Genetic and Environmental Factors Influencing Paediatric Allergic Reactions

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Abstract: *Background*: Paediatric allergic reactions represent a growing global health concern, with conditions such as asthma, atopic dermatitis, food allergy, and allergic rhinitis affecting a substantial proportion of children. Their development is influenced by complex interactions among genetic susceptibility, epithelial barrier dysfunction, immune dysregulation, and environmental exposures that occur from the prenatal period through early childhood.

Objective: To synthesise current evidence on the epidemiology, genetic determinants, and environmental risk factors associated with paediatric allergic reactions, with particular emphasis on mechanisms influencing disease onset, severity, and progression.

Methods: A structured narrative review and analytical synthesis of scientific literature were conducted. Sources included systematic reviews, meta-analyses, prospective cohort studies, and large epidemiological datasets. Evidence was evaluated with attention to temporal relationships between exposures and outcomes, consistency of associations across populations, and biological plausibility. Allergic outcomes were grouped into major clinical phenotypes and immunological markers of sensitisation, while environmental influences were analysed from an exposome perspective.

Results: The global burden of paediatric allergic diseases remains high, with asthma and atopic dermatitis affecting tens of millions of children worldwide. Evidence consistently indicates that epithelial barrier dysfunction and Th2-mediated immune responses are central pathogenic mechanisms. Genetic variants, particularly loss-of-function mutations in the filaggrin gene (FLG), are strongly associated with increased risk and severity of food allergy and atopic dermatitis. Environmental, nutritional, and perinatal exposures – including air pollution ($PM_{2.5}$), caesarean delivery, early-life medication use, dietary factors, and microbial dysbiosis – act as important modifiers of allergic risk and may interact with genetic susceptibility.

Conclusion: Paediatric allergic reactions arise from multifactorial interactions between genetic predisposition and environmental exposures during critical developmental windows. Early identification of high-risk children and preventive strategies targeting modifiable environmental factors are essential for reducing disease burden and improving long-term health outcomes.

Keywords: Atopic dermatitis, exposome, perinatal determinants, antibiotic exposure, comorbidity.

INTRODUCTION

Allergic reactions in childhood represent a pressing problem due to their high prevalence (atopic dermatitis, allergic rhinitis, bronchial asthma, food allergy), early onset, and the risk of progression along the so-called atopic march. The multifactorial nature of these conditions, including hereditary predisposition, epithelial barrier dysfunction, environmental exposures, and immune dysregulation, complicates prevention, early detection, and long-term disease control. These conditions are also associated with a substantial medical and social burden, including reduced quality of life in children, sleep disturbances, impaired learning activity, frequent exacerbations, and high financial costs for families and healthcare systems.

In recent years, increasing attention has been devoted to the exposome framework as a model for understanding the multifactorial origin of paediatric allergic diseases. The exposome encompasses the totality of environmental exposures experienced throughout life, beginning from the prenatal period, including air pollution, nutrition, microbial influences, medications, household chemicals, and psychosocial factors. In childhood allergy, these exposures interact dynamically with genetic susceptibility, epithelial barrier integrity, immune maturation, and microbiome development, shaping sensitisation trajectories and disease severity during sensitive periods of immune development. This framework provides an integrative conceptual perspective, in contrast to traditional approaches focused on isolated environmental or genetic risk factors.

Particular attention has recently been directed toward nutritional determinants during early life, since feeding practices may influence immune maturation, epithelial barrier function, and microbiome development during critical developmental periods. Breastfeeding, dietary diversity, timing of allergen introduction, and

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vitamin D status have been discussed as factors potentially involved in the development of immune tolerance and modification of allergic risk trajectories in childhood. Interactions between nutrition, the gut microbiome, and immune regulation further support the inclusion of nutritional exposures within the exposome framework of paediatric allergic diseases [1, 2].

Previous studies have demonstrated that paediatric allergic diseases are associated with substantial direct and indirect socioeconomic burden, including healthcare costs, reduced quality of life, and impaired daily functioning [3]. Global epidemiological studies based on the Global Burden of Disease (GBD) framework indicate that paediatric allergic diseases remain highly prevalent worldwide, with substantial regional and sociodemographic variability [4]. National epidemiological studies further demonstrate changing patterns of allergic phenotypes in childhood. Using National Health Interview Survey data, Pate *et al.* [5] demonstrated that the prevalence of childhood asthma in the United States declined between 2007 and 2018, whereas other allergic conditions remained widespread. Different phenotypes also showed divergent temporal trends, highlighting the influence of changing environmental exposures and diagnostic practices. Similar heterogeneity was observed in Asian populations. Using Korean population data from 2008-2017, Ha *et al.* [6] described age-related trends in asthma, allergic rhinitis, and atopic dermatitis, further supporting the role of local exposures and critical developmental windows in shaping allergic phenotypes.

Food allergy represents one of the most clinically significant paediatric allergic phenotypes because of its association with severe systemic reactions, including anaphylaxis. Recent epidemiological evidence indicates that food allergy prevalence remains high and continues to increase in many paediatric populations worldwide, particularly among young children, contributing to the growing burden of severe allergic reactions and anaphylaxis [7].

The clinical relevance of allergic conditions in childhood is further reinforced by evidence of broader developmental consequences. In a nationally representative study conducted in the United States of America, Xu *et al.* [8] identified associations between food, respiratory, and skin allergies and attention-deficit hyperactivity disorder. These findings suggest a potential contribution of chronic inflammation, sleep disturbances, and psychosocial stressors to the development of comorbidity.

The epidemiological significance of allergic diseases extends beyond childhood. Findings from the 2021 National Health Interview Survey, reported by Ng and Boersma [9], demonstrated a substantial prevalence of seasonal allergies, eczema, and food allergy among adults in the United States of America. These data highlight the persistent medical and socioeconomic burden of atopic conditions across the life course and support the possibility of long-term persistence or recurrence of allergic phenotypes.

Alongside population-level estimates, evidence has accumulated on molecular determinants of the severity and persistence of paediatric allergic phenotypes, primarily through mechanisms involving the skin barrier. In an early prospective cohort, Virolainen *et al.* [10] identified associations between filaggrin loss-of-function variants and atopic dermatitis phenotypes in an ethnically diverse paediatric population. These findings support a barrier-genetic model as a basis for risk stratification. At the level of clinically relevant food phenotypes, Kalb *et al.* [11] found that FLG loss-of-function mutations were associated with persistence of egg and cow milk allergy, indicating an influence not only on sensitisation onset but also on tolerance development in a proportion of children. At the population level, an urban context further highlights potential links between allergic phenotypes and environmental exposures. Mazur *et al.* [12], within an urbanised agglomeration, analysed the coexistence of atopic dermatitis and food allergy in children and adolescents and examined a possible association with air quality indicators. These observations further support the relevance of an exposomic interpretation of paediatric allergic reactions.

Although numerous studies have examined genetic susceptibility, environmental exposures, or nutritional determinants of paediatric allergic diseases, these factors are frequently analysed in isolation. Less attention has been devoted to integrative approaches that consider the interaction between exposomic influences, epithelial barrier dysfunction, microbiome-related mechanisms, immune maturation, and nutritional exposures within a unified developmental framework. This review aims to address this gap by providing a structured synthesis of current evidence on the interplay between genetic, environmental, microbial, and nutritional factors influencing the onset, progression, and severity of paediatric allergic diseases within the exposome perspective. The objectives of this review were to analyse global prevalence trends and burden of childhood allergic phenotypes; synthesise

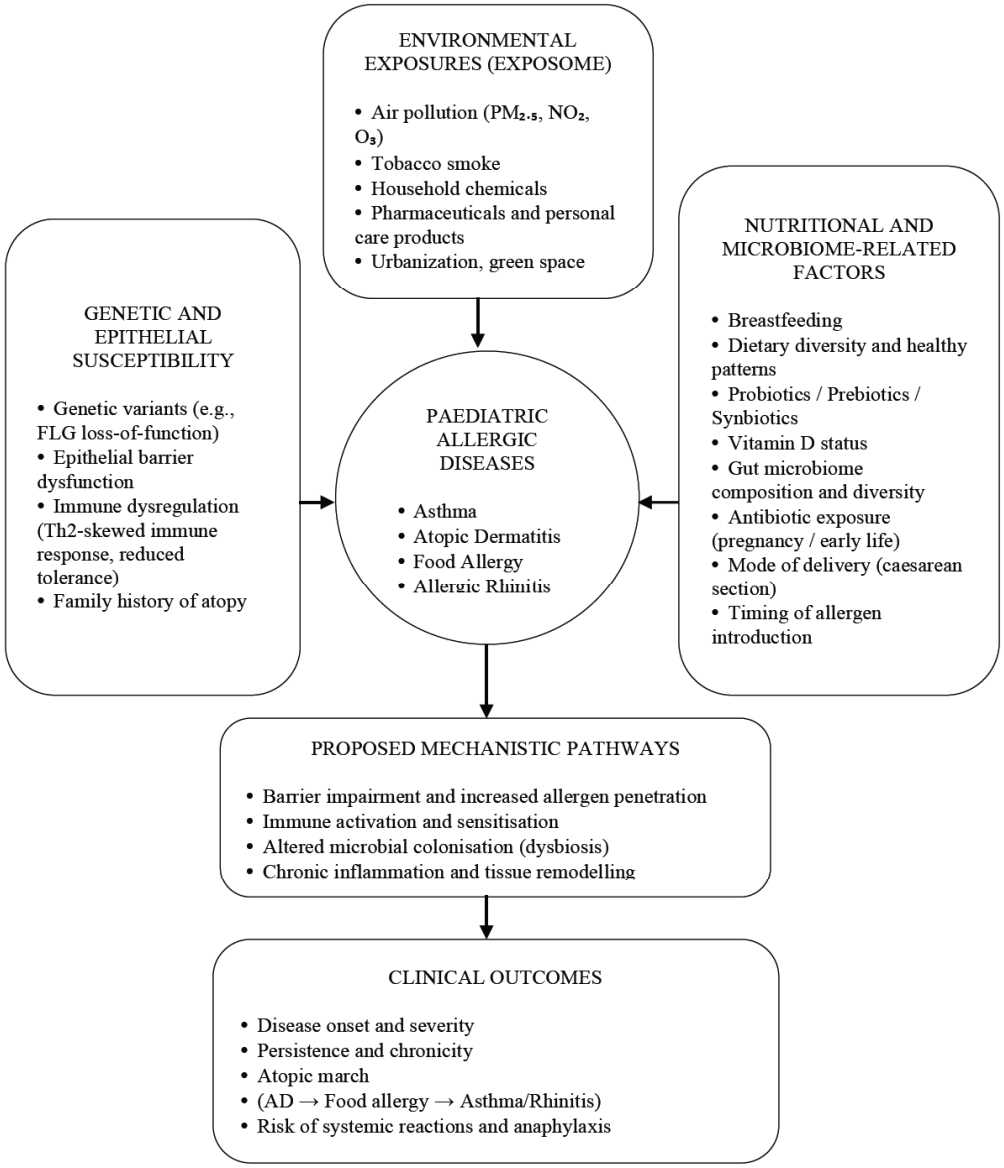

Figure 1: Integrated Exposome Model of Paediatric Allergic Disease Development.
Source: compiled by the authors based on synthesised literature.

the role of barrier-genetic mechanisms, with a focus on FLG variants; and evaluate key exposomic and perinatal risk modifiers and their mechanistic links with allergic disease development.

To facilitate conceptual understanding of the multifactorial mechanisms underlying paediatric allergic diseases, the main exposomic, genetic, microbiome-related, and nutritional interactions discussed in this review are summarised in Figure **1**.

MATERIALS AND METHODS

The methodological approach was based on a combination of narrative review and formalised interpretation procedures, which enabled coherent comparison of heterogeneous sources (cohort studies, meta-analyses, genetic association studies, and guidelines) and reduced the risk of selective interpretation of results. The information base was formed from publications in international bibliographic databases PubMed/MEDLINE, Embase, Web of Science, and Scopus, as well as from clinical guidelines and position papers of international professional societies. The search covered publications from 2020 to 2025, which ensured representativeness of contemporary approaches while also including studies that established foundational concepts of genetic-exposomic interactions. Search strategies employed combinations of controlled terms and free

text, including “paediatric”, “child”, “infant”, “allergic disease”, “atopic dermatitis”, “eczema”, “asthma”, “allergic rhinitis”, “food allergy”, “anaphylaxis”, “gene-environment interaction”, “genetic susceptibility”, “polygenic risk”, “filaggrin”, “exposome”, “air pollution”, “caesarean section”, “antibiotic exposure”, “microbiome”. Language restrictions allowed inclusion of publications in English, while materials in other languages were considered only when a full English abstract provided sufficient information on design, population, exposures, and outcomes. Peer-reviewed studies with clearly defined paediatric populations and validated definitions of exposures and outcomes were included, with priority given to studies that applied multivariable adjustment for key confounders (age, sex, family history of atopy, socio-economic indicators, exposure to tobacco smoke, concurrent infections, and others). Materials without a paediatric analysis, lacking transparency regarding diagnostic criteria, or purely descriptive without an analytical component were not used as a basis for generalised conclusions. The source selection scheme comprised sequential stages: identification of records through database searches and, separately, through guidelines and position papers; duplicate removal; initial screening of titles and abstracts against population criteria (childhood), exposure types (genetic markers, exposomic and perinatal factors), and outcomes (clinically defined allergic phenotypes); full-text assessment of potentially relevant publications; and final inclusion of sources meeting predefined quality criteria and providing quantitative estimates or conceptually significant mechanistic syntheses. To minimise systematic errors, preference was given to meta-analyses, systematic reviews, prospective cohorts, and studies with clear validation of exposures and outcomes, while relevant reference lists in selected reviews were also checked (snowball search) to identify additional primary sources.

Conceptual harmonisation of phenotypes and exposures was performed to improve data comparability. Allergic manifestations were grouped as clinical phenotypes (food allergy, atopic dermatitis, asthma/wheeze, allergic rhinitis, anaphylaxis) and as immunological characteristics of sensitisation (IgE-mediated reactions, specific IgE, skin prick tests), while temporal trajectories of onset and symptom persistence were considered within the “atopic march” framework. Environmental factors were analysed from an exposome perspective, distinguishing external pollutants (notably air pollution), perinatal determinants (for example, mode of delivery), early-life medication exposures (antibiotics), indoor factors (dampness/mould, volatile organic compounds, household chemicals), and biological mediators (microbiome), which potentially mediate the relationship between environment and phenotype.

Analytical synthesis was conducted through a coherent comparison of results across three interrelated parameters: temporal sequence (priority was given to studies where exposure preceded phenotype manifestation), consistency of effects (replication of the direction and magnitude of associations in independent populations), and biological plausibility (agreement with barrier and immune mechanisms, including Th2 polarisation and the role of epithelial signalling). Effect sizes reported in different studies as odds ratio (OR), relative risk (RR), or hazard ratio (HR) were interpreted as relative risk measures, with emphasis on the width of confidence intervals and the stability of estimates after adjustment for confounders; potential non-comparability of OR and RR in the context of high event prevalence was considered as a methodological limitation affecting the strength of conclusions.

Special attention was paid to reconciling genetic and environmental evidence within gene-environment interaction models. When sources reported effect modification analyses (stratification by genotype, family history, sex, or age subgroups), these results were compared across studies and interpreted, with priority given to prospective designs and to studies that corrected for multiple comparisons. For synthesis of the role of the microbiome and epigenetics, an interpretative logic of mediation was applied, where early-life exposures were considered potential drivers of barrier and microbial community changes, and these changes were viewed as links that enhance sensitisation and the development of T2 endotypes; in the absence of formal mediation analysis in primary studies, such links were treated as theoretically grounded rather than as proven causal mechanisms.

The credibility of conclusions was assessed with consideration of the risk of systematic bias typical for observational and genetic studies. For environmental exposures, the likelihood of measurement error, residual confounding, and reverse causality was taken into account, while for genetic studies, population stratification, multiple testing, and transferability of results across populations of different ancestry were considered. Generalisations were developed with

priority given to meta-analyses and large prospective cohorts, and, in the presence of conflicting findings, possible sources of heterogeneity were analysed, including differences in diagnostic criteria, age at assessment, exposure windows, and covariate sets in models.

RESULTS AND DISCUSSION

Population Burden and Epidemiological Trends

The synthesis of global estimates based on GBD 2021 for the child population aged 0-14 years indicates that two fundamental allergic phenotypes, which often underlie paediatric allergic reactions or determine their severity and comorbidity (asthma and atopic dermatitis), remain dominant in absolute terms. In 2021, the global prevalence of childhood asthma amounted to 95.7 million cases, with an age-standardised prevalence of 4,758 per 100,000, whereas atopic dermatitis was estimated at 72.4 million cases, with an age-standardised prevalence of 3,600 per 100,000. A reduction in asthma-associated Disability-Adjusted Life Years (DALYs) in children was also recorded, from 6.9 million (1990) to 4.6 million (2021), which is interpreted as a sign of improved management and control and/or shifts in severity, yet it does not diminish the relevance of the issue due to the continued high number of affected individuals in the population [13].

Within the same GBD estimates, pronounced demographic patterns relevant to the interpretation of allergic reaction risk were described. For asthma, the peak prevalence occurred at ages 5-9 years, with higher rates in boys, whereas for atopic dermatitis, the peak was observed at ages 0-5 years and was more frequent in girls [13]. These age and sex profiles are consistent with the concept of “early windows of vulnerability”, where barrier disruption and early exposures shape sensitisation trajectories, and the respiratory phenotype more often manifests in preschool or early school age.

Nationally representative data from the USA (NHIS, National Health Interview Survey, 2007-2018) indicated that allergic conditions remain widespread even at the level of clinically or self-reported diagnoses. The proportion of children aged 0-17 years with any allergy was 26.4%, including respiratory allergy at 14.7%, skin allergy at 12.7%, and food allergy at 6.4%. Concurrently, divergent trends were observed: the prevalence of “current asthma” declined from 9.1% (2007) to 7.5% (2018); respiratory allergy decreased from 17.2% (2010) to 14.0% (2018); while food allergy increased from 3.9% (2007) to 6.5% (2018). Taken

Table 1: Key Quantitative Indicators of Population Burden and Trends (Selected Sources)

Population	Indicator	Year/period	Value
children aged 0-14 years, global	Asthma prevalence (cases)	2021	95.7 million
	Age-standardised asthma prevalence		4758 per 100,000
	Atopic dermatitis prevalence (cases)		72.4 million
	Age-standardised atopic dermatitis prevalence		3600 per 100,000
	Asthma DALYs	1990 → 2021	6.9 million → 4.6 million
USA, children aged 0-17 years	Any allergy (prevalence)	2007-2018 (pooled)	26.4%
	Respiratory allergy (prevalence)		14.7%
	Skin allergy (prevalence)		12.7%
	Food allergy (prevalence)		6.4%
	Current asthma (trend)	2007 → 2018	9.1% → 7.5%
	Respiratory allergy (trend)		17.2% → 14.0%
	Food allergy (trend)		3.9% → 6.5%
Japan	Food allergy (standardised prevalence)	2010 → 2019	0.325% → 0.797%
Japan, children aged under 6 years	Food allergy (standardised prevalence)		3.377% → 5.726%

Note: AD – atopic dermatitis.
Source: compiled by authors based on Zheng *et al.* [13], Pate *et al.* [14], Liu *et al.* [15].

together, these data support the interpretation of a dynamic restructuring of the allergic pathology profile in childhood, in which some traditional respiratory manifestations decline, while food allergy increases and may play a larger role in severe reactions and comorbidity [14].

Data from Japan, derived from administrative reports from 2010 to 2019, align with the trend of increasing food allergy and add age-specific precision for early childhood. It was shown that the overall standardised prevalence of food allergy increased from 0.325% (2010) to 0.797% (2019), and among preschool children (<6 years) from 3.377% to 5.726%, corresponding to approximately a 1.7-fold increase over the decade. It was further noted that the "high-risk" subgroup (based on adrenaline prescription) accounted for 8.5% of the cohort in 2019, yet the incidence of anaphylaxis or severe allergic reactions within this group was very high, at 227,690 per 100,000 patient-years, highlighting clinical significance despite relatively low overall prevalence [15]. Table **1** summarises the quantitative estimates obtained from three methodologically distinct sources.

The convergence of epidemiological trends across these approaches (the persistence of a high burden of asthma and atopic dermatitis, alongside rising food allergy in certain countries) provides the most reliable basis for concluding that paediatric allergic reactions remain a pressing issue and that preventive strategies focused on early childhood are required.

Genetic Determinants and Epithelial Barrier Dysfunction

Integration of genetic evidence demonstrates that epithelial barrier dysfunction represents a central pathogenic mechanism in paediatric allergic diseases. The epidermal barrier acts as a key interface through which hereditary predisposition to atopic dermatitis may be expressed, while immune dysregulation, particularly Th2 polarisation and epithelial "alarmin" signalling, contributes to chronic inflammation, sensitisation, and polysensitisation. Among the identified genetic associations, FLG mutations remain the most consistently replicated findings. Further progress in this field is expected through the integration of GWAS, polygenic risk models, and epigenetic approaches linking the exposome to allergic phenotypes [16].

A clinically significant link between barrier defects and severe systemic reactions to food allergens was demonstrated in detail in a paediatric cohort of children with atopic dermatitis (n=238), in which genotyping of the most common FLG loss-of-function variants and a multifactorial analysis of associations with concomitant allergic manifestations were performed. The proportion of FLG variant carriers (R501X or 2282del4) was 12.2% (30/238). According to multivariable logistic regression, the presence of FLG loss-of-function variants was associated with a marked increase in the likelihood of severe manifestations of food allergy (OR ≈ 8.9; 95% CI (confidence interval) 3.1-28.3), with severity defined as anaphylaxis and/or the need for adrenaline auto-injector prescription. A separate analysis showed that among clinically confirmed food-allergic patients (n=95), carriage of the FLG variant was associated with a significantly increased risk of reactions to highly allergenic nuts. In the multivariable model, the risk of an allergic reaction to peanut was approximately three times higher (OR 3.2; 95% CI 1.1-9.3), and to hazelnut approximately four times higher (OR 4.1; 95% CI 1.5-13.0) [17]. These findings conceptually support the model "barrier defect → transcutaneous sensitisation → increased risk of severe and/or clinically significant reactions", since reduced skin barrier function allows food proteins and household environmental components to contact antigen-presenting cells of the epidermis more easily, with subsequent development of IgE-mediated responses.

The barrier-genetic line identified in the results (the role of filaggrin and the epidermal barrier) logically aligns with the notion that part of the exposomal and pharmacological influences may exert their effects precisely by exacerbating or persisting epithelial inflammation. In this context, it is important to broaden the "horizon of consequences" of atopic dermatitis beyond the classical "atopic triad". The meta-analysis by Wang *et al.* [18] identified an association of AD with an increased risk of autoimmune diseases, including evidence from both adult and paediatric cohorts. Although direct transfer of autoimmune risk to the paediatric population requires stratification by age and follow-up duration, the presence of the signal itself strengthens the interpretation of AD as a systemic immune-inflammatory condition, in which barrier defects and chronic Th2 activation may combine with broader immune-regulatory disturbances. This provides additional arguments for early inflammation control and for monitoring comorbidities in high-risk groups. Overall, these findings indicate that epithelial tissues function not only as targets of allergic inflammation but

also as active mediators that translate genetic susceptibility and environmental exposures into heterogeneous paediatric allergic phenotypes.

In paediatric asthma, the comparative analysis of gene-ecology interaction approaches demonstrated that "one-dimensional" interaction models (one-variant-one-exposure models) do not adequately reflect the biological complexity of the phenotype and its triggers. As an illustrative example of progress in G×E (gene-environment interaction) approaches, the large 17q12-q21 locus was considered, where interactions with respiratory viral infections and airway epithelial processes helped refine the mechanistic pathways underlying early asthma onset. The need for an "expanded" concept of interactions was substantiated, involving epigenetics, transcriptomics, metabolomics, and proteomics as layers that may explain why identical exposures lead to different severity and different endotypes in children with different genetic backgrounds [19].

Furthermore, in the context of 17q12-q21, attention was drawn to the fact that variants in this region remain the most replicated genetic signal in paediatric asthma, and one promising mechanistic candidate is linked to the regulation of GSDMB expression and/or functional properties in airway epithelium [20]. This aligns with the observation that for both key phenotypes – atopic dermatitis and asthma – the epithelium (skin or airways) acts as the "first line" of interaction with the exposome, and genetically determined features of barrier and innate immune response may determine the severity of clinical reactions and the spectrum of triggers in childhood.

For respiratory phenotypes, findings regarding early symptom onset and subsequent progression align with the notion that preschool wheeze is a heterogeneous phenomenon, and genetic signals are better "read" when phenotyping accounts for trajectories rather than a single assessment. The review by Wolters *et al.* [21] emphasised that genetic approaches are particularly promising for differentiating preschool wheeze subtypes and predicting transition to asthma, but this potential is limited by phenotypic heterogeneity and the influence of environmental triggers, primarily viral infections and airway epithelial responses. This explains why, in the synthesised results, the epithelium (both in skin for atopic dermatitis and in airways for asthma) acted not only as a target of influences, but also as an integrator of signals that translates exposures into inflammation and hyperreactivity.

Exposomal and Environmental Risk Modifiers

The synthesis of evidence on air pollution demonstrates that fine particulate matter ($PM_{2.5}$) is one of the most consistently replicated environmental factors associated with the development of the asthmatic phenotype in childhood and, therefore, with an increased likelihood of respiratory allergic reactions and exacerbations. A global meta-analysis and health impact assessment showed that a 10 μg/m³ increase in long-term $PM_{2.5}$ exposure is associated with a 21.4% (95% CI 11.4-32.3%) increase in the risk of asthma in children. The same study estimated that, in 2019, almost one-third of global asthma cases could be associated with $PM_{2.5}$, shifting the issue from individual risk to population-level prevention and air quality policy [22].

The exposomal evidence received additional support in light of findings that not only the mass of $PM_{2.5}$, but also the chemical composition of fine particles, is clinically relevant. The systematic review and meta-analysis by Li *et al.* [23] indicated that the most influential $PM_{2.5}$ components for childhood asthma risk were black and organic carbon and ammonium, whereas black carbon and sulphates were the key factors for reduced lung function. These findings suggest that different $PM_{2.5}$ components may contribute unequally to epithelial injury and inflammatory responses associated with childhood asthma. Consequently, the preventive potential of air quality policies becomes more targeted: the greatest expected effect may be associated with reducing those fractions that reflect transport and industrial emissions.

An important clarification regarding "windows of vulnerability" is that $PM_{2.5}$ exposure may already be significant in utero, before clinical phenotype manifestation. A meta-analysis demonstrated that prenatal $PM_{2.5}$ exposure was associated with a statistically significant increase in the risk of childhood asthma and wheezing: OR 1.06 (95% CI 1.02-1.11) per 5 μg/m³ during pregnancy. The effect was more pronounced for events in early childhood (up to 3 years): OR 1.15 (95% CI 1.00-1.31) per 5 μg/m³, which aligns with the concept of early programming of immune and epithelial responses and emphasises the relevance of preventive measures during pregnancy [24] (Table **2**).

Perinatal determinants demonstrate comparable stability in their associations, with the most systematically studied factor being delivery by

Table 2: Key Quantitative Estimates for Exposome and Perinatal Risk Modifiers

Factor/exposure	Window of exposure	Outcome	Quantitative estimate
$PM_{2.5}$ (long-term exposure)	Long-term exposure	Childhood asthma	+21.4% risk per 10 μg/m³ (95% CI 11.4-32.3%); in 2019, almost one third of global asthma cases were associated with $PM_{2.5}$
	Pregnancy	Asthma/wheezing	OR 1.06 per 5 μg/m³ (95% CI 1.02-1.11); up to age 3 years OR 1.15 (95% CI 1.00-1.31)
Caesarean section	Perinatal period	Asthma	OR 1.20 (95% CI 1.16-1.25)
		Food allergy	
		Atopic dermatitis/eczema	
Exposome in the context of AD	Early life, critical "dose/timing"	AD as a highly prevalent phenotype	AD affects up to 20% of children; the type, dose, and timing of exposure, and their interaction with barrier function, immunity, and the microbiome are important

Source: compiled by authors based on Li *et al.* [23], Yan *et al.* [24], Liu *et al.* [25], Liu *et al.* [26].

caesarean section. A large systematic review and meta-analysis showed an increased risk of several allergic outcomes in offspring compared with vaginal delivery: asthma OR 1.20 (95% CI 1.16-1.25), allergic rhinitis/conjunctivitis OR 1.15 (95% CI 1.09-1.22), atopic dermatitis/eczema OR 1.08 (95% CI 1.04-1.13), food allergy OR 1.35 (95% CI 1.18-1.54), allergic sensitisation OR 1.19 (95% CI 1.10-1.28). In the AAAAI clinical summary, these estimates were interpreted as +35% for food allergy and +20% for asthma, with very large sample sizes reported (for example, for asthma n≈9.69 million), which emphasises the epidemiological robustness of the trend while also indicating a potential role for modifiers (child age ≤6 years, region latitude, caesarean section rate in the population) that may contribute to heterogeneity [25].

Perinatal influences may contribute to allergic risk through altered microbial colonisation and early immune development. Supporting the role of delivery mode as a marker and potential risk modifier, a meta-analysis by Liu *et al.* [26] established that caesarean section is associated with an increased risk of allergic rhinitis in children; the signal for elective caesarean section was particularly notable (higher risk compared with the overall estimate), and the association was strengthened in the presence of a family history of allergy. These findings support the hypothesis that altered early microbial colonisation after caesarean delivery may influence the development of immune tolerance and susceptibility to allergic diseases. A causal conclusion should remain cautious, however, because of potential confounding (indications for surgery, perinatal complications, differences in breastfeeding, sociodemographic factors). Collectively, these observations support the concept that early-life environmental exposures may modify allergic risk through interactions between microbial colonisation, epithelial maturation, and immune development.

In atopic dermatitis, the exposome includes interacting environmental, behavioural, and biological factors that may influence barrier dysfunction and allergic inflammation. It was emphasised that the exposome encompasses population-level factors (climate change, migration, urbanisation), community-level factors (air pollution, water hardness, sensitisation), and individual factors (diet, microbiome, psychosocial stress, treatment exposure), and the critical element is the interaction of these influences with genetically determined barrier defects and immune shifts [27]. The thesis that atopic dermatitis affects up to 20% of children, presented as an epidemiological basis, further strengthens the argument for the population-level significance of even moderate changes in the exposome. Nutritional exposures may also contribute to this interaction network, particularly by affecting epithelial barrier integrity, immune maturation, and microbiome composition during early childhood.

Findings regarding the role of "new" or previously underestimated chemical exposures (pharmaceutical and cosmetic ingredients, plasticisers, and related substances) conceptually reinforce the exposome component of the model and help explain the potential rise in allergic burden in urban populations. A review by Xie *et al.* [28] synthesised epidemiological and basic evidence on PPCPs (pharmaceutical and personal care products) and atopic dermatitis, highlighting that a range of compounds (including phthalates, parabens, and other common components) show positive

correlations with the risk of, or exacerbations of, atopic dermatitis, and that pregnancy and infancy may be the most sensitive periods. This body of evidence is particularly relevant for interpreting increasing trends in food allergy and dermatological phenotypes in urban populations. The growing "chemical burden" of domestic environments may contribute to epithelial barrier disruption and altered microbial homeostasis, both of which are associated with allergic sensitisation.

Perinatal and Microbiome-Related Influences

A separate block of synthesised results confirms that the microbiome should be considered an "internal" component of the exposome, capable of mediating the connection between early exposures (perinatal conditions, medication exposures, home environment) and the development of allergic phenotypes in childhood. In allergic diseases, microbiome alterations appear to involve structural and taxonomic shifts rather than simple reductions in microbial diversity alone. These patterns reinforce the role of the microbiome as a mediator linking environmental exposures with allergic phenotypes in childhood.

A pilot study comparing gut and skin microbiomes in infants with food allergy and/or atopic dermatitis demonstrated differences in bacterial community structure despite the absence of consistent α-diversity changes. Associations between specific taxa and allergic phenotypes additionally emphasised the potential contribution of the gut-skin axis to early allergic inflammation [29, 30]. No statistically significant differences in α-diversity were found between the allergic and control groups for either faecal or skin samples, but differences in β-diversity and associations between bacterial community structure and allergic phenotypes were observed, with these effects being more pronounced in faecal samples. It was also shown that certain clinical conditions correlated with specific taxa, and correlations between skin and gut were described for particular genera, supporting the role of the gut-skin axis in the development of barrier dysfunction and allergic inflammation during early life.

A similar logic is supported by data in which dysbiotic signals were detected prior to the clinical manifestation of food-allergic disorders, reinforcing the plausibility of a causal contribution from early microbiome "settings". Longitudinal observations in infants with food-allergic disorders demonstrated alterations in the microbiome preceding clinical manifestations, supporting the hypothesis that early dysbiotic shifts may contribute to allergic sensitisation [31 - 33]. Collectively, these observations suggest that microbiome-related alterations may precede clinical manifestation and interact with epithelial and immune mechanisms during early sensitisation. Dietary factors, including breastfeeding patterns, diversity of complementary feeding, and probiotic exposure, may further influence these microbiome-related trajectories during early immune development [34, 35].

Systematic synthesis of evidence on antibiotic exposure confirmed its role as a persistent risk factor for atopic dermatitis and, indirectly, for increased allergic reactivity in children through potential dysbiotic mechanisms. The meta-analysis included 39 studies with a total population of 7,487,925 children; the overall estimate indicated that exposure to antibiotics during pregnancy or early childhood was associated with an increased risk of atopic dermatitis in children (OR 1.22; 95% CI 1.17-1.28), with very high between-study heterogeneity ($I^2 \approx 98\%$) [36]. Notably, subgroup analysis indicated a greater risk with childhood antibiotic exposure than with prenatal exposure, and suggested that the effect magnitude depended on diagnostic criteria, racial and ethnic characteristics of populations, antibiotic frequency and type, and the age at which the outcome was assessed. Although multiple studies report associations between antibiotic exposure and allergic diseases, the magnitude of these effects remains modest and strongly influenced by methodological heterogeneity, publication bias, and residual confounding [36-38]. Consequently, in practical terms, emphasis should be placed not on prohibiting antibiotics, but on rationalising prescriptions and minimising unjustified exposures, especially during early critical windows.

Interactions between microbiome-related exposures and epithelial barrier dysfunction are particularly evident in the field of food allergy, where relevant routes of antigen exposure include not only oral pathways, but also "non-oral" pathways within the living environment [39 - 41]. A review framed within the concept of the external exposome synthesises evidence supporting the dual-allergen hypothesis, according to which early oral exposure to food proteins promotes tolerance, whereas non-oral exposures through the skin or respiratory tract are associated with sensitisation. The authors emphasised that household dust is not only a carrier of food proteins, such as peanut, but also contains adjuvant components, including microbial products, fungal components, and protease allergens, which can modify the immune

response. An experimental observation presented in the work showed that co-exposure to indoor dust and peanut protein, unlike each exposure alone, induced specific IgE and anaphylaxis upon challenge, and it was also emphasised that epicutaneous sensitisation is amplified in the presence of barrier defects [42, 43]. These findings support the interaction between microbiome-related exposures, epithelial barrier dysfunction, and allergic sensitisation in early childhood. Since the results highlighted the microbiome's role as a mediator, analysing the potential of microbiome-oriented interventions is a logical next step. Evidence synthesis in the meta-analysis by Wang and Xu [44] indicated that the use of prebiotics, probiotics, and synbiotics in paediatric populations was associated with reduced incidence of atopic dermatitis (RR 0.74; 95% CI 0.70-0.79) and decreased severity according to SCORAD (WMD − 3.75; 95% CI − 5.08 to 2.42), with more convincing effects observed for multi-strain probiotics, Lactobacillus, and synbiotics. The available evidence suggests moderate but heterogeneous benefits of microbiome-oriented interventions in paediatric allergic diseases [45 - 47]. Therefore, microbiome interventions may be considered an adjunct to prevention and treatment, rather than a substitute for fundamental strategies such as barrier control, avoidance of relevant triggers, and mitigation of environmental risks.

Taken together, these findings support an integrative model in which paediatric allergic reactions develop through interactions between dysbiotic shifts, environmental exposures, medication-related influences, and individual barrier vulnerability. The microbiome appears to function as an important mediator linking the exposome with allergic sensitisation and immune dysregulation during early life. However, the predominance of observational evidence and substantial heterogeneity across studies requires cautious interpretation of causal relationships.

Nutritional and Behavioural Prevention Strategies

Evidence synthesis suggests that modified risk determinants, including behavioural, nutritional, and controlled environmental exposures, can influence trajectories of paediatric allergic phenotypes within critical windows, from pregnancy to preschool age. Specifically, prenatal exposure to pollutants may be associated with early immune shifts, which Pedersen *et al.* [48] interpreted as a mechanistic bridge between maternal exposure and subsequent allergic reactivity in the child. In the broader context of climate change, the potential for increased exposure to pollutants and aeroallergens is emphasised, which may increase the frequency of symptoms and exacerbations in paediatric respiratory phenotypes and necessitates population-level prevention frameworks, as noted by Domingo *et al.* [49]. For the preschool group, an association between exposure to $PM_{2.5}$/PM_{10}, ozone, and nitrogen dioxide with asthma and allergy was further supported, reinforcing the argument of Bobrowska-Korzeniowska *et al.* [50] in favour of early environmental interventions.

Preventive management may be improved by the possibility of stratifying susceptibility. Moll *et al.* [51] demonstrated that polygenic risk models can reflect the heterogeneity of asthma and, accordingly, can justify varying intensities of prevention and exposure control in subgroups with higher genetic burden. At the infection-genetics level, variants at 17q21 have been shown to modify the association between early respiratory infections and subsequent asthma, which conceptually supports the idea of personalised control of virus-induced exacerbations proposed by Smit *et al.* [52]. The mechanistic basis for the roles of rhinoviruses and epithelial innate responses in asthma aligns with the perspectives of Yang *et al.* [53], who argued that some behavioural interventions should aim to reduce the infectious burden and ensure early control of inflammation.

Nutritional interventions are considered the most scalable risk modifiers [54 - 56]. A dose-response meta-analysis showed an association between maternal supplementation with long-chain omega-3 polyunsaturated fatty acids and reduced risk of asthma and wheeze in offspring, supporting the use of such a strategy in high-risk groups, while recognising protocol heterogeneity, as investigated by Jia *et al.* [57]. To prevent atopic dermatitis, a systematic review and meta-analysis by Wang *et al.* [58] found that probiotics can reduce the likelihood of disease development, though effects depend on strains and study design. Separately, machine learning in a preschool cohort demonstrated that breastfeeding, antibiotic exposure, and indoor environmental characteristics jointly contributed to the risk of atopic dermatitis, aligning with the hygiene hypothesis logic of Wang *et al.* [59] and emphasising the value of comprehensive rather than singular preventive recommendations. These observations reinforce a more integrated interpretation of early allergic risk, in which environmental and nutritional exposures interact rather than operate independently. Air pollutants, indoor chemical exposures, and medication-related microbiome

Table 3: Key Exposomic, Microbiome-Related, Genetic, and Nutritional Modifiers of Paediatric Allergic Diseases

Factor/exposure	Main associated outcome	Proposed mechanism	Key evidence
$PM_{2.5}$	Asthma	Epithelial inflammation	Meta-analysis
Caesarean section	Asthma, food allergy	Altered colonisation	Systematic review
Antibiotic exposure	Atopic dermatitis	Dysbiosis	Meta-analysis
FLG variants	Atopic dermatitis, food allergy	Barrier dysfunction	Cohort/genetic studies
Breastfeeding	Reduced allergic risk	Immune tolerance	Cohort studies
Dietary diversity	Improved tolerance	Microbiome maturation	Observational evidence
Probiotics	Reduced atopic dermatitis risk	Microbiome modulation	Meta-analysis

Source: compiled by authors.

disturbances may modify epithelial and immune responses, while breastfeeding, dietary diversity, and microbiome-supportive nutritional strategies may partially counterbalance environmentally induced epithelial and immune disturbances during early allergic sensitisation. In the toxicological dimension, a further manageable direction is the reduction of prenatal metal exposure, which has been associated with the risk of atopic dermatitis in children, supporting the need for sanitary control and individual minimisation measures, as described by Tsai *et al.* [60].

The epigenetic level is considered by Han *et al.* [61] as a key integrator of environment and nutrition to phenotype, since DNA methylation and other epigenetic mechanisms can reflect exposures and potentially explain long-term effects of early interventions. To transition from associations to reproducible, practical risk models, Yang *et al.* [62] argued for exposome-based longitudinal designs with systematic collection of exposure data and biomarkers, which may help develop more targeted preventive strategies.

Summary of the findings indicates that paediatric allergic reactions develop as a multi-layered system of interactions, in which the population burden and divergent phenotype trends determine the scale of the problem, barrier-genetic determinants (notably epithelial barrier disruption and replicated genetic signals) define individual susceptibility and potential severity, exposomal and perinatal influences modify risk within critical early developmental windows, and the microbiome and epigenetic mechanisms act as mediating intermediaries between the environment and phenotype. The convergence of evidence from different source types suggests that the most promising preventive approach is an integrated strategy combining environmental exposure reduction, rational perinatal and pharmacological interventions, nutritional and behavioural support, and risk stratification based on genetic and biomarker characteristics. Particular importance should be given to nutritional determinants during early life, including breastfeeding practices, dietary diversity, micronutrient status, and microbiome-supportive interventions, as potentially modifiable factors in allergic risk. The findings also indicate that environmental and nutritional exposures in early life should be considered as interacting rather than isolated determinants of allergic risk, particularly through their combined influence on epithelial barrier integrity, microbiome development, and immune maturation.

From a practical perspective, the findings favour early-life preventive approaches that integrate nutritional guidance, reduced environmental exposure, rational antibiotic use, and measures promoting healthy microbiome development. Public health approaches may include promoting breastfeeding, balanced complementary feeding with adequate dietary diversity, optimising maternal and childhood vitamin D status, reducing indoor and outdoor pollutant exposure, and providing evidence-based counselling on early allergen introduction for high-risk children.

To improve the clarity and practical usability of the synthesised evidence, the key genetic, exposomic, microbiome-related, and nutritional modifiers associated with paediatric allergic diseases are summarised in Table **3**.

CONCLUSIONS

The synthesis of epidemiological, genetic, environmental, microbiome-related, and nutritional

evidence confirms that paediatric allergic diseases remain a major child health concern associated with substantial clinical and socioeconomic burden. Current evidence supports an integrative model in which allergic phenotypes develop through interactions among genetic susceptibility, epithelial barrier dysfunction, environmental exposures, alterations in the microbiome, and early-life nutritional factors.

Among the most consistently replicated risk modifiers are FLG-related barrier defects, long-term exposure to $PM_{2.5}$, caesarean delivery, and early antibiotic exposure, while breastfeeding, dietary diversity, microbiome-supportive interventions, and appropriate allergen introduction may contribute to the development of immune tolerance and the reduction of allergic risk in susceptible children. These findings emphasise the importance of preventive strategies focused on early developmental periods, combining environmental risk reduction with nutritional and behavioural support.

The review has a narrative and interpretative nature and is based on studies with varying designs, phenotyping approaches, and exposure assessment methods, which may contribute to methodological heterogeneity and limit causal interpretation. Future longitudinal and multi-omic studies integrating exposome profiling, microbiome analysis, and nutritional determinants are needed to improve personalised prevention and early risk stratification in paediatric allergic diseases.

CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

ETHICS STATEMENT AND CONSENT TO PARTICIPATE

This study was based exclusively on previously published literature and did not involve human participants or the collection of primary data. Therefore, ethical approval and informed consent were not required.

AUTHORS' CONTRIBUTION

MZL was responsible for conceptualising the research, designing the study, conducting the primary analysis of the literature and data, and drafting the manuscript. JL contributed to the development of the research methodology, the literature review, the interpretation of the findings, and the critical revision of the manuscript for important intellectual content.

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