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Contents

Pediatric Asthma in Context: From Environmental Risks to Functional and Atopic Insights

Asthma remains the most prevalent chronic respiratory disease in children. The burden of pediatric asthma reflects not only its high prevalence but also the complex relationship between environmental exposures, immune response and genetic predisposition. Over the past decades, advances in epidemiology, biomarker development and lung function assessment continue to refine our understanding of asthma pathophysiology and inform more precise strategies for diagnosis, treatment, and monitoring. The three studies published in this issue provide important perspective on how environmental risk factors, physiological assessment and allergen sensitization influence the course and natural history of pediatric asthma.

The first article by Huang et al., *The effects of fine particulate matter of pediatric airway inflammation and lung function: an epidemiological perspective*,[1] underscores the critical role of environmental pollutants in contributing to airway inflammation and impaired lung function in children. Among the pollutants, fine particulate matter (PM2.5) is one of the most hazardous in urban environment. With the small diameter, it can penetrate deep into the distal airways, triggering oxidative stress, epithelial injury, and immune activation.[2] This is particularly concerning given the widespread presence of PM2.5 in urban settings and its impact on children, whose lung and immune systems are still developing and who are inherently more vulnerable to air pollution. The observed association between PM2.5 exposure and elevated fractional exhaled nitric oxide (FeNO) levels, together with reduction in lung function indices, underscores both biological plausibility of air pollution-induced asthma and the value of non-invasive biomarkers for monitoring its effects.[3] The review also highlights the urgency of comprehensive public health interventions to mitigate PM2.5 exposure in children and the need of research to evaluate the long-term effect of early life PM2.5 exposure.

The study by Lin et al., *Comparative analysis of the correlation among FeNO, impulse oscillometry, and spirometry in the assessment of childhood asthma,*[4] highlight a crucial issue in pediatric asthma care: no single test can capture the full spectrum of the disease activity. The negative correlation between FeNO and FEV1/FVC demonstrated in this study indicates the complementary role of inflammatory and functional assessments in asthma monitoring. In contrast, the lack correlation between FeNO and impulse oscillometry (IOS) indicates the complexity of asthma pathophysiology and suggests that airway inflammation may not always translate into measurable changes in resistance or reactance, or that these relationships are more modulated by other factors such as age, body size, or asthma phenotype. These findings emphasize that each modality captures different aspects of asthma pathophysiology: FeNO as a biomarker of inflammation, spirometry as a measure of airflow limitation, and IOS as a tool for evaluating small airway dysfunction. Combining these modalities offers a comprehensive understanding of airway function and inflammation. For clinicians, using an integrated strategy offers a more precise approach to both diagnosis and long-term monitoring of pediatric asthma, ensuring that treatment decision are aligned with the heterogeneity of the disease expression.

The third article by Tsai et al., *Differential contributions of inhalant and food allergen sensitization to atopic phenotype asthma prevalence among children across age groups,*[5] provides valuable insight into the complex interplay between allergen sensitization in pediatric asthma, in which sensitization profiles evolve with age and contribute differentially to the expression of the atopic phenotype. This study documented a low prevalence of sensitization in early life and predominace of aeroallergen sensitization in adolescent. This indicates the dynamic interaction between immune maturation and environmental exposures, which not only reinforces the role of environmental allergen exposure in sustaining chronic airway inflammation, but also emphasize the critical window for screening and intervention strategies in sensitized children.[6] While food allergies may dominate during infancy and early childhood, aeroallergens such as house dust mite, pollens and animal dander become more important driver of atopic asthma in school-aged children and adolescent. These findings invite a re-evaluation of current clinical approaches that may disproportionately focus on food avoidance, and instead emphasize the value of early screening for inhalant sensitization, proactive environmental control, and tailored counselling for families. Moreover, the strong correlation between main aeroallergen sensitization and atopic asthma prevalence revealed in this study strengthens the argument for prioritizing aeroallergen-focused strategies in both

research and clinical care. In sum, this work enriches our understanding of asthma heterogeneity and provides an evidence-based rationale for age-specific management paradigms that anticipate and address the shifting drivers of atopic disease across childhood and adolescent.

Taken together, these studies provide a multidimensional view of pediatric asthma. From the macro-environmental burden of air pollution, through the practical challenges of clinical assessment, to the immunological underpinnings of allergen sensitization, they collectively emphasize the need for comprehensive and integrated approaches in the management and research of asthma in children. Future research examining whether reductions in PM2.5 exposure alter the course of aeroallergen sensitization of modify biomarker patterns such as FeNO, may clarify the mechanistic pathways linking environment, immunity and lung function. By addressing environmental risks, deploying comprehensive diagnostic strategies, and tailoring interventions to age-specific sensitization profiles, we can better mitigate the burden of childhood asthma and its lifelong consequences.

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Theere are no conflicts of interest.

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Review Article

The Effects of Fine Particulate Matter on Pediatric Airway Inflammation and Lung Function: An Epidemiological Perspective

Ping-Chao Huang[1], Jeffrey Eli Whang[1], Ming-Sheng Lee[1,2], Huei-Shin Chang[1], Jia-Yuh Chen[1], Yi-Giien Tsai[1,2,3,4]

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Abstract

Fine particulate matter ($PM_{2.5}$) exposure is an escalating concern in pediatric respiratory health due to its pervasive presence and detrimental effects. Children are particularly susceptible because of their developing lungs, higher respiratory rates, and increased environmental exposure. $PM_{2.5}$ particles can penetrate deep into the lower airways, carrying toxic substances that trigger oxidative stress and airway inflammation, potentially disrupting normal lung development. Epidemiological studies have linked $PM_{2.5}$ exposure to decreased lung function and elevated levels of fractional exhaled nitric oxide, a noninvasive biomarker of airway inflammation. These effects are particularly pronounced in children with newly developed wheezing symptoms. This review summarizes current epidemiological evidence on $PM_{2.5}$-related airway inflammation and lung function changes in children, highlighting underlying biological mechanisms and underscoring the need for targeted prevention strategies to reduce long-term respiratory harm.

Keywords: Air pollution, asthma, exhaled nitric oxide, lung function, $PM_{2.5}$

Introduction

As reported by the World Health Organization, more than 90% of the global population in 2019 lived in regions where fine particulate matter ($PM_{2.5}$) concentrations exceeded recommended limits. This burden is particularly pronounced in low- and middle-income countries, where rapid industrialization, traffic-related emissions, and limited enforcement of environmental regulations contribute to persistently high exposure levels. In these regions, the impact of air pollution is further exacerbated by constrained healthcare systems and limited access to preventive care, which together increase the vulnerability of children to the health effects of $PM_{2.5}$ exposure.[1]

Children are especially susceptible to air pollution due to several physiological and behavioral factors. Compared to adults, children have developing lungs, faster respiratory rates, larger lung surface areas relative to body mass, and a greater tendency for mouth breathing—all of which increase their inhaled dose of pollutants per unit of body weight.[2] Due to higher respiratory rates, underdeveloped immune defenses, and greater time spent outdoors, children face heightened susceptibility to the harmful effects of airborne pollutants.[3]

Childhood asthma, a complex condition influenced by both genetic predisposition and environmental factors, has been consistently associated with exposure to ambient air pollution.[4] Air pollution not only contributes to the

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onset of asthma but also exacerbates its severity and frequency of symptoms in the pediatric population. Ambient $PM_{2.5}$ exposure has been closely linked to the development and exacerbation of pediatric respiratory diseases, most notably asthma.[5-8] Longitudinal studies have shown that chronic exposure to air pollution is associated with impaired lung function growth in both children and adults.[9-13] Conversely, interventions that improve air quality—such as stricter emission regulations and clean air initiatives—have been linked to significant improvements in lung function development during childhood, highlighting the potential for reversibility and the importance of timely policy action.[13,14] This review aims to synthesize current data on the respiratory health impacts of $PM_{2.5}$ in children, explore relevant pathophysiological mechanisms, and discuss potential public health and clinical interventions to mitigate long-term harm.

$PM_{2.5}$ Exposure and Airway Inflammation in Children

Children are especially sensitive to this powerful oxidant pollutant, which can cause airway inflammation when inhaled. When outdoor air pollution is severe, it can seep indoors, raising levels of indoor particulate matter. One of the primary mechanisms by which $PM_{2.5}$ induces respiratory harm is through the generation of oxidative stress. Prolonged exposure to $PM_{2.5}$ often leads to chronic inflammation, a major contributing factor to respiratory health issues. Exposure to $PM_{2.5}$ contributes to oxidative stress, disrupting the oxidative balance in the respiratory tract by increasing reactive oxygen species, overwhelming antioxidant defenses. This oxidative stress damages airway epithelial cells, impairs alveolar development, and interferes with tissue repair, ultimately compromising lung growth and function in children.[15]

Chronic airway inflammation, a hallmark of asthma, can be intensified by $PM_{2.5}$, which acts as a carrier for harmful substances such as polycyclic aromatic hydrocarbons and transition metals. These pollutants contribute to oxidative stress and inflict damage on airway tissues.[16,17] This persistent inflammatory environment promotes structural remodeling of the airways, including wall thickening, subepithelial fibrosis, and smooth muscle hypertrophy, which are pathognomonic of asthma. Long-term $PM_{2.5}$, exposure has been associated with measurable declines in lung function parameters such as forced expiratory volume in one second (FEV1) and forced vital capacity (FVC), particularly in children with preexisting respiratory conditions.[18] In individuals with severe asthma, $PM_{2.5}$ exposure elicits heightened cytokine responses.[19]

Fractional exhaled nitric oxide (FENO) is a noninvasive biomarker that reflects eosinophilic airway inflammation and serves as an indicator of asthma severity.[20,21] Elevated FENO levels have been linked in various studies to exposure to ambient and traffic-related air pollution over both short and prolonged periods.[5,22-24] At the molecular level, $PM_{2.5}$ exposure may influence FENO expression through epigenetic modifications, such as altered methylation of the inducible nitric oxide synthase (iNOS or NOS2) gene promoter, potentially enhancing nitric oxide production in airway tissues.[25] A meta-analysis confirms underscoring the urgent that even short-term increases in $PM_{2.5}$ are associated with significant elevations in FENO, reinforcing its utility as a biomarker for pollution-induced airway inflammation in children.[22] FENO is particularly valuable in pediatric research due to its noninvasive, cost-effective, and reproducible nature, enabling large-scale monitoring of subclinical inflammation in at-risk populations.[26,27] In mainland China, studies have reported substantial FENO elevations across a wide range of $PM_{2.5}$ concentrations, with increases ranging from 9% to 36.5% per IQR increase in personal $PM_{2.5}$ exposure.[26] Our recent study involving Taiwanese children residing near coal-fired power plants offers important evidence on the impact of long-term $PM_{2.5}$ exposure on asthma prevalence and FENO levels. We observed that annual $PM_{2.5}$ exposure is significantly associated with increased FENO, with each unit rise in $PM_{2.5}$ linked to a measurable elevation after adjusting for confounders.[5]

Impact of $PM_{2.5}$ Exposure on Lung Function

Children are in a critical stage of lung development, making them especially vulnerable to the harmful effects of $PM_{2.5}$. Prolonged exposure can impair lung growth and increase susceptibility to respiratory symptoms later in life. $PM_{2.5}$ can reach the lower respiratory tract, increasing the risk of wheezing and airflow limitation in children.[16] Clarifying how $PM_{2.5}$ exposure affects lung function development is crucial for understanding the mechanisms underlying pediatric asthma and guiding effective prevention strategies.[16,17] Acute $PM_{2.5}$ exposure can also result in transient declines in lung function. Studies have reported immediate reductions in parameters such as forced expiratory volume in one second (FEV1) and peak expiratory flow (PEF), along with increased respiratory symptoms, particularly in children with underlying asthma or heightened airway sensitivity. Notably, children with severe asthma experience a more pronounced decline in lung function following exposure, suggesting that disease severity modifies the inflammatory and functional response to air pollution.[28]

These findings underscore the respiratory vulnerability of pediatric populations to ambient particulate pollution and reinforce the need for continuous monitoring and mitigation efforts.[29-33] These discrepancies may stem from regional differences in pollution levels and composition, individual genetic susceptibility, exposure timing, coexisting allergic or respiratory conditions, and variations

in exposure assessment methods.[11,28,34,35] Nevertheless, cohort studies utilizing land-use regression and ground-level monitoring data—such as those from the European Study of Cohorts for Air Pollution Effects (ESCAPE)—have consistently shown that prolonged $PM_{2.5}$ exposure is associated with measurable declines in lung function, including significant reductions in FEV1 among school-aged children.[9]

The relationship between $PM_{2.5}$ exposure and new-onset wheezing involves several factors, such as airway inflammation, oxidative stress, and hindered lung development.[13,36] Our study demonstrates a strong link between long-term $PM_{2.5}$ exposure and increased wheezing, reduced lung function growth, and elevated FENO levels in children. The effects were especially pronounced in the 207 children with new-onset wheezing, highlighting greater susceptibility among previously asymptomatic individuals. In this group, elevated $PM_{2.5}$ exposure was associated with a significant reduction in FEV_1 by 13 mL and an increase in FENO levels by 0.847 ppb, compared with a reduction in FEV_1 by 9 mL and an increase in FENO levels by 0.387 ppb in the 2914 healthy children [Figure 1].[37] The findings of reduced lung function growth and heightened airway inflammation, particularly in children presenting with new-onset wheezing, underscore the increased vulnerability of the pediatric population to ambient air pollution.[37]

One meta-analysis has demonstrated that each 1 μg/m³ increase in long-term $PM_{2.5}$ exposure is associated with a reduction of 6.1 mL in FEV1 (95% confidence interval [CI] = 2.6–9.6) and 5.4 mL in FVC (95% CI: 7.3–101.6).[30] Tables 1 and 2 in this review summarize current findings on short- and long-term exposure effects, respectively, reinforcing the consistent link between ambient particulate pollution and compromised pulmonary function. These declines in lung function parameters—key indicators of respiratory capacity and health—suggest that sustained exposure to fine particulate matter may hinder optimal lung development and contribute to a progressive decline in pulmonary function over the lifespan. Such findings reinforce growing concerns about the cumulative impact of air pollution on population-level respiratory health, particularly among vulnerable groups such as children and individuals with pre-existing respiratory conditions.

Geographical Disparities and Mitigation Strategies

The adverse impact of $PM_{2.5}$ on pediatric respiratory health highlights an urgent need for targeted policy interventions to protect vulnerable populations.[16,58] Evidence-based strategies, including the use of ultralow-sulfur diesel fuels in school transportation and the implementation of high-efficiency air filtration systems in residential settings, have demonstrated significant benefits. These include reductions in airway inflammation, as evidenced by decreased FENO levels, and improvements in lung function among children with asthma.[59]

Marked geographical disparities in $PM_{2.5}$ exposure and air quality management contribute to differing health outcomes across regions. In highly polluted regions like parts of China and Iran, studies report significant declines in FEV_1 and FVC, reflecting the dose-dependent impact of $PM_{2.5}$.[33,40,52] In contrast, countries with stringent air quality standards—such as those in North America and Western Europe—have observed notable reductions in childhood asthma incidence and improvements in lung function growth following the implementation of cleaner air policies.[54,57] Figure 2 presents meta-regression results of long-term $PM_{2.5}$ exposure on lung function across different continents, based on Zhang *et al*.[58]

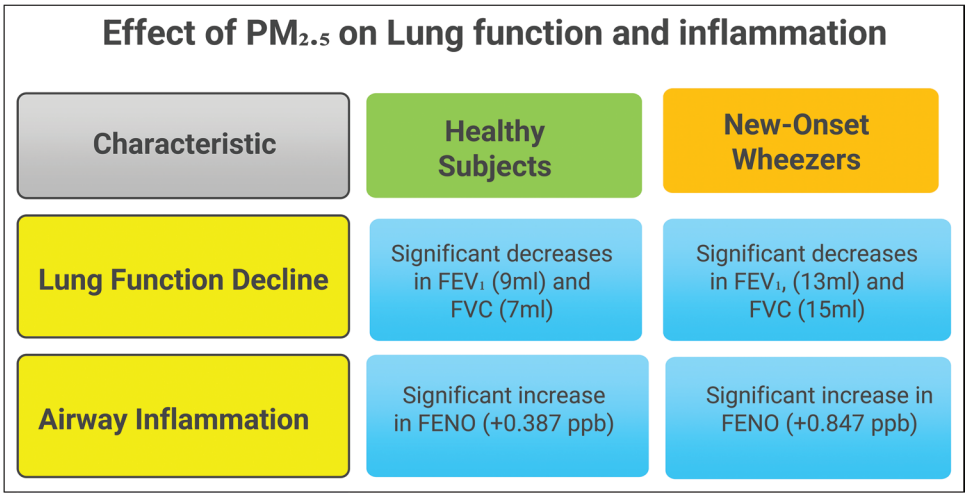

Figure 1: The impact of a 1 μg/m³ increase in annual $PM_{2.5}$ exposure on lung function and FENO changes between 2914 health children and 207 new-onset wheezer children[37]

Table 1: Summary of short-term $PM_{2.5}$ exposure and lung function in the pediatric studies

$PM_{2.5}$ ($\mu g/m^3$)	Region	Cases (*n*)	Age (years)	FEV1 (mL)	PEFR (L/min)	FVC (mL)	Reference
88	Dhaka, Bangladesh	315	12	FEV1: −18.74 mL (95% CI −27.05 to −11.21)	PEFR: −1.20 L/min (95% CI −1.63 to −0.76)		[38]
84.3	Nanjing, China	86	9	FEV1: −18.93 mL (95% CI −28.52 to −9.34)	PEFR: −1.76 L/min (95% CI −3.55 to −0.024)	FVC: −23.22 mL (95% CI −33.25 to −13.19)	[39]
84.3	Ahvaz, Iran	90	12.1	FEV1: −84.62 mL (95% CI −130.57 to −50.27)		FVC: −100.77 mL (95% CI −146.15 to −46.15)	[40]
67.6	Tianjin, China	198	9.5	FEV1: −14.21 mL (95% CI −29.60 to −0.81)		FVC: −21.53 mL (95% CI −39.90 to −3.97)	[41]
67.6	Zhejiang, China	848	9.7	FEV1: −32.56 mL (95% CI −43.71 to −21.41)	PEFR: −4.05 L/min (95% CI −5.36 to −2.73)	FVC: −33.74 mL (95% CI −45.92 to −22.52)	[31]
34	Heshan, China	57	9.8	FEV1: −14.66 mL (95% CI −22.60 to 6.72)			[42]
30.9	Yuge Island, Japan	43	15.1	FEV1: −22.38 mL (95% CI −45.86 to 1.10)	PEFR: −2.48 L/min (95% CI −3.60 to −0.81)		[43]
28.9	Multicentre, Mexico	50	9.3	FEV1: −12 mL (95% CI −24.17 to 0.22)		FVC: −16.57 mL (95% CI −30.17 to −2.49)	[44]
26.1	Taiwan	1494	11.8	FEV1: −8.93 mL (95% CI −42 to 24.15)		FVC: −9.64 mL (95% CI −42.19 to −22.90)	[45]
25	Yotsukaido, Japan	17	11		PEFR: −2.96 L/min (95% CI −4.55 to −1.37)		[46]
24.3	Alta Floresta, Brazil	280	10.4		PEFR: −0.21 L/min (95% CI −0.46 to 0.05)		[35]
19.6	Mato Grosso, Brazil	227	10.3		PEFR: −0.54 L/min (95% CI −0.95 to −0.14)		[47]
12.7	Birmingham, UK	162	9		PEFR: −2.80 L/min (95% CI −5.31 to −0.20)		[48]
11.3	Seattle, USA	17	9	FEV1: −16.12 mL (95% CI −42.61 to 10.37)	PEFR: −2.19 L/min (95% CI −6.49 to 2.12)		[49]
10.7	Shimane Prefecture, Japan	399	8.5		PEFR: −2.41 L/min (95% CI −3.36 to −1.47)		[50]

Age (years) represents the mean age of participants in each study

Table 2: Summary of long-term $PM_{2.5}$ exposure and lung function in the pediatric studies

PM2.5 ($\mu g/m^3$)	Region	Cases (*n*)	Age (years)	FEV1 (mL)	PEFR (L/min)	FVC (mL)	Reference
107.5	Multicentre, China	3273	9	FEV1: −2.7 mL (95% CI −3.5 to −2)		FVC: −3.5 mL (95% CI −4.3 to −2.7)	[51]
54	Liaoning, China	6740	11.6	FEV1: −123.22 mL (95% CI −150 to −94.45)	PEFR: −10.13 L/min (95% CI −13.71 to −6.54)	FVC: −173.29 mL (95% CI −203.29 to −143.33)	[52]
34.5	Taiwan	2941	12	FEV1: −33.60 mL (95% CI −52.73 to −14.87)		FVC: −33.22 mL (95% CI −52.44 to −12.01)	[53]
28.65	Taiwan	5364	9.7	FEV1: −7 mL (95% CI −10 to −4)		FVC: −5 mL (95% CI − 8 to 0)	[37]
16.2	Multicentre, Netherlands	969	12	FEV1: −84.93 mL (95% CI −160.6 to −9.80)		FVC: −94 mL (95% CI 11.76 to 176.25)	[54]
15.9	Multicentre, Netherlands	1058	8			FVC: −381.9 mL (95% CI −731.64 to −36.18)	[55]
13.3	Multicentre, USA	1811	11.2	FEV1: −54.69 mL (95% CI −86.50 to −22.32)		FVC: −40.09 mL (95% CI −85.96 to −11.35)	[10]
12.3	Oslo, Norway	1847	9.8	FEV1: −28.89 mL (95% CI −64.44 to 6.67l)	PEFR: −9.62 L/min (95% CI −15.57 to −3.52)	FVC: −10.83 mL (95% CI −49.72 to 28.06)	[56]
11.5	Boston, USA	614	7.9	FEV1: −71.5 mL (95% CI −182.5 to −39.5)		FVC: −109 mL (95% CI −226 to 8.5)	[57]
11.2	Multicentre, Europe	5921	7	FEV1: −77.19 mL (95% CI −141.67 to −11.16)	PEFR: −10.30 L/min (95% CI −20.15 to −0.20)	FVC: −305.52 mL (95% CI−708.27 to −156.39)	[9]

Age (years) represents the mean age of participants in each study

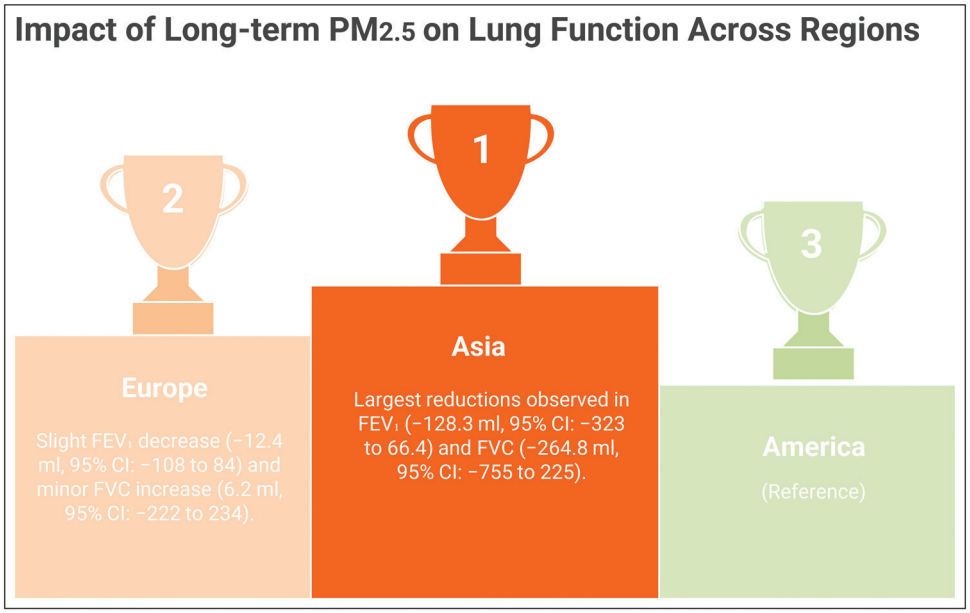

Figure 2: The impact of a 1 $\mu g/m^3$ increase in annual $PM_{2.5}$ exposure on lung function across region in children. The figure now depicts meta-regression results of long-term $PM_{2.5}$ exposure, derived from Zhang *et al.*[30]

underscores the urgent need for targeted policy interventions in regions with elevated $PM_{2.5}$ levels to protect vulnerable pediatric populations.

This review highlights the need for comprehensive strategies to reduce $PM_{2.5}$ exposure. Key interventions include installing air quality monitoring systems in schools, limiting outdoor activities during peak pollution periods, and enhancing indoor air quality with HEPA filters—particularly for children with asthma. Continued longitudinal research is essential to fully understand the long-term effects of early-life $PM_{2.5}$ exposure and to inform evidence-based standards and pediatric respiratory health strategies.

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Conflicts of interest
There are no conflicts of interest.

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Original Article

Comparative Analysis of the Correlation Among Fractional Exhaled Nitric Oxide, Impulse Oscillometry, and Spirometry in the Assessment of Childhood Asthma

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Abstract

Background: Fractional exhaled nitric oxide (FeNO), impulse oscillometry (IOS), and spirometry are three types of noninvasive methods for assessment of pediatric lung function, which could be used to diagnose and evaluate childhood asthma. This study aims to evaluate the correlation among these three methods for childhood asthma evaluation. **Methods:** This retrospective study utilized data from the China Medical University Hospital, Clinical Research Data Repository. Asthma patients aged 6–12 years old who underwent FeNO, IOS, and spirometry testing on the same day were first identified. The data from FeNO, IOS, and spirometry reports were first extracted from the report text. Thereby, the correlation matrices between FeNO and IOS (resistance and reactance) and between FeNO and spirometry (FEV1/FVC ratio) were plotted. The Pearson correlation coefficient (r) and P value were subsequently calculated. **Results:** A total of 337 children with asthma aged 6–12 (male to female 60.8%:39.2%) were ultimately included in the study. The median of FeNO values was 21 ppb, and the median of FEV1/FVC and FEV1 values was 87% and 98.2%, respectively. A statistically significant negative correlation between FeNO and FEV1/FVC was observed ($r = -0.174$, $P = 0.002$). However, there was no significant correlation between FeNO and IOS parameters. **Conclusions:** FeNO, IOS, and spirometry are important methods for evaluation of childhood asthma. In this study, the FEV1/FVC ratio was observed to have a negative correlation with FeNO. However, there is no statistically significant correlation between FeNO and IOS parameters. Therefore, this study concludes that a combination of all three pulmonary functional tests, FeNO, IOS, and spirometry, is the best strategy for evaluating childhood asthma.

Keywords: Childhood asthma, FeNO, IOS, spirometry

Introduction

Lung function tests have attracted interest for the diagnosis and follow-up of childhood asthma in recent years. However, respiratory functional evaluation in young children remains an unresolved problem. For young children who are unable to perform forced expiratory maneuvers properly, impulse oscillometry (IOS) performed during spontaneous breathing without forced expiratory maneuvers may be an alternative tool.[1] IOS emerged over 50 years ago and permits the passive measurement of lung mechanics. By imposing sound waves on normal tiding breathing, flow and pressure disturbances can be detected and utilized to calculate airflow resistance and reactive parameters related to lung volume and pulmonary energy return. Because IOS does not require extensive patient cooperation, it is useful in assessing pulmonary function among pediatric

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patients. Furthermore, IOS parameters can be used for early detection of changes in lung function and proves to be superior to spirometry in predicting disease exacerbation among asthmatic patients and successful in differentiating small airway obstruction from large airway obstruction.[2]

Another method for evaluating pediatric asthma is the use of fractional exhaled nitric oxide (FeNO), which utilizes an endogenous gaseous molecule that can be measured during the breath test to provide information about eosinophilic inflammation.[3] According to Wang *et al.*[4], higher FeNO levels correspond to increased risk of acute exacerbations among patients with moderate-to-severe asthma. The 2017 National Institute for Health and Care Excellence guidelines recommended FeNO as a supporting tool for asthma diagnosis, with a high FeNO result having a 54%–95% positive predictive value (PPV) in adults and 90% PPV among schoolchildren.[4] FeNO has been studied extensively as a marker of respiratory inflammation and incorporated into an algorithm for asthmatic management.[5]

Both IOS and FeNO are methods for diagnosis and follow-up of childhood asthma, but the clinical relationship between these methods and its clinical status are not clear. For the purpose of verifying the association of FeNO, IOS, and spirometry in pediatric asthma, this retrospective, multi-variance study was performed incorporating data from 337 asthmatic children aged 6–12 from 2019 to 2021 in Taichung, Taiwan.

Materials and Methods

Study subjects

This retrospective cohort study was conducted at China Medical University Hospital (CMUH), a tertiary medical center located in central Taiwan. The study utilized data from the iHi Data Platform, which provides a unified dataset encompassing 537,801 patients who received care at CMUH between January 1, 2018, and December 31, 2021.[6]

All patients managed during the study period were evaluated based on the GINA 2016 classification, regardless of their level of clinical control or disease severity.[5] Patient data included information on administrative and demographic details, diagnoses, medical and surgical procedures, prescriptions, laboratory results, physiological monitoring parameters, hospitalization records, and catastrophic illness status as defined by the National Health Insurance Administration. This study was approved by the Big Data Center and the Institutional Review Board of China Medical University Hospital (CMUH109-REC1-024). The original research project was approved for the period from February 27, 2020, to February 26, 2021. An amended version of the research project was subsequently approved, extending the valid period from January 29, 2021, to February 26, 2021, in compliance with the ICH Good Clinical Practice guidelines and applicable governmental laws and regulations..

Study population

From 2018 to 2021, asthmatic patients (older than 6 years old and less than 18 years) who underwent spirometry, IOS, and FeNO on the same day at the outpatient department of CMUH were enrolled. Patients were included irrespective of their current use of asthma controller medications and excluded if they had an acute respiratory tract infection at the time of testing or had more than four concurrent ICD-coded diagnoses during the same clinical encounter, to minimize the inclusion of patients with potentially confounding comorbidities [Figure 1].

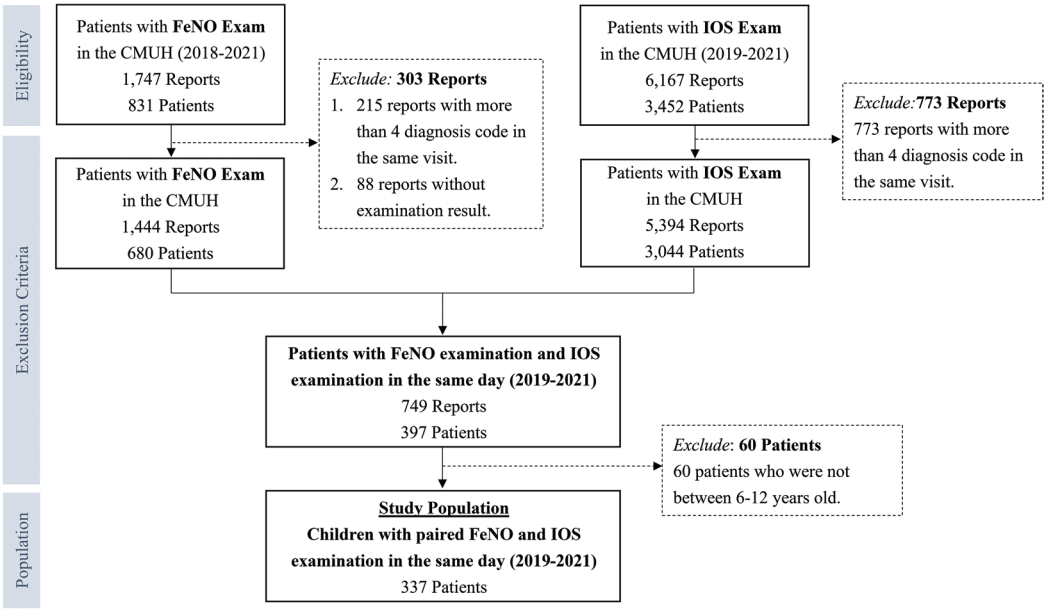

Figure 1: Flow chart. Selection process of the study population

IOS was routinely performed before spirometry. The participants were seated in a chair and squeezed their cheek to reduce the shunting of the upper airway when the examination was conducted under the supervision of experienced technicians.

In this study, the parameters of spirometry, including forced vital capacity (FVC), forced expiratory volume in the first second (FEV1), and ratio of FEV1 to FVC (FEV1/FVC), were collected. The parameters of IOS, including mean values of resistance at 5 Hz (R5) and 20 Hz (R20), reactance at 5 Hz (X5), the area under the curve for negative reactance values (AX), resonance frequency (Fres), and the difference between R5 and R20 (R5–R20), were saved for later analysis.[7,8] FeNO was measured using a CLD 88 (Eco Medics, Duernten, Switzerland) at a constant expiratory flow rate of 50 mL/s.[9] Potential confounding factors such as recent exercise or food intake (nitrate-rich foods, especially leafy vegetables such as lettuce, beetroot, and spinach) influences on FeNO measurements were communicated to patients prior to testing to ensure adherence to standard testing conditions.

Statistical analysis

Patients' characteristics, spirometry results, IOS parameters, and FeNO values were collected. Values with a parametric distribution in the text and tables are expressed as continuous variables and presented as the median (IQR). FeNO, spirometry, and IOS parameters were each subjected to Z-score, log-, and rank-based inverse normal transformations were used to assess the normality. Parameters normally distributed after Z-score or log-transformation were analyzed accordingly; otherwise, rank-based inverse normal transformation was applied. A correlation matrix was used to visualize the relationships among FeNO, spirometry parameters, and IOS parameters after rank-based inverse normal transformation. Pearson's correlation coefficient was calculated to determine the strength of these correlations. A P value of <0.05 was considered statistically significant. All statistical analyses were performed using SAS (version 9.4; SAS Institute Inc., Cary, NC, USA) and R (version 3.5.1; R Foundation for Statistical Computing, Vienna, Austria).

Results

From 2018 to 2021, this study recruited 831 patients who received an FeNO exam and 3452 patients with an IOS exam. After applying the exclusion criteria described in the *Material and Methods* section, a total of 337 asthmatic patients (median age 7.8 years, 205 males and 132 females) who underwent FeNO, IOS, and spirometry on the same day were enrolled in the study [Figure 1]. Baseline demographic and clinical characteristics of 337 patients with paired FeNO and IOS measurements are shown in Table 1.

Figure 2 shows the correlation matrix between FeNO and spirometry parameters (FEV1/FVC and FEV1). FeNO was also compared with IOS parameters (Pre-R5, Pre-R20, R5-R20, X5, Fres, and AX.). The correlation matrices between these two variables are shown in Figures 3 and 4. No statistically significant correlations between FeNO and parameters of IOS were found, but there is a statistically significant negative correlation between FeNO and FEV1/FVC ($r = -0.202$, $P < 0.001$), as shown in Figure 2.

Table 1: Baseline demographic and clinical characteristics of 337 patients for FeNO and IOS

Characteristic[a]	Available *N* (%)	Total (*N* = 337)
Demographic information		
Age (year)	337 (100.0)	7.8 (6.7, 9.5)
Male	337 (100.0)	205 (60.8)
Height (cm)	312 (92.6)	126.1 (118.5, 134.8)
Weight (kg)	334 (99.1)	25.9 (22.0, 34.6)
Body mass index (kg/m^2)[b]	312 (92.6)	16.4 (15.0, 19.2)
Baseline comorbidities[c]		
Asthma	337 (100.0)	294 (87.2)
Allergic disease	337 (100.0)	255 (75.7)
Eczema	337 (100.0)	71 (21.1)
OSA	337 (100.0)	17 (5.0)
FeNO, ppb	337 (100.0)	21.0 (11.0, 40.0)
Lung function		
FEV1/FVC, %	308 (91.4)	87.0 (81.0, 92.0)
FEV1, L	308 (91.4)	1.5 (1.2, 1.8)
FEV1, %	308 (91.4)	98.2 (88.3, 107.4)
FVC, L	308 (91.4)	1.7 (1.4, 2.0)
FVC, %	308 (91.4)	96.0 (88.9, 103.7)
RV, %	64 (19.0)	154.4 (141.9, 194.7)
DLCO SB, %	98 (29.1)	113.2 (101.9, 126.4)
IOS analysis		
Pre R5%	336 (99.7)	119.2 (99.8, 142.5)
Pre R20%	337 (100.0)	106.8 (91.7, 121.3)
R5–R20, kPa/(L/s)	337 (100.0)	0.3 (0.2, 0.5)
Pre R5%–Post R5%	80 (23.7)	44.9 (30.0, 61.3)
X5, kPa/(L/s)	337 (100.0)	−0.2 (−0.3, −0.1)
Resonant frequency, 1/s	333 (98.8)	18.7 (5.1, 23.1)
AX, kPa/L	217 (64.4)	2.3 (1.4, 3.5)

DLCO SB = single breath diffusing capacity of the lung for carbon monoxide, FeNO = fractional exhaled nitric oxide, FEV1 = forced expiratory volume in one second, FVC = forced vital capacity, IOS = impulse oscillometry system, OSA = obstructive sleep apnea.

[a]Categorical variables are presented as frequency (%) and continuous variables are presented as median (IQR).

[b]Body mass index = weight (kg)/height2 (m^2), and both weight and height measured from 1 month before and closest to the index date.

[c]Comorbidities were defined as having the ICD-9 or ICD-10 for asthma (493, J45), allergic disease (477, J30.2, J30.3, J30.5, J30.9, J30.81, J30.89), eczema (692.0–692.6, 692.9, L23.1, L23.3, L23.5-L23.7, L23.9, L24.0–L24.7, L24.9, L25.1, L25.3–L25.5, L25.9, L30.0, L30.2, L30.8, L30.9), OSA (327.2, 780.51, 780.53, 780.57, G47.3) and cerebral palsy (343, G80.0, G80.1, G80.2, G80.4–G80.9) any time prior to the index FeNO/IOS exam

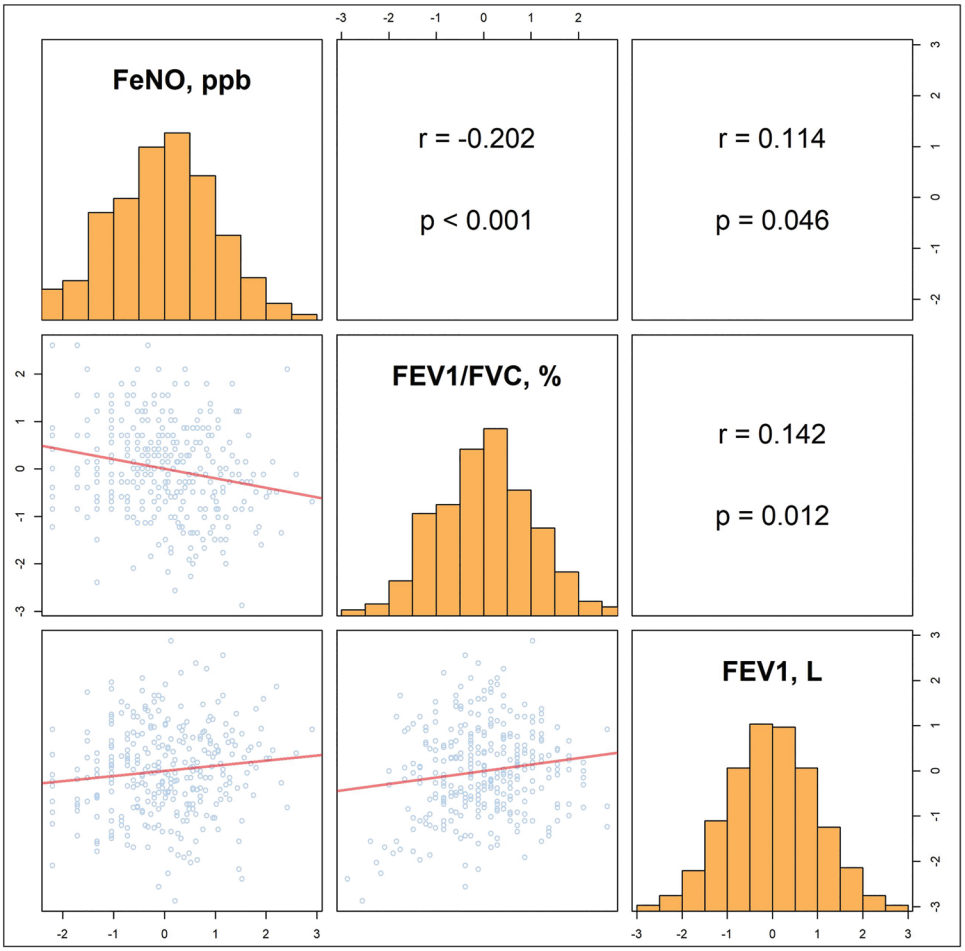

Figure 2: Correlation analysis of the fraction of exhaled nitric oxide and spirometry parameters (FEV1/FVC, EFV1). The pair-wise scatter plots are in the lower and left panels, and the correlations are in the upper and right panels. Rank-based inverse normal transformation was used to standardize the FeNO and spirometry parameters. FeNO = fractional exhaled nitric oxide, FEV1 = forced expiratory volume in one second, FVC = forced vital capacity

Discussion

The present study aimed to elucidate the interrelationships between three pivotal noninvasive methods—FeNO, IOS, and spirometry—in the assessment of pediatric asthma. These methods are integral in diagnosing and managing childhood asthma, each providing distinct insights into pulmonary function and inflammation. We found that the FEV1/FVC ratio was observed to have a negative correlation with FeNO. However, there is no statistically significant correlation between FeNO and IOS parameters.

FeNO and spirometry

FeNO is a noninvasive marker of inflammation used for monitoring asthma and may be a method for early detection of eosinophilic airway inflammation even before symptom presentation and spirometric changes. In Taiwan, the National Health Insurance provides free-of-charge FeNO examinations three times per year (once every 4 months per year) for monitoring the treatment response of pediatric asthma between 6 and 12 years of age. Therefore, patients aged 6–12 were enrolled into the study, and the median (IOR) of FeNO was 21.0 (11.0, 40.0). Conversely, the FEV1/FVC ratio from spirometry is an indicator of airflow obstruction. In our study, a statistically significant negative correlation between FeNO and FEV1/FVC ratio ($r = -0.174$, $P = 0.002$) among asthmatic children was found. It suggests that as airway inflammation (indicated by higher FeNO levels) increases, there is a concurrent decline in the FEV1/FVC ratio, signifying worsening airflow obstruction. This relationship underscores the pathophysiological link between airway inflammation and functional impairment in asthma.

Similar studies conducted internationally confirm this study's findings. In the study by Lo *et al.*[10] from the United Kingdom, 465 children from 5 to 16 years of age were invited for a spirometry and FeNO test. The absolute values for FEV1/FVC were converted into Z-scores and plotted in a scatter plot with corresponding FeNO values.[10] A significant but weak negative correlation between FeNO and FEV1/FVC z-scores ($r = -0.2042$,

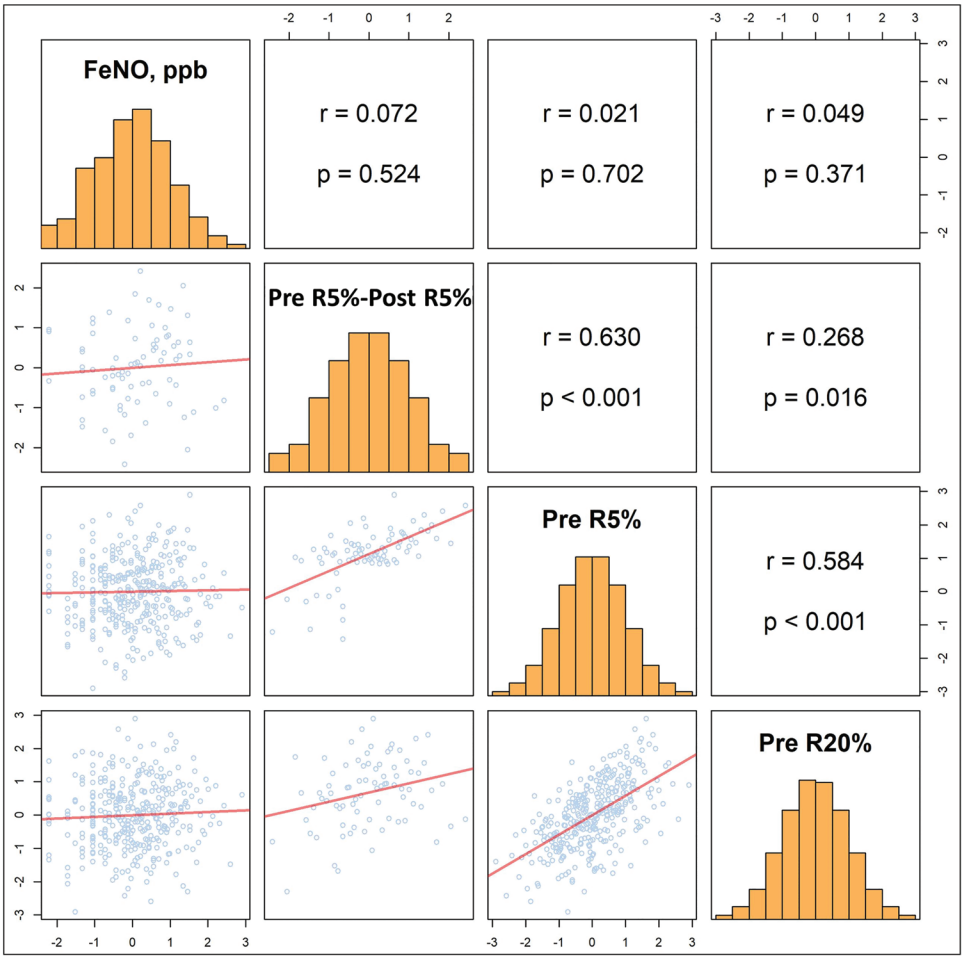

Figure 3: Correlation analysis of fraction of exhaled nitric oxide and impulse oscillometry system parameters (Pre R5%–Post R5%, Pre-R5, and Pre-R20). The pair-wise scatter plots are in the lower and left panels, and the correlations are in the upper and right panels. Rank-based inverse normal transformation was used to standardize the FeNO and IOS parameters. FeNO = fractional exhaled nitric oxide, IOS = impulse oscillometry system

$P < 0.0001$) was likewise discovered. The study by Lo *et al.*[10] shows an even greater negative correlation between FeNO and FEV1/FVC (−0.2042, $P < 0.0001$) compared to this study conducted in Taichung, Taiwan ($r = -0.174$, $P = 0.002$).

Similar results are also found in asthmatic adults worldwide. In Vietnam, the study by Nguyen and Chavannes[11] recruited a total of 410 asthma patients (mean age 42 years; 65% female) with a mean time since asthma onset of 9.5 years. Within this study group, FeNO was found to have a significant inverse correlation with FEV/FVC ($r = -0.143$, $P < 0.05$), corroborating this study's findings in Taiwan. The study by Al Ghobain *et al.*[12] in Saudi Arabia also revealed similar findings. Among 135 adult patients (30% male), a significant negative correlation between FeNO and FEV1/FVC ratio was found ($r = -0.18$, sensitivity 35%, specificity 85%, area under the curve 67%, $P = 0.027$).[12]

However, in the study by Dabbaghzadeh *et al.*[13] researchers found that the mean FeNO value of 28.5 ± 29.1 ppb has a significantly positive correlation with FEV1 (r, 0.232; $P = 0.049$) and a negative correlation with 25%–75% maximum expiratory flow (MEF 25–75) (r, −0.304; $P = 0.009$).[10] These findings diverge from those of previously mentioned studies and of this study in Taiwan. It is difficult to explain the findings of the study by Dabbaghzadeh *et al.*[13] through the basic pathophysiology of asthma because under normal circumstances, airway inflammation in asthma would present with high levels of FeNO and decreased FEV1 due to bronchoconstriction.

FeNO and IOS

FeNO offers insights into airway inflammation, while IOS provides a functional assessment of airway mechanics. According to the Global Initiative for Asthma guidelines, an FeNO level >20 ppb alone is not considered a definitive diagnostic criterion for childhood asthma, but rather one of several supportive indicators. Therefore, in our study, we did not evaluate the predictive values of IOS or spirometry parameters specifically based on an FeNO threshold of >20 ppb. There is no statistically significant correlation between FeNO and IOS parameters in our

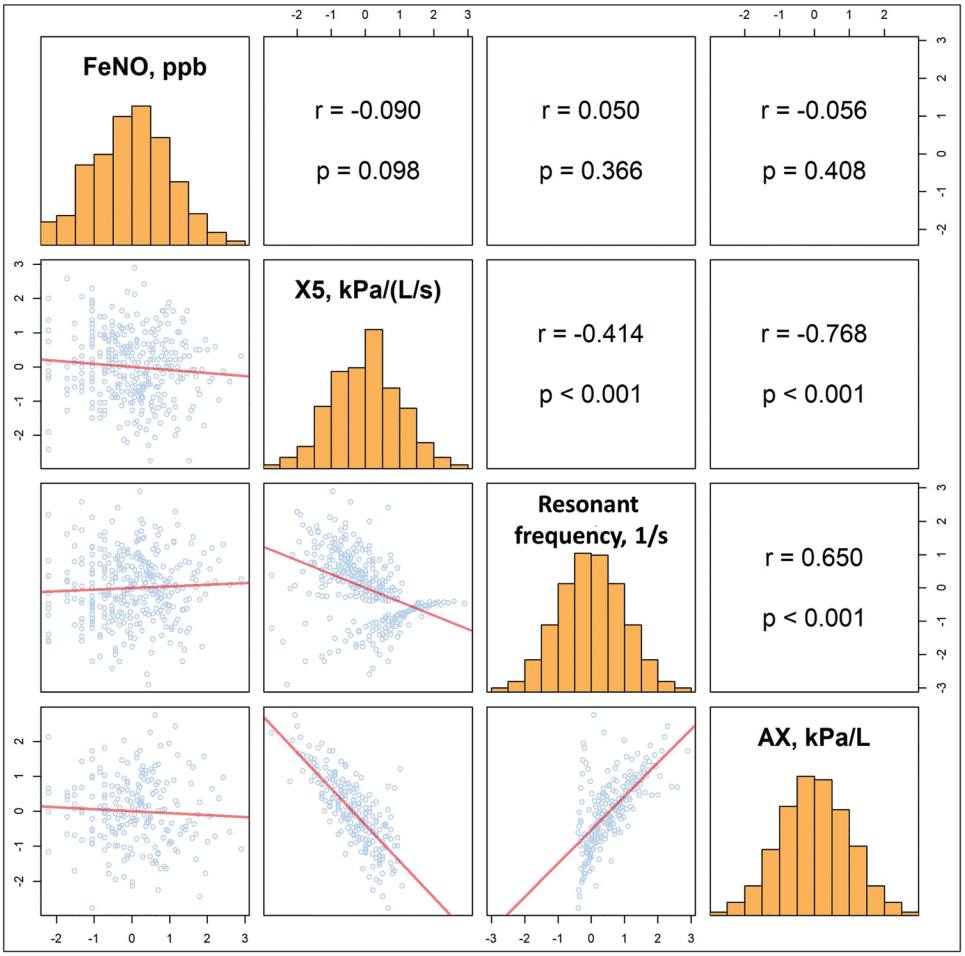

Figure 4: Correlation analysis of fraction of exhaled nitric oxide (FeNO) and impulse oscillometry system parameters (X5, Resonant frequency and reactance area). The pair-wise scatter plots are in the lower and left panels, and the correlations are in the upper and right panels. Rank-based inverse normal transformation was used to standardize the FeNO and lung function parameters. FeNO = fractional exhaled nitric oxide, IOS = impulse oscillometry system

study. A lack of significant correlation between FeNO and IOS parameters in the literatures might suggest that while inflammation is present (as indicated by FeNO), it may not always directly translate to measurable changes in airway mechanics detectable by IOS. This discrepancy highlights the complex nature of asthma, where different pathophysiological processes can occur independently.

The study by Lin *et al.*[14] presented that a combination of FeNO (>20 ppb) with IOS measurements significantly increased the specificity for predicting uncontrolled asthmatic children compared to FeNO alone ($P < 0.01$). In other words, this study showed that the small airway parameter (R5–R20) was the strongest risk factor [OR (95% CI): 87.26 (7.67–993.31)] for uncontrolled asthma patients who also had high FeNO levels. Therefore, combining these two methods can enhance diagnostic accuracy, monitor disease progression, and optimize therapeutic interventions.

However, in our study on asthmatic Taiwanese children, there is a lack of Mid-Expiratory Flow Rate (MEF 25–75) data for analysis. It is a parameter measured during pulmonary function testing, particularly during spirometry. It reflects the flow of air coming out of the lungs during the middle portion of a forced expiration. MEF 25–75 is considered a sensitive measure of small airway function and can detect early changes in the small airways, which might not be apparent in other spirometry parameters like FEV1. The parameter for peripheral airway resistance, R5–R20 in IOS, was also used to represent the small airway condition. However, no statistically significant correlation was found between R5–R20 and FeNO. The lack of correlation between FeNO and IOS parameters could be attributed to the lack of subgroup analyses. To address this concern, prospective studies on the correlation between FeNO and parameter of IOS, such as R5–R20, should be designed and performed in the future.

IOS and spirometry

IOS has shown a highly significant association with spirometry indices and reversibility testing and therefore

may serve as a substitute for spirometry in younger children who fail to properly perform forced expiratory maneuvers.[15] However, its complexity, cost, limited availability, and the need for specialized interpretation can be significant disadvantages compared to the more widely accepted and straightforward spirometry. A systematic review and meta-analysis by Ling *et al*.[16] reported that R5, AX, Fres, and X5 may be able to identify the risk of an acute asthmatic attack. When comparing IOS measurements (R5, R20, and X5) and spirometry in asthmatic patients, current medical literature does report instances of a correlation between IOS parameters and FEV1.[16,17] One such study by Pinto *et al*.[18] explored the relationship between IOS and spirometry among asthmatic preschool children. By incorporating new IOS parameters such as resistance at 5 and 20 Hz (R5–R20), relative difference of R5–20 (R5–20%), and area under the reactance curve (AX) in their study, the authors were able to discover statistically significant negative correlations between R5–20, R5–20%, and AX (IOS parameters) and FEV1 and FEF25-75 (spirometry parameters) (rho: −0.296 to −0.394; all $P < 0.05$). Therefore, IOS could be useful for assessing pulmonary deficits in asthmatic preschool children given its strong correlation with standard spirometry.[17,18,19]

Potential limitations

Because asthma is a result of complex interplay of genetic and environmental factors, environmental factors such as air pollutants, tobacco smoke, respiratory viruses, and allergens could trigger asthma in genetically susceptible individuals.[20] Therefore, asthma may be acquired from previously healthy children that have characteristics that either protect or predispose them to asthma attacks. Medical and family history combined with lung function tests could help physicians accurately diagnose. Unfortunately, lung function tests may not always be available, and such tests are frequently difficult to perform on young children.

To make diagnosis on young children even more difficult, the study by Wu *et al*.[21] found that IOS parameters are closely related to height, age, and weight in healthy children. Specifically, increasing age and height are associated with decreased R5, R20, R5–R20, and Fres and increased value of X_5. Future studies should consider these confounding variables and conduct subgroup analyses after adjusting for differences in height, age, and weight.

Another potential limitation is due to the retrospective nature of the study and a small sample size that could introduce selection bias by the CMUH-Clinical Research Data Repository. Although this study was conducted at a single tertiary center, the findings provide a valuable foundation for future research. Multicenter studies are warranted to further validate and expand the generalizability of these results to broader pediatric populations. Besides, the absence of a healthy control group is a key limitation of our study, and future prospective studies including healthy controls are warranted to strengthen the comparative findings. The omission of the $FEF_{25–75}$ parameter is acknowledged as another limitation of our study as this measurement can provide additional information on small airway function. Additionally, the bronchodilator response test was not included in our analysis because it was not consistently performed for all patients in the dataset. Furthermore, the exclusion criteria [see Figure 1] reduced the original study population of 831 patients with FeNO exam and 3452 patients with IOS exam down to only 337 patients, potentially introducing an additional degree of selection bias.

Nevertheless, this study highlights that among asthmatic children aged 6–12, the FEV1/FVC ratio was found to be negatively correlated to FeNO and that there is no statistically significant correlation between FeNO and IOS parameters. Further studies regarding the correlation between FeNO and IOS should be conducted in the future.

In conclusion, there is no significant correlation between FeNO and IOS parameters in childhood asthma, but a statistically significant negative correlation between FeNO and FEV1/FVC was observed. While this finding suggests a potential link between airway inflammation and airflow limitation, its clinical utility remains to be further established. Further prospective studies with larger cohorts and comprehensive clinical data are warranted to explore the potential diagnostic or monitoring value of this relationship in clinical practice. The findings of this study point to the combination of FeNO, IOS, and spirometry as the most favorable approach to diagnose and treat childhood asthma.

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Author contributions

Writing and drafting: Patrick Wu, Su-Boon Yong and Chien-Heng Lin; Visualization: Su-Boon Yong and Wen-Jue Soong; Data analysis and interpretation: Chieh-Ho Chen and Chien-Heng Lin.

Data availability

The data presented in this study are not publicly available due to privacy or ethical restrictions. Requests to access these datasets should be directed to the.

Informed consent statement

Patient consent was waived due to the retrospective nature of this study.

Institutional review board statement

Ethical review and approval were waived for this study (CMUH109-REC1-024).

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Conflicts of interest

The authors report that they have no conflict of interest to declare regarding this submission.

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Original Article

Differential Contributions of Inhalant and Food Allergen Sensitization to Atopic Phenotype Asthma Prevalence among Children across Age Groups

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Abstract

Background: Allergen sensitization is a critical factor in pediatric asthma development, yet the relative contributions of inhalant and food allergens across age groups remain poorly defined. Understanding these patterns is essential for effective prevention and management strategies. **Methods:** We conducted a retrospective cross-sectional study of 983 children aged 0–18 years diagnosed with asthma between 2006 and 2011. Specific IgE to 36 regionally allergens was measured using the MAST-CLA system. Sensitization was defined as Class ≥2 reactivity. Children with sensitization to any allergen were classified as having atopic phenotype asthma; those without sensitization were classified as non-atopic. All allergens were categorized into main aeroallergens, other aeroallergens, seafood allergens, and other food allergens. Prevalence trends and correlations with atopic phenotype asthma were assessed across nine age groups. **Results:** Overall, 59.4% of children had atopic phenotype asthma. The prevalence of atopic phenotype asthma increased with age, rising from 33.0% in children aged 0–2 years to 82.1% in those aged 13–15 years. Sensitization to main aeroallergens also rose with age, reaching 82.1% in adolescents. In contrast, sensitization to food allergens remained low or declined over time. Correlation analysis showed a strong positive association between main aeroallergen sensitization and atopic phenotype asthma prevalence (r=0.994), while food allergen sensitization showed weak or negative associations. **Conclusions:** Main aeroallergen sensitization is the predominant contributor to age-related increases in atopic phenotype asthma among children. These findings underscore the importance of early detection and targeted management of inhalant allergen sensitization in pediatric asthma care.

Keywords: Allergen, asthma, atopy, children, prevalence, trend

Introduction

Asthma is the most common chronic respiratory disease in children. Asthma affects approximately 300 million individuals worldwide, with prevalence rates ranging from 5% to 20% among children in different regions.[1,2] A substantial proportion of pediatric asthma is associated with atopic sensitization, reflecting the interplay between genetic predisposition and environmental exposures. Although inhalant allergens such as house dust mite, cockroach, and pollen are established triggers of asthma exacerbation, sensitization patterns can vary across regions and developmental stages. The burden of disease is particularly significant in Asia, where urbanization and changing environmental exposures have contributed to rising asthma incidence.[3]

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Early-life sensitization to aeroallergens has been identified as a strong predictor of persistent wheeze and asthma into adolescence.[4-6] Cohort studies in Europe and North America have documented the progression from atopic dermatitis to allergic rhinitis and asthma, supporting the concept of the "atopic march."[7,8] The impact of specific allergen exposures varies by geography, with indoor allergens such as dust mites and cockroach predominating in humid climates,[9,10] while pollen exposure is also common in temperate regions.[11-13] Notably, while the role of aeroallergens in pediatric asthma has been extensively studied, fewer investigations have systematically compared inhalant and food allergen sensitization across age groups. Understanding how sensitization evolves from infancy through adolescence and how it correlates with the prevalence of atopic phenotype asthma is important for early diagnosis, risk stratification, and prevention strategies.

This study aimed to characterize the prevalence of inhalant and food allergen sensitization in asthmatic children across distinct age groups and to evaluate the correlations between sensitization patterns and the prevalence of atopic phenotype asthma in a tertiary care medical center.

Materials and Methods

Study design and setting

This retrospective cross-sectional study was conducted in the Department of Pediatrics at E-Da Hospital, a tertiary medical school hospital, in Taiwan from January 2006 to December 2011. The study was approved by the Institutional Review Board of the E-DA Hospital on August 8, 2018 (Approval No. EMRP-107-077), with a waiver of informed consent due to the retrospective analysis of de-identified data. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.

Participants and age group stratification

Children aged 0–18 years with a physician-diagnosed asthma diagnosis based on the Global Initiative for Asthma (GINA) guidelines were included. Participants were stratified into nine age groups: 0–2, 3, 4, 5, 6, 7–9, 10–12, 13–15, and 16–18 years.

Sensitization to specific allergen groups

Specific IgE to 36 Asian regionally relevant allergens was measured using the Multiple Allergen Simultaneous Test Chemiluminescent Assay (MAST-CLA) system (Hitachi Chemical Diagnostics, Inc., Mountain View, CA). Sensitization to any allergen was defined as a Class ≥2 reactivity.

Thirty-six allergens were divided into four groups. If the asthmatic children had sensitization to any one of these allergens of the group, they were defined as having sensitization to that allergen group; otherwise, they were defined as having no sensitization to that group. Allergens were grouped into four groups: (1) main aeroallergens (six): *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, house dust, cockroach mix, dog, cat; (2) other aeroallergens (14): feather mix, pine mix, cottonwood/willow, eucalyptus, mulberry mix, grass mix, Bermuda grass, ragweed mix 1, pigweed mix, *Alternaria*, *Aspergillus*, *Candida*, *Cladosporium*, and *Penicillum*; (3) seafood allergens (four): crab, shellfish, shrimp, codfish; and (4) other food allergens (12): citrus mix, corn, wheat, vegetable mix, pork, beef, milk, yeast (brewer), soybean, peanut, egg yolk, and egg white.

Definition of atopic phenotype asthma

Children with sensitization to any tested allergen were classified as having atopic phenotype asthma; those without sensitization were defined as non-atopic.

Statistical analysis

Descriptive statistics summarized the distribution of age, sex, and sensitization status. The prevalence of atopic phenotype asthma and sensitization to each allergen group was calculated per age group. Correlations between allergen sensitization prevalence and atopic phenotype asthma percentage were assessed using Pearson's correlation coefficient (r). Trends across age groups were visualized in line and scatter plots. A P value < 0.05 was considered statistically significant. Statistical analyses were conducted using Statistical Package for the Social Sciences (SPSS) software, version 22 for Windows® (SPSS Inc., Chicago, IL, USA).

Results

Study population

A total of 983 children with asthma aged 0–18 years were included. The median age was 5.7 years (IQR 4.2–8.4), and 63.4% were male [Table 1]. Across all age groups, the proportion of male participants was higher than that of female participants.

Prevalence of sensitization to specific allergen groups

The prevalence of sensitization to allergen groups was 56.1% to main allergens, 9.2% to other aeroallergens, 10.9% to seafood allergens, and 11.3% to other food allergens. Main aeroallergen sensitization exhibited a parallel increase with age, ranging from 22.3% in the youngest age group to 82.1% in children aged 13–15 years and 73.7% in those aged 16–18 years. In contrast, sensitization to other aeroallergens, seafood allergens, and other food allergens remained lower and more stable across age groups. Notably, sensitization to other food allergens decreased slightly in older children [Table 1, Figure 1].

Prevalence of atopic phenotype asthma among children with asthma across age groups

Among them, 584 (59.4%) were classified as having atopic phenotype asthma, while 399 (40.6%) were non-atopic. The proportion of atopic phenotype asthma increased progressively with age, from 33.0% in children 0–2 years old to 82.1% in those 13–15 years, before a slight decrease (75.4%) in the 16–18-year group [Figure 1].

Correlation analysis

Correlation analyses demonstrated a very strong positive association between main aeroallergens sensitization and atopic phenotype asthma prevalence across age groups

Table 1: Participants and prevalence (%) of sensitization to allergen groups and atopic phenotype asthma across pediatric age groups

Age group (years old)	0–18	0–2	3	4	5	6	7–9	10–12	13–15	16–18
Case number (*n*)	983	94	123	153	157	110	184	100	39	23
Male (%)	63.4	69.1	67.4	60.1	61.1	63.6	58.7	71	66.7	52.2
Age, median (IQR), years	5.7 (4.2–8.4)	2.4 (1.9–2.8)	3.6 (3.3–3.8)	4.5 (4.2–4.8)	5.4 (5.2–5.7)	6.5 (6.2–6.8)	8.4 (7.6–9.1)	11.1 (10.5–11.9)	14.3 (13.6–15.1)	17.2 (16.6–18.1)
Atopic phenotype percentage (%)	59.4	33	52.8	51.6	47.8	65.5	76.6	72	82.1	73.9
Non-atopic phenotype percentage (%)	40.6	67	47.2	48.4	52.2	34.5	23.4	28	17.9	26.1
Main aeroallergens (%)	56.1	22.3	47.2	47.7	45.2	65.5	75	70	82.1	69.6
Other aeroallergens (%)	9.2	6.4	3.3	9.8	5.7	8.2	12	16	12.8	17.4
Seafood allergens (%)	10.9	3.2	4.9	7.8	10.8	11.8	18.5	19	7.7	0
Other food allergens (%)	11.3	13.8	14.6	13.7	8.9	10.9	10.3	10	5.1	8.7

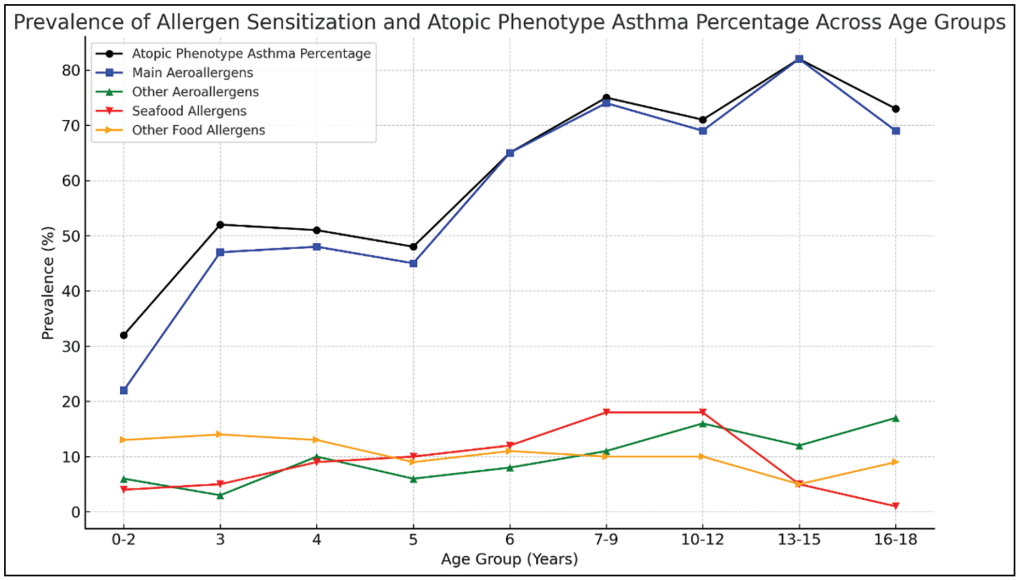

Figure 1: Prevalence of sensitization to allergen groups and atopic phenotype asthma percentage across age groupsLines represent the prevalence (%) of sensitization to allergen groups and the prevalence of atopic phenotype asthma across pediatric age groups. Age groups are categorized as 0–2, 3, 4, 5, 6, 7–9, 10–12, 13–15, and 16–18 years. Prevalence values are expressed as percentages within each group.

Table 2: Association between prevalence of sensitization to allergen groups and atopic phenotype asthma percentage across age groups

Allergens	Pearson's *r*	*P* value	Interpretation
Main aeroallergens	**+0.994**	**<0.001**	Very strong positive correlation
Other aeroallergens	**+0.738**	**0.023**	Positive correlation
Seafood allergens	+0.367	0.331	Weak correlation
Other food allergens	**−0.713**	**0.031**	Negative correlation

Prevalence values are shown as percentages. The data showed Pearson correlation coefficients (*r*) and corresponding *P* value. Bold values indicate significant correlations. A P value < 0.05 was considered statistically significant.

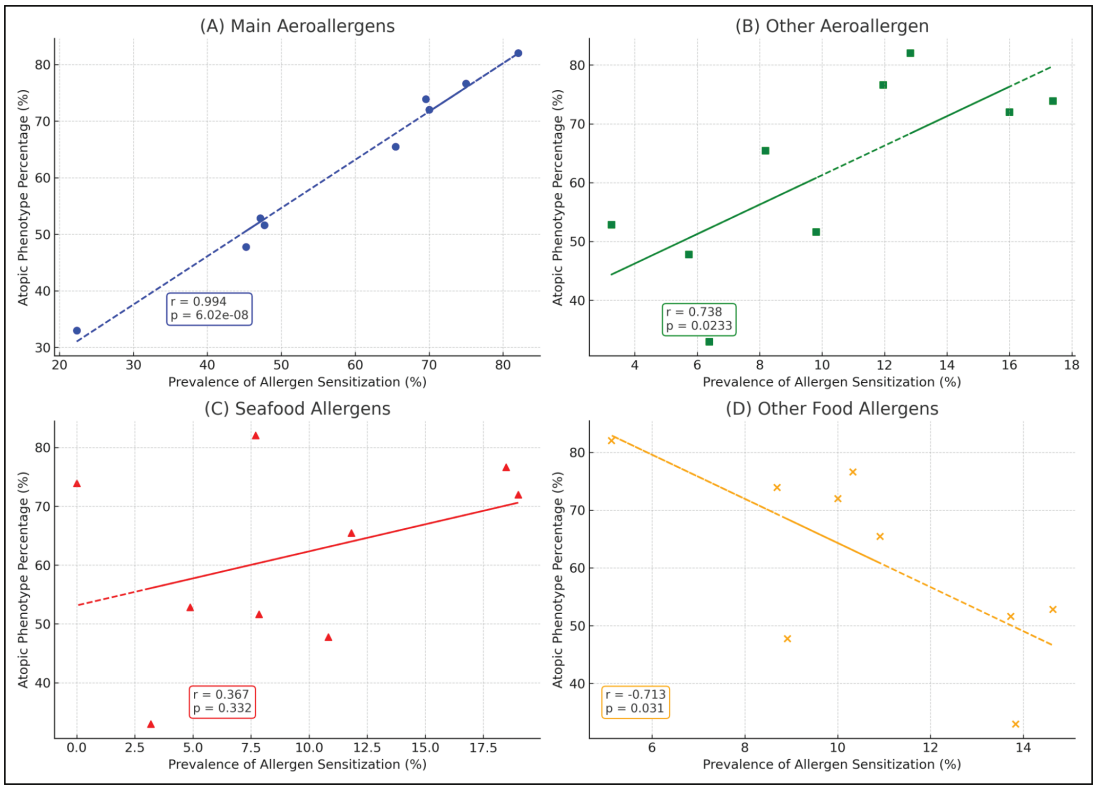

Figure 2: Correlation between prevalence of sensitization to allergen groups and atopic phenotype asthma percentage (individual allergen group panels) Scatter plots display the association between the prevalence of sensitization to each allergen group (*x*-axis) and the prevalence of atopic phenotype asthma (*y*-axis). Each point represents one age group. Regression lines are displayed as dashed lines. Prevalence values are shown as percentages. Pearson correlation coefficients (*r*) and corresponding *P* value are annotated in each panel for clarity. (A) Main Aeroallergens (blue): Very strong positive correlation ($r = 0.994$, $P < 0.001$). (B) Other Aeroallergens (green): Positive correlation ($r = 0.738$, $P = 0.023$). (C) Seafood Allergens (red): Weak correlation ($r = 0.367$, $P = 0.332$). (D) Other Food Allergens (orange): Negative correlation ($r = -0.713$, $P = 0.031$).

($r = 0.994$, $P < 0.001$). Other aeroallergens also showed a strong positive correlation ($r = 0.738$, $P = 0.023$). Conversely, sensitization to seafood allergens showed a weak, nonsignificant positive correlation ($r = 0.367$, $P = 0.332$), while other food allergens were negatively correlated with atopic phenotype asthma prevalence ($r = -0.713$, $P = 0.031$) [Table 2 and Figure 2].

Combined correlation visualization

The combined scatter plot confirmed that among all allergen groups, the main aeroallergens exhibited the most consistent and robust relationship with atopic phenotype asthma prevalence [Figure 3].

Discussion

This study demonstrated that sensitization to main aeroallergens was the predominant factor associated with the increasing prevalence of atopic phenotype asthma across childhood and adolescence. The prevalence of sensitization to main aeroallergens rose steadily with age, closely paralleling the rise in atopic asthma, and exceeded 80% in adolescents aged 13–15 years. In contrast, sensitization to seafood and other food allergens remained relatively stable or declined, showing weak or negative correlations with asthma prevalence.

The prevalence of sensitization to allergen groups was 56.1% to main allergens, 9.2% to other aeroallergens, 10.9% to seafood allergens, and 11.3% to other food allergens. Our findings align with previous large-scale epidemiologic studies showing that inhalant allergen sensitization accounts for most atopic asthma cases in childhood.[14,15] In Thailand, *D. pteronyssinus* is reported as the predominant sensitizing allergen among children with respiratory diseases, with sensitization rates of 63% in those with asthma and allergic rhinitis, 52.7% in allergic rhinitis alone, and 43.5% in asthma alone.[14] The predominance of indoor aeroallergen sensitization in Taiwan and much of Asia reflects climatic, cultural, and behavioral factors. The warm, humid subtropical climate supports year-round proliferation of dust mites, cockroaches, and molds indoors. Traditional bedding materials and limited ventilation in high-rise apartments further increase allergen accumulation. In contrast, countries with distinct seasons have high outdoor pollen levels in spring and summer. Children in these regions spend more time outdoors during pollen seasons, heightening exposure to grass and tree pollens, which are important

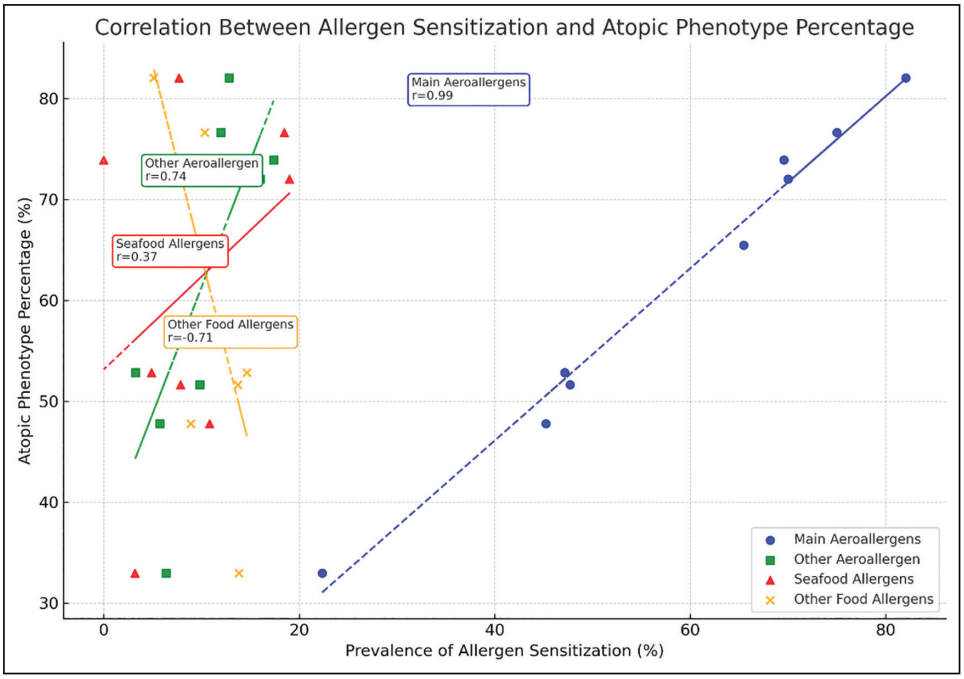

Figure 3: Correlation between sensitization to allergen groups and atopic phenotype asthma percentageScatter plot summarizes the association between the prevalence of sensitization to allergen groups and the prevalence of atopic phenotype asthma. Each point represents one age group. Correlations were computed using Pearson's *r*. Prevalence values were scaled to 0–100% for comparability. Regression lines illustrate the linear association between sensitization to allergen groups and atopic phenotype asthma percentage across the pediatric age spectrum. The blue circles and regression line correspond to main aeroallergens ($r = 0.99$). The green squares and regression line represent other aeroallergens ($r = 0.74$). The red triangles correspond to seafood allergens ($r = 0.37$). The orange crosses represent other food allergens ($r = -0.71$).

risk factors for asthma exacerbations.[16,17] In Jordanian asthmatic children aged 6 months to 14 years, the most common sensitizing allergens were olive pollen (18%), cat fur (13.5%), and *D. pteronyssinus* (11.9%). Notably, allergen sensitization increased significantly with age ($P < 0.001$).[18] In densely populated Asian cities, concerns about pollution, safety, and academic demands result in children spending more time indoors, sustaining chronic exposure to indoor allergens. This pattern may explain why indoor allergens are the main drivers of sensitization in Asian pediatric asthma, while outdoor allergens also play an important role in Western countries.[19-21]

The prevalence of atopic phenotype asthma increased with age, rising from 33.0% in children aged 0–2 years to 82.1% in adolescents. In a cohort study in England, the prevalence of sensitization to any allergen was 19.7% at age 4, 26.9% at age 10, and 41.3% at age 18.[22] In addition, among the 277 Jordanian asthmatic children included, 186 (67%) had atopic phenotype asthma. A significant increase in the prevalence of atopic phenotype asthma was observed across age groups ($P < 0.001$). The prevalence was 0% in children aged ≤1 year, 51.4% in those aged 2–4 years, and 86% among those aged 10 years or older.[18] The increasing prevalence of atopic phenotype asthma with advancing age likely reflects the cumulative effects of prolonged environmental exposure and immunologic maturation.[23] In early childhood, the immune system is still developing tolerance mechanisms, and repeated exposure to inhalant allergens such as dust mite and cockroach antigens can promote a Th2-skewed immune response.[24] This process leads to progressive sensitization characterized by increased production of allergen-specific IgE, mast cell activation, and eosinophilic airway inflammation. Additionally, the maturation of mucosal barrier function and antigen-presenting cell activity during school age may enhance allergen recognition and amplification of allergic inflammation, contributing to the higher likelihood of persistent atopic phenotype asthma in adolescence.

Food allergens, in contrast, are generally less implicated in chronic asthma. Although food allergies commonly manifest during infancy and early childhood, they typically present as acute IgE-mediated reactions involving the skin or gastrointestinal tract rather than sustained lower airway inflammation.[25,26] Over time, many children develop tolerance to common food allergens such as milk, egg, and soy, resulting in a decline in sensitization rates with age. Continuous exposure to inhalant allergens, however, drives persistent airway inflammation and chronic symptoms.[24] This distinction underscores why inhalant allergens are more strongly associated with asthma prevalence and severity in older children. The natural history of food allergy and its limited role in chronic respiratory disease explain the consistently low correlations between food sensitization and asthma observed across pediatric populations.[24,27,28]

Identifying specific allergen sensitizations in children with asthma is essential for precision management and preventing exacerbations. Early detection of sensitization to main aeroallergens enables clinicians to recommend targeted environmental control measures, such as reducing indoor humidity, using dust mite–impermeable bedding covers, and minimizing exposure to pet dander.[1,19-21,24] These interventions can lower allergen burden, decrease airway inflammation, and improve asthma control. Furthermore, recognition of sensitization patterns can guide consideration of allergen immunotherapy (AIT), an evidence-based approach that can modify disease progression and reduce long-term morbidity. AIT modulates allergen-specific Th2 responses and promotes tolerance by enhancing regulatory T-cell activity and the secretion of immunosuppressive cytokines.[29] Guidelines recommend integrating allergen assessment into routine asthma care to inform tailored management strategies.[30,31] Incorporating allergen identification and avoidance strategies into routine asthma care is therefore essential to optimize outcomes.[32-34]

This study's strengths include its large sample size, standardized allergen testing, and detailed age stratification, which together provide a comprehensive picture of sensitization patterns among Taiwanese children with asthma. Our findings extend previous knowledge by quantifying the relative contributions of four allergen groups across distinct age groups in an Asian pediatric population. However, several limitations should be acknowledged. The retrospective, single-center design precludes causal inference and may introduce selection and referral bias, limiting the generalizability of results to other regions. Additionally, environmental exposures such as indoor humidity, air pollution, and genetic predisposition were not assessed, though these factors likely influence sensitization trajectories. To build on these findings, prospective multicenter studies are needed to validate the associations observed here and clarify the temporal sequence of allergen sensitization and asthma development. Future research should also explore gene-environment interactions and assess whether early interventions targeting main aeroallergens can modify disease progression and improve long-term asthma control.

In conclusion, this study demonstrates that inhalant allergen sensitization increases significantly with age in asthmatic children and is strongly correlated with higher prevalence of atopic phenotype asthma. Food allergens play a comparatively minor role beyond early childhood. These findings support the prioritization of early allergen identification, environmental control strategies, and consideration of immunotherapy in managing pediatric asthma.

Consent to participate

Because this study did not pose additional risk to participants, the requirement for informed consent was waived by the IRB.

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Author contributions

Yu-Cheng Tsai, Ya-Ling Huang, and Yu-Tsun Su conceptualized the study, collected grants, and wrote the initial paper; Yu-Tsun Su, Yu-Shen Chen, and Ting-I Lin contributed to data collection and data analysis; Ya-Ling Huang and Ping-Hsuan Hsieh analyzed the blood samples; Ching-Chung Tsai and Yu-Tsun Su contributed to the study design, interpreted data, and edited the paper. All authors approved the final paper as submitted.

Data availability statement

In accordance with the regulations of the Personal Information Protection Act in Taiwan, individual patient-level data cannot be made publicly available. However, de-identified raw data may be obtained from the corresponding author upon request by the editorial staff and with appropriate ethical approval.

Ethical policy and institutional review board statement

The study was approved by the Institutional Review Board of the E-DA Hospital on August 8, 2018 (Approval No. EMRP-107-077).

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Conflicts of interest

There are no conflicts of interest.

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