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Perinatal and Early Childhood Environmental Factors Influencing Allergic Asthma Immunopathogenesis

Jonathan M. Gaffin, MD, MMSc^{a,b}, Watcharoot Kanchongkittiphon^{c,d}, and Wanda Phipatanakul, MD, MS^{b,c}

^aDivision of Respiratory Diseases, Boston Children's Hospital, Boston, MA; USA ^bHarvard Medical School, Boston, MA, USA ^cDivision of Immunology, Boston Children's Hospital, Boston, MA, USA ^dDepartment of Pediatrics, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

Abstract

Background—The prevalence of asthma has increased dramatically over the past several decades. While hereditary factors are highly important, the rapid rise outstrips the pace of genomic variation. Great emphasis has been placed on potential modifiable early life exposures leading to childhood asthma.

Methods—We reviewed the recent medical literature for important studies discussing the role of the perinatal and early childhood exposures and the inception of childhood asthma.

Results and Discussion—Early life exposure to allergens (House dust mite (HDM), furred pets, cockroach, rodent and mold) air pollution (nitrogen dioxide (NO₂), ozone (O₃), volatile organic compounds (VOCs), and particulate matter (PM)) and viral respiratory tract infections (Respiratory syncytial virus (RSV) and human rhinovirus (hRV)) have been implicated in the development of asthma in high risk children. Conversely, exposure to microbial diversity in the perinatal period may diminish the development of atopy and asthma symptoms.

Introduction

Asthma is characterized by airway inflammation mediated through infiltration of eosinophils, neutrophils and mast cells in the airway wall and related airway smooth muscle constriction. Chronic and/or recurrent airway inflammation, mucous hypersecretion, and airway smooth muscle mediated bronchoconstriction conspire to create the airflow limitation, symptoms and signs of asthma.

The epidemic of childhood asthma over the past 30 years highlights the interplay of constitutive host factors with environmental exposures to lead to the development of asthma. In this review we describe the perinatal and early childhood environmental exposures implicated in the development of childhood asthma. We discuss the evidence and known or

Corresponding author: Wanda Phipatanakul, MD, MS, Division of Immunology, Fegan 6, Boston Children's Hospital, 300 Longwood Ave., Boston, MA 02115, USA, Phone: 617-355-6117, Fax: 617-730-0310, wanda.phipatanakul@childrens.harvard.edu, jonathan.gaffin@childrens.harvard.edu, champw@hotmail.com

proposed mechanisms supporting exposures in the respirable environment, early life infectious agents, and microbial gut colonization as it pertains to the development of asthma (schema, Figure 1). Finally we will discuss interventions in the early childhood period that may decrease or delay the inception of asthma.

Environmental Allergens

The allergic asthma phenotype dominates in early life. While a variety of ambient and indoor allergic exposures have been implicated in the development and exacerbation of childhood asthma, the indoor environment is of greatest epidemiologic interest. Infants and children spend the vast majority of their lives in the indoor environment of their home or daycare, are in close proximity to settled dust containing potential allergens, and explore the world through their oral cavity, enabling high level exposure of the physical environment to their mucous membranes and respiratory tract. The paradigm for allergen induction of asthma is from allergen exposure → allergic sensitization → asthma development.

There is a strong relationship between atopy and asthma development¹. Children sensitized to aeroallergens at a young age are likely to have persistent asthma symptoms into late childhood and adulthood and show poorer lung function than those not sensitized. House dust mite (HDM), furred pets, cockroach, rodent and mold, with regional variation, account for the large proportion of aeroallergens associated with sensitization and asthma². In many cases, exposure and sensitivity follow a dose-response relationship³⁻⁶. Evidence supporting this relationship is particularly strong for HDM^{4, 6} and cat⁷⁻¹⁰.

Several birth cohorts have demonstrated the relationship between early atopy and risk for childhood asthma¹¹⁻¹⁵. The Tucson birth cohort showed that early evidence of elevated total IgE and sensitization by skin prick test (SPT) to aeroallergens separates the population of persistent and late onset wheeze from those with early transient wheeze¹³. Children with atopy identified early in life have higher total IgE and larger wheal size compared to those sensitized later¹⁵ which may indicate a greater immunologic impact of earlier exposure to aeroallergens, though the same phenomenon is not seen in food allergy^{11, 16}. Data from the Western Australian Pregnancy Cohort Study confirmed the greater risk of asthma in children with atopy in infancy, independent of lower respiratory tract infections¹⁷.

Children of atopic parents demonstrate the strongest evidence of home allergen exposure and asthma development^{12, 16, 18-23}. Even in children without early wheezing, sensitization by skin prick test or elevated IgE are predictive of asthma at school age^{12, 13}. These associations between early atopy and asthma are carried through to early adulthood¹⁴. The Multicentre Asthma Study¹¹ punctuated the role of atopy in the development of asthma. Ninety percent of the children with non-atopic wheeze in early childhood had remission by age 13 years old compared to only 56% of the atopic wheeze group.

Atopy appears to mediate a large portion of the effect of early viral respiratory tract illness on asthma development, as well. Kusel, et al.¹² found that wheeze and current asthma at 5 years was associated with wheezy and/or febrile lower respiratory illness, but these findings were restricted to allergen-sensitized children under 2 years old. Likewise, Chan-Yeung, et

al.²³ found the strongest association between RSV and diagnosis of asthma at age 7 was in sensitized children.

While development of asthma has been clearly linked to early childhood atopy, the direct link to allergen exposures has been more variable^{4, 6, 8, 24}.

House Dust Mite

House dust mites are microscopic arachnids found in dust and products with woven material or stuffing such as mattresses, pillows, stuffed animals, and bedding²⁵. The most common species are *Dermatophagoides pteronyssinus* (Der p 1) and *Dermatophagoides farina* (Der f 1). Warmth and humidity greater than 50% are the major factors that promote dust mite growth.

Asthma development²⁶⁻²⁹, severity³⁰ and morbidity^{30, 31} have been strongly associated with HDM allergy. More than 50% of children and adolescents with asthma are sensitized to HDM³¹. HDM influences the development of asthma by exposure leading to sensitivity and subsequent asthma. There is strong evidence for a dose-response relationship of exposure to HDM and sensitization in both cross-sectional^{532, 33} and prospective studies^{4, 6, 34} though some studies have not supported this association^{926, 34} or the overall association with asthma development³⁴⁻³⁶.

Early work by Sporik et al.³⁴ demonstrated HDM exposure to be an important factor in the development of childhood asthma, particularly if exposed to high levels in the first year of life. The relative risk of asthma was almost 5-times greater in the subjects who were exposed to high levels of dust mite allergen (>10 µg/g). Tovey and colleagues⁶ showed a non-linear relationship between levels of HDM found in homes and the development of asthma at 5 years of age in a high risk cohort of children. The trends showed increasing prevalence of sensitization and asthma correlating with HDM exposure up to a critical point, achieving statistical significance, and then sharply dropping at the highest level of exposure (>23.40 µg Der p1/g dust). The implications of attenuated disease development with high levels of exposure are unclear, but may indicate high concentrations of non-allergenic immune modifiers such as endotoxin³⁷ and beta-glucans³⁸ that are known to accompany HDM. Celedon, et al.⁴ found a dose response relationship between levels of HDM allergen exposure in high risk infants at age 2 to 3 months and asthma at school age. In this study, the high allergen threshold was 10µg/g so the critical concentration found in Tovey's⁶ study may not have been seen. In addition to the implications for developing asthma, the development of sensitivity to HDM appears to predict poorer lung function than those not sensitized³¹. While the majority of evidence points to a causal relationship between early exposure to HDM, sensitization and asthma, some authors have failed to replicate these findings in general or high risk cohorts⁸.

Pet

Fel d 1, the major cat allergen, is primarily found in cat skin and hair follicles and is produced in sebaceous, anal and salivary glands. It can be carried on small airborne particles ranging from 1 µm to over 20 µm³⁹. Dog allergen, Can f 1, is found in hair, dander and saliva. Airborne levels and particle size distribution is similar to cat allergen. The small

particles of cat and dog allergen can scatter easily in the air and adhere to clothing for further dispersal^{40, 41}. These allergens are found in non-pet homes^{42, 43}, schools^{41, 44, 45} and public places⁴⁴. As such, similar prevalence of sensitivity is found in children who live with a cat and those who do not²⁸.

The Asthma Multicentre Infant Cohort Study⁷⁻⁹ presented data that strongly suggested cat allergen exposure is associated with the development of sensitivity and asthma. Exposure to cat allergen in the child's first 3 months of life demonstrated a dose-dependent relationship with sensitivity and asthma at age 6 years up to a plateau of 1µg fel d1/g of dust. Analysis of the high risk subgroup showed an even greater association with asthma diagnosis at 6 years old with odds ratio greater than 18. This association is corroborated by previously published data^{7, 29, 45}. In areas where HDM is low, dog and cat have been found to be the primary allergen associated with asthma⁴⁶. Increased exposure in sensitized individuals may lead to higher rates of asthma. However, a Norwegian study reported that cat exposure led to an increased risk of asthma by age 10, though did not necessitate sensitization, indicating a potential non-allergic mechanism⁴⁷.

As with HDM, there may be a non-linear exposure to sensitivity and subsequent asthma relationship^{5, 48}. In the German Multicentre Allergy Study⁴⁹ the infants exposed to the highest levels of cat allergen (fel d1) had decreased cat specific IgE levels and high IgG levels corresponding to a low risk phenotype for wheeze. Early exposure to cat has been found protective for asthma in other cohorts, as well^{50, 51, 53, 54} including an already atopic cohort with eczema⁵², though the presence of maternal atopy may adversely affect the risk⁵³.

Dog exposure and asthma is less studied. A meta-analysis by Takkouche, et al.⁵¹ noted a slightly increased, statistically significant, relative risk of asthma in pet owners, not taking into account allergic sensitization. Other birth cohort studies have not been suggestive of an association⁵³.

Pest

The German (*Blattella germanica*) and American (*Periplaneta americana*) cockroach are the most common species to cause allergies. The major allergens, Bla g 1, Bla g 2 and Per a 1, are found in the saliva, fecal material, secretions, cast skins, and debris³⁹. They briefly become airborne on large particles (>10 µm) and quickly settle to the ground. Low socioeconomic status, crowded homes and old buildings are risk factors for cockroach infestation.

Increased cockroach exposure leads to sensitization. The National Cooperative Inner-City Asthma Study (NCICAS), funded by the National Institute of Allergy and Infectious Diseases (NIAID) in the early 1990s, evaluated the home environment of over 1500 inner city children with asthma to determine the etiology of the inner city asthma epidemic. In a subset of 500 asthmatic children from NCICAS, Eggleston et al. demonstrated that the bedroom concentration of cockroach allergen was related to cockroach sensitization³. More recent work by Chew et al. showed the relationship to be dose responsive between inner-city home cockroach level and cockroach sensitization in children⁵⁴.

Several important studies have demonstrated the high prevalence of cockroach in the inner city, the high prevalence of sensitization and relationship between the exposure and poor asthma outcomes in children^{55, 56}. Exposure has been shown to increase the risk of wheeze in children of atopic⁵⁷ and non-atopic parents⁵⁸ in longitudinal studies. Though controversial²⁴, this effect has been seen in both sensitized and non-sensitized children⁵⁹, potentially pointing to non-allergic mechanisms of disease inception.

Biological evidence supports that exposure in the neonatal period can influence the allergy development. Exposure to elevated levels of cockroach allergen at 3 months of life is correlated with T-cell mediated allergic response to cockroach allergen at 2 years of age⁶⁰. Clinically, a dose response relationship has been shown between cockroach allergen exposure and asthma and recurrent wheezing outcomes in high risk children⁶¹.

Mouse

Mus m1 and Mus m2, the major mouse allergens, are found in mouse urine, hair follicles and dander⁶² and carried on particles. They are found in homes with and without mice infestation as they easily migrate on dust particles⁶³. Factors that increase mouse infestation are high population density, clutter and integrity of the home, making older high rise apartments and multifamily dwellings at risk. It is one of the few allergens to span environments from inner city to suburban homes and schools⁶⁴⁻⁶⁶.

Phipatanakul et al. demonstrated that in subjects from the NCICAS, homes with higher mouse allergen concentrations had significantly higher rates of mouse sensitization⁶⁷. In sensitized individuals, exposure affects clinical asthma outcomes^{62, 67, 68}, however a direct link from exposure to asthma development is less clear. Our analysis of data from the Boston Home Allergens and Asthma Study⁶⁹, which included 500 infants of atopic parents, showed significant association between current mouse exposure and current wheeze through 7 years of age, however early exposure at 2-3 months did not predict wheeze or asthma at 7 years. A separate inner city birth cohort study found that wheezing at age 3 years was significantly associated with mouse or cockroach (or both) sensitized children which may be an indication that an allergic sensitization and development of asthma relationship does exist for mouse exposure⁵⁸. Mouse exposure may act as a respiratory irritant⁷⁰, however the association between early exposure and later atopy argues for an allergic sensitization pathway⁶⁹. More research into the role of mouse exposure in the development of asthma is needed.

Timing of Sensitization

Though early sensitization to perennial allergens is associated with asthma in school-age children, debate continues over the actual timing of sensitization.

While there is evidence for T-cell priming *in utero* for maternal vaccination and fetal viral infection, it is likely that the immunogenicity of aeroallergens that could potentially pass through the placental circulation is too weak to produce specific allergic immune response in the fetus^{71, 72}. Evidence for *in utero* sensitization⁷³ has largely been refuted due to the lack

of evidence of allergen specific cytokine and IgE proliferation, relation to exposed allergens⁷⁴ and correlation with childhood sensitization⁷⁵.

Estimates for the critical period within which allergic sensitization leads to asthma range from birth to 8 years^{4, 11, 16, 76-78}. Elevated IgE levels at 6 months of age predict future allergic sensitization⁷⁵ and at 9 months of age are associated with persistent asthma¹³. Kusel, et al.¹² found significant asthma outcomes in children who were sensitized by age 2 years old. This is further supported by laboratory evidence of strong TH2 cytokine response in 11 year olds who showed atopy early in life⁷⁹. Recent evidence, however, suggests that some children may develop transient sensitization. Weber-Chrysochoou, et al. demonstrated that T-cell induced IL-5 proliferation in response to allergen in 18 month olds neither predicted asthma nor was repeatable at age 3 and 5 years⁷⁸.

Air pollution

The steady increase in the prevalence of asthma in westernized countries also shares the trajectory of increasing air pollution and population trends towards urban centers. Air pollution, both in the ambient environment and the indoor environment have been associated with a variety of adverse cardiopulmonary health effects. The pollutants best studied are the gases nitrogen dioxide (NO₂), ozone (O₃), volatile organic compounds (VOCs), and particulate matter (PM) that comprises soot.

While ambient pollutants have been associated with asthma symptoms, exacerbations and decline in lung function⁸⁰⁻⁸², recent evidence has demonstrated elevated pollution exposure *in utero* and in the first year of life may influence the development of asthma in young children⁸³. Indoor air pollution is likely more important than the ambient exposure due to indoor sources and resuspension of particulate pollutants with activity⁸⁴. Exposure to indoor sources of PM_{2.5} and VOCs is directly correlated with FeNO in schoolchildren with and without asthma, indicating potential induction of allergic airway inflammation with these exposures⁸⁵.

These pollutants may act as independent aggravators of the airway epithelium and exert their effects by oxidative injury or direct toxic effects⁸⁶. In addition, particulate matter is known to have adherent allergen particles, making it an easy conduit for allergen-induced airway inflammation in sensitized individuals. Finally, many of these pollutant exposures have been shown to be associated with increased allergic sensitization⁸⁷ raising the possibility of an adjuvant effect on the local allergens⁸⁸. Despite these proposed mechanisms, a recent controlled human subject investigation failed to find convincing evidence of diesel exhaust exposure on allergic airways inflammation in asthmatics, though a slight eosinophil and IL-4 signal may have suggested such a relationship⁸⁹. Some evidence suggests that perhaps air pollution mediates immunologic response and asthma through epigenetic mechanisms. A cross-sectional case control study comparing high and low pollution exposure among children with and without asthma demonstrated that increased exposure to ambient pollution was associated with hypermethylation of the Forkhead box transcription factor 3 (Foxp3) and interferon gamma (IFN- γ) genes leading to impaired regulatory T cell function,

decreased IFN- γ , and associated increasing asthma morbidity^{90, 91}. Further research on the gene-environment determinants and mechanisms of disease are needed.

Nitrogen Dioxide and Ozone

Nitrogen dioxide (NO₂) is a gaseous pollutant found in both the ambient and indoor environment. It is emitted by automobile exhaust, fossil fuel combustion and power plants, leading to the majority of ambient exposure, while indoor home exposures are more commonly due to gas cooking and heating. It has been shown to have a dose-dependent association with incident asthma and wheeze in unselected populations⁹². Recent evidence further links in utero and infancy exposure to the development of childhood asthma⁸³. In children with asthma, exposure to NO₂ has been shown to worsen asthma control based on symptoms and lung function⁹³⁻⁹⁶. It also has a synergistic effect with allergen exposures to elicit airway inflammation and symptoms in allergen-sensitized individuals⁹⁷⁻¹⁰⁰. Mouse models of asthma have shown prolonged allergen induced airway reactivity and augmentation of eosinophilic airway inflammation in the presence of NO₂¹⁰¹.

Nitrogen dioxide and ozone are chief determinants of urban smog via the chemical reaction in ambient air between emitted hydrocarbons and nitrogen oxides from industrial or traffic related sources (USEPA 2006). Bayram et al. demonstrated release of IL-8 and soluble intercellular adhesion molecule 1 (sICAM-1) from human bronchial epithelial cells from non-asthmatic subjects and a greater release of these factors plus GM-CSF and RANTES in response to incubation with O₃ and NO₂.¹⁰² Non-asthmatic and asthmatic airway responses to exposure are likely due to the release of these inflammatory mediators in vivo, with greater response in susceptible hosts. Ozone exposure has also shown to have a dose dependent relationship with intracellular reactive oxygen species and may create susceptibility to inhaled toxins or allergens by creating an environment of epithelial cell permeability¹⁰³. Downstream effects of this disruption of epithelial cell integrity may promote pro-inflammatory mediators, including eicosanoids, cytokines, and adhesion molecules in the airways¹⁰⁴. Newborn rat studies have demonstrated an increase in airway sensory nerves that is associated with later susceptibility to airway reactivity in adulthood¹⁰⁵. This has also been seen in primate models along with the potentiating effect of chronic allergen exposure on nerve distribution¹⁰⁶. The effects of ozone on airway pathology and asthma likely depends on the dose, timing of exposure and relationship with allergens and antigens in the appropriate host¹⁰⁷ and further research is needed to disentangle these relationships.

Particulate Matter

Particulate air pollution (particulate matter, PM) is found in traffic-related and industrial combustion, as well as indoor sources such as cooking exhaust and environmental tobacco smoke^{84, 108}. Fine particles (PM_{2.5}) 2.5 μ m are primarily produced by industrial or motor vehicle combustion and are able to enter the respiratory tract and deposit in the alveoli¹⁰⁹. Fine particles affect respiratory symptoms in children with asthma^{110, 111}. Ambient PM_{2.5} tends to be regionally distributed, however, the black carbon component (7-10%)¹¹² is a particularly sensitive marker for local traffic related pollution¹¹³ and has more spatial variability in the urban setting^{114, 115}. Large epidemiologic studies have tied the

concentration of traffic related air pollution, largely PM_{2.5}, with asthma, hay fever and sensitization to pollen^{116, 117}. Exposure in the first year of life may be the most important determinant of relationship to increased atopic outcomes^{83, 118}. The exact mechanisms of susceptibility in humans have not been fully elucidated, but may be related to innate immune mechanisms as polymorphisms in the tumor necrosis factor (TNF) and toll-like receptor (TLR) 2 & 4 alleles may invoke higher risk of atopic manifestation in conjunction with traffic related pollution exposure^{119, 120}. In human epidemiologic studies it is difficult to parse the many types of ambient and indoor pollutants that may be responsible for the direct immune effects or adjuvant effects with allergen exposures, however in vitro data suggests that the adjuvant effects are driven by the oxidant potential of the exposure leading to eosinophilic infiltration of the airways and mucoid hyperplasia of the respiratory epithelium⁸⁸. Tissue culture of dendritic cells also demonstrates diesel exhaust (at levels found in highway tunnels) directs a Th2-like cytokine response¹²¹ indicating a likely mechanism of allergic immunopathogenesis related to this exposure.

Volatile Organic Compounds

Volatile organic compounds (VOCs) are present in many materials used in household products, solvents, cigarette smoking and pesticides¹²². Frequent use of household aerosols containing VOCs has been shown to lead to 40-50% increase in wheeze and asthma symptoms in adults¹⁰⁸. A case control study by Rumchev et al. demonstrated incident asthma exacerbations with a dose response relative to home exposure to benzene and toluene¹²³. Mechanisms related to allergic diseases were evaluated in the Leipsig Allergy Risk Children Study¹²⁴ and demonstrated differential T cell polarization in children exposed to VOCs in their homes. Children demonstrated reduced numbers of CD8+ peripheral T cells, and higher percentages of IL-4 producing T cells. These findings have been corroborated by cord blood assays in neonates whose mothers were exposed to similar VOC containing products¹²⁵.

Environmental Tobacco Smoke

Environmental tobacco smoke (ETS) is an independent determinant of the development of asthma¹²⁶⁻¹²⁸. Tobacco smoke contains many VOCs and NO₂, which are likely to serve as the conduits to poor respiratory outcomes. In vivo studies also suggest that exposure to ETS is associated with IL-13 and greater serum IgE in children with asthma compared to non-exposed asthmatic children and controls, suggesting an augmentation of the Th2 immunophenotype with exposure¹²⁹.

Infections

Infantile viral infections have long been associated with the development of asthma. The relationship is complicated by the interaction between host and viral infection raising the question of whether children destined to develop asthma suffer disproportionately severe respiratory viral infections early in life or do viral infections stimulate an immunopathologic cascade of events that proceeds to asthma. All children are affected by multiple viral infections early in life. Viral infections are the primary etiology of wheezing illnesses in

infants and preschool aged children, and nearly half of all children will have a wheezy respiratory viral illness before 6 years of age¹³.

Respiratory syncytial virus (RSV) and human rhinovirus (RV) are the most common viruses associated with infantile bronchiolitis and lower respiratory tract infections^{130, 131}. They have drawn the greatest focus as an early life determinant of subsequent asthma development^{130, 132}. Moreover, even though children suffering from wheezy RV infection seem to have a much greater risk of asthma compared to RSV bronchiolitis, the dominance of bronchiolitis during the RSV season may lead to greater number of cases with associated asthma¹³³.

There is a strong association between bronchiolitis in the first year of life and the development of asthma^{134, 135}. RSV is the major cause of bronchiolitis in the first year of life¹³³. It is the leading cause of hospitalizations in infants¹³⁶ and is independently predictive of recurrent wheeze¹³² and early childhood asthma^{132, 134, 137, 138}. RSV bronchiolitis is predictive of asthma even in children without severe bronchiolitis^{130, 135}. One-third of term infants with maternal history of asthma who develop bronchiolitis go on to develop asthma, regardless of bronchiolitis severity¹³⁵.

Ecological data for a causative role of RSV in the development of asthma has been cultivated by Wu and colleagues¹³⁴ pointing to the variation in childhood asthma rates mirroring the timing of infant birth relative to RSV season. If the severe RSV was simply a marker of future asthmatics, the population incidence of asthma should remain stable independent of the timing of birth related to RSV season.

Mechanistically, there is evidence that a single RSV infection has the capacity to cause acute and chronic changes on airway epithelium, produce cytokine precursors, impact dendritic cells that may mediate airway neural pathways, and cause lasting immunomodulatory changes consistent with the asthma phenotype¹³⁹⁻¹⁴¹. Furthermore, the use of Palivizumab, a monoclonal antibody directed at RSV which significantly decrease the severity of RSV bronchiolitis in preterm infants^{142, 143}, has been related to lower rates of asthma development in some studies. Two case control studies have shown efficacy in mitigating long term respiratory outcomes when preterm children received preventive RSV immunoglobulin preparations^{144, 145}. A 7 – 10 year follow up of one group of preterm children showed significantly better measures of airway obstruction, measured by FEV₁/FVC ratio, and asthma morbidity¹⁴⁵. In this small sample, there was no difference in the diagnosis of asthma, however, a nonsignificant, consistent trend in regular use of bronchodilator and inhaled corticosteroid suggested a milder phenotype in the treatment group. Palivizumab decreased the prevalence of physician diagnosed recurrent wheeze by 50% in a cohort of high risk children who were not hospitalized for RSV infection compared to a gestational- and chronological age matched control group¹⁴⁴. This protective effect was preserved even when compared to a control group that was not hospitalized for bronchiolitis, suggesting that even in children with mild or no RSV infection, it is still protective against subsequent recurrent wheeze.

Despite this plausible evidence for a causal role of early life RSV infection leading to subsequent asthma, a Danish population-based twin study found a bidirectional association between severe RSV infection and asthma suggesting that a common predisposing etiologic factor for both conditions may be invoked rather than a true causal relationship¹⁴⁶.

Rhinovirus

Modern diagnostic methods have led to an explosion of literature highlighting the importance of RV lower respiratory tract illnesses (LRTIs) in asthma development. Children hospitalized with RV before 2 years of age are four times more likely to develop asthma than children hospitalized with LRTIs not associated with rhinovirus¹⁴⁷. The Childhood Origins of Asthma (COAST) study found RV wheezing illnesses in the first year of life as a significant predictor of wheezing in the third year of life and asthma at school age in the recruited high risk birth cohort^{130, 148}. In a similar Australian birth cohort from parents with at least one form of atopy, RV in infancy was found to be predictive of current asthma at 5 years, though these findings were restricted to children with evidence of allergic sensitization by 2 years of age¹⁴⁹. This finding was echoed in the COAST study as the highest risk of subsequent asthma was found in those children with RV infection and aeroallergen sensitization¹⁴⁸. Additionally, there was an association between eczema and RV infection in COAST that further complicates the determination of whether causation can be assumed or if atopic children are at higher risk for wheeze with rhinovirus infections.

Mechanistically, in vitro studies of RV infection have demonstrated increased production of mediators of airway remodeling, including, amphiregulin, activin A and vascular endothelial growth factor (VEGF)¹⁵⁰. The VEGF upregulation was mirrored in vivo by nasal sampling in confirmed natural infection¹⁵⁰. Gene based approaches have implicated several immune pathways involved in RV infection, most notably interferon pathways^{151, 152}. In vivo studies have further implicated interferon pathways, specifically low interferon γ (IFN γ) at the time of birth¹⁵³ and infancy¹⁵⁴ in conjunction with increased wheeze in infancy and early childhood.

While the mechanism still needs to be worked out, evidence exists for an inverse correlation between the Fc ϵ R1, the high affinity surface receptor for IgE, on dendritic cells and level of IFN- α release in the setting of viral infection^{155, 156}. Evidence also points to common mediators to allergy and viral illness that are derived from the respiratory epithelium. As recently reviewed by Gavalá¹⁵⁷ et al. “alarmins” including thymic stromal lymphopoietin (TSLP), interleukin (IL)-33 and IL-25 elicited by both agonists alter the balance of innate lymphoid cells and regulatory T cells.

In summary, the epidemiologic data associating RSV and RV with asthma are compelling. However, despite evidence for several potential immunologic pathways for the induction of asthma following infection, the definitive causal relationship is still unclear. Independence from atopic predisposition will be difficult to disentangle.

Microbiome

Since the early 2000s the inverse relationship between farming, particularly traditional dairy farming lifestyle, and the development of asthma has been demonstrated. This relationship is seen early in life and appears to hold true well into adulthood¹⁵⁸. *In utero* and early life exposure to this environment seems to be the key temporal relationship. Evidence suggests a clear augmentation of innate immune function and regulatory T cell function as well as lower Th2 cytokine production in children whose mothers were pregnant in the farming environment^{159, 160}. *In vitro* models are currently working to define which microbial community attributes are important and which immune cells are affected^{161, 162}

A child's contact with cows, straw, and farm milk accounts for the entirety of the protective effect of farm living on the development of asthma¹⁶³. In this cohort, children living on farms also had reduced rates of sensitization and other atopic conditions, but interestingly, these could not be completely explained by the same specific exposures. Farm studies have implicated the rich diversity of microbial exposure both in the animal and home environments are strongly and inversely associated with asthma, implying that the early and persistent microbial environment influences the development of the immune system away from allergic and asthmatic predisposition¹⁶⁴.

In conjunction with these findings of the environmental microbial diversity affecting asthma development, the microbial characteristics of the gut have gained great attention in relation to allergic diseases and asthma. The neonatal gut microbial environment may be significantly affected by route of delivery, exposure to *in utero* or neonatal antibiotics, perinatal stress, use of probiotics, and breastfeeding¹⁶⁵. Birth by c-section has been reported to be associated with childhood asthma across multiple analyses^{166, 167}. Birth passage through the vaginal canal exposes infants to resident vaginal and fecal microbes of the mother which is reflected in their own gut flora. Children born by c-section tend to have delayed colonization with similar flora¹⁶⁸ and instead are colonized with the bacteria of maternal skin¹⁶⁹. Van Nimwegen and colleagues recently reported that children colonized with *Clostridium difficile* at 1 month of age were significantly more likely to suffer from wheeze or asthma through early school age. In children born to atopic parents, there was a 50% reduction in the risk of asthma if the child was born vaginally at home compared to in-hospital vaginal delivery¹⁷⁰. The intestinal microbiome likely influences the immune system in a manner similar to that related to farm exposure, however greater delineation of the mechanism is needed¹⁷¹.

Prevention of Asthma

Perhaps the most convincing evidence for early life environmental exposures influencing the development of asthma would be from randomized controlled interventions to specifically remediate the offending agent and demonstrate lower incidence of asthma development.

Allergen remediation

Allergen remediation strategies¹⁷² directed at cat, dog¹⁷³, mold, mouse¹⁷⁴ and cockroach^{175, 176} can substantially decrease exposure levels in homes. Interventions to

reduce HDM alone¹⁷⁷⁻¹⁷⁹ have been effective and seem to improve early outcomes. However, long term analyses of single HDM-directed interventions have not prevented allergy and asthma^{78, 180}.

Recent meta-analyses have shown multifaceted allergen remediation programs to be protective^{181, 182} against the development of asthma with 20-50% reduction in odds^{172, 173}, though other studies have been disappointing^{77, 183}. The most protective effect was seen in children with greater than 5 years of follow-up¹⁸², indicating a true decrease in risk to those prone to develop atopic asthma. Macdonald, et al.¹⁸¹ found that the decrease in physician diagnosed asthma did not carry over to the outcome of parental report of wheeze raising the question of whether there was mitigation of severity rather than prevention of disease. Those without physician diagnosis may not have presented with such significant symptoms to warrant asthma diagnosis.

The best preventative effect of allergen avoidance was the Canadian Childhood Asthma Primary Prevention Study¹⁸⁴, a multifaceted intervention randomized controlled trial in a high risk birth cohort. In this study, the intervention was avoidance of house dust mite, pets, and environmental tobacco smoke starting prenatally, and encouragement of breastfeeding with delayed introduction of solids. HDM interventions included encasing parents' and infants' mattresses and box springs, weekly hot water wash of all bedding and application of benzyl benzoate to carpets and upholstery before birth and at 4 and 8 months of age. Children receiving the intervention had significantly less physician diagnoses of asthma, wheeze in the past 12 months and wheeze apart from colds when evaluated at age 7 years. The protective effect on physician diagnosed asthma was a relative risk of 0.44 (95% CI 0.25-0.79; P=0.006). Interestingly, there was no difference between the groups for the outcome of atopy despite reduced allergen levels during the intervention¹⁸⁵. Arshad, et al.¹⁸⁶ also observed significantly fewer asthma symptoms at age 8 years old in a high risk birth cohort intervention focused on HDM and food allergen avoidance in early life, but this cohort did show a significant decrease in atopy at the 8 year time point.

Intervention studies of this kind have many limitations. First, while allergen reduction is achievable^{183, 187}, the level of reduction may not be low enough to avoid an allergen mediated immune reaction¹⁸⁸. Second, several prospective studies used educational programs to enforce their interventions, rather than providing the intervention, which may have allowed for suboptimal adoption of the stringent avoidance regimens¹⁸⁹. Finally, in high risk cohorts it is likely that control group families actively avoid allergen exposures as a consequence of public knowledge or allergies affecting other family members. Acknowledging these limitations, the body of evidence supports multifaceted avoidance strategies in high risk individuals, though the direct biologic affect remains to be elucidated.

Antiviral therapies

In preterm infants without bronchopulmonary dysplasia, Palivizumab, a monoclonal antibody against RSV, reduces respiratory morbidity up to 78%¹⁴². Recent findings in late preterm children without BPD suggests that prophylaxis through infancy may decrease recurrent wheeze in the first year of life by 10%¹⁹⁰ and by up to 50% at three years of

age^{144, 191}, an effect dominated by the children of non-atopic parents¹⁹². While encouraging, further longitudinal studies are necessary to evaluate the effect of palivizumab prophylaxis to decrease the incidence of asthma in childhood.

Recent evidence suggests that anti-allergen immunotherapy to cross-link the FcεR1 receptor may diminish viral induced asthma symptoms¹⁵⁶. However, there are no studies, to date, investigating how Omalizumab, an FDA approved anti-IgE monoclonal antibody, may prevent or delay the onset of asthma.

Probiotics

Early studies on the effect of probiotics to affect asthma development by influencing the perinatal microbiome have been mixed. A recent meta-analysis by Elazab et al. found significant decrease in the risk of atopic sensitization associated with pre and post-natal administration of probiotics, however there was no effect on asthma or wheeze¹⁹³. A birth cohort study subsequently published also found no effect of probiotic infused milk product consumption and asthma at 3 years of age¹⁹⁴.

While alterations of the physical environment have been studied, little attention has been given to the approach of altering the immune constitution of high risk individuals. In this respect, immunomodulators, such as Omalizumab may be of future interest.

Conclusions

Perinatal and early childhood environmental exposures may promote (or prevent) the subsequent development of childhood asthma by mechanisms centered on airway injury and immunologic programming. Environmental allergens are the best studied of these exposures, however a significant body of evidence is growing in support of elevated risk of perinatal exposure to indoor air pollution, viral infection, and a potentially lower risk of atopy with exposure to a diverse microbiome.

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Figure 1.

The potential consequences of early childhood environmental exposures on the development of asthma in genetically predisposed children.