Invited Review Article

Insights from the COCOA birth cohort: The origins of childhood allergic diseases and future perspectives

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ABSTRACT

The ongoing COhort for Childhood Origin of Asthma and allergic diseases (COCOA) study is a prospective birth cohort investigating the origin and natural courses of childhood allergic diseases, including atopic dermatitis, food allergy, allergic rhinitis and asthma, with long-term prognosis. Initiated under the premise that allergic diseases result from a complex interplay of immune development alterations, environmental exposures, and host susceptibility, the COCOA study explores these dynamic interactions during prenatal and postnatal periods, framed within the hygiene and microbial hypotheses alongside the developmental origins of health and disease (DOHaD) hypothesis. The scope of the COCOA study extends to genetic predispositions, indoor and outdoor environmental variables affecting mothers and their offsprings such as outdoor and indoor air pollution, psychological factors, diets, and the microbiomes of skin, gut, and airway. We have embarked on in-depth investigations of diverse risk factors and the pathophysiological underpinnings of allergic diseases. By employing multi-omics approaches—proteomics, transcriptomics, and metabolomics—we gain deeper insights into the distinct pathophysiological processes across various endotypes of childhood allergic diseases, incorporating the exposome using extensive resources within the COCOA study. Integration with large-scale datasets, such as national health insurance records, enhances robustness and mitigates potential limitations inherent to birth cohort studies. As part of global networks focused on childhood allergic diseases, the COCOA study fosters collaborative research across multiple cohorts. The findings from the COCOA study are instru-

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diseases; DOHaD, developmental origins of health and disease; ECHO, Exposome and Child Health with Omics;
ETS, environmental tobacco smoke;
GST, glutathione-S-transferase;
LTL, leukocyte telomere length;
NACMAAS, National Asthma Campaign Manchester Asthma and Allergy Study;
PSKC, Panel Study on Korean Children;
PM, particulate matter; PM2.5, particulate matter with a diameter of less than 2.5 μg;
PM10, particulate matter with a diameter of less than 10 μg; TEWL, transepidermal water loss; TRAP, traffic-related air pollution

mental in informing precision medicine strategies for childhood allergic diseases, underpinning the establishment of disease trajectories.

Introduction

The escalating prevalence of allergic diseases has frequently been attributed to environmental shifts, particularly urbanization and industrialization. Recent data from Western nations, however, indicate that this trend may be reaching a plateau or even experiencing a decline.[1] Nevertheless, many Asia—Pacific countries, including Korea, continue to undergo such environmental transitions. The precise factors underlying the elevated and rising incidence of allergic diseases in these regions remain elusive. Comprehensive exploration of the causal elements and mechanisms necessitates prospective, long-term birth and child cohort studies. A significant number of such population-based studies have been initiated over recent decades, designed to enhance our understanding of the natural course of allergic diseases and to identify specific determinants and factors influencing their persistence or transient nature across an individual's lifetime.

The COhort for Childhood Origin of Asthma and allergic diseases (COCOA) study, initiated in November 2007, is an ongoing birth cohort concentrating on elucidating the etiological aspects of allergic diseases. It evaluates the dynamic interaction between genetic predispositions and environmental factors,[2] thereby affirming the developmental origins of health and disease (DOHaD) hypothesis, postulating that prenatal development significantly influences future health outcomes. Over its 15-year duration, the COCOA study has been steadfastly committed to evaluating the consequential effects of assorted environmental factors on the manifestation and progression of allergic diseases (Fig. 1). These factors include indoor environment exposures, such as house dust mites, environmental tobacco smoke (ETS), and air pollutants (Table 1). Additionally, outdoor air pollutants, maternal and child psychosocial stress, dietary patterns, microbiome, environmental chemicals, and heavy metals have also been examined. In the critical stages of life, by scrutinizing the interaction between these factors and the child's genetic/epigenetic background, the COCOA study seeks to augment our knowledge of allergic disease pathogenesis. Simultaneously, we are actively elucidating the underlying mechanisms of these interactions using multi-omics techniques. Our aim is to identify biomarkers associated with new biological significance that can predict the onset and prognosis of allergic diseases in early life. This methodology offers the potential for the discovery of meaningful indicators that could facilitate early diagnosis and intervention in allergic diseases.

Many risk alleles and loci associated with allergic diseases have been identified via genome-wide association studies (GWAS),[3] including those in recent studies focusing on Korean children.[4,5] However, the GWAS approach is generally limited to detecting common variants with small effect sizes and employs inherently circumscribed statistical methods, regardless of gene—gene and gene—environment interactions. Our research has identified numerous interactions between candidate genetic variants and environmental factors relevant to allergic diseases, occurring in prenatal[6—8] and early life[9,10] periods. By leveraging the multi-layered omics data amassed from the COCOA cohort, we plan to elucidate gene-environment interactions implicated in allergic diseases.

This review outlines the strategic approach and key findings of the COCOA study, underscoring their potential applicability in the clinical context. Additionally, we propose future research trajectories to further deepen our understanding of allergic diseases.

Outdoor environmental factors in allergic diseases

An abundance of international studies underscores the adverse health impacts caused by ambient air pollution. Evidence from a comprehensive, nationwide, prospective epidemiological study in Korean children indicates a correlation between residential proximity to high-traffic roadways and an increased risk of developing airway hyperresponsiveness (AHR).[11] In the COCOA study, traffic-related air pollution (TRAP), a principal source of outdoor air pollution, was evaluated via its marker, particulate matter (PM). The study suggests that the impact of PM on allergic diseases could vary based on the exposure dose and critical timing of exposure in susceptible individuals.[12]

Previous investigations into the association between air pollution and atopic dermatitis (AD) have yielded inconsistent results, largely dependent on the specific types of air pollution, the exposure dose, and the period of exposure.[13] Early-life environmental exposure can influence structural and immune development, potentially inciting allergic diseases.[14] Our results from the COCOA study elucidate that prenatal exposure to PM with a diameter of less than 2.5 μg ($PM_{2.5}$) was associated with the development of AD in early childhood. This association was modulated by a range of factors, including gender, maternal anxiety, and vitamin D levels in cord blood.[15,16] Furthermore, exposure to outdoor $PM_{2.5}$ and PM with a diameter of less than 10 μg (PM_{10}) during pregnancy, particularly in the first trimester, heightened the risk of early life AD through skin barrier dysfunction, as indicated by transepidermal water loss (TEWL).[17]

Aligned with embryological differentiation, the structural evolution of airways during the saccular (27—36 weeks of gestation) and alveolar stages (from 36 weeks of gestation to 2 years postpartum) potentially represent vulnerable windows for the development of asthma in response to environmental factors.[18] A Taiwanese birth cohort study indicated that both prenatal and postnatal exposure to $PM_{2.5}$ heightened the risk of preschool asthma development.[19] Furthermore, both prenatal and postnatal PM_{10} exposure were
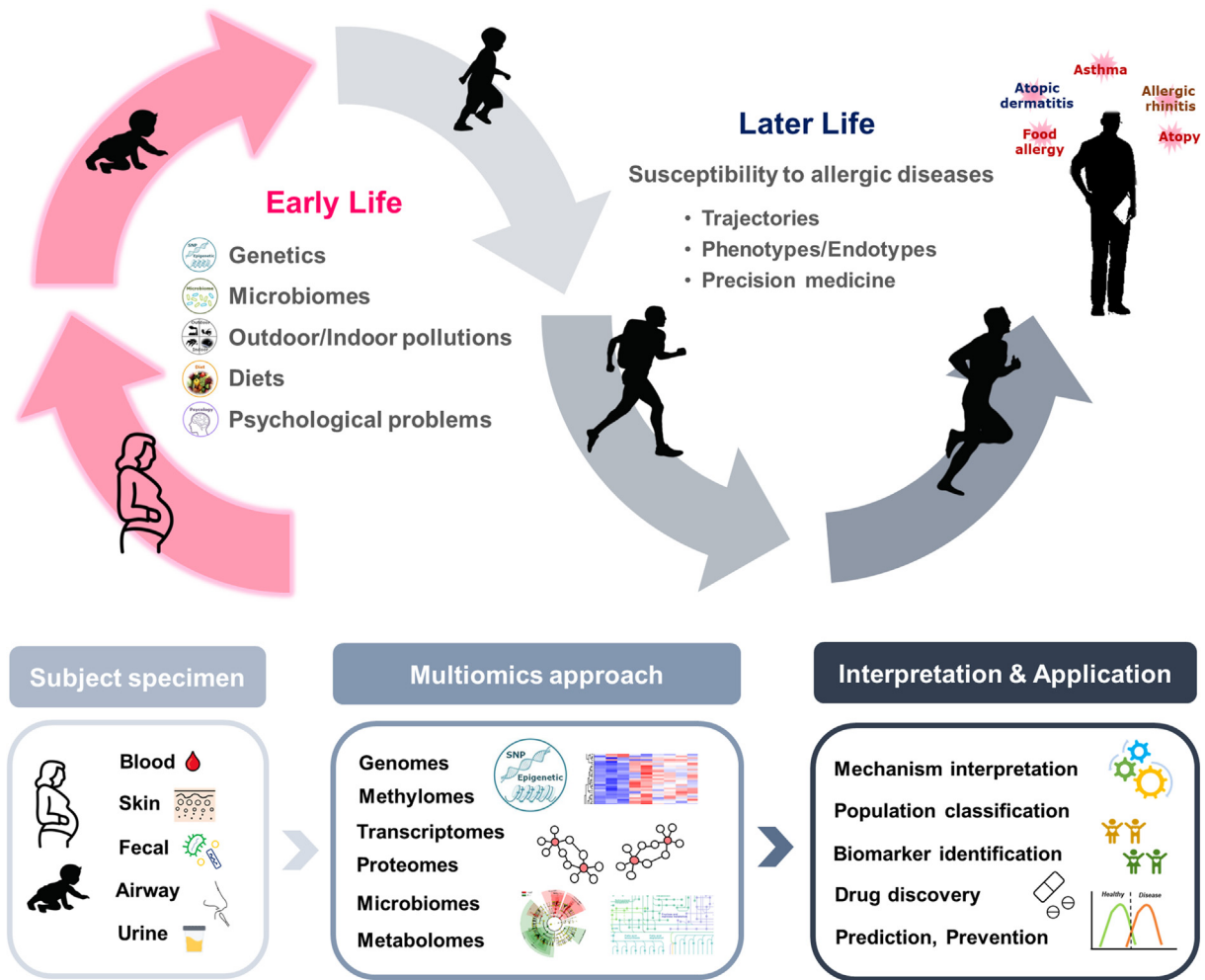
Fig. 1. An overview of the COCOA study.

linked with AHR in a Korean schoolchildren cohort study, with the risk of a newly diagnosed asthma in children aged 7 with AHR significantly amplified by PM_{10} exposure during the second trimester.[20] An investigation within the Asthma Coalition on Community, Environment, and Social Stress (ACCESS) project associated childhood asthma with $PM_{2.5}$ exposure at 16–25 weeks of gestation.[21] In the context of the COCOA study, PM_{10} exposure during 26–28 weeks of gestation was tied to childhood asthma, with the association modulated by gender and *NRF2* genotype.[6]

Air pollution's contribution to the pathogenesis of allergic diseases is potentially mediated through several mechanisms including oxidative stress, airway remodeling, and inflammatory and immunological responses (Fig. 2).[6,22] Genetic and epigenetic alterations elicited by air pollution have also been postulated as potential pathways contributing to allergic disease development.[23] In the COCOA study, high levels of prenatal $PM_{2.5}$ exposure during the first trimester, in conjunction with low vitamin D levels in cord blood, were implicated in the development of early-onset persistent AD, mediated by alterations in placental deoxyribonucleic acid (DNA) methylation.[16] Moreover, fetal growth retardation was influenced by alterations in placental *ARRDC3* methylation due to $PM_{2.5}$ exposure during mid-pregnancy,[24] a condition that may also serve as a risk factor for allergic diseases.[25] These results underline the importance of considering a multitude of interacting factors concurrently with air pollution exposure. It is also paramount to extend future research to explore the influence of these factors on

lung development, as well as their linkage to adult respiratory health within ongoing birth cohort studies.

Indoor environment factors in allergic diseases

Children reportedly spend nearly 80% of their time in indoor environments[26] where concentrations of specific pollutants often exceed outdoor levels by two to five-fold.[27] Energy-efficient building designs and the incorporation of synthetic building materials, in conjunction with the use of pesticides and household cleaners, may further augment the concentrations of certain indoor pollutants.[28] The 2019 Coronavirus Disease (COVID-19) pandemic has drastically modified lifestyles, with an observed shift toward increased indoor living and reliance on food delivery services employing single-use packaging, a potential source of chemical agent release. Consequently, rising apprehension over the health impacts of indoor environments, particularly in relation to air quality, has triggered a need for further investigations into the correlation between indoor environmental factors and the rise of childhood allergic diseases.[29,30]

Indoor environmental factors encompass aeroallergens (such as house dust mites, animal dander, mold, cockroach and rodents), chemical pollutants (including nitrogen dioxide, carbon monoxide, particulate matter, ozone, and volatile organic compounds), bacteria, and ETS. The COCOA study has documented the detrimental impact of lead and chromium in cord blood on the persistence and

Table 1
Data collection instruments and timeline of the COCOA study.

Age		26 w	36 w	0	1 M	6 M	1 Y	2 Y	3 Y	4 Y	5 Y	6 Y	7 Y	8 Y	9 Y	10 Y	11 Y	12 Y	13 Y	14 Y	15 Y	16 Y	17 Y	18 Y	19 Y
Enrollment		O																							
Physical examination				O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O
Questionnaires	Health/Environmental questionnaire	O			O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O			O
	Dietary	O			O	O	O						O		O				O			O			O
	Psychological development/	O			O	O	O	O	O	O			O		O			O	O	O					
	Maternal stress	CESD, PSS					CESD, CBCL		CESD	CESD, CBCL		CESD, CBCL		CNT					CNT	YSR	CNT					
Air pollution	Indoor dust/pollutants collection		O		O								O												
	Outdoor air pollution		O				O		O				O		O			O			O				O
Clinical test	Skin prick tests		O						O				O		O			O			O				O
	Total/Specific IgE		O				O		O				O		O			O			O				O
	Transepidermal water loss				O	O			O				O		O		O	O			O				O
	Impulse oscillometry									O															
	FeNO										O														
	Bronchial challenge test												O												
	Pulmonary function test														O		O			O			O		
	Bone age									O						O									
	Body composition analysis												O		O				O			O			
	Sex hormones/Lipid profile													O											
Sample collection	Blood (serum, plasma, DNA/RNA stabilization tube)		O	Cord blood			O		O				O		O				O			O			O
	Urine		O						O				O		O	O			O			O			O
	Stool				O	O	O	O	O				O		O	O			O			O			O
	Skin swab				O	O	O	O					O		O	O			O			O			O
	Oropharyngeal swab				O	O	O	O					O		O										
	Nasopharyngeal swab																	O	O			O			O
	Tape strips				O	O	O	O					O												

CBCL, Child Behavior Checklist; CESD, Center for Epidemiologic Studies Depression; CNT, Complexity navigation test; DNA, Deoxyribonucleic acid; FeNO, Fractional exhaled nitric oxide; IgE, Immunoglobulin E; M, month; PSS, Perceived Stress Scale; RNA, Ribonucleic acid; Y, Years; YSR, Youth Self-Report.
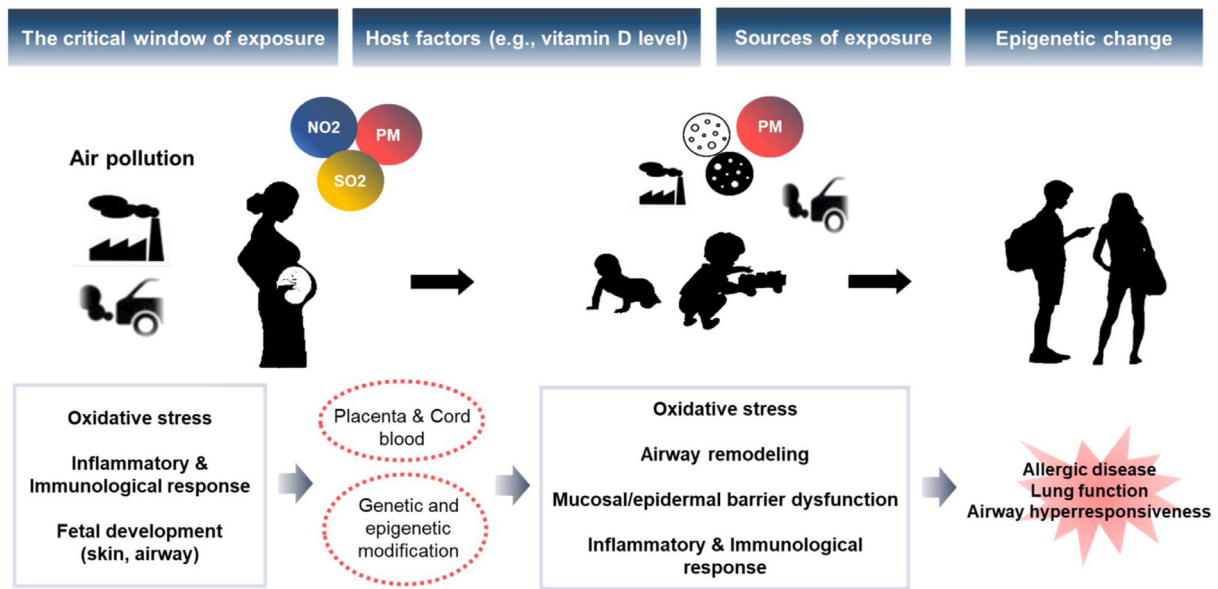
Fig. 2. The impact of particulate matter exposure during the critical periods on the development of allergic diseases.
NO$_2$, nitrogen dioxide; PM, particulate matter; SO$_2$, sulfur dioxide.

severity of AD.[31] Moreover, dog ownership, during any phase from pregnancy up to the child's first year, was found to reduce the risk of sensitization to aeroallergens while concomitantly increasing the risk of non-atopic AHR and non-atopic asthma at seven years of age.[32]

Despite a limited number of studies elucidating the role of early life mold exposure on the risk of childhood asthma and rhinitis,[33,34] investigations concerning AD have been notably scarce. Within the framework of the COCOA study, it was determined that prenatal mold exposure heightened the risk of AD during the first two years of life, particularly in infants exhibiting elevated TEWL levels. This suggests that exposure to mold during critical prenatal periods may precipitate AD development in concert with skin barrier dysfunction.[35] Infants with AD who were exposed to mold during pregnancy exhibited significantly increased total serum IgE levels, indicating the potential influence of mold on AD via IgE-mediated allergic inflammation.[36] An association was also discerned between the environmental mycobiome at 36 weeks of pregnancy and AD.[36]

A plethora of factors, including weather conditions, outdoor pollutants, socioeconomic status, lifestyle modifications, and activities (e.g., smoking, heating, and cooking), significantly impact indoor air quality.[27,37,38] The health consequences of indoor air pollutants can markedly vary, contingent on their sources, levels, compositions, and the races or ethnicities of the exposed population.[39,40] As such, the exploration of the role of indoor air pollutants in childhood allergic diseases across different geographical and cultural contexts is essential. To fully understand this relationship, researchers should supersede single-exposure methodologies and adopt an exposomal approach within birth cohorts. Awaiting the findings of the exposome research conducted as part of the COCOA cohort study, specifically the Exposome and Child Health with Omics-COCOA (ECHO-COCOA) study, we anticipate garnering invaluable insights regarding the role of the indoor environment in the etiology of childhood allergic diseases. Birth cohort studies with long-term follow-ups afford the opportunity to identify causal associations between early life or lifelong exposure to diverse indoor environments and childhood allergic diseases, in addition to elucidating their natural courses.

Nutritional factors in allergic diseases

Dietary habits indisputably represent a crucial environmental exposure. Historically, research exploring the correlation between diet and allergic diseases in children predominantly concentrated on examining individual foods, either as single nutrients or allergens.[41–43] The principal objective of these studies was to ascertain whether specific foods or nutrients either incite or impede the onset of allergic disease (Fig. 1). With the COCOA study, we scrutinized both maternal diet during pregnancy and the child's diet at varying ages to evaluate the hypothesis that interplay with factors, both dietary and non-dietary, could influence the development of allergic diseases (Table 1). We uncovered a correlation between prenatal antioxidant intake and the occurrence of respiratory diseases during infancy[44] and observed that dietary patterns during pregnancy can influence the onset of allergic diseases in infants.[7] Our findings suggest that prenatal antioxidant intake may exert a protective influence against respiratory tract infections in early childhood, contingent on genetic mutations linked to innate immunity, such as CD14.[44] Though the correlation is not exclusive to prenatal antioxidant intake, we additionally identified a relationship between antioxidant consumption and AR in school-age children.[45,46] These findings infer that antioxidant intake might potentially mitigate respiratory tract infections and assuage symptoms of allergic diseases in children.[45]

Traditional investigations into the effects of dietary factors on health tend to focus on individual nutrients. But, their overall impact on health warrants assessment via an analysis of dietary patterns. Maternal dietary patterns, such as the Mediterranean diet, can confer a protective effect against the development of allergic diseases in children.[46,47] However, most dietary pattern studies are cross-sectional studies, and longitudinal studies on the effects of maternal diet patterns during pregnancy on allergic diseases in offspring are few and show inconsistent results.[48–51] These few longitudinal studies have presented inconsistent results, possibly attributable to the lack of consideration of individuals' genetic backgrounds.[48–51] Specific genetic polymorphisms, particularly in CD14, which regulate the pro-inflammatory response, and in glutathione-S-transferase (GST), which is instrumental in
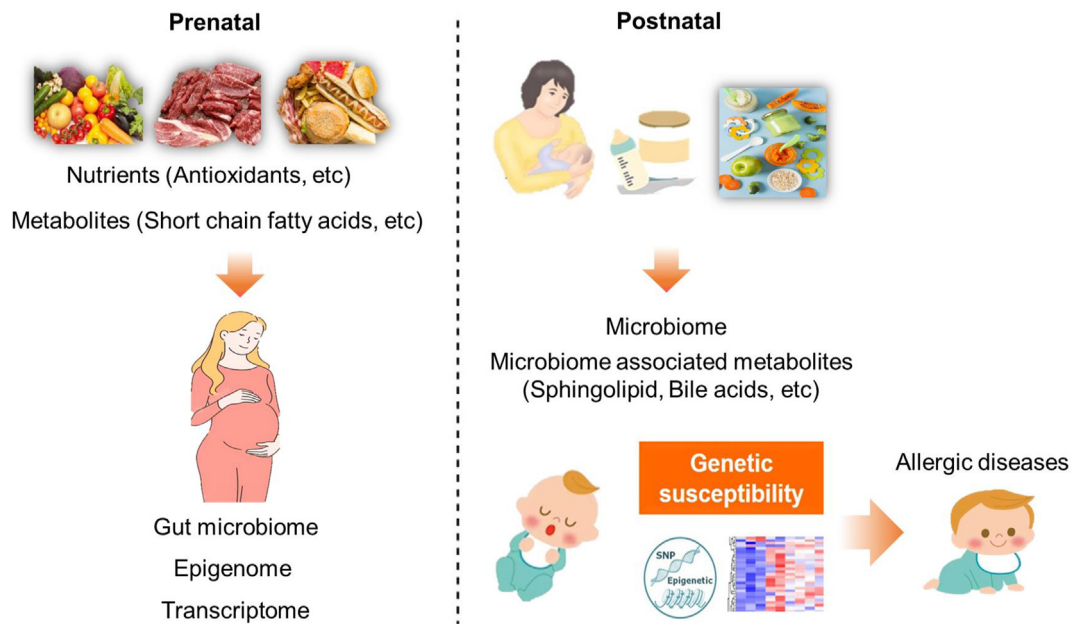
Fig. 3. Effects of maternal diet during pregnancy and child's diet at various ages on allergic disease development and potential underlying mechanisms.

detoxification pathways, could potentially heighten susceptibility to food allergy in infants whose mothers follow a confectionery-rich diet.[7] Conversely, a vegetable-rich dietary pattern during pregnancy has been associated with a protective effect against the development of allergic diseases, particularly in individuals with low genetic susceptibility.[46] Therefore, future assessments of diet's influence on allergic diseases should consider the interplay between diet and genetic factors.

The COCOA study has primarily focused on investigating the impact of maternal diet during pregnancy on offspring's health. Going forward, the study aims to elucidate how children's diet at specific ages can influence the development and natural course of allergic diseases. In addition, the study has explored dietary intake, including feeding type, as a critical determinant of gut microbiome composition, which in turn plays a substantial role in the development of allergic diseases.[52] The gut microbiome can modulate the development of the human immune system through direct interactions or by generating metabolites that partake in immune processes.[53] Thus, diet-induced shifts in microbiota partly explain the mechanisms through which diet can modulate the risk of allergic diseases and inflammation (Fig. 3).

Microbiome in allergic diseases

The "hygiene hypothesis" and "microbial hypothesis" have been posited to delineate the origin of allergic diseases.[54] These theories align on the premise that dysbiosis within barrier organs, such as the gut, skin, and airway, stemming from varied environmental exposures, can modulate immune system development, particularly in susceptible individuals, and thereby fundamentally influence the development of allergic diseases. Within the framework of the COCOA study (Fig. 1), we sequentially collected stool, skin swab, and airway samples at specific intervals in early life to discern the pathophysiology of allergic diseases (Table 1), characterized by unique endotypes and phenotypes, and to devise personalized therapeutic strategies.

The COCOA study endeavored to characterize the functional role of distinct gut microbiota at the strain level. We also sought to enhance our understanding of AD pathogenesis by integrating transcriptome, metagenome, and metabolite data (Fig. 4).[55] Feeding patterns during infancy were shown to differently influence gut colonization and immune development in healthy infants and those with AD.[52] For instance, in the breastfed cohort, robust colonization and healthy immune development were noted among healthy infants, whereas those with AD exhibited suboptimal gut microbiome colonization and a reduction in functional genes associated with immune development.[52] Conversely, in the mixed-fed cohort, healthy infants demonstrated colonization with mucin-degrading bacteria, which serve as a nutritional source for other gut microbiota. Infants with AD, however, showed suboptimal colonization and reduced numbers of mucin-degrading bacteria, resulting in a diminished presence of some functional genes.[52] In a separate animal study, we discovered that oral administration of *Ruminococcus gnavus*, a type of mucin-degrading gut bacteria, ameliorated TEWL levels, skin inflammation, and clinical scores in AD. It also resulted in the down-regulation of T helper 2-related cytokine mRNA and upregulation of interleukin-10 and Foxp3 in the skin, along with increased fecal butyrate levels.[56] These findings propose that alterations in gut microbiome and functional genes can modulate host immune cell functions, thus playing a role in the development of AD.[52]

Additionally, alterations in gut microbiota—spanning composition, function, and metabolite profiles—have been linked to the natural courses of AD in infants.[57] In particular, persistent AD up to two years of age in children has been associated with decreased levels of *Clostridium* and *Akkermansia*, along with elevated *Streptococcus* concentrations within gut microbiota. These children also exhibit diminished gut microbial functional genes associated with oxidative phosphorylation.[57] In contrast, children with transient AD have been characterized by lower *Streptococcus* and increased *Akkermansia* levels, alongside decreased butyrate and valerate concentrations in fecal samples.[57]

The interactions between host genetic factors and gut microbiota may influence the evolution of allergic diseases through modulating the immune system. However, studies addressing these interactions remain scarce. Within the context of the COCOA study, an increase in *Streptococcus* within the gut microbiota of infants with AD and those with GA + AA of *IL-17* (rs2275913) variant was observed at six
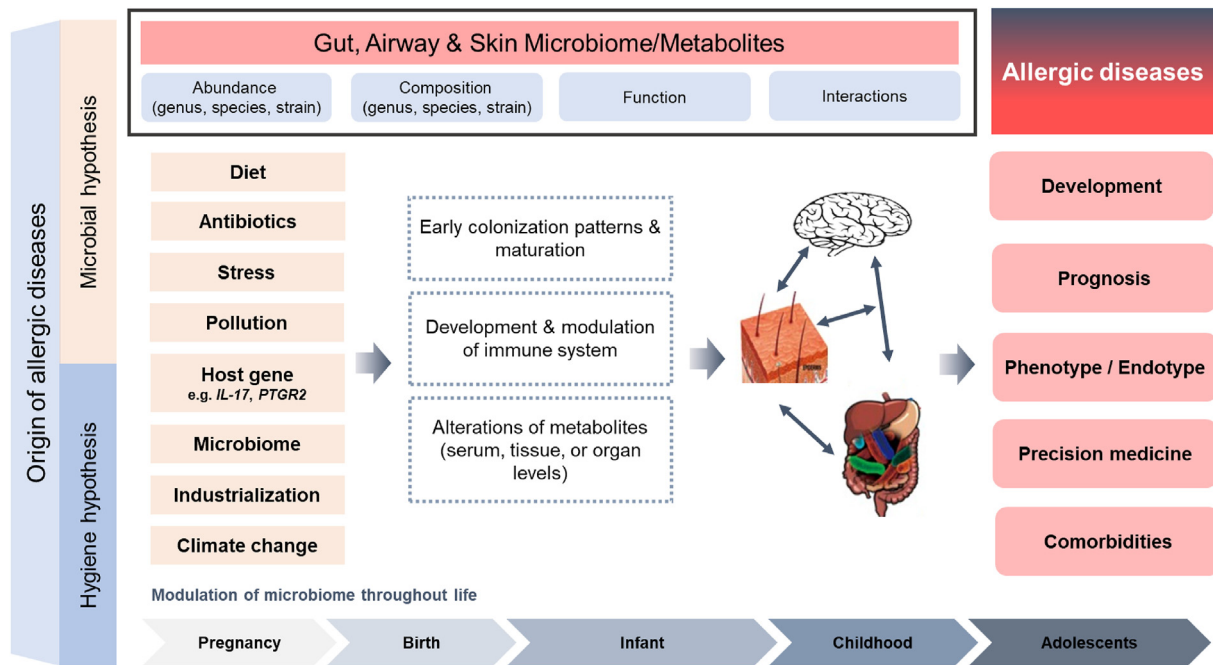
Fig. 4. The potential mechanisms underlying the association of the microbiome with the development of allergic diseases.
IL, interleukin; PTGR2, Prostaglandin Reductase 2.

months of age.[9] Additionally, decreased levels of short chain fatty acids, such as butyrate and valerate, demonstrated in the fecal samples of AD infants with the GA + AA of *IL-17* (rs2275913) variant.[9] Lower colonization of *Clostridium* was linked to increased functional genes related to oxidative phosphorylation in healthy infants carrying the GG variant of *IL-17* (rs2275913).[9] Transcriptome analysis of fecal samples indicated elevated levels of lactate dehydrogenase A-like 6B, which is involved in the conversion of pyruvate to lactate, in infants with AD.[9] This increase in *Streptococcus* within the gut microbiome might contribute to the development of AD through modulating the immune system in early life.[9] One study investigating the relationship between host genetics and gut microbiota in AD revealed that the interplay between dysregulated *PTGR2* expression and the abundance of *Bifidobacterium* might affect the risk of AD with differences in severity.[58] In another study, we explored the interactions between the host and the gut microbiome, focusing on the dynamics of gut microbiome in infants with AD.[44] While the gut microbiome matures with age in both healthy and AD infants, in the latter, the gut microbiome was observed to mature in a direction detrimental to health, characterized by abnormal short chain fatty acid production and increased IgE production.[59] These findings suggest that early life disruption in gut microbiome development and associated metabolite disturbances may contribute to AD onset during early childhood, primarily through unbalanced microbiome–host interactions.[59] Furthermore, gut linoleic acid metabolites were found to be associated with milder AD during infancy, potentially due to the inhibition of anti-inflammatory effects of gut linoleic acid.[60]

Looking forward, research focusing on the microbiome in various allergic diseases, as well as sensitization, will persist in an effort to elucidate the pathophysiology of allergic diseases and establish therapeutic targets. An ongoing integrated study is examining the gut-skin-airway microbiome in relation to the immune development stage in children and exploring the connection between gut-skin-airway microbiome, related metabolites, and allergic diseases using a multi-omics approach, aiming to uncover the origin of allergic diseases in children.

Maternal psychosocial stress and the child's neurodevelopment in allergic diseases

The potential influence of maternal distress, including anxiety and depression, as a prenatal factor affecting the development of non-communicable diseases in children is increasingly recognized.[61,62] In line with this, the COCOA study has been systematically gathering data on maternal prenatal and perinatal stress levels, life satisfaction, as well as children's developmental, behavioral, and psychological stress information, with an aim to elucidate their associations with the offspring's allergic disease incidence (Fig. 1, Table 1).

Recent birth cohort investigations have lent credibility to the association between maternal psychological distress and the onset of AD, asthma, and allergic rhinitis in progeny.[63,64] Several mechanisms, including oxidative stress and hypothalamic-pituitary-adrenal axis imbalances, have been postulated as potential pathways in these contexts.[65,66] Nevertheless, these mechanisms have already been implicated as fundamental pathways in the pathogenesis of cardiovascular diseases and mental illnesses. The delineation of specific mechanisms driving the development of allergic diseases, distinct from those related to metabolic syndrome or neuropsychiatric diseases, remains elusive (Fig. 5).

In relation to this, our research has unearthed several findings corroborating this association. Foremost, maternal psychological distress escalates the risk of AD development in offspring. As per the epidemiological data extracted from COCOA participants, prenatal maternal distress amplified the risk of AD in children, with hazard ratios for depression and anxiety being 1.31 (95% CI, 1.02–1.69) and 1.41 (95% CI, 1.06–1.89), respectively.[67] Furthermore, we have suggested that prenatal distress could lower the ratio of glutathione-to-glutathione disulfide in the placenta and decrease the levels of placental 11β-hydroxysteroid dehydrogenase type 2, thereby providing potential mechanistic insights.[67] While assessing leukocyte telomere length (LTL) as a potential biomarker for this risk, we discerned no association concerning the development of asthma[68] and AD.[69] However, cord-blood LTL was
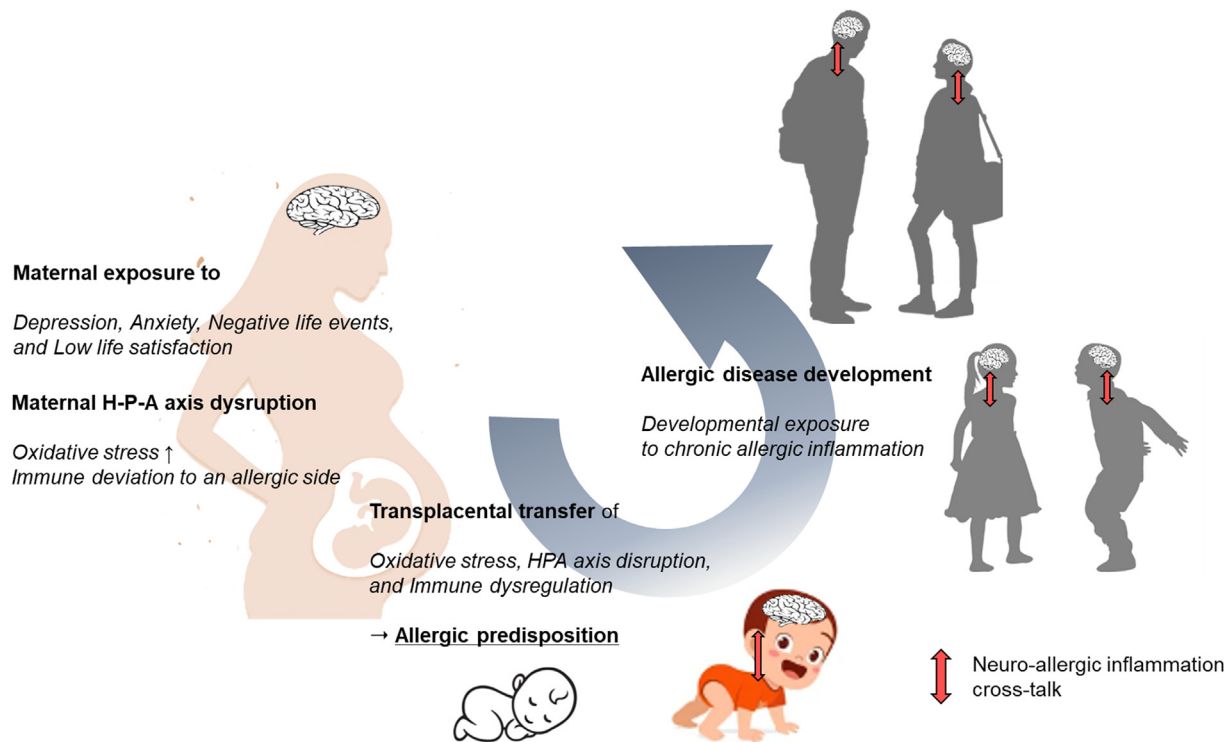
Fig. 5. The mechanisms underlying the associations of maternal psychological distress and children's behavioral problems with the development of allergic diseases. HPA axis, Hytothalamic pituitary adrenal axis.

comparatively shorter in prenatally stressed infants than in their unstressed counterparts, a difference that remained significant at the one-year milestone.[69]

Another area of scientific exploration concerns the potential correlation between children's developmental/behavioral problems and allergic diseases. Despite growing interest in this intriguing relationship, the underlying mechanisms have yet to be thoroughly elucidated.[70] To date, the National Asthma Campaign Manchester Asthma and Allergy Study (NACMAAS) birth cohort is the only research group to suggest that children's mental health issues may precede the onset of childhood wheezing.[71] However, this study fell short in defining the mechanistic underpinnings that might substantiate this causal relationship. Previous investigations have postulated various mechanisms, including chronic inflammation, inflammatory cytokines, and other immune factors that influence neurotransmitter systems and brain function, leading to allergic inflammation.[70] Given this background, the COCOA study is further investigating the association between early life behavioral issues in children and the subsequent emergence of childhood allergic diseases, in addition to potential underlying mechanisms (Fig. 5).

A consistent correlation has been found between prenatal maternal psychological distress and subsequent allergic diseases in children, a finding supported by multiple birth cohort studies worldwide.[64,70] Hence, our research endeavors extend beyond merely delineating epidemiologic risk factors; we also aim to identify potential biomarkers that may elucidate the underlying mechanisms of this association and offer targets for early intervention (Fig. 1). We currently postulate that epigenetic modifications in specific genes and shifts in the microbiome may play

pivotal roles in this relationship. However, definitive evidence supporting this hypothesis remains to be uncovered.

Future perspective

In the initial decade of the COCOA study, our focus was primarily directed toward establishing a comprehensive database system, thereby constructing a robust cohort. Concurrently, we devoted attention to investigating risk factors influencing the development of allergic diseases, with an emphasis on perinatal and early life periods, identified as critical windows of susceptibility. Within this cohort, pediatric allergists rigorously assess the health status of each participant during every visit through detailed physical examinations. This methodology is crucial, offering potential insights into the future trajectory of allergic diseases. As we continue to lengthen the follow-up period for our subjects, we persist in our exploration of the natural courses of allergic diseases from infancy through adolescence. Furthermore, we plan to conduct studies evaluating the health implications of exposure to various detrimental environmental factors, such as metals, polycyclic aromatic hydrocarbons, persistent organic pollutants, and volatile organic compounds. These investigations, stratified by lifelong exposome exposure and distinct endotypes identified via multi-omics and machine learning, are ongoing. These studies will leverage serial multi-omics and exposome analyses, incorporating gut microbiome data.

The integration of COCOA study with data from the nationwide health insurance system enables us to mitigate potential drawbacks and amplify the advantages of the cohort study. Our multifaceted approach is poised to unveil novel biomarkers capable of predicting both development of allergic diseases and responses to treatment,

elucidating the intricate interplay of numerous factors that contribute to the progression of allergic diseases. This comprehensive approach has the potential to provide innovative perspectives on preventive measures and precision medicine for allergic diseases in children.

Additionally, we have joined international collaborative efforts in childhood allergic disease research, such as the Asian Allergy Birth Cohort Network (A2BC Network), encompassing ten birth cohorts from eight Asian countries. This collaboration enhances the robustness of our research findings and facilitates multinational research initiatives. The shared data and knowledge aid in discerning the health effects of rapidly changing lifestyles and environmental diversity on allergic disease prevalence in Asian children.

Conclusions

To elucidate the origins of childhood allergic diseases, the COCOA study has conducted and will continue to pursue an exhaustive examination of a myriad of factors—particularly those encountered in the perinatal and postnatal periods—in conjunction with genetic susceptibility and their complex interactions. Through the integration of sequential multi-omics data with exposome information, the COCOA study provides in-depth insights into the unique pathophysiological pathways characteristic of diverse endotypes of allergic diseases, thereby paving the way for precision medicine. The longitudinal monitoring of the COCOA study will continue, providing pivotal information regarding the development and trajectories of allergic diseases from prenatal periods through adolescence, and ideally, extending into adulthood.

Acknowledgments

Conflict of interest

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