



REVIEW

Better understanding of childhood asthma, towards primary prevention – are we there yet? Consideration of pertinent literature [version 1; referees: 2 approved]

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Abstract

Asthma is a chronic disease, characterized by reversible airway obstruction, airway inflammation and hyper-reactivity. The prevalence of asthma has risen dramatically over the past decade, affecting around 300,000,000 people. The etiology is multifactorial, with genetic, epigenetic, developmental and environmental factors playing a role. A complex interaction between the intrauterine environment, the developing immune system, the infant's microbiome and infectious organisms may lead to the development of allergic sensitization and asthma. Thus, a large number of studies have investigated the risk factors for childhood asthma, with a meticulous search of modifiable factors that could aid in primary prevention.

We present a current literature review from 2014-2017, as well as older classic publications, on the pathogenesis and the potential modifiable factors for primary prevention of asthma. No ideal preventive measure has yet been found. Rather, creating favorable prenatal and postnatal environments, minimal exposure to hostile environmental factors, prevention of infections in early life, allergic desensitization and nutritional modifications could possibly reduce asthma inception. In the era of personalized medicine, identifying individual risk factors and tailoring specific preventive measures is warranted.

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Introduction

Asthma is a chronic disease, characterized by episodes of reversible airflow obstruction. The prevalence of allergic diseases and asthma has risen substantially over the past decades. Currently, it is the most common non-communicable disease, affecting around 300,000,000 people, especially in developed countries, leading to enormous public health costs¹. In a recent study, the total annual health care expenditure attributable to asthma for school-aged children in the United States was 5.92 billion US dollars². Currently, no available therapeutic regimens can cure asthma, and the burden of asthma will continue to be driven by the increased but, as yet, poorly explained prevalence³.

Population-based birth cohorts on asthma and allergies may provide insights into the development and natural history of the diseases. Over 130 birth cohorts have been initiated in the last 30 years⁴. These birth cohorts have improved our understanding of asthma inception, progressions and persistency. Thus, they may help in targeting the ambitious and important goal of primary prevention of asthma. The Tucson birth cohort, developed in 1995 by Martinez *et al.* is the “classic” and most utilized model. This cohort proposed three categories of wheezing phenotypes at early age: transient wheezers (wheezing symptoms before 3 years, no wheezing at age 6), late onset wheezers (no wheeze until 3 years, wheezing at age 6), and persistent wheeze (wheezing in the first 3 years, wheezing at 6 years). This latter group of persistent wheezers can be divided into non-atopic and atopic. One third of all children aged 3 or younger had lower respiratory tract illnesses with wheezing; however, by the age of 6 close to 60 percent of these children no longer had wheezing symptoms. Transient early wheezers were found to have lower levels of lung function compared to other groups of wheezers, possibly reflecting congenitally smaller airways⁵. Understanding the trajectory of early wheezing may help identify early predictors of later childhood persistent asthma. This is of utmost importance in identifying preventive interventions that could potentially reduce the inception of asthma⁶.

The etiology of asthma is multifactorial; genetic, epigenetic, developmental and environmental factors play a role, as do the interactions between them^{1,3}. Two important risk factors have been identified: the development of allergic sensitization and wheezing respiratory tract illnesses at an early age. Since both allergic sensitization and viral/bacterial illnesses occur in children who do not develop asthma, it is crucial to identify genetic and environmental factors that activate, interfere with and direct the immune system toward the development of asthma⁷. Moreover, it has been found that environmental factors affecting a critical period in lung development (during pre- and postnatal periods) are associated with the development of allergic diseases and asthma. Epigenetic pathways could mediate the gene-environment interactions⁸ and may explain the impact of external environmental factors on disease development.

Taking into account the significant burden of asthma, it is crucially important to find preventive measures. Strategies targeting asthma prevention can be primary (e.g. infants at high-risk for asthma) or secondary, dealing with children who have

developed allergic sensitization or the first manifestations of allergic diseases (e.g. eczema or wheezing)⁹. However, the heterogeneity and complex natural history of the disease serve as a barrier for the use of a single prevention strategy and suggest the importance of individualized risk assessment and multiple prevention measures with personalized primary prevention strategies³. This review discusses research from the past 3 years, focusing on childhood asthma and primary preventions. We conducted a PubMed search of observational studies and clinical trials, including systematic reviews and meta-analyses, from 2014 to 2017. We also included older classic publications; thus, the search included studies dealing with potentially modifiable factors (both prenatal and postnatal) implicated in the inception of asthma. Environmental factors, early life respiratory infections, host factors and nutritional interventions will also be discussed.

Environmental factors

Favorable environment

The “farm effect”. The importance of favorable environmental exposures in the development of asthma was demonstrated by epidemiologic studies showing significant protection from asthma and allergic diseases in children raised on traditional dairy farms. In particular, it was found that children who lived on farms were exposed to a greater variety of environmental microorganisms than controls. Endotoxin, a cell wall component of Gram negative bacteria, along with peptidoglycan, is widespread in stables and other farming environments and exposure to such microbial compounds was found to be inversely correlated with the risk of atopy¹⁰. Higher diversity of microorganism exposure was correlated with a reduced prevalence of asthma and atopy¹¹. Compelling data exist showing that the “farm effect”¹² is not only present in childhood but also exerts an effect during pregnancy, influencing the developing fetal immune system. The farming environment has been linked with lower rates of asthma in offspring, although early-life farm exposure was shown to boost this effect¹³. A recent study with the Amish community using traditional farming and the Hutterite community using industrialized farming evaluated asthma prevalence in children with similar genetic ancestries and lifestyles¹⁴. Asthma prevalence and allergic sensitization was 4 and 6 times lower in the Amish community, whereas median endotoxin levels in Amish house dust was 6.8 times higher. The authors used a murine model of experimental allergic asthma to assess the effects of dust extracts found in Amish and Hutterite households on immune and airway responses. Experiments in humans and mice indicated that the traditional farm environment guards against asthma via interaction with and molding of the innate immune response. Hence, it is evident that altering innate immune signaling, as by farm environment, may be the primary target of asthma protection. However, the interventions required to create a farm effect without living on a farm are as yet unknown.

Pets. Several prospective birth cohort studies found a decreased prevalence of atopic disease in children having daily contact with pets, in particular cats and dogs, during early infancy¹⁰. Exposure to two or more dogs or cats in the first year of life was associated with a significantly lower risk of atopy (adjusted OR 0.23, 95% CI 0.09-0.60)¹⁵. Another study found that living with

a cat was inversely related both to having a positive skin test to cat (RR, 0.62 [0.47–0.83]) and incidence of physician-diagnosis of asthma (RR, 0.49 [0.28–0.83]). The effect was most pronounced among the children with a family history of asthma. Ownership of a dog resulted in weaker protective trends¹⁶. A pooled analysis of individual participant data of 11 prospective European birth cohorts of 22,000 children concluded that pet ownership in early life did not appear to either increase or reduce the risk of asthma¹⁷. However, a large nationwide cohort study (1,011,051 children) in Sweden found that dog exposure during the first year of life was associated with a decreased risk of asthma in school-aged children (OR 0.87, 95% CI 0.81-0.93) and in children 3 years or older (HR 0.90, 95% CI 0.83-0.99). Exposure to farm animals was correlated with a lowered risk of asthma in both children of school and preschool age. These results were independent of parental asthma¹⁸.

However, the effect of exposure to dogs and farm animals was less pronounced in children younger than 3 years of age. These young children may reflect a group of children with transient wheeze and not persistent asthma⁵. Taken together, most (but not all) studies support the theory of protective effects of having pets on asthma development.

Day care attendance. The effect of day care attendance on asthma development is complex. In a study involving 1,035 children followed since birth as part of the Tucson study, children with older siblings or day care attendance were more likely to have frequent wheezing at the age of 2 years, but less likely to have frequent wheezing from the age of 6 to 13 years¹⁹. Different results were obtained in a birth cohort of 762 children²⁰. In this study, day care attendance at 12 months was associated with an increased risk of asthma [OR 1.8, 95% CI 1.1-3.0]. A multivariate logistic model showed that day care attendance and number of lower respiratory infections at 12 months were associated with asthma [OR 1.2 (1.1-1.5); OR 1.4 (1.2-1.7), respectively]. Nevertheless, day care attendance of greater than 37.5 hours per week was associated with a lower risk of asthma [OR 0.6 (0.4-0.9)]. Hence, day care during infancy can either increase or reduce the risk of asthma.

Prevention of allergic sensitization

There is a clear association between asthma and allergy²¹. Most school age children and adolescents with asthma also have allergic sensitization. Early allergic sensitization is a risk factor for asthma development. In children of preschool age, researchers have found a sequential relationship of allergic sensitization followed by virus-induced wheezing. Exposure to allergens may increase asthma severity in susceptible patients (for example, an asthmatic patient exposed to dust mite allergens may develop increased airway hyper-reactivity)²². Therefore, prevention of allergic sensitization is a major path for primary prevention of asthma.

A Cochrane review in 2009 found that multifaceted interventions (reducing exposure to both inhalant and food allergens) 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). Monofaceted interventions (reducing exposure to either inhalant or food allergens) did not produce significant effects²³. Another interventional study assessed the effectiveness of a multifaceted intervention program for the primary prevention of asthma in high-risk infants. The interventions were initiated shortly before birth and applied until 1 year of age, and included avoidance of house dust mites, pets, environmental tobacco smoke, encouragement of breast-feeding, and delayed introduction of solids. These measures resulted in a 4-fold reduction in the risk of asthma (adjusted OR, 0.26; 95% CI 0.08-0.88) in the children who did not develop atopy by 1 year of age; however, in children with early, persistent atopy, the risk of asthma was not reduced²⁴. Moreover, attempts to reduce exposure to house dust mites, known to be strongly associated with atopic sensitization and the development of asthma in childhood, were not found to be effective in the primary prevention of disease³. Lynch *et al.* examined a birth cohort and a nested case-control study to assess the factors linking contact with allergens and bacteria in the first 3 years of life with the inception of recurrent wheeze and atopy. As the authors put forward, increasing allergen exposure in the first 3 years correlated with allergic sensitization, and allergic sensitization correlated with recurrent wheeze. However, there was a negative association between contact with cockroach, mouse and cat allergens in the first year and recurrent wheeze (OR 0.60, 0.65, and 0.75, respectively, $p \leq 0.01$)²⁵.

Overall, the reported nature of the relationship between exposure and sensitization varies widely among studies, from no significant association to a simple linear dose–response relationship or a ‘bell-shaped’ dose–response model with a protective effect of high allergen exposure. A recent study assessed the potential role of immunotherapy to alter the natural course of allergic march from allergic sensitization to asthma. The study included 812 children (5–12 years), with grass pollen allergic rhinoconjunctivitis and no medical history or signs of asthma. Children were double blinded and randomly allocated to receive immunotherapy or placebo for three years and were followed for two additional years²⁶. The study showed reduced risk of experiencing asthma symptoms and using asthma medication, but did not show an effect on the time to onset of asthma.

Hence, the relationship of atopic desensitization and asthma is complex and is likely determined by the type of allergen, the timing, pattern, route of exposure (inhaled, oral, transcutaneous), dose, as well as other environmental factors and individual genetic predispositions²¹. Thus, the role and the measures of prevention of sensitization in the development of IgE-mediated sensitization asthma are yet to be determined.

Hostile environment

Air pollution. Air pollutants, representing a complex exposure to inorganic and organic components, are known to exacerbate asthma symptoms and might play a role in initiation of this disease. Particulate matter (PM) carries both environmental pollutants, such as polycyclic aromatic hydrocarbons (PAHs)—formed during incomplete combustion of fossil fuels and oil products—as well as agents causing immune stimulation—such as pollens, endotoxin and fungal spores. Air pollutants probably

cause oxidative injury to the airways, leading to inflammation, remodeling, and an increased risk of sensitization. The idea that air pollution can cause exacerbations of pre-existing asthma is supported by evidence-based studies, but evidence suggests that air pollution might cause new-onset asthma as well, both in children and in adults²⁷. In a recent epidemiologic review, Schulz *et al.* concluded that early life and school-age exposures to air pollution has a negative impact on lung function, at least up to adolescence²⁸. In a Canadian birth cohort study, postnatal exposure to traffic-related air pollution increased the risk for the development of atopy to any allergens (adjusted OR 1.16; 95% CI 1.00-1.41)²⁹.

Gauderman *et al.* found an association between improvements in air quality in southern California and measurable improvements in lung-function development in children³⁰. Consequences of exposure to pollutants, pre- or postnatal, represent a complex interaction between the environment, the host and epigenetic factors. In children, PAH exposure has been associated with changes in DNA methylation, as well as impaired function of regulatory T cells³¹. Epigenetic processes translate environmental exposures into regulation of the identity, gene expression profile, and activity of specific cell types that participate in the pathophysiology of the disease. Further discussion of the effects of air pollution is beyond the scope of this review.

Tobacco smoke. There is evidence indicating a consistent detrimental effect of prenatal exposure and postnatal environmental smoking on childhood wheezing illnesses. Environmental tobacco smoke (ETS) during critical periods of lung development (prenatally, i.e. during pregnancy, and during early life) is considered a substantial risk factor for childhood allergic diseases. ETS induces over-expression of Toll-like receptors on the surface of the airway epithelium, increases oxidative stress and activates dendritic and innate lymphoid cells through the production of cytokines, such as IL-1, IL-25 and IL-33. The result is a higher susceptibility to allergen sensitization and a further risk for asthma³². Genetic polymorphism on chromosome 17q21 was found to be predictive of childhood-onset asthma, and the risk was further increased by early-life exposure to environmental tobacco smoke^{33,34}.

In a meta-analysis, ETS was associated with an increased risk of elevated specific IgE (OR 1.12; 95% CI 1.00-1.25) and positive skin prick test (OR 1.15; 95% CI 1.04-1.28). The relationship was stronger in young children and in prospective studies³⁵. In another meta-analysis of 79 prospective studies, ETS was found to increase the risk of wheeze by age 2 years by 70%; prenatal smoking was related to a 40% increased risk. The risk of asthma decreased with age (30% at age 3–4 years, 23% at 5–18 years)³⁶. In a cohort study of 27,993 mother–child pairs, children of mothers exposed to passive smoking whilst pregnant but no other smoking exposure had an increased tendency to develop wheeze up to 2 years old (OR 1.11; 95% CI 1.03–1.20) in comparison with control pairs. Exposure to passive smoke postnally, in addition to their mothers' prenatal passive exposure, further increased the risk (OR 1.29; 95% CI 1.19–1.40). The risk was highest with passive neonatal exposure in addition to prenatal active smoking (OR 1.73; 95% CI 1.59–1.88)³⁷. Thus, ETS was found to be

an important but avoidable risk factor for the development of allergic disease in children³⁵. Smoking is a modifiable risk factor in asthma. There is definitely a need for robust measures to reduce prenatal and postnatal smoking as a strategy for primary prevention of asthma.

Early life respiratory infections

Infections

Childhood asthma and infant respiratory viral infection are the most frequent chronic and acute illnesses of childhood, respectively. Over the years, it has been possible to make links between these diseases and spot common clinical traits. Early life respiratory syncytial virus (RSV) and human rhinovirus (HRV) lower respiratory tract infections (LRTIs) have been found to be strongly associated with increased asthma risk. During early infancy, RSV is a more common cause of severe LRTI. With advancing age, the situation is reversed, with HRV becoming more common. In spite of continuous research, the role of these respiratory viruses in the inception of asthma is still under debate³⁸.

Respiratory syncytial virus (RSV). Severe RSV bronchiolitis requiring hospitalization is considered a risk factor for future asthma. In the RSV Bronchiolitis in Early Life Study, 50% of patients hospitalized with RSV had a physician diagnosis of asthma at age 7 years³⁹. Another study found that 21% of infants hospitalized for RSV bronchiolitis had asthma at age 6 years, compared to 5% in controls⁴⁰. There is a direct relationship between the severity of the initial RSV bronchiolitis and the risk of subsequent asthma, while environmental factors may further augment the risk⁴¹. Thus, the association between early life RSV LTRI and later wheezing is consistent across most studies with large effect sizes and severity dose-response relationship.

The pathway from early-life infections with RSV to asthma is the result of complex interactions between the specific type of the virus, genetic, and environmental factors. RSV induces persistent airway damage and bronchial hyper-responsiveness⁴². It has been suggested that RSV infection affects Th1/Th2 balance in early childhood, thereby inducing an atopic state and may, therefore, be involved in the inception of asthma⁴³. There is data that suggest that in utero exposure to RSV is followed by dysregulation of neurotrophic pathways, predisposing to postnatal airway hyperreactivity upon reinfection with the virus⁴⁴.

Palivizumab (monoclonal antibody) prophylaxis in the first year of life reduces recurrent wheezing in children aged 1 to 3 years⁴⁰. Palivizumab resulted in a relative reduction of 61% (95% CI 56-65) in the total number of wheezing days during the first year of life⁴⁵. However, the substantial cost, the need to treat a large population early in life (before RSV infection), and the need for parenteral administration limit its widespread use⁴¹. While there is evidence that palivizumab prophylaxis reduces wheezing, its long-term impact on the development of atopic asthma remains controversial. In a follow-up study of children aged 2 to 5 years, palivizumab administration resulted in a 68% reduction in wheezing in the families of non-asthmatics and an 80% reduction in wheezing in non-atopic families, but no protection was achieved in atopic families⁴⁶. Similarly, in a recent

prospective multicenter observational cohort study of 444 pre-term infants, palivizumab prophylaxis administration significantly reduced subsequent physician diagnosis of recurrent wheezing up to 6 years, but did not reduce the incidence of atopic asthma, casting doubt on the suggestion that RSV prevention may decrease atopic asthma inception⁴⁷. Carroll *et al.* looked at infants at high-risk for severe RSV and whether a link could be found between better adherence to immunoprophylaxis and decreased childhood asthma. Analysis revealed that 70% or greater adherence decreased the odds of asthma compared to those with 20% or less adherence (OR 0.62; 95% CI 0.50-0.78)⁴⁸. Recently, in two prospective birth cohort studies, HRV infection was significantly more common among infants administered with RSV immunoprophylaxis (OR, 1.65; 95% CI 1.65-2.39)⁴⁹.

Taken together, the impact of palivizumab on the development of atopic asthma after RSV infection is still controversial. A definitive large-scale randomized clinical trial (RCT) measuring the effect of the prevention of RSV on childhood asthma is yet to be done. A large study evaluated 607 children aged 12 to 71 months at the beginning of a LRTI. Administration of azithromycin significantly reduced the odds of progression to severe LRTI (HR 0.64; 95% CI 0.41-0.98, $p=0.04$)⁵⁰. A relatively small double-blind placebo-controlled trial found a protective effect of azithromycin therapy during RSV bronchiolitis on subsequent recurrent wheeze⁵¹. Currently, a larger study assessing asthma prevention following RSV by azithromycin is being conducted (NCT02911935).

Other strategies to prevent RSV are under investigation. There are some efforts to develop a specific vaccination against RSV. Recently, a genetically engineered, live attenuated vaccine was found to be effective in a phase I study⁵². Another innovative approach includes immunization of pregnant women that potentially will decrease airway hyperreactivity upon postnatal reinfection with the virus⁵³.

In conclusion, although there is a clear association between RSV and asthma, the role of strategies to prevent RSV (palivizumab, azithromycin, vaccine) in asthma prevention has yet to be confirmed.

Human rhinovirus (HRV). HRV has been increasingly recognized as an etiologic factor in preschool wheeze, as well as a significant risk factor in the development of asthma⁴¹. Episodes of wheezing during which HRV was found in the upper airways have been found to be a strong predictor of subsequent asthma⁵⁴. HRV wheezing illnesses were found to increase the risk of asthma by 10-fold at 6 years of age⁵⁵. Lee *et al.* analyzed 1,445 samples collected from 209 infants enrolled in the COAST (Childhood Origins of ASThma) cohort study; these infants had an increased risk for developing allergies and asthma. HRV species A and C were about 7 times more likely to cause moderate to severe illness. These results firmly indicate that antiviral therapies aiming at lowering HRV-related morbidity in those infants at high risk ought to be directed towards HRV-A and HRV-C species.

As with RSV, the mechanism by which severe early-life HRV causes future asthma remains uncertain. Postulated mechanisms are airway epithelial injury and/or creating the appropriate pro-inflammatory allergenic milieu; alternatively, wheezing viral LRTI may serve as a marker for asthma susceptibility. Several studies suggest that the initial wheezing HRV LRTI may serve as a marker for asthma tendency, while early-life severe RSV bronchiolitis may have a causative role in the development of asthma⁴¹. Thus, preventive measures are aimed at decreasing the incidence and severity of infections caused by HRV. A recent study⁵⁶ identified day-care attendance (OR 5.0; 95% CI 2.3-10.6), high eosinophil blood counts (OR 2.6; 95% CI 1.2-5.7) and exposure to tobacco smoke (OR 2.5; 95% CI 1.1-15.6) as significant risk factors for HRV LRTI. Hence, restricting children's exposure to tobacco smoke may limit dissemination of viruses to younger children, counteract severe respiratory diseases, and thus may reduce sequelae.

An RCT assessed the efficacy of oral corticosteroid treatment during the first HRV LRTI to reduce the frequency of subsequent wheezing within 12 months. The study failed to show reduction in post HRV wheezing; however, children with a high viral load treated with prednisolone had a longer time to the next wheezing episode compared to placebo⁵⁷.

Strategies for developing an effective vaccine⁵⁸ or for preventing viral contact and invasion by forming a barrier on the host mucosa⁵⁹ are being developed; however, currently there is no approved strategy against HRV. Limiting viral spread is the main available protective measure.

Host factors

The microbiome

The whole host-microbe system benefits from the essential ecosystem services provided by microbial communities (microbiota) and the host environment in which they reside. Such services include making vital resources, nutrient bioconversion, and guarding against harmful microbes. Disease can arise from a shortfall in these beneficial functions or the maladaptive functions introduced by pathogenic microbes.

With the advent of 16s rRNA sequencing, a strong association between the host microbiome and asthma has emerged. The microbiome can be modulated by various environmental factors, including diet, prebiotic and probiotic, and early-life microbial exposures. Recently, the nasopharyngeal microbiome of 33 healthy infants was compared to 99 infants with confirmed RSV. The abundance of the dominant genera was significantly different between the groups, suggesting that RSV alters the infant nasopharyngeal microbiome and, thereby, may contribute to asthma development⁶⁰.

Affecting the microbial dysbiosis was suggested as a target for the prevention of asthma⁶¹. Herein, we will discuss the potential role of a prebiotic and probiotic diet in the prenatal and postnatal period.

Prenatal. Prenatal prebiotic and probiotic supplementation may alter maternal gut bacteria and influence maternal immune function. There is an inconsistent effect on the offspring of mothers supplemented during pregnancy, and a comprehensive 2016 World Allergy Organization review found a lack of evidence to support the use of prebiotics during pregnancy⁶².

Maternal urinary tract infection during pregnancy increased the likelihood of asthma (OR 1.21; 95% CI 1.2-1.220)³. Several studies have reported an association between the use of over-the-counter antipyretics during pregnancy or infancy and an increased risk (OR 1.26; 95% CI 1.02-1.58) of asthma in early childhood, but not mid-childhood⁶³. In a recent review, the maternal use of antibiotics or paracetamol during pregnancy was suggested as a modifiable risk factor for childhood asthma⁶⁴.

Postnatal. Microbial gut colonization typically starts at the time of birth, and is influenced by the bacterial load of maternal microbiota, type of delivery (cesarean section vs. vaginal delivery), feeding (formula vs. breast-feeding), and the use of antibiotics.

In a retrospective cohort study including 321,287 births, there was no difference in the risk of asthma following planned compared to unscheduled cesarean surgery. However, compared to vaginal delivery, planned cesarean delivery resulted in a small increase in the risk of asthma requiring hospital admission (adjusted HR 1.22; 95% CI 1.11-1.34) and salbutamol inhaler prescription at age 5 years (adjusted HR 1.13; 95% CI 1.01-1.26)⁶⁵. In another study, cesarean section increased the risk of childhood asthma by 34% in univariate analysis and 11% after adjusting for other environmental exposures and covariates⁶⁶. Infants born via cesarean section have higher rates of *Clostridium*, *Klebsiella*, *Bacteroides*, and several other species at age 1 to 6 months, which predispose them to a higher risk for asthma, atopy and allergic rhinitis⁶⁷. In the newborn period, the gut microbiota plays a crucial role in maintaining the structure and function of the mucosal immune system. Gut-associated mucosal lymphoid tissue becomes reactive to pathogenic bacteria but tolerant to “beneficial” bacteria. T regulatory cells (Treg) are the key players in immunological tolerance; changes in their number or function are associated with the development of allergy⁶⁷. In a recent systematic review, the early microbiota of children who later developed allergies showed lower bacterial diversity; moreover, a predominance of Firmicutes, a higher prevalence of *Escherichia coli*, *Clostridium difficile*, and a lower prevalence of *Lactobacillus* were found⁶⁸.

In the Canadian Healthy Infant Longitudinal Development (CHILD) Study, Arrieta *et al.* evaluated the gut microbiota of 319 individuals. They found that those at risk of asthma showed transient gut microbial dysbiosis in their first 100 days of life, with reduced levels of *Faecalibacterium*, *Veillonella*, *Lachnospira*, and *Rothia*. Moreover, when these four bacterial taxa were introduced to germ-free mice, they showed decreased airway inflammation, suggesting a causal role of these bacteria in asthma development⁶⁹.

Several animal and human studies have examined the role of the postnatal use of prebiotics and probiotics in the prevention of

allergic diseases. A meta-analysis reported data from 4,755 children (2,381 in the probiotic group, 2,374 controls). Infants treated with probiotics had a significantly lower risk of eczema (RR 0.78; 95% CI 0.69-0.89). No significant difference in terms of prevention of asthma (RR 0.99; 95% CI 0.77-1.27) or wheezing (RR 1.02; 95% CI 0.89-1.17) was found. Another meta-analysis concluded that controlled studies have not yielded sufficient evidence to date to recommend prebiotics and probiotics for the primary prevention of asthma⁷⁰.

Perinatal and postnatal suggested modifiable behaviors were natural childbirth, breastfeeding, increased outdoor activities, diet and the judicious use of antibiotics and antipyretics. These measures may help restore the neonatal microbiome and may reduce the risk for allergic diseases⁷¹.

Nutritional prevention

Dietary interventions during pregnancy are attractive because they are inexpensive and follow the accepted practice of folic acid supplementation³. Several nutritional supplements have been investigated; we will discuss the main recent findings.

Current evidence suggests that maternal diet during pregnancy influences the developing immune system of the fetus. Interestingly, maternal weight gain or obesity during pregnancy was found not only to increase maternal asthma exacerbations⁷² but also the risk for childhood asthma⁶⁴. Thus, efforts to prevent childhood asthma focus on early prenatal and postnatal interventions. The Mediterranean diet (MD) comprises fruit, vegetables and grains, a moderate intake of dairy products and a low intake of meat. This diet has been suggested to have a potential protective role in asthma. In a recent pilot study involving 30 pregnant women, the introduction of MD was feasible and acceptable, with 93% of participants retaining the diet⁷³. In a meta-analysis, MD was associated with a lower prevalence of “asthma ever” (OR -0.86; 95% CI 0.74–1.01), as well as “current wheeze” (OR -0.85; 95% CI 0.75–0.98) and “current severe wheeze” (OR -0.66; 95% CI 0.48–0.90)⁷⁴.

Thus, although MD has been suggested to be beneficial to general health, its impact on asthma prevention is still not proven and requires a large epidemiological study; assessing the mechanism, the relevant window of exposure and addressing specific components of the diet is warranted.

Vitamins

Most studies focus on vitamin D supplementation and the results are inconclusive. Vitamin D has the ability to regulate inflammation and modulate immune responses and cell growth. Experimental data suggest that vitamin D may affect the developing lung and immune system during the prenatal and postnatal periods. Additionally, observational studies have suggested an association between maternal intake of vitamin D, cord blood vitamin D levels and persistent and recurrent wheezing in early childhood⁷⁵. In an RCT, 623 pregnant Danish women receiving 400 IU/d of vitamin D during the third trimester of pregnancy were randomized to receive an additional 2400 IU/d or placebo. Follow-up of the children (N=581) was completed when the

youngest child reached age 3 years. Persistent wheeze was diagnosed in similar rates (16% and 20%) of children whose mothers received supplemental vitamin D and placebo, respectively (hazard ratio 0.76; 95% CI 0.52-1.12; $p=0.16$). The results suggest that 2800 IU/d during the third trimester of pregnancy cannot reduce the risk of persistent wheeze in the offspring through age 3 years. In the Vitamin D Antenatal Asthma Reduction Trial (VDAART) RCT, 881 pregnant women at risk of having children with asthma were randomized to 4,000 international units (IU)/d vitamin D or placebo plus 400 IU/d of vitamin D. Supplementation with 4400 IU/d resulted in a 20% reduction of recurrent wheeze or asthma (hazard ratio 0.8; 95% CI 0.6-1) that did not reach statistical significance ($p=0.051$)⁷⁶. A secondary analysis of the data revealed that the largest protective effect was found in women with higher initial vitamin D levels who were randomized to the intervention group (adjusted OR 0.13; 95% CI 0.02-0.99)⁷⁷. This suggests that higher vitamin D levels in early pregnancy may be required for asthma/recurrent wheeze prevention in early life.

A meta-analysis reporting data from 2,456 children demonstrated that prenatal supplementation of vitamin D significantly decreased recurrent wheeze (RR 0.812; 95% CI 0.67-0.98). Postnatal vitamin D administration was found to be associated with a reduction in upper respiratory tract infections⁷⁸; however, its role in primary asthma prevention remains unclear. Thus, a large randomized double-blind controlled study is currently being conducted to assess the role of postnatal vitamin D supplementations on multiple end points, including allergy, atopy and asthma later in life (NCT01723852)⁷⁹.

Vitamin C and E studies have not undergone meta-analysis due to high heterogeneity; these vitamins did not appear to have a significant preventive effect on recurrent wheeze⁸⁰.

To conclude, currently there is no sufficient evidence regarding any of the vitamins in the inception and prevention of asthma. Larger double-blind studies are required to recommend their routine use.

Antioxidants and fish oil

Antioxidants reduce reactive oxygen species and there are several reports about the inverse associations between intake of antioxidants and allergic diseases. Total antioxidant capacity (TAC) assesses the combined activity of all the dietary antioxidants. A study in 2,359 Swedish children found that higher dietary TAC was inversely associated with the sensitization to aeroallergens (OR 0.73; 95% CI 0.55-0.97) and the risk of allergic asthma (OR 0.57; 95% CI 0.34-0.94). Interestingly, the relationship was modified by exposure to air pollution. A stronger inverse association between dietary TAC and allergy was observed in children with low exposure to air pollution. The authors postulated that high TAC may not be enough to counteract the high oxidative stress caused by air pollution⁸¹.

More than a decade ago, Hodge *et al.* examined the relation between certain food consumption and asthma. They found a significantly reduced risk of current asthma in children who ate fresh, oily fish (OR 0.26; 95% CI 0.09-0.72; $p<0.01$)⁸².

Later on, observational studies suggested an association between low levels of dietary fish-oil derived fatty acids (FA) and the risk of asthma and wheezing. In an RCT, 736 pregnant women were assigned to receive 2.4 gr of fish oil or placebo (olive oil). In the treatment group, there was a 30.7% reduction in the risk of persistent wheeze or asthma. The effect was most prominent in the women with low FA levels at randomization; moreover, the effect of the intervention remained at age 5 years, suggesting that it is not restricted to the “transient wheezers”⁸³.

Taken together, dietary interventions may aid in the primary prevention of asthma. Antioxidants, MD and fish oil seem to have a beneficial effect. Vitamin D is associated with asthma, but evidence for its role in primary prevention is still lacking. Other vitamins studied (such as C and E) failed to show a beneficial effect.

Stress

Stress has been suggested to modify the normal lung morphogenesis and maturation during pregnancy and the postnatal period. Stress may affect neuroendocrine, autonomic and immune function programming, thereby leading to increased asthma inception. Prenatal maternal stress was found to alter innate and adaptive immune response in cord blood mononuclear cells, suggesting that prenatal stress may impact the expression of allergic diseases and increase the risk for later childhood wheezing^{84,85}.

Postnatally, maternal behavior was found to influence the development of hypothalamic-pituitary-adrenal (HPA) responses to stress in rodents, mediated by changes in glucocorticoid receptor (GR) expression⁸⁶. Dreger *et al.* found that exposure to maternal distress restricted to the first year of life resulted in a 40% increase in cortisol levels in children; beyond the postnatal period, response to stress differed according to the presence of asthma⁸⁷. A recent study in a high-risk birth cohort found that maternal stress at age 2 and 3 years and maternal depression at any age were positively associated with recurrent wheeze ($p<0.05$ and $p\leq 0.01$, respectively)⁸⁸. Moreover, both active and passive stressors in asthmatic patients were associated with an increased activation of the sympathetic nervous system⁸⁹. Taken together, the data suggest that prenatal as well as postnatal maternal distress may contribute to asthma development in children; thus, lowering early life stress may help decrease asthma.

Conclusions

Asthma is a chronic inflammatory disease, and genetic, infectious, nutritional and environmental factors play a role in its pathogenesis. In recent years, there has been some advance in the concept of primary prevention of asthma. However, there is no consensus on the relative importance of risk factors associated with asthma inception and none of the primary prevention or intervention strategies investigated has provided sufficient evidence to lead to widespread implementation in clinical practice. Current findings suggest that the major preventing measures during pregnancy are avoiding of passive and active smoking and the possible modification of maternal microbiome (e.g. lifestyle, diet, nutritional supplements). Avoiding unnecessary caesarean delivery is the main perinatal

measure that may affect asthma. Postnatally, the most important measures are preventing severe neonatal respiratory infection, increasing favorable environment and behaviors (e.g. mimicking farm residence, breastfeeding) and decreasing hostile environments (e.g. smoking and air pollution). Unfortunately, gaps in knowledge still exist. The exact immune pathways that predispose certain infants (and not others) to asthma following early life viral infections are not fully understood. Additionally, although there is a clear association between allergy and asthma, its role in the primary prevention of asthma is under debate. Moreover, none of the suggested therapies or interventions can serve as a sole solution for the prevention of asthma inception. Instead, the combination of several pre- and postnatal factors, such as creating a favorable environment with minimal exposure to a hostile environment, attempts to beneficially affect the maternal and infant microbiome, with prevention of infections in early life, is expected to be more effective. This should be achieved by extensive educational and public health efforts to reduce tobacco

smoking and air pollution, to implement dietary interventions in pregnant women, and to encourage breastfeeding and childhood vaccinations.

Future research should focus on the prevention of RSV and HRV, possibly by vaccine development. Moreover, in the era of personalized medicine, a test that would recognize the specific asthma phenotype and endotype of each patient, as well as his or her own risk factors, would enable tailoring specific preventive measures for the individual patient.

Competing interests

The authors declared that they have no competing interests.

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References



- Jackson DJ, Hartert TV, Martinez FD, *et al.*: **Asthma: NHLBI Workshop on the Primary Prevention of Chronic Lung Diseases.** *Ann Am Thorac Soc.* 2014; **11**(Suppl 3): S139–45.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Sullivan PW, Ghushchyan V, Navaratnam P, *et al.*: **The national cost of asthma among school-aged children in the United States.** *Ann Allergy Asthma Immunol.* 2017; **119**(3): 246–252.e1.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
- Beasley R, Semprini A, Mitchell EA: **Risk factors for asthma: is prevention possible?** *Lancet.* 2015; **386**(9998): 1075–85.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Bousquet J, Gern JE, Martinez FD, *et al.*: **Birth cohorts in asthma and allergic diseases: report of a NIAID/NHLBI/MedALL joint workshop.** *J Allergy Clin Immunol.* 2014; **133**(6): 1535–46.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Martinez FD, Wright AL, Taussig LM, *et al.*: **Asthma and wheezing in the first six years of life. The Group Health Medical Associates.** *N Engl J Med.* 1995; **332**(3): 133–8.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Panico L, Stuart B, Bartley M, *et al.*: **Asthma trajectories in early childhood: identifying modifiable factors.** *PLoS One.* 2014; **9**(11): e111922.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Jackson DJ, Gern JE, Lemanske RF Jr: **The contributions of allergic sensitization and respiratory pathogens to asthma inception.** *J Allergy Clin Immunol.* 2016; **137**(3): 659–65;quiz 666.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Potaczek DP, Harb H, Michel S, *et al.*: **Epigenetics and allergy: from basic mechanisms to clinical applications.** *Epigenomics.* 2017; **9**(4): 539–71.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
- Elenius V, Jartti T: **Vaccines: could asthma in young children be a preventable disease?** *Pediatr Allergy Immunol.* 2016; **27**(7): 682–6.
[PubMed Abstract](#) | [Publisher Full Text](#)
- von Mutius E, Schmid S: **The PASTURE project: EU support for the improvement of knowledge about risk factors and preventive factors for atopy in Europe.** *Allergy.* 2006; **61**(4): 407–13.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Ege MJ, Mayer M, Normand AC, *et al.*: **Exposure to environmental microorganisms and childhood asthma.** *N Engl J Med.* 2011; **364**(8): 701–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
- Wlasiuk G, Vercelli D: **The farm effect, or: when, what and how a farming environment protects from asthma and allergic disease.** *Curr Opin Allergy Clin Immunol.* 2012; **12**(5): 461–6.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Douwes J, Cheng S, Travier N, *et al.*: **Farm exposure in utero may protect against asthma, hay fever and eczema.** *Eur Respir J.* 2008; **32**(3): 603–11.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Stein MM, Hrusch CL, Gozdz J, *et al.*: **Innate Immunity and Asthma Risk in Amish and Hutterite Farm Children.** *N Engl J Med.* 2016; **375**(5): 411–21.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
- Ownby DR, Johnson CC, Peterson EL: **Exposure to dogs and cats in the first year of life and risk of allergic sensitization at 6 to 7 years of age.** *JAMA.* 2002; **288**(8): 963–72.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
- Perzanowski MS, Rönmark E, Platts-Mills TA, *et al.*: **Effect of cat and dog ownership on sensitization and development of asthma among preteenage children.** *Am J Respir Crit Care Med.* 2002; **166**(5): 696–702.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Lødrup Carlsen KC, Roll S, Carlsen KH, *et al.*: **Does pet ownership in infancy lead to asthma or allergy at school age? Pooled analysis of individual participant data from 11 European birth cohorts.** *PLoS One.* 2012; **7**(8): e43214.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
- Fall T, Lundholm C, Örtqvist AK, *et al.*: **Early Exposure to Dogs and Farm Animals and the Risk of Childhood Asthma.** *JAMA Pediatr.* 2015; **169**(11): e153219.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
- Ball TM, Castro-Rodriguez JA, Griffith KA, *et al.*: **Siblings, day-care attendance, and the risk of asthma and wheezing during childhood.** *N Engl J Med.* 2000; **343**(8): 538–43.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Cheng G, Smith AM, Levin L: **Duration of day care attendance during infancy predicts asthma at the age of seven: the Cincinnati Childhood Allergy and Air Pollution Study.** *Clin Exp Allergy.* 2014; **44**(10): 1274–81.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Custovic A: **To what extent is allergen exposure a risk factor for the development of allergic disease?** *Clin Exp Allergy.* 2015; **45**(1): 54–62.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Jackson DJ, Evans MD, Gangnon RE, *et al.*: **Evidence for a causal relationship between allergic sensitization and rhinovirus wheezing in early life.** *Am J Respir Crit Care Med.* 2012; **185**(3): 281–5.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
- Maas T, Kaper J, Sheikh A, *et al.*: **Mono and multifaceted inhalant and/or food allergen reduction interventions for preventing asthma in children at high risk of developing asthma.** *Cochrane Database Syst Rev.* 2009; (3): CD006480.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Chan-Yeung M, Ferguson A, Watson W, *et al.*: **The Canadian Childhood Asthma**

- Primary Prevention Study: outcomes at 7 years of age.** *J Allergy Clin Immunol.* 2005; **116**(1): 49–55.
[PubMed Abstract](#) | [Publisher Full Text](#)
25. Lynch SV, Wood RA, Boushey H, *et al.*: **Effects of early-life exposure to allergens and bacteria on recurrent wheeze and atopy in urban children.** *J Allergy Clin Immunol.* 2014; **134**(3): 593–601.e12.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
26. Valovirta E, Petersen TH, Piotrowska T, *et al.*: **Results from the 5-year SQ grass sublingual immunotherapy tablet asthma prevention (GAP) trial in children with grass pollen allergy.** *J Allergy Clin Immunol.* 2017; pii: S0091-6749(17)31088-6.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
27. Guarneri M, Balmes JR: **Outdoor air pollution and asthma.** *Lancet.* 2014; **383**(9928): 1581–92.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
28. Schultz ES, Litonjua AA, Melén E: **Effects of Long-Term Exposure to Traffic-Related Air Pollution on Lung Function in Children.** *Curr Allergy Asthma Rep.* 2017; **17**(6): 41.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
29. Sbihi H, Allen RW, Becker A, *et al.*: **Perinatal Exposure to Traffic-Related Air Pollution and Atopy at 1 Year of Age in a Multi-Center Canadian Birth Cohort Study.** *Environ Health Perspect.* 2015; **123**(9): 902–8.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
30. Gauderman WJ, Urman R, Avol E, *et al.*: **Association of improved air quality with lung development in children.** *N Engl J Med.* 2015; **372**(10): 905–13.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
31. Yang IV, Lozupone CA, Schwartz DA: **The environment, epigenome, and asthma.** *J Allergy Clin Immunol.* 2017; **140**(1): 14–23.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
32. Yang HJ: **Impact of perinatal environmental tobacco smoke on the development of childhood allergic diseases.** *Korean J Pediatr.* 2016; **59**(6): 319–27.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
33. Bouzigon E, Corda E, Aschard H, *et al.*: **Effect of 17q21 variants and smoking exposure in early-onset asthma.** *N Engl J Med.* 2008; **359**(19): 1985–94.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
34. Moffatt MF, Gut IG, Demenais F, *et al.*: **A large-scale, consortium-based genomewide association study of asthma.** *N Engl J Med.* 2010; **363**(13): 1211–21.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
35. Feleszko W, Ruszczyński M, Jaworska J, *et al.*: **Environmental tobacco smoke exposure and risk of allergic sensitisation in children: a systematic review and meta-analysis.** *Arch Dis Child.* 2014; **99**(11): 985–92.
[PubMed Abstract](#) | [Publisher Full Text](#)
36. Burke H, Leonardi-Bee J, Hashim A, *et al.*: **Prenatal and passive smoke exposure and incidence of asthma and wheeze: systematic review and meta-analysis.** *Pediatrics.* 2012; **129**(4): 735–44.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
37. Vardavas CI, Hohmann C, Patelarou E, *et al.*: **The independent role of prenatal and postnatal exposure to active and passive smoking on the development of early wheeze in children.** *Eur Respir J.* 2016; **48**(1): 115–24.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
38. Feldman AS, He Y, Moore ML, *et al.*: **Toward primary prevention of asthma. Reviewing the evidence for early-life respiratory viral infections as modifiable risk factors to prevent childhood asthma.** *Am J Respir Crit Care Med.* 2015; **191**(1): 34–44.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
39. Bacharier LB, Cohen R, Schweiger T, *et al.*: **Determinants of asthma after severe respiratory syncytial virus bronchiolitis.** *J Allergy Clin Immunol.* 2012; **130**(1): 91–100.e3.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
40. Zomer-Kooijker K, van der Ent CK, Ermers MJ, *et al.*: **Increased risk of wheeze and decreased lung function after respiratory syncytial virus infection.** *PLoS One.* 2014; **9**(1): e87162.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
41. Beigelman A, Bacharier LB: **Early-life respiratory infections and asthma development: role in disease pathogenesis and potential targets for disease prevention.** *Curr Opin Allergy Clin Immunol.* 2016; **16**(2): 172–8.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
42. Jafri HS, Chavez-Bueno S, Mejias A, *et al.*: **Respiratory syncytial virus induces pneumonia, cytokine response, airway obstruction, and chronic inflammatory infiltrates associated with long-term airway hyperresponsiveness in mice.** *J Infect Dis.* 2004; **189**(10): 1856–65.
[PubMed Abstract](#) | [Publisher Full Text](#)
43. Román M, Calhoun WJ, Hinton KL, *et al.*: **Respiratory syncytial virus infection in infants is associated with predominant Th-2-like response.** *Am J Respir Crit Care Med.* 1997; **156**(1): 190–5.
[PubMed Abstract](#) | [Publisher Full Text](#)
44. Piedimonte G, Walton C, Samsell L: **Vertical transmission of respiratory syncytial virus modulates pre- and postnatal innervation and reactivity of rat airways.** *PLoS One.* 2013; **8**(4): e61309.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
45. Blanken MO, Rovers MM, Molenaar JM, *et al.*: **Respiratory syncytial virus and recurrent wheeze in healthy preterm infants.** *N Engl J Med.* 2013; **368**(19): 1791–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
46. Simões EA, Carbonell-Estrany X, Rieger CH, *et al.*: **The effect of respiratory syncytial virus on subsequent recurrent wheezing in atopic and nonatopic children.** *J Allergy Clin Immunol.* 2010; **126**(2): 256–62.
[PubMed Abstract](#) | [Publisher Full Text](#)
47. Mochizuki H, Kusuda S, Okada K, *et al.*: **Palivizumab Prophylaxis in Preterm Infants and Subsequent Recurrent Wheezing. Six-Year Follow-up Study.** *Am J Respir Crit Care Med.* 2017; **196**(1): 29–38.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
48. Carroll KN, Gebretsadik T, Escobar GJ, *et al.*: **Respiratory syncytial virus immunoprophylaxis in high-risk infants and development of childhood asthma.** *J Allergy Clin Immunol.* 2017; **139**(1): 66–71.e3.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
49. Achten NB, Wu P, Bont L, *et al.*: **Interference Between Respiratory Syncytial Virus and Human Rhinovirus Infection in Infancy.** *J Infect Dis.* 2017; **215**(7): 1102–6.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
50. Bacharier LB, Guillbert TW, Mauger DT, *et al.*: **Early Administration of Azithromycin and Prevention of Severe Lower Respiratory Tract Illnesses in Preschool Children With a History of Such Illnesses: A Randomized Clinical Trial.** *JAMA.* 2015; **314**(19): 2034–44.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
51. Zhou Y, Bacharier LB, Isaacson-Schmid M, *et al.*: **Azithromycin therapy during respiratory syncytial virus bronchiolitis: Upper airway microbiome alterations and subsequent recurrent wheeze.** *J Allergy Clin Immunol.* 2016; **138**(4): 1215–1219.e5.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
52. Karron RA, Luongo C, Thumar B, *et al.*: **A gene deletion that up-regulates viral gene expression yields an attenuated RSV vaccine with improved antibody responses in children.** *Sci Transl Med.* 2015; **7**(312): 312ra175.
[PubMed Abstract](#) | [Publisher Full Text](#)
53. Saso A, Kampmann B: **Vaccination against respiratory syncytial virus in pregnancy: a suitable tool to combat global infant morbidity and mortality?** *Lancet Infect Dis.* 2016; **16**(8): e153–63.
[PubMed Abstract](#) | [Publisher Full Text](#)
54. Martinez FD: **New insights into the natural history of asthma: primary prevention on the horizon.** *J Allergy Clin Immunol.* 2011; **128**(5): 939–45.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
55. Jackson DJ, Gangnon RE, Evans MD, *et al.*: **Wheeze rhinovirus illnesses in early life predict asthma development in high-risk children.** *Am J Respir Crit Care Med.* 2008; **178**(7): 667–72.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
56. Nicolai A, Frassanito A, Nenna R, *et al.*: **Risk Factors for Virus-induced Acute Respiratory Tract Infections in Children Younger Than 3 Years and Recurrent Wheezing at 36 Months Follow-Up After Discharge.** *Pediatr Infect Dis J.* 2017; **36**(2): 179–83.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
57. Jartti T, Nieminen R, Vuorinen T, *et al.*: **Short- and long-term efficacy of prednisolone for first acute rhinovirus-induced wheezing episode.** *J Allergy Clin Immunol.* 2015; **135**(3): 691–8.e9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
58. Lee S, Nguyen MT, Currier MG, *et al.*: **A polyvalent inactivated rhinovirus vaccine is broadly immunogenic in rhesus macaques.** *Nat Commun.* 2016; **7**: 12838.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
59. Mukherjee PK, Esper F, Buchheit K, *et al.*: **Randomized, double-blind, placebo-controlled clinical trial to assess the safety and effectiveness of a novel dual-action oral topical formulation against upper respiratory infections.** *BMC Infect Dis.* 2017; **17**(1): 74.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
60. Rosas-Salazar C, Shiels MH, Tovchigrechko A, *et al.*: **Nasopharyngeal Microbiome in Respiratory Syncytial Virus Resembles Profile Associated with Increased Childhood Asthma Risk.** *Am J Respir Crit Care Med.* 2016; **193**(10): 1180–3.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
61. Chung KF: **Airway microbial dysbiosis in asthmatic patients: A target for prevention and treatment?** *J Allergy Clin Immunol.* 2017; **139**(4): 1071–81.
[PubMed Abstract](#) | [Publisher Full Text](#)
62. Cuello-Garcia CA, Fiocchi A, Pawankar R, *et al.*: **World Allergy Organization-McMaster University Guidelines for Allergic Disease Prevention (GLAD-P): Prebiotics.** *World Allergy Organ J.* 2016; **9**: 10.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
63. Sordillo JE, Scirica CV, Rifas-Shiman SL, *et al.*: **Prenatal and infant exposure to**

- acetaminophen and ibuprofen and the risk for wheeze and asthma in children. *J Allergy Clin Immunol.* 2015; **135**(2): 441–8.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
64. Castro-Rodríguez JA, Forno E, Rodríguez-Martínez CE, *et al.*: **Risk and Protective Factors for Childhood Asthma: What Is the Evidence?** *J Allergy Clin Immunol Pract.* 2016; **4**(6): 1111–22.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
65. **F** Black M, Bhattacharya S, Philip S, *et al.*: **Planned Cesarean Delivery at Term and Adverse Outcomes in Childhood Health.** *JAMA.* 2015; **314**(21): 2271–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
66. **F** Wu P, Feldman AS, Rosas-Salazar C, *et al.*: **Relative Importance and Additive Effects of Maternal and Infant Risk Factors on Childhood Asthma.** *PLoS One.* 2016; **11**(3): e0151705.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
67. Hendaus MA, Jomha FA, Ehlayel M: **Allergic diseases among children: nutritional prevention and intervention.** *Ther Clin Risk Manag.* 2016; **12**: 361–72.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
68. **F** Melli LC, do Carmo-Rodrigues MS, Araújo-Filho HB, *et al.*: **Intestinal microbiota and allergic diseases: A systematic review.** *Allergol Immunopathol (Madr).* 2016; **44**(2): 177–88.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
69. **F** Arrieta MC, Stiemsma LT, Dimitriu PA, *et al.*: **Early infancy microbial and metabolic alterations affect risk of childhood asthma.** *Sci Transl Med.* 2015; **7**(307): 307ra152.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
70. Azad MB, Coney JG, Kozyrskyj AL, *et al.*: **Probiotic supplementation during pregnancy or infancy for the prevention of asthma and wheeze: systematic review and meta-analysis.** *BMJ.* 2013; **347**: f6471.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
71. Bloomfield SF, Rook GA, Scott EA, *et al.*: **Time to abandon the hygiene hypothesis: new perspectives on allergic disease, the human microbiome, infectious disease prevention and the role of targeted hygiene.** *Perspect Public Health.* 2016; **136**(4): 213–24.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
72. **F** Ali Z, Nilas L, Ulrik CS: **Excessive gestational weight gain in first trimester is a risk factor for exacerbation of asthma during pregnancy: A prospective study of 1283 pregnancies.** *J Allergy Clin Immunol.* 2017; pii: S0091-6749(17)30673-5.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
73. **F** Sewell DA, Hammersley VS, Robertson A, *et al.*: **A pilot randomised controlled trial investigating a Mediterranean diet intervention in pregnant women for the primary prevention of allergic diseases in infants.** *J Hum Nutr Diet.* 2017; **30**(5): 604–14.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
74. Garcia-Marcos L, Castro-Rodríguez JA, Weinmayr G, *et al.*: **Influence of Mediterranean diet on asthma in children: a systematic review and meta-analysis.** *Pediatr Allergy Immunol.* 2013; **24**(4): 330–8.
[PubMed Abstract](#) | [Publisher Full Text](#)
75. von Mutius E, Martínez FD: **Inconclusive Results of Randomized Trials of Prenatal Vitamin D for Asthma Prevention in Offspring: Curbing the Enthusiasm.** *JAMA.* 2016; **315**(4): 347–8.
[PubMed Abstract](#) | [Publisher Full Text](#)
76. **F** Litonjua AA, Carey VJ, Laranjo N, *et al.*: **Effect of Prenatal Supplementation With Vitamin D on Asthma or Recurrent Wheezing in Offspring by Age 3 Years: The VDAART Randomized Clinical Trial.** *JAMA.* 2016; **315**(4): 362–70.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
77. **F** Wolsk HM, Harshfield BJ, Laranjo N, *et al.*: **Vitamin D supplementation in pregnancy, prenatal 25(OH)D levels, race, and subsequent asthma or recurrent wheeze in offspring: Secondary analyses from the Vitamin D Antenatal Asthma Reduction Trial.** *J Allergy Clin Immunol.* 2017; **140**(5): 1423–1429.e5.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
78. **F** Martineau AR, Jolliffe DA, Hooper RL, *et al.*: **Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data.** *BMJ.* 2017; **356**: i6583.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
79. Helve O, Viljakainen H, Holmlund-Suila E, *et al.*: **Towards evidence-based vitamin D supplementation in infants: vitamin D intervention in infants (VIDI) - study design and methods of a randomised controlled double-blinded intervention study.** *BMC Pediatr.* 2017; **17**(1): 91.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
80. **F** Vahdaninia M, Mackenzie H, Helps S, *et al.*: **Prenatal Intake of Vitamins and Allergic Outcomes in the Offspring: A Systematic Review and Meta-Analysis.** *J Allergy Clin Immunol Pract.* 2017; **5**(3): 771–778.e5.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
81. **F** Gref A, Rautiainen S, Gruzieva O, *et al.*: **Dietary total antioxidant capacity in early school age and subsequent allergic disease.** *Clin Exp Allergy.* 2017; **47**(6): 751–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
82. Hodge L, Salome CM, Peat JK, *et al.*: **Consumption of oily fish and childhood asthma risk.** *Med J Aust.* 1996; **164**(3): 137–40.
[PubMed Abstract](#)
83. **F** Bisgaard H, Stokholm J, Chawes BL, *et al.*: **Fish Oil-Derived Fatty Acids in Pregnancy and Wheeze and Asthma in Offspring.** *N Engl J Med.* 2016; **375**(26): 2530–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
84. Chiu YH, Coull BA, Cohen S, *et al.*: **Prenatal and postnatal maternal stress and wheeze in urban children: effect of maternal sensitization.** *Am J Respir Crit Care Med.* 2012; **186**(2): 147–54.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
85. Wright RJ, Visness CM, Calatroni A, *et al.*: **Prenatal maternal stress and cord blood innate and adaptive cytokine responses in an inner-city cohort.** *Am J Respir Crit Care Med.* 2010; **182**(1): 25–33.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
86. Weaver IC, Szyf M, Meaney MJ: **From maternal care to gene expression: DNA methylation and the maternal programming of stress responses.** *Endocr Res.* 2002; **28**(4): 699.
[PubMed Abstract](#) | [Publisher Full Text](#)
87. Dreger LC, Kozyrskyj AL, HayGlass KT, *et al.*: **Lower cortisol levels in children with asthma exposed to recurrent maternal distress from birth.** *J Allergy Clin Immunol.* 2010; **125**(1): 116–22.
[PubMed Abstract](#) | [Publisher Full Text](#)
88. **F** Ramratnam SK, Visness CM, Jaffee KF, *et al.*: **Relationships among Maternal Stress and Depression, Type 2 Responses, and Recurrent Wheezing at Age 3 Years in Low-Income Urban Families.** *Am J Respir Crit Care Med.* 2017; **195**(5): 674–81.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
89. **F** Plourde A, Lavoie KL, Raddatz C, *et al.*: **Effects of acute psychological stress induced in laboratory on physiological responses in asthma populations: A systematic review.** *Respir Med.* 2017; **127**: 21–32.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)

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