

Early life exposures: impact on asthma and allergic disease

Anita L. Kozyrskyj, Salma Bahreinian and Meghan B. Azad

Department of Pediatrics, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, Alberta, Canada

Correspondence to Anita Kozyrskyj, Department of Pediatrics, Faculty of Medicine and Dentistry, University of Alberta, 8226a Aberhart Centre, 11402 University Avenue, Edmonton, Alberta, T6G 2J3, Canada
Tel: +780 407 8672; e-mail: kozyrskyj@ualberta.ca

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Purpose of review

To identify and discuss recent studies relating prenatal and early-life environmental exposures to the development of asthma and allergic disease.

Recent findings

New studies show that prenatal and early-life stress can alter infant immune profiles, increasing risk for asthma and allergy. Mounting evidence implicates indoor and outdoor air pollution in the origins of allergic disease, while Vitamin D intake and a Mediterranean diet may be protective. The role of early-life fever and infection remain controversial, with recent studies yielding conflicting results and new evidence indicating that previous studies may have been confounded. New studies are increasingly focused on environmental ‘imprinting’ of the infant gut microbiota, which is a critical determinant of immune system development. Early exposures impacting the intestinal microbiota include mode of delivery, infant diet, and use of antibiotics – factors that are also associated with childhood asthma and allergic disease.

Summary

This overview highlights environmental exposures during the in-utero and ex-utero time periods that are potential stimuli for the early programming of asthma and allergy. Special consideration is given for the potential role of intestinal microbiota. Future studies in this field promise to inform health policy and intervention strategies for the prevention of asthma and allergic disease.

Keywords

allergic disease, asthma, early life exposures, fetal programming, infant gut microbiota

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Introduction

The hygiene hypothesis, supported by provocative evidence from farm lifestyle and endotoxin studies [1], has revolutionized modern conceptions about environmental origins of allergic disease. However, it fails to explain the co-existing epidemic in autoimmune disease or the high rates of asthma and allergy among the urban poor in the United States. This deficiency has fuelled the continued search for alternate environmental explanations. Originating as the Barker hypothesis, ‘early programming’ has been a dominant theory for the origins of cardiovascular and metabolic disease [2]. Also known as ‘developmental plasticity’, this concept describes the ability of physiologic systems in the fetus and infant to adapt to environmental stimuli during critical time windows [3•]. As immune and lung development occur largely *in utero* and during early childhood [4•], early programming is a plausible pathway for allergic and respiratory disease [5]. Epigenetic mechanisms – the imprinting of environmental experiences on infant gene expression – are thought to be at the root of developmental plasticity in relation to allergic disease [3•,6]. However, environmental imprinting on the infant micro-

biome is also relevant to respiratory health and allergic disorders [7]. This overview highlights environmental exposures during the in-utero and ex-utero time periods that are potential stimuli for the early programming of asthma and allergy. These include stress, nutrition, infection, and pollution. As the genetics and epigenetics of allergic disease are discussed elsewhere in this special issue, we will focus on the impact of early environmental exposures, with special consideration for the role of the infant intestinal microbiota.

Stress and distress

The importance of stress in early-life programming of cardiovascular and metabolic disease is steadily being informed by studies of stress and adversity during pregnancy and infancy. We have come full-circle from initial constructs of asthma and allergies as psychosomatic diseases in the 1950s, to recent-decade investigations of early-life stress as a contributor to asthma initiation and exacerbation [8]. New research describing allergic immune profiles in cord blood provides evidence that prenatal maternal stress modulates fetal innate and adaptive immune responses [9••]. Indeed, mother’s anxiety

during pregnancy has been found to increase the likelihood of asthma at school-age [10]. During infancy, both maternal and paternal distress appear to play independent roles in precipitating wheeze [11]. However, accumulating evidence indicates that the perinatal period is not the only critical window for stress exposure. We and others have previously shown that long-term exposure to maternal anxiety/depression in early childhood increases risk of recurrent wheeze and asthma in preschool and school-age children [12]. Recent studies further suggest that cumulative exposure to multiple psychosocial and environmental stressors throughout childhood can synergistically increase the risk for childhood asthma. For example, Franco *et al.* [13•] found that exposure to household violence increased the likelihood of developing asthma before age 3, with a greater effect observed among children also living in poor housing conditions.

Our understanding of the mechanisms by which early-life stress predisposes children to asthma and allergic disease continues to improve. New findings emphasize that early-life stress can alter cardiopulmonary maturation [14] and cause long-term dysregulation of the hypothalamic-pituitary-adrenocortical (HPA) axis and autonomous nervous system (ANS), which in turn alters immune system regulation and increases risk for asthma development [15•]. HPA dysfunction in asthmatic children was recently demonstrated by Dreger *et al.* [16•], who observed blunted or lower cortisol levels in asthmatic versus healthy children. This type of impaired stress response agrees with the concept of allostatic load, whereby metabolic activities, HPA and ANS function are distorted after repeated exposure to stress [17]. Allostatic load has been proposed as the link between neighborhood violence, psychosocial stress and higher asthma morbidity in inner-city populations [18]. We are currently studying the relevance of allostatic load to asthma development in a general population of children [19]. Dysregulation of the ANS, measured as impaired sympathovagal balance, has been observed in children with asthma [20]. This imbalance has also been found in children with depression, which may explain the higher incidence of depression observed in children with asthma [21•].

Nutrition and nutrients

Parallel increases in overweight and asthma among children over the last quarter century have prompted research on maternal or childhood nutrition as a determinant of persistent asthma. Previous cross-sectional studies [22,23] in Greece and Spain have reported that a Mediterranean diet (MD: rich in vegetable, fruit, olive oil, and antioxidants) is protective against wheeze and asthma in children. A new multinational survey has

Key points

- Environmental exposures during both in-utero and ex-utero time periods are involved in the early programming of asthma and allergy.
- Important exposures include maternal and family stress, maternal and infant nutrition, indoor and outdoor air pollution, and early-life infection.
- Environmental exposures such as birth mode, infant diet, and use of antibiotics may ‘imprint’ the infant microbiome, ultimately influencing immune development and allergic disease.

reproduced these findings, showing that Mediterranean diet protects against childhood asthma, but not allergic sensitization [24••]. There is also evidence that maternal adherence to Mediterranean diet during pregnancy may be protective against persistent wheeze in childhood [25], although others have failed to confirm this association [26•,27]. In parallel, new studies have found that a Western diet is associated with increased risk for asthma [24••], and that fast food consumption may counteract the protective effects of prolonged breastfeeding [28].

Accumulating evidence suggests that Vitamin D may be implicated in asthma development. New longitudinal studies [29,30••] confirm previous reports that high Vitamin D intake during pregnancy provides protection against recurrent wheeze and asthma in offspring. However, a recent meta-analysis [31••] reported weak evidence for the beneficial effects of prenatal vitamin D intake. Although cellular effects of Vitamin D and antioxidants present compelling arguments for a nutrition pathway in early programming of allergic disease, it should be noted that women who are depressed or stressed during pregnancy are more likely to have poor eating habits [32]. As existing observational studies have not adequately adjusted for these biases, future diet intervention studies will be required to determine the role of nutrition in asthma development and prevention.

Pollution and chemicals

Recent reviews have summarized the evidence implicating indoor and outdoor air pollution in the development of childhood asthma [33,34]. Early-life exposure to air pollution is considered especially harmful, as the respiratory epithelium of the developing lung exhibits increased permeability to toxins [33]. Similarly to previous reports, a new Canadian birth cohort study [35••] found that modest exposure to traffic-related pollutants during the first year of life was associated with up to 12% increased risk for asthma diagnosis at age 4. Equivalent exposures were associated with up to 50% increased risk for asthma in a high-risk birth cohort from the same geographical area [36•], suggesting that infants who are genetically

predisposed to asthma may be especially sensitive to air pollution.

New studies are increasingly focusing on indoor air pollution as a determinant of asthma morbidity, since children spend up to 90% of their time indoors. Important indoor pollutants include particulate matter, nitrogen dioxide, and airborne mouse allergen [34]. Mounting evidence further suggests that early-life exposures to household chemicals play a role in allergic airway disease. For example, Choi *et al.* [37^{••}] have found that bedroom concentration of propylene glycol and glycol ethers (PGEs, which are widely used in water-based paint, cleaning fluids and polyvinyl chloride pipes) is significantly associated with elevated risks of asthma, allergic rhinitis, and eczema in children.

Viruses, microbes, and fever

Exposure to external micro-organisms is central to the hygiene hypothesis, but evidence for early-life infection as a modifier of allergic disease is inconsistent at best. Initial evidence for an association with early-life viral exposure came from studies of respiratory syncytial virus (RSV) infection, many of which documented a positive association with childhood wheeze or asthma [38^{••}]. Two recent follow-up studies [39[•],40[•]] support this literature, showing that RSV hospitalization before age 2 is associated with up to a 14-fold higher risk of asthma, persisting into adulthood. However, another study [41[•]] found no difference in asthma prevalence among twin pairs discordant for RSV hospitalization.

New evidence suggests that viral infections besides RSV may also influence the development of atopy or wheeze in children, although results have been conflicting. For example, the common cold has been reported to increase risk of early wheeze [42^{••}], while nose or throat infection was shown to be protective [43[•]]. Similarly, early measles infection may predict later rhinitis and bronchial hyper-responsiveness [44], while chicken pox, herpes virus type 6, and Epstein–Barr virus are apparently protective against atopic sensitization [45–47]. In light of these conflicting reports, further research is required in order to determine whether viral damage to the lung epithelium, or viral unmasking of host susceptibility are causal pathways to allergic disease.

A novel and substantial association with gastrointestinal infection has been documented in the Dutch Kind, Ouders en gezondheid: Aandacht voor Leefstijl en Aanleg (KOALA) birth cohort: diarrhea with fever during the first 3 months of life (a presumed indicator of viral gastroenteritis) resulted in a four-fold elevated risk for wheeze at age 2 [42^{••}]. In parallel, new research in developing countries has shown that gastrointestinal infection with helminthes

is also associated with wheeze and atopic sensitization in preschool children [48,49]. Notably, the KOALA results are consistent with existing literature on the association of fever or paracetamol use during infancy with later development of asthma [50]. Recently, however, the latter association was proven to be confounded by the presence of respiratory tract infections [51^{••}]. Extending earlier publications on fever during pregnancy, a new body of literature on chorioamnionitis also indicates a high likelihood of asthma development, especially in very premature infants [52,53^{••}]. It remains to be proven whether paracetamol use in pregnancy is simply a marker for infection; however, a newly published meta-analysis determined that prenatal use of paracetamol for pain, rather than infection, remained significantly associated with an increased risk of childhood asthma [54^{••}].

Imprinting on the intestinal microbiome

A Darwinian perspective would challenge the notion that sporadic and unpredictable infections during infancy are crucial to the development of the human immune system. Rather, as supported by mounting evidence, the continuous and predictable presence of microbiota in the human intestine is more likely to shape immune system development during infancy [7,55[•]]. Since the early 2000s, we have known that infants who ultimately develop allergic disease harbor a distinct gut microbiota [56]. With advances in the DNA sequencing methods used to study microbiota composition, understanding how early environmental exposures may imprint the infant microbiome has become a top priority in health research. Several studies have contributed new findings in the past year, providing further evidence for the so-called ‘microflora hypothesis’.

Since the newborn’s first microbial exposure is to maternal microbiota during birth, followed by dietary exposures, three environmental factors have been the focus of study: mode of delivery, infant nutrition, and antibiotic use [55[•]]. New studies [57,58[•]] have described altered fecal microbiota profiles in caesarean section delivered infants beginning at 1 day after birth and persisting to 6 weeks of age. A previous meta-analysis [59] reported a 20% increase of asthma in children born by caesarean section, but there is considerable heterogeneity among recent studies. For example, a UK medical record linkage study [60] documented that caesarean delivery was not associated with hospital admission for ‘asthma’ beyond age 1, while a Canadian study [61] found an association with asthma at age 9, though it was limited to first-time caesarean section only.

Following birth, exclusive breastfeeding has been associated with ‘beneficial’ gut microbiota when compared with formula-fed infants [62,63]. New research suggests that

the beneficial effects of breast milk may be attributable to the prebiotic properties of human milk oligosaccharides [64], or the transfer of intestinal bacteria from mother to infant via breast milk [65[•]]. In parallel, studies [66[•],67[•]] continue to find that breastfeeding protects against recurrent wheeze and asthma in later childhood.

Antibiotics suppress commensal bacteria and can lead to the emergence of pathogens such as *Clostridium difficile* [55[•]]. Recent reports [62,68] have confirmed previously documented associations of antibiotic use by newborns with altered infant microbiota profiles, including long-term reduction in microbiota diversity. Additional studies [53^{••}] have accounted for prenatal exposure to antibiotics. Concurrently, new studies [69[•]–71[•]] continue to find that antibiotic use during infancy is associated with increased risk for atopic disease later in childhood. Nevertheless, this association remains controversial since a number of studies appear to be confounded by reverse causation or confounding-by-indication, as described by Penders *et al.* [72^{••}] in their meta-analysis. Well designed prospective birth cohort studies will be required to fully characterize the impact of caesarean delivery, formula-feeding and antibiotic use on child health, and to empirically validate the ‘microflora hypothesis’ in the context of allergic disease.

New and revisited hypotheses

Recent developments will help further the connection between environmental exposures, microbiota, and allergic disease. Using evolutionary principles, Raison *et al.* [73^{••}] have proposed the ‘Old Friends’ hypothesis, which posits that micro-organisms in the internal and external human environment, such as intestinal microbiota and pseudo-commensals in soil and water, train the immune system in tolerance as a means of promoting their own survival. ‘Old Friends’ microbes are differentiated from pathogens by their ability to activate host production of anti-inflammatory, rather than pro-inflammatory, cytokines. With the gradual reduction or disappearance of ‘Old Friends’ organisms, persons’ living modern lifestyles lack this critical immune system training, and are subsequently at risk for inappropriate inflammatory responses to harmless environmental antigens. Pseudo-commensals include *Helicobacter pylori*, whose colonization in humans has declined over the last 50 years. Inverse associations of *H. pylori* with asthma and allergy were first reported in the USA [74], and have recently been confirmed in other countries [75,76]. Changes to nutrition in modern lifestyles also support the ‘Old Friends’ hypothesis, since plant fiber serves as an important substrate for microbiota [77]. Further, Vitamin D is thought to be essential for mediating signals from microbiota to dendritic and T-regulatory cells in the training of the immune system [78[•]].

The protective effect of maternal exposure to farm animals, and the risk associated with prenatal maternal stress, raise the possibility that stimulation of the maternal immune system during pregnancy generates signals capable of training the fetal immune system [79]. Maintenance of the placental microenvironment in a ‘noninflamed’ steady state represents the ideal for healthy fetal development. How this balance is achieved remains unknown, but conceivably, it is disrupted by in-utero infections, maternal stress, poor nutrition, and exposure to chemical pollutants. Placental balance may also be a function of the mother’s parity and paternal antigens. As nulliparity or a new partner increases risk for preeclampsia, it has been hypothesized that nulliparous women have a lower activity of T-regulatory cells specific to paternal antigens [80]. Indeed, a recent study [81] has shown that children born to preeclamptic mothers are more likely to develop atopy.

Conclusion

To conclude this review of current theses on environmental determinants of allergic disease, we return to the early programming hypothesis. New evidence supports the concept that increased fetal and infant exposure to stress, Western diet, infection, and chemical pollutants may create an adverse environment, with resulting changes to lung and immune physiology affecting health and survival in the short and long term. Declining exposure to ‘Old Friend’ microbes and disruption of microbiota development may affect immune system training. Consistent with the programming hypothesis, we have summarized the recent literature on early-life environmental exposures that may influence the development of atopy in children. Future studies in this field promise to inform health policy and intervention strategies for the prevention of asthma and allergic disease.

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Conflicts of interest

None declared.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

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