

## REVIEW ARTICLE

# Gene-environment interactions in childhood asthma revisited; expanding the interaction concept

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**Abstract**

Investigation of gene-environment interactions (GxE) may provide important insights into the gene regulatory framework in response to environmental factors of relevance for childhood asthma. Over the years, different methodological strategies have been applied, more recently using genome-wide approaches. The best example to date is the major asthma locus on the 17q12-21 chromosome region, viral infections, and airway epithelium processes where recent studies have shed much light on mechanisms in childhood asthma. However, there are challenges with the traditional single variant–single exposure interaction models, as they do not encompass the complexity and cumulative effects of multiple exposures or multiple genetic variants. As such, we need to redefine our traditional GxE thinking, and we propose in this review to expand the GxE concept by also evaluating other omics layers, such as epigenetics, transcriptomics, metabolomics, and proteomics. In addition, host factors such as age, gender, and other exposures are very likely to influence GxE effects and need firmly to be considered in future studies.

**KEYWORDS**

asthma, children, environmental exposure, epigenetics, genetics, genome-wide interaction study, methylation, omics

## 1 | INTRODUCTION

The traditional gene-environment interaction (GxE) concept is based on the hypothesis that a particular gene variant determines disease risk following environmental exposure. As such, investigation of GxE may provide insights into the gene regulatory framework in response to relevant environmental factors and novel asthma loci that would perhaps go unnoticed without investigating the role of interactions with the environment or other host factors.<sup>1</sup> In addition, interaction studies may contribute to developing more accurate preventive and

therapeutic strategies for the clinical management of asthma using precision-medicine approaches.

GxE studies have evolved from linkage screenings to candidate gene studies followed by genome-wide interaction studies, GWIS.<sup>2</sup> Although hypothetically very attractive, with the central dogma that a combination of genes and environments determine your disease risk, surprisingly few convincing asthma examples that replicate across studies have been identified throughout the years, despite major efforts.<sup>3,4</sup> One potential reason for this lack of robust GxE findings is that the numerous toxic effects from hundreds of

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different compounds and metabolites, for example, cigarette smoke or air pollutants, are too complex to be captured by single variant interaction effect analyses. The same argument may apply to other factors, such as diet or microbial exposures. Additional exposures, nicely captured by the exposome concept,<sup>5</sup> and subtle ethnic differences may also influence GxE interaction effects thereby reducing the chances to replicate GxE findings across studies from different geographical and/or ethnic backgrounds.

As discussed below in this article, many gene variants cumulatively sum up to disease risk rather than single variants with large effects, and it is therefore perhaps unlikely that we will find single variant–single exposure interaction effects. Instead, GxE effects may be seen primarily using combinations of many genetic variants in the model or at other omics layers such as epigenetics, transcriptomics, metabolomics, or proteomics, rather than at the level of single-nucleotide polymorphisms (SNP).<sup>1,6,7</sup>

In this article, we are reviewing the recent GxE literature in childhood asthma with the main focus on papers published in the last years. To get a comprehensive picture of the key elements in GxE studies, we are also briefly summarizing the role of some selected environmental exposures and the current state of knowledge for asthma genetics, including the major 17q12-21 locus and the role of the airway epithelium. In addition, we are expanding the GxE concept by reviewing studies on other omics layers and pinpointing important aspects of future GxE studies going forward.

## 2 | KEY ENVIRONMENTAL EXPOSURES

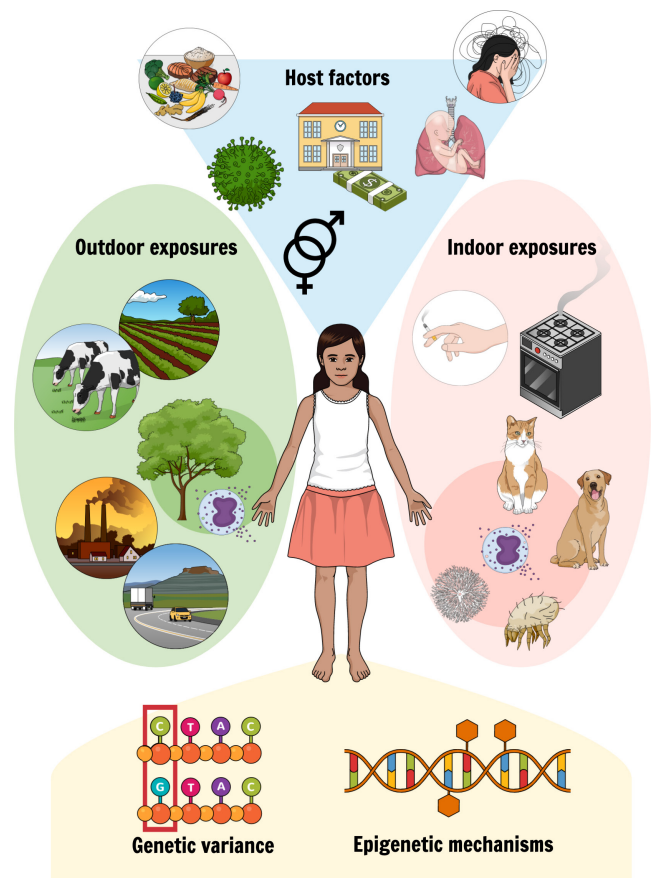
Children have underdeveloped lungs and an immature immune system and are thus very susceptible to adverse effects caused by environmental exposures.<sup>8,9</sup> In general, children have a higher respiratory rate and spend more time outdoors than adults, being inherently more exposed and vulnerable to the effects of environmental exposures.<sup>9</sup> Despite the numerous environmental factors evidenced to play a key role in asthma, early-life tobacco smoke, outdoor and indoor air pollutants, farming environment, and microbial exposures have been the most frequently studied (Figure 1).<sup>3</sup>

Air pollution constitutes one of the most important environmental contributors to disease today and is known to both cause and aggravate pre-existing asthma.<sup>8,10</sup> Air pollutants irritate the mucosa of the respiratory tract, causing airway inflammation and hyperreactivity.<sup>10</sup> In recent decades, children have been spending a proportionally larger part of the day indoors, meaning that indoor exposures at home and in school constitute a substantial part of the complete environmental setting.<sup>11</sup> Nonetheless, tobacco smoke has been most extensively studied in relation to asthma.<sup>3</sup>

Exposure to outdoor air pollution in early life has been linked to asthma onset during childhood by effects on inflammation and anti-oxidation.<sup>12</sup> This has also been linked to poorer lung function and respiratory infections in children.<sup>8-10</sup> Also, prenatal maternal exposure may increase offspring asthma risk.<sup>8</sup> Indeed, epigenetic changes,

### Key Message

The study of gene-environment interactions is a powerful approach to provide insights into the molecular mechanisms involved in childhood asthma. Nonetheless, this concept should be expanded, including the exploration of other omics layers and host factors beyond solely environmental exposures in interaction with genetic variants.



**FIGURE 1** Overview of the environmental and host factors in interaction with the genetic variation affecting childhood asthma. Outdoor exposures are shown on the left-hand side, including farming environment, outdoor allergens, and ambient air pollution. Indoor factors are illustrated on the right: for example, tobacco smoke, cooking and heating, allergens from furred pets, house dust mites, and molds. Host factors are presented on top comprising age (not shown), gender, SES, psychosocial and perinatal factors, and diet and respiratory infections in early life. These interact with the individual's genetic composition and epigenetic modifications altering the risk of asthma-related traits

maternal systemic inflammation, and oxidative stress in the placenta have been hypothesized to contribute.<sup>8,10</sup>

On the contrary, a farming environment during childhood is in general thought to decrease the risk of asthma, and the effect is particularly marked if the exposure occurs *in utero* or during the first

year of life.<sup>4,13</sup> One proposed mechanism is that rural areas bring about differential exposure to a larger number of diverse microbial products compared with urban settings, and this difference is thought to modify immunological responses and subsequently decrease asthma risk.<sup>4,13</sup>

Respiratory infections and wheezing early in life are well known to increase the risk of asthma.<sup>4,13</sup> One suggestion is that this association is dependent on host factors, causing wheezing in vulnerable children with abnormal lung physiology, concomitant sensitization, and increased genetic predisposition for asthma.<sup>13</sup> In summary, these pieces of evidence demonstrate the substantial contribution of environmental exposures in the modification of asthma susceptibility and disease progression.

### 3 | ASTHMA GENETICS

The complex etiology of asthma has been established to be the result of intricate interactions between numerous factors. Among these, the substantial contribution of the individual's genetic composition to different asthma-related traits has been demonstrated through heritability estimates ranging from 30% to 90%.<sup>14</sup> Indeed, adult-onset asthma has been suggested to have a weaker genetic component<sup>15</sup> and to share genetic factors with other comorbidities.<sup>15</sup> Nonetheless, the contribution of genetic variants specific and shared among different age groups has been described for different asthma-related traits.<sup>16,17</sup>

The methodological approaches and study design in the field of asthma genetics since its beginning more than 30 years ago have been extensively reviewed elsewhere.<sup>18,19</sup> The first decades were characterized by hypothesis-driven approaches that evolved into genome-wide association studies (GWAS)<sup>18,19</sup> triggered by the numerous limitations of the former strategies and the development of genome-scale genotyping platforms.<sup>18,19</sup> The main findings of the GWAS of asthma susceptibility published until 2019 have been previously described in detail, which have revealed the association of nearly 40 genomic regions.<sup>18,19</sup> To the best of our knowledge, a total of 78 articles have reported results of genome-wide explorations in different asthma-related traits based on GWAS Catalog records (<https://www.ebi.ac.uk/gwas/>) by the time of writing (February 2022).

Most of the asthma association signals reported to date are located in non-coding regions and the functional insights into the majority of asthma loci are still quite limited, which also hampers the possibility to draw firm conclusions from GxE studies.<sup>20</sup> However, evidence of potential implications in the regulation of the transcription of nearby genes in immune and pulmonary cells has been described for some of the association signals identified.<sup>20</sup> Nevertheless, the causal molecular and cellular mechanisms through which the genetic variation may influence the development of asthma are not completely understood.<sup>21</sup>

The numerous advantages of GWAS have substantially increased the power to detect novel asthma loci compared with previous

approaches. However, the genetic factors identified to date only account for a small proportion of the total estimated heritability, hampering their capacity to predict the risk of developing asthma or certain related traits.<sup>20,22</sup>

### 4 | INTERACTIONS BETWEEN GENES AND THE ENVIRONMENT

Today, global trends in asthma incidence vary by country.<sup>23</sup> Given the strong heritable character of asthma, and that genetic risk can be assumed to be relatively stable overtime, the effect of the interplay between a wide range of environmental exposures and genetic factors on asthma prevalence is likely substantial.<sup>23,24</sup> Specifically, there is considerable evidence of the influence of GxE in processes related to innate immunity, antioxidation, and pulmonary capacity. Indeed, the effect size of the genetic determinants might be partially influenced by the individual's environmental exposures.<sup>25</sup> Thus, the effect allele of a certain genetic variant could be associated with the protection or risk of different asthma-related phenotypes in different environmental settings.<sup>26</sup> *Vice versa*, the influence of environmental factors on asthma development may be modified by the genetic composition.<sup>26</sup>

The field of GxE in asthma has drastically evolved together with technological advances over the last decades following a similar pattern to asthma genetics.<sup>2,4</sup> First, GxE investigations were mostly focused on the evaluation of a reduced panel of variants across the genome or within a specific region of interest. The interaction with exposure to tobacco smoke in family members in relation to the development of childhood asthma through linkage screenings was the most common scenario.<sup>2,4</sup> Nonetheless, candidate gene-based strategies have been the most predominant over the years. A detailed description of the main findings of the studies carried out until 2019 was reported by Morales et al.<sup>3</sup> Briefly, genes encoding proteins involved in mechanisms related to asthma pathophysiology, antioxidation, and detoxification as well as environmental exposure to tobacco smoke, outdoor air pollutants, and microbes have been the main actors in the GxE field.<sup>3</sup> Despite reports on the effect of numerous environmental factors on childhood asthma, the availability of detailed and diverse exposure data is often limited,<sup>4</sup> tobacco smoke being the most accessible and extensively explored factor along with the trajectory of GxE investigations.

The interaction of the genetic composition with traffic-related air pollution has been widely explored, which could be categorized as the second most studied environmental exposure in asthma research. As a result, several genes have been identified to potentially modify the risk to develop asthma in children exposed to traffic-related air pollution (e.g., *GSTP1*, *B4GALT5*, *ADCY2*, *DLG2*, *GSTM1*, *TNF*, *TLR2*, and *TLR4*).<sup>3</sup>

Nonetheless, the effects of indoor exposures on the genetic risk of asthma-related traits have also been evaluated. For instance, exposure to house dust mite allergens and molds has been proposed

TABLE 1 Summary of the GxE interaction studies of asthma-related traits published between 2019 and 2022

Type of study	Trait	Definition of trait	Exposure	Population	Age group	Sample size (cases/controls)	Region studied (reason of selection)	References
Candidate gene-environment interaction study	Asthma susceptibility	Doctor's diagnosis	Childhood environment tobacco smoke	European	Children	359 (48/311)	NAT71 (involved in xenobiotic metabolism; previous association with hair cotinine levels)	[33]
		History of recurrent asthma symptoms and positive bronchial provocation	Household mold	Asian	Children	1447 (608/839)	ADRB2, GSDMB, ICAM1, IL13, IL4, IL4R, STAT6 (inflammation-related genes; SNPs previously linked to childhood asthma, asthma, and/or any environment interaction)	[38]
		History of asthma symptoms and/or low lung function	Tobacco smoking	Asian	Adults <sup>a</sup>	1292 (430/862)	IL6, IL7R (encoded proteins involved in asthma pathophysiology; previous associations with asthma)	[29]
		Asthma-related immunomodulation (IL10 and IL13 levels)	Heavy metals (Pb and Cd)	Asian	Children	155	IL10, IL13 (encoded proteins involved in asthma immunomodulation; previous associations with asthma)	[37]
		Doctor's diagnosis before 10 years of age	Childhood environment tobacco smoke	Mixed (Latino, African American, European)	Adults	441 (259/182)	IL1RN (previous associations with asthma)	[34]
Asthma susceptibility/severity		History of symptoms, low lung function, and use of any asthma medications	Occupational exposure to irritants	European	Adults <sup>a</sup>	509 (48/461)	422 genes involved in the response to oxidative stress pathway	[30]
		Doctor's diagnosis/History of asthma symptoms and/or exacerbations	Childhood environment tobacco smoke	European	Children	669 (444/225)	NFE2L2 (encoded protein involved in antioxidant defense; previous associations with asthma, interaction with traffic-related air pollution)	[32]
Allergic sensitization		Cord blood total IgE levels	Prenatal exposure to cats/dogs, pre-natal maternal active or second-hand smoking, maternal atopy, age, pre-pregnancy BMI, delivery mode, infants' gender, and season of birth	Asian	Children	989	IL13, IL4, IL4RA, FCER1B, ADRB2 (previous associations with asthma/atopy)	[34]
Lung function in asthma		Pre-bronchodilator FEV <sub>1</sub>	Air pollution (SO <sub>2</sub> )	African American	Children	661	KITLG (variants associated with FEV <sub>1</sub> ; previous implications in allergic inflammation in asthma)	[36]
GWIS	Time of asthma onset	Doctor's diagnosis, standard questionnaires	Childhood environment tobacco smoke (maternal smoking during pregnancy/parental smoking during early childhood)	European	Children	8273 (2874/5399)	Whole genome (Rsq ≥ 0.5, MAF ≥ 1%)	[35]

TABLE 1 (Continued)

Type of study	Trait	Definition of trait	Exposure	Population	Age group	Sample size (cases/controls)	Region studied (reason of selection)	References
	Asthma treatment response (ICS)	History of asthma exacerbations despite ICS use <sup>b</sup>	Age	European	Adults/children	783 (407/376)	Whole genome (Rsq ≥ 0.9, MAF ≥ 1%)	[86]
	Asthma treatment response (BDR)	100 × (post-FEV <sub>1</sub> - pre-FEV <sub>1</sub> ) / pre-FEV <sub>1</sub> <sup>b</sup>	Age	European	Adults/children	892	Whole genome (MAF ≥ 5%)	[85]

Abbreviations: BDR, bronchodilator response; Cd, cadmium; FEV<sub>1</sub>, forced expiratory volume in one second; GWIS, gene-environment interaction study; GxE, gene-environment; ICS, inhaled corticosteroids; IgE, immunoglobulin E; IL10, interleukin 10; IL13, interleukin 13; MAF, minor allele frequency; NA, not available; Pb, lead; Rsq, imputation quality score; SO<sub>2</sub>, sulfur dioxide.

<sup>a</sup>The detailed results of this study were not included in this review.

<sup>b</sup>History of any emergency room visits, hospitalizations, or need for oral corticosteroids use because of asthma.

<sup>c</sup>Spirometry measurements before or after two puffs of albuterol.

to potentially modify the effects of several genes on asthma exacerbations (*IL9*), airway responsiveness (*TGFB1*), and childhood-onset asthma (*IL4*), respectively.<sup>27,28</sup> Although most of the environmental factors have been found to increase the genetic risk to develop asthma, certain exposures, such as a farming environment, have been suggested to provide a protective effect in interaction with *TLR6*, *GRM1*, and *NOD1* polymorphisms against childhood-onset asthma.<sup>3,4</sup>

These findings demonstrate that candidate gene-based GxE investigations have allowed pinpointing genes that might be of relevance in asthma in the context of specific environmental settings. However, these strategies have been characterized by a limited statistical power to detect significant interactions despite substantial efforts to combine several studies through meta-analyses.<sup>1</sup> Thus, these have opened the doors to GWIS in the last years with the potential of being a powerful unbiased strategy to identify novel genetic loci interacting with environmental exposures.<sup>2</sup> This method shares similar principles with GWAS with the only addition of the interaction effect between genetic variants across the whole genome and a certain exposure factor in the evaluation of the association with an asthma outcome. Despite the numerous advantages of GWIS, only a very limited number of studies using this approach to childhood-onset asthma had been published until 2019, as reviewed by Morales and colleagues.<sup>3</sup> These revealed the role of the interaction of the most widely studied environmental factors with variants at genes previously known to be involved in asthma pathophysiology.<sup>3</sup> However, limited replication of loci reported by candidate GxE studies was found.<sup>3</sup>

To our knowledge, a total of 12 GxE studies have been published from April 2019 to the time of writing (February 2022; Table 1), including nine using a candidate-gene interaction approach and only three GWIS. The effects of the environment on the genetic composition and *vice versa* have been mostly investigated in childhood traits, except for two studies focused on adults.<sup>29,30</sup> Additionally, the exploration of gene interactions with early-life environmental exposure to tobacco smoke in asthma susceptibility remains the most studied setting (Table 1). As a result, these studies have suggested interaction effects of known asthma genes with environmental tobacco smoke exposure during childhood (*IL1RN*, *NFE2L2*),<sup>31,32</sup> and a novel locus for asthma susceptibility (*NAT1*)<sup>33</sup> (Table 2). Furthermore, the association of *in utero* exposure with genetic variants in asthma has been evaluated.<sup>34</sup> Additionally, Sugier et al.<sup>35</sup> carried out one of the few GWIS published to date evaluating the effects of tobacco smoke. Specifically, the significant interaction of four novel loci with exposure to cigarette smoke was revealed to potentially influence the time-to-asthma onset in children from European populations<sup>35</sup> (Table 3).

Gene interactions with other environmental exposures have also been explored in the last 3 years, although to a lesser extent. Indeed, only two studies evaluated the interaction with different air pollutants, suggesting interaction effects of genes previously linked to asthma or lung function measurements (*IL13*, *KITLG*)<sup>36,37</sup> (Table 2). Furthermore, one large study recently suggested that the combination of mold exposure and the effect allele of an

TABLE 2 Summary association results of candidate-gene interaction studies conducted in childhood asthma in 2019–2022

Trait	Exposure	Population	Sample size	Chr. region <sup>c</sup>	SNP	Position <sup>a</sup>	Nearest gene(s)	Effect allele	OR (95% CI) <sup>b</sup>	p-value	Reported phenotype association for the effect allele	References					
Asthma susceptibility	Childhood environment tobacco smoke	Mixed (Latino, African American, European American)	441	2q13	rs2234678	113875565	IL1RN	G	9.10 (NA)	0.037	Increased risk for childhood asthma after early exposure to tobacco smoke	[31]					
					rs392503	113884195	IL1RN	G	8.70 (NA)	0.021							
					rs1794067	113886384	IL1RN	A	8.50 (NA)	0.013							
Asthma susceptibility	Household mold	Asian	1447	17q12	rs7216389	38069949	GSDMB	T	3.21 (1.77–5.99)	<0.05 <sup>c</sup>	Increased asthma risk after exposure to visible mold	[38]					
					rs4921580	18071000	NAT1	G	NA	7.0x10 <sup>-3</sup>	Increased risk for childhood asthma in presence of parental tobacco smoking	[33]					
Asthma susceptibility	Parental tobacco smoking (hair cotinine levels)	European	359	8p22	rs4921581	18071095	NAT1	A	NA	0.042							
					rs7003890	18077310	NAT1	A	NA	0.030							
					rs13253389	18071907	NAT1	A	NA	0.048							
Asthma susceptibility	Parental tobacco smoking (parents' report)	European	359	8p22	rs4921581	18071095	NAT1	A	NA	0.014	Increased risk for childhood asthma in presence of parental tobacco smoking	[33]					
					rs13253389	18071907	NAT1	A	NA	0.020							
Asthma severity	Childhood environment tobacco smoke	European	669	2q31.2	rs10183914	178097666	NFE2L2	A	1.99 (1.11–3.65)	0.020	Increased risk for childhood asthma in interaction with SHS exposure	[32]					
					rs1806649	178118152	NFE2L2	A	2.55 (1.28–5.34)	0.010							
Asthma severity	Heavy metals (Pb)	Asian	155	5q31.1	rs1800925	131992809	IL13	T	8.45 (2.61–27.32)	<0.001 <sup>c</sup>	Lower IL13 levels in interaction with exposure to high Pb levels	[37]					
					rs20541	131995964	IL13	T	5.37 (1.96–14.79)	<0.001 <sup>c</sup>							
Asthma severity	Childhood environment tobacco smoke	European	669	2q31.2	rs6726395	178103229	NFE2L2	A	0.21 (0.05–0.70)	0.016	Increased asthma severity in interaction with SHS exposure	[32]					
					rs2243250	132009154	IL4	C	1.41 (1.04–1.91)	0.027	Increased cord blood IgE levels in interaction with maternal atopy	[34]					
Allergic sensitization	Maternal atopy	Asian	989	5q31.1	rs58475486	89143324	KITLG	T	1.38 (NA)	3.0x10 <sup>-3</sup>	Protective genetic effect on FEV <sub>1</sub> in interaction with exposure to air pollution in the last year	[36]					
					rs111289668	89195377	KITLG	G	1.51 (NA)	0.037							
					rs73440122	89195898	KITLG	C	1.48 (NA)	0.051							
					rs17016065	89198057	KITLG	G	1.22 (NA)	0.026	Protective genetic effect on FEV <sub>1</sub> in interaction with exposure to air pollution in the last year						
					rs17016066	89198297	KITLG	A	1.22 (NA)	0.026							
					rs1398303	89205094	KITLG	A	1.23 (NA)	0.021							
					rs61924868	89205352	KITLG	T	1.23 (NA)	0.023							
					rs73429415	89213087	KITLG	A	1.22 (NA)	0.026							
					Lung function in asthma	Air pollution (SO <sub>2</sub> ) in the past year	African American	661	12q21.33	rs58475486	89143324	KITLG	T	1.38 (NA)	3.0x10 <sup>-3</sup>	Protective genetic effect on FEV <sub>1</sub> in interaction with exposure to air pollution in the last year	[36]
										rs111289668	89195377	KITLG	G	1.51 (NA)	0.037		



TABLE 2 (Continued)

Trait	Exposure	Population	Sample size	Chr. region <sup>c</sup>	SNP	Position <sup>a</sup>	Nearest gene(s)	Effect allele	OR (95% CI) <sup>b</sup>	p-value	Reported phenotype association for the effect allele	References
	Air pollution (SO <sub>2</sub> ) in the first year of life	African American	640	12q21.33	rs73440122	89195898	KITLG	C	0.73 (NA)	0.045	Decreased FEV <sub>1</sub> in interaction with exposure to air pollution during the first year of life	

Abbreviations: CI, confidence interval; FEV<sub>1</sub>, forced expiratory volume in one second; IgE, immunoglobulin E; IL13, interleukin 13; NA, not available; Pb, lead; SHS, second-hand tobacco smoke; SNP, single nucleotide polymorphism; SO<sub>2</sub>, sulfur dioxide.

<sup>a</sup>Chromosomal region.

<sup>b</sup>Positions based on GRCh37/hg19 build.

<sup>c</sup>Odds ratio for the effect allele.

<sup>d</sup>The p-value was not reported by the original publication.

intronic *GSDMB* variant could be associated with an increased risk to develop asthma in Asian children<sup>38</sup> (Table 2), consistent with previous studies.<sup>38</sup>

## 5 | ROLE OF AIRWAY EPITHELIUM IN GENE-ENVIRONMENT INTERACTIONS

The airway epithelium, extending from the nasal cavity to the small airways in the lungs, is an intricate structure composed of several cell types with dynamic and complex tasks.<sup>39</sup> This tissue upholds respiratory homeostasis and comprises the first line of defense against exogenous components in the surrounding air.<sup>40</sup> Several mechanisms are involved, including mucociliary function, structural protection, and coordination of immunological responses.<sup>40</sup> Airway epithelial dysfunction and remodeling have a significant role in asthma pathogenesis and have been linked to disease onset and progression.<sup>41</sup> Several asthma susceptibility genes are expressed in airway epithelial cells and/or have a direct role in epithelial functionality.<sup>41</sup> Intricate genetic and epigenetic mechanisms—functionally relevant genetic modifications without changes in the underlying nucleotide sequence—as well as environmental exposures are believed to drive part of the observed dysfunction and alter the response to insults.<sup>40-42</sup> The effect of the exposure to certain environmental factors early in life on the modification of the risk and severity of asthma later in childhood<sup>40,41</sup> is partially dependent on the functionality and integrity of the airway epithelium.<sup>40,43</sup> Indeed, environmental exposures can trigger an inflammatory response and the disruption of the barrier and mucociliary function, as well as the maintenance of respiratory homeostasis.<sup>40,41</sup> Children with a predisposed dysfunctional epithelium are particularly vulnerable to these adverse effects.<sup>40</sup>

Respiratory infections are common insults in young children, particularly rhinovirus (RV) infections, which have been linked with epithelial dysfunction, wheezing, and subsequent asthma.<sup>40</sup> Wheezing and asthma share some pathomechanisms in common such as inflammation, smooth muscle hyperreactivity, and mucus hyperplasia.<sup>40</sup> RV is detected in most children who receive medical care for asthma exacerbations and is known to exacerbate pre-existing asthma.<sup>40</sup> Impaired epithelial barrier and functionality, as well as dysregulated immune responses, have been suggested as perpetuating mechanisms, perhaps even more so in children with a predisposition for epithelial dysfunction and future asthma.<sup>40,44</sup> In fact, children with RV infections show impaired epithelial wound repair, which is magnified in asthmatic airways.<sup>44</sup>

### 5.1 | The 17q12-21 locus: a central marker of asthma in interaction with the environment

The 17q12-21 chromosome region stands out as the most widely and consistently associated signal in different populations, making it a potential central genetic marker in asthma.<sup>15</sup> This region consists of a dense block of SNPs located at a core region harboring *ZBPB2*, *GSDMB*,

*ORMDL3*, and *IKZF3*, together with flanking genes such as *PGAP3*, *ERBB2*, and *GSDMA*.<sup>15,20</sup> Additionally, there is strong evidence of the modification of the effects of genes at this locus in childhood asthma by environmental exposures, specifically, those in early life.<sup>45</sup>

Interestingly, RV or respiratory syncytial virus infections of the lower respiratory tract during infancy have been strongly associated with genotypes at the 17q12-21 locus, increasing the risk to develop childhood-onset asthma.<sup>45</sup> This has been evidenced to be substantially enhanced by the combination with environmental tobacco smoke exposure.<sup>46</sup> Among the genes located in this genomic region, *ORMDL3* and *GSDMB* have been the main actors.<sup>45</sup> Genetic variants at the 17q12-21 locus previously associated with asthma have been linked to the expression patterns of these together with *ZBPB2*.<sup>15,20</sup> The *ORMDL3* expression levels have been proposed to regulate the viral replication in bronchial and airway epithelial cells.<sup>47</sup> Thus, upregulation of *ORMDL3* could potentially trigger the viral load increase and hamper the recovery capacity of these cells after infection.<sup>45</sup> This process could be mediated by the sphingolipid pathway<sup>47</sup> and decreased expression of the RV receptor ICAM-1,<sup>48</sup> leading to a hindered response to lung injury.<sup>48</sup> These pieces of evidence might explain the increased susceptibility of children carrying effect alleles of 17q12-21 variants associated with increased expression levels of *ORMDL3* to experience recurrent wheezing after RV infection.

Exposure to farm animal sheds, which harbor high levels of microorganisms, and household cat allergens has been proposed to be potentially beneficial against respiratory infections and the development of childhood asthma in subjects carrying the effect allele of 17q12-21 variants associated with increased asthma risk.<sup>49,50</sup>

## 6 | EXPANDING THE GENE-ENVIRONMENT CONCEPT

### 6.1 | Challenges of conventional GxE strategies

Despite the advances in the GxE methodological approaches in the lifetime of this field, we are still far from having a complete picture of the complex interactions between the individual's genetic composition and the environment. Indeed, major novel GxE findings have not been detected as expected.<sup>3,4</sup> This could be partially explained by the modest associations in terms of effect size and significance levels detected by the very limited number of GWIS carried out in the last few years<sup>3,4</sup> in a context of highly restrictive threshold conditions, limited robustness, and consistency across different studies.<sup>1,3</sup> The strict requirement for very large sample sizes is difficult to achieve in most asthma studies.<sup>3,4</sup> Additionally, frequent high correlation among environmental factors hampers the capacity to discern the influence of each of them in the modification of the protective or detrimental effect of genetic variants on different asthma-related traits.<sup>4</sup> Also, most GxE studies carried out until now have been focused on asthma status with a scarce exploration of more specific endotypes, which are likely to interact with different environmental exposures and genetic determinants.<sup>51</sup>

TABLE 3 Summary results of GWIS of childhood asthma-related traits published between 2019 and 2022

Trait	Exposure	Population	Sample size	Chr. region <sup>d</sup>	SNP	Position <sup>a</sup>	Nearest gene(s)	Effect allele	OR (95% CI) <sup>b</sup>	p-value	Reported phenotype association for the effect allele	References
Time of asthma onset	Childhood environment tobacco smoke (maternal smoking during pregnancy/parental smoking during early childhood)	European	8273	2p22	rs232542	38328178	CYP11B1	C	1.33 (1.18–1.50) <sup>d</sup>	4.10 × 10 <sup>-6</sup>	Increased risk of childhood asthma in interaction with early-life tobacco smoke exposure	[35]
				2p22	rs232540	38329395	CYP11B1	C	1.33 (1.18–1.50) <sup>d</sup>	4.80 × 10 <sup>-6</sup>		
				2p22	rs151313	38332182	CYP11B1	T	1.33 (1.18–1.50) <sup>d</sup>	5.00 × 10 <sup>-6</sup>		
				2p22	rs232535	38332303	CYP11B1	C	1.33 (1.18–1.50) <sup>d</sup>	5.00 × 10 <sup>-6</sup>		
				13q21	rs17742723	70635410	KLHL1	T	1.54 (1.30–1.82) <sup>d</sup>	6.70 × 10 <sup>-7</sup>		
				13q21	rs1372284	70639940	KLHL1	G	1.47 (1.25–1.72) <sup>d</sup>	3.90 × 10 <sup>-6</sup>		
				13q21	rs2439614	70641136	KLHL1	C	1.53 (1.30–1.80) <sup>d</sup>	4.00 × 10 <sup>-7</sup>		
				13q21	rs7334050	70645872	KLHL1	G	1.58 (1.34–1.86) <sup>d</sup>	4.30 × 10 <sup>-8</sup>		
				13q21	rs9542173	70646892	KLHL1	T	1.56 (1.32–1.85) <sup>d</sup>	1.30 × 10 <sup>-7</sup>		
				13q21	rs299526	70655360	KLHL1	C	1.49 (1.27–1.76) <sup>d</sup>	1.60 × 10 <sup>-6</sup>		
				14q22	rs7493885	51317418	NIN	G	1.37 (1.20–1.56) <sup>d</sup>	2.90 × 10 <sup>-6</sup>		
				14q22	rs1951474	51317832	NIN	T	1.37 (1.20–1.56) <sup>d</sup>	3.10 × 10 <sup>-6</sup>		
				14q22	rs8020067	51318210	NIN	G	1.37 (1.20–1.56) <sup>d</sup>	3.10 × 10 <sup>-6</sup>		
				20p12	rs187097	14911406	FLRT3	C	1.31 (1.17–1.48) <sup>d</sup>	5.40 × 10 <sup>-6</sup>		
				20p12	rs13037508	14928945	FLRT3	A	1.48 (1.27–1.72) <sup>d</sup>	4.90 × 10 <sup>-7</sup>		



TABLE 3 (Continued)

Trait	Exposure	Population	Sample size	Chr. region <sup>d</sup>	SNP	Position <sup>a</sup>	Nearest gene(s)	Effect allele	OR (95% CI) <sup>b</sup>	p-value	Reported phenotype association for the effect allele	References		
Asthma treatment response (ICS)	Age	European	783 <sup>c</sup>	1q21.3	rs509061	153133123	SPRR2G	C	2.08 (1.5–2.89)	$1.28 \times 10^{-5}$	Poorer ICS response in older ages	[84]		
				1q21.3	rs77668680	153135101	SPRR2G	CAG	2.23 (1.58–3.14)	$4.23 \times 10^{-6}$				
				1q21.3	rs524887	153136507	SAMD13	G	2.23 (1.58–3.14)	$4.57 \times 10^{-6}$				
				5q11.2	rs72755727	57526702	PLK2	T	2.67 (1.71–4.17)	$1.72 \times 10^{-5}$				
				5q11.2	rs1477347	57532962	PLK2	A	2.71 (1.73–4.24)	$1.31 \times 10^{-5}$				
				5q11.2	rs2052548	57536732	PLK2	C	2.73 (1.74–4.27)	$1.18 \times 10^{-5}$				
				5q11.2	rs72755734	57538754	PLK2	G	2.72 (1.74–4.26)	$1.22 \times 10^{-5}$				
				5q11.2	rs6892109	57550096	PLK2	T	2.7 (1.73–4.22)	$1.34 \times 10^{-5}$				
				5q11.2	rs12658947	57552464	PLK2	G	2.69 (1.72–4.2)	$1.51 \times 10^{-5}$				
				5q11.2	rs12659412	57552715	PLK2	C	2.69 (1.72–4.2)	$1.51 \times 10^{-5}$				
				5q34	rs290119	163268101	MAT2B	A	2.38 (1.6–3.53)	$1.76 \times 10^{-5}$				
				5q34	rs290122	163268306	MAT2B	T	2.38 (1.6–3.53)	$1.76 \times 10^{-5}$				
				5q34	rs58836160	163268787	MAT2B	TA	2.38 (1.6–3.53)	$1.76 \times 10^{-5}$				
				6q24.2	rs2328386	143144958	HIVEP2	T	0.33 (0.2–0.55)	$1.86 \times 10^{-5}$				
				8q24.12	rs34338452	119473789	SAMD12	A	2.24 (1.57–3.19)	$7.58 \times 10^{-6}$				
				8q24.12	rs10094604	119475295	SAMD12	T	2.28 (1.6–3.24)	$4.73 \times 10^{-6}$				
				12q24.31	rs28520411	121973317	KDM2B	A	2.3 (1.58–3.35)	$1.45 \times 10^{-5}$				
				12q24.31	rs28663167	121988899	KDM2B	T	2.38 (1.62–3.48)	$8.52 \times 10^{-6}$				
				15q23	rs34631960	71833069	THSD4	C	2.33 (1.61–3.38)	$7.08 \times 10^{-6}$				
				16p13.3	rs6500715	5784292	RBFOX1	C	0.47 (0.34–0.65)	$5.51 \times 10^{-6}$				
Asthma treatment response (BDR)	Age	European	892	3q11.2	rs832073	97697002	RIOX2	T	1.27 (1.15–1.40)	$3.00 \times 10^{-6}$	Poorer BDR in older ages	[85]		
				8p23.1	rs4840337	8198306	PRAG1	C	1.27 (1.15–1.39)	$1.00 \times 10^{-6}$				
				18p11.32	rs1439427	1845637	METTL4	A	0.51 (0.38–0.68)	$3.00 \times 10^{-6}$	Improved BDR in older ages			

Abbreviations: BDR, bronchodilator response; CI, confidence interval; ICS, inhaled corticosteroids; NA, not available; SNP, single nucleotide polymorphism.

<sup>a</sup>Chromosomal region.

<sup>b</sup>Positions based on GRCh37/hg19 build.

<sup>c</sup>Odds ratio for the effect allele.

<sup>d</sup>The association results from the discovery phase are shown.

<sup>e</sup>The effect size was reported in terms of hazard ratios by the original publication.

It is important to note that GxE investigations of asthma have been characterized by an overrepresentation of European populations, hampering the translation of findings into other ancestry groups.<sup>52</sup> Indeed, the potential of recently admixed populations in GWIS has been demonstrated, although presenting additional challenges.<sup>4</sup> The utility of the screening of these populations through an alternative to conventional admixture mapping analyses has been suggested to substantially increase the statistical power to detect GxE effects.<sup>53</sup>

On the other hand, other types of genetic variation beyond common SNPs harbored at autosomes are expected to reveal novel asthma loci with functional implications in interaction with environmental exposures.<sup>2</sup> Polygenic risk score (PRS) approaches show an increased potential to detect significant GxE in complex traits compared with methods based on individual SNPs.<sup>54,55</sup> Mendelian Randomization (MR) strategies also promise to provide additional insights into the causality and directionality of GxE,<sup>56</sup> although they have been scarcely applied to evaluate the mechanisms underlying asthma.<sup>57</sup>

## 6.2 | GxE approaches beyond genetic variation

High-throughput sequencing approaches and methods to simultaneously measure large sets of biomarkers promise high advances to disentangle the molecular mechanisms underlying asthma in interaction with environmental exposures exploring several layers of biological information.

### 6.2.1 | Epigenetics: a well-established field in the GxE investigations

Environmental exposures can not only modify the risk of asthma-related traits provided by the genetic information, but also they are able to induce epigenetic changes, for example, methylation at regions enriched on cytosine and guanine nucleotides (CpG sites), post-transcriptional control by noncoding RNAs, and histone modifications. As a result, the gene expression and phenotype are modified without altering the DNA sequence.<sup>58</sup> These modifications last for a varied time and are dynamic with the possibility of even being transferred transgenerationally.<sup>58</sup> For instance, grandmaternal smoking has been demonstrated to predispose to childhood asthma in the offspring, potentially mediated by epigenetic mechanisms.<sup>59</sup>

It has been suggested that several environmental factors associated with asthma might induce epigenetic changes, and differential methylation patterns at birth and in childhood have been linked with this disease.<sup>60</sup> Thus, their study could shed light on the mechanisms of GxE and the development of asthma-related phenotypes.<sup>2</sup> The potential of epigenetics in the GxE investigation of childhood asthma is also reinforced by epigenetic mechanisms in airway epithelial cells, involved in the host immune response and the regulation of the development, functionality, and repair of the

airway epithelium,<sup>61</sup> which is crucial in the interaction with the environment, as mentioned above. In fact, changes in DNA methylation near genes involved in the immune response and asthma pathogenesis in nasal epithelial cells and blood were detected in asthmatic subjects following RV infection.<sup>62,63</sup> These epigenetic mechanisms in airway epithelial cells may have different roles: to further aggravate the disease mechanisms or to try to repair the dysfunctional epithelium.<sup>61</sup> Here, we will focus on DNA methylation changes which is perhaps the most studied epigenetic mechanism in childhood asthma.

Tobacco smoke has also been extensively studied in asthma from an epigenetic perspective. Interestingly, a large meta-analysis of 13 pediatric cohorts identified circa 3000 CpGs differentially methylated in neonate blood following maternal smoking during pregnancy. These methylation changes were observed to persist to a later time in childhood, increasing the risk to develop asthma.<sup>64</sup> Furthermore, air pollution has been widely linked to epigenetic changes, which might modulate immune responses in the airways and provide an increased risk of asthma.<sup>65</sup> For instance, three studies identified differentially methylated regions associated with traffic-related air pollution exposure that mapped to *FOXP3* and *IL-10* in peripheral blood mononuclear cells (PBMCs), buccal epithelial cells, and saliva and were linked to decreased lung function, wheezing, and asthma.<sup>65,66</sup> *FOXP3* has also been found to be differentially methylated in T cells from children in association with exposure to air pollution and second-hand smoke.<sup>67</sup> Furthermore, the hypomethylation of the *NOS3* promoter was associated with traffic-related air pollution exposure.<sup>68</sup> However, epigenetic changes associated with air pollution exposure can differ between individuals with distinct characteristics, which has been demonstrated by the identification of enhanced changes in CpG methylation following outdoor air pollution exposure in the *IL4* promoter and *NOS2A* in serotopic children or patients with a history of concomitant sensitization to cockroaches.<sup>69</sup>

The timing of environmental exposures might have a critical role in the effect of epigenetic changes. Specifically, exposures during the prenatal and perinatal periods have been proposed as a potential crucial mechanism in asthma-related traits, causing epigenetic modifications also in later stages of the development that can persist across the lifespan.<sup>25</sup> This has been demonstrated by the identification of differentially methylated CpGs mapping to genes previously linked to asthma and lung health in newborns of mothers that had been exposed to traffic-related air pollution.<sup>70</sup> Similarly, exposure to tobacco smoke *in utero* has been associated with epigenetic changes in offspring<sup>71</sup> and, subsequently an increased risk for asthma in childhood.<sup>59</sup>

Several studies have reported differential DNA methylation profiles in nasal epithelial cells from children with asthma and/or atopy, with CpG sites mapping to genes with known effects on immune responses and epithelial functionality.<sup>60,72</sup> Different methylation patterns in airway epithelial cells might differ between allergic diseases and asthma, and even different asthma phenotypes.<sup>72,73</sup>

## 6.2.2 | Emerging omics approaches in the GxE field

The exploration of additional omics layers has been proven very useful to provide an alternative perspective to better understand the GxE in asthma. The evaluation of differential gene expression patterns in cells or tissues in response to a certain environmental exposure in transcriptomic studies has been highlighted for its capacity to discern different GxE effects in well-controlled in vitro environments.<sup>4</sup> Some studies have suggested the existence of transcriptional changes in PBMCs after RV infection.<sup>74,75</sup> McGeachie et al.<sup>76</sup> also demonstrated the influence of the patient's age on the expression of *SMARCD1* in lymphocytes with effects on asthma control despite inhaled corticosteroids (ICS) use. Nonetheless, the analysis of transcriptome data obtained through NGS technologies (RNA-seq) in the GxE field is highly promising, which can be demonstrated by the recent evidence of changes in gene expression levels that might affect asthma in interaction with psychosocial factors.<sup>77</sup>

It has been proposed that the exploration of the proteome in interaction with multiple environmental factors could facilitate the identification of relevant disease proteins.<sup>78</sup> Although no proteomic studies accounting for interactions with the environment have been conducted in asthma research to date, it is a promising field that deserves further exploration. Similarly, metabolic profiling outstands for its capacity to capture the history of the response to exposures overtime.<sup>79</sup> Liang and colleagues<sup>80</sup> recently revealed significant metabolic changes related to inflammatory processes and oxidative stress after exposure to traffic-related air pollution in patients with asthma, suggesting a valuable alternative approach to conventional GxE conventional methods.

Additionally, the study of the microbiome—genetic characterization of the human microbiota—has been evidenced to be of special relevance for disorders with an important contribution to processes related to the immune system.<sup>81</sup> Indeed, the composition and abundance of the gut and airway microbiome have been demonstrated to be influenced by environmental exposures across the lifespan, modifying the risk to develop asthma.<sup>82</sup> Thus, this offers an alternative framework to understand the GxE in asthma-related traits.

## 6.3 | Exploring host factors in GxE

Environment-related factors have had the leading role in the GxE investigations (mainly air pollution and tobacco smoke) with a clear underrepresentation of host characteristics (Table 1), despite their implication in the modification of the genetic risk to develop different asthma-related traits (Figure 1).<sup>26,32</sup>

### 6.3.1 | Age and gender

It is well known that the prevalence of asthma and related phenotypes differ by gender and age across the lifespan. Childhood-onset asthma is more prevalent in prepubertal men although with

a less severe phenotype, even though the lifetime risk of asthma is higher in women.<sup>83</sup> A complex network of different factors has been proposed to play an important role,<sup>83</sup> including genotype-by-sex interactions. For instance, two SNPs at the *IFNG* gene were associated with a decreased risk for the development of childhood asthma in women compared with men of the same age with a history of wheezing early in life.<sup>84</sup> Moreover, age has been proposed to be an important modifier of the association of genetic variants with other asthma-related traits apart from susceptibility, such as treatment response. Indeed, two recent GWIS explored interactions with age in the response to the most commonly used asthma medications (short-acting beta-2 agonists [SABA] and ICS) in European populations<sup>85,86</sup> (Table 1). Interestingly, age-related modifications of genetic associations at several loci previously linked to asthma pathophysiology were revealed in asthma exacerbations despite ICS and bronchodilator response in pediatric and adult asthma patients (Table 3). However, there is contradictory evidence regarding the contribution of genetic factors in the response to asthma treatment dependent on age, demonstrating the need for further investigation,<sup>16,17</sup> including the exploration of the influence of GxE.

### 6.3.2 | Socioeconomic and psychosocial factors

Socioeconomic status (SES) has been suggested to affect the transmission of intergenerational asthma risk through GxE mechanisms.<sup>87</sup> Children of parents with asthma and lower SES are more probably exposed to unhealthy environmental risk factors compared to children with higher SES.<sup>87</sup> Thus, it has been suggested that genetics might play a larger role in asthma onset in families with higher SES,<sup>87</sup> demonstrating the potential of the investigation of the effect of the interaction with SES on the modification of the genetic risk to develop childhood asthma.

On the other hand, psychosocial factors, such as stress, have been evidenced to affect the expression of genes linked to asthma and inflammation, worsening asthma symptoms.<sup>77</sup> This association can be extended to maternal psychosocial experiences, which can increase the risk to develop childhood-onset asthma, potentially by modifying lung development or immune responses.<sup>88</sup> Moreover, parental depression implying negative changes in the child's mood has been associated with a decreased expression of the glucocorticoid receptor and  $\beta_2$  adrenergic receptor in whole blood, which can influence the response to asthma treatment and disease control.<sup>89</sup> Thus, decreasing socioeconomic and health disparities as well as improving the psychosocial environment for expecting mothers and for families with young children may reduce asthma onset.<sup>77</sup>

### 6.3.3 | Pharmacological therapies

Some studies have suggested that certain medications might affect asthma onset, but findings have not been consistent to date. The role of both prenatal and childhood paracetamol and antibiotic use

has been speculated to increase the risk of asthma and/or wheezing. However, their role, and the influence of confounding factors such as the indication and reverse causation needs further investigation, and might muddle the observed effect.<sup>90</sup> Moreover, the regular use of inhaled  $\beta$ -agonists at a young age to treat wheezing symptoms might aggravate airway hyper-responsiveness, which may play a role in future asthma development in children.<sup>13</sup>

### 6.3.4 | Early life-related factors

Perinatal factors relating to birth conditions and newborn characteristics might affect asthma risk and lung function in the early years. Indeed, preterm birth and bronchopulmonary dysplasia increase the risk of asthma, wheezing illness, and impaired lung function in childhood.<sup>90</sup> Additionally, the prenatal maternal diet has been evidenced to affect the development of childhood-onset asthma in the offspring.<sup>90</sup> Supplementation regimens during pregnancy with increased vitamin D intake and fish oil have been suggested to promote appropriate fetal lung growth and subsequently improved lung function and a decreased risk of asthma and/or wheezing in the offspring.<sup>13,91</sup> Nonetheless, there are contradicting views on how breastfeeding affects future asthma risk. Some studies have suggested the protective effect of breastfeeding against lower respiratory symptoms during the first year of life in those children carrying the effect alleles of *GSDMB*, *GSDMA*, and *ORMDL3* variants previously associated with an increased risk to develop childhood asthma.<sup>92</sup> Thus, we could hypothesize that those breastfed infants could experience a lower risk to develop viral infections, partly contributed by 17q12-21 genetic variants, and therefore wheezing, reducing the risk to develop childhood-onset asthma.

On the other hand, diet and body composition in childhood affect both asthma susceptibility and severity. Increasing the intake of fruits and vegetables and eating less fast foods as well as adopting a Mediterranean diet have been linked to a decreased asthma risk.<sup>13</sup> Moreover, a positive association between high body mass index (BMI), sedentary behavior, and asthma symptoms in children from high-income countries has been reported. Thus, overweight or obese asthmatic children have worse asthma control and more severe symptoms.<sup>90</sup> This raises concerns about the future as the prevalence of childhood obesity and sedentary behavior are globally increasing.<sup>11,13</sup>

## 7 | GOING FORWARD

Despite methodological and conceptual challenges with GxE interaction studies, recent data have led to new insights into childhood asthma pathophysiology. This is perhaps best exemplified by the 17q12-21 asthma locus, where studies have taught us important lessons on GxE effects in that associations with SNPs at this major locus seem to be restricted to childhood asthma

onset, thereby highlighting the importance of age and related factors. This locus primarily reflects early-life susceptibility to respiratory viruses common to all asthma and wheezing children. Cumulatively, these pieces of evidence demonstrate the potentially crucial role of the 17q12-21 region in key processes in the airway epithelium in response to pathogenic and beneficial microbe exposure.

Going forward, we propose that the future of GxE investigations in childhood asthma research should be characterized by solid attempts to overcome the limitations of the conventional methodological approaches discussed in this review. The horizon of this field needs to be widely expanded by exploring alternative methods such as PRS, MR, and admixture mapping, as well as combining different omics layers.

Additionally, it is very important to gather efforts to evaluate a more complete set of environmental exposures, for example through an exposome approach, to better understand the molecular and cellular mechanisms involved in childhood asthma taking into account the important role of the environment.<sup>5</sup> A continued and refined use of single-cell techniques could be used to further elucidate the role of the airway epithelium in asthma, understand how the airways adapt to exposures and discern those factors with a key role and in what time frame.<sup>41,42</sup> Additionally, longitudinal and functional studies are needed to provide insights into the biological mechanisms underlying the observed associations and to pinpoint precisely which environmental exposures give rise to the epigenetic changes that modify the asthma risk.<sup>1,58</sup> Utilizing several types of genomic data and assessing co-exposures in large study populations could also illuminate the reported complex interactions and elucidate how genetic variance affects epigenetic mechanisms even on a single-cell level.<sup>1,58</sup>

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