Primary Prevention of Asthma: Will It Be Possible in the Future?

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Abstract

Purpose of Review Asthma is a major public health problem in both the developed and developing world. Asthma is a complex heterogeneous disease with a multifactorial etiology involving genetic, epigenetic, viral, microbial and environmental exposures.

Recent Findings New studies have provided significant novel information on the interplay between inherited and modifiable risk factors in the development of asthma, suggesting possible primary preventive measures.

Summary Multi-faceted interventional strategies targeted to the personalized risk profile will likely be most effective in primary prevention of asthma.

Introduction

What is asthma?

Asthma is a broad term covering a heterogeneous group of airway diseases that are characterized by inflammation of the airways and reversible airflow obstruction [1, 2]. There remains significant ongoing discussion on the exact definition of asthma, particularly in early childhood when diagnosis is complicated by the high prevalence of transient forms of wheezing in infancy and preschool

age. It is a complex syndrome covering many different phenotypes, distinguishable by observable characteristics. Phenotypes include allergic asthma, non-allergic asthma, exercise-induced, obesity-related, and eosinophilic asthma (characterized by a marked eosinophilic airway inflammation). There is increasing interest in defining endotypes, which distinguish asthma variants by their underlying pathophysiological mechanisms.

However, the robustness of these defined endotypes has yet to be evaluated in prospective clinical studies [3].

Regardless of the method of classification, the worldwide prevalence of asthma has increased significantly over the past 60 years [4, 5]. Advances on improving the assessment and management of asthma, and public health focus on asthma has resulted in a 42% reduction in age-standardized asthma death rates between 1990

and 2013 [6]. Despite the decrease in mortality, asthma is still an important cause of morbidity, and effective primary intervention strategies to decrease development of asthma remain a vital health care need.

In this paper, the current evidence for the risk factors for asthma, and interventions that have been studied for primary prevention of asthma are reviewed (Table 1).

Risk factors for asthma

Genetics

The pathogenesis of asthma is widely recognized to begin early in life.

Genetic predisposition is an important component of asthma risk. A family history of asthma or atopy clearly increases the risk of developing asthma in the child. Despite many advances, the genetic basis of asthma is as yet poorly defined, and cannot be clinically translated. Many loci across many chromosomes have been associated with asthma—however the heterogeneity of populations and asthma phenotypes, methodological limitations, variable gene expression, and difficulty to correlate with objective diagnostic tools of asthma have complicated the endeavor to fully define the genetic basis of asthma. In addition, the rapid increase in asthma prevalence over the last 25 years, and the differences in asthma prevalence in populations with similar genetics in different environments [1, 7], all suggest that gene-environmental interactions are key in the pathogenesis of asthma.

The association between the 17q21 locus, in particular between genes that code for the orsomucoid-like 3 protein (ORMDL3), and childhood asthma has been shown in multiple cohorts [8, 9]. Among the many genes associated with asthma are included polymorphisms in a number of immune response genes,

Table 1. Risk factors for development of asthma

Non-modifiable
Genetic predisposition
Currently modifiable
Environmental tobacco smoke
Environmental airway pollution
Obesity
Vitamin D deficiency
Potentially modifiable
Viral wheezing illness in early life
Allergic sensitization
Disordered microbiome
Atopic dermatitis

suggesting immune perturbations that may be responsible both for asthma, and increased susceptibility to RSV: CX3CR1, TLR-4, SP-A, SP-D, IL-10, CCR5, TLR-10, IL-4, IL-13, IL-8, IL-18, TNF, TLR-4, MS4A2, VDR, IL-4R α , RANTES, TGF- β 1, and ADAM33 [10].

Viruses—RSV, rhinovirus, meta-pneumovirus

Infection with certain respiratory viruses in infancy, particularly respiratory syncytial virus (RSV) and rhinovirus (RV), has been associated with a marked increase in risk of subsequent childhood asthma. Severe RSV/RV disease is associated with a higher risk of subsequent asthma. RSV-induced bronchiolitis has been recognized to be associated with later development of asthma in many prospective long-term studies with outcomes up to 18 years [11]. The role of RV-induced bronchiolitis in the progression to asthma has been better identified in recent decades because of the increased sensitivity of PCR techniques, particularly in RV diagnostics. RV-induced wheezing is more highly associated with asthma risk than wheezing episodes caused by RSV or other viruses. A recent meta-analysis of 15 studies has confirmed the association between RV-induced wheezing and the development of childhood asthma [1, 12]. Meta-pneumovirus lower respiratory tract infections has also been associated with subsequent wheezing in childhood, although a definitive association with asthma was not established [13].

Data from high-risk birth cohorts (with at least one atopic parent) showed an additive effect of early allergen sensitization upon the increased risk of asthma following RV wheezing illness [14, 15], that this risk appears to be heightened in the susceptible host suggests the “double hit” hypothesis in which viral infection provokes wheezing in a genetically predisposed infant, and/or that an interaction between viral infection and aero-allergen sensitization leads to the development of asthma [16].

Genetically predisposed susceptibility to both viral wheezing illness and allergic sensitization appear to be linked—several genes have been associated with both increased risk of RSV/RV infection and increased risk of asthma, suggesting a genetic susceptibility to both [17]. In a collaborative study involving two birth cohorts, the 17q21 genotype was strongly associated with both risk of RV-induced wheezing and subsequent asthma following an episode of RV-induced wheezing [18]. The prevalence of RV-induced bronchiolitis in the first year of life has been as high as 50–80% in infants with recurrent moderate-to-severe respiratory illnesses from atopic families.

Interactions between allergic sensitization and viral infection in the inception of asthma have been well described, though results are still controversial. The developmental sequence between allergic sensitization and viral wheezing illness has been difficult to determine conclusively. In vitro and animal studies have shown that RSV infection is associated with increased predominant production of Th2 cytokines and enhanced airway sensitization to allergens [19]. Longitudinal studies have demonstrated that RSV lower respiratory tract infections precede atopic sensitization [20]. Conversely, a longitudinal multistate Markov model in a high-risk birth cohort study (COAST study) identified a sequential relationship with allergic sensitization preceding viral wheezing, with no evidence that viral wheezing led to sensitization [21]. This association has also been seen in emergency department studies in which detection of a respiratory virus,

detectable allergen-specific IgE, and/or the presence of eosinophilic inflammation were identified as risk factors for subsequent acute wheezing [22, 23].

The mechanisms by which viral-induced wheezing increases the risk of childhood asthma have been proposed to be multifactorial and mutually interactive with allergic sensitization. Both RV infections and allergens can enhance the airway epithelial cell production of IL-25 and IL-33 which promotes type 2 airway inflammation and remodeling. Children with allergic airways have impaired antiviral responses, and high-affinity IgE receptor cross-linking has been shown to impair virus-induced interferon-gamma responses, with subsequent enhanced viral replication and increased type 2 airway inflammation [11, 24].

The viral wheezing illness may itself cause airway damage during a critical time window of lung development, with resultant long-term effects [25]. Viral infections have also been proposed to interact with microbiome to promote dysbiosis (imbalance in a microbial ecosystem) towards an environment that promotes allergic disease. Acute RSV infection in infancy is associated with a nasopharyngeal microbiome composition similar to the composition seen in infants who later develop asthma [26], and with airway microbiomes dominated by *H influenzae* or *Streptococcus* species, which are in turn associated with enhanced innate immune activation [11].

Allergic sensitization

Allergic sensitization is highly associated with subsequent development of abnormal lung function, and persistent wheezing in childhood. Prospective studies with long-term follow-up have also suggested that these effects on lung function and symptoms persist into adulthood [27]. There is growing recognition that sensitization patterns are heterogeneous and diverse. Definition of sensitization patterns has moved from dichotomous classifications (positive or negative, atopic or non-atopic) to data-driven classification according to associations with eventual asthma. Different subgroups of sensitization have been proposed, differing in their risk factors, associations with asthma progression and response to treatment.

Timing of onset of sensitization and the nature of sensitization appear to be discriminative in predicting which risk of subsequent asthma. Children who are highly sensitized [28], sensitized early in life [29, 30], or sensitized to multiple allergens [30, 31] have a higher risk of developing asthma. Sensitization in childhood to specific allergens, such as house-dust mites, dogs, or cats [32] have been reported to be strongly associated with asthma development [33].

There is strong evidence for a dose-response relationship of exposure to HDM and sensitization [34, 35]. Tovey et al. demonstrated a non-linear relationship between levels of household HDM and the development of asthma in a high-risk cohort of children, with a trend of increasing prevalence of sensitization and asthma correlating with HDM exposure up to a critical level and a sharp drop at the highest level of exposure [34]. The mechanism for the attenuated disease development with high levels of HDM exposure is unclear—high concentrations of endotoxin and beta-glycans from fungus are known to accompany HDM and may play a protective role, demonstrating the complex interplay between different environmental exposures in the pathogenesis of asthma.

The strongest effects of sensitization are seen in high-risk birth cohorts, as demonstrated in several longitudinal birth cohort studies [32, 36, 16]. The Childhood Asthma Prevention Study in a high-risk cohort showed that a correlation between early atopy (positive SPT at 18 months) in children who never wheezed and later development of asthma [16].

New computational approaches such as longitudinal latent class analysis have used data-driven methods in conjunction with clinical analysis to better define subgroups with asthma, and highlighted allergic sensitization as an important feature [37]. Age and sex stratification for SPT and IgE values have also been investigated as a means of better correlating sensitization data with eventual asthma [38]. The use of component resolved diagnostics determining sensitization to specific molecular components of allergen has allowed more precise identification of sensitization trajectories that are significantly associated with subsequent development of asthma [39].

Microbiome/hygiene hypothesis

The rising prevalence of atopic diseases has been attributed to the “hygiene hypothesis,” which had its origins in observations that decreasing family size was associated with increased hay fever incidence [40]. The hypothesis was that this effect was mediated by a lower degree of sibling-related childhood infections and microbial exposure. This effect has also been demonstrated in the protective effects of rural farm life exposure [41] and exposure to pets (particularly dogs). The hygiene hypothesis has since then been extended to the “old friends” hypothesis, which postulates that microbes with which the human race has coevolved with have developed mechanisms to modulate and regulate the immune system [42, 43]. With changes in lifestyle and living conditions, the “old friends” are being lost with decreased microbial diversity, and the loss of these archaic microbes plays an essential part in the increased incidence of asthma and allergic diseases. Changes in the diversity and composition of gut microbiota of infants have been shown to be associated with a subsequent increased risk of wheezing [44], and similar findings have also been reported in the nasal microbiome [45].

Further study on gene-environment interactions in early farm exposure has found that a number of single-nucleotide polymorphisms linked to farming, such as in genes transcribing CD14 or Toll-like receptors (TLR) [46]. A recent farm study reported on associations with asthma risk alleles on chromosome 17q21 suggesting that the same genotype represents a genetic risk to asthma, which is simultaneously susceptible to environmental influences [47].

Environmental tobacco smoke

Meta-analysis of studies examining the effect of exposure to environmental tobacco smoke has shown increased risk of wheezing and subsequent asthma [48]. A meta-analysis of 79 prospective studies showed an increased risk of wheeze by 2 years of 70% [49]. Although the risk was highest when prenatal passive exposure was combined with prenatal active smoking, passive exposure alone increased the risk of subsequent wheeze [50].

Second-hand smoke exposure has been shown to increase severity of infant viral respiratory infection, apart from directly increasing the risk of developing asthma. Neonates born to maternal smokers have altered neonatal innate

immune responses with high Th2 responses, cord blood IgE levels, and decreased innate TLR responses as compared to infants of non-smokers [51, 52].

Obesity

Obesity, being a heterogeneous disorder itself, is both a risk factor and disease modifier for asthma, and this is mediated through a number of different underlying mechanisms. Obesity often precedes incident asthma, and obesity-induced increases in asthma risk can start in prenatal life [53]. Maternal obesity and weight gain during pregnancy have been shown to be independently associated with a 15–30% increased risk of asthma [53, 54]. The classical Th2 inflammation described in asthma is attenuated in the obese state, and obesity skews CD4 cells towards Th1 polarization [55], and increases secretion of obesity-related pro-inflammatory cytokines such as IL-6 [56]. Adipose tissue produces adipokines and other cytokines that can affect the lungs and airways [57]. Higher leptin levels in obese adults and children have been shown to correlate inversely with airway reactivity and lung function [58, 59]. Hyperglycemia and hyperinsulinemia can cause epithelial damage and airway smooth muscle proliferation leading to airway hyperresponsiveness and remodelling [60].

Eczema

The “atopic march” describes the sequential development of atopic dermatitis in infancy to asthma and allergic rhinitis in later childhood, and was derived from numerous longitudinal cohort studies following the prevalence of allergic diseases from infancy to adolescence [61, 62]. One proposed mechanism for the role of atopic dermatitis in the development of asthma has been through the pathway of epicutaneous sensitization leading to subsequent airway sensitization [63].

In a Canadian birth cohort, atopic dermatitis with allergic sensitization was shown to be a risk factor for subsequent asthma, although this risk was not shown in atopic dermatitis without sensitization. There was a positive additive effect of atopic dermatitis and allergic sensitization on the risk of subsequent asthma [64]. Conversely, in another large birth cohort, wheezing and atopic dermatitis were seen as an early co-manifestation, with no clear sequential emergence between the onset of atopic dermatitis and asthma, between suggesting that the relationship of atopic dermatitis in early childhood to asthma in later childhood cannot be explained through simple linear progression, as in the classical atopic march [65]. A subsequent meta-analysis of four birth cohorts found a twofold increased risk of asthma at school age in children with atopic dermatitis in the first 4 years of life [66]. However, latent variable modeling of two large population-based birth cohorts showed only a small proportion (7%) of atopic children followed trajectory profiles resembling the atopic march [67].

The diverse findings from different cohorts may represent the heterogeneity of atopic dermatitis, or reflect common genetic and/or environmental risk factors resulting in the co-manifestation of both atopic dermatitis and asthma. Although genes associated with atopic dermatitis do not overlap with those associated with asthma, the expression of proteins by genetic regions involved in both asthma and atopic dermatitis are mainly located in epithelial tissue [68]. This suggests that epithelial barrier dysfunction may be a common first

step leading to subsequent sensitization and development of asthma. The subgroup of children with early atopic dermatitis who also develop allergic sensitization appear to be at higher risk of subsequent asthma, however better characterization of this group, and identification of the pathophysiological mechanisms involved, are required before primary preventive strategies can be formulated for these children.

Interventions

Interventions targeting viral infections

Prophylactic administration of pavilizumab, a monoclonal antibody against RSV, has been shown to reduce recurrent wheezing in high-risk children aged 1–3 years, but did not decrease the incidence of atopic asthma [15, 69]. Another study found that the use of early azithromycin at the beginning of a lower respiratory tract infection (LRTI) decreased progression to severe LRTI (HR 0.64, 95% CI 0.41–0.98, $p = 0.04$) [70]. A large study assessing asthma prevention following RSV with early administration of azithromycin is in progress.

Data from birth cohorts suggest that certain strains of HRV (HRV-A and HRV-C) are more highly associated with increased severity of illness. This finding suggests that “asthma-genic” strains may be a valuable target for vaccine or small molecule development. Administration of a short course (3 day) of oral corticosteroids during the first HRV LRTI showed no reduction in subsequent wheezing. However, children with a high HRV viral load treated with prednisolone had a longer time to the next wheezing episode compared to placebo [71].

The clear association between viral infection (particularly HRV & RSV) and the development of asthma has made it a prime target for intervention. A number of promising antiviral agents are in development, targeting aspects of the viral life cycle including receptor binding, fusion, uncaring, translation, and replication; however, none of these candidate drugs have been progressed to a phase 3 clinical trial [72]. At present, interventional strategies targeting the prevention or amelioration of viral infection have not yet been shown to be effect in preventing subsequent asthma. Until then, limiting viral spread through universal precautions and prophylactic passive immunization with RSV (pavilizumab) remain the main available protective measures.

Allergen avoidance

A number of large scale interventional studies have focused on aero-allergen avoidance for the primary prevention of asthma. A Cochrane review in 2009 pooled the results of 3 multifaceted and 6 mono-faceted intervention studies with a total of 3271 children at high-risk of developing asthma [73]. Multifaceted interventions resulted in a significant decrease in asthma compared to usual care (< 5 years: OR 0.72, 95% CI 0.54 to 0.96; > 5 years: OR 0.52, 95% CI 0.32 to 0.85). All three multi-faceted interventional trials targeted reduction in house-dust mite, food, and pet allergen exposure [74–76]. Two of the studies also targeted reduction to environmental tobacco smoke [74, 76]. Most mono-faceted interventional studies have focused on house-dust mite avoidance in the home. However, significant house-dust mite exposure also occurs outside the home, on public transport, in schools and other environments, demonstrating the difficulty of true “real-life” house-dust mite avoidance [77]. Mono-

faceted interventions (reducing exposure to either inhalant or food allergens) did not produce significant effects.

The relationship between exposure and sensitization is widely variable between studies, and with different allergens and populations, varying from simple linear dose-response relation, a "bell-shaped" dose-response model with a protective effect of high allergen exposure or no significant association. Individual interventions to reduce aero-allergens have not been shown to be effective in reducing risk of asthma. Given the complex pathogenesis of asthma and its heterogeneous nature, multifaceted interventions addressing different risk factors may be more effective in preventing development of asthma.

Immunotherapy

Allergen-specific immunotherapy (AIT) is the only known disease modifying treatment in allergic disease. The use of early immunotherapy to modify the natural progression of the allergic march has been proposed as a primary prevention strategy. However at present, there is no evidence base for immunotherapy as primary prevention of asthma or secondary prevention for development of asthma in sensitized children with other allergic diseases. A recent trial assessed the potential role of grass pollen immunotherapy in preventing developing of asthma in grass pollen sensitized children with allergic rhinoconjunctivitis [78]. The intervention group had a reduced risk of experiencing asthma symptoms and asthma medication, but there was no effect on time to onset of asthma.

Interventions to prevent sensitization have also been attempted in children at high-risk of developing asthma. Holt and colleagues designed a trial to investigate multi-allergen immunotherapy (to HDM, cat and timothy grass) in a high-risk infants with no allergic sensitization. Unfortunately, the trial was stopped when pilot data preliminary data showed no difference in immunological parameters between intervention and control groups, suggesting insufficient transmucosal allergen delivery [79]. A large-scale RCT of HDM immunotherapy in 111 high-risk infants showed decrease in sensitization to allergens as a whole, but no treatment effect on HDM sensitization or wheezing [80]. A recent meta-analysis of 32 studies found no conclusive evidence that allergen immunotherapy reduced the risk of developing a first allergic disease or long-term reduction in the risk of sensitization [81].

There has been increasing recognition of the importance of epithelial barrier in immunity and development of tolerance, particularly with regard to epicutaneous sensitization, and food allergy. Studies assessing the association of atopic dermatitis with asthma have shown that this risk is highest or indeed only present in children with both atopic dermatitis and early sensitization [64, 65]. Although not effective in a general high-risk cohort, for a subgroup of young children with atopic dermatitis who are at risk of early sensitization, early immunotherapy with house-dust mite may potentially decrease the risk of sensitization and subsequent development of asthma.

Microbiome

Many well-known environmental factors have been associated with decreased development of atopy and asthma, including farm residence, cohabitation with

dogs, vaginal birth, and day care attendance; all are increasingly recognized to exert their effects through changes in the maturation and composition of the microbiome. Recognition of this connection between microbial dysbiosis and the development of asthma has led to attempts to modify the gut microbiome in early life. However, randomized trials of prenatal or early life administration of probiotic and prebiotic treatments have shown no effect on asthma incidence [82, 83].

Bacterial lysates are immunoregulatory cellular extracts that have been found to reduce allergic airway inflammation. The best studied is OM-85 BV, which contains extracts from eight species: *Staphylococcus aureus*, *Streptococcus* species, *Klebsiella* species, *Neisseria catarrhalis*, and *Hemophilus influenzae*. OM-85 BV has been shown to reduce recurrent respiratory tract infections in adults and children, and has been used in clinical practice for this indication [84, 85]. A multicenter placebo-controlled randomized clinical trial evaluating the effectiveness of OM 85 BV in preventing severe wheezing lower respiratory tract infection in high-risk infants, is currently in progress (NCT02148796) [86].

Environmental air pollution and environmental tobacco smoke

Exposure to environmental air pollutants, such as nitric oxide, ozone, and polycyclic aromatic hydrocarbons (PAH) is a risk factor for abnormal lung development and asthma [87, 88]. Longitudinal cohort studies have shown an association between early exposure to nitrogen dioxide and nitric oxide, and subsequent asthma [89–91]. Cohort studies of asthmatic and non-asthmatic children in geographical areas that undertook significant pollution reduction strategies demonstrated improvements in FEV1 associated with declining levels of nitrogen dioxide [92]. As a public health strategy, interventions to reduce air pollution are feasible and will show demonstrable benefit in reducing the morbidity of asthma.

Vitamin D

Vitamin D has been showed to influence modulation of immune responses and regulation of inflammation. Observational studies have suggested an association between decreased maternal vitamin D intake, low cord blood vitamin D levels, and early childhood wheezing [93]. However, randomized controlled trials of maternal vitamin D supplementation during pregnancy have not shown a reduced risk of persistent wheeze or asthma [94, 95]. Subgroup analysis of the Vitamin D Antenatal Asthma Reduction Trial (VDAART) showed the largest protective effect in women with higher initial vitamin D levels who were randomized to the intervention group—suggesting that higher vitamin D levels may be required to show a beneficial effect on asthma prevention [94].

Obesity

Weight loss interventions in obese adult patients with asthma have shown significant improvements in both asthma control and lung function with sufficient weight loss (at least 5% of body weight, in adults) [96, 97]. Pediatric studies of weight loss interventions for obesity and asthma have been limited to small group before/after comparisons [98, 99]. There have been no reported controlled trials on prevention of obesity as primary

prevention strategy for asthma. Interventions targeting reduction of obesity should begin in prenatal life, given the evidence that maternal obesity and pregnancy-related weight gain increases the risk of asthma in offspring [53, 54]. There are also intriguing associations between infant BMI peaks and early childhood cardio-metabolic markers suggesting that a trajectory towards obesity may begin in infancy. This underlines the fact that the infant and early childhood period are a prime window for multi-faceted interventions for prevention of asthma [100]. Effective public health measures are needed to address target lifestyle factors for obesity such as the increase in sedentary behavior and consumption of high calorie foods. Reduction of childhood obesity should be part of any multi-interventional strategy for primary prevention of asthma.

Conclusion

Developing effective and feasible primary prevention methods is inherently difficult for asthma due to the heterogeneity and complex natural history of the disease. There is a large range of potential risk factors and intrinsic difficulty in establishing causality from observational association studies or untangling the complex multi-factorial interplay between genome, microbiome, and viral interactions in early life. Progress in interventional studies has been slowed by the resources required for adequately powered randomized controlled trials with extended follow-up beyond infancy. Primary prevention strategies that focus on a single risk factor or intervention are clearly inadequate.

Many of the risk factors are well-known and likely to apply to a broad range of phenotypes. These include the effect of tobacco exposure, indoor and outdoor pollution, and childhood obesity, which are risk factors that can be addressed by public health measures. Multi-faceted interventions are most likely to be effective in primary prevention of asthma—through a combination of public health interventions addressing the risk factors mentioned above, and interventions to prevent/ameliorate respiratory viral infections and reduce aero-allergen sensitization. Further work on refining asthma phenotypes will allow personalization of interventions towards the specific risk factors of particular phenotypes or endotypes, thus increasing the efficacy of primary preventive measures.

Respiratory micro-organisms remain a major modifiable risk factor. Further research is required to characterize asthma-genic viral strains to inform vaccine development, identify protective host factors that prevent asthma development after viral respiratory infections, and characterize the microbiome and its complex interactions with respiratory viruses, in order to develop effective interventional strategies for primary prevention.

Further advances in defining asthma phenotypes is necessary to elucidate the common and different risk factors across phenotypes, allowing both broad and narrowly targeted intervention methods. More evidence could be gleaned from novel approaches to interventional trials such as platform trials [101], which are biomarker-driven trials with Bayesian statistical methods that allow investigation of the efficacy and safety of several interventions in different phenotypic groups.

Compliance with Ethical Standards

Conflict of Interest

The authors declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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