



In-utero exposures and the evolving epidemiology of paediatric allergy

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Purpose of review

Emerging evidence suggests that the rising prevalence of early-onset 'noncommunicable' diseases, such as paediatric atopy, is related to modern environmental changes, the effects of which appear to commence *in utero* or even preconception. Here, we review how recent publications have contributed further to our understanding of the influence of in-utero exposures on the predisposition to immune dysregulation, with a particular focus on the evolving epidemiology of paediatric allergy.

Recent findings

New evidence suggests that inter-individual variations in immune function development are principally driven by nonheritable factors, for example periconceptional environment. One of the most significant influences is maternal nutrition during pregnancy. New studies further support a healthy balanced maternal diet that contains immunomodulatory nutrients, prebiotics and probiotics, which benefit multiple aspects of fetal development, including immune development. In addition, declining maternal biodiversity, maternal stress and exposures to environmental pollutants further interact to have adverse influences on the developing immune system.

Summary

The in-utero period appears to be a critical time point. Further investigations of gene–environmental interaction mechanisms are essential prior to further recommendations of early-life preventive strategies to reduce the growing global burden of allergic disease, as well as other 'noncommunicable' diseases.

Keywords

allergic disease, developmental origins of health and disease, early immune development, gene–environmental interactions, noncommunicable diseases

INTRODUCTION

The impact of modern diet, lifestyle and environmental factors on human health can be clearly seen in dramatic changes in the epidemiology of disease over the last century. Chronic inflammatory 'non-communicable' diseases (NCDs) have superseded infectious diseases as the most common causes of mortality and morbidity in most regions of the world. Even in childhood, when infectious conditions remain common, the 'antibiotic age' has heralded a decline in morbidity and mortality from bacterial infection. An associated decline in microbial diversity in early life is thought to be one of the major culprits in the increasing early onset of NCDs including allergic diseases. Although the significance may have been overlooked until recently, it is increasingly evident that allergy is a central element in the changing modern disease profile, sharing many risk factors with other NCDs. As one of the most common and earliest onset NCDs, paediatric allergy is arguably the earliest

evidence of the environmental impact on the developing immune system. It is also a useful early barometer in evaluating strategies to improve immune health as part of life-course strategies to prevent NCDs.

Interestingly, the profile of childhood allergic disease appears to be still evolving. Although the prevalence of respiratory allergies, such as allergic rhinitis and asthma, has reached a plateau or even declined [1] in many high-income regions, the rate

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Curr Opin Allergy Clin Immunol 2015, 15:402–408

DOI:10.1097/ACI.0000000000000209

KEY POINTS

- The in-utero period appears to be a critical time point for environmental exposures to influence genomic inheritance of the developing immune system.
- A better understanding of nutritional-programming of immune health, nutritional-epigenetics and the biological processes sensitive to nutritional exposures in early life may lead to dietary strategies that provide more tolerogenic conditions during early immune programming.
- The role of antenatal microbial exposures must not be underestimated and requires further detailed investigation.

of early-onset diseases such as food allergy and eczema are continuing to rise, in what we have described as 'a second wave' of the allergy epidemic [2]. The reasons for this are unclear, but suggest evolving environmental influences. Greater understanding of the mechanisms of potential gene–environmental interactions provides new perspectives on how the maternal environment can induce systemic, mitotically heritable, stable epigenetic alterations in gene expression, which have the capacity to alter disease predisposition. As well as the external environment, endogenous maternal factors including psychological and metabolic stress may also influence the developing fetus. Rising rates of maternal allergic disease and maternal obesity are also likely to influence the predisposition to inflammation in the offspring. A better understanding of the underlying mechanisms of these gene–environment interactions is an essential element of early-life preventive strategies to reduce the burden of NCDs in society. Here, we review how recent publications have contributed further to our understanding of the influence of in-utero exposures on the predisposition to immune dysregulation, with a particular focus on the evolving epidemiology of paediatric allergy.

MECHANISMS OF EARLY ENVIRONMENTAL IMPACT ON ALLERGIC GENETIC PREDISPOSITION

Although genetic predisposition plays a major role in allergic disease risk, inter-individual variations in immune function are principally driven by nonheritable factors [3]. A recent 'systems-level' study of 204 different parameters in monozygotic and dizygotic twins (including cytokines, cell subsets and cellular responses) showed that nonheritable influences dominantly influence immune function.

Variability increased with age reflecting the cumulative influences of the environment. In other studies, monozygotic twin pairs exhibit substantial discordance in DNA methylation at metastable epialleles, suggesting that stochastic establishment of epigenotype at some loci is exquisitely sensitive to maternal periconceptional environment [4].

It is also possible, but not yet known, that mucosal and skin integrity is specifically influenced by antenatal events. The mucosal immune system is already active before birth [5] when mucosal contact with environment begins. The fetus breathes, swallows and can detect flavours and tastes in amniotic fluid. It is not yet clear what effects cytokines, allergens and other environmental factors known to pass into amniotic fluid [6] may have on the developing mucosal surfaces and uncornified fetal skin, which may be more permissive to these elements. Any factors that induce low-grade inflammation *in utero* could potentially influence mucosal integrity, which appears to be a critical factor in the rising predisposition to food allergy and eczema. For example, inflammatory processes such as chorioamnionitis are known to induce fetal gut inflammation [7] with mucosal injury and loss of the tight junctional proteins. It is possible that the associated abnormalities of epithelial development and mucosal integrity could predispose to that very early mucosal immune dysregulation associated with the appearance of clinical food allergy and eczema in the early postnatal months [8]. It also remains to be seen whether these host mucosal disturbances could interfere with normal gut colonization, which may depend on the local host environment as well the prevailing microbial diversity.

Thus, in considering the impact of the role of the early environment in the allergy epidemic, it is important to consider how environmental changes influence the predisposition to systemic immune dysregulation and Th2 responses, the vulnerability of particular organs and tissues to disease, and how early maternal exposures may lead to either tissue-specific changes in gene expression or systemic epigenomic changes that modify phenotype and disease predisposition in offspring.

MATERNAL NUTRITION HAS A FUNDAMENTAL INFLUENCE ON IMMUNE DEVELOPMENT

Maternal diet is fundamental for all aspects of fetal development providing the nutrients required for normal structural and functional development of all organ systems. Dietary patterns and specific nutrients can have profound effects on both tissue-specific patterns of gene expression, and systemic

metastable epialleles [4]. A better understanding of nutritional-programming of immune health, nutritional-epigenetics and the biological processes sensitive to nutritional exposures in early life may lead to dietary strategies that provide more tolerogenic conditions during early immune programming and reduce the burden of many inflammatory diseases, not just allergy.

General dietary patterns

Modern high-fat, low-fibre diets may have unfavourable effects on the gut microbiome contributing to low-grade systemic inflammation, metabolic dysregulation and potentially chronic diseases [9], with growing speculation that this may also impact fetal development in pregnancy (as discussed further below). Modern food processing is also more likely to generate inflammatory 'danger signals' through nonenzymatic glycation and oxidation of proteins and lipids. The resulting advanced glycation end products ('AGEs') initiate and propagate inflammation through innate immune pathways and are implicated in many inflammatory processes. These 'danger signals' are known to contribute to the development of atopic disease [10,11], although their role *in utero* and early infancy is not yet clear.

Immunomodulatory nutrients

Specific nutrients that have been investigated for their immunomodulatory effects and potential for allergy protection include n-3 polyunsaturated fatty acids (PUFA), antioxidants, vitamin D (in the form of supplements when nondietary sources are inadequate) and dietary fibre (including prebiotic oligosaccharides).

Adding to the well established anti-inflammatory effects of n-3 PUFA [12] and the allergy protective effects of fish oil supplementation during pregnancy on offspring [13], new studies [14[■],15] show that this may be mediated, at least in part, through anti-inflammatory effects on the placenta. The cellular mechanisms through which n-3 PUFAs exert their effects include their ability to modify the production and actions of a range of distinct classes of lipid-derived mediators, thereby mitigating the harmful effects of inflammation and oxidative stress. Recent studies identified a new class of n-3 PUFA-derived mediators known as 'specialized pro-resolving lipid mediators' (SPMs), which include the resolvins, protectins and maresins [16]. For the first time, we recently reported that fish oil supplementation during pregnancy significantly increased SPM precursors, namely 18-hydroxyeicosapentaenoic

acid (18-HEPE) and 17-hydroxy docosahexaenoic acid (17-HDHA), in the placenta, as well as placental docosahexaenoic acid (DHA) levels [14[■]]. This is consistent with our previous reports of reduced oxidative stress [17] and cytokines [including interleukin (IL)-13] [18] in cord blood following maternal fish oil supplementation. We now have new evidence that previously observed effects of n-3 PUFA on neonatal T-cell function may be mediated by epigenetic changes in histone acetylation of key genes, including IL-13 and protein kinase C (PKC), in patterns that are associated with allergy protection (submitted for publication). Others have also shown that maternal PUFA supplementation may epigenetically modulate global DNA methylation and the Th1/Th2 homeostasis in offspring, particularly with maternal smoking, which is a source of considerable oxidative stress to the fetus [19]. Although we have also observed some effects of in-utero n-3 PUFAs exposure on the CD4(+) T-cell methylation profile, the effect sizes were small and insignificant with little evidence that n-3 PUFA supplementation in pregnancy substantially alters the developing fetal methylome [20].

Maternal antioxidants (such as zinc, selenium, vitamins A and C) protect the fetus from oxidative stress. One recent population study [21[■]] has shown a weak protective relationship between maternal vitamin A and E intakes and the risk of childhood respiratory allergy, while another did not [22[■]]. The latter instead found lower activity of glutathione peroxidase enzyme 3 in cord blood of children who developed atopic dermatitis during the first year of life [22[■]], suggesting that an imbalance in the antioxidant defense system at birth may predispose to an allergic phenotype. Others have investigated the role of antioxidant supplementation to reduce the adverse effects of oxidative stressors such as maternal smoking [23], with some protective effects on the placenta [24[■]]. Although not all studies have shown that vitamin supplementation at conception protects against oxidative stress [23], one recent randomized controlled trial showed that supplemental vitamin C (500 mg/day) in pregnant smokers improved newborn lung function results and decreased wheezing in infancy compared with the placebo group [25[■]], suggesting that prenatal oxidative balance is important for lung development.

On the basis of population studies linking various allergic outcomes with rising rates of vitamin D insufficiency and mechanistic studies that provide biological pathways of influence, including immune development, lung development and skin barrier function (recently reviewed) [26], vitamin D has also been implicated as an environmental and dietary factor of interest. Although observational

studies continue to report associations between vitamin D status and allergic outcomes [27], evidence from well designed and adequately powered clinical trials of vitamin D supplementation in pregnancy and early life are needed [28].

Other specific nutrients have been associated with increased allergic risk, namely folate supplementation. However, the evidence is neither consistent nor compelling (as reviewed recently by Miles and Calder [29]), and there is no justification to change current recommendations for women to consume 400 µg of folic acid per day from preconception to 12 weeks gestation to reduce the risk of neural tube defects.

Recent interest has emerged in the role of dietary fibre as an important immunomodulatory factor, through anti-inflammatory effects of short-chain fatty acid metabolites. Colonic microflora ferment dietary fibre to produce short-chain fatty acids (SCFA) (acetate, butyrate and propionate), which have been shown in a series of landmark studies [30–32] to mediate the protective immunomodulatory effects of the commensal bacteria. A high-fibre diet significantly increases SCFA metabolites in both faeces and serum [33], with systemic suppression of allergic airways responses [34]. Seminal studies [30,31] have shown that these microbial-derived dietary fibre metabolites (butyrate) induce tolerogenic dendritic cells and Treg differentiation, mediating these effects through epigenetic changes, including chromatin modification at the *Foxp3* locus. In both adults and infants, prebiotic oligosaccharides selectively stimulate growth of immunomodulatory gut microbiota, with favourable effects on colonization, metabolic and immune parameters [33,35]. So far, most human intervention studies have focused on improving postnatal infant colonization, and these have not generally examined the metabolic effects of SCFA. We propose that the effects of modulating the maternal microbiome with prebiotic fibre begin *in utero*, and that the effects on the developing immune system are mediated, at least in part, by SCFA and associated metabolic changes. There may be additional postnatal effects through breast milk and infant colonization. One recent study [36²²] shows that prebiotic supplements (8 g/day in pregnancy and lactation) alter gene expression in breast milk and significantly increases immune-modulatory cytokines (IL-27) in both colostrum and breast milk. Thus, maternal interventions to increase dietary fibre earlier in pregnancy, when fetal responses are first initiated, are likely to be more effective, given the importance of the maternal microbiome in pregnancy for both immune and metabolic homeostasis.

DECLINING MATERNAL BIODIVERSITY IN PREGNANCY

Although the maternal microbiome is an important determinant of postnatal infant colonization, it also has newly recognized antenatal effects on multiple aspects of fetal development. Contrary to the long-standing belief that the womb is ‘sterile’ paradigm, maternal microbial transfer to the offspring begins during healthy pregnancy, with microbes detected in normal amniotic fluid placental and fetal membranes, cord blood and meconium. The maternal microbiome adapts during pregnancy to modulate both metabolism and immune function [37], and this is highly responsive to dietary changes (as discussed above), providing important metabolic and immune influences on the fetus [33]. Modern, refined low-fibre diets are a major determinant of disruptions in ‘gut homeostasis’ and immune maturation [33,38]. Changes in diet lead to rapid changes in microbiome composition, even within a single day [39], making this an important target in improving gut biodiversity. This essentially means there are both direct immunomodulatory effects of microbial exposure and the indirect effects mediated by their metabolites released in to the systemic circulation.

Many other changes associated with a modern lifestyle are likely to be influencing the biodiversity of gut microflora, including antibiotics, sealed housing, environmental chemicals and generally cleaner environmental conditions. Most of these factors are interconnected. New studies support previous evidence that maternal antibiotic use during pregnancy increases asthma risk in offspring [40]. In animal models, different antibiotics given in the perinatal period can selectively modify the resident gut microbiota profile in ways that differentially alter susceptibility to inflammatory lung disease in offspring [41²³]. Epidemiological studies indicate that rich microbial environment (such as the German farming environment) during pregnancy affords greater allergy protection than postnatal exposure alone [42]. More recent studies from the same group reveal that antenatal farm exposure was associated with hypomethylation of immune regulatory genes such as *ORMDL1* and *STAT6* in cord blood and hypermethylation of genes associated with IgE regulation (*RAD50*, *IL-13* and *IL-4*) [43], consistently with the previously observed allergy protective effects of the farming environment. There is also emerging evidence that, in addition to previous effects on T regulatory gene expression, maternal farming may also modulate T(h)17 markers in cord blood [44]. Similarly, in other settings, other sources of microbial exposure, namely, helminth infection during pregnancy, have been associated with the lower rate of allergic disease in

offspring [45[■]]. Thus, although postnatal microbial exposure is critical for immune maturation and allergy protection, the role of the antenatal period must not be underestimated and requires further detailed investigation.

IMPACT OF MATERNAL HEALTH AND LIFESTYLE BEHAVIOUR

Other factors in maternal health and general lifestyle have the potential to affect fetal development, including neighbourhood environment [46,47]. Recent studies also suggest that maternal psychological distress adversely affects lung development in the fetus and contribute to an increased risk of childhood asthma [48[■]]. Adverse life maternal events during mid-late pregnancy have also been associated with an increasing risk of allergic disorders including asthma and eczema in the offspring [49[■]]. This is also consistent with earlier studies linking salivary cortisol levels in infancy and allergic sensitization and allergic symptoms, suggesting a role of an altered hypothalamo-pituitary-adrenal (HPA) axis in the etiological process of allergies [50].

EFFECT OF MATERNAL SMOKING AND EXPOSURE TO OTHER POLLUTANTS AND TOXINS

There is growing evidence for the role of environmental pollutants such as smoking on small non-coding RNA molecules, such as microRNA (miRNA), which play a critical role in posttranscriptional regulation of gene expression, including pathways involved in immune regulation. New studies reveal that maternal tobacco smoke exposure during pregnancy correlates with miRNA-223 expression in newborn blood, with an effect on cord blood Treg cell numbers and subsequent allergy risk [51]. This is also consistent with previous studies showing maternal smoking in pregnancy is associated with reduced regulatory T-cells in cord blood, which were associated with an increased allergic phenotype in the offspring [52]. This provides additional mechanisms for the well known adverse effects of smoking, which remains an essential target in preventing many NCDs.

Exposure to a broad range of other modern environmental pollutants during the prenatal period has been associated with an increased risk of paediatric asthma and other allergic diseases, including organic chemicals, heavy metals and traffic-related particles [53–55]. Among these, the effect of prenatal exposure of diesel exhaust particles (DEPs) has been studied most extensively. A range of mechanisms are implicated in the mucosal

inflammation induced by DEPs, including adjuvant effects in the presence of allergen [56], induction of thymic stromal lymphopoietin [57], Th2 and Th17 responses [56], and inhibition of interferon-gamma (IFN- γ) [58]. There is growing evidence that in-utero exposure to DEPs is associated with epigenetic effects in both mice [59] and humans [60] with augmented IgE production of following allergen sensitization associated with hypermethylation of *IFN- γ* and hypomethylation of the *IL4* locus in the offspring [59]. New animal models reveal that offspring of mice exposed to DEPs are prone to allergic sensitization mediated through natural killer (NK) cells as the primary source of Th2 and Th17-type cytokine in asthma development [61[■]]. They also demonstrated a relationship between asthma susceptibility and increased transcription of genes known to be specifically regulated by oxidative stress.

There is also growing interest in other environmental chemical pollutants that contaminate food and water supplies, such as bisphenol (BPA), phthalates and a range of persistent organic pollutants. A recent study [62[■]] on prenatal exposure to BPA and high molecular weight phthalates, measured in urine samples collected during the first and third trimesters, was associated with an increased risk of asthma symptoms and respiratory tract infections in children to 7 years of age. The mechanisms of effect are not yet clear [63,64]; however, there is previous evidence that in-utero effects of BPA may be mediated by epigenetic changes early in development, which can change offspring phenotype by stably altering the epigenome in animal models [65]. There are an increasing number of organic and inorganic pollutants that may have epigenetic effects (reviewed in more detail elsewhere) [66], many of which are difficult to avoid because they contaminate a wide range of consumer goods, cosmetics, plastics, toys, soil, foods and the water supply. This highlights the need for ongoing research and efforts to reduce environmental contamination.

CONCLUSION

Recent evidence links multiple changes in modern dietary intakes, lifestyle factors and surrounding environments to adverse influences on the developing immune system and increasing prevalence of early childhood inflammatory disease including allergic disease. The in-utero period appears to be a critical time point and is likely to influence genomic inheritance on the developing immune system. Studies have also shown that antenatal exposures have a significant epigenetic effect on

Table 1. Environmental exposures during pregnancy and their potential gene interaction

Environmental exposure during pregnancy	Potential gene interaction
n-3 PUFA (fish oil)	Epigenetically modifies histone acetylation of key genetic patterns, including IL-13 and PKC, which are associated with allergy protection (submitted for publication)
Dietary fibre	Epigenetic modification at the FOXP-3 locus that induce tolerogenic dendritic cells (DCs) and Treg cells differentiation [30,31]
Farm environment	Hypomethylation of immune regulatory genes such as <i>ORMDL1</i> and <i>STAT6</i> in cord blood and hypermethylation of genes associated with IgE regulation (<i>RAD50</i> , <i>IL13</i> and <i>IL14</i>) [43]
Cigarette smoke	Associated with miRNA-223 expression in newborn blood that affects cord blood Treg cell numbers [51]
Diesel exhaust particles	Increase IgE production through hypermethylation of the <i>IFN-γ</i> and hypomethylation of the <i>IL4</i> locus in offspring [59]

fetal gene expression, thereby altering predisposition to allergic diseases and potentially other NCDs (Table 1). Future integrated research on the interplay between multiple in-utero exposures and the development of allergic diseases will provide the much needed evidence upon which to base allergy prevention recommendations.

Acknowledgements

None.

Financial support and sponsorship

S.P. is supported by a Practitioner Fellowship from the National Health and Medical Research Council (NHMRC) of Australia.

Conflicts of interest

There are no conflicts of interest.

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