

Potential Strategies and Targets for the Prevention of Pediatric Asthma



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KEYWORDS

• Asthma • Prevention • Microbiome • Vitamin D

KEY POINTS

- Exposure to a diverse microbial environment is likely protective versus asthma development, with a “critical window” of opportunity to alter the host microbiome in early infancy.
- Fetal exposure to appropriate amounts of vitamin D or fish oil could prevent recurrent wheeze or asthma.
- Modification of the host response to allergens via allergen immunotherapy may help to prevent asthma, although the duration of the effect is unclear.
- Prevention of viral respiratory tract infections shows promise for asthma prevention.

INTRODUCTION

Asthma is the most common chronic disease of childhood, resulting in missed school days and significant social and economic burden for both families and the health care system.^{1–3} Identification of potentially modifiable environmental and host risk factors for asthma development (**Fig. 1**) has allowed for the beginning of a paradigm shift from disease treatment toward primary asthma prevention, and studies are underway to determine how best to prevent the development of asthma in children. This article reviews the effect of environmental exposures, host factors, and treatment of viral illnesses on the evolution of childhood asthma; summarizes successful primary prevention strategies; and identifies future areas of need.

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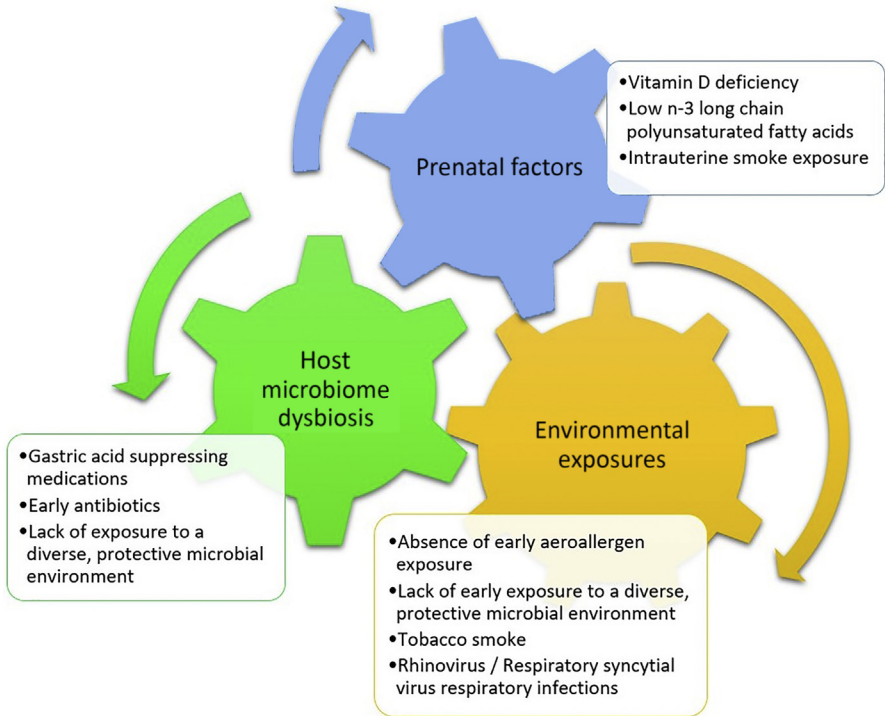


Fig. 1. Factors associated with an increased risk of asthma development.

MODIFIABLE ENVIRONMENTAL EXPOSURES: AEROALLERGENS AND ENVIRONMENTAL TOBACCO SMOKE

Multiple epidemiologic studies have demonstrated significant correlations between irritant and aeroallergen exposures, or lack thereof, and the subsequent development of recurrent wheeze or asthma in children.^{4–6} Asthma prevalence is notably higher in developed countries, suggesting that the identification and alteration of modifiable environmental risk factors could decrease the risk of developing asthma. Although earlier studies yielded conflicting results regarding early aeroallergen exposure and asthma development, current data suggest that exposure to high levels of concomitant allergens and diverse environmental bacteria in the first year of life among high-risk children growing up in an urban environment is associated with reduced likelihoods of recurrent wheeze and asthma at ages 3 and 7 years.^{4,7} Rural farming environments rich in microbes and aeroallergens also seem to be protective for asthma, allergic rhinitis (AR), and atopic sensitization.⁸

To evaluate the effects of the urban environment on asthma development, the Inner-City Asthma Consortium initiated the Urban Environment and Childhood Asthma study, an ongoing birth cohort assessing the factors associated with asthma development among inner-city children with at least 1 atopic parent.⁹ Higher indoor levels of cockroach, mouse, and cat allergens during infancy were associated with a lower risk of asthma development at age 7 years,⁴ suggesting that early indoor allergen avoidance is unlikely to be an effective strategy to reduce asthma prevalence, at least among inner-city children.

Environmental tobacco smoke exposure, including during the prenatal period, has been identified as another independent predictor of asthma development among

the Urban Environment and Childhood Asthma cohort; children with higher levels of umbilical cord cotinine were at heightened risk of developing asthma.⁴ A 2012 meta-analysis of 79 prospective studies concluded that prenatal or postnatal passive smoke exposure is associated with a 30% to 70% increased risk of incident wheeze in children (odds ratio, 1.7 in children aged ≤ 2 years; 95% confidence interval, 1.35–2.53) and a 21% to 85% increase in incident asthma (odds ratio, 1.85 in children aged ≤ 2 years; 95% confidence interval, 1.24–2.35).⁵ Recently, a systematic review of 2 population-based birth cohorts demonstrated that smoke exposure at any age is associated with impaired lung function associated with persistent wheeze and asthma.⁶ These results strongly suggest that interventions to decrease prenatal and postnatal smoke exposure may reduce asthma incidence and improve lung function in children.

HYGIENE HYPOTHESIS AND MICROBIOME DYSBIOSIS

The “hygiene” or “old friends” hypothesis postulates that decreased contact with microbial pathogens early in life leads to immune tolerance defects, resulting in heightened susceptibility to atopic disorders.¹⁰ Early life exposures, including antibiotics, formula feeding, and gastric acid suppressive medications, may modify commensal intestinal microflora, causing dysbiosis and subsequent redirection toward a proallergic and proasthmatic T helper 2 phenotype.^{11,12} Acid-suppressing medications decrease the digestion of proteins and may affect antigen processing. A recent cohort study of almost 800,000 children found positive associations between the use of gastric acid-reducing medications in the first 6 months of life and subsequent asthma (adjusted hazard ratio, 1.25 [95% confidence interval, 1.21–1.29] for H2 receptor blockers; adjusted hazard ratio, 1.41 [95% confidence interval, 1.31–1.52] for proton pump inhibitors). In the same study, antibiotic use in the first 6 months of life was associated with a 2-fold increased risk of childhood asthma (adjusted hazard ratio, 2.09; 95% confidence interval, 1.29–1.40).¹¹

Increasing evidence supports a key association between respiratory and gastrointestinal microbiota and asthma, with notable differences in the microbiota between asthmatic and nonasthmatic individuals.^{13,14}

Although previously thought to be relatively devoid of bacteria, sequencing of 16S ribosomal RNA has facilitated the discovery of a diverse microbial population within the human lower respiratory tract.¹⁵ The respiratory microbiome changes throughout the first few years of life, reaching an adultlike composition around the age of 3, although neonates nasopharyngeally colonized with *Streptococcus pneumoniae*, *Haemophilus influenzae*, and/or *Moraxella catarrhalis* at just 1 month of age are at 2 to 4 times greater risk for recurrent wheeze and asthma.^{16,17} Examination of the lung microbiota of asthmatic patients consistently reveals more proteobacteria including *H influenzae*, *Pseudomonas*, *Neisseria*, and *Burkholderia* than in nonasthmatic individuals, independent of age, asthma severity, or treatment with corticosteroids.^{13,18} Therapeutic strategies targeting the airway microbiome could be potentially valuable in asthma prevention, though this has not yet been pursued.

The influence of the gut microbiome on atopy development is an ongoing area of study, with evidence of a “critical window” in which intestinal dysbiosis perhaps irreversibly alters human immune development.¹⁹ Perinatal antibiotic exposure is associated with higher serum IgE levels and fewer colon regulatory T cells in murine models,²⁰ and infants at risk of asthma have transient intestinal dysbiosis in the first 100 days of life that is not apparent at 1 year of age, suggesting that prenatal or neonatal intervention is crucial if modification of this dysbiotic state is targeted as

an intervention to prevent asthma.²¹ A study of 319 children enrolled in the Canadian Healthy Infant Longitudinal Development (CHILD) cohort found a significant reduction in the abundance of 4 genera—*Faecalibacterium*, *Lachnospira*, *Veillonella*, and *Rothia* (collectively termed FLVR)—in the stool of children who went on to develop atopic wheezing. Upon inoculation with FLVR, germ-free mice produced offspring with significantly reduced airway inflammation, implying a causal role of these 4 genera in protection from asthma.²¹ Although there is no evidence to date for a protective effect of infant or maternal probiotic administration with either *Lactobacillus* or *Bifidobacterium* genera on the development of incident wheeze or lower respiratory tract infection (RTI) in infants,²² perhaps supplementation with the FLVR genera could reduce the risk of asthma.

A striking example of the hygiene hypothesis is the farm effect, a well-studied phenomenon wherein children residing on farms have a significantly lower risk of recurrent wheeze and asthma, with a protective effect related to the diversity of microbial exposure.^{17,23,24} To determine the effect of a traditional farming environment on immune response, a landmark 2016 study evaluated environmental exposures and immune profiles of children in distinct US Amish and Hutterite agricultural populations.²⁵ Despite similarities in lifestyle and genetic ancestry, Amish children have a strikingly lower prevalence of asthma and allergic sensitization relative to Hutterite children²⁶; compared with Hutterites' large, industrialized farms, the Amish live on single dairy farms and use livestock for transportation. The authors found differences in microbial dust composition, significantly higher endotoxin levels in Amish house dust (6.8 times that of Hutterite homes), and profound disparities in innate immune cell phenotype and function between the 2 populations.²⁵ Interestingly, a subsequent analysis showed that, in a mouse model, inhalation of Hutterite barn dust can inhibit allergen-induced airway hyperresponsiveness and specific IgE. Overall, these findings suggest that Hutterite children perhaps lack early access to protective exposures, although specific protective microbes were not identified.

These findings may be generalizable to a larger and more diverse population, because aeroallergen concentration is directly correlated with differences in house dust microbiota in the Urban Environment and Childhood Asthma inner-city cohort discussed elsewhere in this article.^{4,9} The homes of children who did not develop asthma more often contained *Kocuria*, an organism known to produce a macrolide with activity against *Staphylococcus* species, and *Bifidobacterium* and *Acinetobacter*, both of which protect against aeroallergen sensitization in mouse models.^{27,28} In contrast, homes with a child who developed asthma were more likely to be enriched with the taxa *Staphylococcus*, *Haemophilus*, *Corynebacterium*, and *Sphingomonas*.⁴ These disparities suggest that modification of environmental bacterial exposures in early life may influence the risk of asthma development, presumably through modification of the child's gastrointestinal and airway microbiomes.

EFFECTS OF MATERNAL DIET AND NUTRITIONAL SUPPLEMENTATION

Another factor is the westernized lifestyle, with increased time spent indoors and a diet dominated by processed, modified foods generally deficient in vitamins and minerals.²⁹ Increasing evidence points to the effect of the maternal diet on susceptibility to atopic disorders, raising the possibility that altering the prenatal diet is a potentially effective and inexpensive method of primary prevention for multiple inflammatory diseases.³⁰ The strongest data linking maternal dietary supplementation and asthma prevention exist for maternal vitamin D and fish oil, with limited data on folate.

Vitamin D has beneficial effects on innate and adaptive immunity, and maternal vitamin D is involved in fetal immune system development and lung maturation.^{31,32} Vitamin D deficiency has long been proposed as a risk factor for asthma, and the recent increase in the prevalence of vitamin D deficiency mirrors the increase in asthma.³³ Higher maternal vitamin D intake is associated with reduced rates of recurrent wheeze in early childhood.^{34,35}

Although a metaanalysis of 34 observational studies concluded that significant evidence does not exist to support an impact of vitamin D supplementation on asthma,³⁶ randomized controlled trials have yielded encouraging results. A study of 623 women from the Copenhagen Prospective Studies on Asthma (COPSAC₂₀₁₀) cohort randomized women to receive either 2400 or 400 IU vitamin D from 24 weeks' gestation through delivery. Children born to mothers receiving the higher dose of vitamin D had nonsignificant but lower risk of persistent wheeze (hazard ratio, 0.76; 95% confidence interval, 0.52–1.12).³⁷ Similarly, the Vitamin D Antenatal Asthma Reduction Trial (VDAART) randomized 881 pregnant women at risk of having a child with asthma to either 4400 or 400 IU vitamin D daily starting at 10 to 18 weeks' gestation. The incidence of asthma or recurrent wheeze by age 3 years was 6.1% lower in children of women who received 4400 IU daily, although statistical significance was not attained ($P = .051$).³⁸ A follow-up study showed that children of mothers with an initial vitamin D level of greater than 30 ng/mL who were randomized to the intervention group had a significantly lower risk of asthma or recurrent wheeze by age 3 years (adjusted odds ratio, 0.42; 95% confidence interval, 0.19–0.91) compared with those with initial levels of less than 20 ng/mL randomized to placebo, suggesting that adequate vitamin D levels as early as in the first trimester (and potentially before conception), and maintained throughout pregnancy, may be necessary for asthma prevention.³⁹ This finding was replicated in combined analysis of the VDAART and COPSAC₂₀₁₀ cohorts, with a risk reduction of almost 50% in offspring of mothers with initial vitamin D level of greater than 30 ng/mL who received supplementation.⁴⁰ Additional studies are necessary to further evaluate this question.

In 1997, Black and Sharpe⁴¹ described an association between the increase in atopy with changes in dietary fat consumption in the Western diet, namely the increased use of plant-based oils containing omega-6-polyunsaturated fatty acids (n-6 PUFAs) such as linoleic acid, reduced use of animal fats (butter/lard), and decreased consumption of oily fish products containing n-3 long chain PUFAs (LCPUFAs). Because linoleic acid is a precursor to arachidonic acid, the increase in n-6 PUFA consumption can be linked to the production of prostaglandins including prostaglandin E₂, which promotes T helper 2 cell differentiation. Dietary supplementation of asthmatic patients with n-3 LCPUFAs is ineffective,⁴² but its use in preventing asthma has shown promise. Although a 2015 Cochrane review found little evidence to support maternal n-3 PUFA supplementation for reduction of allergic disease in children,⁴³ significant heterogeneity in included studies limited the findings; 2 recent large randomized controlled trials showed a benefit of prenatal fish oil supplementation on the prevention of wheeze in offspring.^{44,45}

In 1 study, 736 women were randomized to receive either 2.4 g fish oil daily versus olive oil placebo starting at 24 weeks gestation, and 695 children were followed for 5 years. Children whose mothers received fish oil had a 30.7% overall reduced risk of persistent wheeze or asthma, with the greatest benefit seen in mothers with the lowest baseline LCPUFA levels before randomization (54.1%), with a number needed to treat of 6.⁴⁵ The second study examined adult offspring (aged 18–19 years) of mothers randomized to 2.7 g fish oil (vs olive oil vs no intervention) in the third trimester. Maternal fish oil supplementation was associated with a decreased

probability of asthma medication prescription and an in-hospital discharge diagnosis of asthma in adult offspring.⁴⁴ These findings suggest a potentially beneficial effect of fish oil supplementation during pregnancy, although capsules are generally unpalatable and it may be challenging for some mothers to take multiple pills or to afford the financial cost of supplementation.⁴⁶ Of note, initial blood levels of n-3 LCPUFAs correlated with reported maternal fish ingestion; feasibly, targeting women with the least fish intake would be most advantageous, because the study doses of 2.4 to 2.7 g fish oil are roughly 20 times the normal daily n-3 LCPUFA intake in the United States.⁴⁵

Prenatal folate exposure was formerly thought to be a risk factor for childhood atopy, owing to its ability to donate methyl groups and thereby epigenetically modify DNA.⁴⁷ Results of studies are mixed, and many studies do not include blood folate levels.^{48,49} A recent prospective cohort study actually found a modest decrease in the odds of wheeze at age 3 among offspring of women high plasma folate levels in the second trimester (adjusted odds ratio, 0.67; 95% confidence interval, 0.46–0.97), although the finding was not replicated for third trimester folate levels.⁵⁰ These data certainly do not support a harmful effect of prenatal folate exposure on childhood atopic disease.

MODIFYING THE IMMUNE RESPONSE TO ALLERGENS

AR affects 2% to 25% of children, with steadily increasing prevalence.⁵¹ Often preceding the development of asthma, AR is an independent risk factor for asthma development.^{51,52} Although strict early avoidance of environmental allergens has generally not proven beneficial in the prevention of asthma in the general population,⁵³ evidence from small trials suggests that treatment of AR with allergen immunotherapy can prevent progression of AR to allergic asthma.^{54–56} The first randomized trial designed to assess the efficacy of subcutaneous immunotherapy included 44 subjects with AR and bronchial hyperresponsiveness monosensitized to dust mite. After 2 years of subcutaneous immunotherapy, the methacholine provocative dose to elicit a 20% decrease in the Forced expiratory volume in 1 second increased 4-fold in the treatment group, and no treatment subjects developed asthma (vs 9% of placebo subjects).⁵⁷ Similar results were produced in children with AR sensitized to birch and/or grass pollen, with persistence of the preventative effect for at least 10 years.⁵⁸

Asthma prevention results are not as robust for sublingual immunotherapy, although recently published results of the GRAZAX Asthma Prevention (GAP) study are somewhat encouraging. In 812 nonasthmatic children with AR sensitized to Timothy pollen, sublingual Timothy immunotherapy (GRAZAX, ALK-Abello, Denmark) given for 3 consecutive allergy seasons did not decrease incident asthma in 2-year follow-up, although asthma symptoms and medication use were reduced compared with placebo (odds ratio, 0.66; $P < .36$).⁵⁹

Whereas a 2017 metaanalysis of 32 studies of allergen immunotherapy administered by any route found a short-term protective effect versus asthma (relative risk, 0.40; 95% confidence interval, 0.30–0.52), there was inconclusive evidence that benefit was maintained.⁶⁰ Well-conducted randomized controls with long-term outcomes are lacking.

Studies evaluating the effects of disruption in the atopic march, specifically in the prevention of atopic dermatitis and food allergy, have generally been precluded from examining asthma outcomes owing to short duration.⁶¹ The PreventADALL multinational birth cohort (NCT02449850) seeks to determine if early, low-cost interventions could alter the course of atopic disease; infants are randomized to 1 of 4

groups, including observation only, early emollient use, early food introduction, and a combination of early interventions. Because these children will be studied through 2044, long-term outcomes, including effects on asthma prevention, will be possible. Also of note, a recent follow-up of the Learning Early About Peanut (LEAP) cohort noted that early consumption of peanut in high-risk infants is disease and allergen specific, and although reducing the risk of peanut allergy, this approach does not prevent the development of other atopic diseases, including asthma.⁶²

ALTERING THE IMMUNE RESPONSE TO MICROBES

Viral RTIs are the most common cause of recurrent wheeze in infants, and wheezing illnesses in the context of infections with human rhinovirus and respiratory syncytial virus (RSV) are strong predictors of asthma development in children.^{63,64} In 1 cohort, RSV bronchiolitis requiring hospitalization during infancy conferred a 50% likelihood of physician-diagnosed asthma by age 7 years, potentially mediated by the chemokine CCL5 (RANTES).⁶⁵ In the high risk for atopy Childhood Origins of ASThma (COAST) cohort, wheezing with human rhinovirus infection in the first year of life was associated with an increased risk of school-age asthma by 3-fold, and 90% of children with wheeze during human rhinovirus infection in the third year of life had developed asthma at age 6 years.⁶⁶

Several therapies to decrease the incidence or severity of these RTIs have been evaluated, including prophylactic vaccination, antiinflammatory therapies, and immunostimulatory agents, under the premise that prevention or modulation of the acute illness will confer long-term protection from recurrent wheezing and asthma.

To identify a causal relationship between initial RSV infection and recurrent wheeze, the MAKI trial evaluated the effect of the anti-RSV monoclonal antibody palivizumab administration during RSV season in 429 otherwise healthy late preterm infants. Compared with placebo, palivizumab treatment reduced the number of wheezing days by 61% in the first year of life, even outside of RSV season, suggesting that primary prevention of RSV was an effective strategy in reducing all-cause wheezing.⁶⁷ After 6 years, this mode of RSV prevention was associated with decreased parent-reported wheeze but not in physician-diagnosed asthma or lung function.⁶⁸ Clinical trials of a maternal RSV vaccination (NCT02624947) and of an extended half-life anti-RSV monoclonal antibody (NCT 02878330) are underway. However, with an estimated direct cost of \$10,665 for 5 monthly doses, it is not feasible to dose every infant with a full season of palivizumab therapy.⁶⁹

Macrolide antibiotics have been proposed as a more cost-effective strategy, because these agents exhibit both antineutrophilic and antibacterial effects.⁷⁰ After azithromycin was shown to attenuate airway inflammation in a mouse model of viral bronchiolitis,⁷¹ a pilot study of 40 infants hospitalized with RSV bronchiolitis randomized subjects to either 14 days of azithromycin versus placebo. Compared with placebo, azithromycin decreased upper airway IL-8 levels and resulted in decreased recurrent wheeze and fewer days with wheezing.⁷² Interestingly, azithromycin modified the upper airway microbiome, with significantly decreased *Moraxella* abundance in the treatment group. Lower *Moraxella* abundance was independently associated with decreased odds of recurrent wheeze.⁷³ An ongoing trial (NCT02911935) aims to evaluate the effects of azithromycin on the upper airway microbiome and on recurrent wheeze during the preschool years.

Because most RTIs are viral, with hundreds of possible etiologies, vaccination for each individual virus is not a feasible prophylactic solution. Immunostimulatory agents enhance innate and adaptive immune response to infection by targeting the gut–lung

immune axis.⁷⁴ Of the immunostimulatory agents, OM-85 BV (Broncho-Vaxom, OM Pharma, St. Gallen, Switzerland) is the most well-studied in RTI prevention. OM-85 BV is a bacterial lysate immunomodulator composed of 21 lyophilized strains of common respiratory pathogens, including *Haemophilus influenza*; *Streptococcus pneumoniae*, *pyogenes*, and *viridans*; *Klebsiella pneumoniae* and *ozaenae*; *Staphylococcus aureus*; and *M catarrhalis*, thought to exert efficacy by inhibiting T helper 2-mediated inflammation via gut dendritic cell activation and regulatory T-cell mobilization to the lung. Randomized controlled trials have demonstrated the efficacy of OM-85 BV in a reduction of the rate and duration of wheezing in children with recurrent RTIs.^{74,75} A Cochrane analysis demonstrated a decrease in acute RTIs by 36%,⁷⁶ and an ongoing 36-month phase II trial is examining if OM-85 BV given regularly for 2 years to at-risk children ages 6 to 18 months of age (NCT02148796) decrease the likelihood of recurrent wheeze.

SUMMARY AND FUTURE CONSIDERATIONS

The increase in asthma prevalence necessitates the identification and alteration of modifiable risk factors to promote primary disease prevention. Evidence suggests that maternal diet modification resulting in fetal exposure to appropriate amounts of vitamin D or fish oil could prevent recurrent wheeze or asthma, and that early exposure to a diverse microbial environment is likely protective, with a likely critical window of opportunity to alter the host microbiome in very early infancy. Modification of the host response to allergens via specific allergen immunotherapy may prevent asthma, although the typical subcutaneous route of administration is time constraining. The prevention and modification of viral RTIs, a known risk factor for asthma, also shows promise and is under intense investigation. Immunostimulatory agents may also have a role in enhancing innate and adaptive immune response to infection by targeting the gut-lung immune axis. Ongoing trials and longitudinal birth cohort studies will help to identify additional protective strategies, because asthma prevention is clearly multifactorial.

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