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Strategies to alter the natural history of childhood asthma

K Lee-Sarwar[1], **L Bacharier**[2], and **A Litonjua**[3]

[1]Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Boston, MA

[2]Division of Pediatric Allergy, Immunology and Pulmonary Medicine, Department of Pediatrics, Washington University School of Medicine, St Louis, MO and St Louis Children's Hospital, St Louis, MO

[3]Channing Division of Network Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA

Abstract

Purpose of review—Asthma exhibits significant heterogeneity in occurrence and severity over the lifespan. Our goal is to discuss recent evidence regarding determinants of the natural history of asthma during childhood, and review the rationale behind and status of major efforts to alter its course.

Recent findings—Variations in microbial exposures are associated with risk of allergic disease, and the use of bacterial lysates may be a promising preventive strategy. Exposure to air pollution appears to be particularly damaging in prenatal and early life, and interventions to reduce pollution are feasible and result in clinical benefit. E-cigarette use may have a role in harm reduction for conventional cigarette smokers with asthma, but has undefined short- and long-term effects that must be clarified. Vitamin D insufficiency over the first several years of life is associated with risk of asthma, and vitamin D supplementation reduces the risk of severe exacerbations.

Summary—The identification of risk factors for asthma occurrence, persistence and severity will continue to guide efforts to alter the natural history of the disease. We have reviewed several promising strategies that are currently under investigation. Vitamin D supplementation and air pollution reduction have been shown to be effective strategies and warrant increased investigation and implementation.

Keywords

asthma; vitamin D; microbiome; tobacco; pollution

Corresponding Author: Kathleen A. Lee-Sarwar, MD, Fellow in Allergy & Immunology, Brigham and Women's Hospital, Address: Brigham and Women's Hospital, Channing Division of Network Medicine, 181 Longwood Ave, Boston MA 02115, Telephone: (617) 780-7339, klee-sarwar@partners.org.

Conflicts of interest

None.

Introduction

Asthma is a developmental disease: the majority of cases are diagnosed by age 6 [1], and lung function abnormalities may be present in early infancy [2–4]. However, diagnosis in early childhood may be difficult as preschool wheeze has a variety of causes including bronchiolitis [5,6]. Almost 50% of children report wheeze before age 6, but 40% of these children experience resolution of wheeze between the ages of 3 and 6 [7].

The existence of distinct trajectories of childhood wheeze, and of asthma more generally, represents a challenge to the elucidation of the natural history of the disease. Several phenotypes of preschool wheeze have been identified and indices have been developed to predict development of subsequent asthma by mid-childhood [8,9]. Children with preschool wheeze in the Tucson Children's Respiratory Study cohort were categorized in three groups: early transient wheezers with symptoms by age 3 and resolution by age 6, persistent wheezers with symptoms by age 3 that persisted at age 6, and late-onset wheezers with symptom onset between ages 3 and 6 [7]. Approaches employing machine learning computational techniques to distinguish asthma phenotypes have largely corroborated the existence of groups defined by early life wheeze (transient or prolonged), late-onset wheeze, and persistent wheeze (controlled or troublesome) [10,11]. This work has led to the identification of major risk factors for persistent wheeze, including atopy, relatively high asthma morbidity in early life, and maternal history of asthma [5,6,10].

Though childhood wheeze may resolve by adulthood [12,13], lung function abnormalities frequently persist later in life [14–16]. A recent study demonstrated distinct trajectories of lung function in nearly 700 children with mild-to-moderate asthma followed to an average age of 26 with annual lung function assessments [17**]. Four patterns were identified based on FEV1 measurements with approximately equal numbers of subjects in each group: normal lung development, normal lung growth with an early decline in lung function, reduced lung growth with no early decline in lung function, and reduced lung growth with an early decline in lung function. Risk factors for abnormal longitudinal patterns include maternal smoking, reduced lung function at enrollment, increased airway hyperresponsiveness, vitamin D insufficiency, and male sex.

While additional research is needed to further characterize asthma subtypes and determinants of their courses over the lifespan, there have been advances in strategies to alter the natural history of asthma. In this review, we discuss medical management in early childhood, prevention of smoke and air pollution exposure, modification of microbial exposures, and vitamin D supplementation. Other relevant topics reviewed elsewhere in this issue include allergy and viral respiratory infection prevention (reviewed by Daniel Jackson) and prenatal exposures (reviewed by Tina Hartert).

Medical Management in Early Childhood

Among medical treatments for control of recurrent preschool wheeze, which are reviewed in this issue by Avraham Beigelman, inhaled corticosteroid use has accrued the most evidence of effectiveness [18–21], with less evidence supporting use of leukotriene inhibitors [22]. A

recent multicenter randomized crossover trial demonstrated heterogeneity in response to treatment: 74% of 230 children age 12–59 months who require a daily controller medication had a differential response to treatment with daily inhaled corticosteroids, intermittent inhaled corticosteroids, and leukotriene receptor antagonists. Of those with differential response to treatment, daily inhaled corticosteroids had the highest probability of producing the best response [23].

As the prevalence of and morbidity from asthma and wheeze are high during early childhood, interventions during this period may be expected to impact lung function and asthma control later in life. Unfortunately, randomized placebo-controlled trials have not found that inhaled corticosteroid treatment during the preschool years alters the natural history of asthma or persistent wheeze [24–26], though no trials have investigated consistent and long-term use of daily controller therapy [5]. Anti-IgE therapy with omalizumab is currently under investigation as a treatment to prevent asthma in high-risk preschool children (NCT02570984).

Prevention of Smoke Exposure in the e-Cigarette Era

There is abundant evidence that smoke exposure worsens [27–31] and smoking cessation improves [32,33] asthma control and lung function. Electronic cigarettes, or e-cigarettes, are battery-powered nicotine delivery systems that are thought to reduce toxic and carcinogenic exposures compared to combustible conventional cigarettes [34*,35,36].

E-cigarette use has become widespread in the United States. In 2014, 12.6% of adults had ever used an e-cigarette, and 3.7% were current users [37]. The majority of adult users of e-cigarettes were current or former users of conventional cigarettes, suggesting that e-cigarettes do not promote widespread initiation of smoking or relapse in those with remote smoking histories [37]. However, e-cigarette use is also frequent in adolescents, with 44.9% of students in grades 9–12 reporting having ever used an electronic vapor product [38], and 5.3% of middle school and 16.0% of high school students reporting current e-cigarette use in 2015 [39]. In Florida, e-cigarette use among high school students in 2012 was actually more frequent among students who reported having asthma than among those without asthma [40]. Though these numbers may decrease with the ban on sale of e-cigarettes to those under age 18 implemented in 2016 in the United States, they raise concern that e-cigarettes may promote initiation of smoking among adolescents and young adults, including those with asthma.

On the other hand, though evidence is mixed regarding the effectiveness of e-cigarette use for smoking cessation [36,41,42], it may be useful for harm reduction in smokers with asthma. A prospective study of 18 subjects with mild-to-moderate asthma who switched from conventional to e-cigarette use found significant improvements over two years of follow-up in respiratory symptoms, lung function, airway hyperresponsiveness, and tobacco consumption with no significant change in asthma exacerbation rate [43*,44]. Despite this encouraging research, toxicity varies significantly between e-cigarette products [45,46] and long-term effects of e-cigarette use remain unknown [34*,35,36]. Until these effects are

clarified, other safer methods of smoking cessation should be used before e-cigarettes in patients with asthma.

Prevention of Early Life Exposure to Air Pollution

Exposure to air pollutants, such as nitrogen dioxide, ozone, and particulate matter, is a major risk factor for abnormal lung development and function [47–51] and has been linked to increased asthma prevalence and reduced asthma control [52–59, 60*]. Recent evidence highlights the impact of air pollution exposure in prenatal and early life on lung function later in life. Schultz, *et al* reported on longitudinal exposure to nitric oxide and particulate matter with an aerodynamic diameter of <10 μm in 2,278 subjects followed from birth [61*, 62]. There was a negative association between air pollution exposure in the first year of life and FEV1 at age 16, and later air pollution exposures appeared to have additional negative effects. Another study utilizing administrative databases of medical visits over a 10-year period in a Canadian population-based cohort of over 65,000 subjects found that prenatal nitrogen dioxide exposure was associated with asthma that persisted past age 6, but not with "transient asthma" that resolved by age 6 [63].

Interventions to reduce air pollution are feasible and result in demonstrable benefit. Between 1994 and 2011, aggressive pollution reduction strategies were implemented in southern California. Over this period, three separate large cohorts of children were followed between the ages of 11 and 15 including annual lung function measurements [64**]. Improvements in 4-year growth of FEV1 and FVC were associated with declining levels of nitrogen dioxide and particulate matter with aerodynamic diameters <2.5 μm and <10 μm. This association held in children both with and without asthma, and the proportion of children with FEV1 values of less than 80% of the predicted value at age 15 declined significantly from 7.9% to 6.3% to 3.6% across the three cohorts. This important study builds on prior research showing reduced asthma morbidity in association with decreased traffic during the Olympic Games in both Atlanta in 1996 and Beijing in 2008 [65–67].

Potential Benefit of Immunostimulant Microbial Exposures

The ecological community inside and outside the body has emerged as a major environmental exposure of interest in asthma pathogenesis. Culture-independent high-throughput methods have revolutionized the identification and quantification of genetic material, and knowledge has rapidly accumulated regarding the microbial composition of human living environments and bodies [68*,69]. These developments occurred concomitantly with the proposal and evolution of the "hygiene hypothesis," which posits that reduced microbial exposure accounts for the rising prevalence of allergic disease [70].

The hygiene hypothesis is based on the now well-documented finding that risk of allergic disease is reduced in association with a variety of environmental exposures, among which household size was the first to be identified [68*,69,70]. Wu and colleagues recently showed that exposures in early infancy may be particularly important [71*]. In a population-based birth cohort of 136,098 infants, maternal urinary tract infection and antibiotic use during pregnancy, mode of delivery, infant antibiotic use, and having older siblings at home were

associated in a cumulative and dose-dependent manner with increased risk of childhood asthma; of these, infant antibiotic use was the strongest predictor.

As many of the same exposures that are linked to reduced risk of allergy have come to be recognized as determinants of human microbial composition, including residence on a farm, cohabitation with a dog, day care attendance, and vaginal birth, the hygiene hypothesis has evolved into a “microbiota hypothesis” in which environmental factors reduce allergic disease via modification of the host microbiome [68*,69,72*]. Other recognized asthma risk factors may also act via perturbations of the human microbiome. For example, acute respiratory syncytial virus infection during infancy is associated with a nasopharyngeal microbiome composition similar to the composition seen in infants who later develop asthma [73].

The microbiota hypothesis is supported by a growing body of evidence. The gut microbiome differs between those with and without asthma [74–76], and between members of communities with different degrees of industrialization and prevalence of allergic disease [68*,72*,77]. Oropharyngeal colonization and gut microbiome composition as early as age 1 month have been associated with risk of subsequent atopy and asthma [78–81]. Evidence primarily from animal models demonstrates a role of the gut microbiome in the development of immune tolerance mechanisms [82], and exposure to bacterial species associated with protection from allergic disease in human studies has been shown to reduce experimentally-induced airway inflammation in mice [74, 83–85].

Synthesizing and building on this body of evidence, Stein and colleagues recently reported on children from Hutterite and Amish agricultural communities in the United States [86*]. These populations have similar ancestry and agricultural lifestyles, but Hutterites use more industrialized farming practices. Hutterite children demonstrated higher prevalence of allergic disease, differences in the microbial composition of dust in participants’ homes, and differences in innate immune cell frequencies and phenotypes compared to Amish children. In a mouse model, intranasal dust extracts from Amish, but not Hutterite, homes significantly inhibited airway hyperreactivity and eosinophilia.

It may soon be possible to predict risk of asthma based on early infancy microbiome data. Fujimura and colleagues recently used 16S rRNA sequencing of stool samples provided between ages 1 and 11 months to categorize 298 birth cohort participants into three distinct microbiota compositional states, each of which was associated with significantly different risk for multisensitized atopy at age 2 and doctor-diagnosed asthma at age 4 [87].

The recognition of a connection between early microbial interactions and risk of asthma has led to attempts to modify gut colonization to prevent asthma. Unfortunately, several randomized trials have failed to show that prenatal and early life probiotic and prebiotic treatments reduce asthma incidence [88–94].

Bacterial lysates, immunoregulatory cellular extracts that have been found to reduce allergic airway inflammation in mouse models, may be an effective alternative [95–97]. The most studied bacterial lysate is OM-85 BV, which contains extracts derived from 8 bacterial species: *Staphylococcus aureus, Streptococcus* species*, Klebsiella* species*, Neisseria*

catarrhalis and *Haemophilus influenzae*. Several trials, though generally small and with significant heterogeneity, have demonstrated that bacterial lysate treatment reduces recurrent respiratory tract infections in adults and children [98–101], and OM-85 BV has been used for decades for this indication in Europe [95]. A small clinical trial of 75 children between ages 1 and 6 with recurrent wheeze found a nearly 40% reduction in number of wheezing attacks and a reduction in duration of wheezing attacks over one year of follow-up in those randomized to OM-85 BV treatment [102]. Non-randomized clinical data further support a potential benefit of OM-85 BV in asthma [103]. The effectiveness of OM-85 BV in preventing severe wheezing lower respiratory tract infection in high-risk infants is currently under study in a multi-center placebo-controlled randomized clinical trial (NCT02148796).

Vitamin D Supplementation

Vitamin D deficiency is common worldwide and several of its myriad physiological consequences are central to asthma pathogenesis, including effects on lung development and immune function [104–108]. The role of vitamin D over the first decade of life was recently studied by Hollams, *et al* in a birth cohort of children at high risk of asthma that measured 25-hydroxyvitamin D levels at 7 visits between birth and age 10 [109*]. Though there was no overall longitudinal association between vitamin D level and asthma or wheeze, in a subgroup of 80 subjects in whom vitamin D levels were available from all follow-up visits, the total number of vitamin D-deficient follow-ups per child was positively associated with asthma and wheeze at age 10. There were inverse relationships between vitamin D levels and early allergic sensitization, nasopharyngeal colonization with *Streptococcus*, and early febrile lower respiratory infections – factors associated with asthma in this cohort [110] – suggesting that an effect of vitamin D deficiency on subsequent asthma may be partly modulated by allergic sensitization, respiratory tract bacterial colonization and/or infection in infancy [109*]. This suggests that preventing vitamin D deficiency throughout childhood may be important in prevention of these disorders.

The efficacy of vitamin D is better established for the management than for the prevention of asthma. A Cochrane review of placebo-controlled trials, including 435 children and 658 adults, concluded that vitamin D is likely to reduce the risk of severe asthma exacerbation and healthcare use due to asthma, though children and those with severe asthma were underrepresented in the included studies [111**]. These findings are in accordance with other systematic reviews [112,113].

As many processes affected by vitamin D begin before or shortly after birth, there has been considerable interest in a possible role of prenatal and early life vitamin D supplementation in asthma prevention [104]. Observational studies, though heterogeneous and inconsistent, and a growing body of clinical trial data suggest a protective effect of vitamin D supplementation during pregnancy and early infancy [114–117]. This and other prenatal interventions are reviewed in detail in this issue by Tina Hartert.

The dose of vitamin D needed for prevention remains undefined. In pregnancy, doses of 2,400 to 4,400 UI daily appear safe [116,117]. However, a single dose recommendation for all patients may not suffice, and future studies will need to define whether a level-based

dosing regimen (i.e. to target a pre-specified level) may be a better strategy. Likewise, in infancy and early childhood, the dose of vitamin D supplementation or the desired level of 25-hydroxyvitamin D to prevent asthma remain undefined. The study by Hollams, *et al* will need to be verified in other cohorts. The current recommended daily allowance for vitamin D in children is 600 IU daily [118]. However, given the high prevalence of vitamin D deficiency in many countries, it remains to be seen whether individualized supplementation to target a specified level in children rather than prescribing a specific intake for all children, will be more effective in preventing the development of asthma.

Conclusion

The determinants of the diverse trajectories of lung function and asthma morbidity that are observed throughout the lifespan remain to be fully defined. This area of study progresses in parallel with and enables the recognition of risk factors for asthma and the evaluation of interventions to reduce asthma risk. We have highlighted active areas of research, including the search for medical treatments that could be given in the preschool years to prevent persistent wheeze, the undefined role of e-cigarette use in smokers with asthma, and whether microbial exposures can be manipulated to reduce asthma risk. These lines of investigation will hopefully yield additions to the armamentarium of effective strategies to modify the natural history of asthma. Evidence is accumulating that reducing air pollution and avoiding vitamin D deficiency in childhood lead to improved outcomes and attention should be paid to these exposures.

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Key Points

- Efforts are ongoing to describe and predict trajectories of asthma occurrence and severity over the lifespan.
- A large and growing body of evidence has linked microbial exposures and risk of allergic disease, and the use of bacterial lysates in asthma prevention is currently under study.
- Interventions to reduce air pollution are feasible, result in demonstrable improvement in lung function development, and may have the greatest impact during prenatal and early life.
- The health effects of e-cigarette use in those with asthma must be clarified before a role of e-cigarette use in smokers with asthma can be defined.
- Vitamin D plays an important role in immune and pulmonary development, and vitamin D supplementation reduces asthma exacerbations in adults with mild-to-moderate asthma.