intramuscular adrenaline. Additionally, AI can analyze patterns in the patient's health data to predict potential exacerbations or allergic reactions, allowing patients to take preemptive action. For example, if an AI system detects an increase in environmental allergens that typically trigger a patient's asthma, it can alert the patient to take preventive measures, such as using inhalers or avoiding certain activities. Despite being required by law, some restaurants fail to show the allergy list or don't consider the possibility of contamination. In the near future, AI could be able to identify and indicate the existence of allergens in a meal by detecting traces.

Moreover, AI can facilitate telemedicine consultations, where patients can report their symptoms and receive guidance without needing to visit the doctor's office. Simulation scenarios, supported by virtual reality, can be valuable in enhancing a patient's autonomy in treating and managing their condition. This empowers patients to handle minor issues independently while having support readily available if needed.

2.2 Facilitating the transfer of information

AI technology offers an opportunity to streamline the transition process. By analyzing vast amounts of data, including electronic health records, laboratory results, and treatment protocols, AI algorithms can provide comprehensive insights to improve continuity of care. AI can be instrumental in building a patient's report, encompassing history, recent therapies, comorbidities, and treatment advances. The assignment of disease risk (such

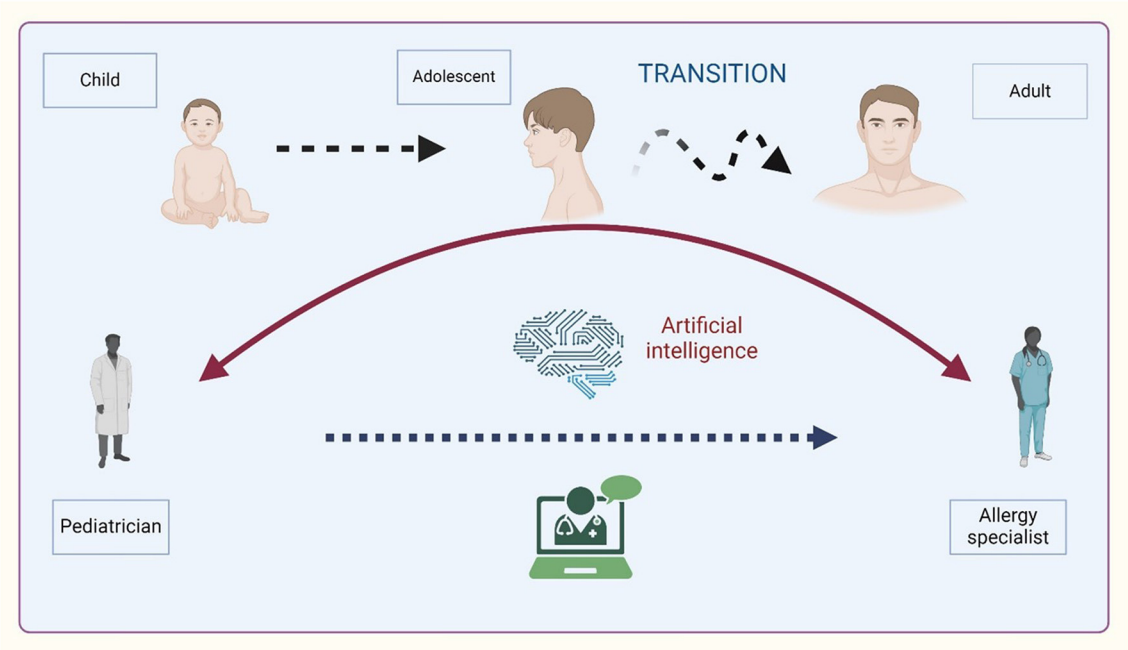

FIGURE 1
Overview of asthma transition from childhood to adulthood. Created with BioRender.com.

as asthma exacerbation or anaphylaxis) and the construction of predictive models can further support clinicians in making informed decisions during the transition period. By extracting insights from electronic health records, AI systems can ensure that the new healthcare provider is well-informed about the patient's condition and previous treatments.

3 Limitations of AI in the transition of allergy care

While AI offers significant potential benefits in managing the transition of allergy care from childhood to adulthood, several limitations must be considered. First, the accuracy and effectiveness of AI systems heavily rely on the quality and comprehensiveness of the data they are trained on. Incomplete or biased data can lead to incorrect predictions and recommendations, potentially jeopardizing patient safety. The effectiveness of AI in healthcare heavily relies on the quality and diversity of the datasets used for training algorithms. High-quality, diverse datasets are crucial to avoid biased or inaccurate predictions. Bias in AI can arise from unrepresentative data that fails to include various demographic groups, leading to disparities in healthcare outcomes. For instance, an AI system trained predominantly on data from a specific ethnic group may not perform well for individuals from different backgrounds. A recent study highlighted how biased datasets can lead to significant disparities in healthcare delivery and outcomes (13). Ensuring data diversity and quality helps create more equitable AI applications in healthcare, providing accurate predictions and treatment recommendations for all patient groups. The deployment of AI in healthcare also brings to the forefront significant ethical and privacy issues. Healthcare providers must ensure that AI applications comply with stringent regulatory standards to protect patient information. Robust data protection measures are essential to safeguard patient information and maintain confidentiality. This involves implementing stringent security protocols and ensuring compliance with regulations such as the General Data Protection Regulation (GDPR) (14). Additionally, transparency in AI algorithms is critical to building trust among patients and healthcare providers. Transparent algorithms allow stakeholders to understand how decisions are made, facilitating accountability and ethical use (15).

While AI offers substantial benefits, it is crucial to recognize that it cannot replace the expertise and empathy of healthcare professionals. AI should be viewed as a complementary tool that enhances the capabilities of healthcare providers rather than replacing them. The human touch, characterized by empathy, ethical judgment, and nuanced understanding of patient needs, remains irreplaceable. For example, while AI can analyze data and suggest diagnoses, the interpretation of these suggestions and the delivery of care require the human element to ensure compassionate and personalized patient care (16).

Moreover, there is a need for extensive training for both healthcare professionals and patients to effectively use AI-driven technologies. Resistance to change and a lack of trust in AI systems among patients and clinicians can also hinder widespread adoption. Ensuring a balanced approach that leverages AI's strengths while acknowledging its limitations is crucial for the successful integration of AI in transitional allergy care.

A graphical overview of asthma transition is illustrated in Figure 1.

4 Discussion and conclusion

Overall, AI has the potential to revolutionize the transition of patients with asthma and allergic diseases by improving personalized care, risk stratification, treatment optimization, remote monitoring, patient education, and provider collaboration. We think AI is a great tool to help doctors, who should learn how to use and manage it according to its appropriate use. Healthcare providers may improve patient transition experiences and guarantee continuity of treatment across the lifespan by leveraging AI-driven solutions.

Author contributions

CI: Conceptualization, Writing – original draft. AK: Conceptualization, Data curation, Writing – original draft. GD: Conceptualization, Writing – original draft. FD: Conceptualization, Supervision, Writing – review & editing. MM: Conceptualization, Supervision, Writing – review & editing.

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Respiratory, cardio-metabolic and neurodevelopmental long-term outcomes of moderate to late preterm birth: not just a near term-population. A follow-up study

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Introduction: Moderate-to-late preterm infants constitute the majority within the preterm infant population. Most research on preterm infants has focused on very preterm children, often treating moderate-to-late preterm infants as similar to full-term infants. Our objective was to compare clinical, respiratory, cardio-metabolic and neurodevelopmental outcomes in adolescents aged 12–15 years born moderate and late preterm with a control group of the same age born full-term.

Methods: Observational cross-sectional study, comparing moderate-to-late preterm (32–36^{+6} weeks' gestational age) with full-term adolescents (37–41^{+6} weeks' gestational age; 75 each group). Perinatal and neonatal history were collected as well as data on respiratory evolution (ISAAC questionnaire for asthma symptoms for adolescents 13–14 years), anthropometric values, learning difficulties, behavioral test (screening questionnaire for high-performance autism spectrum disorder and evaluation test for attention deficit hyperactivity disorder), skin prick test, pulmonary function test, echocardiogram and blood pressure. A blood test with metabolic profile was conducted.

Results: Moderate-to-late preterm adolescents had more current asthma [$p = 0.008$, OR3 (95% CI 1.26–7.14)] and longer duration of combined treatments to control asthma (inhaled corticosteroids and anti-leukotrienes; $p = 0.048$). Forced vital capacity <80% was detected more often in moderate-to-late preterm patients ($p = 0.013$). When assessing right ventricle, moderate-to-late preterm adolescents showed better tricuspid annular plane systolic excursion z-score ($p = 0.003$), shortening fraction ($p < 0.001$) and E/A ratio z-score ($p = 0.002$). Regarding left ventricular assessment, moderate-to-late preterm group had smaller ventricle diastolic diameter ($p = 0.04$) and lower posterior wall z-score values ($p = 0.037$). They also showed a better S'wave z-score ($p = 0.027$), E wave ($p = 0.005$), E/A ratio ($p = 0.003$) and a higher septal myocardial performance index z-score ($p = 0.025$). Moderate-to-late preterm adolescents presented lower weight z-score ($p = 0.039$), body mass index z-score ($p = 0.013$), Waterlow

weight index ($p = 0.006$) and higher undernutrition index [$p = 0.04$; OR 1.4 (95% CI 1–1.9)]. Although there were no differences in neurodevelopmental survey or behavioral tests.

Conclusion: Our findings underscore the importance of extended follow-up for this predominant group of premature infants to identify potential respiratory, cardiac and anthropometric issues that may emerge in the future.

KEYWORDS

moderate to late preterm, premature birth, asthma, lung function, cardiovascular risk, metabolic risk, developmental disabilities

Introduction

Preterm infants account for 10.6% of livebirths (1). Preterm birth, defined as birth before 37 weeks, is a very heterogeneous group. Moderate-to-late preterm (MLP) infants, which are defined as birth between 32 and 36 weeks' gestation and represents 85% of all preterm births (1, 2).

Previously, MLP infants have been considered "near" to term. However, recent publications (3, 4) report that MLP births have higher rates of morbidity and mortality compared to full-term children, especially in the first year of life. In addition, most recent studies (5, 6) suggest cardiovascular, neurodevelopmental and respiratory adversity in their evolution (Figure 1). These studies have revealed that MLP birth can be associated with poor growth (7, 8), increased blood pressure (4, 9), dyslipidemia or insulin resistance (10, 11), but outcomes in the adolescence have been inconsistent.

Lung development is also affected in MLP births. Compared with term, MLP children suffer more bronchiolitis, requiring hospitalization, and asthma especially in childhood (12–14). As the age of infants born MLP increases, a lower prevalence of asthma has been reported (15). It has been described in MLP infants a similar forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV_1), but lower mean forced expiratory flow between 25% and 75% of FVC ($FEF_{25–75}$) than in term infants (15, 16). However, the impact of MLP birth on asthma prevalence and lung function during adolescence remains unclear.

The premature developing brain is exposed to an extrauterine environment during their development. Prematurity is associated to higher risk of cognitive, motor, behavioral and neurosensory deficit. In particular greater prevalence of behavioral and psychiatric disorders have been described in MLP patients (17, 18).

In all these studies, it remains unclear whether the outcomes are associated with gestational age and whether they persist into adulthood. The long-term evolution of MLP adolescents needs to be well characterized to implement specific guidelines, targeted screening, and early treatment to improve their prognosis.

The aim of this study was to characterize the clinical, respiratory (asthma evolution, skin prick test and lung function), cardio-metabolic (hypertension, morphological or functional cardiac

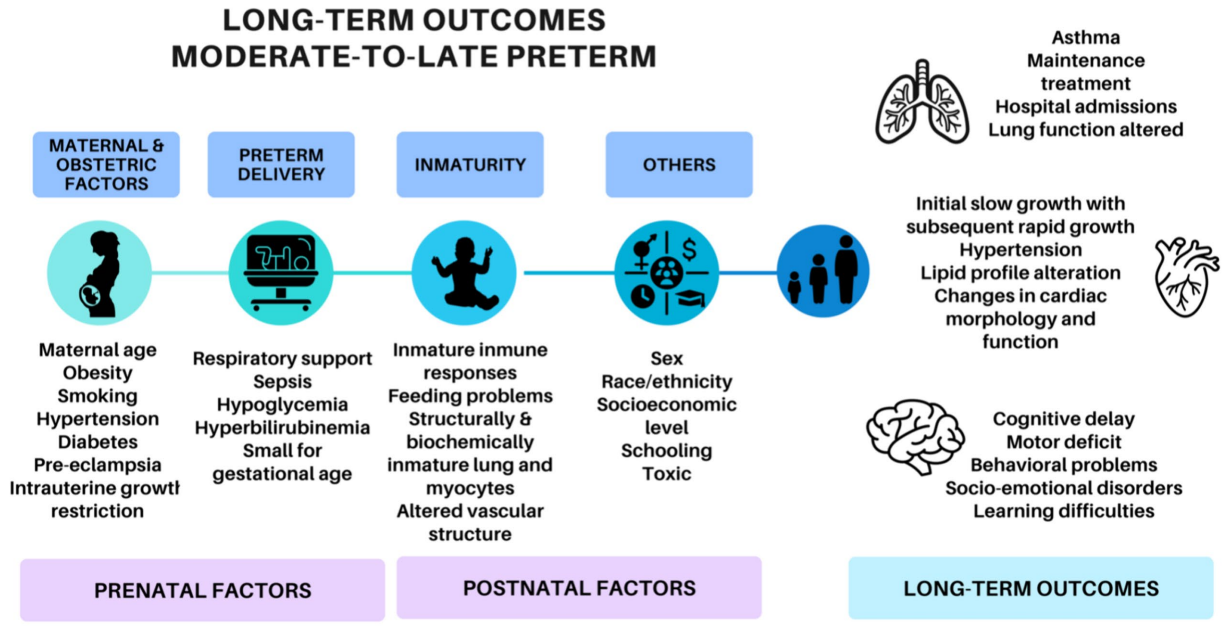

FIGURE 1
Factors involved in the development of the long-term outcomes of moderate-to-late preterm adolescents.

changes, growth disturbance and metabolic disorders) and neurodevelopmental outcomes (behavioral, social and learning diseases) among adolescents born with moderate and late prematurity, in comparison to their full-term counterparts.

Methods

An observational analytic cross-sectional study was performed. All adolescents aged 12 to 15 years, with a history of MLP birth (32–36^6 weeks of gestational age), born from 1 January 2006 to 31 December 2007, in the Severo Ochoa University Hospital, were invited to participate in the study. A control group of adolescents aged 12 to 15 years born at term (≥37 weeks) was also included. Furthermore, moderate preterm adolescents (MP) (32–33^6 weeks of gestational age) were compared with late preterm and full-term adolescents (LPFT) (34–41^6 weeks of gestational age).

The study sample was obtained from the birth registry of the Severo Ochoa University Hospital. A list was generated with all the MLP and full-term infants, arranged in chronological order according to date of birth. All the parents of the MLP patient were contacted by telephone to inform them of the study and, if interested in participate, to arrange an appointment. Each MLP patient was matched with a full-term control, the one immediately after the MLP patient who accepted to be included in the study.

The study was approved by the Ethics Committee of the Severo Ochoa Hospital. Written informed consent was obtained from all the patients and their parents after full explanation of the study protocol. All methods were carried out in the accordance with relevance guidelines and regulations.

Perinatal and neonatal medical history were collected from medical history (newborn measurements were presented with Fenton z-score) (19). The same respiratory, cardiologic, metabolic and neurological evaluation was conducted in both, cases and controls, as described below.

The frequency of asthma, allergy, abnormal lung function, hypertension, functional cardiac changes, growth disturbance, metabolic disorders and behavioral, social and learning diseases was compared between MLP and full-term adolescents and between MP and LPFT adolescents.

Respiratory evaluation

A specific questionnaire was used to obtain information on wheezing episodes, hospital admissions, maintenance medication, and family history of respiratory disease. The International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire for asthma symptoms for adolescents 13–14 years (20), previously validated and translated to Spanish, was answered by adolescents. *Current asthma* prevalence was estimated by the percentage of children with an affirmative answer to question number 2 (*wheezing or whistling in the chest in the past 12 months*), which has demonstrated the higher correlation with current asthma prevalence in validation studies (20, 21).

Skin prick test was performed to evaluate allergic sensitization for common inhaled allergens. Standardized Allergens (ALK-Abelló) were used with a positive control (10 mg/mL histamine) and negative control (glycerol-saline carrier solution). Positive test was considered when the papule diameter was greater than the positive control (22).

Lung function was evaluated by spirometry, according with the established guidelines (23) using Easy on-PC spirometer (NDD, New diagnostic design medical technologies). At least three reproducible maneuvers were performed, selecting the one with best FEV-1 and FVC values. The percentages were given with Zapletal (24) and z-score of predicted values with reference values of *Global Lung Function Initiative* (25). The variables collected were: FVC, FEV_1, FEV_1/FVC and $FEF_{25–75}$. The results were normal when FEV_1 and FVC were ≥80%, ratio FEV_1/FVC > 80% and $FEF_{25–75}$ ≥ 65% (26). Bronchodilator test was positive when FEV_1 increased >12% compared to the baseline after administration of 400 mcg of salbutamol (27).

Cardiologic evaluation

Blood pressure (BP) was measured oscillometrically with EarlyVue VS30 (Philips Healthcare, EEUU). Results were presented with z-scores of National High Blood Pressure Education Working Group on High Blood Pressure in Children and Adolescents 2004 (28), being considered pathological if >95th percentile (29). Echocardiogram to evaluate the cardiac function was performed using Vivid Pro7 and 9 (General Electric Healthcare, United States). Measurements were obtained using M-mode, power-doppler, continuous-doppler and myocardial performance index (MPI) and the results were presented with z-scores (30–32).

Metabolic assessment

The follow-up included current anthropometric measurements [weight, height, body mass index presented with Carrascosa 2010 z-score (33)], Waterlow index (34) and abdominal perimeter [presented with Moreno z-score (35)]. Body mass index and abdominal perimeter were considered pathological > 2standard deviations-SD (36, 37). Laboratory tests with metabolic profile (LDL-low-density lipoprotein, HDL-high-density lipoprotein, cholesterol, triglycerides, glycated hemoglobin-HbA1c) were performed. Cholesterol values ≥ 200 mg/dL, HDL < 40 mg/dL, LDL ≥ 130 mg/dL, triglycerides ≥ 150 mg/dL and HbA1c ≥ 6.5% were considered as pathologic (37, 38).

Neurologic evaluation

Learning disabilities and social development were evaluated. Behavioral tests [*Asperger Syndrome Screening Questionnaire*–ASSQ (39) and attention deficit hyperactivity disorder-ADHD assessment scale (40)] were carried out. The ASSQ was considered abnormal when the score was greater than 19 points. The test ADHD was pathological if the patient obtained >30 points, >10 points in attention deficit/hyperactivity subscale or 11 points in the behavioral disorder subscale (41, 42).

Statistical analysis

To calculate the sample size, the expected prevalence of asthma in preterm adolescents was expected to be about 25–30% (43) vs. 10%

(44) in the control group. The minimal sample size required, with an alpha error of 5% and a power of 80%, was 90 patients in each group. All the analysis was performed using the Statistical Package for the Social Sciences (SPSS) Version 23.0.

Absolute and relative frequencies were used to describe qualitative variables. Continuous variables were described using median and interquartile range-IQR (non-normal distribution). Comparisons were performed with Student's test, Chi^2 and Mann–Whitney test. p-value < 0.05 was regarded as statistically significant. To control for potentially confounding variables and to examine the independent contribution of the explicative variables on the likelihood of developing asthma, a backward stepwise binomial logistic regression model was built. All the variables with p-value < 0.1 were introduced in the multi-variate analysis. Adjusted odds ratios (OR) with 95% confidence intervals (CI) were calculated.

Results

A total of 150 children (75 preterm and 75 full-term) were included, with mean age 13 years (IQR 13–14). Preterm adolescents were younger (13 years, IQR 12–13) than the full-term ones (14 years, IQR 13–14) ($p < 0.001$). Perinatal characteristics are presented in Table 1.

Respiratory health

The responses to the ISAAC questionnaire for asthma symptoms are displayed in Table 2. *Current asthma* (Question 2) was more frequent in the MLP group compared to the full-term one [$p = 0.008$, OR 3 (95% CI 1.26–7.14)] as well as in the MP group in comparison with the LPFT group [$p = 0.003$; OR 3.22 (95% CI 1.56–6.62)]. The frequency of *asthma ever* (Question 6) showed a tendency to be more common in the MLP group, although it did not reach statistical significance ($p = 0.08$).

After logistic regression, *current asthma* and *asthma diagnosis ever* in adolescents were independently associated to neonatal respiratory support and allergic sensitization (Table 3).

Respiratory evolution and family history of asthma/allergic sensitization of preterm and full-term children are shown in Table 4. No differences were observed in asthma chronic treatment prescription or duration of inhaled corticosteroids or anti-leukotrienes treatment. However, MLP patients were more likely to receive longer combined treatment with both drugs simultaneously ($p = 0.048$). The risk of hospital admission due to respiratory causes were similar in both groups.

Overall, spirometry measurements were within normal limits in both groups. A higher proportion of children with FVC < 80% was observed in the MLP group ($p = 0.013$). Additionally, when comparing MP with LPFT adolescents, FVC < 80% and FEF_{25-75} < 65% were more often found in the MP group ($p = 0.021$ and $p = 0.046$, respectively). Data are represented in Table 5.

TABLE 1 Perinatal characteristics of moderate-to-late preterm adolescents vs. the full-term group.

	Moderate-to-late preterm	Full-term	*p*-value	Odds ratio 95% (confidence interval)
	N = 75	*N* = 75		
Male gender	36 (48%)	41 (54.7%)	0.414	0.8 (0.6–1.2)
Multiple pregnancy	33 (44%)	2 (2.7%)	**<0.001**	2.6 (2–3.3)
Intrauterine growth restriction	2 (2.7%)	0	0.497	Not available
Preeclampsia	11 (14.7%)	2 (2.7%)	**0.009**	1.8 (1.3–2.4)
Chorioamnionitis	2 (2.7%)	1 (1.3%)	1	1.3 (0.6–3)
Gestational diabetes	9 (12%)	4 (5.3%)	0.245	1.4 (0.9–2.1)
Maternal smoking in pregnancy	9 (12%)	18 (24%)	**0.056**	1.6 (1–2.8)
Maternal age**	32 (IQR 31–35)	32 (IQR 29–35)	0.395	
Lung maturation	20 (26.7%)	0	**0.001**	Not available
Gestational age (weeks)**	35 (IQR 34–36)	39 (IQR 38–40)	**<0.001**	
Newborn weight (g)**	2,300 (IQR 2,090–2,650)	3,280 (IQR 3,040–3,600)	**<0.001**	
Newborn weight (z-score Fenton 2013)**	−0.4 [IQR (−0.8) − 0.3]	−0.3 [IQR (−0.8) − 0.2]	0.864	
Neonatal resuscitation	35 (46.7%)	10 (13.3%)	**<0.001**	2.0 (1.5–2.7)
Noninvasive mechanical ventilation	15 (20%)	0	**<0.001**	Not available
Invasive mechanical ventilation	2 (2.7%)	0	0.497	Not available
Patient ductus arteriosus	4 (5.3%)	0	0.120	Not available
Sepsis	10 (13.3%)	2 (2.7%)	**0.031**	1.7 (1.3–2.4)
Hyperbilirubinemia with phototherapy	39 (52%)	0	**<0.001**	Not available
Hypoglycemia	16 (21.3%)	1 (1.3%)	**<0.001**	2.1 (1.6–2.6)

**Median (interquartile range-IQR). Values in bold are statistically significant.

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TABLE 2 Affirmative answers to the ISAAC Questionnaire for asthma symptoms in moderate-to-late preterm vs. full-term adolescents and in moderate preterm vs. late preterm and full-term at the follow up (12–15 years of age).

Answer	Moderate and late preterm	Full-term	*p*-value	Odds ratio 95% (confidence interval)
	N = 75	*N* = 75		
1. Have you ever had wheezing episodes at any time?	52 (69.3%)	48 (64%)	0.488	1 (0.8–1.3)
2. Have you had wheezing episodes in the last 12 months?	18 (24%)	6 (8%)	**0.008**	3.0 (1.2–7.1)
3. How many wheezing episodes have you had in the last 12 months? None 1–3 4–12 >12	 57 (76%) 14 (18.6%) 2 (2.7%) 2 (2.7%)	 69 (92%) 2 (2.7%) 3 (4%) 1 (1.3%)	0.095	Not available
4. How many times had you had symptoms in the night in the last 12 months? Never Less than once a week More than once a week	 66 (88%) 7 (9.3%) 2 (2.7%)	 73 (97.3%) 2 (2.7%) 0	0.627	Not available
5. Wheezing episodes have you interrupted while speaking in the last 12 months?	5 (27.8%)	0	0.28	Not available
6. Have you ever been diagnosed with asthma?	29 (38.7%)	19 (25.3%)	0.08	1.5 (0.9–2.9)
7. Have you had wheezing episodes while practicing sports?	12 (16%)	9 (12%)	0.48	1.3 (0.6–2.9)
8. Have you had dry in the last 12 months?	7 (9.3%)	2 (2.7%)	0.166	3.5 (0.7–16.3)

	Moderate preterm	Late preterm and full-term	*p*-value	Odds ratio 95% (confidence interval)
	N = 17	*N* = 133		
1. Have you ever had wheezing episodes at any time?	9 (52.9%)	91 (68.4%)	0.202	0.8 (0.5–1.2)
2. Have you had wheezing episodes in the last 12 months?	7 (41.2%)	17 (12.8%)	**0.003**	3.2 (1.6–6.6)
3. How many wheezing episodes have you had in the last 12 months? None 1–3 4–12 >12	 10 (58.8%) 5 (29.4%) 1 (5.9%) 1 (5.9%)	 116 (87.2%) 11 (8.3%) 4 (3%) 2 (1.5%)	0.877	Not available
4. How many times had you had symptoms in the night in the last 12 months? Never Less than once a week More than once a week	 13 (76.5%) 4 (23.5%) 0	 126 (94.7%) 5 (3.8%) 2 (1.5%)	0.355	Not available
5. Wheezing episodes have you interrupted while speaking in the last 12 months?	5 (27.8%)	0	0.280	Not available
6. Have you ever been diagnosed with asthma?	8 (47.1%)	40 (30.1%)	0.157	1.5 (0.9–2.7)
7. Have you had wheezing episodes while practicing sports?	5 (29.4%)	16 (12%)	0.052	2.4 (1–5.8)
8. Have you had dry in the last 12 months?	3 (17.6%)	6 (4.5%)	0.066	3.9 (1–14.2)

Values in bold are statistically significant.

TABLE 3 Multivariate analysis of risk factors independently associated with current asthma and asthma diagnosis ever in the whole cohort of 12–15-year adolescents moderate-late preterm and full-term children.

		Adjusted odds ratio	Confidence interval 95%	*p*-value
Current asthma	Neonatal respiratory support	4.7	1.5–15.2	**0.009**
Asthma diagnosis ever		2.9	1.1–7.8	**0.032**
Current asthma	Allergic sensitization	5.7	1.7–18.3	**0.004**
Asthma diagnosis ever		4.8	2.2–10.7	**<0.001**

Values in bold are statistically significant.

TABLE 4 Comparison of respiratory evolution during the follow up of moderate-to-late preterm vs. full-term adolescents and in moderate preterm vs. late preterm and full-term at 12–15 years of age.

	Moderate and late preterm	Full-term	*p*-value
	N = 75	*N* = 75	
Chronic asthma treatment	23 (30.7%)	24 (32%)	0.860
Duration of anti-leukotrienes treatment (months)**	33 (IQR 15–46.5)	36 (IQR 16.5–48)	0.862
Duration of inhaled corticosteroids treatment (months)**	24 (IQR 7.5–30)	48 (IQR 12–48)	0.081
Duration of inhaled corticosteroids + antileukotrienes (months) **	36 (IQR 24–60)	24 (IQR 12–42)	**0.048**
Respiratory admissions	27 (36%)	22 (29.3%)	0.384
Respiratory ICU admissions	2 (2.7%)	0	0.155
Allergic sensitization	33 (45%)	34 (45.9%)	0.811
Parental asthma	29 (38.7%)	26 (34.7%)	0.611
Parental atopy	22 (29.3%)	14 (18.7%)	0.126

	Moderate preterm	Late preterm and full-term	*p*-value
	N = 17	*N* = 130	
Chronic asthma treatment	7 (41.2%)	40 (30.1%)	0.353
Duration of anti-leukotrienes treatment (months)**	0	36 (IQR 15–48)	-
Duration of inhaled corticosteroids treatment (months)**	8 (IQR 8)	31.5 (IQR 15–45)	0.308
Duration of inhaled corticosteroids + antileukotrienes (months) **	36 (IQR 21–39)	24 (IQR 12–48)	0.251
Respiratory admissions	7 (41.2%)	42 (31.6%)	0.427
Respiratory ICU admissions	1 (5.8%)	1 (0.7%)	0.214
Passive smoking	3 (17.6%)	70 (52.6%)	**0.009**
Allergic sensitization	9 (52.9%)	58 (43.9%)	0.483
Parental asthma	(4823.5%)	32 (24.1%)	1
Parental atopy	9 (52.9%)	46 (34.6%)	0.139

ICU, Intensive Care Units. **Median (interquartile range-IQR). Values in bold are statistically significant.

After bivariate analysis, the variables associated with lower lung function (FEV_1 z-score, $FEV_1 < 80\%$, FVC z-score and $FVC < 80\%$) were: MLP, male gender, *current asthma, asthma diagnosis ever*, wheezing with exercises and chronic asthma treatment (Table 6).

Cardiometabolic results

BP values were similar in MLP and full-term adolescents, with no differences in the prevalence of hypertension. In relation to metabolic disease as dyslipidemia or diabetes, lower HDL values were found only in one MLP and in 4 full-term adolescents. Hypertriglyceridemia was detected in one full-term patient and hypercholesterolemia and high LDL values in only one MLP adolescent. No child presented pathological HbA1c hemoglobin values or metabolic disease (Table 7).

Right ventricular function and morphology data are showed in Table 8. MLP adolescents had better TAPSE ($p = 0.025$), TAPSE z-score ($p = 0.003$), shortening fraction ($p < 0.001$) and E/A z-score ($p = 0.002$) than full-term ones. When MP adolescents were compared with LPFT, a smaller right ventricular diastolic diameter and their z-score were observed ($p = 0.006$ and $p = 0.046$, respectively). However, no differences regarding right ventricular function were observed.

Regarding the left ventricular assessment, MLP adolescents had smaller ventricular diastolic diameter compared to full-term children ($p = 0.04$) and lower posterior wall z-score values ($p = 0.037$). They also had better S′ wave z-score ($p = 0.027$), E' wave z-score ($p = 0.005$), E/A ratio ($p = 0.003$) and higher septal MPI z-score ($p = 0.025$). When comparing MP vs. LPFT, no differences in left ventricular morphology and function were found. Data obtained in the assessment of left ventricle are shown in Table 9.

Anthropometric data

No significant differences could be detected between both groups regarding the anthropometric measurements at birth, according to their gestational age (presented with Fenton 2013 z-score). In the follow-up, MLP adolescents had lower weight ($p < 0.001$) and lower weight z-score ($p = 0.039$) than the full-term ones. They also showed lower body mass index ($p = 0.002$) and lower body mass index z-score ($p = 0.013$) than the control group. No differences were found in height or abdominal circumference between the two groups. The Waterlow weight index was lower in the MLP group ($p = 0.006$) and there was a higher percentage of MLP patients with undernutrition index [$p = 0.04$; OR 1.4 (95% CI 1–1.9)]. These differences were also observed when comparing the MP patients with the group composed of LPFT. MP adolescents also had lower weight ($p = 0.022$), weight z-score ($p = 0.017$), body mass index ($p = 0.011$), body mass index z-score ($p = 0.011$) and lower Waterlow weight index ($p = 0.039$).

TABLE 5 Lung function comparisons between moderate-to-late preterm and full-term counterparts and in moderate preterm vs. late preterm and full-term at the follow up (12–15 years of age).

	Moderate and late preterm	Full-term	*p*-value	Odds ratio (confidence interval 95%)
	N = 73	*N* = 74		
FEV_1 (% predicted)**	101.5 (IQR 89.5–110.9)	99.3 (IQR 89.2–107.3)	0.914	
FEV_1 z-score**	0.1 [IQR (−0.9) − 0.9]	−0.1 [IQR (−0.9) − 0.6]	0.955	
$FEV_1 < 80\%$	7 (9.5%)	3 (4%)	0.209	2.4 (0.6–8.8)
FVC (% predicted)**	101.5 (IQR 88.8–108.5)	101.6 (IQR 95.5–109.7)	0.214	
FVC z-score**	0.2 [IQR (−0.7) – 0.8]	0.1[IQR (−0.4) – 0.8]	0.547	
FVC < 80%	6 (8.2%)	0	**0.013**	Not available
FEV_1/FVC (% predicted)**	94.1 (IQR 88–105.1)	94.9(IQR 89.8–104.1)	0.077	
FEV_1/FVC z-score**	0.7 [IQR (−1.5) − 0.9]	−0.7 [IQR (−1.4) − 0.6]	0.071	
$FEV_1/FVC \leq 80\%$	3 (4.1%)	4 (5.4%)	1	0.8 (0.2–3.2)
FEF_{25-75} (% predicted)**	98.4 (IQR 85.8–119.2)	93.9 (IQR 77.5–112.6)	0.341	
FEF_{25-75} z-score**	−0.5 [IQR (8–1.6) – 1.1]	−0.3 [IQR (−1.3) − 0.4]	0.579	
$FEF_{25-75} < 65\%$	7 (9.5%)	6 (8.1%)	0.78	1.2 (0.4–3.3)
Bronchodilator test positive	3 (4.1%)	4 (5.4%)	0.628	0.7 (0.2–3.2)

	Moderate preterm	Late preterm and full-term	*p*-value	Odds ratio (confidence interval 95%)
	N = 17	*N* = 130		
FEV_1 (% predicted)**	90.9 (IQR 83.9–106.8)	101.4 (IQR 90–109.5)	0.133	
FEV_1 z-score**	−0.8 [IQR (−1.4) – 0.4]	0.1 [IQR (−0.8) – 0.8]	**0.050**	
$FEV_1 < 80\%$	3 (17.6%)	7 (5.4%)	0.093	3.2 (0.9–11.5)
FVC (% predicted)**	97.8 (IQR 81.2–108.9)	101.8 (IQR 94.1–109.3)	0.306	
FVC z-score**	−0.2 [IQR (−1.6) − 0.8]	0.2 [IQR (−0.5) − 0.8]	0.241	
FVC < 80%	3 (17.6%)	3 (2.3%)	**0.021**	7.6 (1.7–34.9)
FEV_1/FVC (% predicted)**	94.1 (IQR 90–109.2)	99.6 (IQR 93.4–104.3)	0.830	
FEV_1/FVC z-score**	−0.9 [IQR (−1.3) − 1.7]	−0.1 [IQR (−0.9) – 0.7]	0.767	
$FEV_1/FVC \leq 80\%$	2 (11.8%)	5 (3.8%)	0.187	3.0 (0.6–14.5)
FEF_{25-75} (% predicted)**	87.6 (IQR 69.5–95.4)	98 (IQR 80.7–114.9)	0.089	
FEF_{25-75} z-score**	−0.6 [IQR (−1.5 – 0.2)]	−0.1 [IQR (−0.9) − 0.7]	**0.070**	
$FEF_{25-75} < 65\%$	4 (23.5%)	9 (6.9%)	**0.046**	3.4 (1.2–9.8)
Bronchodilator test positive	0	7 (5.4%)	1	Not available

FEV 1: Forced expiratory volume in one second; FVC: Forced vital capacity; FEF 25-75: Mean forced expiratory flow between 25-75% of FVC. Predicted values presented with Zapletal; Z-score values presented with Global Lung Initiative. Values in bold are statistically significant. **Median (interquartile range-IQR).

TABLE 6 Variables associated to lower lung function values in moderate-to-late preterm and full-term adolescents (12–15 years of age).

		p-value	Odds ratio	Confidence interval 95%
FEV_1 z-score	Male gender	0.062		
	Current asthma	0.002		
	Wheezing with exercises	0.030		
	Chronic asthma treatment	0.014		
$FEV_1 < 80\%$	Current asthma	0.001	7.7	2.3–25.2
	Asthma diagnosis ever	0.012	5.0	1.3–18.3
	Wheezing with exercises	0.006	6.0	1.9–18.9
FVC z-score	Male gender	0.011		
	Current asthma	0.023		
FVC < 80%	MPL	0.013	Not available	
	Asthma diagnosis ever	0.073	4.2	0.9–22.4
	Chronic asthma treatment	0.077	4.4	0.8–23.1

FEV 1: Forced expiratory volume in one second; FVC: Forced vital capacity.

TABLE 7 Blood pressure and metabolic disease in moderate-to-late preterm vs. full-term adolescents and in moderate preterm vs. late preterm and full-term at the follow up (12–15 years of age).

	Moderate and late preterm	Full-term	*p*-value
	N = 75	*N* = 75	
Systolic blood pressure**	113 (IQR 105–118)	115 (IQR 108–121)	0.064
Systolic blood pressure z-score**	0.4 [IQR (−0.3) − 1]	0.4 [IQR (−0.2) − 1]	0.434
Diastolic blood pressure**	68 (IQR 64–74)	68 (IQR 66–72)	0.614
Diastolic blood pressure z-score**	0.7 (IQR 0.1–1)	0.6 (IQR 0.2–0.8)	0.426
Hypertension (SBP or DBP ≥ p 95)	3 (4%)	4 (5.3%)	1
Cholesterol ≥ 200 mg/dL	1 (1.3%)	0	1
HDL < 40 mg/dL	1 (1.3%)	4 (5.3%)	0.367
LDL ≥ 130 mg/dL	1 (1.3%)	0	1
Triglycerides ≥ 150 mg/dL	0	1 (1.3%)	1
HbA 1c ≥ 6.5%	0	0	Not available

	Moderate preterm	Late preterm and full-term	*p*-value
	N = 17	*N* = 133	
Systolic blood pressure**	112 (IQR 104.5–119)	115 (IQR 107–120)	0.460
Systolic blood pressure z-score**	0.2 [IQR (−0.3) − 1]	0.4 [IQR (−0.2) − 1]	0.654
Diastolic blood pressure**	68 (IQR 63–76.5)	68 (IQR 65–72)	0.609
Diastolic blood pressure z-score**	0.4 [IQR (−0.1) − 1]	0.4 (IQR 0.1–0.8)	0.868
Hypertension (SBP or DBP ≥ p 95)	1 (5.9%)	6 (4.5%)	0.577
Cholesterol ≥ 200 mg/dL	1 (1.3%)	0	1
HDL < 40 mg/dL	1 (1.3%)	4 (5.3%)	0.367
LDL ≥ 130 mg/dL	1 (1.3%)	0	1
Triglycerides ≥ 150 mg/dL	0	1 (1.3%)	1
HbA 1c ≥ 6.5%	0	0	Not available

High Blood Pressure z-scores presented with scores of National High Blood Pressure Education Working Group on High Blood Pressure in Children and Adolescents 2004. LDL, low-density lipoprotein; HDL, high-density lipoprotein; HbA1c, glycated hemoglobin. **Median (interquartile range-IQR).

TABLE 8 Right ventricular function and morphology in moderate-to-late preterm vs. full-term adolescents and in moderate preterm vs. late preterm and full-term at the follow up (12–15 years of age).

	Moderate and late preterm	Full-term	*p*-value
	N = 75	*N* = 75	
Basal diameter (mm)**	19.3 (IQR 17.9–21.4)	19.9 (IQR 18.3–22)	0.239
z-score basal diameter**	−0.2 [IQR (8–0.6) – 0.1]	−0.3 [IQR (−0.6) – (−0.1)]	0.601
TAPSE (mm)**	23.3 (IQR 21.3–25.3)	22.2 (IQR 21–23.3)	**0.025**
TAPSE z-score**	0.7 [IQR (−0.5) – 1.8]	−0.1 [IQR (−0.7) – 0.8]	**0.003**
Shortening fraction (%)**	37.8 (IQR 32.7–42.9)	30 (IQR 27–32)	< **0.001**
S′ wave (cm/s)**	14 (IQR 13–16)	14 (IQR 13–15)	0.208
S′ wave z-score**	0.1 [IQR (−0.5) – 0.7]	−0.1 [IQR (−0.5) – 0.5]	0.074
E/A ratio**	1.9 (IQR 1.7–2.2)	1.8 (IQR 1.6–2.1)	0.199
E/A ratio z-score**	0.5 (IQR 0.1–1)	0.1 [IQR (−0.3) – 0.8]	**0.002**
E/E' ratio**	3.2 (IQR 2.7–4)	3.2 (IQR 2.8–3.8)	0.937
E/E' ratio z-score**	−0.2 [IQR (−0.7) – 0.3]	−0.4 [IQR (−0.7) – 0.2]	0.341
MPI**	0.3 (IQR 0.3–0.4)	0.3 (IQR 0.3–0.3)	0.763
MPI z-score**	−0.7 [IQR (−1.1) – (−0.2)]	−0.7 [IQR (−1) – (−0.3)]	0.957

	Moderate preterm	Late preterm and full-term	*p*-value
	N = 17	*N* = 132	
Basal diameter (mm)**	18.4 (IQR 17.6–19.4)	19.9 (IQR 18.3–21.8)	**0.006**
z-score basal diameter**	−0.6 [IQR (−0.8) – (−0.1)]	−0.2 [IQR (−0.6) – 0.1]	**0.046**
TAPSE (mm)**	23.4 (IQR 19.7–26.8)	22.7 (IQR 21–24)	0.429
TAPSE z-score**	0.4 [IQR (−1.1) – 2.3]	0.2 [IQR (−0.6) – 1]	0.758
Shortening fraction (%)**	31.3 (IQR 28.8–35.7)	32.7 (IQR 29–39.5)	0.423
S′ wave velocity (cm/s)**	14 (IQR 13–16)	14 (IQR 13–15)	0.617
S′ wave z-score**	0.1 [IQR (−0.5) – 0.8]	0.1 [IQR (−0.1) – 0.9]	0.819
E/A ratio**	1.8 (IQR 1.5–2.3)	1.9 (IQR 1.7–2.1)	0.754
E/A ratio z-score**	0.4 (IQR 0.1–0.5)	0.4 [IQR (−0.1) – 0.9]	0.819
E/E' ratio**	3.2 (IQR 2.9–4)	3.2 (IQR 2.7–3.9)	0.631
E/E' ratio z-score**	−0.4 [IQR (−0.6) – (−0.4)]	−0.3 [IQR (−0.7) – 0.3]	0.901
MPI**	0.3 (IQR 0.3–0.4)	0.3 (IQR 0.3–0.3)	0.120
MPI z-score**	−0.4 [IQR (−0.9) – 0.5]	−0.7 [IQR (−1.1) – (−0.2)]	0.085

TAPSE, tricuspid annular plane systolic excursion; MPI, myocardial performance index. **Median (interquartile range-IQR). Values in bold are statistically significant.

Anthropometrics data of both group of adolescents are shown in Table 10.

After logistic regression, the variables independently associated with undernutrition at 12–15 years of age (Waterloo index weight < 90%) were: male gender [$p < 0.001$; OR 4.65 (95% CI 2.17–9.98)] and MLP birth [$p = 0.016$; OR 2.5 (95% CI 1.19–5.25)].

Neurological

Neurodevelopmental outcomes are shown in Table 11. No differences were found in the neurodevelopmental and behavioral tests, although MP infants, in comparison with LPFT ones, reported more social problems ($p < 0.001$).

Discussion

To our knowledge, this is the first study to evaluate the global development of MLP patients in adolescence and to compare it with children of the same age born at term. Our results show that MLP adolescents are not the same as full-term, with some differences, but also with some similarities.

In relation to the respiratory evolution, MLP adolescents, exhibited, in our study, higher prevalence of current asthma, with a threefold increased risk compared to full-term children,

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TABLE 9 Left ventricular morphology and function in moderate-to-late preterm vs. full-term adolescents and in moderate preterm vs. late preterm and full-term at the follow up (12–15 years of age).

	Moderate and late preterm	Full-term	*p*-value
	N = 75	*N* = 75	
Left ventricle diastolic diameter (mm)**	44.1 (IQR 42.2–46.5)	46 (43.6–48.9)	**0.04**
Left ventricle diastolic diameter z-score**	−0.2 [IQR (−0.7) − 0.3]	−0.1 [(−0.6) − 0.3]	0.622
Interventricular septum (mm)**	6.7 (IQR 5.8–7.6)	6.7 (6.1–7.6)	0.334
Interventricular septum z-score**	-0.3 [IQR (−0.9) − 0.2]	−0.5 [IQR (−0.9) − 0.2]	0.343
Left posterior wall (diastole) (mm)**	7 (IQR 6.6–7.8)	7.3 (6.3–7.9)	0.644
Left posterior wall z-score**	0.4 [IQR (−0.1) − 0.7]	0.2 [IQR (−0.6) − 0.8]	0.037
Shortening fraction (%)**	40 (IQR 37–45)	40 (IQR 37–43)	0.529
Ejection fraction (%)**	70 (IQR 68–75)	71 (IQR 67–75)	0.440
S′ wave velocity (cm/s)**	13 (IQR 12–14)	13.5 (IQR 12–14)	0.600
S′ wave velocity z-score**	0.8 (IQR 0.1–1.1)	0.4 (IQR (−0.4) − 0.9)	**0.027**
E wave velocity (cm/s)**	22 (IQR 20–23)	20 (IQR 18–24)	0.054
E wave velocity z-score**	0.4 [IQR (−0.2) − 1]	0.1 [IQR (−0.5) − 0.6]	**0.005**
E/A ratio**	2 (IQR 1.6–2.6)	1.7 (IQR 1.5–2.2)	**0.002**
E/A ratio z-score**	0.1 [IQR (−0.6) − 1]	−0.4 [IQR (−0.9) − 0.3]	**0.003**
E/E' ratio**	4.1 (IQR 3.6–4.5)	4.2 (IQR 3.4–5.1)	0.079
E/E' ratio z-score**	−0.6 [IQR (−1) − (−0.3)]	−0.4 [IQR (−1.1) − 0.2]	0.118
Septal MPI**	0.3 (IQR 0.3–0.4)	0.3 (IQR 0.2–0.3)	0.144
Septal MPI z-score**	−0.8 [IQR (−1.2) − (−0.2)]	−1 [IQR (−1.5) − (−0.5)]	**0.025**
Lateral MPI**	0.2 (IQR 0.2–0.3)	0.2 (IQR 0.2–0.3)	0.258
Lateral MPI z-score**	−1.1 [IQR (−1.6) − 0.6]	−1.1 [IQR (−1.4) − 0.6]	0.453

	Moderate preterm	Late preterm and full-term	*p*-value
	N = 17	*N* = 133	
Left ventricle diastolic diameter (mm)**	43.4 (IQR 41.2–46.2)	45.6 (IQR 42.9–47.9)	0.088
Left ventricle diastolic diameter z-score**	−0.1 [IQR (−0.6) − 0.2]	−0.1 [IQR (−0.6) − 0.3]	0.885
Interventricular septum (mm)**	7 (IQR 5.5–7.8)	6.7 (IQR 6–7.6)	0.924
Interventricular septum z-score**	−0.1 [IQR (−1) − 0.4]	-0.4 [IQR (−0.9) − 0.1]	0.397
Left posterior wall (diastole) (mm)**	7 (IQR 6.5–7.7)	7.1 (IQR 6.5–7.8)	0.537
Left posterior wall z-score**	0.5 (IQR 0.1–0.8)	0.3 [IQR (−0.3) − 0.7]	0.418
Shortening fraction (%)**	44 (IQR 37.5–45)	40 (IQR 37–43)	0.339
Ejection fraction (%)**	75 (IQR 67.5–76)	70 (IQR 67–75)	0.317
S′ wave velocity (cm/s)**	13 (IQR 11.5–14)	13 (IQR 12–14)	0.644
S′ wave velocity z-score**	0.4 [IQR (−0.2) − 0.8]	0.6 (IQR 0.1–1.1)	0.324
E wave velocity (cm/s)**	22 (IQR 20–23)	21 (IQR 19–23)	0.206
E wave velocity z-score**	0.4 [IQR (−0.1) − 0.8]	0.4 [IQR (−0.4) − 0.7]	0.429
E/A ratio**	1.8 (IQR 1.6–2.2)	1.8 (IQR 1.5–2.5)	0.821
E/A ratio z-score**	−0.3 [IQR (−0.7) − 0.2]	-0.2 [IQR (−0.8) − 0.8]	0.687
E/E' ratio**	4 (IQR 3.1–4.4)	4.2 (IQR 3.5–4.8)	0.129
E/E' ratio z-score**	−0.7 [IQR (−1.3) − (0.3)]	−0.5 [IQR (−1) − (−0.1)]	0.224
Septal MPI**	0.3 (IQR 0.3–0.4)	0.3 (IQR 0.2–0.3)	0.137
Septal MPI z-score**	−0.6 [IQR (−1.1) − 0.2]	−0.8 [IQR (−1.4) − (−0.3)]	0.054
Lateral MPI**	0.3 (IQR 0.2–0.3)	0.2 (IQR 0.2–0.3)	0.458
Lateral MPI z-score**	−1 [IQR (−1.3) − (−0.1)]	−1.1 [IQR (−1.5) − (−0.7)]	0.312

MPI, myocardial performance index. **Median (interquartile range-IQR). Values in bold are statistically significant.

TABLE 10 Comparison of anthropometrics characteristics of moderate-to-late preterm vs. full-term adolescents and in moderate preterm vs. late preterm and full-term at the follow up (12–15 years of age).

	Moderate and late preterm	Full-term	*p*-value	Odds ratio (confidence interval 95%)
	N = 75	*N* = 75		
Weight (kg)**	51.5 (IQR 43.5–60)	55.5 (IQR 49.8–66.3)	**0.001**	
Weight z-score (SD)**	−0.3 [IQR (−0.8) − 0.6]	0.1 [IQR (−0.6) − 1]	**0.039**	
Height (cm)**	160 (IQR 153.5–172.5)	162.5 (IQR 160–167.7)	**0.001**	
Height z-score (SD)**	0.2 [IQR (−0.6) − 1.6]	0.1 [IQR (−0.4) − 0.6]	0.78	
BMI (kg/m^2)**	19.4 (IQR 17–23)	21.4 (IQR 19–25.6)	**0.002**	
BMI z-score (SD)**	−0.4 [IQR (−0.9) − 0.5]	0.1 [IQR (−0.5) − 1.2]	**0.013**	
BMI ≥ 2 SD	5 (6.7%)	4 (5.3%)	1	1.2 (0.4–4.5)
Abdominal circumference (cm)**	69 (IQR 64–79.5)	72 (IQR 66–80)	0.224	
Abdominal circumference z-score (SD)**	0.1 [IQR (−0.5) − 1.6]	0.4 [IQR (−0.5) − 1.7]	0.645	
Abdominal circumference ≥ 2 SD	17 (22.7%)	17 (22.7%)	1	1.0 (0.5–1.8)
Waterloo Index Weight (%)**	94.7 (IQR 83–108.4)	102.1 (IQR 89.4–123.4)	**0.006**	
Waterloo index height (%)**	99.8 (IQR 97.3–106.2)	98.9 (IQR 98.4–102.5)	0.883	
Waterloo Index weight < 90%	32 (42.6%)	20 (26.6%)	**0.04**	1.4 (1–1.9)
Waterloo index height < 90%	7 (9.3%)	7 (9.3%)	1	1 (0.4–2.7)

	Moderate preterm	Late preterm and full-term	*p*-value	Odds ratio (confidence interval 95%)
	N = 75	*N* = 75		
Weight (kg)**	47.2 (IQR 42.9–56.6)	55 (IQR 46.9–65.2)	**0.022**	
Weight z-score (SD)**	−0.5 [IQR (−0.9)-(−0.1)]	−0.1 [IQR (−0.6) − 1]	**0.017**	
Height (cm)**	162 (IQR 154–168.5)	161.5 [IQR 155.5–166.3]	0.922	
Height z-score (SD)**	0.1 [IQR (−0.7) − 0.8]	−0.1 [IQR (−0.6) − 0.7]	0.887	
BMI (kg/m^2)**	18.1 (IQR 17–21)	20.4 (IQR 18–25)	**0.011**	
BMI z-score (SD)**	−0.6 [IQR (−1) − (−0.1)]	−0.1 [IQR (−0.7) − 1.1]	**0.011**	
BMI ≥ 2 SD	9 (6.7%)	0	0.598	Not available
Abdominal circumference (cm)**	67 (IQR 64.2–73.2)	70 (IQR 65.7–80.2)	0.098	
Abdominal circumference z-score (SD)**	−0.1 [IQR (−0.8) − 0.7]	0.3 [IQR (−0.5) − 2]	0.113	
Abdominal circumference ≥ 2 SD	0	34 (25.5%)	**0.013**	Not available
Waterloo index weight (%)**	92.3 (IQR 81.7–102.3)	98.7 (IQR 86.5–120.6)	**0.039**	
Waterloo index height (%)**	99.8 (IQR 96.3–103.1)	99.4 (IQR 97.3–103.3)	0.87	
Waterloo index weight < 90%	7 (41.1%)	45 (33.8%)	0.055	1.2 (0.6–2.2)
Waterloo index height < 90%	2 (11.7%)	12 (9%)	0.661	1.3 (0.3–5.3)

SD, standard deviation. Weight, height, body mass index presented with Carrascosa 2010 z-score. Waterlow index (20) and abdominal perimeter presented with Moreno z-score. **Median (interquartile range-IQR). Values in bold are statistically significant.

particularly at lower gestational ages. Furthermore, the MLP group was more likely to undergo longer combined chronic asthma treatment. In summary, these data might indicate that moderate and late birth should be acknowledged as a risk factor for asthma development, not only in the early years of life, but also in adolescence. Several studies have described higher prevalence of asthma in MLP births especially during childhood (4, 43, 45–47). However, the duration of this increased risk is a matter of controversy. Kotecha et al. (48) reported similar respiratory morbidity, including asthma, in 37 born MLP and 34 born full-term at 13–14 years of age. In contrast, Thunqvist et al. (49) found that female subjects, born moderate to late preterm, reported significantly more respiratory symptoms at both, 8 and 16 years of age, than females born term. Additionally, according to the meta-analysis by Been et al. (50), the strength of the association between preterm birth and wheezing disorders is similar between children

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TABLE 11 Neurodevelopmental outcome of moderate-to-late preterm vs. full-term adolescents and in moderate preterm vs. late preterm and full-term at the follow up (12–15 years of age).

	Moderate and late preterm	Full-term	*p*-value
	N = 75	*N* = 75	
Learning disability	20 (26.7%)	22 (29.3%)	0.716
Social development	3 (4%)	0	1
Attention deficit hyperactivity disorder	6 (8%)	2 (2.6%)	0.276
ASSQ < 19 points	0	0	Not available
ADHD > 30 points	3 (4%)	3 (4%)	1
ADHD subtype hyperactivity > 10 points	4 (5.3%)	3 (4%)	0.719
ADHD subtype persistent inattention > 10 points	5 (6.7%)	6 (8%)	0.772
ADHD subtype combination of both > 18 points	2 (2.7%)	4 (5.3%)	0.681
ADHD subtype impulsivity > 11 points	7 (9.3%)	4 (5.3%)	0.366

	Moderate preterm	Late preterm and full-term	*p*-value
	N = 17	*N* = 133	
Learning disability	4 (23.5%)	38 (28.6%)	0.780
Social development	3 (17.6%)	0	**<0.001**
Attention deficit hyperactivity disorder	1 (5.9%)	7 (5.3%)	1
ASSQ < 19 points	0	0	Not available
ADHD > 30 points	1 (5.9%)	5 (3.8%)	0.523
ADHD subtype hyperactivity > 10 points	1 (5.9%)	6 (4.5%)	0.581
ADHD subtype persistent inattention > 10 points	2 (11.8%)	9 (6.8%)	0.364
ADHD subtype combination of both > 18 points	2 (11.8%)	4 (3%)	0.140
ADHD subtype impulsivity > 11 points	2 (11.8%)	9 (6.8%)	0.364

ASSQ, Asperger Syndrome Screening Questionnaire; ADHD, attention deficit hyperactivity disorder. Values in bold are statistically significant.

aged younger and older 5 years. This heterogeneity in the results may be related to various factors, especially the different gestational age of the included patients and their varied age at the time of follow-up, as well as the diversity in the definition of asthma used by different authors. We must also consider other factors that may affect the development of asthma such as a history of asthma, respiratory syncytial virus infection, genetics or the role of inflammasome as an immunomodulator (51). As previously described, we did not find any differences in allergic sensitization rates based on gestational age (14, 16).

Although the rate of asthma admissions did not differ between the preterm and full-term groups, MLP patients did experience higher rate of intensive care unit admissions than full-term children. Our data, according to other reports (12, 16, 45, 52) suggest that, compared to full-term, MLP infants may experience more severe asthma exacerbations (52, 53).

Regarding asthma treatment, no differences were found when the proportion of patients under chronic treatment was compared (30.7 and 32%). However, the duration of combined inhaled corticosteroid/anti-leukotriene treatment was significantly longer in MLP patients, suggesting, a more severe asthma course among MLP adolescents. Other studies have also described similar percentages of chronic asthma treatment in MLP children, such as Perez-Tarazona et al. (16), (28.4%) or Yaacoby-Bianu et al. (54). In contrast, only 8% of moderate preterm children and 5.7% of late preterm in the cohort of Haataja et al. (45) was prescribed asthma treatment.

In relation to lung function, airway obstruction has been described in MLP births during childhood (14, 55). However, the lung function data during school age are controversial (48, 49, 54, 56) and in adolescence most studies (5, 15, 16, 57) indicate that FVC and FEV_1 values are comparable to those observed in full-term, with only $FEF_{25–75}$ values slightly lower or at the lower limit of normality. Overall, the results of pulmonary function tests in our study showed no significant differences between MLP and full-term children. However, the MP group showed lower FEV_1 values when compared with LPFT. Furthermore, the probability of FVC values less than 80% and $FEF_{25–75}$ less than 65% was seven and three times higher, respectively, in the MP group. Similar results were observed in previously reports (15, 16, 57). The presence of normal lung function in late adolescents preterm might be related to the pulmonary plasticity described in this group as age progresses (56). On the other hand, the mild lung function impairment is maintained in the most premature (57, 58) with the MP adolescents having, in our cohort, lower FEV_1 and $FEF_{25–75}$ z-score with a higher percentage of FVC less than 80% and $FEF_{25–75}$ less than 65%. These data suggest that, albeit mild, late preterm infants maintain a mild obstructive and restrictive pulmonary pattern in adolescence, that deserves ongoing monitoring over time to confirm its progression and to implement preventive pulmonary rehabilitation measures aimed at improving thoracic mobility (59, 60).

In our series, no patient had a diagnosis of bronchopulmonary dysplasia. However, Manti el al (61) did not find significant differences in lung function values between very preterm patients (<32 weeks of

gestational age) with or without bronchopulmonary dysplasia, at preschool age.

Prematurity has extensively been described as a cardiovascular risk factor (9, 62–64). In our study, no differences in BP values could be demonstrated between MLP and full-term children, even when analyzing separately MP children as a group of greater vulnerability. Several prior publications (4, 9, 64, 65) have noted minimal differences in BP, particularly among infants under 32 weeks, with even smaller variances observed in late preterm infants, primarily identified through continuous blood pressure monitoring. In addition to gestational age, there may be other factors such as a history of small for gestational age (63), female sex (9, 64) as well as other cardiovascular risk factors (obesity, sedentary lifestyle, metabolic disorders, etc.) and prenatal factors (pre-eclampsia, use of corticosteroids or fetal growth, among others) that may influence the increase in BP levels (63–65).

A reduction in cardiac cavity size, coupled with an increase in mass, diminished stroke volume, and decreased end-diastolic volume, along with observed alterations in myocardial deformation and reduced relaxation, have been noted in the hearts of very premature infants (11, 66, 67). These factors collectively contribute to hypertrophy rather than the hyperplasia seen in the third trimester of gestation. Consequently, these alterations lead to shifts in cardiac morphology and affect both systolic and diastolic functions, particularly in the left ventricle. It is important to note that not all studies have reported the same extent of cardiac remodeling, and variations may depend on factors such as perinatal and postnatal care practices, a history of pulmonary hypertension or obesity (64, 66, 68). Regarding cardiac morphology and function in MLP group, our observations revealed a diminished size of the right ventricle with maintained function, consistent with the findings reported by Lewandoski et al. (66). They similarly observed a reduced right ventricle size paired with a larger ventricular mass, though their results exhibited a more pronounced effect. This variation might be partially attributed to the heightened sensitivity of magnetic resonance in detecting changes in ventricular morphology compared to the ultrasound scan utilized in our study. Additionally, the individuals included by Lewandoski et al. (66) were young adults, potentially exposed to various cardiovascular risk factors not yet present in our adolescent patients. Lastly, it is noteworthy that Lewandoski et al. (66) incorporated, not only preterm patients, but also those classified as small for gestational age, a condition with well-documented negative cardiovascular effects. On the other hand, our results are consistent with those published by Arroyas et al. (57), who detected no differences in the morphological assessment of the right ventricle in MLP group. They included patients of the same age than ours and used the same imaging technique (ultrasound) as in our study.

With respect to right ventricular function, Arroyas et al. (57) found a trend toward lower systolic function and worse diastolic function in very premature infants and in those with bronchopulmonary dysplasia. However, these trends were not evident in our study population.

In the evaluation of left ventricle morphology, we observed slightly smaller size z-score values in MLP adolescents and larger septal and posterior wall z-score values. This aligns with studies on preterm infants, which have described a correlation between ventricular size and gestational age, indicating smaller sizes in the more premature infants (66, 69). Additionally, an increase in septal and posterior wall z-score values was noted, a feature independent of blood pressure (66).

In the assessment of the left ventricle function, we observed better diastolic function data in MLP children compared with term children (E-wave velocity, E/A ratio and their respective z-score values). However, no differences were detected in systolic function values, except for the S-wave′ z-score. Notably, these results were not observed in the MP group. Similarly, global left ventricle function (septal MPI index) exhibited higher z-score values in both MLP and MP adolescents. It is crucial to underscore that despite the statistical significance of these differences, they probably lack clinical relevance, as all patients exhibited figures considered normal for their respective age. Our findings on left ventricle function contrast with previously available publications (11, 57, 66, 69) where poorer systolic and diastolic function data were reported in very preterm children. However, it is essential to consider several factors that distinguish these studies from ours. Firstly, the study population in these previous studies consisted of very preterm infants, with an age range between 18 and 40 years, which is significantly older than our cohort. Also, these patients belonged to an era characterized by neonatal care practices markedly different from those of today (such as the use of mechanical ventilation, surfactation or corticosteroids, prenatal factors that influence cardiac remodeling), as well as their patients had a higher cardiovascular risk, since they exhibited hypercholesterolemia, hypertriglyceridemia and insulin resistance, factors not present in our adolescent patients. Additionally, the cardiological assessments were conducted using magnetic resonance imaging, offering a different and potentially more sensitive approach compared to our study.

From an anthropometric point of view, MLP adolescents had less weight and body mass index, without differences in their height when compared to full-term children. The growth of MLP children has been studied in the different stages of development, showing a slower growth in the neonatal and school period (4, 7), followed by a progressive catch-up. When this catch-up occurs is still uncertain, although our results are similar to the findings of Bergmann et al. (8), who observed a slower growth in their premature infants. As far as we know, there are no available data about the nutritional status of MLP children in adolescence. According to our results MLP adolescents have 1.5 times more undernutrition than their full-term pairs. These alterations in anthropometric data had been previously described in selected MP births, but as mentioned above, they are described here for the first time in MLP group.

Catch-up growth has been associated with higher prevalence of obesity in this group of age and possibly, higher cardiovascular risk in adulthood (9, 70). In our study, both groups, MLP and full-term, presented high percentage of pathological abdominal circumference (71), although the percentage of MLP patients with pathological body mass index (>2SD) was similar to the general population (71). However, it is important to highlight that these children have not yet made the catch-up growth and therefore, the risk of obesity might increase later in life.

In our series, no metabolic alterations were found in the MLP group. There has been much controversy in previous publications on this issue. Some studies have described some alterations in the lipid

profile, in glycemic values, with increased insulin resistance, and higher frequency of metabolic syndrome (9, 10). However, these studies included young adults, adolescents or even smoking adults as well as patients with different risk factors such as very premature births. In contrast, other studies with a design similar to ours have also reported no metabolic alterations in preterm infants, aligning with our findings (62–64).

Focusing on the neurodevelopment, behavioral, socioemotional and learning difficulties have been described in preterm compared to term infants at 36 months of life (72). Although significant risk factors related to severe prematurity certainly exist, the comparison between the two groups (term and late preterm) demonstrates a similar development pathway in our study, although a higher percentage of social problems was detected in MLP patients. We did not find significant differences related to learning difficulties or need for school or out-of-school support between both groups. This result contrasts with data from other authors (17, 73, 74) who described lower school performance in MLP infants. However, it is worth it considering that these learning difficulties have been observed mainly at school age, but there have not been many follow-up studies in adolescence. According to our results, Alterman et al. (75) confirm previous studies, finding greater learning difficulties at lower gestational age but in the early stages; however, in adolescence only very preterm children had lower academic performance. On the other hand, cognitive problems detected through intelligence questionnaires or other standardized tests are more precise than those reported by the parents as in our study.

In our cohort, MLP adolescents exhibited a notably low prevalence of issues in social relationships, 4%, in contrast to findings reported in other studies (18, 76, 77), such as the study by Palumbi et al. (18), which reported a prevalence of around 30%. The elevated prevalence rates observed in the study by Palumbi et al. (18) could be attributed to the selective sampling of MLP individuals with neuropsychiatric disorders, along with the utilization of diagnostic tests specifically designed to identify these disorders in the studies conducted by Johnson et al. (76) and Polić et al. (77). However, significant differences in social development were observed in the comparison of MP group, suggesting an increase in problems in social relationship with decreasing gestational age.

According to other publications (78, 79) 8% of our MLP adolescents had scores considered diagnostic of ADHD compared to 3% of terms adolescents. Some publications (78, 80, 81) have indicated a higher frequency at lower gestational age, with a risk up to 1.5 times higher in MLP infants compared to full-term. These data were not confirmed in our sample, probably due to the use of different diagnostic scales between studies and different age of the patients.

Few studies refer to the subtypes of ADHD. Preterm birth has been mainly related to inattention disorders (72, 82, 83) with higher risk detected with more severe neonatal pathology and lower gestational age. However, in our sample of MLP adolescents, no significant increase in attention disorders was observed, nor there was a higher risk at a lower gestational age. It is important to consider that the characteristics of the disorder may vary based on gender, age, or developmental stage assessed during the evaluation, warranting further research for the complete validation of this screening scale (41, 84).

The primary limitation of our study was the sample size, which, although larger than in some other studies, proved insufficient for detecting certain differences, particularly in the domain of cardiovascular assessment and in identifying the most vulnerable subgroup of MPs. Additionally, patient recruitment had to be conducted in two stages due to a temporary interruption caused by the confinement measures implemented during the SARS-CoV-2 pandemic. Furthermore, the study faced limitations associated with the requirement for specific diagnostic tests or more sensitive imaging techniques to detect subtle differences.

In summary, despite all possible limitations, our findings provide an overview of the clinical situation of adolescent MLP and suggest that MLP patients should be regarded as a population at heightened risk of developing pathologies, mainly respiratory, minimal alterations on cardiological assessment and possibly anthropometric changes after growth, which may emerge later in life, potentially resulting in significant morbidity and mortality. Therefore, close follow-up of this majority group of preterm infants from the neonatal period to adulthood could be of interest, especially or those with additional risk factors. Prolonged monitoring of this predominant cohort of preterm infants may allow the identification of subtle alterations compared to term and very preterm infants, facilitating early implementation of interventions to mitigate the risk of future morbidity.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Comité de Ética de la Investigación con medicamento (CEIm), Hospital Universitario Severo Ochoa, Leganés, Madrid, Spain. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

PA-L: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. MA: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. MB: Investigation, Supervision, Visualization, Writing – original draft, Writing – review & editing. SR-G: Investigation, Methodology, Validation, Writing – original draft, Writing – review & editing. IO: Investigation, Methodology, Validation, Writing – original draft, Writing – review & editing. MG-G: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration,

Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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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

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Artificial intelligence and wheezing in children: where are we now?

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Wheezing is a common condition in childhood, and its prevalence has increased in the last decade. Up to one-third of preschoolers develop recurrent wheezing, significantly impacting their quality of life and healthcare resources. Artificial Intelligence (AI) technologies have recently been applied in paediatric allergology and pulmonology, contributing to disease recognition, risk stratification, and decision support. Additionally, the COVID-19 pandemic has shaped healthcare systems, resulting in an increased workload and the necessity to reduce access to hospital facilities. In this view, AI and Machine Learning (ML) approaches can help address current issues in managing preschool wheezing, from its recognition with AI-augmented stethoscopes and monitoring with smartphone applications, aiming to improve parent-led/self-management and reducing economic and social costs. Moreover, in the last decade, ML algorithms have been applied in wheezing phenotyping, also contributing to identifying specific genes, and have been proven to even predict asthma in preschoolers. This minireview aims to update our knowledge on recent advancements of AI applications in childhood wheezing, summarizing and discussing the current evidence in recognition, diagnosis, phenotyping, and asthma prediction, with an overview of home monitoring and tele-management.

KEYWORDS

wheezing, machine learning, artificial intelligence, asthma, digital health

Introduction

Wheezing is a musical sound, high-pitched and continuous, emitted from the chest during exhalation and resulting from the narrowing of the intrathoracic airway and expiratory flow limitation (1). The prevalence of wheezing disorders in preschool children varies worldwide and appears to have increased during the last decade (2). It is estimated that about one in three children experiences wheezing during the first 3 years of life (3). Viral infections trigger most wheezing episodes, involving up to 30–50% of preschool children (4). Generally, such episodes are mild and transient. However, one-third of preschoolers develop recurrent wheezing, which is defined as four or more episodes in the previous year (5). Recurrent wheezing has a significant impact on quality of life as well as on healthcare resources (6). Indeed, the economic burden of wheezing for the European Union is estimated at EUR 5.2 billion (7).

Artificial intelligence (AI) and machine learning (ML) encompass approaches such as data mining methodologies, predictive analytics, and advanced statistics for pattern recognition and neurocomputing (8). The application of AI technologies in paediatric allergology and

pulmonology has increased, contributing to disease detection, risk profiling, and decision support (9, 10). Additionally, the COVID-19 pandemic has shaped healthcare systems, resulting in an increased workload and the necessity to reduce access to hospital facilities. Indeed, several studies have investigated the applications of AI and ML during the COVID-19 pandemic (11). Overall, such approaches could help address current issues in managing preschool wheezing, including phenotyping and improving parent-led/self-management, while reducing economic and social costs.

This minireview aims to summarize and discuss the current evidence on possible applications of AI in recognizing and monitoring wheezing in children and predicting future asthma development, progressing from deep phenotyping to patient-tailored management (Figure 1). We conducted a literature search in the PubMed database, selecting articles published over the last 10 years. We used medical subject headings (MeSH terms) and free-text terms related to wheezing, machine learning, artificial intelligence, and asthma and limited the search to clinical trials, randomized controlled trials, meta-analyses, and systematic reviews. Additionally, we manually consulted the reference lists of the retrieved articles. Manuscripts were selected by the authors (L.V. and S.M.), considering full manuscripts published in English in peer-reviewed journals.

Can artificial intelligence recognize and monitor wheezing in children?

Parents and doctors often use "wheezing" to describe various respiratory sounds, such as crackles (12). The cheapest and non-invasive method for assessing wheezing is auscultation using a phonendoscope, which is operator-dependent and does not allow recording. Therefore, there is an increasing demand for an automatic, more objective, shareable, and reproducible method to assist doctors in diagnosing and monitoring patients with respiratory diseases (13).

The electronic stethoscope is an innovative version of the classic model, offering the ability to record and store chest sounds, allowing remote access. Many devices enable sound amplification, which is helpful for teaching (13). However, the digital data collected are subject to human interpretation and inter-operator variability, challenges that can be addressed by AI and ML technologies. These technologies have demonstrated good accuracy in recognizing respiratory sounds, particularly wheezing in children (Supplementary Table S1).

AI-assisted home stethoscopes can provide reliable information on asthma exacerbations. A recent study evaluated StethoMe for the automatic detection of pathological lung sounds (wheezes, crackles, and rhonchi) at home in 90 patients (0–18 years), demonstrating its efficacy in identifying asthma exacerbation across all ages (14). StethAid® is a device with a decision support system based on deep learning, an artificial neural network technology, used in an emergency department to recognize wheezing (15). The device recorded lung sounds from patients aged 2–18 years experiencing asthma exacerbation. These recordings were converted into spectrograms, serving as input for two deep learning models: ResNet-18 and Harmonic Networks. Both models were trained and validated to identify wheezing sounds from clear breathing sounds with good sensitivity, specificity, and accuracy. Specifically, ResNet-18 achieved 77% sensitivity, 70.1% specificity and 73.9% accuracy, while Harmonic Networks achieved 83.7% sensitivity, 84.4% specificity, and 84% accuracy.

A recent study by Ajay Kevat et al. (16) demonstrated high accuracy in recognizing children's lung sounds using AI-enhanced digital stethoscopes, although differences were noted between various devices. AI stethoscopes can store diaries of wheezing episodes, enabling remote monitoring (14). Limitations of these devices include high cost, complexity of use, incompatibility with software and/or

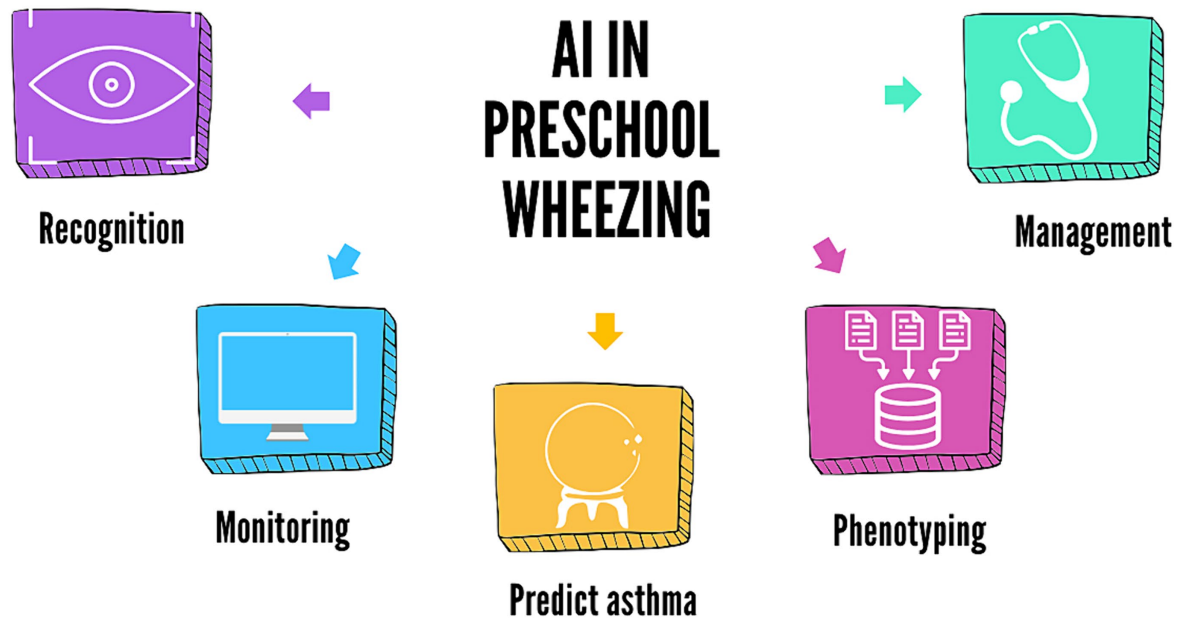

FIGURE 1
Possible applications of AI in preschool wheezing.

operating systems, and technical constraints (e.g., limited data memory, duration of autonomy, and varying frequency characteristics) (15).

Another device for analyzing lung sounds is PulmoTrack® (17–19), which utilizes chest sensors with an external microphone to capture and cancel environmental noises. Its effectiveness was evaluated in a study (17) involving 120 infants during sleep, demonstrating that computerized wheezing detection is more objective, non-invasive, and standardized compared to medical auscultation. The device also proved beneficial in intensive care settings for managing patients with wheezing (20).

The HWZ-1000 T device (Omron Healthcare Corporation, Kyoto, Japan) was evaluated in a study (21) involving 374 children. Wheeze was detected by auscultation with a stethoscope and recorded using the wheeze recognition algorithm device (HWZ-1000T), based on the sound characteristics of wheezing. The device accurately identified wheezing (sensitivity 96.6%, specificity 98.5%, positive predictive value 98.3%, and negative predictive value 97.0%).

In the study by Dramburg et al. (22), 20 infants and preschool children (9–72 months) diagnosed with wheezing in the past year were recruited. All their families were requested to use the WheezeScan® digital wheeze detector (OMRON Healthcare Co., Ltd.) twice daily and simultaneously monitor the child's respiratory symptoms through a smartphone clinical diary for 30 days. The results were displayed on an integrated screen that could be transmitted via Bluetooth to a PC or mobile device (e.g., smartphone or tablet). The study concluded that using the WheezeScan® Detector is straightforward and safe for children with wheezing. The support of a digital wheezing detector enhances parents' self-efficacy in managing asthma and wheezing, boosting their confidence in handling their child's wheezing at home. The WheezeScan® demonstrated good sensitivity (83.3%) and specificity (100%) in wheezing recognition, albeit with limited visits (22). In a more recent study (23), the analysis of WheezeScan® revealed no significant differences in wheeze control between study groups, with no impact on quality of life and minimal differences in parental efficacy in wheezing management.

Smartphone devices also play a role in integrating AI in Medical Practice. The ResAppDx® algorithm (24) analyses cough using a microphone integrated into the smartphone, alongside symptoms reported by the patient and/or parents. Automated cough analysis has demonstrated good diagnostic accuracy for common childhood respiratory diseases and it is non-invasive and feasible even in resource-limited environments (24). Another smartphone-based algorithm for detecting cough sounds was evaluated (25), comparing training data that included recordings of children coughing and ambient audio with everyday noises. The algorithm achieved an accuracy of 99.7% and a specificity of 99.96% when tested on the coughs of 21 children between 0 and 16 years hospitalized for lung diseases. This suggests that smartphone applications can be used for clinical follow-up and as a digital endpoint in clinical trials (25).

AI algorithms for wheezing recognition have some limitations, such as difficulty in correlating certain respiratory sounds with specific illnesses and considering that paediatric cough sounds vary with age due to respiratory and vocal system development. It should also be acknowledged that digital devices remain limited when compared to traditional lung auscultation for patients with severe airflow obstruction, who may have silent lungs without wheezing (19), and that the effectiveness of a digital device can be influenced by various factors such as age and cultural background. In conclusion, while many studies highlight the effectiveness and applicability of AI digital devices in detecting wheezing, others have yet to achieve similar results. Therefore, more studies will be necessary to assess their effectiveness in recognizing wheezing in children.

Can artificial intelligence predict asthma outcomes in children with wheezing?

Most children with asthma experience symptoms in early life, but these are typically transient, often disappearing by school age (6–13 years) (26). Therefore, it can be challenging to differentiate asthma from other wheezing disorders at this age (26). Over the last few decades, considerable effort has been dedicated to predicting asthma in children to identify earlier those at high risk and provide them with the best treatment option (26).

Previous studies based on population birth cohorts have identified distinct wheezing phenotypes (clusters) with associated early-life factors and outcomes, paving the path to predict wheezing trajectory and thereby develop targeted management (27). In this context, predictive models have been developed, considering various risk factors associated with asthma development, such as parental history of atopy and asthma, eczema and atopic dermatitis, allergic sensitization, and eosinophilia. However, they have rarely included environmental exposures and socioeconomic status (28). One of the most widely used models is the Asthma Predictive index (API) (29) and its modified version (mAPI) (30). Other models, such as the Isle of Wight score (31) and the Prevention and Incidence of Asthma and Mite Allergy (PIAMA) risk score, have also been developed (32); however, they have included children with recurrent chest infections, potentially misreporting episodes of wheezing (33).

Other predictive tools include the Leicester asthma prediction tool (34), the University of Connecticut (ucAPI) (35), and the Asthma Detection and Monitoring (ademAPI) (36), which also incorporate predictors such as 10 exhaled breath condensate biomarkers, 17 volatile organic compounds, and 31 genes. Although the ademAPI is the most comprehensive and sophisticated model, demonstrating reasonable specificity (88%) and sensitivity (90%), as well as the best positive and negative LRs (8.8 and 0.13, respectively), compared to other predictive models (33), its implementation in clinical practice remains challenging due to high cost (33). Even the original API, which includes only four items and a blood sample for eosinophil count, shows a good positive LR but a low negative LR, making it less effective in ruling out asthma (33). One of the more recent models is the CHILDhood Asthma Risk Tool (CHART) (37), which can identify children from 2 years of age at high risk of persistent wheezing and likely to develop asthma. Thanks to its simplicity, CHART could be used as a screening tool in primary care.

Overall, the models mentioned above indicate that the wheeze pattern alone cannot predict asthma progression. For this purpose, ML approaches have demonstrated better predictive performance and generalizability compared to regression-based models (27). In this context, artificial neural networks (ANNs) constitute a type of AI technique that learns the potential relationship between input–output mapping from a given dataset without prior knowledge or assumptions

about the data distribution (38). This sets them apart from common statistical tests and makes them suitable for classification and prediction tasks.

One of the initial studies in this research field (26) employed Principal Component Analysis (PCA) for feature extraction, followed by the Least Square Support Vector Machine (LSSVM) classifier for pattern classification, resulting in a ML model with an accuracy of 95.54% in predicting asthma. More recently, a study (39) from the Isle of Wright birth cohort applied ML approaches to predict school-age asthma (at the age of 10 years) in early life (Childhood Asthma Prediction in Early life, CAPE model) and at preschool age (Childhood Asthma Prediction at Preschool age, CAPP model). Recursive Feature Elimination (RFE) with a random forest algorithm was used for feature selection. Seven ML classifiers were then implemented to identify the best classification algorithm: two Support Vector Machines (SVM), a decision tree, a random forest, Naive Bayes, Multilayer Perceptron, and K-Nearest Neighbours. Finally, the models were also validated in the Manchester Asthma and Allergy Study (MAAS) cohort. The SVM algorithms demonstrated the best performance for CAPE and CAPP, showing excellent sensitivity in predicting persistent wheezing. Interestingly, the study was implemented by incorporating genetic and epigenetic information (40), which marginally improved performance and indicated that genetic and epigenetic markers for the broader phenotype of "diagnosed with asthma" are unlikely to have clinical utility (41).

A limitation of using the scores mentioned above is the challenge of ruling out asthma rather than identifying it. However, in clinical practice, they can assist in identifying patients at high risk of developing asthma who are likely to respond to ICS, as shown in a latent class analysis (LCA) (42). This analysis showed that ICS treatment reduced exacerbations in children with persistent wheezing and conditions such as "sensitization with indoor pet exposure" and "multiple sensitization and eczema."

Ultimately, the global diffusion of electronic health records (EHRs) created a need for automated chart review to diagnose asthma in children. Kaur et al. (43) developed a natural language processing (NLP) algorithm to identify children meeting API criteria. This NLP-API predicted asthma in preschoolers with a sensitivity of 86%, specificity of 98%, positive predictive value of 88%, and negative predictive value of 98%. Such an index has the potential to be utilized by healthcare systems to identify children meeting API criteria, even in early childhood (e.g., < 3 years old), thereby improving access to preventive and therapeutic interventions for asthma and monitoring their outcomes (9, 43).

Nonetheless, using AI algorithms and ML for predicting asthma outcomes in children may raise potential ethical concerns. Firstly, AI algorithms are trained on a large volume of personal data from EHRs, including clinical, imaging, and even genomic data, so it appears clear that ensuring privacy is critical, while overprotection of the data collection, usage, and sharing can slow down the innovation in AI training (44). To overcome this important limitation and preserve privacy, new techniques are emerging in AI such as the generation of synthetic data that mirrors the real-world dataset, but even this approach can not ensure full privacy, especially in small datasets, as patients from a specific region (45) or in a particular age range. Moreover, if AI algorithms are trained in a limited dataset, they can inadvertently present some gender, socioeconomic, and ethnic bias, that can exacerbate health inequalities in underrepresented social groups (44, 46), resulting in incorrect predictions, and leading to misdiagnosis when these biases are not corrected or prevented during the elaboration of the training dataset (44).

For these reasons, taking also in consideration that AI can actually make mistakes, AI can not be held morally accountable, having a role only as a decision support aid for clinicians (44). If used in clinical practice to provide therapeutic recommendations, to inform prognosis or risk of future events, informed consent should be provided to patients, explaining to them if AI has been used, clarifying which type of AI and how it was involved in the decision process, informing also about potential pitfalls (47).

Can artificial intelligence identify wheezing endotypes in preschool children?

Wheezing has been classified into different phenotypes since the first population-based cohort studies aimed to understand its heterogeneity (41).

The initial study was the Tucson Children's Respiratory Study (5), which identified three patterns of preschool wheezing (early transient, late-onset, and persistent), each associated with different risk factors. Subsequent studies have further defined additional phenotypes and temporal patterns, such as the Avon Longitudinal Study of Parents and Children (ALSPAC) (4, 48), the Prevention and Incidence of Asthma and Mite Allergy (PIAMA) birth cohort (49), the Viva project (50).

This approach assumes that patterns of symptoms and/or biomarkers assessed in longitudinal or cross-sectional studies reflect the underlying mechanisms, leading to the identification of asthma endotypes, but this assumption is uncertain (51).

ML approaches such as LCA have also been used in preschool wheezing (4, 52–54) and childhood asthma (55, 56).

An interesting study (57) focused on the longitudinal trajectory of wheezing exacerbations using an ML approach (k-means clustering), which identified two types of trajectories from birth to adolescence. The k-means clustering revealed that a shorter duration of breastfeeding was one of the early risk factors for frequent exacerbations. Additionally, children with frequent exacerbations showed increased airway resistance and, at 8 years of age, a lower lung function with higher FeNO levels, with evolution to asthma at 16 years of age.

ML approaches have also contributed to identifying specific genes, as demonstrated by Lin et al. (58), who employed Weighted Gene Co-expression Network Analysis (WGCNA) to identify gene co-expression modules associated with pediatric asthma. They subsequently used ML algorithms (random forest, lasso regression algorithm, and support vector machine with recursive feature elimination) to classify asthma cases and controls based on the 11 identified genes that can potentially explain the pathophysiology of difficult asthma and serve as biomarkers for diagnosis and targets for future advanced treatments.

Notably, as Saglani et al. (51) highlighted, we should be cautious about assuming that clusters identified in these studies represent "true" wheezing endotypes. The limitations of these studies include the identification of different risk factors for the same disease (wheezing) using the same technique (LCA), differences in the characteristics of the wheezing trajectories, the temporal description of wheezing in these clusters that may not align with the temporal presentation of symptoms, and ultimately, the diverse pathological mechanisms that can lead to wheezing within the same cluster. For example, persistent wheezing can

arise from recurrent airway infections due to impaired immunological responses or from allergen sensitization and exposure (51).

Considering these limitations, ML has identified more intermediate phenotypes with one certainty across all studies: all wheezing phenotypes, even the transient ones, lead to impaired lung function in early adulthood (41). Moreover, the results obtained so far need validation in further longitudinal studies involving larger populations of preschool children.

Conclusion

The applications of AI in preschool wheezing have encompassed various research topics, including phenotyping, delineating trajectories using data from EHR, predicting future asthma development and exacerbations, and identifying early risk factors and genetic markers. There are also several applications for clinical practice, such as wheezing recognition using AI-augmented stethoscopes or smartphones and telemonitoring (59).

Although AI could support clinicians in their daily practice, some questions must be addressed, especially when caring for children. Regulatory requirements are of foremost importance in protecting sensitive data and maintaining privacy. Additionally, AI approaches and their results must be rigorously validated before we adopt them in our routines.

In conclusion, AI could enhance the management of preschool wheezing, from recognition to identifying children potentially at high risk of exacerbation and asthma, thereby enabling an AI-tailored treatment. Furthermore, we should consider AI's utility in case of future pandemics, particularly in telemonitoring and telemanagement. However, we must be mindful of its limitations and work to address them to ensure the safety of children's data.

Author contributions

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Genetic biomarker prediction based on gender disparity in asthma throughout machine learning

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Background: Asthma is a chronic respiratory condition affecting populations worldwide, with prevalence ranging from 1–18% across different nations. Gender differences in asthma prevalence have attracted much attention.

Purpose: The aim of this study was to investigate biomarkers of gender differences in asthma prevalence based on machine learning.

Method: The data came from the gene expression omnibus database (GSE69683, GSE76262, and GSE41863), which involved in a number of 575 individuals, including 240 males and 335 females. Theses samples were divided into male group and female group, respectively. Grid search and cross-validation were employed to adjust model parameters for support vector machine, random forest, decision tree and logistic regression model. Accuracy, precision, recall, and F_1 score were used to evaluate the performance of the models during the training process. After model optimization, four machine learning models were utilized to predict biomarkers of sex differences in asthma. In order to validate the accuracy of our results, we performed Wilcoxon tests on the genes expression.

Result: In datasets GSE76262 and GSE69683, support vector machine, random forest, logistic regression, and decision tree all achieve 100% accuracy, precision, recall, and F_1 score. Our findings reveal that XIST serves as a common biomarker among the three samples, comprising a total of 575 individuals, with higher expression levels in females compared to males ($p < 0.01$).

Conclusion: XIST serves as a genetic biomarker for gender differences in the prevalence of asthma.

KEYWORDS

asthma, gender disparity, machine learning, biomarker, prevalence

1 Introduction

Asthma is a chronic respiratory condition affecting populations worldwide, with prevalence ranging from 1–18% across different nations (1). This ailment is characterized by diverse respiratory symptoms and variable airflow limitation. Asthma represents a complex interplay between genetic and environmental factors, giving rise to a heterogeneous spectrum of clinical manifestations, airway inflammation, and remodeling (2). Presently, there is compelling evidence linking asthma to various inflammatory pathways (3), suggesting that this condition is not solely a straightforward, monocausal disease but rather a multifaceted and diverse syndrome with an array of inflammatory mechanisms (4).

The overall prevalence of asthma was estimated to be 4.2% (95% CI: 3.1–5.6) in a sample of 45.7 million Chinese adults. Among children, boys exhibit a higher asthma prevalence compared to girls; however, in women, the prevalence is approximately 20% higher than in men (5). Notably, this discrepancy may change during puberty. The higher prevalence in boys compared to younger girls can be partially attributed to the relatively smaller size of their airways in comparison to their lungs. A prospective study involving 19-year-old children revealed that 21% of those diagnosed with asthma at the age of 7 experienced resolution, 38% had recurrent asthma, and 41% had persistent asthma. Remission was more frequent among boys, but less noticeable in girls and patients with severe asthma or sensitivity to fur animals (6).

Despite the crucial role played by environmental factors in asthma development, genetic factors have also been identified as key contributors. Studies investigating the heritability of asthma (the extent of population phenotypic variation attributed to genetic variation among individuals within the population) have estimated it to range from 35 to 95% (7). Dogs and cats are the most prevalent domestic pets, and individuals with anaphylactic responses may experience significant asthma-related morbidity due to exposure to allergens from these animals (8). Approximately 25 to 65% of children with persistent asthma display sensitivity to these allergens (9, 10).

Research has confirmed that the severity of asthma and its diverse clinical phenotypes may be linked to specific pathogenic moleculars, identified as the asthma biomarkers (11). Elevated levels of type 2 cytokines such as IL-5, IL-4, IL-13, IL-25, IL-33, periostin, dipeptidyl peptidase-4, osteopontin, fractional exhaled nitric oxide, bromotyrosine, prostaglandin D2 and leukotriene E4, and thymic stromal lymphopoietin (TSLP) are emblematic biomarkers for the detection and diagnosis of T2-high asthma; conversely, for the diagnosis and monitoring of low T2 type asthma, only a limited number of available biomarkers are mediated by Th1 and Th17 cells, including TNF-α, IL-1β, IL-6, IL-8, IL-17, folliculin, S100A9, myeloperoxidase, neutrophil elastase, and brain-derived neutrophil factor (12). Moreover, asthma biomarkers are often closely associated with genetic factors, encompassing genetics, epigenetics, and transcriptomic studies (13). In light of these factors, the application of machine learning and artificial intelligence technologies will enhance the precision in identifying biomarkers for different asthma phenotypes.

Machine learning is a crucial branch of artificial intelligence, with its core focus on enabling algorithms to self-optimize through training datasets, thereby making predictions or decisions on unseen data (14). Machine learning and artificial intelligence have been widely applied in the medical field, such as in image recognition, intelligent diagnostics, healthcare, and biomarker prediction (15, 16). Ding et al. (17) explored asthma-related lipid metabolism-associated biomarkers in mouse samples through five types of machine learning models, ultimately identifying cholesterol 25-hydroxylase (CH25H) as a central lipid metabolic gene in asthma. Lin et al. (18) based on weighted gene co-expression network analysis and machine learning, found 11 hub genes from the GSE135192 data set that could serve as novel diagnostic markers and therapeutic targets for pediatric asthma. Camiolo et al. (19) performed machine learning classification of bronchial epithelial cell gene expression data and found that L18R1 (IL-18 receptor 1) was inversely associated with lung function and was highly expressed in the most severely asthmatic population.

Gender differences are another reason for asthma attacks. Asthma prevalence rises in boys during childhood. In contrast, the prevalence and severity of asthma increases as women become older. Gender differences in asthma prevalence have attracted widespread attention. In this study, we used machine learning to explore potential biomarkers.

2 Method

The process of this study is depicted in Figure 1. Firstly, we selectively extract three samples (GSE69683, GSE76262, and GSE41863) from the gene expression omnibus (GEO) database and categorize them into male and female groups based on gender. The data came from the gene expression omnibus database[1] (20), which is a gene expression public database created in 2000 and contains high-throughput gene expression data around the world (21). Subsequently, we optimized the parameters of four machine learning models: support vector machine, random forest, logistic regression, and decision tree. We then input the optimized parameters into the machine learning models to predict biomarkers of gender-specific difference associated with asthma prevalence. Lastly, we validate our findings through the Wilcoxon test.

2.1 Data source

Data were obtained from three samples including No. GSE69683 (22), No. GSE76262 (23), and No. GSE41863 (24), in which we divided asthma patients into male group and female groups, involving a number of 575 individuals, including 240 males and 335 females (Table 1). Data set about GSE41863, GSE69683, and GSE76262 was

Abbreviations: CI, Confidence interval; GEO, Gene expression omnibus; TP, True positive; TN, True negative; FP, False positive; FN, False negative; XIST, X-inactive specific transcript; TSIX, TSIX transcript XIST antisense RNA; TXLNGY, Taxilin gamma Y-linked; USP9Y, Ubiquitin specific peptidase 9 Y-linked; ZFY, Zinc finger protein Y-linked; TTTY10, Testis expressed transcript, Y-linked 10; TTTY14, Testis expressed transcript, Y-linked 14; TTTY15, Testis expressed transcript, Y-linked 15; UTY, Ubiquitously transcribed tetratricopeptide repeat containing, Y-linked; DDX3Y, DEAD-box helicase 3 Y-linked; EIF1AY, Eukaryotic translation initiation factor 1A Y-linked; KDM5D, Lysine demethylase 5D; RPS4Y1, Ribosomal protein S4 Y-linked 1.

1 https://www.ncbi.nlm.nih.gov/geo/

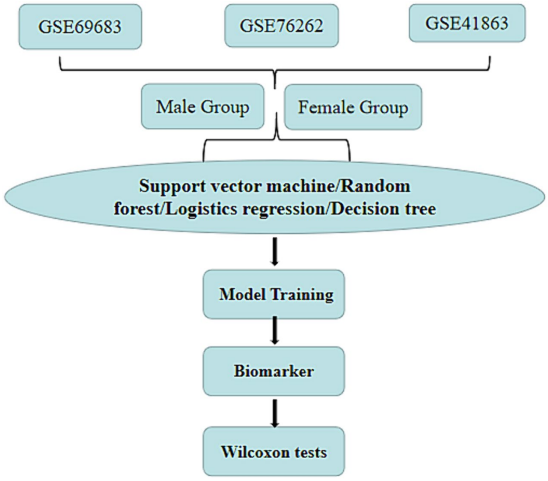

FIGURE 1
The flowchart of the research.

TABLE 1 Gender distribution in the sample.

Datasets	Female	Male	Age
GSE69683	243	170	≥27
GSE76262	70	47	—
GSE41863	22	23	—

obtained from sputum cells, blood sample and induces sputum, respectively. Subjects in GSE69683 were divided into severe, moderate, and healthy group according to grade of severity. Severe and moderate asthma subjects were merged, and divided into male and female group.

2.2 Machine learning

Grid search and cross-validation were used to adjust model parameters for support vector machine, random forest, decision tree and logistic regression model. Parameter settings are shown in Table 2. For support vector machine model, kernel was setting as linear, and penalty coefficient was setting from 0.0005 to 100. N_estimators and Max_depth of random forest were from 10 to 500, and from 1 to 70, respectively. As for logistic regression model, *C* was setting from 0.001 to 11. Accuracy, precision, recall, and F_1 score were used to evaluate the classification performance of the models during the machine learning process. As depicted in Table 3, TP represents the number of correctly classified positive samples, TN represents the number of correctly classified negative samples, FP represents the number of samples falsely classified as negative, and FN represents the number of positive samples incorrectly classified. All the aforementioned operations were carried out in Python3.7 software.

2.3 Statistical analysis

In order to validate the accuracy of our results, we performed Wilcoxon test on the genes from the GSE69683, GSE76262, and GSE41863. The Wilcoxon test was operated in the website https://www.home-for-researchers.com/#/.

TABLE 2 Parameter settings based on grid search for model optimization.

Model	Parameters	Setting
Support vector machine	Kernel	Linear
	C	0.0005, 0.001, 0.005, 0.01, 0.05, 0.1, 0.5, 1, 5, 10, 20, 100
	Gamma	100, 50, 40, 30, 20, 15, 11, 9, 5, 7, 3, 1, 0.1, 0.01, 0.001
Random forest	N_estimators	10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 150, 200, 300, 400, 500
	Max_depth	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 70, 80, 90, 100
Logistics regression	*C*	0.001, 0.003, 0.005, 0.007, 0.009, 0.1, 0.3, 0.5, 0.7, 0.9, 1, 3, 5, 7, 9, 11
Decision tree	Criterion	Gini, Entropy
	Max_depth	1, 3, 5, 7, 9, 15, 20, 25, 30, 35, 40, 50, 100, 200
	Max_leaf_nodes	1, 3, 5, 7, 9, 11, 15, 20, 30, 40, 50, 100

3 Result

3.1 Model training

The parameter optimization results for support vector machine, random forest, logistic regression, and decision tree using the grid search-cross validation method are shown in Table 4. For all three samples, the optimal parameters for support vector machine are *C* = 0.005, Gamma = 100, and kernel = linear. For sample GSE69683, the optimal parameters for random forest are Max_depth = 2 and N_estimators = 150. For sample GSE76262, the optimal parameters are Max_depth = 4 and N_estimators = 300. Lastly, for sample GSE41863, the optimal parameters are Max_depth = 90 and N_estimators = 20.

The performance of each model with the optimal parameters obtained during training is shown in Figure 2. In datasets GSE76262 and GSE69683, support vector machine, random forest, logistic regression, and decision tree all achieve 100% accuracy, precision, recall, and F_1 score, described in Figures 2A,B. However, in the dataset GSE41863, the random forest achieved an accuracy of 88%, a recall rate of 75%, an F_1 score of 76%, and a precision of 80% (Figure 2C).

3.2 Biomarker prediction

Table 5 presents the intersection of the top 20 important genes in the feature ranking among four models when the model reaches its optimum. During blood sample GSE69683, support vector machine, random forest, logistic regression, and decision tree all ranked X-inactive specific transcript (XIST) among the top 20 genes. The intersection of support vector machine, random forest, and logistic regression models comprises TSIX, TTTY10, TTTY14, TTTY15, TXLNGY, USP9Y, UTY, and ZFY genes (Table 6) in blood sample GSE69683.

The intersection of support vector machine, random forest, decision tree, and logistic regression models induces sputum sample GSE76262 are TSIX and XIST. The intersection of support vector machine, random forest, and logistic regression models consists of DDX3Y, EIF1AY, KDM5D, and RPS4Y1 genes in GSE76262.

In sputum cell sample GSE41863, the intersecting genes ranked among the top 20 by all four models are TXLNGY, USP9Y, UTY, XIST, and ZFY. The intersection of support vector machine, random forests, and logistic regression models includes TSIXT and TTY15.

In order to validate the accuracy of our results, we performed Wilcoxon tests on the genes from the GSE69683 (XIST), GSE76262 (TSIX and XIST) and GSE41863 (TXLNGY, USP9Y, UTY, XIST, and ZFY). As depicted in Figure 3, within the GSE 76262 dataset, there were 47 males (represented by the blue color) and 70 females (represented by the red color). TSIX and XIST exhibited higher expression in females and lower expression in males, with statistical significance ($p < 0.001$). The same result about XIST is observed in the GSE69683 and GSE41863 data sets, as illustrated in Figures 4, 5E. As shown in Figure 5, the expression of TXLNGY, USP9Y, UTY, and ZFY is significantly higher in males compared to females, with statistical significance ($p < 0.001$).

4 Discussion

Asthma is a common chronic inflammatory disease of the airways, characterized by variable and recurrent symptoms, reversible airflow obstruction, and bronchospasm (25). The etiology of asthma is complex and likely involves the interaction between genetic factors and environmental factors that are not fully understood yet. This study, based on machine learning, was purposed to investigate the genetic biomarkers that caused sex differences in asthma.

TABLE 3 Evaluating indicators.

Evaluation index	Function definition
Recall	$\text{Recall} = \frac{TP}{TP + FN} * 100\%$
Specificity	$\text{Specificity} = \frac{TN}{TN + FP} * 100\%$
Precision	$\text{Precision} = \frac{TP}{TP + FP}$
F_1-score	$F_1\text{score} = 2\frac{\text{Precision} * \text{Recall}}{\text{Precision} + \text{Recall}}$
Accuracy	$\text{Accuracy} = \frac{TP + TN}{TP + TN + FP + FN} * 100\%$

The gender disparity in the incidence of asthma has attracted considerable attention among scholars. The physiological variances in pulmonary development and structure may contribute to this phenomenon. Sex differences in lung development between males and females begin as early as weeks 16–24 of gestation (26). Female fetuses have smaller airways and a lower number of respiratory bronchioles compared to males; however, they exhibit a faster rate of maturation (27). Upon reaching adulthood, males and females are exposed to potentially distinct occupational and familial triggering factors that may influence asthma. Females have a greater opportunity to utilize cleaning agents within their domestic environment compared to males (28). Certain chemical substances present in these cleaning agents have the potential to induce respiratory allergic reactions or inflammation, subsequently leading to the onset of asthma.

The number of genes associated with the X chromosome was thought to influence the immune response and the development of autoimmune diseases, such as asthma. Taking toll-like receptor (an X-linked gene involved in innate immunity) as an example, TLR7-mediated HLADR + CD3–CD19-cell production of IFN-α was significantly upregulated in healthy women compared to healthy men. This suggests that the presence of two X chromosomes plays an important role in enhancing innate and adaptive immune responses (29). TLR7 could be capable of escaping X-chromosome inactivation in female immune cells, similar to TLR8, which also could evade X-chromosome inactivation in human monocytes and CD4 T cells. The co-dependent transcription of the active X chromosome and the escape from X-chromosome inactivation (XCI) both lead to higher protein abundance of TLR8 in female cells, which may impact the response to viruses and bacteria, as well as influence the risk of developing inflammation and autoimmune diseases (30).

The X-inactive-specific transcript (XIST) gene serves as a primary regulatory factor for X chromosome inactivation in mammals. In this study whether it's a blood sample, an induced sputum sample, or a sputum cell sample, XIST ranked at the top of all four machine learning models in our predictions. XIST produces a long non-coding (lnc) RNA that accumulates throughout the entire length of the transcribed chromosome, recruiting factors to modify the potential chromatin and silence X-linked genes in cis. Previous studies have established a significant correlation between XIST and lung pathologies. In the context of lung cancer, Li et al. (31) discovered that XIST in metastatic non-small cell lung cancer (NSCLC) tissues facilitates TGF-β-induced EMT, as well as cell invasion and metastasis, through modulation of the miR-367/miR-141-ZEB2 axis. Additionally, XIST expression is elevated in response to the nicotine derivative nitrosamine ketone (NNK) in lung injury, influencing the aberrant expression of miR-328-3p (32).

TABLE 4 The optimal parameters for the four models.

Model	Support vector machine			Random forests		Decision tree			Logistic regression
	C	Gamma	Kernel	Max_ depth	N_ estimators	Criterion	Max_ depth	Max_leaf_ nodes	C
GSE69683	0.0005	100	Linear	2	150	Gini	1	3	0.001
GSE76262	0.0005	100	Linear	4	300	Gini	1	3	0.1
GSE41863	0.0005	100	Linear	90	20	Gini	5	20	0.003

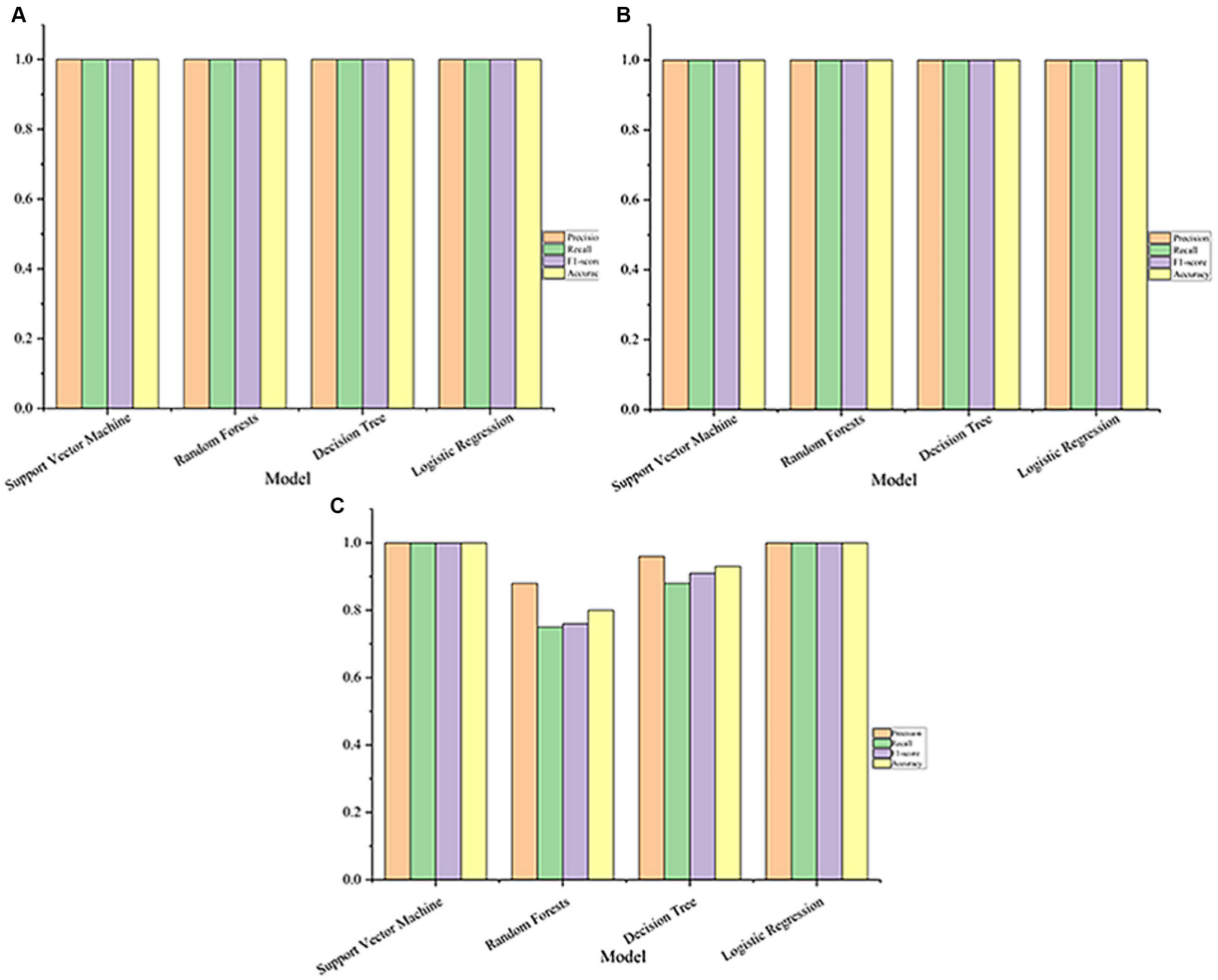

FIGURE 2
The performance of the machine learning model on the dataset (**A**, GSE76262; **B**, GSE69683; **C**, GSE41863).

TABLE 5 Intersection of the top 20 genes ranked by feature importance among four models.

Model	GSE69683	GSE76262	GSE41863
Support vector machine Random forests Decision tree Logistic regression	XIST	TSIX XIST	TXLNGY USP9Y UTY XIST ZFY

TABLE 6 Intersection of the top 20 genes ranked by feature importance among three models.

Model	GSE76262	GSE69683	GSE41863
Support vector machine Random forests Logistic regression	DDX3Y EIF1AY KDM5D RPS4Y1	TSIX TTTY10 TTTY14 TTTY15 TXLNGY USP9Y UTY ZFY	TSIXT TTY15
Random forests Decision tree Logistic regression	TXLNGY USP9Y	Support vector machine Random forests Decision tree	ZNF107 ZNF471

Furthermore, XIST plays a role in acute lung injury (ALI), Li et al. (33) observed upregulation of XIST in a lipopolysaccharide (LPS)-ALI mouse model and in lung endothelial cells; knockdown of XIST inhibited the LPS-induced inflammatory response and apoptosis in these cells. While numerous studies have substantiated the association between XIST and various lung diseases, its relationship with asthma has been less explored. In the present study, we elucidate the connection between XIST and asthma, and propose its potential as a biomarker for gender disparities in asthma prevalence. Fagerberg et al. (34) utilized next-generation sequencing to analyze the transcriptomes of 95 different human organs and tissues based on a total of 27 individuals' samples. They discovered the expression of the XIST gene in human lung tissue. In our

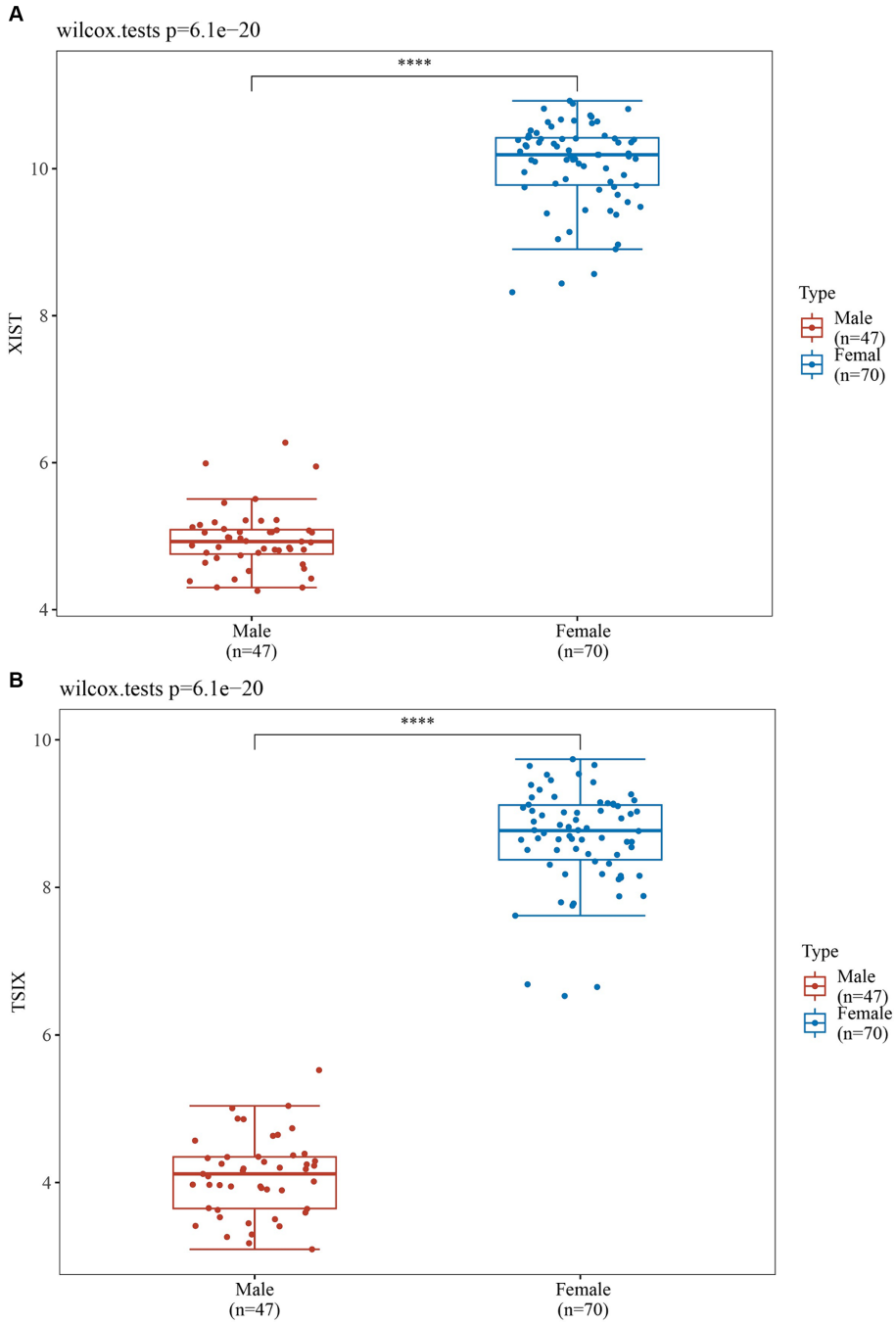

FIGURE 3
Results of Wilcoxon tests on GSE76262 (**A**, XIST; **B**, TSIX).

analysis of three samples from a cohort of 575 individuals, we observed elevated expression of XIST exclusively in females. Currently, there is a lack of reports regarding the gender differences in XIST expression in the context of asthma. However, the high expression of XIST has been shown to be associated with primary biliary cholangitis in females, XIST can stimulate the proliferation and differentiation of initial $CD4^+$ T cells, which considered to be the reason for the high incidence of PBC in females (35). In addition, Yu et al. (36) confirmed that dysregulation of XIST may bias the differentiation selection of this immune cell, with dysregulation of XISL evident in CD11c + atypical B cells in female patients but not in male patients. These results indicate that XIST may affect gender differences in asthma by targeting the proliferation and differentiation of immune cells.

Asthma is associated with sex hormone levels and obesity, and some published researches revealed that XIST is involved in regulating these biological processes. XIST is associated with the expression of sex hormones. Armoskus et al. (37) employed gene expression microarrays to identify 90 potential genes that were differentially expressed in male and female mice's neocortex/hippocampus, and

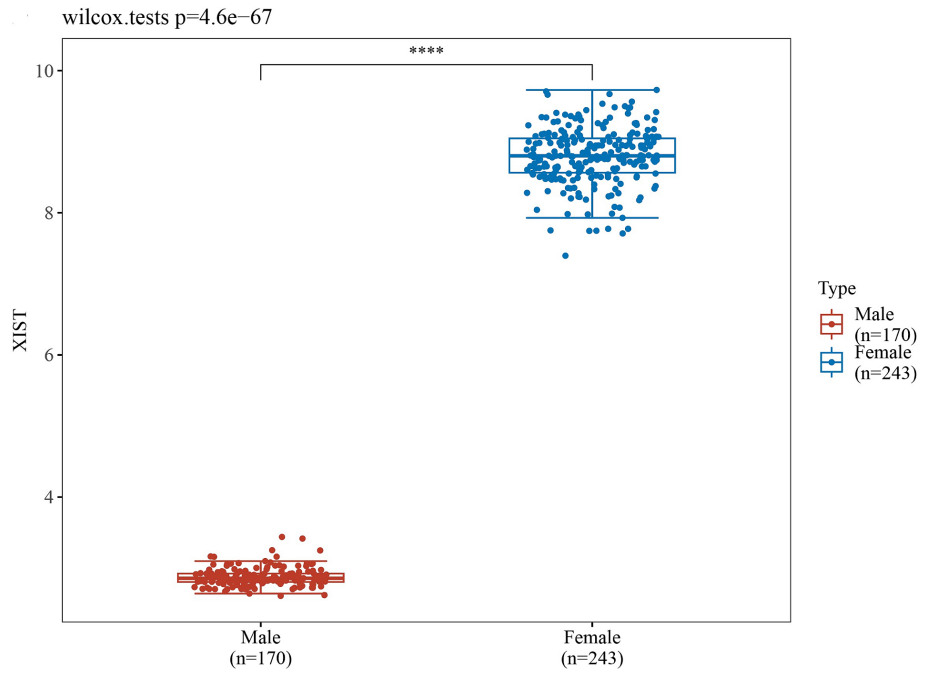

FIGURE 4
Results of Wilcoxon tests on GSE69683.

PCR reverse transcription revealed dimorphic expression of the XIST gene. XIST is implicated in androgen/estrogen signaling pathways, protein modification, and cell proliferation/death, all of which are linked to differences in neurodevelopment, cognitive function, and neurological illness between sexes. Wang et al. (38) discovered that the lncRNA XIST was down-regulated in late-onset hypogonadism, and that XIST siRNA increased cell apoptosis, increased caspase3 activity, and decreased testosterone levels. XIST also regulates obesity-related processes. XIST may assist regulate intramuscular fat metabolism, according to Yang et al. (39), who used bioinformatics analysis and machine learning to uncover potential tissue-specific indicators of swine fat accumulation. Wu et al. (40) discovered that XIST expression was substantially higher in female than male persons in human adipose tissue. XIST expression increased considerably *in vitro* during brown fat cell development. Brown preadipocyte development was impeded by XIST knockdown, but XIST overexpression facilitated full differentiation. Yao et al. (41) used lncrNA-mirNA-mrna networks to identify possible functional lncRNAs in metabolic syndrome (including abdominal obesity), and discovered that XIST was the most relevant lncRNA.

Abnormal proliferation and activation of immune cells are considered to be the key to the pathogenesis of asthma. TH2 cell was generally considered to be the main immune cell responsible for asthma, but increasing evidence shows that asthma was related to B cells (42, 43). Previous research has demonstrated the crucial role of B cells in regulating lung function and airway remodeling in mouse models of asthma (44). Mechanistic investigations have revealed that B cells contribute to the asthmatic process by initiating and sustaining T helper (Th) cell-mediated immune responses (45). A recent study highlighted the connection between the initiation of the Th response and innate lymphoid cells type 2 (ILC2s). ILC2s reside on mucosal surfaces, including the lungs, and are capable of producing type 2 cytokines such as interleukin-5 (IL-5) and interleukin-13 (IL-13), which are pivotal in the pathogenesis of allergic disorders and asthma (46). Notably, IL-13 can induce B cell class switching and the production of immunoglobulin E (IgE), collectively exacerbating the progression of asthma (47). Habener et al. (48) found that IgA + memory B cells were significantly increased in peripheral blood mononuclear cells of asthmatic patients, especially in asthmatic patients with small airway dysfunction. Wypych et al. (45) also confirmed that B cells participate in the pathogenesis of asthma mouse models by amplifying Th cell effects. What is exciting is that the latest study confirmed that XIST was required to maintain the homeostasis of B cells. On the one hand, XIST prevents the escape of x-linked genes with DNA hypomethylation promoters in B cells. On the other hand, XIST maintains X inactivation through sustained deacetylation of H3K27ac, revealing the regulatory role of XIST in B cells (36). Interestingly, XIST dysregulation was found in infiltrating B cells of rheumatoid arthritis joint tissues, which is a chronic inflammatory condition in the same family as asthma (36), suggesting the potential of XIST in the treatment of chronic inflammation, which indirectly justifies the conclusion of the present study that XIST can be used as a therapeutic target for asthma. The study conducted by Zhou et al. (49) provides additional support for our findings. They obtained peripheral blood samples from 137 pediatric asthma patients and 59 healthy children. Through bioinformatics analysis, it was revealed that XIST is significantly upregulated in pediatric asthma patients.

Jiang et al. (50) employed bioinformatics approaches to analyze the hub genes and signaling pathways involved in severe asthma. Through protein–protein interaction network analysis and module analysis, they identified 11 hub genes within key modules. Jiang's study also involved the GSE76226 dataset, yet it yielded no overlapping

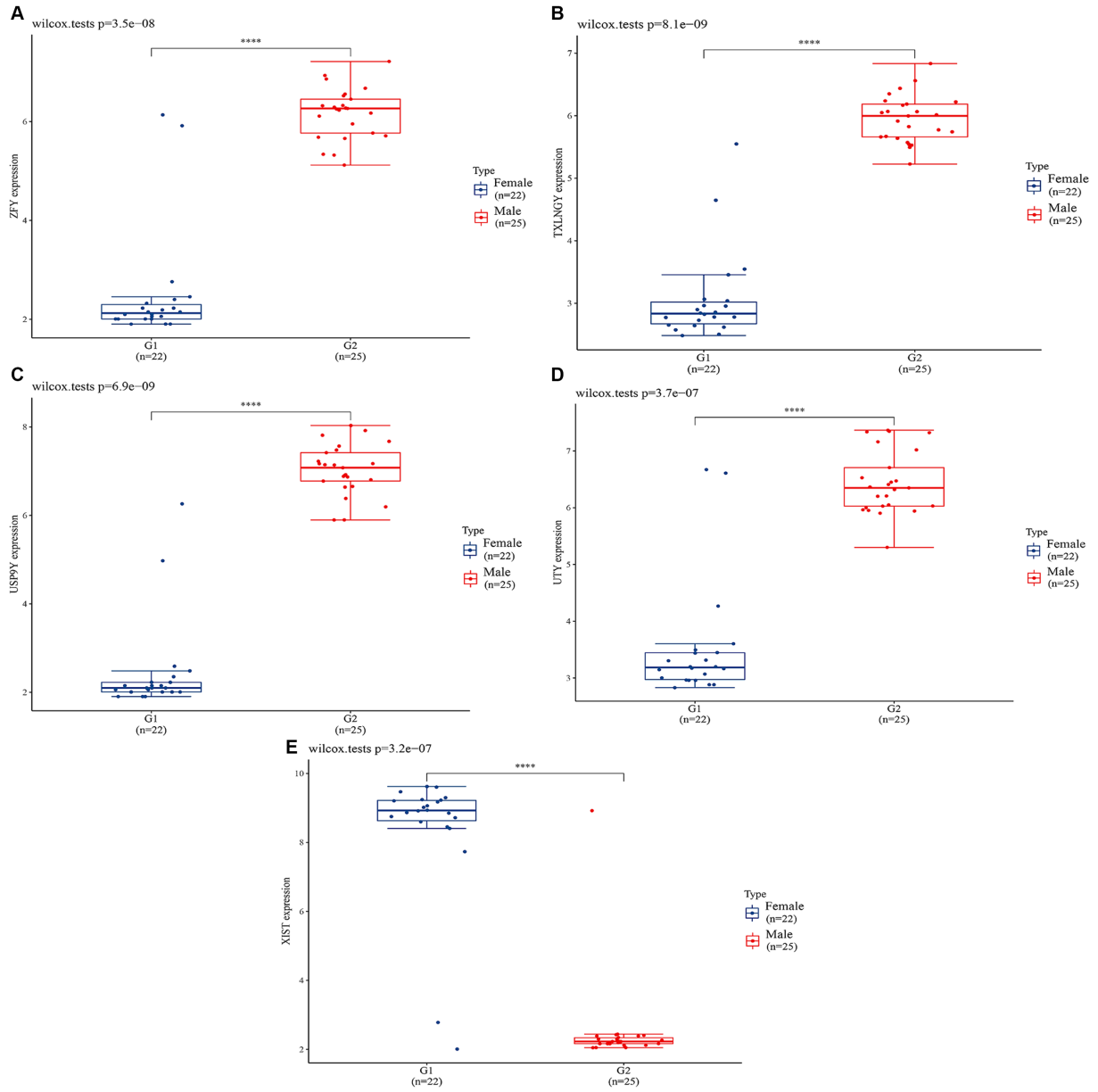

FIGURE 5
Results of Wilcoxon tests on GSE41863 (**A**, ZFY; **B**, TXLNGY; **C**, USP9Y; **D**, UTY; **E**, XIST).

results with our predicted genes. We speculate that the probable reason lies in the different methodologies employed: this study utilized machine learning models with parameter optimization techniques to screen for potential genes, whereas Jiang et al. analyzed the top 5,000 genes from three datasets.

We must acknowledge the limitations of this study. Firstly, it is based on predictive analysis of existing databases to identify gender-specific differences in asthma prevalence genes, suggesting XIST as a potential biomarker. However, experimental validation is lacking, and we plan to address this in future experiments. Secondly, our analysis utilized three datasets, with one dataset including age information (over 18 years old), as our preliminary literature review revealed a reversal in asthma prevalence between males and females during adolescence.

5 Conclusion

The study, based on machine learning, found genetic biomarkers that caused sex differences in asthma rates around puberty, which has attracted widespread attention. Grid search was used to train and adjust parameters of support vector machine, decision tree, logistic regression and random forest. Results revealed that XIST was a potential genetic biomarker associated with gender differences in asthma prevalence.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession

number(s) can be found at: https://www.ncbi.nlm.nih.gov/geo/, GSE69683, GSE76262 and GSE41863.

Author contributions

CC: Writing – original draft. FY: Writing – review & editing. XM: Writing – original draft. FP: Writing – original draft, Writing – review & editing. XS: Writing – original draft, Writing – review & editing. CW: Writing – original draft, Writing – review & editing. YS: Writing – original draft, Writing – review & editing. HD: Writing – original draft, Writing – review & editing. DL: Writing – original draft, Writing – review & editing. NZ: Writing – original draft, Writing – review & editing. XW: Writing – original draft, Writing – review & editing. TW: Writing – original draft, Writing – review & editing. PW: Writing – original draft, Writing – review & editing.

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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.

The reviewer CT declared a shared affiliation with the authors XM and XS to the handling editor at the time of review.

Publisher's note

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Epidemiological investigation of allergic rhinitis in children aged 6–12 years in Bayannur City, China

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Background: Allergic rhinitis (AR) is an inflammatory condition of the nasal mucosa triggered by exposure to non-harmful substances. Over the past decade, the prevalence of AR in Chinese children has been steadily increasing. However, detailed epidemiological data on AR in children from Bayannur City are lacking.
Methods: This study randomly selected six primary schools in Bayannur City. Electronic questionnaires were distributed via the web, and parents and children completed the questionnaires by scanning the two-dimensional code within a designated timeframe. Statistical analysis was performed on the collected data.
Results: A total of 4,754 valid responses were obtained. The self-reported prevalence of AR among children in Bayannur city was 39.79%. Multivariate analysis revealed that male gender, belonging to an ethnic minority, a history of food or drug allergies, frequent antibiotic use (≥3 times per year in the past two years, with each course lasting ≥3 days), and residence in urban or pastoral areas was associated with an increased prevalence of AR in children. The proportion of children experiencing moderate to severe AR hat impacted their studies or daily life was 48.78%. Chronic AR was reported in 56.71% of cases. Among AR patients with other allergic conditions, the incidence rates were as follows: bronchial asthma 35.99%, upper airway cough syndrome (UACS) 64.32%, secretory otitis media (SOM) 22.41%, obstructive sleep apnea hypopnea-syndrome (OSAHS) 49.58%, allergic dermatitis (AD) 48.72%, and allergic conjunctivitis (AC) 85.20%. The prevalence of AR was 50.30% in urban areas, 13.733% in rural areas and 20.90% in pastoral areas. Seasonal effects on AR prevalence were notably significant in urban and pastoral regions.
Conclusions: The prevalence of AR among children in Bayannur city was 39.80%. Of those with AR, 48.72% experienced significant impacts on their learning or daily life, while only 14.80% had no other allergic conditions. There were significant variations in the prevalence and onset of AR among children between urban, agricultural and pastoral areas.

KEYWORDS

allergic rhinitis, children, epidemiology, China, Bayannur City

1 Introduction

Allergic rhinitis (AR) is a non-infectious condition characterized by inflammation of the nasal mucosa in response to exposure to allergens such as dust mites, pollen, dairy products, and eggs (1). The primary symptoms include runny nose, sneezing, nasal congestion, and itchy nose. AR affects approximately 25% of the global population (2),

with the majority of individuals exhibiting symptoms before the age of 20, and nearly 50% of patients showing symptoms by age 6 (3). AR not only disrupts daily activities, academic performance, and sleep in children but also increases the risk of physiological disorders such as depression and bipolar disorder in severe cases (4). In children aged 6–12 years, AR can significantly impact sleep quality, facial development, and vocal function (5). Additionally, AR often coexists with bronchial asthma, upper respiratory syndrome, allergic dermatitis, allergic conjunctivitis and other allergic diseases, which collectively impair children's development and physical and mental health.

According to 2019 report, the prevalence of AR in Chinese children was 15.8%, of which the prevalence rates in central China, South China, Northwest China, Taiwan, Southwest China, North China and East China were 17.20%, 15.99%, 15.62%, 15.33%, 15.07%, 14.87%, and 13.94%, respectively (6). Limited large-scale epidemiological data on AR in Inner Mongolia exist. A 2015 large-scale epidemiological survey by Ma Tingting et al. reported a self-reported AR prevalence of 26.6% among children aged 0–17 years in six grassland regions of Inner Mongolia (44.5% in Xilin Hot, 21.8% in Duolun County, 45.4% in Erenhot, 10.8% in Tongliao City, 27.5% in Zalute Banner, and 15.3% in Kailu County) (7). In 2019, allergen testing of 129 patients with AR from central and western Inner Mongolia (including Hohhot, Baotou, Ulanqab, Ordos and Bayannur) revealed Artemisia muisia as the predominant allergen (8).

Bayannur City situated in the western Hetao Plain of Inner Mongolia Autonomous Region, has a long-term resident population of approximately 1.5 million. Bayannur Meteorological Bureau reports an increase in annual average temperatures and sunshine over the past 60 years, with no significant change in precipitation but a gradual decrease in humidity (9). Artemisia plants are widespread in Bayannur, with artemisia pollen being the major allergen in the Inner Mongolia Autonomous Region of China (7). Recent rapid industrialization and urbanization in Bayannur City have further exacerbated air quality, creating an environment conducive to the spread of AR.

According to the 2023 China Health and Health Statistics Yearbook, Bayannaoer City, with its relatively low economic development, allocates a smaller proportion of its total budget to health expenditures compared to more developed regions. Consequently, per capita health expenditures are below the national average, and attracting public health professionals remains challenging. Additionally, the city's medical and health infrastructure is underdeveloped, resulting in suboptimal treatment options for AR. Currently, the primary methods for treating AR include drug therapy and surgical intervention. For mild symptoms or early-stage cases, hormone + antihistamine therapy is employed alongside nasal cavity irrigation using physiological saline. Severe cases or those with significant nasal septum hypertrophy may require partial resection of the inferior nasal concha. However, specific immunotherapy, including sublingual and subcutaneous allergen immunotherapy widely used globally, is not yet available in Bayannur.

Despite recent large-scale epidemiological studies on AR in Inner Mongolia's major cities, such as Hohhot, Xilin Hot, and Tongliao, detailed prevalence data for Bayannur City remains scarce. Therefore, this study aims to provide a comprehensive analysis of AR prevalence among children aged 6–12 years in Bayannur City, thereby addressing the current gap in epidemiological data for this region.

2 Methods

2.1 General information

2.1.1 Sample size calculation

$$n = \frac{t^2 pq}{d^2}$$

n: sample size; p: Estimated overall prevalence; q = 1-p; d: Tolerance error.

Assuming α is 0.05, t = 1.96, and d = 0.1p, previous studies reported that the prevalence of AR in Inner Mongolia was 17.10%, with an estimated sample size of n = 1,940. To account for the cluster sampling method and to minimize error, the sample size was increased by 50%, resulting in a minimum sample size of 2,929 people.

2.1.2 Random sampling

This cross-sectional study was conducted in Bayannur City, China, which is administratively divided into one district (Linhe District); two counties (Wuyuan County and Dengkou County), and four flags (Urat Front flag, Urat Middle flag, Urat Rear flag, and Hangjin Rear flag). Based on the selection criteria, 89 primary schools, with 75,629 students, were included. Among the 89 primary schools, which were numbered from 1 to 89, six were randomly selected using a lottery method. All children aged 6–12 years from the selected schools who met inclusion criteria were invited to participate. From October 1 to October 15, 2023, electronic QR codes containing informed consent forms and questionnaires were distributed to the parents of the selected children. Parents scanned the QR codes, completed the questionnaires with their children, and submitted them within the specified timeframe. This study was approved by the Ethics Committee of Bayannur City Hospital.

2.2 Method

2.2.1 Questionnaire design

The questionnaire consisted of four sections. The first part included the basic information of the children, such as gender, ethnicity, and contact number; The second section was the risk factors, which included information on breastfeeding duration, delivery method, history of food allergies, and other relevant factors. The third section focuses on the diagnosis and classification of AR, while the fourth section addresses the presence of other allergic concomitant diseases.

The reliability of the questionnaire was ensured by referencing international authoritative questionnaires and having it reviewed by experts in allergy science and epidemiology. During the distribution of the questionnaires, rhinologists provided explanations to students and parents. After completion, two study members verified the reliability of the responses. Finally, all responses were imported into an Excel spreadsheet, and after inclusion and exclusion criteria were applied, the eligible samples were coded numerically for statistical analysis.

2.2.2 Partition and diagnosis

Partition: The Land Use Master Plan (2006–2020) provided the basis for area classification (10). Urban areas were considered as concentrated residential zones engaged in industrial, commercial, and service activities. This includes cities, organized towns, development zones, and parks. The agricultural area was characterized by economic activities centered around agriculture, specifically river irrigation farming in the southern Hetao plain, covering approximately 1,147,800 hectares. The pastoral area referred to areas designated for grazing or nomadic activities, including the Wolf Mountain area to the west of the Chashitai Mountain and the northern Urat High Plain, encompassing approximately 10,441,600 hectares. Other areas include small fishing areas, forested areas, and mixed settlements that do not fit into the primary classification.

Diagnosis of AR: Diagnosis was based on the International Study of Asthma and Allergy in Childhood (ISAAC) (11) combined with the Score for Allergic Rhinitis (SFAR) (12). The SFAR scores range from 0 to 16, with a cutoff of 7 points. Scores ≥7 were considered positive for AR, while scores <7 were deemed negative. Participants with positive questionnaire results or a history of positive allergic reactions were classified as AR-positive (Table 1).

Classification of AR: Classification followed by the 2019 update of Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines (13). Based on AR severity, it was divided into mild and moderate to severe. Mild was defined as having no symptoms and does not interfere with daily activities and sleep. Moderate to severe was defined as having at least one nasal symptom (runny nose, stuffy nose, itchy nose, or sneezing) that disrupts daily activities and sleep. It can be further divided into continuous and intermittent based on duration. Persistent AR was defined as nasal symptoms that occur more than four days per week for over four consecutive weeks; otherwise, AR is intermittent.

TABLE 1 SFAR scores.

Item	Mark
Repeated sneezing, nasal congestion or runny nose in the past year (except when you have a cold)	1 for each symptom 3 total
Rhinoconjunctivitis positive	1
Duration of nasal symptoms	Season 1 Perennial 1
Nasal symptoms trigger	Pollen/dust mites/dust 2 Hair (cat/dog, etc.) 1
Conscious of allergic symptoms	2
Family history of allergies	2
Past positive allergy tests	2
Previous diagnosis of allergic symptoms	1

AR concomitant symptoms were defined based on questions. Asthma was determined based on the question "Has your child ever been diagnosed with asthma by a doctor?" The options were Yes or No. Similarly, upper airway syndrome (UACS), secretory otitis media (SOM), sleep apnea-hypopnea syndrome (OSAHS), allergenic dermatitis (AD), and allergic conjunctivitis (AC) were defined.

2.2.3 Inclusion and exclusion criteria

Inclusion criteria: (1) children aged 6–12 years; (2) Residing in Bayannur City for ≥1 year; (3) Parents who have the reading ability and who consent to participate in the survey.

Exclusion criteria: (1) Family members who decline to participate; (2) Inability to accurately assess the child's condition; (3) Incomplete or erroneous questionnaires.

2.3 Statistical analysis

SPSS26.0 software was used for data analysis. The Class I error value α was set to 0.05 (both sides). Descriptive analysis for categorical variables was presented as counts and percentages, while quantitative data with a normal distribution were expressed as mean ± standard deviation. For sample size >2,000, the Kolmogorov-Smirnov test was used to evaluate the normality of continuous variables. The Pearson Chi-square test was used to examine the correlation between independent and dependent variables. Univariate logistic regression analysis was performed to identify influencing factors, yielding odds ratios (OR), and 95% confidence intervals (95% CI). Moreover, a correlation was considered statistically significant if $P < 0.05$. Independent variables from univariate analysis were included in multivariate logistic regression analysis, and demographic data including gender, ethnicity, and age were adjusted for Model I. Model II was corrected for breastfeeding duration, delivery mode, history of food or drug allergies, antibiotic use, environmental exposure to smoking, dietary habits, and zoning based on model I.

3 Results

3.1 Demographic data analysis

3.1.1 Self-reported prevalence of AR

Out of 6 primary schools, 6,225 students were enrolled, and 5,006 questionnaires were collected, yielding an overall response rate of 80.41%. Of these, 4,754 questionnaires were valid, resulting in an effective recovery rate of 94.97%. The sample comprised 2,501 males and 2,253 females, with a male-female ratio of 1.11:1. The prevalence of AR was 39.80% (1,892/4,754), which is higher than reported in other major cities in Inner Mongolia.

3.1.2 AR distribution in the population

The prevalence of AR was 43.06% (1,077/2,501) in males and 2,253 (815/2,253) in females. There were significant differences in AR prevalence between males and females ($X^2 = 23.476$, $P < 0.05$). The prevalence of AR was 38.22% (1,524/3,988) in Han

nationality and 48.04% (368/766) in minority nationality, with a significant difference observed between these groups ($X^2 = 25.900$, $P < 0.05$). The mean age of AR patients was 9.19 ± 1.811, while that of non-AR patients was 9.23 ± 1.860, with no significant difference ($X^2 = 9.127$, $P > 0.05$). Gender and nationality significantly affect AR prevalence, but age does not (Table 2).

3.1.3 AR general situation correlation analysis

The prevalence of food allergy was 34.50% (1,405/4,072), showing a significant correlation between food allergy and AR prevalence, ($X^2 = 332.048$, $P < 0.05$). Drug allergy prevalence was 36.55% (1,519/4,156), also significantly correlated with AR prevalence, ($X^2 = 145.521$, $P < 0.05$). The prevalence of AR among those with frequent antibiotic use was 38.95% (634/1,276), with a significant correlation between antibiotic use frequency and AR prevalence ($X^2 = 71.181$, $P < 0.05$). Dietary habits revealed that 32.86% (69/32.86) of patients with AR were vegetarian, 39.67% (1,653/4,167) consumed both meat and vegetables, and 45.09% (170/377) had a meat-based diet. A significant correlation was found between dietary habits and AR prevalence ($X^2 = 8.663$, $P < 0.05$), with a higher prevalence in meat-based diets. Among these variables, food allergy had the strongest association with AR prevalence (Table 2).

The prevalence of AR in relation to breastfeeding duration was 35.77% (176/492) for <6 months, 40.74% (264/648) for 0–6 months, and 40.18% (1,452/3,614) for >6 months. There was no significant difference in the prevalence of AR with different duration of breastfeeding ($X^2 = 3.785$, $P > 0.05$). For different birth modes, the prevalence of AR was 39.15% (1,128/2,881) for vaginal deliveries and 40.79% (764/1,873) for C-sections, with no significant correlation ($X^2 = 1.270$, $P > 0.05$). AR prevalence was 62.38% (373/598) in smoking-exposed environments compared to 40.80% (900/2,207) in non-exposed environments, with no significant correlation ($X^2 = 1.656$, $P > 0.05$). Breastfeeding time, birth mode, and exposure to smoking were not significant independent risk factors for AR (Table 2).

TABLE 2 Demographic data.

Variable	Total cases	AR cases (%)	X^2	P
Sex			23.476	<0.05
Male	2,501	1,077 (43.06)		
Female	2,253	815 (36.17)		
Nation			25.900	<0.05
The Han nationality	3,988	1,524 (38.22)		
Minority nationality	766	368 (48.04)		
Age				
Average age/years	9.21 ± 1.841	9.23 ± 1.860	9.127	0.164
6	318	201 (63.21)		
7	785	464 (59.11)		
8	652	399 (61.20)		
9	862	497 (57.66)		
10	772	447 (57.90)		
11	678	427 (62.98)		
12	687	427 (62.15)		
Duration of breastfeeding			3.785	0.15
0	492	176 (35.77)		
0–6 month	648	264 (40.74)		
>6 month	3,614	1,452 (40.18)		
Birth			1.270	0.26
Eutocia	2,881	1,128 (39.15)		
Caesarean section	1,873	764 (40.79)		
Food allergy			332.048	<0.05
No	4,072	1,405 (34.50)		
Yes	682	487 (71.41)		
Drug allergy			145.521	<0.05
No	4,156	1,519 (36.55)		
Yes	598	373 (62.38)		
Antibiotic use			71.181	<0.05
No	3,478	1,258 (36.17)		
Frequently	1,276	634 (49.69)		
Exposure to smoking			1.656	0.20
No	2,207	900 (40.80)		
Yes	2,547	992 (38.95)		
Eating habit			8.663	<0.05
Vegetarianism	210	69 (32.86)		
Balanced diet	4,167	1,653 (39.67)		
Meat-Based	377	170 (45.09)		
Subzone			390.001	<0.05
City center	2,312	1,163 (50.30)		
Rural area	750	103 (13.73)		
Pasturing area	445	93 (20.90)		
Other	1,247	533 (42.74)		

AR, allergic rhinitis.

3.1.4 AR region distribution characteristics

The prevalence of AR was 50.30% (1,163/2,312) in urban areas, 13.73% (103/750) in agricultural areas, 20.90% (93/445) in pastoral areas, and 42.74% (533/1,247) in other areas. AR prevalence was significantly higher in urban areas compared to other regions ($P < 0.05$). Among the four regions, urban areas had the highest impact on AR prevalence (Table 2).

3.2 Analysis of risk factors for AR

3.2.1 Single factor logistics regression analysis

Logistic regression analysis was performed on 11 possible related risk factors such as gender, ethnicity, age, breastfeeding time, and the mode of delivery. Male (OR = 1.334, 95% CI = 1.187–1.500), ethnic minority (OR = 1.459, 95% CI = 1.280–1.746), food allergy (OR = 4.747, 95% CI = 3.967–5.666), drug allergy (OR = 2.878, 95% CI = 2.411–3.435), frequent use of antibiotics (OR = 1.743, 95% CI = 1.531–1.948), 50/50 meat and vegetable diet (OR = 1.344, 95% CI = 1.001–1.804) and meat diet (OR = 1.678, 95% CI = 1.1.180–2.378), urban area (OR = 6.358, 95% CI = 5.085–7.949) and pastoral area (OR = 1.660, 95% CI = 1.219–2.260) were potential risk factors for AR ($P < 0.05$). No significant correlation was noted between age, birth mode, breastfeeding time and exposure to a smoking environment and AR ($P > 0.05$) (Table 3).

3.2.2 Multi-factor logistics regression analysis

Multivariate Logistic regression analysis was conducted to evaluate potential risk factors for AR while controlling for confounding variables. Model I was adjusted for gender, ethnicity,

and age. Model II, which was based on Model I, was further adjusted for breastfeeding duration, mode of delivery, history of food and drug allergies, antibiotic use, environmental exposure to smoking, dietary habits, and geographic zoning. The statistical results including OR, 95% CI, and *P*-value were analyzed.

TABLE 3 Univariate logistic regression analysis of AR in children.

Variable	*OR*	95% CI		*P*
		Lower	Upper	
Sex, male	1.334	1.187	1.500	<0.05
Nation, minority nationality	1.495	1.280	1.746	<0.05
Age				
6	1			0.31
7	1.185	0.902	1.556	0.22
8	1.125	0.849	1.490	0.41
9	1.237	0.945	1.619	0.12
10	1.247	0.949	1.639	0.11
11	1.024	0.773	1.355	0.87
12	1.055	0.798	1.395	0.71
Duration of breastfeeding				
0		1		0.15
0–6 month	1.234	0.969	1.572	0.08
>6 month	1.206	0.991	1.457	0.06
Birth, Caesarean section	1.071	0.951	1.206	0.26
Food allergy, Yes	4.741	3.967	5.666	<0.05
Drug allergy, Yes	2.878	2.411	3.435	<0.05
Antibiotic use, Frequently	1.743	1.531	1.984	<0.05
Exposure to smoking, Yes	0.198	0.825	1.041	0.93
Eating habit				
Vegetarianism		1		<0.05
Balanced diet	1.344	1.001	1.804	<0.05
Meat-based	1.678	1.180	2.387	<0.05
Subzone				
Rural area		1		<0.05
City center	6.358	5.085	7.949	<0.05
Pasturing area	1.660	1.219	2.260	<0.05
Other	4.689	3.702	50,939	<0.05

The results indicated that the prevalence of AR in males was 1.349 times higher than in females (OR = 1.394, 95% CI = 1.184–1.537, $P < 0.05$). The prevalence was 1.487 times higher in ethnic minorities compared to Han individuals (OR = 1.487, 95% CI = 1.238–1.1.786, $P < 0.05$). Patients with a positive history of food allergies had a prevalence of AR 3.728 times higher than those without (OR = 3.728, 95% CI = 3.049–4.558, $P < 0.05$). A positive history of drug allergies was associated with a 2.093-fold increase in AR (OR = 2.093, 95% CI = 1.693–2.588, $P < 0.05$). The prevalence of AR increased 1.817 times in patients with frequent antibiotic use (OR = 1.817, 95% CI = 1.566–2.108, $P < 0.05$). Compared to rural areas, the prevalence of AR increased 7.292 times in urban areas (OR = 7.292, 95% CI = 5.707–9.317, $P < 0.05$), 1.673 times in pastoral areas (OR = 1.673, 95% CI = 1.199–2.334, $P < 0.05$), and 4.865 times in other areas (OR = 4.865, 95% CI = 3.766–6.286, $P < 0.05$). Therefore, being male, belonging to an ethnic minority, having food or drug allergies, residing in urban or pastoral areas, and exposure to other specific environmental factors were identified as significant independent risk factors ($P < 0.05$), (Table 4).

Regarding dietary habits, compared to a vegetarian diet, balanced diets (OR = 1.147, 95% CI = 0.819–1.607) and meat-based diets (OR = 1.346, 95% CI = 0.92–2.010) did not show statistically significant effects on AR prevalence. Hence dietary habits were not considered independent risk factors for AR (Table 4).

3.3 Comparison of AR negative, total samples and AR positive three types combined with other allergic diseases

The non-AR group was a sample of children with a negative diagnosis of AR and the presence of other allergic diseases. Specifically: Asthma 4.05% (116/2,862), UACS 14.50% (415/

TABLE 4 Multivariate logistic regression analysis of AR in children.

Influencing factor	Crude OR (95% CI)	Adjust OR (95% CI)	
		Model I	Model II
Sex, male	1.334 (1.187–1.500)*	1.350 (1.185–1.537)*	1.349 (1.184–1.537)*
Nation, minority nationality	1.495 (1.280–1.746)*	1.490 (1.240–1.789)*	1.487 (1.238–1.786)*
Food allergy, Yes	4.741 (3.967–5.666)*	3.726 (3.049–4.554)*	3.728 (3.049–4.558)*
Drug allergy, Yes	2.878 (2.411–3.435)*	2.090 (1.691–2.584)*	2.093 (1.693–2.588)*
Antibiotic use, Frequently	1.734 (1.531–1.984)*	1.815 (1.566–2.105)*	1.817 (1.566–2.108)*
Eating habit			
Vegetarianism	1	1	1
Balanced diet	1.334 (1.001–1.804)*	1.151 (0.822–1.611)	1.147 (0.819–1.607)
Meat-based	1.678 (1.180–2.387)*	1.349 (0.904–2.012)	1.346 (0.902–2.010)
Subzone			
Rural area	1	1	1
City center	6.358 (5.085–7.949)*	7.337 (5.757–9.352)*	7.292 (5.707–9.317)*
Pasturing area	1.660 (1.219–2.260)*	1.677 (1.202–2.339)*	1.673 (1.199–2.334)*
Other	4.869 (3.702–5.939)*	4.876 (3.776–6.298)*	4.865 (3.766–6.286)*

Model I: Adjusted for gender, ethnicity, and age.
Model II: On the basis of model I, we adjusted for breastfeeding duration, mode of delivery, history of food allergy, history of drug allergy, antibiotic use, exposure to smoking environment, dietary habits, and zoning.
*$P < 0.05$.

2,862), SOM 2.80% (80/2,862), OSAHS 19.88% (569/2,862), AD 11.76% (337/2,862), AC 6.77% (191/2,862). In the Totality group, there were other instances of allergic disease in the 4,754 valid questionnaires. Asthma 16.70% (797/4,754), UACS 34.33% (1,632/4,754), SOM 10.60% (504/4,754), OSAHS 31.70% (1,507/4,754), AD 26.48% (1,259/4,754), AC 37.93% (1,803/4,754). AR group refers to AR positive at the same time as other allergic diseases. Specifically: Asthma 35.99% (681/1,892), UACS 64.32% (1,217/1,892), SOM 22.41% (424/1,892), OSAHS 49.58% (938/1,892), AD 48.72% (922/1,892), AC 85.20% (1,612/1,892).

The prevalence of concomitant allergic diseases was significantly higher among patients with AR compared to healthy children and the overall sample ($P < 0.05$). Allergic conjunctivitis was the most common comorbidity, affecting 85.20% of patients with AR, while secretory otitis media was less common (Table 5). Compared with the above three groups, the non-AR group exhibited the lowest prevalence of other allergic diseases, with a significant difference from the AR groups. Patients with AR were more likely to suffer from additional allergic diseases (Figure 1).

3.4 Classification of AR patients

Among the 1,892 patients, 43.29% had intermittent AR, while 56.71% had persistent AR. In terms of severity, 51.22% of patients had mild AR, and 48.78% had moderate to severe AR. Persistent AR was more prevalent, with more than half of the patients experiencing severe symptoms. Thus, AR was more severe in children aged 6–12 years in Bayannur City (Table 6).

TABLE 5 Children with other allergic diseases.

Item	Totality	non-AR	AR	X^2	P
Asthma	797 (16.7)	116 (4.05)	681 (35.99)	832.742	
UACS	1,632 (34.33)	415 (14.50)	1,217 (64.32)	1,254.177	
SOM	504 (10.60)	80 (2.80)	424 (22.41)	462.384	<0.05
OSAHS	1,507 (31.70)	569 (19.88)	938 (49.58)	463.927	
AD	1,259 (26.48)	337 (11.76)	922 (48.72)	799.023	
AC	1,803 (37.93)	191 (6.67)	1,612 (85.20)	2,862.00	

UACS, upper airway cough syndrome; SOM, secretory otitis media; OSAHS, obstructive sleep apnea hypopnea syndrome; AD, allergic dermatitis; AC, allergic conjunctivitis.

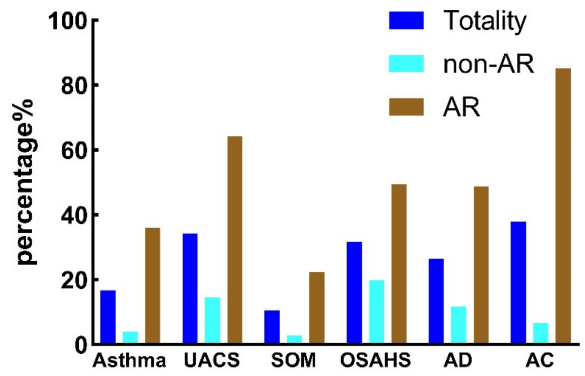

FIGURE 1
Comparison of samples from different groups with other complications.

TABLE 6 Classification of AR in children.

Item	Number of cases	X^2	P
Classification by time		3,362.590	<0.05
Intermittent AR	819 (43.29)		
Persistent AR	1,073 (56.71)		
Classified according to severity		3,294.753	<0.05
Mild AR	969 (51.21)		
Moderate to severe AR	923 (48.78)		

AR, allergic rhinitis.

3.5 Prevalence of AR in children in urban, agricultural and pastoral areas

Among 2,312 valid questionnaires, 1,163 were AR-positive, yielding a prevalence rate of 50.30%. Seasonal distribution showed that AR prevalence was 15.48% (180/1,163) from March to May, 54.00% (628/1,163) from June to August, 22.96% (267/1,163) from September to November, and 33.28% (33/1,163) from December to February. A total of 4.73% (55/1,163) of cases did not exhibit clear seasonal patterns. Of the 750 valid questionnaires in rural areas, 103 were AR-positive, giving a prevalence rate of 13.73%. Seasonal distribution in rural areas was 29.13% (30/103) from March to May, 28.16% (29/103) from June to August, 14.56% (15/103) from September to November, and 4.85% (5/103) from December to February, 23.30% (24/103) of cases showing no obvious seasonality. Among 445 valid questionnaires in pastoral areas, 93 were AR-positive, resulting in a prevalence rate of 20.90%. Seasonal distribution in pastoral areas was 13.98% (13/93) from March to May, 46.24% (43/93) from June to August, 21.51% (20/93) from September to November, and 5.38% (5/93) from December to February, with 12.90% (12/93) showing no clear seasonal trend. The prevalence of AR varied significantly across different months in urban areas (Table 7).

3.6 Comparison of AR in urban, agricultural and pastoral areas in different seasons

The prevalence of AR in urban areas was highest during the summer months from June to August, showing the greatest seasonal variation compared to agricultural and pastoral areas. The epidemic characteristics of AR in pastoral areas and urban areas were similar, but urban areas were more typical of seasonal influences. In contrast, the prevalence rate of AR in rural areas changed slightly in one year. However, the prevalence of AR was highest in rural areas without seasonal effects (Figure 2).

4 Discussion

AR is a prevalent chronic disease in children, placing a significant burden on families and posing challenges for

TABLE 7 Comparison of AR among children in urban, agricultural and pastoral areas in different seasons.

Variable	City area AR positive (n = 1,163)		Rural area AR positive (n = 1,163)		Pasturing area AR positive (n = 1,163)	
	(n)	(%)	(n)	(%)	(n)	(%)
3–5 month	180	15.48	30	29.13	13	13.98
6–8 month	628	54.00	29	28.16	43	46.24
9–11 month	267	22.96	15	14.56	20	21.51
12–2 month	33	2.84	5	4.85	5	5.38
No concentrated onset period	55	4.73	24	23.30	12	12.90

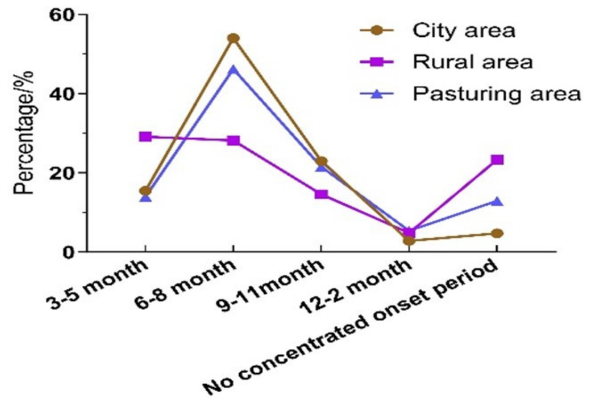

FIGURE 2
The prevalence of AR in different regions at different times.

healthcare and preventive sectors. The first phase of the ISAAC survey (14), which has been validated and used worldwide, surveyed 700,000 children across 156 centers in 56 countries and reported that developed countries had the highest prevalence of AR among the surveyed countries. The ISAAC Phase 3 study further reported an increase in AR prevalence globally, ranging from 0.8% and 39.7%, affecting both developed and developing countries alike (15). In Europe, the self-reported AR prevalence in the city of Zagreb, Croatia, was 35.70% (16), and 36.2% in Budapest, Hungary (17). In the Middle East, the self-reported prevalence of AR was 39.90% among 851 people in Saudi Arabia (18). The prevalence of AR in children aged 6–18 years in Turkey is 43.20% (19). In Asia, a South Korean study of 12,919 children aged 6–18 revealed a 27.60% increase in AR prevalence over a decade (20), while recent cross-sectional studies in Japan indicate rising rates of nasal conjunctivitis (21). In China, large-scale surveys from 2005 to 2011 across 11 cities revealed significant increases in self-reported AR among adults in eight of these cities (22). Other studies have also reported the regional prevalence of AR in different regions of China. For example, the prevalence of AR among children in Taipei City (23), Xiamen City (24), Zaoyang City (25), and Xilingol League grassland area of Inner Mongolia (26) were 42.80%, 13.70%, 24.31%, and 39.96%, respectively. Given the global rise in AR prevalence, detailed data for Bayannur City are limited. Therefore, this study addressed this gap by conducting a cross-sectional survey of 4,754 children aged 6–12 years in Bayannur City using an electronic questionnaire. The self-reported prevalence rate of AR in children in Bayannur City was 39.80%, which is notably high compared to some developed regions in Europe and Asia, and higher compared to other cities in China.

AR is recognized as the most common allergic disease worldwide, often attributed to a combination of genetic predisposition and environmental factors (27). It involves the abnormal activation of NOD-like receptor thermal protein domain associated protein 3 (NLRP3) and an imbalance in the distribution of CD4-positive cells (Th1), particularly the overexpression of Th2 cells, leading to AR development (28). Our survey, which considered various AR risk factors, revealed through multivariate regression analysis that being male, belonging to an ethnic minority, having a history of food or drug allergies, frequent antibiotic use, and long-term residence are independent risk factors for AR in Bayannur City. A national study in South Korea suggests that sex differences in hormone production and BMI may influence the risk of allergic diseases (29). The higher prevalence of AR among male children in our city might be attributed to such factors. Ethnic minorities also exhibit a higher prevalence of AR. Although there is limited research on racial and ethnic differences in AR, studies by Kim, Yuhree et al. (30) have indicated that individuals of certain non-white races, such as Black and Hispanic populations, experience a higher incidence and persistence of allergic diseases, along with a lower quality of life compared to non-Hispanic whites. Modi et al. (31) also reported significant differences in the effectiveness of subcutaneous allergen immunotherapy (SCIT) across various racial and ethnic groups. A 2010 report highlighted substantial racial and ethnic disparities in health status in the United States, noting that certain diseases are more prevalent in specific populations (32). Therefore, we speculated that these disparities may be due to differences in genetic responses to allergens among ethnic minority individuals compared to Han children, though such studies are lacking. Children with a history of food and drug allergies exhibit a higher prevalence of AR, likely due to heightened sensitivity. The association between frequent antibiotic use and increased AR prevalence is attributed to changes in gastrointestinal flora. Reports suggest that early antibiotic use correlates positively with AR prevalence in children (33).

Additionally, some studies suggest that dietary patterns can influence AR risk. For instance, high vegetable intake and low meat consumption may reduce the risk of AR by decreasing n-6 fatty acid intake (34). Additionally, a study in the United States

found that differences in birth patterns between vaginal and cesarean deliveries lead to abnormal microbial colonization or ecological disorders in infancy, potentially affecting allergic disease development (35). Breast milk contains immunoglobulin (Igs), cytokines, and dietary antigens that may regulate immunity. Although direct evidence is lacking, numerous studies have associated breastfeeding duration with allergic disease prevalence in children (36). Research in India has indicated that common indoor air pollutants, such as tobacco smoke, organic compounds from new furniture, and formaldehyde, may increase AR risk in children (37). However, our study found that dietary habits, breastfeeding duration, birth mode, and exposure to smoking are not independent risk factors for AR among children aged 6–12 years in Bayannur City. This suggests that while the independent risk factors for AR are consistent with findings from other regions, the high prevalence observed in Bayannur City may be attributable to unique environmental factors specific to the area.

As previously mentioned, Bayannur City is situated in the grassland region of the northern border of China, between 40°13′–42°28′ north latitude, near the border with Mongolia. Over the past 60 years, air humidity in this region has declined steadily (9). This dry climate may contribute to the high prevalence of AR. Additionally, extensive cultivation of artemisia plants in Bayannur City (38). plays a significant role, as allergen pollen is a major allergen in northern China and contributes substantially to AR prevalence. Epidemiological studies indicate that outdoor air pollution, driven by increased fossil fuel combustion, comprises airway mucous membrane permeability, enhancing allergen penetration and allergic reactions (39). Research conducted in Germany on over 85% of the population revealed that higher degrees of urbanization correlate with increased incidence of respiratory allergic diseases (40). Outdoor air pollutants, including NO_2, SO2, and particulate matter, are known to elevate AR prevalence in urban areas (41). Moreover, low humidity and water (through hydration) contribute to pollen rupture, which, combined with wind dispersion, increases the concentration of airborne pollen and its allergenic effects (42). Recent industrialization and urbanization in Bayannur City have led to a decline in air quality. According to the Bayannur City Statistics Bureau, industrial production relies predominately on fossil fuels, which constitute 95.30% of energy sources. Therefore, we hypothesized that these environmental factors contribute to the high prevalence of AR among children in Bayannur City. While congenital genetic factors cannot be altered, adjusting children's living conditions and environments could potentially reduce the occurrence of AR.

Studies show that the prevalence of allergic diseases in urban children was significantly higher than that in rural children. Rural living may offer some protection against AR, respiratory allergies, and atopic sensitization (10). Japanese research has also suggested that the height of residence impacts AR prevalence, with bungalows providing a protective effect compared to buildings with 2–5 floors in urban areas (43).This city is situated in the Hetao Plain region of China, characterized by its flourishing agriculture and animal husbandry. Farmers and herdsmen gradually form a breeding state of double baling of grass and livestock and construction of net fences, and their living environment is different from that of urban areas (44). According to the seventh national census, the city is home to over 110,000 ethnic minorities, including 85,000 Mongolians. This concentration of livestock production and pastoral area contributes to a unique environment. The medical services available to residents in Bayannur's farming and pastoral areas are relatively underdeveloped, with limited health education and resources. This lack of access to medical care and education is reflective of a broader global issue, where disparities exist between urban and rural health resources. Based on the characteristics of the natural environment, the distribution of population characteristics, and the low resources of medical and health care in this region, we further studied the prevalence of AR among children aged 6–12 years in urban, agricultural, and pastoral areas. Our study found that the prevalence of AR among children aged 6–12 years in urban areas was higher compared to those in pastoral and agricultural areas. This observation aligns with the understanding that rapid urbanization contributes to increased AR prevalence. However, our findings also revealed a higher prevalence of AR in pastoral areas compared to rural areas, thereby contributing to the global data on AR prevalence in rural and pastoral settings.

Leynaert et al. have shown a positive correlation between the severity and duration of AR and the prevalence of asthma (45, 46). Additionally, Japanese researchers have identified olfactory dysfunction in children with moderate to severe AR (47). Chronic AR patients are also at a higher risk for depression, bipolar disorder, and increased suicidal tendencies (4). Antonella Gambadauro et al. found that AR is linked not only to attention deficit hyperactivity disorder (ADHD) but also that patients with severe AR combined with ADHD exhibit better compliance with AR treatment than those with mild AR. This compliance is inversely correlated with inattention symptoms in children with ADHD (48). This compliance is inversely correlated with inattention symptoms in children with ADHD. Thus, addressing emotional and behavioral aspects is crucial in managing AR effectively, particularly for the 48.78% of children in our study with server AR.

The abnormal activation of NLRP3 contributes to AR and other type 2 inflammatory conditions, including asthma, atopic dermatitis, and various respiratory, gastrointestinal, and skin diseases (49, 50). Consequently, AR patients are often accompanied by other allergy symptoms. Reports indicate that 19%–38% of patients with AR may have asthma, and among patients with both diseases, more than 75% develop the secondary condition within two years if not concurrently present (51). Furthermore, AR is recognized as a significant risk factor for otitis media effusion, alongside bacterial infection and eustachian tube obstruction (52). In our study, only 14.709% of children with AR in Bayannur City did not have any concurrent allergic conditions, aligning with global trends. Therefore, parents and medical personnel need to monitor the presence of other allergic comorbidities while actively preventing and treating AR.

To address the high incidence of AR among children in Bayannur City, several preventive and medical recommendations

are proposed. Bayannur City should consider vegetation cover instead of wormwood to reduce the main allergens. Concurrently, efforts to transition from fossil fuels to cleaner energy sources could help reduce air pollution. Moreover, public health campaigns should emphasize preventive measures such as wearing masks and goggles to minimize allergen exposure, promoting regular physical exercise and a healthy diet, and reducing the early and frequent use of antibiotics to improve immunity. Children and parents should also be encouraged to seek medical attention when AR or accompanying symptoms are observed initially to avoid worsening symptoms. For AR treatment, current practices in Bayannur City primarily involve medication and surgery. However, the introduction of specific immunotherapy and desensitization therapy should be pursued to help patients build tolerance to allergens and alleviate symptoms. Future advancements might include gene modification therapies to address hypersensitivity comprehensively. These strategies could serve as a model for other areas with similar medical and environmental conditions.

It should be noted that there are limitations to this study. This study is a large-scale epidemiological survey, and the sample size was expanded to minimize sampling error and potential selection bias. The conclusions drawn are based on self-reported data, which, while extensive, could be enhanced by incorporating physical examinations by specialists and laboratory examinations for allergen detection. These additional measures would improve the accuracy of the prevalence data.

This is an area for future research to obtain more precise data on AR prevalence among children in this region.

To mitigate the occurrence of deviation, we also implemented relevant measures. First, the sample size was increased, and random sampling was employed. All team members underwent professional training before distributing questionnaires. They emphasized the anonymity, lack of innovation, and importance of the questionnaire when they visited schools in person. The contents of the questionnaire were explained in detail, and support from the municipal Education Bureau was secured to bolster the trust and attention of children and parents. Second, the questionnaire included a verification question: "In the past year, have you or your child been diagnosed with allergic rhinitis by a healthcare provider?". This question helped validate some of the responses. Finally, after completing the report, the team members contacted 10% of the parents by telephone to verify the accuracy of the data. The questionnaire results were verified against medical records from local hospitals to minimize errors related to questionnaire completion.

5 Conclusions

Not only in Inner Mongolia or China, children aged 6–12 in Bayannur City have a high prevalence of AR in the world. And nearly half of the symptoms were severe enough to interfere with daily life. Prevention departments and medical and health institutions should strengthen the prevention and treatment of AR in the region. In addition to genetic factors, we preliminarily speculate that the most influential factor of AR in this region is the natural environment. Therefore, we call on the government departments to target the reduction of wormwood in the future development, while reducing the use of fossil fuels and improving air quality. This study is the first large-scale epidemiological investigation on children's AR in Bayannur City, and we hope that the data from this study can provide a data basis for the epidemiology of children's AR in China. At the same time, we also hope that this study will increase attention to the current prevalence of childhood AR in grassland regions around the world.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/Supplementary Material.

Author contributions

XY: Investigation, Software, Visualization, Writing – original draft. LL: Conceptualization, Funding acquisition, Investigation, Resources, Writing – review & editing.

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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.

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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.2024.1422323/full#supplementary-material

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Efficacy of omalizumab after discontinuation: a retrospective single-center observational study in children with severe asthma

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Introduction: Several trials documented safety and efficacy of omalizumab, but there are a few data about its effects after discontinuation. This study aims to evaluate the maintenance of efficacy of omalizumab in pediatric asthmatic patients one year after its suspension.
Methods: A retrospective analysis was conducted on 17 subjects aged 6–18 years, divided into two groups: Group A (9 patients) who discontinued omalizumab after 18 months, and Group B (8 patients) who continued the therapy. Data on respiratory function (FEV1%), the number of exacerbations, need for hospitalizations, use of oral corticosteroids, and Asthma Control Test (ACT) scores were collected and analyzed at three time points: baseline (T0), after 18 months of treatment (T1), and 36 months (T2).
Results: In Group A, significant differences were observed between T0 and T1, and T1 and T2, in FEV1% values, the number of exacerbations, the need for oral corticosteroids, and ACT scores. Group B showed significant differences in these parameters over time, with a notable reduction in exacerbations and improvement in ACT scores. The comparative analysis revealed that Group B had a higher number of exacerbations compared to Group A at T0 and greater use of oral cortico-steroids at T1. By T2, Group A had a higher ACT score than Group B at T0, whereas Group B showed higher ACT scores at T2 compared to Group A.
Discussion: The study confirmed the efficacy and safety of omalizumab, with its benefits persisting one year after treatment discontinuation in terms of lung function, reduction in exacerbations, decreased need for oral corticosteroids, and improved quality of life. Further research is necessary.

KEYWORDS

children, discontinuation, omalizumab, persistence of efficacy, severe asthma

1 Introduction

Omalizumab is a humanized recombinant monoclonal antibody approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) as add-on treatment for patients ≥6 years old with moderate-to-severe persistent allergic asthma and unsatisfactory response to inhaled corticosteroid (ICS), high serum immunoglobulin E

(IgE) levels (30–1,500 IU/ml) and positive specific serum IgE to at least one aeroallergen (1–3). Furthermore, omalizumab is recommended for patients aged 12 years and above with chronic spontaneous urticaria (CSU), as well as for adults (aged 18 years and above) with nasal polyps (1–3). In addition, several studies are ongoing involving omalizumab as an add-on treatment to oral immunotherapy (OIT) or as monotherapy in food allergy (FA) (4). Indeed, on February 16, 2024, the FDA approved omalizumab for the reduction of allergic reactions, including anaphylaxis, that may occur with an accidental exposure to one or more foods in adults and children aged 1 year and older with FA (5).

Omalizumab binds to the Cϵ3 domain of the Fc region of circulating IgE, forming inert complexes that do not activate the complement system, thereby reducing serum IgE levels. It also inhibits the interaction between IgE and their high-affinity (FcϵRI) and low-affinity (FcϵRII/CD23) receptors, which are present on the membranes of mast cells, basophils, eosinophils, neutrophils, dendritic cells, and lymphocytes. This reduces the expression of these receptors and inhibits the release of inflammatory mediators (6–8). Additionally, omalizumab acts on IgE bound to B-cell receptors (BCRs). The synthesis of IgE is regulated by the interaction between the IgE-BCR complex and CD21 on B cells, which are induced to synthesize IgE by soluble CD23 (sCD23). The binding of omalizumab to the IgE-BCR complex prevents IgE synthesis and induces cellular apoptosis (9). Finally, omalizumab can enhance the antiviral response in patients with allergic asthma, particularly those with high serum IgE levels who are more susceptible to viral-induced exacerbations, especially from respiratory viruses like Rhinovirus and Influenza virus (10, 11). This effect is attributed to its action on plasmacytoid dendritic cells, which typically produce interferon (IFN), particularly IFN-α, following interactions between virions and Toll-Like Receptors (TLRs) expressed on their plasma membrane (12). Compared to healthy individuals, patients with allergic asthma exhibit increased expression of FcϵRI on dendritic cells and elevated IgE levels, which correlates with a significant down-regulation in TLRs expression and a reduced production of IFN-α in response to viral infections (12). Therefore, treatment with omalizumab also improves the TLR-mediated antiviral response, enhancing IFN-α production by dendritic cells (12). The drug is administered as a subcutaneous injection. In asthmatic subjects, the dosage and frequency of administration are personalized for each patient, established by a nomogram based on the patient's weight (kg) and baseline total serum IgE levels (13, 14).

Several studies in the literature documented the efficacy and safety of omalizumab. Specifically, omalizumab showed its efficacy after 12–16 weeks of treatment improving the number of exacerbations and hospitalizations, the need for rescue therapy and the quality of life (QoL) of patients and their caregivers (15–20).

Despite the clear benefits of omalizumab in the management of severe asthma, nowadays, stopping therapy is still debatable, as well as the criteria for safely suspending treatment are not well-defined. Factors such as stable lung function, reduced exacerbation frequency, and the ability to maintain asthma control were considered, but standardized guidelines are lacking. The decision is further complicated by the limited data available in current literature regarding the persistence of omalizumab beneficial effects after discontinuation among adult and, particularly, pediatric patients (18, 21–28).

The aim of the following study was to assess the sustained efficacy of omalizumab therapy in pediatric patients with severe asthma one year after treatment discontinuation. Specifically, our evaluation focused on several key indicators of asthma control, including Forced Expiratory Volume in the 1st second (FEV1%), number of annual exacerbations, need for hospitalization and oral corticosteroid (OCS) use, and QoL.

2 Materials and methods

2.1 Study design

This study was a retrospective, single-center, observational analysis focusing on pediatric patients with severe asthma. We collected a range of demographic and clinical data, including FEV1% values, number of exacerbations, data about need for hospitalization and OCS, scores from the Asthma Control Test (ACT).

2.2 Subjects and eligibility criteria

The study population consisted of pediatric patients of both genders, aged 6–18 years old, affected by severe asthma. The following inclusion criteria were adopted: age major than 6 years old; confirmed diagnosis of severe asthma in agreement with the current guidelines (1, 29); therapy with omalizumab administered for at least 18 months; discontinuation of omalizumab treatment for at least one year. Patients with good control of the disease, in terms of FEV1% (≥90%), number of exacerbations (<3/year), need for hospitalization (0/year), need for OCS (0/year) and ACT score (≥20), were candidates for discontinuing treatment.

2.3 Data analysis

The data were analysed using Microsoft Excel version 2023 and the Statistical Package for Social Sciences (SPSS) software version 22.0. Data were considered statistically significant with a p value <.05. The continuous variables were categorized using descriptive statistics and expressed as mean ± standard deviation (SD). The ordinary variables were expressed as percentage. Fisher's exact test or the Pearson Chi-squared test (Pearson coefficient of correlation) for qualitative variables and the paired t-test for continuous variables were used.

2.4 Ethics

All study participants, along with their parents, received comprehensive information and provided written informed consent

as part of the study protocol. The study protocol was designed and conducted in compliance with Good Clinical Practice (GCP) standards and adhered to the ethical principles outlined in the Declaration of Helsinki with successive amendments. The Local Ethics Committee confirmed that no ethical approval was required for this retrospective observational study.

3 Results

17 children and adolescents affected by severe asthma and treated with omalizumab were included in the final analysis. Based on the suspension of omalizumab, the enrolled population was stratified into two groups: Group A, including 9/17 (53%) patients who stopped omalizumab; Group B, including 8/17 (47%) patients who continued the treatment with omalizumab. The clinical and demographic features of the enrolled population are shown in Table 1.

Regarding Group A, 6/9 (67%) were male and 3/9 (33%) were female. 8/9 (89%) were Caucasian and 1/9 (11%) was Asian. 8/9 (89%) presented comorbidities: 6/9 (67%) allergic rhinitis (AR), 2/9 (22%) atopic dermatitis (AD) and 1/9 (11%) eosinophilic esophagitis (EoE). The mean age at the diagnosis of asthma was 7.5 ± 2.9 years old. The mean age at the start of omalizumab was 10.6 ± 3.5 years old, with a mean duration of therapy of 2.1 ± 0.9 years, and a mean age at the treatment discontinuation of 12.5 ± 3.8 years old. None of the patients developed adverse drug reactions (ADRs) due to omalizumab. All the patients continued therapy with ICS/Long-Acting Beta2-Agonist (LABA) during and post-treatment with omalizumab. 8/9 (89%) stopped omalizumab treatment according to patient and/or caregivers request, 1/9 (11%) suspended omalizumab for moving abroad. Before the suspension, the asthma control of the disease was evaluated according to the previously reported criteria. Regarding Group B, 4/8 (50%) were male and 4/8 (50%) were female. 8/8 (100%) were Caucasian. 8/8 (100%) presented comorbidities: 7/8 (87.5%) AR, 2/8 (25%) FA, 1/8 (12.5%) CSU and Hashimoto thyroiditis (HT) and 1/8 (12.5%) polycystic ovary syndrome (PCOS). The mean age at the diagnosis of asthma was 6.8 ± 2.0 years old, with a mean age at the start of the treatment with omalizumab of 11.0 ± 3.6 years old. 1/8 (12.5%) patient developed mild and transient headache because of omalizumab administration. All the patients continued therapy with ICS/LABA during treatment with omalizumab. No monoclonal antibodies were administered before omalizumab in both groups. The dosage and frequency of omalizumab administration were established by the nomogram, as previously stated.

Regarding Group A, the statistical analysis was conducted at baseline (T0), at 18 months of treatment (T1), considered a common reference for mid-treatment assessment, and one year after the suspension of omalizumab (T2). The results are reported in Table 2. The following changes were reported: in FEV1% values T0: 87.4 ± 7.8 vs. T1: 104.6 ± 13.8 ($p = .005$) vs. T2: 119.2 ± 7.1 ($p = .012$); in the number of exacerbations: T0: 5.9 ± 2.3 vs. T1: 3.5 ± 2.1 ($p = .036$) vs. T2: 1.8 ± 0.7 ($p = .025$); in the number of patients who needed hospitalization: T0: 67% vs. T1: 0% ($p = .001$) vs. T2: 11% ($p = .332$); in the number of patients who needed OCS: T0: 100% vs. T1: 11% ($p = .000$) vs. T2: 56% ($p = .048$); and in ACT score: T0: 14 ± 1.6 vs. T1: 21.7 ± 2.6 ($p < .000$) vs. T2: 18.2 ± 5.5 ($p = .013$).

Regarding Group B, the statistical analysis was conducted at baseline (T0), at 18 months (T1) and at 36 months of treatment (T2). The results are reported in Table 3. The following changes were reported: in FEV1% values T0: 84.1 ± 10.6 vs. T1: 97.5 ± 12.7 ($p = .044$) vs. T2: 112.6 ± 13.3 ($p = .035$); in the number of exacerbations: T0: 9.1 ± 2.7 vs. T1: 4.7 ± 0.7 ($p = .000$) vs. T2: 2.0 ± 0.7 ($p < .000$); in the number of patients who needed hospitalization: T0: 87.5% vs. T1: 0% ($p = .008$) vs. T2: 11% ($p = .148$); in the number of patients who needed OCS: T0: 100% vs. T1: 62.5% ($p = .059$) vs. T2: 12.5% ($p = .040$); and in ACT score: T0: 12.2 ± 1.2 vs. T1: 19.5 ± 2.9 ($p = .000$) vs. T2: 22.6 ± 1.5 ($p = .020$).

Finally, a comparative analysis between Group A and Group B was performed. The results are shown in Table 4. Specifically:

TABLE 1 Demographic and clinical findings of the enrolled population ($n = 17$).

Children's characteristics	Group A ($n = 9$)	Group B ($n = 8$)
Gender, *n* (%)	Male, 6 (67)	Male, 4 (50)
	Female, 3 (33)	Female, 4 (50)
Race, *n* (%)	Caucasian, 8 (89)	Caucasian, 8 (100)
	Asian, 1 (11)	
Comorbidities, *n* (%)	AR, 6 (67)	AR, 7 (87.5)
	AD, 2 (22)	FA, 2 (25)
	EoE, 1 (11)	CSU and HT, 1 (12.5)
		PCOS, 1 (12.5)
Age at the diagnosis of asthma, mean (SD), years	7.5 (2.9)	6.8 (2.0)
Age at omalizumab initiation, mean (SD), years	10.6 (3.5)	11.0 (3.6)
Treatment duration, mean (SD), years	2.1 (0.9)	—
Age at the treatment discontinuation, mean (SD), years	12.5 (3.8)	—
Adverse drug reactions, *n* (%)	0	1 (12.5)
Discontinuation reasons, *n* (%)	Patients and/or caregivers request, 8 (89)	—
	Transfer abroad, 1 (11)	

AR, allergic rhinitis; AD, atopic dermatitis; CSU, chronic spontaneous urticaria; EoE, eosinophilic esophagitis; FA, food allergy; HT, Hashimoto thyroiditis; *n*, number; PCOS, polycystic ovary syndrome; SD, standard deviations.

TABLE 2 Results of the statistical analysis of Group A ($n = 9$).

Variables	T0	T1	*p*	T2	*p*
FEV1, mean (SD), %	87.4 (7.8)	104.6 (13.8)	=.005	119.2 (7.1)	=.012
Exacerbations, mean (SD), *n*/year	5.9 (2.3)	3.5 (2.1)	=.036	1.8 (0.7)	=.025
Need for hospitalization, *n* (%)	67	0	=.001	11	=.332
Need for OCS, *n* (%)	100	11	=.000	56	=.048
ACT score, mean (SD)	14 (1.6)	21.7 (2.6)	=.000	18.2 (5.5)	=.013

ACT, Asthma Control Test; FEV1%, Forced Expiratory Volume in the 1st second; *n*, number; OCS, oral corticosteroid; SD, standard deviations.

TABLE 3 Results of the statistical analysis of Group B ($n = 8$).

Variables	T0	T1	*p*	T2	*P*
FEV1, mean (SD), %	84.1 (10.6)	97.5 (12.7)	=.044	112.6 (13.3)	=.035
Exacerbations, mean (SD), *n*/year	9.1 (2.7)	4.7 (0.7)	=.000	2.0 (0.7)	<.000
Need for hospitalization, *n* (%)	87.5	0	=.008	11	=.148
Need for OCS, *n* (%)	100	62.5	=.059	12.5	=.040
ACT score, mean (SD)	12.2 (1.2)	19.5 (2.9)	=.000	22.6 (1.5)	=.020

ACT, Asthma Control Test; FEV1%, Forced Expiratory Volume in the 1st second; *n*, number; OCS, oral corticosteroid; SD, standard deviations.

TABLE 4 Results of the comparative analysis between Group A and Group B.

Variables	*p* T0	*p* T1	*p* T2
FEV1%	=.472	=.286	=.213
Number of annual exacerbations	=.017	=.141	=.529
Need for hospitalization	=.342	=.124	=.362
Need for OCS	=.500	=.002	=.168
ACT score	=.025	=.132	=.046

ACT, Asthma Control Test; FEV1%, Forced Expiratory Volume in the 1st second; OCS, oral corticosteroid.

FEV1%: $p = .472$ (T0), $p = .286$ (T1), $p = .213$ (T2); number of exacerbations: $p = .017$ (T0), $p = .141$ (T1), $p = .529$ (T2); number of patients who needed hospitalization: $p = .342$ (T0), $p = .124$ (T1), $p = .362$ (T2); number of patients who needed OCS: $p = .002$ (T1), $p = .168$ (T2); ACT score: $p = .025$ (T0), $p = .132$ (T1), $p = .046$ (T2).

4 Discussion

Children and adolescents with severe asthma face different challenges; their condition not only compromises their physical health, but also has a profound impact on their QoL, potentially hindering their daily activities, overall growth, and developmental progress (30, 31). The burden of severe asthma can lead to frequent absences from school, physical activity limitations, and psychological stress (31). Omalizumab is widely used as a long-term treatment for managing severe, persistent asthma, making it crucial to understand whether its therapeutic benefits endure after the treatment is discontinued, especially in pediatric patients.

Our study aimed to analyze whether stopping omalizumab treatment would lead to a deterioration in asthma control or if the clinical improvements achieved during the therapy could be sustained even without continued pharmacological intervention. This evaluation is particularly important as discontinuing biologic therapy represents a delicate step for patients, families, and healthcare providers. Understanding the persistence of treatment benefits could influence clinical decision-making regarding the long-term management strategies for pediatric subjects with severe asthma. Nopp et al. described the clinical and immunological state of 18 adult patients with severe allergic asthma 3 years after omalizumab was stopped. 12/18 (66.7%) patients reported improved or unchanged asthma control compared with ongoing treatment in terms of FEV1%, QoL at questionnaires and downregulation of basophil allergen sensitivity (22). These data were confirmed by additional studies. Humbert et al. conducted a real-life study to assess omalizumab treatment patterns in adult and pediatric asthmatic patients and describe asthma control at omalizumab initiation and discontinuation. 16,750 adults and 2,453 children started omalizumab, with a median treatment persistence before discontinuation of 51.2 months in adults and 53.7 months in children. Among adults who discontinued omalizumab while asthma was controlled, 70%, 39% and 24% remained controlled and did not resume omalizumab at 1, 2 and 3 years after suspension, respectively. These proportions were higher in children (76%, 44% and 33%, respectively). Over 2 years of follow-up after discontinuation, rate of hospitalizations for asthma (none before the suspension, 1.3% and 0.6% at 2 years in adults and children respectively) and use of OCS (20.0% and 20.2% before the stop, 33.3% and 24.6% at 2 years in adults and children respectively) remained stable (23). Recently, Ferraro et al. conducted a prospective study on a cohort of 20 pediatric subjects who discontinued omalizumab after at least 2 years of treatment. Patients were evaluated at T0 (when omalizumab was discontinued) and after 3 (T1), 6 (T2) and 12 (T3) months after the suspension in different items: number of asthma exacerbations, asthma control according to Global Initiative for Asthma (GINA), Composite Asthma Severity Index (CASI), and spirometry. Furthermore, the Pediatric Asthma Quality of Life Questionnaire (PAQLQ) was administered at T0 and T3. The study showed omalizumab's clinical and functional effect for at least 1 year after discontinuation; only one child resumed omalizumab for worsening asthma, suggesting that a minority of children with severe allergic asthma may depend on biological therapy (24). Regarding our study, we analyzed and statistically correlated 5 items (FEV1%, number of exacerbations, need for hospitalization, need for OCS, and ACT score) at baseline (T0), at 18 months (T1) and at 36 months (T2) in two pediatric cohorts of severe asthmatic patients treated with omalizumab: Group A, including 9 subjects who stopped omalizumab; Group B, including 8 subjects who continued the treatment. In Group A, we found a statistically significant correlation in FEV1% values ($p = .005$ and =.012), number of exacerbations ($p = .036$ and =.025), number of patients who needed OCS ($p = .000$ and =.048) and ACT score ($p = .000$ and =.013) between T0 and T1, and T1 and T2, respectively, demonstrating the persistence of omalizumab efficacy one year after its discontinuation. In Group B, a statistically relevant correlation was detected in FEV1% values ($p = .044$ and =.035), number of exacerbations ($p = .000$ and <.000) and ACT score ($p = .000$ and =.020) between T0 and T1, and T1 and T2, respectively, confirming current literature data on the efficacy of omalizumab in pediatric subjects with severe asthma. Additionally, the comparative analysis performed between the two groups at T0, T1 and T2, did not document a statistically significant difference in FEV1% values and in the number of patients who required hospitalization. Patients in Group B showed a higher number of exacerbations at T0 ($p = .017$) and greater use of OCS ($p = .002$) at T1 compared to Group A. Finally, patients in Group A showed higher ACT

scores than Group B at T0 ($p = .025$), whereas Group B showed higher ACT scores at T2 compared to Group A ($p = .046$).

In their retrospective analysis, Silver et al. showed that the most common reasons of discontinuation were lack of symptoms control, exacerbations, cost, and patient re-quest, highlighting the complexity of care for this group of subjects and the need for assessment the reasons for discontinuation, including both clinical and non-clinical factors (25). Therefore, establishing the criteria for discontinuation remains an essential aspect, as suggested by Kupryś-Lipińska et al. (26). Their findings highlighted that the decision to stop omalizumab should be individual and based on benefits and risks, especially in patients with a long history of severe asthma, treated with high doses of OCS before the introduction of omalizumab, near-fatal asthma events and/or worsening of asthma during previous trials of omalizumab discontinuation (26). In our study, all patients discontinued omalizumab after a strict assessment of asthma control, based on evaluation of respiratory function, number of asthma exacerbations, need for hospitalization, need for OCS, and ACT score, as previously described. However, it is desirable to establish consistent criteria for discontinuing treatment in patients receiving omalizumab or other monoclonal antibodies.

Another challenge is establishing the duration of the omalizumab efficacy once suspended. *in vitro* studies showed that IgE production decreases throughout treatment, reaching a new equilibrium after about 5 years. It was suggested that IgE production could increase slowly after discontinuation, returning to baseline after 15 years, meaning patients would not need omalizumab indefinitely (32). Vennera et al. conducted an open, prospective study evaluating 49 adult patients who voluntarily agreed to stop omalizumab after 6 years of treatment. A total of 19 subjects (38.8%) developed asthma exacerbations: 12 patients relapsed in the first year of follow-up, and 7 within 13 and 48 months vs. 30 patients (61.2%) who did not relapse. These results suggest that the efficacy of omalizumab after 6 years of treatment may persist for at least 4 years after discontinuation of therapy (28). Regarding our study, all the patients presented satisfactory asthma control one year after the suspension. Nobody needs to restart treatment with omalizumab or other monoclonal antibodies. Still, a continuous follow-up is necessary to determine the optimal therapy duration and maintain its efficacy at the stop in long-term studies.

5 Conclusion

Our study provides additional real-world evidence on the maintenance of omalizumab efficacy following treatment discontinuation, contributing to the broader understanding of its impact on asthma management. Despite the limited sample size, our retrospectively collected data confirmed the efficacy and safety of omalizumab, demonstrating sustained benefits in key clinical parameters, including FEV1%, annual exacerbation rate, need for OCS, and QoL. However, our study was not designed to establish definitive criteria for determining when omalizumab should be discontinued or continued. Given the potential for variability in patient response, individuals who discontinue treatment should be closely monitored to ensure sustained asthma control. While our findings contribute to the ongoing discussion on omalizumab discontinuation, further prospective, long-term studies with larger cohorts are essential to develop evidence-based guidelines for treatment cessation once optimal asthma control has been achieved.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

All study participants, along with their parents, received comprehensive information and provided written informed consent as part of the study protocol. The study protocol was designed and conducted in compliance with Good Clinical Practice (GCP) standards and adhered to the ethical principles outlined in the Declaration of Helsinki with successive amendments. The Local Ethics Committee confirmed that no ethical approval was required for this retrospective observational study.

Author contributions

SFR: Formal analysis, Software, Visualization, Writing – original draft, Writing – review & editing. CL: Data curation, Visualization, Writing – original draft. FG: Investigation, Visualization, Writing – review & editing. GP: Funding acquisition, Visualization, Writing – review & editing. GC: Validation, Visualization, Writing – review & editing. LC: Validation, Visualization, Writing – review & editing. SG: Data curation, Investigation, Visualization, Writing – review & editing. PR: Resources, Validation, Visualization, Writing – review & editing. SM: Conceptualization, Methodology, Supervision, Validation, Visualization, Writing – review & editing.

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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.

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Decoding bronchopulmonary dysplasia in premature infants through an epigenetic lens

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This review provides a comprehensive overview of the evolving insights into the epigenetic mechanisms associated with bronchopulmonary dysplasia (BPD). It specifically highlights the roles of DNA methylation, histone modifications, and RNA regulation in the development of BPD in premature infants. BPD results from complex interactions among genetic factors, environmental exposures, and neonatal stressors. Key findings suggest that intrauterine hypoxia, hyperoxia, and nutrition can lead to epigenetic alterations, affecting gene expression and methylation, which may serve as biomarkers for early BPD detection. RUNX3 is identified as a critical transcription factor influencing lung development and inflammation, while changes in DNA methylation and histone dynamics in cord blood are linked to immune dysregulation associated with BPD. The role of m6A RNA methylation regulators from the IGF2BP family affects mRNA stability and gene expression relevant to BPD. Additionally, specific histones and microRNAs, particularly from the miR-17∼92 cluster, are implicated in pulmonary development and vascular regulation. Long non-coding RNAs (lncRNAs), such as MALAT1, also play a role in gene regulation via competitive endogenous RNA networks, indicating their potential as biomarkers and therapeutic targets. The interplay of these epigenetic mechanisms underscores the need for further research to develop targeted interventions aimed at reducing BPD severity and enhancing health outcomes for at-risk neonates.

KEYWORDS

epigenetics, bronchopulmonary dysplasia, DNA methylation, RUNX3, microRNAs, long non-coding RNAs

Introduction

Bronchopulmonary dysplasia (BPD) is a chronic lung disease predominantly affecting premature infants, resulting from inadequate lung development often associated with mechanical ventilation and supplemental oxygen use (1, 2). These interventions can induce inflammation and scarring, particularly harming the alveoli, which are crucial for gas exchange (3). BPD primarily impacts infants born before 28 weeks of gestation who require respiratory support, with high-pressure ventilation and elevated oxygen levels exacerbating the condition. Symptoms of BPD include rapid or labored breathing, shortness of breath, apnea, wheezing, and cyanosis, which indicates low blood oxygen levels (4). Diagnosis typically relies on the necessity for supplemental oxygen after 28 days of life or upon reaching 36 weeks of postmenstrual age (PMA), often supplemented by chest X-rays and blood tests (5, 6). The severity of BPD is classified as mild, moderate, or severe based on the level of respiratory support required and the infant's overall health, which guides treatment decisions and predicts long-term outcomes (7).

Epigenetics, a rapidly advancing field, examines how non-genetic factors influence gene expression without altering the DNA sequence, emphasizing the complex interplay between genetic predispositions and environmental factors, particularly in relation to diseases (8, 9). In the context of BPD, both genetic and environmental influences encountered before and after birth significantly contribute to its development (2, 7). Adverse prenatal conditions, such as intrauterine hypoxia, hyperoxia, and maternal smoking, have been associated with lasting changes in gene expression through epigenetic modifications, potentially increasing the risk of BPD and affecting future generations. Additionally, psychosocial stress may alter the epigenetic landscape, potentially accelerating biological aging and heightening the risk of developing BPD (10). Ongoing research into these epigenetic changes holds promise for improving perinatal health strategies and facilitating more personalized medical and public health interventions (11). Notable findings include alterations in DNA methylation linked to critical pathways involved in lung maturation, hematopoiesis, inflammation, and cellular mechanisms in infants predisposed to BPD (12).

Recent studies employing epigenome-wide association studies (EWAS) have identified a substantial number of differentially methylated CpG sites, with 275 sites exhibiting differential methylation at a false discovery rate of less than 1%. Remarkably, approximately 64% of these CpGs were hypomethylated in BPD cases compared to controls. Among these, the CpG site cg23328237, situated in the 3' untranslated region (UTR) of an unidentified gene, demonstrated a particularly strong association with BPD. The differentially methylated loci corresponded to 386 nearby genes, highlighting the extensive implications of methylation changes on gene expression pertinent to lung development and BPD pathology (12). Moreover, studies revealed that higher nucleated red blood cell (NRBC) content in preterm cord blood significantly influenced DNA methylation profiles. Elevated NRBC percentages correlated with lower birth weight (BW) and gestational age (GA), as well as hypomethylation of markers associated with tobacco smoke exposure (12, 13). Transcriptomic analyses indicated that gene expression changes in cord blood cells were reflective of cell cycle regulation, developmental processes, and pulmonary disorders related to BPD. Additionally, intrauterine hypoxia was found to elicit epigenetic changes, including altered DNA methylation, histone acetylation, and variations in miRNA expression (10).

Current research highlights the potential of specific epigenetic biomarkers as predictors of BPD risk, emphasizing the need for further studies to validate these findings and explore epigenetic therapies for prevention and treatment. This review aims to clarify the complex relationship between BPD and epigenetic mechanisms, focusing on how epigenetic modifications may influence the pathophysiology of this chronic lung condition. By synthesizing existing literature, we highlight the role of various epigenetic factors—such as DNA methylation, histone modification, and non-coding RNAs—in modulating inflammatory and fibrotic responses in the lungs of preterm infants. We also assess the clinical implications of these changes for early diagnosis and the development of targeted therapeutic strategies. The manuscript is structured to first discuss research progress on epigenetic mechanisms in BPD, followed by an examination of the epigenetic regulation of immune responses, epigenome-wide association studies, and the influence of environmental factors. It further explores the role of RUNX3, cord blood epigenetics, m6A methylation, histone modifications, microRNA dysregulation, long non-coding RNAs, competitive endogenous RNA networks, sex differences, and DNA methylation in animal models, concluding with a discussion on DNA methylation clocks for assessing health outcomes in preterm infants. Ultimately, this review aspires to deepen our understanding of BPD from an epigenetic perspective and to guide future research initiatives.

Materials and methods

This review aims to synthesize existing literature on BPD in premature infants, emphasizing epigenetic factors. A systematic approach was employed to gather relevant studies from multiple databases, including PubMed, Scopus, Web of Science, Google Scholar, Embase, Cochrane Library, CINAHL, and PsycINFO, using keywords such as "bronchopulmonary dysplasia," "premature infants," "epigenetics," "DNA methylation," "histone modification," "RNA regulation," "genetic factors," "environmental exposures," "neonatal stressors," "intrauterine hypoxia," "hyperoxia," "nutrition," "RUNX3," "immune dysregulation," "m6A RNA methylation," "IGF2BP," "microRNAs," "MALAT1," "therapeutic targets," and "non-coding RNA." Studies published up to November 2024 were included, focusing on peer-reviewed articles, reviews, and clinical studies that explore epigenetic mechanisms influencing BPD in preterm infants, with only English-language studies considered. Relevant information was extracted from selected articles, including study design, sample size, demographic data, and key findings related to epigenetic mechanisms, paying special attention to methodologies like genomic analyses and methylation profiling. The extracted data were categorized based on various epigenetic mechanisms, such as DNA methylation patterns, histone modifications, and the role of non-coding RNAs, allowing for an analysis of patterns and correlations between epigenetic changes and BPD severity. A narrative synthesis integrated findings from diverse

studies, highlighting the interplay between genetic susceptibility, environmental factors, and epigenetic modifications in BPD pathophysiology. Gaps in the current literature were identified, and recommendations for future research directions were formulated. Since this review involved synthesizing existing literature rather than direct research with human subjects or animals, ethical approval was not required, although adherence to ethical standards in research reporting was maintained. The outcomes of this systematic review aim to contribute to a deeper understanding of the epigenetic underpinnings of BPD in premature infants and may inform future therapeutic strategies.

Research progress in the epigenetic mechanisms of BPD

Bronchopulmonary dysplasia poses a substantial risk to premature infants, manifesting as inadequate lung development with potential long-term consequences (14). The disorder arises from a complex interplay of genetic predisposition, environmental exposures, and prenatal and postnatal risk factors (15). Epigenetic mechanisms, especially DNA methylation, have emerged as key regulators of gene expression in the context of BPD (16). Alterations in gene expression and DNA methylation during lung development suggest that epigenetic changes may play a critical role in BPD's pathogenesis (16, 17). Factors such as intrauterine hypoxia, hyperoxia, and disturbances in chromatin remodeling pathways have been linked to BPD development (18, 19). Intrauterine hypoxia triggers epigenetic mechanisms that affect lung plasticity, leading to inflammation during lung development and impeding the growth of alveoli and blood vessels. This disruption results in an imbalance in lung development, contributing to BPD. Epigenetic therapies, such as DNMT inhibitors, HDAC inhibitors, and miR modulators, can promote lung development and lower the risk of neonatal chronic lung disease (Figure 1). Environmental influences, particularly hypoxia and hyperoxia, have been shown to impact epigenetic programming within lung development and BPD (19, 20). For instance, hyperoxia-induced methylation changes, including reduced expression of the RUNX3 gene, have been documented in a rat model of BPD, suggesting a connection between epigenetic modifications and disease development (19). Further, disruptions in gene expression related to chromatin remodeling pathways have been observed in premature infants at risk for BPD, implying a crucial role for epigenetic dysregulation in susceptibility to the disorder (18). EWAS have revealed DNA methylation loci affiliated with BPD, underscoring the significance of epigenetic changes in the disease's development (21). Additionally, variations in the expression of microRNAs and their relationship with DNA methylation patterns have been noted in severe cases of BPD, further emphasizing the role of epigenetic regulation in determining disease severity (22). Moreover, differences in DNA methylation among very preterm infants have been linked to serious neonatal morbidities, including BPD, highlighting the influence of these epigenetic changes on health outcomes (23). The regulation of the immune system has also been shown to be affected by epigenetic modifications in experimental models of BPD, suggesting a connection between epigenetics and immune responses regarding the disorder (24). Furthermore, analyses of the epigenome and transcriptome of cord and peripheral blood from preterm infants at risk for BPD have provided valuable insights into the epigenetic factors underlying susceptibility (21). Table 1 presents critical insights into the epigenetic mechanisms and their implications BPD. Together, these findings illustrate a complex interplay between epigenetic modifications, gene expression, and immune responses in the pathogenesis of BPD.

Epigenetic regulation of immune responses in BPD

Epigenetic regulation is a pivotal factor in modulating immune responses associated with BPD in preterm infants. It encompasses mechanisms such as DNA methylation, histone modifications, and non-coding RNAs that together influence gene expression and immune function (25). Studies indicate that preterm infants exhibit DMRs in their placentas and cord blood compared to full-term infants, which align with genes that play significant roles in immune regulation and inflammation. The altered DNA methylation patterns are believed to exacerbate the heightened inflammatory responses characteristic of BPD, particularly due to increased methylation of inflammation-related genes that sustain inflammatory processes central to BPD pathogenesis (26). In addition, variations in histone acetylation and methylation can modify chromatin structure, thereby affecting gene expression tied to immune responses and lung development by altering the accessibility of transcription factors. Non-coding RNAs, particularly microRNAs, also play a crucial role by post-transcriptionally regulating gene expression and influencing the differentiation and activation pathways of immune cells (27). Moreover, m6A RNA methylation is instrumental in modulating immune responses related to BPD, with changes in m6A methylation regulators, such as IGF2BP1/2/3, linked to the disease and its immune environment (28, 29). These epigenetic alterations impact immune cell composition and signaling pathways, highlighting the significance of DNA and histone modifications during lung development and injury.

In the context of BPD, immune dysregulation creates an imbalance between pro-inflammatory and anti-inflammatory signals. Preterm infants frequently display increased levels of regulatory T cells (Tregs) in early life, potentially acting as a protective mechanism before the onset of BPD (30). While Tregs initially contribute to mitigating inflammation, their efficacy may be undermined in the inflammatory milieu of BPD, causing them to adopt a more inflammatory phenotype that could exacerbate lung injury. Additionally, oxidative stress stemming from hyperoxia can inflict inflammatory damage on alveolar epithelial cells, further worsening the inflammatory state in BPD. Changes in gut microbiota and blood transcriptomes are also associated with immune dysregulation in preterm infants, compounding this chronic lung condition (31). The polarization and activation of macrophages are essential processes, with DNA methylation influencing gene expression throughout lung development. Understanding the interplay between epigenetics and immune function is vital for developing targeted therapeutic strategies to address environmental factors that induce epigenetic

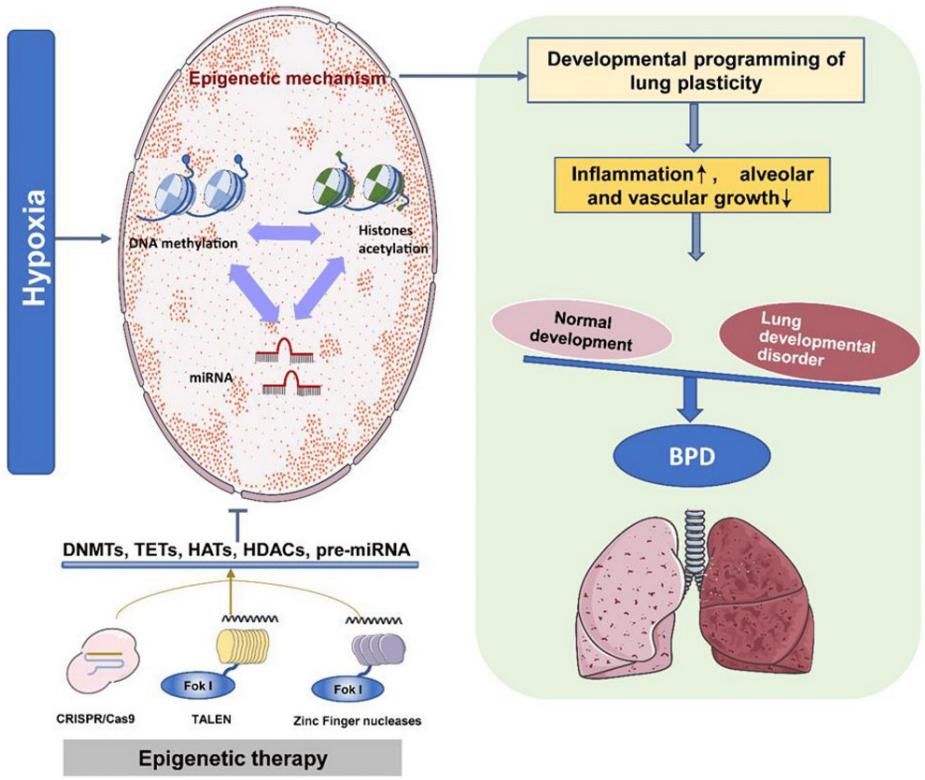

FIGURE 1
The epigenetic program regulates bronchopulmonary dysplasia (BPD) development. Intrauterine hypoxia triggers various epigenetic mechanisms that coordinate lung plasticity. This results in inflammation during lung development, inhibiting the growth of alveoli and blood vessels. Consequently, the balance between normal and abnormal lung development is disrupted, leading to BPD. Epigenetic therapies utilizing DNMT inhibitors, histone deacetylase (HDAC) inhibitors, and miR modulators can enhance lung development and mitigate the onset of neonatal chronic lung disease. This figure is derived from a study by Tong et al. (10).

modifications. This relationship highlights the potential for interventions targeting specific epigenetic alterations to improve immune function and reduce the risk of BPD in preterm infants (32, 33). The adaptability of immune cells, particularly Tregs, suggests a protective role against excessive immune activation; however, their responses may vary significantly based on the surrounding activation environment. Continued research is essential to explore these epigenetic mechanisms and their clinical applications in preventing or alleviating BPD in vulnerable populations.

Epigenome-wide association studies in BPD

Epigenome-wide association studies have revealed the epigenetic mechanisms behind BPD, highlighting the role of epigenetic modifications in understanding the disease's etiology and identifying potential biomarkers for early detection. Cuna et al. (16) investigated the effects of DNA methylation on gene expression during lung alveolar septation in murine and human models. They identified 95 genes in mice that showed an inverse relationship between expression and methylation during normal septation, focusing on genes vital for lung development, particularly those associated with Wnt signaling and the extracellular matrix. In human samples, 23 genes demonstrated differential methylation and reciprocal expression changes in BPD compared to preterm and term lung tissues, particularly involving detoxifying enzymes and TGF-β signaling. Importantly, 20 genes and three pathways were common to both murine and human studies, emphasizing DNA methylation's key role in regulating gene expression linked to normal and abnormal alveolar septation (16). Wang et al. (12) studied the connections between GA, BW, and blood cell composition in premature infants with BPD. Analyzing cord blood DNA from 14 BPD-affected preterm infants and 93 unaffected ones, they found significant associations with GA (p < 1.0E-04) and BW (p < 1.0E-02). A negative correlation was noted between nucleated red blood cell (NRBC) percentage and both BW and GA, with NRBC-rich samples exhibiting a hypomethylation profile associated with tobacco exposure. They identified 38 differentially methylated CpGs tied to pathways involved in lung maturation and hematopoiesis, and observed an increased epigenetic mutation burden in infants who developed BPD (adjusted p = 0.02). While the sample size was small, transcriptomic changes in cord blood highlighted critical biological processes related to lung development and cell proliferation (12). In a 2020 study, Everson et al. (23) sought to identify PMA-associated CpGs while minimizing the detection of surrogate markers during buccal swab collection. Their EWAS revealed that infants with more health complications had longer NICU stays, which influenced

TABLE 1 Essential insights into epigenetic mechanisms and their implications for bronchopulmonary dysplasia (BPD).

Section	Key points
RUNX3 role	– RUNX3 is critical for lung development and BPD regulation. – Disruption in RUNX3 expression is linked to abnormal lung architecture and impaired alveolarization. – RUNX3 may serve as a prognostic marker and therapeutic target for BPD. – DNA methylation and H3K27me3 alterations affect RUNX3 in BPD models. – Increased DNMT1 and DNMT3b expression correlates with decreased RUNX3 levels in hyperoxia models.
Cord blood modifications	– Methylation alterations impact immune responses in premature neonates. – Epigenetic markers in cord blood DNA are associated with BPD risk. – Studies show differential patterns of hypomethylation and hypermethylation in BPD patients. – Specific genes (e.g., CTSH, SPOCK2) linked to BPD identified through epigenome-wide association studies. – Elevated neutrophil-to-lymphocyte ratio (NLR) may indicate higher BPD risk.
m6A methylation	– m6A modification regulates mRNA metabolism and gene expression. – IGF2BP proteins are involved in BPD pathogenesis, promoting mRNA stability. – YTHDF2 reduces mRNA stability, affecting hematopoietic stem cell proliferation. – METTL3 enhances hyperoxia-induced pyroptosis in BPD. – Down-regulation of several m6A regulators is observed in BPD cohorts.
Histone modifications	– Histone acetylation/deacetylation regulates gene transcription. – Changes in histone modification patterns (e.g., hyperacetylation of H2A.Z and H3K9) are linked to BPD. – Histone deacetylase 3 (HDAC3) is pivotal in abnormal pulmonary angiogenesis and alveolar development. – Targeting histone acetylation and chromatin remodeling may offer therapeutic avenues.
MicroRNA dysregulation	– Specific microRNAs (e.g., miR-21, miR-34a, miR-431) are differentially expressed in BPD. – miR-17∼92 cluster downregulation correlates with BPD severity. – Elevated levels of miR-421 target FGF10, exacerbating inflammation and apoptosis in BPD. – miR-29b administration may enhance lung phenotype in severe BPD models.
Long non-coding RNAs	– lncRNAs play roles in transcription, RNA metabolism, and chromatin modification. – Differential expression of lncRNAs (e.g., MALAT1, lncRNA_AK096792) is observed in BPD. – lncRNA_AK096792 may serve as a biomarker for BPD.
Competitive endogenous RNA networks	– ceRNA networks regulate gene expression in BPD. – Dysregulated ceRNA networks may serve as therapeutic targets and biomarkers.
Animal model studies	– Animal models help explore epigenetics of BPD. – Sex-specific differences in epigenetic responses to hyperoxia are noted. – DNA methylation may hinder alveolarization in neonatal rats.
Neonatal epigenetic clocks	– NEOage clocks assess biological maturity and predict health outcomes in preterm infants. – Initial findings link epigenetic clocks to BPD development and risk assessment.

DNA methylation. They identified significant epigenetic signals with varying associated CpGs at different significance thresholds, incorporating PMA as a covariate for some CpGs. A separate analysis identified ten genome-wide significant CpGs, three of which were intergenic, with cg09787236 on 6q13 deemed the most significant. Notably, cg26838315 (10q21.1) exhibited lower DNA methylation levels with increased PMA, and sensitivity analyses indicated that adjustments for immune cell proportions did not affect the results. Analysis of differentially methylated regions (DMRs) identified 1,744 candidate regions, none of which reached Bonferroni-adjusted significance; however, seven DMRs had regional *p*-values within the FDR 10% threshold (23). Comparative analyses of existing EWAS enhance the understanding of the epigenetic landscape related to BPD, revealing strong connections between specific DNA methylation patterns and the risk of developing the condition. This underscores the urgent need for further research into these biomarkers for early detection and intervention, suggesting that integrating epigenetic and transcriptomic data could inspire innovative therapeutic strategies to mitigate BPD's impact on vulnerable populations.

Role of environmental factors in the epigenome of BPD

Environmental factors significantly affect the epigenome of preterm infants, influencing their risk of BPD through various mechanisms. Preterm infants often face challenges such as underdeveloped lungs due to lower GA, leading to epigenetic changes that hinder lung maturation. Low BW can also cause detrimental modifications that impact lung function and immune development (4, 12). Exposure to neonatal stressors like mechanical ventilation and oxygen therapy disrupts DNA methylation in immune-related genes, resulting in chronic inflammation and impaired lung growth (34). Intrauterine hypoxia induces epigenetic alterations, including changes in DNA methylation and histone acetylation, which compromise alveolarization and increase BPD risk (10). Practices in neonatal intensive care units can further contribute to lung injury and epigenomic changes by downregulating genes related to mitochondrial biogenesis. Additionally, variations in the airway microbiome influence immune development and modify the epigenetic landscape, potentially worsening BPD. Recent studies, such as those by Wang et al. (12) and Cho et al. (21), highlight the impact of environmental factors on the epigenome, revealing differential methylation of inflammatory genes crucial for lung development and linking epigenetic changes to transcriptomic signatures in immune responses. Maternal stress, nutrition, and pollutant exposure can disrupt DNA methylation, as noted by Song and Bhandari (35), while glucocorticoid exposure during critical development stages has been shown to alter DNA methylation, increasing BPD susceptibility. Understanding the interactions among gestational conditions, inflammatory responses, and environmental exposures is essential for identifying biomarkers for early detection and developing strategies to mitigate BPD severity, ultimately improving health outcomes for vulnerable infants (35). Recent research has explored the connection between air pollution and epigenetic markers associated with BPD in preterm

infants, indicating that exposure to pollutants like nitrogen dioxide (NO2) and particulate matter (PM) can alter DNA methylation patterns. Long-term NO2 exposure is linked to significant global hypomethylation in gene bodies and shores of CpG islands, crucial for regulating genes involved in lung development and inflammation. Studies on prenatal exposure have revealed both global and locus-specific DNA methylation changes in placental and cord blood samples, with higher levels of ozone (O3) correlating with reduced methylation in neonates (36). A review indicated that air pollution impacts DNA methylation throughout the lifespan, suggesting that early-life exposure significantly influences respiratory health and elevates BPD risk. While the mechanisms by which air pollution modifies the epigenome are still being studied, these changes are believed to sensitize the immune system, increasing the likelihood of inflammatory conditions like BPD (37). Understanding these pathways is vital for developing targeted interventions and identifying potential biomarkers for early BPD risk associated with environmental pollutants, underscoring the necessity for future research to focus on specific environmental exposures and their epigenetic effects to enhance therapeutic approaches.

Maternal smoking during pregnancy is a significant risk factor for BPD in infants, particularly those born prematurely who may require supplemental oxygen and respiratory support. A systematic review of 171,772 infants revealed a strong association between maternal smoking and an increased risk of moderate to severe BPD, with a pooled risk ratio of 1.126. However, no significant correlation was found for all BPD cases or severe BPD specifically (38). The harmful chemicals in tobacco smoke, particularly nicotine, can cross the placental barrier and hinder fetal lung development. Animal studies indicate that maternal smoking results in increased oxidative stress and inflammation in offspring's lungs, leading to structural changes that heighten the risk of respiratory problems (39). Moreover, smoking during pregnancy is associated with preterm birth, another known BPD risk factor, underscoring the importance of smoking cessation for better neonatal outcomes. Tobacco smoke can also induce epigenetic changes in offspring, affecting DNA methylation, microRNA expression, and histone modifications, which may disrupt lung development-related gene expression, such as that of the AHRR and CYP1A11 genes (38, 40). These epigenetic alterations can interfere with crucial developmental pathways and contribute to long-term health issues, potentially increasing the risk of respiratory diseases like asthma and chronic obstructive pulmonary disease (COPD) (41).

RUNX3's role in BPD development

The Runt-related transcription factor 3 (RUNX3) is crucial for lung development, especially in the differentiation of lung epithelial cells and the establishment of pulmonary vasculature (42). The subcellular localization of RUNX3 is vital for its functional activity; when RUNX3 is localized in the cytoplasm, it has been associated with tumorigenesis (43). RUNX3 modulates gene expression through post-transcriptional mechanisms that involve DNA methylation at the 5′-terminal and transcription start sites (44). This process is primarily mediated by DNA methyltransferases (DNMTs), with a particular emphasis on DNMT1 and DNMT3b (45). Furthermore, the tri-methylation of lysine 27 on histone H3 (H3K27me3), driven by EZH2, contributes significantly to this regulatory framework (46). The expression levels of RUNX3 play a crucial role in determining its effectiveness, while H3K27me3 trimethylation represents a common epigenetic alteration linked to its activity (47).

RUNX3's role in the development of BPD highlights its regulatory capacity in lung maturation and inflammatory responses (25). Research indicates that the expression of RUNX3 is frequently altered in BPD, which may result in abnormal lung structure and impaired alveolar development. In particular, diminished levels of RUNX3 in lung tissue from patients with BPD may induce epithelial-mesenchymal transition (EMT) in alveolar type II (AT2) cells, negatively impacting alveolar growth (48). Furthermore, studies involving mouse models of asthma have shown that the mislocalization of Runx3 protein is associated with allergic inflammation and increased airway hyper-responsiveness (49). These findings suggest that RUNX3 could be utilized as both a prognostic biomarker and a potential therapeutic target for BPD. Recent research has identified a correlation between DNA methylation and alterations in H3K27me3 in the promoter region of the RUNX3 gene within a hyperoxia-induced neonatal mouse model of BPD. Specifically, RUNX3 protein is prominently expressed in bronchioles and alveolar epithelial cells on embryonic day 17.5 throughout the pulmonary tissue of mice. Investigations into the cellular mechanisms suggest that epigenetic modifications of the RUNX3 gene significantly impact BPD development. Given the established role of DNA methylation in this condition, it is hypothesized that decreased expression of essential pulmonary development genes, such as RUNX3, may be linked to these epigenetic alterations (50). Zhu et al. (19) explored the relationship between RUNX3 protein levels and DNMT expression in alveolar type 2 (AT2) cells, reporting a marked increase in DNMT1 protein expression after 1 day of hyperoxia exposure, with DNMT3b levels rising notably from day ten onward and inversely correlating with RUNX3 protein levels. While both control and experimental AT2 cell groups showed elevated methylation, the hyperoxia group exhibited significantly higher methylation levels, particularly noticeable from day fourteen. Consequently, hypermethylation of the RUNX3 promoter in AT2 cells from the hyperoxia model group was evident compared to control cells. This study emphasizes the interplay between DNA methylation and H3K27me3 in a rat model of hyperoxia-induced BPD, highlighting the combined effects of DNMT3b-mediated DNA methylation and EZH2-mediated H3K27me3 on the downregulation of RUNX3 protein during the later stages of BPD. Early identification and intervention targeting these epigenetic pathways may alleviate the impacts of environmental and genetic factors on premature infants, thereby reducing the risk of developing BPD (19). Additionally, the findings underscore the significance of Runx3 in the pathophysiology of BPD in neonatal rat models and its relationship with EMT under hyperoxic conditions. A notable decrease in Runx3 protein and mRNA in BPD-derived alveolar type 2 cells correlates with critical pulmonary development markers, implying that low Runx3 expression may promote EMT, thereby hindering alveolar maturation. Experimental evidence indicates that Runx3 knockdown in RLE-6TN cells under TGF-β1 stimulation initiates EMT, whereas its overexpression inhibits this process, establishing Runx3 as a vital regulator

of EMT dynamics. Furthermore, in a hyperoxia model, the significant downregulation of RUNX3, alongside the upregulation of DNMT3b and EZH2, along with epigenetic modifications, indicates a complex regulatory mechanism influencing RUNX3 expression. Treatments with JMJD3 and DZNep effectively reversed RUNX3's hyperoxia-induced downregulation, suggesting potential therapeutic strategies to alleviate BPD by targeting Runx3's epigenetic regulation and related pathways (19, 50). A better understanding of the molecular mechanisms governing RUNX3's role in BPD may lead to the discovery of novel therapeutic targets for this complex condition.

Impact of cord blood epigenetics on BPD in preterm infants

Methylation alterations and transcriptional dysregulation are believed to have impacted neutrophil and lymphocyte levels, as well as T cell and adaptive immune responses, in premature neonates. These changes may also have influenced inflammation, phagocytosis, cellular assembly, and DNA damage repair (51, 52). Modifications in methylation and disrupted transcription could have affected the ratios of neutrophils and lymphocytes and the functions of T cells and adaptive immune responses. Such modifications likely played a role in various biological processes relevant to premature neonates, including inflammation, phagocytosis, cellular assembly, and DNA damage repair (53, 54). A methylation-based framework has indicated a positive correlation between reduced BW and GA with increased levels of nucleated red blood cells (NRBCs). However, variability exists, as some larger and more mature infants present high levels of NRBCs. Highlighting the significance of GA in neonatal health, researchers have investigated integrating cord blood DNA methylation data into predictive models for GA. This integration has led to the identification of epigenetic gestational age (EGA) acceleration, which reflects the difference between GA estimated from DNA methylation (epigenetic maturity, EGA) and GA determined through ultrasound or last menstrual period (chronological GA) (55–57).

As shown in Figure 2, The analysis of cord blood genes and pathways associated with BPD reveals significant insights into the condition's underlying mechanisms, particularly when considering epigenetic modifications. A comprehensive examination of differentially expressed genes in BPD cases, when compared to non-BPD controls, highlights enriched pathways and Gene Ontology (GO) terms, as visually represented in a dot plot. This pathway analysis has been rigorously adjusted for various covariates, including cell type proportions, sex, gestational age, and birth weight. Notably, pathways identified through cord blood epigenome-wide association analysis (EWAS) are underscored for their relevance to BPD. Furthermore, utilizing Ingenuity Pathway Analysis (IPA), the interleukin-2 (IL-2) pathway emerges as a crucial modulator of both epigenomic and transcriptomic changes in blood cell development and function, which are instrumental in the pathogenesis of BPD. Key molecules within this network, including SIRT1, TREX1, and IRF2, play significant roles in regulating cytokine signaling and transcriptional processes, thereby potentially influencing the progression and severity of BPD. This multifaceted approach underscores the intricate interplay of genetic and epigenetic factors in BPD's development and progression, highlighting potential avenues for therapeutic intervention (21).

In a detailed examination involving 54 preterm infants, Cohen et al. (18) discovered changes in histone acetyltransferase binding activity along with pathways linked to chromatin remodeling. While the individual genes analyzed did not exhibit statistical significance within the cord blood samples, the associated pathways did yield significant findings. In a study conducted by Cho et al. (21) on preterm infants, epigenetic markers in cord blood DNA associated with the risk of BPD were identified. These markers were linked to specific genes such as cathepsin H (CTSH, cg24847366) and SPOCK2 (cg17958658). The study proposed that alterations in the cord blood methylome, related to processes such as lung and tissue development, cell cycle regulation, leukopoiesis, immune-mediated inflammation, and T and B cell responses, could serve as indicators for the potential development of BPD. Furthermore, EWAS on cord blood samples have revealed differential patterns of hypomethylation and hypermethylation of CpG islands in patients diagnosed with BPD, including alterations in the SPOCK2 gene and genes involved in the pathway of reactive oxygen species production (21). Similarly, Cho et al. (21) investigated DNA methylation and gene expression in cord and venous blood within the first month following premature birth, unveiling molecular and cellular differences in newborns later diagnosed with BPD. A notable correlation was observed between GA and reduced lymphocyte proportions, paired with increased granulocyte proportions in both cord and peripheral blood samples. These variations were also reflected in the neutrophil-to-lymphocyte ratio (NLR), particularly in extremely premature newborns who subsequently developed BPD. Elevated NLR values in the early weeks of life may signal a greater risk for subsequent BPD development, corroborating findings from previous research that indicated higher NLR values in infants with BPD at each time point assessed (21). In 2022, Wang et al. conducted an analysis of DNA methylation in cord blood to investigate the relationship between GA, BW, and the distribution of cord blood cell types, specifically NRBCs, in a small cohort of preterm infants with and without BPD. The study noted no significant differences in the methylation-based estimated proportions of various cell types within cord blood DNA between infants with BPD and their counterparts without the condition. Furthermore, no differences in cell-type composition were observed among non-BPD infants who did not require supplemental oxygen. Their results demonstrated that the composition of cord blood cells, inferred from methylation patterns, varied with BW and GA, establishing that higher levels of NRBCs were associated with lower BW and DNA hypomethylation (12).

m6A methylation in gene regulation related to BPD

N6-methyladenosine (m6A) is recognized as the predominant internal modification present in messenger RNA (mRNA) within eukaryotic cells. This modification plays a pivotal role in regulating multiple facets of mRNA metabolism, including splicing,

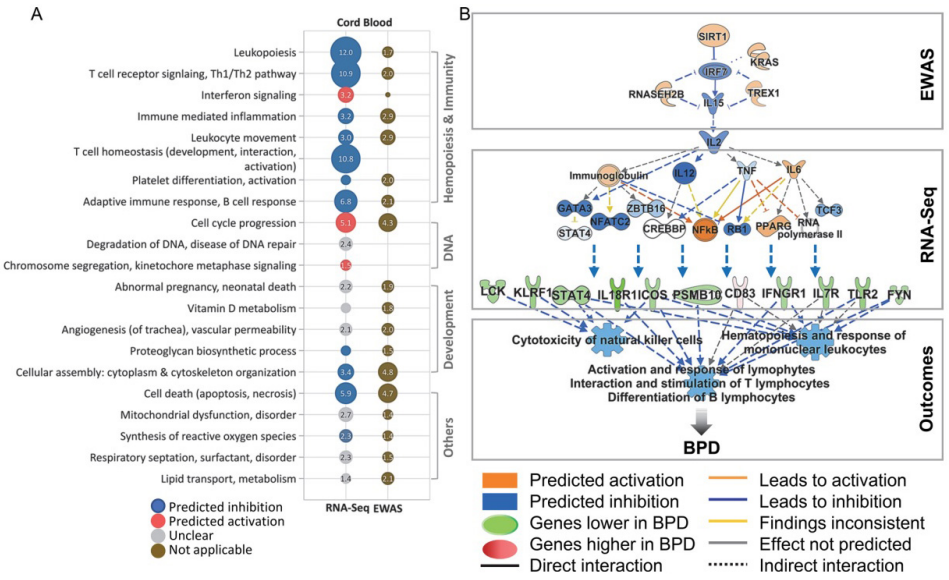

FIGURE 2
Overview of cord blood genes and pathways linked to bronchopulmonary dysplasia (BPD) and a comparison of epigenetic changes. **(A)** The dot plot illustrates enriched pathways and gene ontology (GO) terms from differentially expressed genes in BPD cases versus non-BPD controls, with pathway analysis adjusted for covariates like cell type proportions, sex, gestational age, and birth weight. Pathways related to cord blood epigenome-wide association studies (EWAS) are highlighted for their relevance to BPD. Circle size represents pathway or GO significance, while color indicates activation trends. **(B)** Ingenuity Pathway Analysis (IPA) identifies interleukin 2 (IL-2) as a crucial factor influencing epigenomic and transcriptomic changes in blood cell development and function during BPD pathogenesis. Key molecules in this network—SIRT1, TREX1, and IRF2—play roles in regulating cytokine signaling and transcription, potentially impacting BPD progression. This figure is derived from a study by Cho et al. (21).

stability, localization, and translation. The dynamic and reversible characteristics of m6A modification enable precise control over gene expression in response to various cellular signals and environmental stimuli (58, 59). m6A is implicated in numerous biological processes such as neuronal development, tumorigenesis, gametogenesis, and both physiological and pathological events. Importantly, m6A modification is involved in mRNA quality control, guiding improperly processed mRNAs for nuclear retention and degradation (59, 60). The regulation of m6A is mediated by "writers" (for example, METTL3, METTL14, RBM15, WTAP, KIAA1429), "erasers" (such as ALKBH5 and FTO), and "readers" (including IGF2BPs and YTHDFs). Overall, m6A modification is a significant posttranscriptional alteration that influences various biological functions (59, 61). The advent of adenosine deamination sequencing (AD-seq) has enabled the detection of m6A in RNA with single-base resolution, offering critical insights into the roles of m6A in cellular processes. Recent research has illuminated the involvement of m6A modification in the development and progression of various diseases (62, 63). However, the precise mechanisms through which m6A affects BPD remain incompletely understood.

Modifications in m6A RNA methylation regulators, particularly IGF2BP1/2/3, have been observed in BPD. Analyses of differentially expressed genes underscore the significant influence of IGF2BP in BPD pathogenesis. The IGF2BP family of m6A reader proteins (IGF2BP1/2/3) targets mRNA transcripts by recognizing the m6A consensus motifs "GGAC," promoting the stability, storage, and translation of certain mRNA targets. The absence of IGF2BPs is associated with widespread decreases in the regulation of target genes (64). Functional enrichment analysis of IGF2BP-targeted genes reveals their significant roles in DNA replication, the cell cycle, cell proliferation, and cancer. Unlike IGF2BP1/2/3, the m6A reader YTHDF2 decreases the stability of target mRNAs, promoting their degradation (65). YTHDF2 inhibits the Wnt signaling pathway, crucial for cellular communication and influencing development, cell proliferation, and differentiation. It achieves this by binding to and degrading mRNAs of key genes such as ccnd1, c-Myc, and Axin2, which reduces the proliferation and differentiation of hematopoietic stem cells. As an m6A "writer," METTL3 is vital for mRNA stability, preferentially binding to m6A-modified RNAs, typically near stop codons and in 3'-UTRs. This modification is associated with various biological functions and pathological events, with high METTL3 expression linked to poor survival in lung cancer patients. Furthermore, METTL3-mediated m6A modification of GPX4 and STAT2 promotes ferroptosis in conditions like NET-induced sepsis-associated acute lung injury and neonatal pneumonia (59). In a 2023 study, Xu et al. (66) revealed that METTL3 enhances hyperoxia-induced pyroptosis in BPD by inhibiting the LC3-conjugation pathway, shedding new light on BPD development. Additionally, the FTO "eraser" reduces m6A methylation in human cells through the demethylation of m6A. Suppressing FTO activity and elevating m6A levels fosters the recruitment of YTHDF1, leading to the increased translation of MYC and thereby contributing to tumorigenesis (66). According to Bao et al. (91), demonstrated that the expression of several m6A regulators—namely YTHDF1, YTHDF2, ZC3H13, FTO, ELAVL1, LRPPRC, RBM15B, METTL14, CBLL1, and FMR1—was down-regulated in the BPD cohort compared to controls, whereas

the levels of IGF2BP1, IGF2BP2, and IGF2BP3 were found to be elevated (64).

Histone modifications and their role in BPD pathogenesis

The pathogenesis of BPD is closely associated with histone modifications, particularly the dynamic processes of acetylation and deacetylation. Histone acetylation generally activates gene transcription, while deacetylation represses it (67). Notable changes in histone modification patterns, such as hyperacetylation of H2A.Z and H3K9, have been observed at gene loci implicated in BPD, including NOS3 and STAT3. These alterations may contribute to the dysregulated vascular responses seen in children diagnosed with BPD (68).

Histone acetyltransferases (HATs) facilitate the addition of acetyl groups to lysine residues on histones, which neutralizes their positive charge, reducing their affinity for DNA and leading to a more relaxed chromatin structure that promotes gene activation (69). Research by Chao et al. (68) examining mice in a hyperoxic environment—used to model BPD—demonstrated elevated expression levels of NOS3 and STAT3 mRNA in lung endothelial cells, alongside changes in histone acetylation at the H2A.Z and H3K9 loci. In vitro cell culture experiments further supported the notion that histone acetylation at these loci is a significant factor in BPD development in premature infants (70). Notably, infants born before 28 weeks of gestation exhibit two epigenetic pathways associated with BPD—histone acetylation and chromatin remodeling. Targeting these pathways may offer promising therapeutic avenues (12).

Histone deacetylation, mediated by histone deacetylases (HDACs), results in the silencing of transcription by promoting tight nucleosome binding to DNA. Class I HDACs, such as HDAC1 and HDAC2, are primarily located in the nucleus and play essential roles in embryonic development, cellular proliferation, and differentiation (71). HDAC3 is particularly important in abnormal pulmonary angiogenesis and alveolar development associated with BPD, activating specific pathways that accelerate abnormal lung blood vessel and air sac growth (72). Reduced levels and activity of HDACs due to preterm birth or environmental stress contribute to lung development issues in BPD (48). Enhancing HDAC activity may provide a protective effect against BPD through inflammation reduction. Additionally, sirtuin-3 (Sirt3), another NAD-dependent deacetylase, helps protect lung cells from BPD-related damage by influencing FOXO1 activity. Studies using chorioamnionitis models, where lipopolysaccharides (LPS) were injected into the amniotic cavity of pregnant mice, revealed obstructed lung development similar to BPD phenotypes. Evaluating lung tissue from these newborns highlighted significant reductions in HDAC1 and HDAC2 expression compared to controls, suggesting these enzymes' protective roles in alveolar development (73, 74). A related study examined Silent Information Regulator 1 (Sirt1) through tracheal aspirate fluid samples from 51 infants, finding lower Sirt1 levels in those with BPD, indicating a significant link between histone deacetylation and BPD progression (75). Londhe et al. (76) proposed that reduced expressions of HDAC1 and HDAC2 can lead to alveolar dysplasia, particularly in hyperoxic conditions. Systemic sepsis has been shown to trigger acute inflammatory responses in developing lungs, potentially leading to phenotypes resembling BPD in premature infants. Evidence suggests that HDAC inhibitors may worsen sepsis, further influencing inflammatory responses and impairing lung development, pointing to a significant role for these inhibitors in BPD etiology (76). These findings indicate that histone modifications are crucial regulators in the development and treatment of BPD, offering insights into the molecular mechanisms involved in lung development and dysplasia.

MicroRNA dysregulation in BPD

Several microRNAs, including miRNA-21, miRNA-34a, miRNA-431, Let-7f, and miRNA-335, have been identified as differentially expressed in lung tissues affected by BPD. These microRNAs provide valuable insights into the underlying mechanisms contributing to BPD (77). Notably, microRNAs are implicated in critical processes such as branching morphogenesis and secondary septation, both essential for lung development and alveolarization. Additionally, specific microRNA signatures have been detected in the tracheal aspirates of preterm infants with severe BPD, suggesting their potential as biomarkers for assessing disease severity (78). The miR-17∼92 cluster, which is transcribed as a single unit, undergoes posttranscriptional modification to produce six distinct miRNAs: miR-17, miR-18a, miR-19a, miR-19b, miR-20a, and miR-92. These miRNAs exhibit high expression levels during lung development and have been shown to activate the EZH1-p65-Pgf axis through the inhibition of miR-17, leading to abnormal pulmonary angiogenesis and impaired alveolarization in BPD mouse models (79).

Research indicates that approximately 20 miRNAs are up-regulated and 26 are down-regulated in the alveolar compartment during BPD, highlighting their significant role in the disease's onset and progression. In a pivotal study conducted by Rogers et al. (79) in 2015, it was found that all components of the miR-17∼92 cluster were downregulated in infants who succumbed to BPD as compared to those who died from other causes. The study further reported increased methylation in the promoter region of this cluster, associated with elevated expression of DNMTs (DNMT-1, 3a, and 3b) (79). Another investigation by the same group revealed substantial promoter methylation within the lung miR-17∼92 cluster in a severe BPD model. While control mice exhibited approximately 2% promoter methylation, mice subjected to LPS/O2 conditions presented with an alarming 98% methylation rate. Importantly, the research established circulating plasma miR-17 levels as an early indicator of disease severity, detectable just 5 days post-birth, prior to the onset of clinical symptoms (22). These findings point toward a model where alterations in miR-17∼92 cluster expression are driven by increased promoter methylation mediated by DNMTs. In addition to miR-17∼92, the work of Lal et al. (81) revealed that decreased expression of miR-876-3p at birth can effectively predict severe BPD in very low BW infants. Enhancing miR-876-3p activity has been linked to improvements in abnormal alveolar structures, suggesting its potential as a predictive biomarker for preventing BPD in this vulnerable population (80, 81). Further research by Sun et al.

utilized microarray technology to analyze peripheral blood from neonates with BPD and a control group, identifying significantly elevated levels of serum miR-495-5p in the BPD group. This miRNA was found to target 117 genes involved in processes such as apoptosis, cell death, autophagy, transcriptional regulation, and angiogenesis, indicating its possible role in regulating BPD development (82).

Clinical studies have corroborated the reduced expression of miR-29b in the serum of premature infants diagnosed with BPD. Animal studies indicated that administering miR-29b could enhance lung phenotype in severe BPD models, hinting at its potential as a new therapeutic avenue for the prevention or treatment of severe BPD. In hyperoxia-induced BPD mouse models, high-throughput sequencing has identified 201 differentially expressed miRNAs, including miR-342 and miR-335, with notable down-regulation of miR-150, miR-126, and miR-151, while miR-21 and miR-34a were found to be up-regulated (83, 84). The expression of miR-30a significantly increased in neonatal mice lung tissue after prolonged hyperoxia exposure, demonstrating a gender difference, as female mice showed higher levels than male mice. Additionally, the expression level of miR-34a in the lung tissues of newborn mice exposed to hyperoxia has been shown to significantly increase; inhibiting miR-34a expression has been demonstrated to ameliorate BPD symptoms and associated pulmonary hypertension (85, 86). Conversely, overexpression of miR-34a exacerbates these symptoms, suggesting that miR-34a inhibitors could serve as potential therapeutic agents for BPD management (87). MiR-421 targets fibroblast growth factor 10 (FGF10). In hyperoxia-induced BPD models, researchers observed elevated miR-421 levels and reduced FGF10 levels in lung tissues. This dysregulation worsens inflammation and increases cell apoptosis in BPD lung tissue, suggesting that down-regulating miR-421 could be a potential therapeutic strategy to alleviate its harmful effects in BPD pathology (88).

Long non-coding RNAs in BPD

Long non-coding RNAs (lncRNAs), which are defined as non-coding RNAs longer than 200 bases, represent about 80% of all ncRNAs. These molecules are crucial in various biological processes, including transcription, translation, RNA metabolism, chromatin modification, stem cell maintenance and differentiation, autophagy, apoptosis, and embryonic development. Due to their significant links with various diseases, lncRNAs have become key targets in research aimed at understanding disease mechanisms, thereby providing insights for treatment and prevention strategies (89). lncRNAs serve both as scaffolds for chromatin modification complexes and as direct transcription regulators. For example, some antisense lncRNAs bind to the 3' UTR of mRNA, affecting its stability and interaction with microRNAs, while also performing various nuclear functions (90). A landmark study by Bao et al. first documented variations in lncRNA expression in lung tissues of mice exposed to hyperoxia. Specifically, they found that in the BPD group, 882 lncRNAs were up-regulated and 887 down-regulated, suggesting a potential role in BPD's onset and progression and paving the way for a better understanding of its molecular mechanisms (91).

In a follow-up analysis of the GSE25286 dataset from the Gene Expression Omnibus (GEO), researchers examined the expression of the 8,778-base pair lncRNA, Metastasis Associated Lung Adenocarcinoma Transcript 1 (MALAT1), in the lung tissue of BPD mice. The results showed significant up-regulation of MALAT1 in the BPD group, with peripheral blood samples from premature infants also indicating increased MALAT1 levels in those affected by BPD. These findings suggest a close association between MALAT1 expression and the onset and progression of BPD, offering valuable clinical insights (92). Further research in China compared lncRNA_AK096792 levels in umbilical cord blood from premature infants with those in peripheral venous blood from neonates diagnosed with BPD. Results revealed significantly higher levels of lncRNA_AK096792 in the umbilical cord blood of the BPD group compared to the non-BPD group, with even higher levels in the peripheral blood of children with BPD than in umbilical samples, indicating its potential as a BPD biomarker. In another study, Cheng et al. (94) established a neonatal mouse model of BPD using hyperoxia and utilized Illumina sequencing to analyze lncRNA expression differences between affected and control groups. Their analysis identified 30,225 genes in the hyperoxia group and 30,361 lncRNA-related gene expressions in controls, revealing significant variations in lncRNA expression profiles. Among 1,175 different lncRNAs identified, 544 were up-regulated and 631 down-regulated (93). Gene Ontology (GO) enrichment analysis revealed 673 functional enrichment differences primarily related to biological processes such as cell positioning. Moreover, KEGG enrichment analysis indicated lncRNA involvement in 257 KEGG pathways, with nine lncRNAs validated experimentally. The significant differences in validated lncRNAs between the hyperoxia and control groups led researchers to propose that lncRNAs contribute to BPD development, thus presenting new perspectives for exploring the biological processes underlying the condition (94).

Competitive endogenous RNA networks in BPD

Competitive endogenous RNA (ceRNA) networks are essential regulatory systems in which non-coding RNAs (ncRNAs) and messenger RNAs (mRNAs) compete for shared microRNA (miRNA) binding, thereby influencing gene expression and various biological processes and diseases. In BPD, studies highlight the significance of lncRNA-mediated ceRNA networks in regulating GTPase activity, ERK1 and ERK2 signaling pathways, chromosome regulation, and cell cycle control in mouse models (90). Extracellular signal-regulated kinases 1 and 2 (ERK1/2) are key components of the mitogen-activated protein kinase (MAPK) signaling pathway, which is critical for cellular processes such as proliferation, differentiation, and survival. This pathway is activated by stimuli like growth factors, cytokines, and oncogenes, involving a series of phosphorylation events that transmit signals from the cell membrane to the nucleus (95). Dysregulated ceRNA networks have also been associated with lung cancer, particularly lung adenocarcinoma, affecting multiple biological functions and offering prognostic and diagnostic potential. Studies, including those by Li et al. (96) have identified several novel lncRNAs as promising biomarkers and therapeutic targets for BPD,

while Dong et al. (97) highlighted specific regulatory axes like miR17hg-miR-130b-3p-Robo2 and GM20455-miR-34a-5p-Brinp1. This research has enhanced our understanding of the molecular mechanisms underlying BPD, which mainly affects premature infants. The ceRNA hypothesis suggests that various RNA molecules—lncRNAs, miRNAs, and mRNAs—interact through shared miRNA response elements (MREs), with lncRNAs and circular RNAs (circRNAs) acting as "sponges" that sequester miRNAs, thereby regulating target mRNA expression.

Recent studies identified 445 differentially expressed genes and 155 differentially expressed miRNAs in neonates with BPD compared to healthy controls, enabling the construction of ceRNA networks that highlight specific lncRNAs crucial for regulating miRNA activity in BPD. Functional validation through quantitative real-time PCR (qPCR) in animal models has confirmed the biological relevance of these interactions, improving our understanding of lung development and injury mechanisms in neonates (98). This knowledge clarifies the pathogenesis of BPD and suggests potential therapeutic strategies, indicating that targeting specific lncRNAs or miRNAs within these regulatory networks could effectively mitigate lung injury and improve outcomes for affected infants. Notably, lncRNAs in the ceRNA framework act as miRNA "sponges," preventing miRNAs from binding to target mRNAs, resulting in increased gene expression, while miRNAs can also enhance gene expression by competing with lncRNAs. Dysregulated lncRNA-miRNA interactions have been linked to BPD, with studies showing that in a mouse model, the ceRNA axis involving miR17hg, miR-130b-3p, and the roundabout guidance receptor 2 (Robo2) was disrupted, leading to the upregulation of miR17hg and Robo2 and downregulation of miR-130b-3p (99). Similarly, another regulatory axis involving GM20455, miR-34a-5p, and BMP/retinoic acid-inducible neural specific 1 (Brinp1) exhibited dysregulation, with GM20455 and Brinp1 upregulated and miR-34a-5p downregulated. Additionally, an analysis of circRNAs in BPD identified three upregulated circRNAs—hsa_circ_0007054, hsa_circ_0057950, and hsa_circ_0120151—that contribute to immune dysregulation and inflammatory responses through their interactions with miRNAs (30, 100). These findings indicate that dysregulated lncRNA-miRNA interactions significantly contribute to BPD pathogenesis, particularly affecting immune responses, inflammation, and lung development, highlighting the potential for targeting specific ceRNA axes as a novel therapeutic strategy against BPD.

The role of Sex differences and DNA methylation in animal models

Ethical concerns have been raised regarding the practice of drawing blood from premature infants for research, primarily due to the invasive nature of the procedure and the complications associated with repeated use of cannulas. To address these challenges, researchers are encouraged to explore alternative methodologies, such as animal models, which can provide valuable insights into the epigenetics of BPD and enhance our understanding of its biological impacts (101). Animal models have proven particularly useful in examining sex-specific epigenetic variations following exposure to hyperoxia, as clinical outcomes for BPD often differ based on biological sex (67). Studies involving male and female mice have shown distinct patterns of histone acetylation in genes critical for lung development, highlighting the importance of sex as a variable in BPD research. For instance, chromatin immunoprecipitation targeting the H3K27ac histone modification has demonstrated significant sex-related differences in the epigenetic response to hyperoxia. Specifically, female mice exhibit an upregulation of miR-30a, a microRNA that targets genes linked to angiogenesis (102). This finding is significant as it indicates that female mice exhibit more substantial changes in angiogenesis-related gene expression, particularly in the Delta-like 4 (Dll4) gene, which is essential for the Notch signaling pathway. These mechanisms may help maintain pulmonary vascular development in females after exposure to high oxygen levels compared to males (103). This signaling pathway is a conserved intercellular mechanism vital for various biological processes, including embryonic development, cell fate determination, and tissue homeostasis in multicellular organisms (104).

Recent animal studies have begun to illuminate the role of DNA methylation modifications in the development of BPD. For instance, research by Chen et al. has drawn parallels between the lung phenotype observed in hyperoxic lung injury models and the underlying pathophysiology of BPD. This investigation employed DNA methylation co-immunoprecipitation techniques to analyze whole-genome DNA methylation profiles in rat lung tissue, revealing that DNA methylation may hinder alveolarization processes induced by hyperoxia in neonatal rats (94). Complementary work by Bik-Multanowski et al. (105) utilized microarray technology to explore methylation levels in the lung tissue of neonatal rat models of BPD resulting from hyperoxic exposure. Their findings demonstrated increased DNA methylation levels in the promoter regions of key genes, such as transforming growth factor beta receptor 1 (TGFBR1) and cyclic adenylate response element binding protein 1 (CREB1), indicating a potential role for DNA methylation in the pathogenesis of BPD (105). Further research has demonstrated that hyperoxic conditions can profoundly affect the phosphatidylinositol-3-kinase (PI3K)-protein kinase B (AKT) signaling pathway in mouse models of BPD. Notable changes in the expression of genes associated with BPD, along with hypermethylation of key components within this signaling pathway, strengthen the hypothesis that epigenetic modifications play a critical role in the regulatory mechanisms underlying BPD development (74, 106). The PI3K-AKT signaling pathway is essential for regulating numerous cellular processes, including growth, survival, proliferation, and metabolism (107). Overall, these findings emphasize the necessity of utilizing animal models to dissect the intricate epigenetic landscape associated with BPD, drawing attention to both sex-specific differences and the impact of DNA methylation pathways.

DNA methylation clocks for assessing preterm health outcomes

DNA methylation-based epigenetic clocks, or neonatal aging epigenetic clocks (NEOage clocks), show promise in evaluating biological maturity and predicting health outcomes for preterm infants. These clocks align with chronological age, allowing for an assessment of neonatal development related to both immediate and long-term health issues (108, 109). Recent research links

NEOage clocks to the development of BPD, demonstrating their effectiveness in estimating clinical GA and identifying epigenetic biomarkers early associated with BPD. Studies emphasize DNA methylation as a biomarker for biological age and disease progression in preterm infants, highlighting specific CpG site patterns that expose the gap between biological and chronological ages (110). NEOage clocks provide better predictions of PMA and postnatal age (PNA) in very preterm infants compared to conventional methods. Evidence suggests that accelerated biological aging, as indicated by these clocks, correlates with increased risks of neonatal morbidities, including moderate to severe BPD. However, the variability in DNA methylation during early development complicates accurate measurement. Integrating NEOage clocks into clinical practice could improve risk assessment for preterm infants, though factors such as developmental differences and population characteristics may influence their accuracy (111). Ongoing research seeks to refine these clocks and address clinical implementation challenges. In 2021, Graw et al. (109) introduced four NEOage clocks specifically for estimating PMA and PNA, analyzing DNA methylation at certain CpG sites in very preterm infants. The Neonatal Neurobehavior and Outcomes in Very Preterm Infants (NOVI) study collected buccal cell samples from 542 infants to evaluate DNA methylation levels. The resulting NEOage clocks demonstrated strong correlations with actual ages and were compatible with Illumina EPIC and 450K arrays (109). Further research in 2023 by Paniagua et al. (111) found that infants with neonatal morbidities, especially BPD, exhibited signs of accelerated epigenetic aging. While some neurobehavioral traits showed varying levels of age acceleration, most did not significantly correlate with early-life age acceleration. A lower GA at birth appears to be a key factor influencing these associations. Although additional studies are necessary to clarify the relationship between NEOage clocks and BPD, initial findings are promising for managing this common neonatal lung condition (111).

Potential applications of epigenetic findings in clinical practice

The exploration of epigenetic mechanisms in BPD has yielded significant insights applicable to clinical practice, particularly in developing diagnostic biomarkers and personalized therapies to improve outcomes for preterm infants. Specific epigenetic markers, such as DNA methylation patterns and altered microRNA levels, hold promise for creating diagnostic tools that could facilitate early identification of at-risk infants through routine screenings. This integration of epigenetic data into clinical assessments allows for targeted monitoring and interventions, potentially reducing the incidence and severity of BPD. Furthermore, understanding individual variability in epigenetic modifications can lead to personalized treatment strategies, enhancing therapy effectiveness through tailored interventions such as DNMT inhibitors, HDAC inhibitors, and microRNA modulators. Insights from epigenetic research can also inform targeted interventions addressing specific risk factors, such as promoting smoking cessation programs and reducing exposure to environmental pollutants during pregnancy. Additionally, epigenetic markers may serve as indicators for monitoring disease progression and treatment response, enabling healthcare providers to adjust care plans accordingly. The influence of maternal nutrition and environmental conditions on epigenetic programming underscores the importance of tailored nutritional support and optimized care environments. Integrating epigenetic findings into clinical protocols can enhance the standard of care for preterm infants, while collaboration among clinicians, geneticists, and researchers can lead to comprehensive care plans that consider both clinical and environmental factors in BPD management. Overall, the application of epigenetic findings in clinical practice represents a significant advancement in the prevention and management of BPD, contributing to the evolution of precision medicine in neonatology.

Limitations

Research on the epigenetic mechanisms underlying BPD offers both advantages and limitations. A significant advantage is the potential to identify novel biomarkers and therapeutic targets, enhancing our understanding of the complex interactions between genetics, environmental factors, and nutrition in BPD development. Insights from EWAS could facilitate early detection and intervention, ultimately improving health outcomes for premature infants. The focus on environmental influences underscores the need for better care practices in neonatal intensive care units and preventive measures against pollution and maternal malnutrition. However, limitations include relatively small sample sizes in some studies, which may affect the generalizability of findings, and the dynamic nature of epigenetic modifications that can vary over time and with different exposures. Establishing causal relationships between epigenetic changes and BPD remains a significant challenge, necessitating further research to validate biomarkers for clinical use. The exploration of specific factors such as RUNX3, histone modifications, microRNA dysregulation, and lncRNAs highlights their potential as prognostic biomarkers and therapeutic targets, though complexities in gene regulation and reliance on animal models may complicate the translation of findings to human populations. Additionally, the study of sex differences and DNA methylation through animal models provides controlled experimental insights but may not fully replicate human conditions, emphasizing the need for continued research to bridge the gap between experimental results and clinical applications. Overall, while promising avenues for understanding and treating BPD exist, further studies are essential to address these challenges and translate findings into effective clinical practices.

Implications and future directions

Research on epigenetic mechanisms in BPD holds significant implications for healthcare, particularly in enhancing clinical practices for managing at-risk premature infants. The findings from this study could lead to improved management strategies and highlight the necessity for further exploration of these mechanisms, paving the way for future research on long-term outcomes and potential therapies. By identifying specific DNA methylation patterns associated with BPD, opportunities arise for early detection and monitoring, enabling healthcare providers

to recognize at-risk infants through routine screenings and implement timely interventions. Future studies should prioritize longitudinal research to assess the stability and predictive value of identified epigenetic biomarkers over time, evaluate their effectiveness in predicting BPD risk and outcomes, and explore the interplay between genetic predispositions and environmental factors to gain deeper insights into epigenetic modifications and their long-term effects on lung development. Investigating the impact of various therapeutic interventions on epigenetic changes in preterm infants with BPD is crucial for developing personalized treatment strategies. Additionally, examining the influence of maternal health, nutrition, and lifestyle on the epigenetic profiles of both mothers and infants could inform preventative measures and interventions. Integrating multi-omics approaches—combining genomics, transcriptomics, and epigenomics—could provide a comprehensive understanding of the biological mechanisms underlying BPD, ultimately guiding future research and clinical practice. Addressing environmental factors, such as maternal smoking and air pollution, during prenatal care is vital for reducing BPD risks, while reassessing neonatal care practices in light of stressors like mechanical ventilation is essential for optimizing outcomes. Monitoring inflammatory responses is also crucial, as elevated markers can indicate BPD progression and prompt timely interventions. Continued research into therapeutic targets, including long non-coding RNAs and microRNAs, is critical for developing effective treatments and biomarkers. A multidisciplinary approach involving neonatologists, geneticists, and public health experts is necessary to comprehensively address the complexities of BPD. By integrating epigenetic insights into clinical protocols, care can be enhanced, while ethical considerations in research emphasize the importance of safe methodologies that prioritize the well-being of vulnerable populations. Overall, these insights underscore the significance of a holistic patient management approach that considers both biological and chronological age to improve outcomes for preterm infants affected by BPD.

Conclusion

In summary, the intricate interplay of genetic and epigenetic factors, including the roles of RUNX3, histone modifications, microRNA dysregulation, lncRNAs, and DNA methylation, is crucial in understanding the pathogenesis of BPD in premature infants. Research has revealed that these epigenetic mechanisms significantly influence lung development, immune responses, and inflammatory processes associated with BPD. RUNX3 has emerged as a potential prognostic biomarker and therapeutic target, while epigenetic modifications in cord blood DNA can help identify at-risk infants for preventive strategies. The dynamic processes of histone acetylation, the role of microRNAs, and the interactions between lncRNAs and microRNAs further underscore the importance of the epigenetic landscape in BPD. Additionally, advancements like NEOage clocks for assessing biological age through DNA methylation hold promise for predicting health outcomes. Together, these insights underscore the need for a comprehensive understanding of BPD's etiology and the potential for innovative therapeutic strategies that could improve the health trajectories of vulnerable neonatal populations.

Author contributions

SD: Conceptualization, Writing – original draft, Writing – review and editing. RB: Conceptualization, Writing – original draft, Writing – review and editing. MG-T: Investigation, Writing – original draft, Writing – review and editing. MD: Investigation, Methodology, Writing – original draft, Writing – review and editing. SA: Methodology, Writing – original draft, Writing – review and editing. ASha: Investigation, Writing – original draft, Writing – review and editing. MY: Data curation, Writing – original draft. AShi: Investigation, Writing – review and editing. AM: Investigation, Writing – original draft. HN: Conceptualization, Investigation, Methodology, Writing – original draft, Writing – review and editing.

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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.

Generative AI statement

The authors declare that no Generative AI was used in the creation of this manuscript.

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Monitoring respiratory function with telemedicine devices in asthmatic children

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Introduction: Pediatric asthma requires continuous monitoring, traditionally reliant on in-person assessments. Home-based telespirometry offers a promising approach, enabling regular lung function testing, early exacerbation detection, and improved disease management while reducing the burden of in-person visits. However, its effectiveness and accuracy compared to clinical measurements need further evaluation. This study aimed to assess the feasibility and reliability of home spirometry in children with moderate asthma and to compare home-based lung function measurements with those obtained under clinical supervision.

Methods: Eleven children (aged 8–17 years) with moderate asthma were trained to use a handheld spirometer and an associated mobile app. Participants performed home spirometry at least four times per week over a 12-month period, following ERS/ATS standards. Key respiratory parameters, including forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), FEV_1/FVC ratio (Tiff), peak expiratory flow (PEF), and forced mid-expiratory flow (FEF_{25-75}), were recorded. Data was transmitted to a clinical cloud system for real-time monitoring. Measurement reliability was assessed based on ERS/ATS acceptability criteria, and statistical analyses included mixed ANOVA model, and Bland–Altman analysis with confidence intervals to compare home and clinical measurements.

Results: Home spirometry demonstrated a high rate of reliable measurements, with no significant decline in reliability over time. A positive correlation was observed between the number of home spirometry recordings and the reliability of FEV_1 and FVC measurements. Comparisons between clinical and first home spirometry measurements showed strong correlations, particularly for FVC. Bland–Altman analyses confirmed good agreement between home and clinical assessments, with narrow limits of agreement for FVC, FEV_1, and Tiff, whereas PEF and FEF_{25-75} showed greater variability. When expressed as percentage predicted values, similar trends were observed, with FVC% showing the strongest correlation.

Conclusion: The difference in peak flow indices measured at home and lung function labs in asthmatic children highlights the importance of patient education, and the reliabilities indicate the need for frequent assessments. The strong agreement with clinical measurements supports its potential

integration into routine asthma care, enabling more accessible and continuous disease management.

KEYWORDS

pediatric asthma, telespirometry, home spirometry, lung function monitoring, telemedicine

Introduction

Pediatric asthma poses an increasing challenge for global healthcare systems, necessitating innovative approaches to management and monitoring. Conventional care models, primarily reliant on face-to-face consultations, often fall short in effectively addressing the complexities of asthma management in children (1). This inadequacy is underscored by the rising prevalence of asthma exacerbations, which can lead to significant morbidity and increased healthcare utilization (2–4). The Global Initiative for Asthma (GINA) emphasizes that assessing symptom control alone is insufficient, clinicians must also evaluate patients' risk factors for exacerbations and accelerated lung function decline (5). Consequently, there is a clear need for more effective monitoring strategies, as timely detection of exacerbations is critical for preventing severe outcomes and optimizing treatment (6–8).

Recent advancements in telemedicine have opened a new era for asthma control, particularly through the implementation of telespirometry. This technology allows for regular home lung function testing, enabling patients to monitor their respiratory status without the need for frequent clinic visits (9–11). Studies have shown that home spirometry can enhance patient engagement and provide valuable data for clinicians, facilitating timely interventions in exacerbation scenarios (12–15). The feasibility of telespirometry has been demonstrated in various contexts, including chronic respiratory diseases, where it has proven effective in monitoring lung function and improving patient outcomes (8, 12, 13, 16–18). Furthermore, the integration of digital health interventions has the potential to transform asthma care by providing real-time feedback and personalized management strategies (6, 7, 15).

Recent studies have demonstrated the potential of home spirometry and telemonitoring tools to improve asthma management by enabling regular lung function assessment outside clinical settings. However, most of these earlier studies focused on adult populations (9, 19, 20) or short-term monitoring (21–23), and there remains limited data on long-term feasibility and technical reliability in children. Moreover, variability in study design, measurement standards, and patient selection complicates direct comparisons (10, 14, 18, 23, 24). This underscores the need for further pediatric-focused research that addresses these gaps under real-world conditions.

Our study aims to assess the feasibility of telespirometry specifically in the pediatric population, focusing on the reliability of home measurements. By evaluating the accuracy and consistency of these home-based assessments, we aimed at contributing to the establishment of a framework for integrating telespirometry into routine asthma management (25). This approach not only aligns with current trends in digital health but also addresses the pressing need for more accessible and efficient monitoring solutions for children with asthma (26). As healthcare systems continue to evolve, the incorporation of telemedicine into asthma care could significantly enhance the quality of life for pediatric patients while alleviating some of the burdens on healthcare providers (6, 7, 24, 27).

Materials and methods

Participants

The study was approved by the National Institute of Pharmacy and Nutrition, Hungary (No. OGYÉI/8725/2020; address: Hungary, 1051 Budapest, Zrínyi u. 3., dated 16 March 2020) and conducted in accordance with the 1964 Declaration of Helsinki and its amendments. Written informed consent was obtained from all participants, and the trial was registered in the European Union Drug Regulating Authorities Clinical Trials Database under the name *Telemonitoring of Lung Function by Spirometry* (NCT04447664).

Participants were required to be under 18 years old with moderate asthma (GINA stages 2–3) (5, 28, 29) and willing to perform home telespirometry as instructed. Exclusion criteria included poor overall health, recent asthma exacerbation requiring clinical care, or any condition deemed unsuitable by the investigator. Participants could withdraw at any time. The study adhered to CONSORT guidelines, with the patient flow chart presented in **Figure 1**. Of 16 eligible participants, five were excluded: one due to internet access issues, two declined participation for personal reasons, and two were ineligible for using IT tools.

Spirometry

Measurements

Children with moderate asthma ($n = 11$, aged 8–17 years) were trained to use a handheld spirometer (Uscom SpiroSonic Ultrasonic Spirometer, Uscom Europe, Budapest, Hungary) at the Department

Abbreviations: ATS, American Thoracic Society; CONSORT, Consolidated Standards of Reporting Trials; ERS, European Respiratory Society; FEF_{25-75}, mean forced expiratory flow between 25% and 75% of the FVC; FEV_1, forced expiratory volume in the first second; FVC, forced vital capacity; GINA, Global Initiative for Asthma; GLI, Global Lung Function Initiative; PEF, peak expiratory flow; SD, standard deviation.

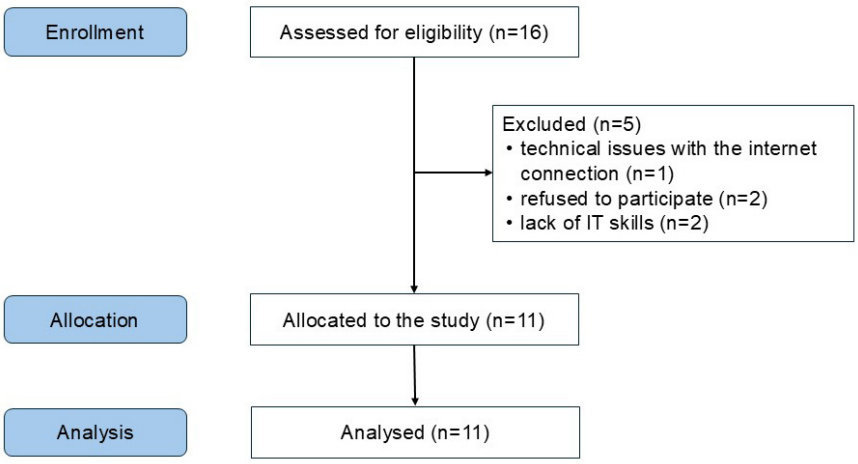

FIGURE 1
Patient flow chart. A total of 16 participants were assessed for eligibility, meeting criteria including informed consent, being under 18 years old, and the ability to cooperate. Five participants were excluded: one due to internet access issues, two declined participation for personal reasons, and two were ineligible due to insufficient IT skills. The remaining 11 children were enrolled in the study, completed the allocated intervention, and were included in the final analysis.

of Pediatrics and Pediatric Healthcare Center, University of Szeged. The spirometer is a factory-calibrated device that requires no manual recalibration and is clinically approved and certified by international regulatory bodies, including the FDA and CE.

After training, respiratory function parameters were measured in the clinic under specialist supervision. Participants then used the spirometer at home for one year, performing measurements at least four times per week per ERS/ATS standards (30). More frequent measurements were encouraged during periods of asthmatic symptoms. Additionally, an asthma control test, integrated into the app, was completed at least weekly, preferably after each spirometry session.

Before each measurement session, the app automatically performed a zero-flow calibration. The child was then prompted to carry out the prescribed spirometry maneuvers. After each attempt, the app validated the technical quality of the effort and displayed the resulting spirometry curves and numerical parameters. Once three acceptable and reproducible measurements were obtained, the full dataset, including all calculated values and flow-volume loops, was automatically uploaded to a secure clinical database. In cases where participants did not complete the recommended number of weekly measurements, the assistance team contacted the parents to inquire about the cause. This follow-up helped sustain engagement and identify potential technical issues or motivational challenges.

Data management with mobile and web-based applications

Following informed consent, demographic and medical data were recorded into the web-based clinical portal and linked to the patient's unique identifier within the mobile application. A pediatric pulmonologist provided instructions to both children and their caregivers on proper spirometer use, including managing the Bluetooth connection, performing the pre-measurement calibration, and navigating the Android-based mobile application during spirometry sessions.

The mobile app calculated key spirometry parameters, including forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), FEV_1/FVC ratio (Tiffeneau index: Tiff), peak expiratory flow (PEF), and mean forced expiratory flow between 25% and 75% of FVC (FEF_{25-75}). Predicted values and corresponding percentages were derived based on the Global Lung Function Initiative (GLI) reference standards (31). According to ERS/ATS guidelines (30), the acceptance criteria required that the difference between the largest and the next largest FEV_1 and FVC values be less than 0.1 L in three measurements per session.

Results were instantly transmitted to a clinical cloud system for real-time review by clinicians, enabling continuous monitoring and timely interventions. The web portal available to clinicians provided secure access to patient data, including graphical displays of previous spirometry measurements, an automated alert system for abnormal values, integrated messaging tools (e.g., push notifications and email), and comprehensive measurement histories. Timestamps were automatically created in the log-files for each measurement activity. This infrastructure enabled continuous remote monitoring and facilitated more proactive and individualized patient follow-up.

Statistical analysis

The sample size estimation was based on a significance test for the Pearson correlation coefficient. The test was designed with 80% power, an expected effect size of $\rho = 0.7$, and a one-sided alternative hypothesis (positive correlation), using a commonly accepted significance level of 5%. The calculation yielded a minimum

required sample size of 11. This analysis was performed using G*Power (version 3.1.9.7, Universität Düsseldorf, Germany).

Agreement between clinical and home spirometry measurements was primarily evaluated using Bland–Altman analyses (32), with limits of agreement calculated as the mean difference ± 1.96 standard deviations (SD) and accompanied by 95% confidence. Pearson's correlation coefficients were calculated to assess linear associations, acknowledging that correlation does not imply agreement. These analyses were conducted for both absolute and percentage predicted spirometry values to assess measurement consistency across parameters.

The association between the number of home spirometric measurements and the number of reliable FEV_1 and FVC estimates was analyzed using Pearson's correlation test. As the study involved repeated spirometric measurements per subject over time, introducing both within-subject and between-subject variability, a mixed ANOVA approach with an interaction term was applied. The sphericity test failed; therefore, the Greenhouse–Geisser correction was used. Statistical analyses were performed using SigmaPlot for Windows (version 15, Systat Software, Inc., Chicago, IL, USA), and mixed ANOVA was performed using IBM SPSS Statistics version 29.0.0 (Build 241), with significance set at $p < 0.05$. All reported p-values are two-sided.

Results

The demographic and clinical characteristics of the children are summarized in Table 1, including gender distribution, age, asthma severity and duration, and allergen sensitization. Most participants had mild persistent asthma and were on varying treatment regimens. The majority experienced at least one exacerbation requiring medical consultation in the past year.

A time series of home spirometric parameters obtained in two representative children with moderate asthma are demonstrated in Figure 2. Relatively stable periods supplying reproducible values in the recorded outcomes are interrupted by temporary deteriorations in FEV_1, FVC, PEF, and FEF_{25-75} in both children.

Figure 3 demonstrates the relationships between the number of home spirometric measurements performed by the children and the number of reliable estimates for FEV_1 and FVC based on ERS/ATS criteria. A positive correlation was observed for both parameters, with reliability increasing as the number of home measurements increased (FEV_1: $r = 0.65$, $p < 0.05$; FVC: $r = 0.56$, $p < 0.05$).

Figure 4 illustrates the rate of reliable FEV_1 and FVC measurements over the 12-month period. No significant interaction effect was observed, indicating no differential change over time between subjects. Overall, no statistically significant difference was detected in the shape of the trends. The between-subjects effect was also not significant, while the within-subject effect (i.e., the effect of time) yielded the lowest p-value but did not reach statistical significance at the 5% level.

Relationships between spirometry outcomes obtained under pulmonologist supervision in the lung function laboratory and those derived from the first home measurement are demonstrated in Figure 5. Bland–Altman analyses revealed good agreement between the clinical and first home measurements, with narrow

TABLE 1 Demographic data and clinical characteristics of the children involved in the study.

Demographic data		
Gender	Female/male	8/3 (0.72)
Age (years)	Mean ± SD [min–max]	12.9 ± 3.1[8–17]
Body mass (kg)	Mean ± SD [min–max]	49.5 ± 18.5 [25–75]
Height (cm)	Mean ± SD [min–max]	153.5 ± 14.4 [130–174]
BMI (kg/m^2)	Mean ± SD [min–max]	20.5 ± 5.7 [13.9–32.9]
Overweight/obesity (IOTF criteria > 25)		3/11 (0.27)
Age at diagnosis of asthma	Mean [min–max]	4.72 [1–11]
Duration of asthma (years)	Mean [min–max]	8.11 [4–15]
Atopy-allergy		
Prick test or serum IgE (positive for inhalative allergens)		
	House dust mite	6/11 (0.54)
	Pollen	7/11 (0.63)
	Mold	1/11 (0.09)
	Dog dander	3/11 (0.27)
	Cat dander	3/11 (0.27)
Atopic dermatitis		1/11 (0.09)
Allergic rhino-conjunctivitis		8/11 (0.72)
Food allergy		2/11 (0.18)
Treatment (according to GINA 2024)		
SABA (as required)	(Step 1)	0/11
ICS only	(Step 2)	3/11 (0.27)
LTRA only	(Step 2)	2/11 (0.18)
Combined ICS + LTRA	(Step 3)	2/11 (0.18)
Combined ICS + LABA/RABA	(Step 3)	2/11 (0.18)
Combined LTRA + ICS + LABA/RABA	(Step 4)	2/11 (0.18)
Severity (GINA level)		
Intermittent (level 1)		0/11
Mild persistent asthma (level 2)		9/11 (0.82)
Moderate persistent (level 3)		2/11 (0.27)
Severe persistent (level 4)		0/11
Asthma control		
> 1 medical consultation for asthma exacerbation in previous year		10/11 (0.91)
> 1 hospitalization for asthma in the previous year		1/11 (0.09)
> 1 hospitalization in intensive care for asthma, ever		0/11
Control according to GINA score	Well controlled	5/11
	Partly controlled	6/11 (0.54)
	Uncontrolled	0/11 (0.45)
ACT score < 20 (uncontrolled)	[min–max]	3/11 (0.27) [11–19]

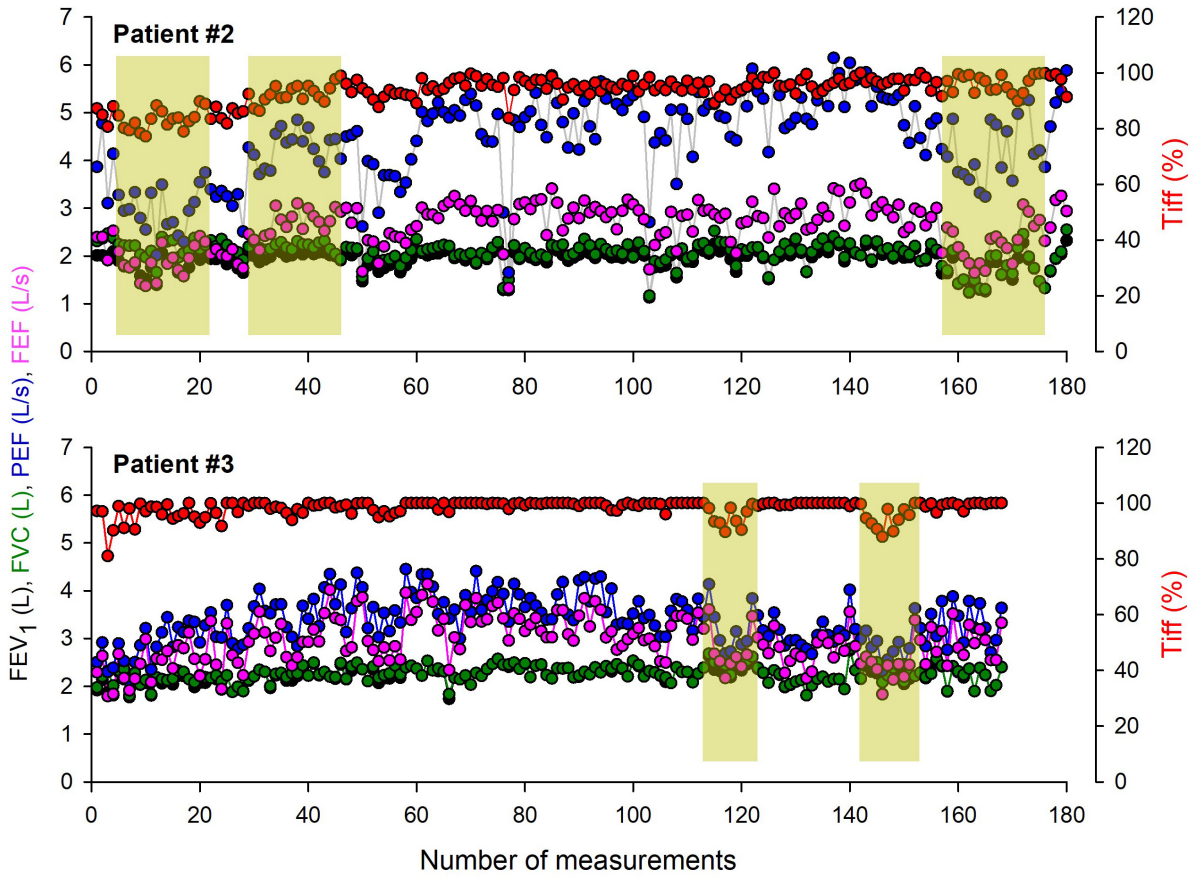

FIGURE 2
Time series of home spirometry parameters recorded over a one-year monitoring period in two representative children with moderate asthma. The graphs illustrate key respiratory function parameters, including forced vital capacity (FVC), forced expiratory volume in the first second (FEV_1), FEV_1/FVC ratio (Tiffeneau index), peak expiratory flow (PEF), and forced mid-expiratory flow (FEF_{25-75}). Periods requiring specialist intervention are highlighted, indicating clinical deterioration, symptom exacerbation, or significant deviations from baseline values.

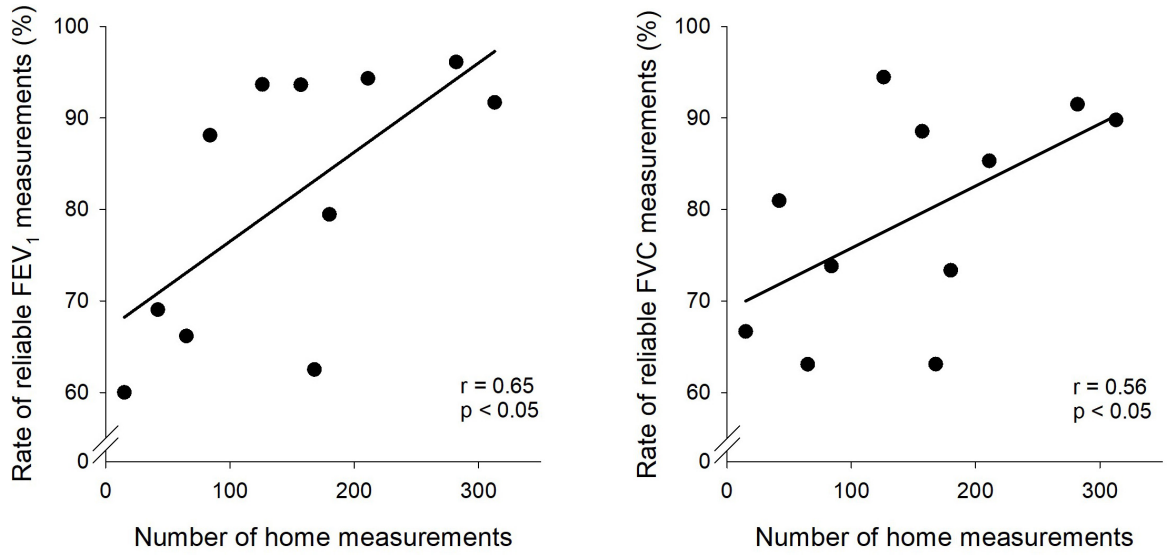

FIGURE 3
Association between home spirometry frequency and measurement reliability. Scatter plots depict the relationship between the number of home spirometry measurements and the reliability of forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) measurements.

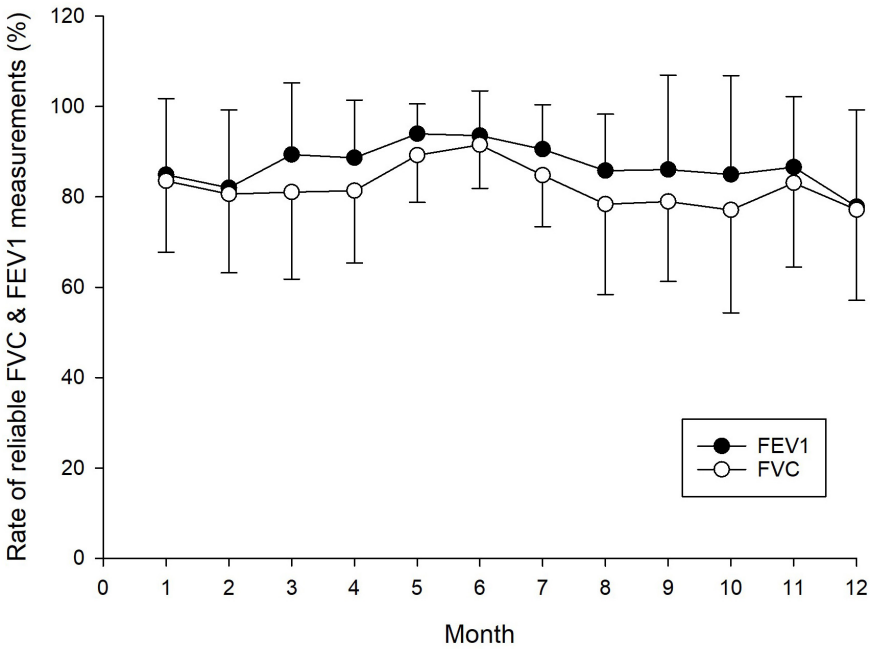

FIGURE 4
Reliability of home spirometry measurements over a 12-month period, showing the rate of reliable forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) measurements. Each data point represents the mean and standard deviation of reliable FEV_1 and FVC measurements.

limits of agreement for FVC (0.75 L), FEV_1 (0.69 L), and Tiff (10.0%) and somewhat wider limits of agreement for PEF (3.0 L/s) and FEF_{25-75} (1.6 L/s). Statistically significant correlations were observed between the clinical and home recordings, with the strongest correlation for FVC ($r = 0.966$, $p < 0.001$) and the least robust associations for PEF ($r = 0.71$, $p < 0.05$).

Expressing the spirometric parameters as percentage predicted values exhibited similar trends to those observed for their absolute values, as demonstrated in Figure 6. The narrowest limits of agreements were obtained by the Bland–Altman analyses for Tiff% (11.8%) and were intermediate for $FEV_{1\%}$ (23.7%) and FVC% (23.8%), and were the widest for $FEF_{25-75\%}$ (46.3%) and PEF% (52.7%). FVC% showed the strongest ($r = 0.93$, $p < 0.001$), while PEF% demonstrated the weakest correlation ($r = 0.74$, $p < 0.05$).

Ninety-five percent confidence intervals for the bias and limits of agreement for all key parameters, in both absolute and percentage predicted values, are presented in Table 2.

Discussion

The present study evaluated the feasibility of home lung function assessments in a vulnerable pediatric population with asthma bronchiale, focusing on the reliability, accuracy, and consistency of home-based spirometric measurements. Our results demonstrate a high acceptance rate in obtaining home spirometry parameters (> 60%) and generally stable lung function over the 12-month study period, with occasional temporary declines in key lung function outcomes. A positive correlation was observed between the number of home spirometry measurements and the reliability of FEV_1 and FVC estimates. Throughout the 12-month period, the rate of reliable FEV_1 and FVC measurements remained stable, with no significant temporal effects. Comparisons between clinical and initial home spirometry measurements showed strong correlations and good agreement, particularly for FVC and FEV_1. When expressed as percentage predicted values, similar trends were observed, with FVC% exhibiting the strongest correlation and PEF% the weakest. The narrowest limits of agreement were found for the Tiffeneau index, while PEF% and $FEF_{25-75\%}$ displayed the greatest variability.

In the present study, significant correlations were observed between the number of home measurements and the reliability of spirometry results in children with asthma (Figure 3). Accordingly, an increased frequency of home spirometry measurements in asthmatic children increases patient familiarity with the procedure and minimizes potential measurement errors, thereby leading to improved accuracy and reliability of spirometric outcomes (13). This finding is in line with the results of earlier studies emphasizing a positive correlation between the regularity of home measurements and the reliability of spirometry results, and underscoring the necessity for frequent assessments to augment the accuracy of monitoring processes (33).

The reliability of measurements in this study was defined based on ATS/ERS acceptance criteria (30). Accordingly, at least three technically acceptable spirometry tests were required for each child, ensuring that the two largest FVC and FEV_1 values differed by no more than 0.1 liter. The rate of reliable FVC and FEV_1 measurements during home spirometry was approximately 80% and remained stable throughout the 12-month follow-up period (Figure 4). Notably, a significant proportion of home measurements met the acceptance criteria established by international guidelines (30). This performance is substantially higher than that reported in adults with asthma (22) and in children with acute asthma exacerbations (34).

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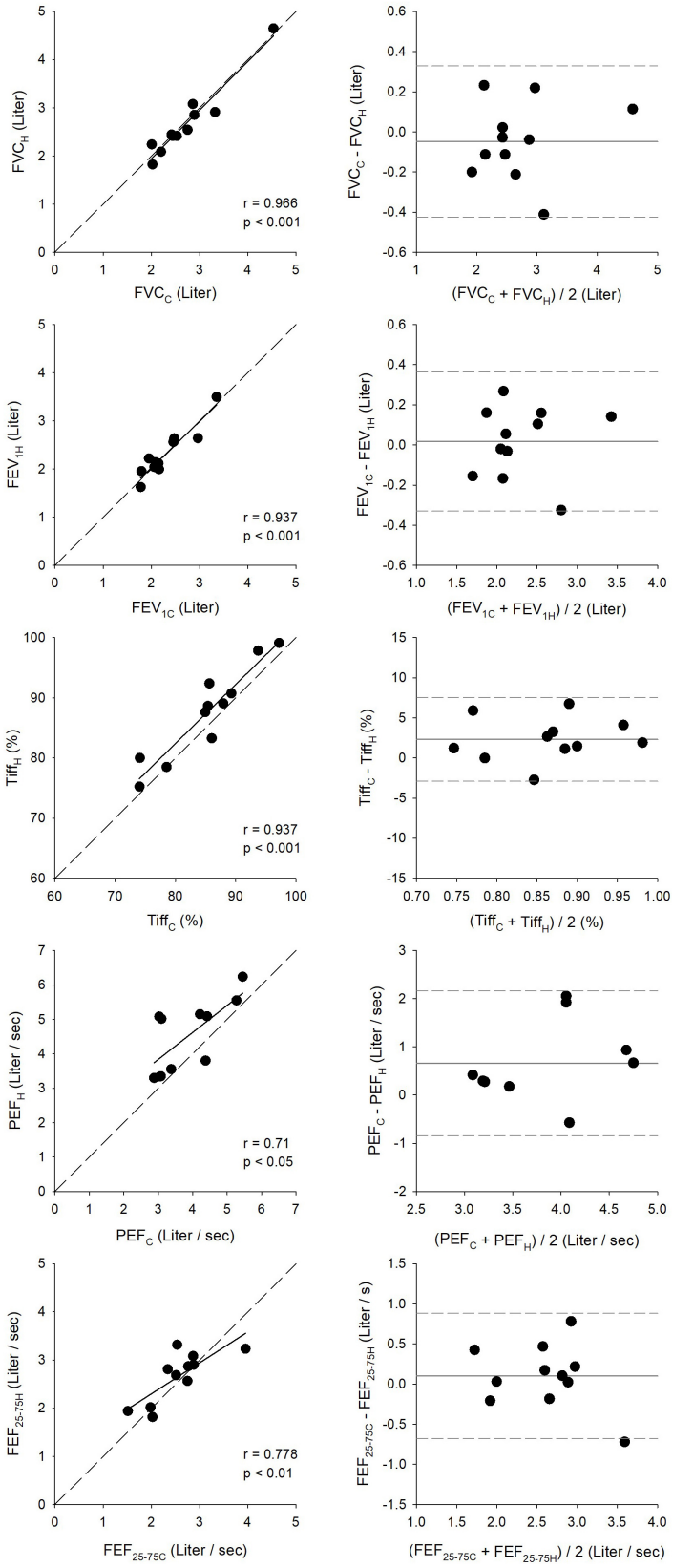

FIGURE 5
Correlation and agreement between clinical (C) and first home (H) spirometry measurements. The left panels show correlations between key respiratory parameters measured during clinical visits and first home assessments, including forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), peak expiratory flow (PEF), and forced mid-expiratory flow (FEF_{25-75}). The right panels present Bland–Altman plots, illustrating agreement and measurement consistency between clinical and home recordings.

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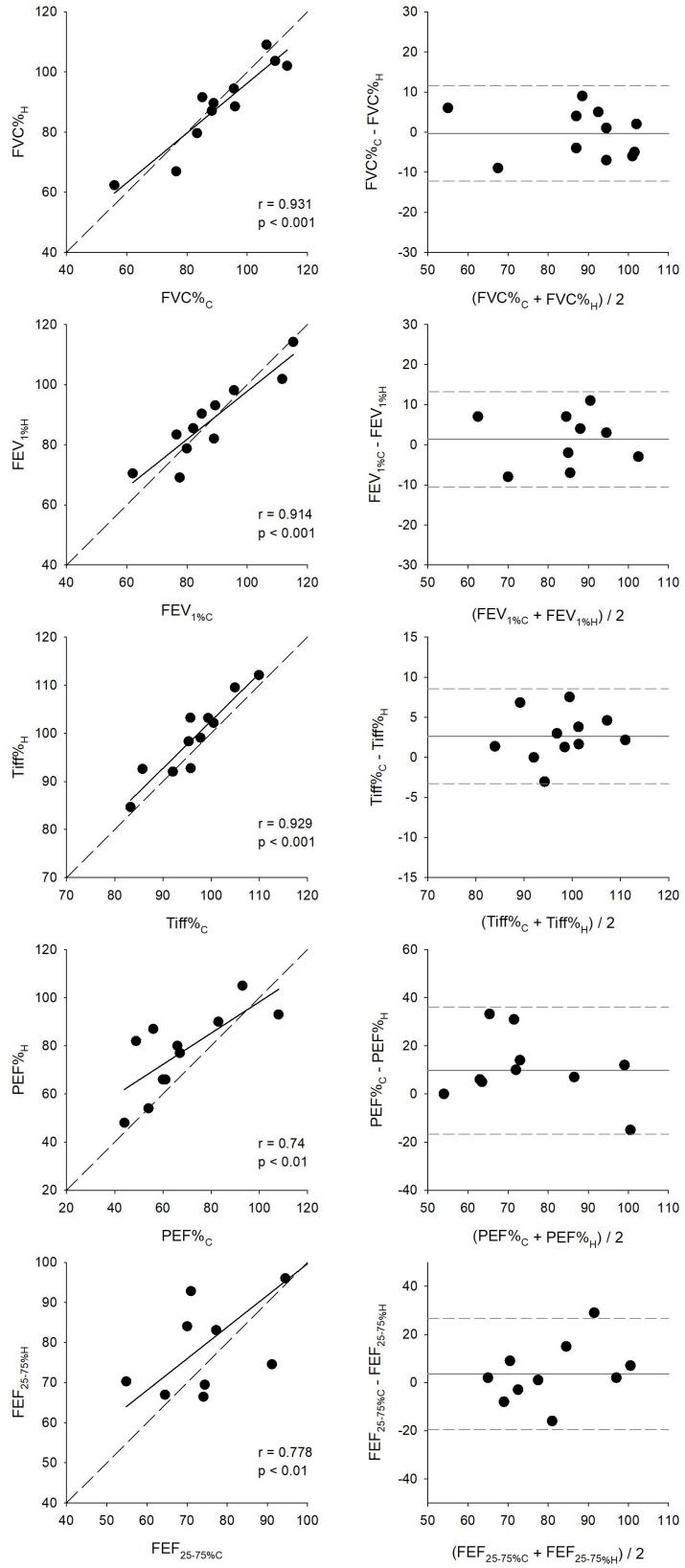

FIGURE 6
Scatter plots compare key respiratory parameters between clinical (C) and first home (H) spirometry measurements, including the percentage of forced vital capacity (FVC%), forced expiratory volume in the first second (FEV_1%), FEV_1/FVC ratio (Tiffeneau index, Tiff%), peak expiratory flow (PEF%), and forced mid-expiratory flow ($FEF_{25-75\%}$). All values are expressed as percentages of the predicted values set by the Global Lung Function Initiative (GLI). Correlation coefficients (*r*) and significance values (*p*) indicate the level of agreement between clinical and home measurements. Bland–Altman plots assess measurement consistency by displaying the mean difference between clinical and home values against their averages.

TABLE 2 Bland–Altman analysis of agreement between clinical and first home spirometry measurements, including bias, limits of agreement, and their 95% confidence intervals (CI).

Parameter	Bias (CI)	Lower limit (CI)	Upper limit (CI)
FVC (L)	0.048 (−0.180, 0.083)	−0.426 (−0.654, −0.198)	0.329 (0.102, 0.557)
FVC%	−0.36 (−4.50, 3.78)	−12.26 (−19.43, −5.09)	11.54 (4.36, 18.71)
FEV_1 (L)	0.017 (−0.103, 0.138)	−0.329 (−0.538, −0.121)	0.363 (0.155, 0.572)
FEV_1%	1.36 (−2.77, 5.49)	−10.50 (−17.65, −3.35)	13.23 (6.08, 20.38)
Tiff (%)	0.023 (0.005, 0.042)	−0.029 (−0.060, 0.003)	0.076 (0.044, 0.107)
Tiff%	2.65 (0.59, 4.70)	−3.25 (−6.81, 0.30)	8.55 (4.99, 12.11)
PEF (L/s)	0.657 (0.134, 1.180)	−0.846 (−1.751, 0.06)	2.160 (1.254, 3.065)
PEF%	9.75 (0.57, 18.92)	−16.62 (−32.51, −0.73)	36.11 (20.22, 52.00)
FEF_{25-75} (L/s)	0.100 (−0.171, 0.372)	−0.679 (−1.149, −0.210)	0.880 (0.410, 1.350)
FEF_{25-75}%	3.55 (−4.51, 11.61)	−19.62 (−33.58, −5.66)	26.71 (12.75, 40.67)

These findings underscore the feasibility of telemedical lung function monitoring through home spirometry, provided that children receive adequate training and parental supervision (13, 35–37). The high technical reliability of home-based spirometry in pediatric asthma presents a promising opportunity for enhanced disease management, potentially reducing the need for frequent specialist visits while minimizing associated risks, such as infection exposure and disruptions to daily activities (38).

Strong correlations and good agreement were observed between key spirometric parameters measured in clinical and home settings, whether expressed as absolute values or as percentages of predicted values (**Figures 5**, **6**). The mean differences for FEV_1 and FVC were within the Minimal Clinically Important Difference limits of 100–200 mL (or 5–10% of predicted values) (39). These findings highlight the potential of telespirometry for remote lung function monitoring in children with asthma. While strong agreement was observed for FVC and FEV_1, the wider limits of agreement for PEF and FEF_{25-75} suggest poorer reproducibility. These parameters are known to be more effort-dependent and technically variable, particularly in pediatric populations (40–42). Therefore, although trends in PEF and FEF_{25-75} may still offer useful context, they should be interpreted cautiously for distant clinical decision-making.

Interestingly, Tiff and PEF values measured at home were higher than those obtained in the clinical environment using the same handheld spirometer. This discrepancy may be attributed to comprehensive patient education, which ensured accurate home measurements. Furthermore, these findings suggest that home spirometry may yield more reliable and representative lung function data, as children perform the tests in a familiar, stress-free environment, potentially minimizing anxiety or the white-coat effect commonly observed in clinical settings. The absence of external pressures from a clinical environment or physician presence may enable children to perform spirometry in a more relaxed and natural manner, leading to consistently higher Tiff and PEF values in home assessments. These results are in accordance with earlier findings demonstrating strong correlations and good agreements between spirometric outcomes measured in clinical and home settings (22, 43).

A methodological limitation of the present study is the relatively small number of children included in the follow-up of lung function via telespirometry. This can be attributed to the technically demanding measurement conditions and the extended study duration of one year. Nevertheless, the data analyses yielded clear and statistically robust results, demonstrating convincing correlation coefficients and rational limits of agreement. Thus, the inclusion of this pediatric population was sufficient to draw well-founded conclusions on the reliability, accuracy, and consistency of home-based lung function measurements with high confidence. The relatively small sample size reflects the feasibility-focused design of the study, consistent with accepted practices for pilot investigations. Despite this limitation, the statistically significant correlations, as well as the consistent reliability outcomes observed, provide meaningful support for the feasibility of home telespirometry in pediatric asthma. Another limitation is the absence of a control group, such as standard hospital-based monitoring. Since our primary aim was to assess the technical performance and reliability of home spirometry rather than clinical outcomes, a control group was not incorporated by design.

In summary, the results of the present study support the feasibility and reliability of home spirometry for long-term respiratory monitoring in asthmatic children with digital literacy. The positive correlation between the rate of reliable home spirometry and the number of measurements demonstrates the importance of practice, besides training. The strong agreement with clinical measurements suggests that home spirometry could serve as a valuable tool for remote patient monitoring, potentially improving asthma control and management in this particularly vulnerable population. Moreover, the stability of reliability over time indicates that frequent at-home monitoring can provide consistent and clinically useful data, reinforcing its potential integration into routine pediatric patient care. Thus, the integration of telespirometry into asthma management for children has the promise to represent a significant advancement in healthcare delivery. Telespirometry enables long-term monitoring of spirometric data over weeks or months, tailored to the patient's clinical needs. It not only facilitates timely intervention during exacerbations but also empowers patients and their families to take an active role in managing the condition.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by the National Institute of Pharmacy and Nutrition, Hungary (No. OGYÉI/8725/2020; address: Hungary, 1051 Budapest, Zrínyi u. 3., dated 16 March 2020). The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

KK: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – original draft, Writing – review and editing. ZN: Conceptualization, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing – original draft, Writing – review and editing. FP: Conceptualization, Formal Analysis, Funding acquisition, Investigation, Methodology, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review and editing. JT: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review and editing. FR: Data curation, Formal Analysis, Writing – review and editing.

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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.

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