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The Role of the Early-Life Environment in the Development of Allergic Disease

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SYNOPSIS

A consensus has been reached that the development of incident allergic disorders are likely strongly influenced by early life exposures. An overview of several prenatal and early life factors that have been investigated for their associations with development of childhood allergy is presented. Delivery mode, the gut microbiome, Vitamin D, folate, breastfeeding, pets, antibiotics, environmental tobacco smoke and airborne traffic pollutants are discussed. Despite a large proportion of the studies suggesting an effect, overall no risk factors clearly increase or reduce the risk of allergic outcomes.

Keywords

asthma; allergy; IgE; prenatal; eczema; atopic dermatitis

The developmental origins of health and disease (DOHaD) hypothesis suggests that a child's environment from conception through 1000 days greatly influences a child's risk for chronic disease. Although not well tested in association with immunological diseases such as allergies and asthma, recent studies have focused on early-life risk factors and the development of allergic diseases later in life.^{1–3} This review summarizes studies of prenatal and early postpartum exposures and the subsequent development of allergy-related outcomes with a focus on delivery mode, the gut microbiome, nutritional factors, and exposure to animals, medications and airborne pollutants. Further, these early life factors are reviewed in the context of disease incidence (occurrence) rather than disease exacerbation or management.

Delivery Mode

Birth by cesarean section may increase the risk of allergic disease. The mechanism is not known, but recent human microbiome research suggests that lack of exposure to beneficial

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microbes present in the birth canal may affect the colonization of the child's gut microbiome and subsequent immune development. Comparisons of studies correlating delivery mode and allergy are also impacted by variability in outcome definitions (parental report versus clinical evaluation).

No association between delivery mode and eczema diagnostic codes was found in the West Midlands General Practice Research Database (n=24,690)⁴ or a Kaiser Permanente Northwestern birth registry cohort (n=7872).⁵ In a Japanese birth cohort, no association was found between delivery mode and maternal report of physician-diagnosed eczema.⁶ A meta-analysis resulted in a similar conclusion,⁷ as did the Finnish SKARP study (n=4799).⁸ However, in the KOALA study, children born via c-section were more likely to have parental-reported eczema.⁹

No association between delivery mode and skin prick test results at age 7 was found in the ALSPAC cohort.¹⁰ A meta-analysis concluded that children born by c-section were more likely to have food allergy/sensitization but not inhalant sensitivity.⁷ Similar associations with food allergy were reported in a systematic review¹¹ and in the KOALA birth cohort.⁹ Among offspring of non-allergic parents in the PIAMA study (n=2917), children born via c-section were more likely to have positive allergen-specific IgE testing.¹² Among Boston children, c-section was associated with positive skin prick tests or allergen-specific IgE at age 9 years,¹³ as it was among 8 year old children whose parents were allergic in the Republic of Cyprus (skin prick tests).¹⁴

A meta-analysis concluded that c-section is associated with increased asthma risk⁷ while such an association was only seen among girls in the Kaiser Permanente study⁵ and restricted to children born by emergency c-section in a registry report from Sweden.¹⁵ In contrast, the West Midlands General Practice Research Database report found no association.⁴ Several studies using questionnaire data have reported associations between c-section and increased asthma frequency,^{12,14} while others failed to confirm this finding.^{8,10} Questionnaire data may not provide sufficient specificity for defining asthma as an outcome; hence, the emergence of conflicting results.

Microbiome

Intensive interest in the influence of the human microbiome, in particular the gut microbiome, on the developing immune system and allergy has been ignited with the recent development of culture-independent tools to more comprehensively measure bacterial community composition.^{16,17} However, even prior to these technologies, investigators postulated that mechanisms underlying the Hygiene Hypothesis were linked to alterations in patterns of "normal" infant intestinal microbial colonization.^{18,19} Small studies using culture-dependent methods indicated differences in the prevalence of intestinal microorganisms between atopic and non-atopic infants,²⁰ although subsequent studies did not find confirm differences linked to food sensitization or atopic eczema using culture-dependent assessments.²¹ In 2001, Kalliomaki assessed fecal samples from a small birth cohort (n=76), using both culture-dependent and culture-independent bacterial measures. The study demonstrated that culture-independent approaches detected fecal microbial

differences that distinguished children who developed allergic sensitization.²² Murray et al. used a similar approach in a case-control study of 33 pairs of children and found that the ratio of bifidobacteria to total fecal bacteria was lower in children with eczema at age 4 years.²³

The Netherlands KOALA birth cohort was the first to study selected fecal bacteria phylogroups (n=5) in a large group of infants (n=1032) using quantitative real-time PCR. Microbial colonization patterns were associated with several proposed risk factors linked to allergy development, such as mode of delivery, breast feeding, antibiotic use and birth order.²⁴ Another European group demonstrated distinct fecal bacterial composition patterns among populations of children with varied prevalences of allergy.²⁵ Penders et al. later related fecal bacteria in the KOALA study to atopic outcomes at age 2 years and found that increased *E. coli* and *C. difficile* were associated with eczema and the latter with recurrent wheeze and allergic sensitization.²⁶ A 2007 review of 17 studies stressed the importance of considering the techniques used to measure the presence of bacteria as well as and the timing of measurement.²⁷

Other recently reported birth cohort studies have addressed the relationship of the intestinal microbiome and allergic outcomes, with most suggesting associations.^{9,28–31} Investigators can now take advantage of advances in 16S rRNA gene deep sequencing and array technologies that allow comprehensive detection of microbial communities on a large scale.^{32,33} For instance, in a group of 40 Swedish infants, low fecal microbial diversity measured with 16S rDNA 454-pyrosequencing was associated with atopic eczema.³⁴ It is clear that studies of the infant gut microbiome and atopic outcomes need to appropriately consider other factors, many mentioned in this review, such as mode of delivery, diet and breastfeeding patterns, antibiotic use and other environmental factors that may affect the maternal and infant gut microbiome (e.g., animals, daycare, vitamin D). For example, data from infants in the Canadian CHILD study and the Detroit area WHEALS birth cohort, using these new high-throughput technologies, suggest that pets are associated with distinct infant gut and environmental microbiome signatures, respectively.^{35,36}

Vitamin D

Interest in vitamin D's role in allergic disease has grown tremendously in recent years, particularly since vitamin D supplementation is perceived as low-risk and non-invasive. Overall, the evidence that vitamin D modifies the incidence of allergy-related outcomes is mixed. Studies including a direct measure of vitamin D (25-hydroxyvitamin D [25(OH)D] or 25(OH)D₂ or 25(OH)D₃) that clearly precede childhood allergy are reviewed below. We have excluded studies using food frequency questionnaires since they approximate dietary vitamin D intake rather than reflect bioavailable levels, which are also influenced by sun exposure, supplement intake, genetic variation in vitamin D metabolism and variable dietary absorption. Further, early vitamin D levels beyond the prenatal period have not been well studied so discussion is limited to reports measuring either prenatal maternal or cord blood vitamin D.

Although considered a treatment of atopic dermatitis (AD),³⁷ there is limited evidence detailing the relationship between early life vitamin D levels and childhood AD risk. In a birth cohort of 440 English infants (age 9 months), children whose mothers had the highest quartiles of 25(OH)D during pregnancy had an increased risk of AD.³⁸ However, there was no association between prenatal 25(OH)D levels and eczema (assessed by questionnaire) among 7–8 year old children in the ALSPAC birth cohort.³⁹ Considering cord blood, 25(OH)D₃ was weakly inversely associated with eczema (by clinical examination or parental report of doctor diagnosis) at 1 year of age in an Australian cohort (n=231) with at least 1 allergic parent.⁴⁰ Cord blood 25(OH)D levels were also inversely associated with AD (assessed by questionnaire) by age 5 years in children in the EDEN birth cohort (n=239).⁴¹ These conflicting results could be due to the use of outcomes based on questionnaire versus clinical examination. Also, correlations between prenatal and cord blood vitamin D levels are variable which could account for some inconsistencies.

Prenatal 25(OH)D levels were not associated with childhood skin prick test results in either the ALSPAC cohort³⁹ or the Southampton Women's Survey (n=860).⁴² Associations were not found between cord blood 25(OH)D₃ and skin prick tests in the Perth cohort⁴⁰ or cord blood 25(OH)D and allergic rhinitis (AR) in the EDEN cohort.⁴¹ Weisse et al. reported that higher prenatal and cord blood 25(OH)D₃ were associated with increased risk of food allergy (report of doctor diagnosis) at age 2 years in the German LINA cohort (n=272).⁴³ In the Tucson Infant Immune Study, high cord blood 25(OH)D levels were associated with increased rates of having a positive skin prick test while both high and low 25(OH)D levels were associated with higher levels of total IgE.⁴⁴

A study in Southampton, UK, although limited by loss to follow-up, found that higher 25(OH)D levels in late pregnancy were associated with increased frequency of asthma at age 9.³⁸ No association was found between prenatal 25(OH)D level and lung function in the ALSPAC cohort³⁹ or with childhood asthma in the Southampton Women's Study.⁴² Cord blood 25(OH)D was not associated with asthma at age 5 years in the EDEN study⁴¹ or New Zealand Allergy and Asthma cohort (n=922).⁴⁵

Folate

The evidence that folate or its synthetic form (folic acid) is associated with risk of allergy is decidedly mixed. Study of this relationship is complicated by the fact that in parallel with the allergy epidemic, folic acid has been added to numerous foods and recommended for pregnant women to prevent birth defects.⁴⁶ In the Netherlands' KOALA birth cohort (n=837), prenatal erythrocyte folic acid levels were not associated with AD at 2 year examination.⁴⁷ However, among children carrying a mutation in the methylenetetrahydrofolate reductase gene, cord blood folate was associated with a report of physician diagnosed eczema at ages 4 and 6 years in the Generation R birth cohort in the Netherlands.⁴⁸ No association was reported between prenatal or cord folate levels with doctor diagnosis or observation of eczema in an Australian birth cohort (n=484);⁴⁹ however, higher folate supplement ingestion during the third trimester led to higher risk of eczema by age 1 year. Folic acid-only supplements and prenatal supplements with folic acid, multi-vitamin supplements or vitamin D complex were not associated with parental reported

eczema in children through age 8 years in the PIAMA study.⁵⁰ Interpretation is further complicated by the heavy reliance on parental report of AD versus study-specific validated reports or clinical evaluations.

Prenatal intracellular folic acid was not associated with total IgE or sensitization in the KOALA birth cohort.⁴⁷ Cord blood folate between 50 and 70 nmol/l was associated with lower risk of positive skin test results at 1 year compared to higher or lower levels in a birth cohort from Western Australia (n=484); but no association with prenatal folate was evident.⁴⁹ Sensitization (sIgE 0.70 IU/ml) at age 8 years was not associated with prenatal folic-acid supplements in the PIAMA birth cohort.⁵⁰ However, higher folate levels through age 8 years were associated with sensitization (including foods), in the COAST cohort.⁵¹

A recent meta-analysis reported a lack of association between maternal folic acid supplementation and risk of asthma in their children.⁵² Neither cord blood folate, nor prenatal folic acid supplements were associated with recurrent wheeze at age 1 year in Western Australia (n=484).⁴⁹ Maternal folic acid supplementation was associated with wheeze at age 1 year, but not other time points through 8 years, or with asthma symptoms at any age in the PIAMA cohort (n=3786).⁵⁰ Cord blood folate was not associated with diagnosed asthma, wheeze, exhaled nitric oxide or lung function (interrupter resistance) at age 6 years in the Generation R birth cohort (n=2001).⁴⁸ Prenatal intracellular folic acid levels were inversely associated with asthma (diagnosis and/or asthma medications in last 12 months) at age 6 to 7 years in the KOALA birth cohort.⁴⁷ Child folate levels were not associated with wheeze in the COAST cohort.⁵¹

Breastfeeding

The American Academy of Pediatrics recommends breastfeeding for at least a year with exclusive breastfeeding in the first 6 months (with vitamin D supplementation).⁵³ While widely investigated regarding a role in allergy prevention, a consensus on breastfeeding remains elusive. Many publications have analyzed different breastfeeding characteristics including duration of breastfeeding, maternal diet during lactation⁵⁴ or age at complementary food introduction.^{55–57} Furthermore, breast milk varies in composition^{58–60} and some women alter their diet while breastfeeding based on varying recommendations, which further complicates study interpretation. Among possible mechanisms, breastfeeding may alter a child's gut microbiome and immune development.^{61,62} Breastfeeding may also alter a child's risk of respiratory infections through maternal antibody transfer⁶¹ or impact childhood nutrient intake such as vitamin D. Recent publications on breastfeeding provide mixed results for commonly investigated allergic outcomes: AD,^{56–61;63–65} sensitization/sIgE,^{59;61;66–68} and asthma.^{56–58;61;68–73}

Pets

Numerous studies have reported that prenatal or early life exposures to mammals, including pets and livestock, are inversely associated with pediatric allergy. Protective associations have been reported for total IgE, atopic sensitization, and clinical disorders such as AD, allergic rhinitis and asthma. Most reports on livestock exposure have been based in the Alpine areas of Europe, whereas domestic pet studies have been conducted worldwide. The

theory that animal exposure is protective for allergy has been linked to the Hygiene Hypothesis with the concept that environments with animals are less hygienic, although studies have not identified what specific animal exposure characteristics might afford protection. Hypotheses implicate high levels of allergen exposure, animal transport of outdoor substances into the home, increased physical activity associated with animal ownership, or even decreased stress levels. Recently, attention has focused on the impact an animal may have on a child's microbial environment or the microbial population inhabiting the child's gastrointestinal tract, skin and respiratory tract. Thus the "Hygiene Hypothesis" has evolved into the "Microbiome Hypothesis", or perhaps, better, the "Microbiome Dysbiosis Hypothesis".¹⁶ Studies initially were limited to analyzing culturable bacteria,⁷⁴ but the Human Microbiome Project and sequencing technology have expanded knowledge and assessment of entire microbial populations consisting of thousands of taxa in samples ranging from environmental residential dust to human stool, skin and airway samples.

Several reviews and meta-analyses have summarized early life cat and dog exposure as risk factors for allergic conditions.^{75–79} Results have been less consistent for cats than dogs.⁷⁶ Dog exposure has been associated with less risk for allergy, especially allergic sensitization.^{75–77} A study from the Cincinnati CCAAPS cohort found that infants with dogs were less likely to have an eczema diagnosis at age 1 year (Odds Ratio=OR=0.62, 95% confidence interval (CI) 0.40–0.97) and at age 4 years.⁸⁰ Two meta-analyses also suggested inverse relationships between early dog (but not cat) exposure and eczema.^{79,81} In the European PASTURE/EFRAIM cohort, prenatal exposure to more farm animals, cats or dogs was associated with significant or borderline significant decreased odds ratios for AD by age 2 years.⁸² A large Australian study of 5276 infants found that first year exposure to dogs was associated with less egg allergy (OR=0.72, 95% CI 0.52–0.99), with a similar but non-significant risk estimate for cat exposure.⁸³ The Detroit area Childhood Allergy Study found that early exposure to two or more cats or dogs was associated with a lower prevalence of sensitization to all inhalant allergens at age 6 years.⁷⁵ Inverse associations have been less evident for asthma.

The timing of exposure to pets appears critical, with prenatal or infancy exposure more consistently inversely associated and later exposure sometimes positively associated with allergic outcomes. A recent meta-analysis of eleven European birth cohorts did not find associations between cat exposure and current asthma, allergic asthma, allergic rhinitis or allergic sensitization in mid-childhood.⁷⁸ However, dogs were inversely associated with allergic sensitization (OR=0.65, 95% CI 0.45–0.95) with borderline significant findings for allergic rhinitis (OR=0.77, 95% CI 0.55–1.07) and current asthma (OR=0.77, 95% CI 0.58, 1.03).

Inconsistent results may relate to differences in study populations with respect to genetic factors, the prevalence of local pet keeping and unmeasured risk factors associated with pet exposure.^{84,85} Therefore, although not settled, there is no consistent evidence that early pet exposure increases the risk for allergic disorders, and some evidence of a protective effect. In recent years, many think that both pet and livestock exposure reflects a complex causal pathway in which they contribute to allergic disease development through their impact on the infant's environmental and human microbiome.⁷⁴

Medications

Antibiotic use in the first years of life as a risk factor for allergic disorders is an attractive hypothesis. Antibiotic use has increased in parallel with the increasing prevalence of allergic conditions which can be linked through plausible mechanisms, including decreased duration or number of bacterial infections and consequent effects on the immune system, or more recently, effects on the immune system due to gastrointestinal dysbiosis. Numerous studies have addressed this hypothesis with respect to asthma. A recent exquisitely detailed review identified 45 studies through 2012 that focused on early childhood antibiotics and pediatric asthma.⁸⁶ Indeed, several meta-analyses and reviews have addressed this topic.^{86–90} These reviews all reach similar conclusions – that studies associating early antibiotic use and asthma are typically fraught with biases. A particular challenge is to disentangle early respiratory infections as risk factors and/or early markers of asthma themselves versus their role as the most common indication for antibiotic use during infancy. Studies that attempt to account for this complicated pathway generally show little or no associations. A large 2011 cross-sectional study distinguished between three common asthma phenotypes; transient wheezing, early onset wheezing/asthma, and late onset wheezing/asthma at age 6–7 years, but not allergic versus non-allergic disease.⁹¹ They demonstrated associations between antibiotics and disease under age 2 years that were strong but eventually dissipated to a weak, albeit statistically significant association, with disease onset at later time points. These authors cautioned against the conclusion of a potential causal association. In contrast, a 2014 finding from 62,576 children in a nationwide health insurance plan yielded remarkably similar findings but the authors recommended heightened caution regarding unnecessary use of antibiotics in infants.⁹² Acetaminophen (paracetamol) use during pregnancy and infancy has also been under investigation as a risk factor for childhood asthma, with parallel results and methodological concerns as respiratory infections are also linked to acetaminophen use.⁸⁶

Fewer studies have addressed antibiotic use and the outcomes of AD or sensitization where reverse causation may be of less concern. Jordan et al. identified 12 publications focused on antibiotic use during pregnancy and childhood eczema and summarized the results as equivocal.⁹³ Results from the Dutch KOALA birth cohort followed through age 2 years did not indicate associations of eczema or atopic sensitization with antibiotic use, which they reported as being consistent with other cohort studies.^{88,94,95} A Belgian birth cohort followed through age 4 years reported that prenatal exposure to antibiotics was associated with AD but not sensitization, but no association of post-natal antibiotic exposure to either outcome was apparent.⁹⁶ Even fewer studies address early antibiotic exposure and allergic rhinitis. An early Boston cohort analysis found no evidence of an association⁹⁴ and a 2008 study from a high risk Australian birth cohort deploying propensity score analyses was also consistent with no associations for allergic rhinitis (or any other allergic outcome).⁹⁷

Airborne Exposures – Tobacco Smoke and Traffic Related Airborne Pollution

It is well established that many airborne irritants and pollutants trigger wheezing and exacerbations of asthma as well as upper respiratory tract symptoms. However, the specific

impact of early life pollutant exposure on the development of childhood atopy is less clear. Since many pollutants are airway irritants, studies with outcomes related to airway symptoms are excluded and discussion of potential relationships of early-life exposure pollutants to allergy will be limited to two of the most extensively studied environmental exposures – environmental tobacco smoke (ETS) and traffic-related air pollutants (TRAP).

Environmental Tobacco Smoke

Tobacco smoke contains over 5000 chemical substances with nearly 100 linked to poor health.⁹⁸ Exposure to ETS has been one of the most studied early life risk factors for allergy and asthma. This section will summarize studies that address the potential impact of early life passive-smoke exposure on the risk for the development of childhood atopy.

In 1998, Strachan et al, completed a systematic review of ETS and its association with allergy-related outcomes including a quantitative meta-analysis of 12 qualifying reports of the effects of parental smoking on positive childhood allergen skin prick tests. Parental smoking during pregnancy or infancy was not associated with increased likelihood of allergen skin prick positivity (pooled OR=0.87, 95% CI 0.62 to 1.24). Furthermore, the results of subsequent studies potentially linking ETS to allergic rhinitis, eczema, and sensitization have been mixed.^{99–102}

However, results from subsequent prospective cohort studies have suggested that early life ETS may increase allergic sensitization among specific subgroups of children. In the German Multicenter Allergy Study (MAS) cohort, 342 children were assessed for outcomes reported at age of 3 years. Compared to unexposed children, those who were pre- and post-natally exposed to ETS had a higher likelihood of sensitization to food allergens (OR=2.3, 95% CI 1.1–4.6) with a similar estimate among those exposed only post-natally (OR=2.2, 95% CI 0.9–5.9). No association with inhalant allergens was evident.¹⁰³ Among one-year old children in the CCAAPS cohort, those living in homes where >20 cigarettes/day were consumed had higher risk of allergic rhinitis defined by the combination of prior rhinitis symptoms and a positive skin prick test at 12 months of age to at least one of 15 allergens (OR=2.7, 95% CI 1.04–6.8).¹⁰⁴ In a large Swedish cohort, prenatal maternal smoking was not associated with risk for IgE sensitization. However, a dose-response relationship was reported between postnatal ETS exposure during the first several months of life and the likelihood of having a positive specific IgE test among 2534 children at age 4 yrs (any of 14 allergens: adjusted OR=1.28, 95% CI 1.01–1.62; food allergens only: aOR=1.46, 95% CI 1.11–1.93; cat allergen aOR=1.96, 95% CI 1.28–2.99).¹⁰⁵

Some studies suggest interactions between ETS exposure and inherited predisposition for allergy. Among 10 year old MAS cohort children with two allergic parents and compared to those not exposed to ETS, routine maternal smoking during and after pregnancy was associated with increased allergic sensitization (sIgE > 0.35 kU/l) to at least one of nine common food or inhalant allergens measured at seven time points up to age 10 (aOR =4.8, 95% CI 1.3–18.2). Elevated risk was still apparent among children with one allergic parent (aOR =1.8, 95% CI 1.1–2.9) but absent among children with 2 non-allergic parents (aOR =0.7, 95% CI 0.4–1.3). Paternal smoking or occasional maternal smoking was not associated

with altered risk of sensitization.¹⁰⁶ In stark contrast to the MAS report, early life ETS exposure increased childhood allergen sensitization only among children with non-allergic mothers in the Detroit WHEALS birth cohort.¹⁰⁷ Several methodological differences may have contributed to these discrepant findings including the use of a propensity score statistical analysis that reduces inherent imbalances in the distribution of baseline characteristics among the exposed and non-exposed populations as well as varied classifications of ETS exposure levels.

The data regarding potential associations of ETS to allergic disease (other than asthma) is also a matter of ongoing debate with little definitive prospective data published. A large cross-sectional study of nearly 7800 French children at age 10 that reported no impact on atopy from childhood exposure to parental smoking at any time from pregnancy forward did present evidence of inverse associations between maternal smoking (current and during pregnancy) with eczema and current ETS with hay fever.¹⁰⁸ However, the authors speculated that “reverse causation” could provide a plausible explanation for their findings.

Traffic Related Air Pollution (TRAP)

Motor vehicle traffic volume, resultant pollutant exposure and allergic disease prevalence have increased in parallel during recent decades. This has stimulated investigators to scrutinize the impact of traffic related air pollution (TRAP) on the development of allergy-related disorders. TRAP is a complex mixture of inhaled substances including carbon monoxide, nitrogen oxides (NO), benzene, sulfur dioxides, ozone and particulate matter (PM) with the primary source of vehicular PM being derived from diesel exhaust. The mechanism(s) responsible for potential associations of TRAP to atopy remain uncertain. However, experimental studies have demonstrated that diesel exhaust particle (DEP) exposure can increase symptoms in patients with established disease, enhance allergic inflammation, and induce the development of Th2- driven allergic immune responses.^{109–111} Specifically, polyaromatic hydrocarbons (a major component of DEPs) enhance IgE production.¹¹²

The evidence supporting a role for TRAP in the induction of allergic sensitization is mixed.¹¹³ Several early studies suggested linkage of atopy with exposure to nitrogen oxides,^{114,115} ozone,¹¹⁶ and PM,^{117,118} but other studies failed to find substantial associations between allergy and these same components.^{119,120} Factors that may explain the discrepant findings include varying and inefficient methods to approximate individual-level exposures and a limited ability to measure key qualitative variations in the composition of particulate air pollution.¹²¹ Recent prospective data from several European birth cohorts is reflective of the overall literature and these reports are summarized below.

Morgenstern and colleagues reported on data from GINI and LISA, two Munich-based birth cohorts.¹²² In this report, a complex exposure assessment method combining local air pollution measurement and the geographic proximity of the participant’s home to major roads was applied. The exposure variable included evaluating addresses for road proximity at birth and was adjusted with available data at ages 2, 3 and 6 years. At age 6 years, prior exposure to higher concentrations of PM_{2.5} (particles <2.5 µm) was associated with an

increased odds of sensitization to any of nine inhalant allergens (aOR=1.45, 95% CI 1.12–1.74). This finding was driven by pollen allergen sensitization (aOR=1.52, 95% CI 1.23–1.87) but not “indoor” allergens including cat, dog, dust mite, and mold. In addition, when compared to homes located more than 1000 meters from a major road, those living in closer proximity exhibited higher risk for sensitivity to pollens (within 250 meters) or any allergen (within 50 meters). They also reported associations between PM_{2.5} exposure and hay fever (aOR=1.59, 95% CI 1.11–2.27) and NO₂ exposure and physician diagnosed eczema (aOR=1.18, 95% CI 1.00–1.39).

Similar findings were found among a large prospective cohort of infants in Sweden where traffic-related pollutants exposure during the first year of life was associated with higher rates of pollen sensitization (sIgE) at age 4 years. This association was noted with both inhalable PM (OR=2.3, 95% CI [1.23–4.29) and traffic-related NOs (OR=1.67, 95% CI 1.1–2.5).¹²³ However, when the cohort was evaluated at age 8 years, the impact of these first year exposures on sensitization was no longer present.¹²⁴ However, new sensitization to food allergens with onset between the ages of 4 and 8 years was associated with exposure to NOs (aOR=2.30, 95% CI 1.10–4.82).

First and second year exposure to NO₂, PM_{2.5} and PM₁₀ were analyzed for associations with positive skin tests (10 allergens) among 9–10 year old participants in a Norwegian birth cohort.¹²⁵ No associations were found. Although lifetime pollutant exposure was marginally associated with higher rates of dust mite and cat sensitization, the effect appeared to diminish with adjustment for socioeconomic factors. Similarly, among 8 year old participants in the Dutch PIAMA birth cohort, no altered risk for allergen sensitization or eczema was apparent in association with estimated levels of exposure to soot, PM_{2.5} or NO₂ at their original birth address.¹²⁶ However, a higher rate of hay fever was associated with PM_{2.5} exposure among a subpopulation of children that had never moved from their birth address (aOR=1.43, 95% CI 1.01–2.04).

A soon-to-be-published meta-analysis of five large European birth cohorts (including several of the aforementioned studies) does not present any convincing associations between multiple measures of air pollution (PM_{2.5}, PM_{2.5-10}, PM₁₀, “blackness” of PM_{2.5} filters, NOs, traffic intensity and traffic load) either currently or at birth to common food or inhalant allergen sensitization among children up to 10 years of age.¹²⁷ Thus, there is conflicting data regarding potential associations of early life exposure to pollutants and the development of allergy. However, recent data suggest that studies that consider an individual’s genetic variation in response to oxidative stress as well as pollution exposure levels may further advance our understanding.¹²⁸

Future Considerations/Summary

We have summarized reports addressing potential linkage between early-life exposure to several factors and an altered risk for childhood allergy. However, previous and emerging data not discussed herein also suggest other potential factors that may modulate risk. A partial listing includes viruses, allergens, polyunsaturated fatty acids, antioxidants, a variety of specific medications and non-traffic related pollutants (e.g., bisphenol, endotoxin,

phthalates, PCBs, volatile organic compounds, etc.). Other exposures that are more difficult to quantify, such as stress and magnetic field exposure, have also been implicated in studies.

Although existing reports all have methodological limitations, we must properly leverage what we have learned from important epidemiological studies. While large cohort and cross-sectional studies based on questionnaire data help us to recognize patterns and associations, future longitudinal epidemiological cohort studies with enhanced and detailed exposure measurements and outcome classifications based on comprehensive clinical examinations are needed to more precisely assess true relationships. Use of disease phenotypes and endotypes will also improve our understanding of relationships with exposures.^{129,130} Challenges will persist in identifying modifiable risk factors; however, teams of scientists with diverse expertise in clinical care, epidemiology, statistics, microbiology, genetics and molecular science will be needed to work together to have the greatest impact on this critical area of investigation.

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Key Points

1. Brief summaries of several prenatal and early life risk factors that have been analyzed for potential associations with the development of childhood allergy are presented.
2. The results and conclusions from individual studies of a single risk factor are often conflicting and may be due to considerable variability in the specific allergy-related outcomes evaluated as well as the methods used to measure an individual's exposure to the risk factor.
3. Teams of scientists with diverse expertise are needed to work together to have the greatest impact on understanding risk factors for allergic diseases.