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Review Article

Diet and Childhood Asthma

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Abstract

Asthma is a multifactorial disease. The increasing incidence of asthma in the last 6 decades may be related to the changes in population dietary habits with eating fewer fruits and vegetables and more processed foods. Diet plays an important role in the pathogenesis of asthma. Poor nutrition could also increase the likelihood of having asthma symptoms. Inadequate maternal nutrition during pregnancy could adversely impact childhood respiratory health, particularly during critical periods of embryonic and fetal growth and could increase the risks of asthma, chronic obstructive airway disease, and impaired lung functions. There are some controversies about the protective effect of breastfeeding on asthma. The effect of breastfeeding on asthma is influenced by different factors including duration of breastfeeding, the age of the child; hereditary factors as presence or absence of maternal asthma and atopy in the child, and environmental factors as exposure to tobacco smocking. With the new advancement of infant formula, as in partially or extensively hydrolyzed cow's milk formula, the incidence of wheezing was significantly decreased than in infants fed with regular cow's milk. The effect of bottle feeding is not only related to the milk but it could be also related to the plastic products used in the feeding bottles. Early or delayed weaning may be associated with increased risk of asthma and should not be started before 17 wk or delayed beyond 26 wk of age. Food allergy not only increases the incidence of childhood asthma, but also increases risk of asthma mortality and morbidity. However, the relationship between diet and asthma remains uncertain and needs further investigational studies.

Keywords Children; Asthma; Maternal Diet; Breastfeeding; Bottle feeding; Weaning; Food Allergy; Obesity

Introduction

The increasing incidence of asthma in the last 6 decades may be related to changes in population dietary habits with eating fewer and fewer fruits and vegetables and more processed foods. Poor nutrition could also increase the likelihood of having asthma symptoms. High calories diet increases the incidence of obesity and hence may increase the severity of asthma symptoms. However, the relationship between diet and asthma remains uncertain, a possible mechanism by which these dietary changes may affect asthma includes airway inflammation [1]. As the diet has been linked to the development of the fetus and child; nutrition can affect the possibility of developing asthma in all stages of life even before and during conception. According to fetal programming theory or Barker hypothesis; suboptimal fetal nutrition, due to maternal obesity or underweight, insufficient dietary intake, or placental dysfunction might affect fetal growth and lung development together with long term physiologic or metabolic changes [2]. Bottle-fed infants are more liable to develop asthma and bronchitis more often than their breast-fed counterparts. In this article, the effects of diets on the predisposition to asthma as well as the protective role of the diet against asthma will be discussed.

Maternal Diet

Asthma, like other common diseases, has at least a part of its origin early in life. Maternal nutrition during pregnancy could affect the intrauterine environment and the quality of the substrates necessary for many important processes including lung maturation and development of the immune system and consequently the fetal growth. As a result, inadequate maternal nutrition during pregnancy could adversely impact childhood respiratory health, particularly during critical periods of embryonic and fetal growth [3]. Maternal macronutrients deficiency may be associated with low birth weight which could increase the risks of asthma, chronic obstructive airway disease, and impaired lung functions in adults, as well as increases the risks of respiratory symptoms in early childhood [4]. Maternal malnutrition could also encourage neonatal T-helper (Th)-cell responses to allergens being with more shifts toward Th2-cell responses, increasing the risk of asthma and allergic diseases in childhood [5]. The fetus immune system has the ability to respond to the in utero allergens exposure from 22 weeks of gestation with thymus organogenesis and T cell development in the thymus. Prenatal stress challenges including maternal malnutrition or allergen exposure could alter fetal immune system and may contribute to the etiopathogenesis of asthma [6]. The ability of the fetus to mount an immune response to food allergens stimulated some physicians to try to decrease the risk of developing food allergy and other atopic conditions by restricting the diet of pregnant mothers [7].

Thus allergenic food intake by the pregnant mothers could increase the risk of sensitization in the fetus and subsequent allergic diseases including asthma [8]. Many studies have explored the effects of certain nutrients or dietary supplements consumed by pregnant women on the possibility of development of asthma in their offspring. Some studies showed that pregnant mothers consuming less nuts or nut products or intake of more fish, apples, anti-oxidants, omega-3 poly-unsaturated fatty acids and vitamin D may have less risk of wheezing or asthma in children [9].

Lower maternal intake of micronutrients such as iron, folate, vitamin B12, vitamin E or vitamin D during pregnancy may induce fetal epigenetic changes that could influence gene expression and airway epithelial cell signalling with a higher incidence of asthma and wheeze in the offspring children. Low dietary antioxidant intake is an important factor in rising asthma prevalence. It reduces the natural antioxidant defence capacity of the fetal lungs and decreases the ability of antioxidants to act on fetal development of the airways and/or on the first interaction between an allergen and the immune system [10]. Prenatal antioxidant supplementation might influence fetal lung growth and development and reduce infant respiratory morbidity. High maternal intake of antioxidants during pregnancy is controversial. Study done by Greenough et al. [11] showed that high-dose antenatal vitamin C and E supplementation did not improve infant respiratory outcome and was associated with increased healthcare utilisation and cost of care. On the other hand, study done

by Miyake et al. [12] showed that higher maternal vitamin E consumption during pregnancy was significantly inversely related to the risk of infantile wheeze, but not eczema. Vitamin E increases the activity of COX-2 and the production of prostaglandin E-2 (PGE-2) by macrophages which promotes the differentiation of T cells to Th-2 lymphocytes which increase the activity of T cells [13].

Maternal anaemia, is an important parameter that could indicate overall maternal malnutrition. Gestational anaemia could be associated with either recurrent wheeze in first year of life, wheeze by 3 years of age or development of asthma at 6 years of age. There is an inverse relationship between cord iron levels and early childhood wheezing. Because fetal iron stores during pregnancy typically last only through the first 6 months of life; it is expected that maternal anaemia is mostly associated with early life respiratory outcomes (particularly 1st year of life) [14]. Maternal iron deficiency anaemia may be associated with other maternal micronutrients and vitamins deficiency including: selenium, zinc, vitamin D, vitamin C, vitamin E and folic acid. These deficiencies may lead to impaired fetal body, lung and airway growth and subsequently lead to an increased risk of asthma in childhood and development of increased infant susceptibility to respiratory disease [3].

Increased prevalence of allergic asthma in humans may in part be related to increased perinatal dietary supplementation with methyl donors such as folic acid. Some studies in mouse models showed that excess amount of dietary methyl donors could alter promoter DNA methylation, induce hypermethylation with suppression of regulatory genes in lung tissue, reduce the expression of key genes that regulate adaptive immunity, and enhance the severity of allergic airway disease [15]. However; a more recent study showed that higher serum folate levels are associated with lower total IgE levels and a lower risk of allergic sensitization and wheeze in children 2 years and older. Future studies are needed to define the temporal relationships among serum folate levels and allergy and asthma and to determine whether these associations, if causal, are mediated by epigenetic changes or by other mechanisms [16].

Increased maternal consumption of calcium and total dairy products, milk, and cheese during pregnancy significantly decrease the risk of wheeze in infants aged 16–24 months. The effects of these dairy products are mainly due to the calcium and Vitamin D content. Higher vitamin D intake during pregnancy may have a protective effect against childhood wheeze and eczema. The efficacy of vitamin D in reducing the risk of wheezing is a dose dependant. Children whose mother had consumed daily 4.309 mg or more of vitamin D during pregnancy had a significantly reduced risk of wheeze and eczema, suggesting a threshold effect rather than a monotonic trend [17]. The dietary calcium is the major source of the calcium present in the body fluids, whether in blood, in interstitial spaces or within the cell cytosol or organelles. Calcium is important for the development and maturation of lymphocytes. It is important for signalling activation cascades and (CD)83 differentiation and responsiveness to Toll-like receptor, B-cell receptor and cytokine receptor signals. So, higher maternal calcium intake during pregnancy might down regulate the calcium-sensing mechanism on B cells, resulting in a decreased risk of allergic disorders in the offspring [18, 19]. Some studies showed that low levels of zinc in the diet of pregnant women could increase the likelihood that their children would develop wheezing and asthma in childhood [20,21].

A recent study by Maslova etal. [22] showed that increase maternal intake of peanuts and tree nuts during pregnancy was inversely associated with asthma in children at 18 months of age. They suggested that women should not decrease peanut and tree nut intake during pregnancy. Consumption of peanuts and tree nuts during pregnancy might even decrease the risk of allergic disease development in children [22]. In another recent study in Finland, low maternal consumption of leafy vegetables, malaceous fruits, and chocolate were positively associated with the risk of wheeze in children. They also found that high maternal consumption of fruit and berry juices was positively associated with the risk of allergic rhinitis in children. However; they found no associations between maternal food consumption and asthma [23]. Higher maternal intake of alpha-linolenic acid and docosahexaenoic acid during pregnancy may reduce the risk of infantile wheeze. However, maternal intake of n-6 polyunsaturated fatty acids, especially linoleic acid, during pregnancy may increase the risk of childhood eczema [24]. The intake of fish during pregnancy has controversial preventive effects against the development of childhood asthma and allergic disease. However, definite effects of maternal diet during pregnancy on development of offspring asthma still need more studies.

Breastfeeding

There is no doubt that breastfeeding is the most favourable nutrition for infants. Exclusive breastfeeding is preferable up to the age of 6 months. Breastfeeding has many nutritional, growth, and immunological benefits during a critical period of the infant's life when its own immune system is immature. Breastfeeding may also reduce the risk of certain chronic childhood disorders including asthma. However, there are some controversies about the protective effect of breastfeeding on asthma. Most of the studies concerned about the role of breastfeeding in protection against asthma were observational because randomised controlled trials (RCTs) are impossible with breastfeeding. These observational studies were subjected to several confounding factors and biases because of the multi-factorial nature of asthma, and because of the recall bias in recording feeding practices retrospectively. Another bias in observational studies is that the mothers of high-risk infants may be more inclined to breastfeeding than those of low-risk infants [25].

Fredriksson et al. [26] showed that the lowest prevalence of asthma was found in children who were breastfed from four to six months. They showed U-shaped rather than a linear relation between the duration of breastfeeding and the risk of asthma and chronic respiratory symptoms. They found that the lowest risk with breastfeeding was from four to nine months for asthma and seven to nine months for persistent wheezing, cough and phlegm. They also showed that optimal breastfeeding duration was 4 to 6 months. Breastfeeding less than 4 months increases the risk of asthma and chronic respiratory symptoms while prolonged breastfeeding was also associated with an increased risk of the studied outcomes. A previous study done by Oddy et al. [27] showed that exclusive breastfeeding for at least 4 months was associated with a significant reduction in the risk of asthma and atopy at age 6 years and with a significant delay in the age at onset of wheezing and asthma being diagnosed by a doctor. Another cohort study done by Elliott et al. [28] agreed that breastfeeding had a modest protective effect against wheeze and asthma in early childhood but this effect lasts only till the sixth year of life. On the other hand; Kramer et al. [29] assessed whether exclusive and prolonged breastfeeding reduces the risk of asthma and allergy at 6 years of age. They found no significant difference in allergy and asthma symptoms reported by parents or the results of allergy skin

prick tests among the group with exclusive breastfeeding and the group without strict prolonged exclusive breastfeeding. Their results did not support a protective effect of prolonged and exclusive breastfeeding on asthma or allergy.

The effect of breastfeeding on asthma is influenced by different factors. Gdalevich et al. [30] showed in their meta-analysis; the evidence of hereditary factors on protective effect of breastfeeding against asthma. They showed a protective effect of 3 months of exclusive breastfeeding only in children of atopic parents, whereas there was no effect in children of non-atopic parents. Kull et al. [31] showed that at the age of 4 years, children who had been exclusively breastfed for four months or more exhibited a reduced risk of asthma compared with children breastfed for less than four months. On contrary to Gdalebich study; Kull et al. [31] found that the beneficial effects of breastfeeding were more pronounced in children who did not have a parent with atopic disease than in those with an atopic parent.

The relationship between breastfeeding and asthma or recurrent wheeze varies with the age of the child and the presence or absence of maternal asthma and atopy in the child. Wright et al. [32] found that while associated with protection against recurrent wheeze early in life; breastfeeding was associated with an increased risk of asthma and recurrent wheeze beginning at the age of 6 years, but only for atopic children with asthmatic mothers. Exposures to environmental factors could also modify the relation between breastfeeding and asthma. Study done by Nafstad et al. [33] showed that the effects of exposure to environmental tobacco smoke (ETS) on the risk of asthma were stronger among children who were breastfed less than 6 months compared those breastfed 6 months or longer. Chulada et al. [34] showed also that breastfeeding might reduce the prevalence of asthma and recurrent wheezing in children exposed to environmental tobacco smoke, but not in unexposed children.

There are different theories to explain the preventive effect of breastfeeding against asthma. Breast milk contains traces of food proteins consumed by the mother that could promote tolerance to these foods. Breastfeeding may stimulate the early induction of an oral tolerance capacity in human neonates and may thereby prevent some forms of food allergy in the pediatric population [35]. Some factors present in the breastmilk may have the ability to modulate mucosal immune processes including a variety of maternal leukocytes (macrophages, Neutrophils, nd lymphocytes), cytokines and chemokines including IL-1 β, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, IL-13, TNFα, TGF {transforming growth factor}β, INFγ, and granulocyte-colony stimulating factor, monocytes chemotactic protein 1), Ig A, factors that promote gut maturation, oligosaccharides, nucleotides and that control the growth of intestinal microbiota and long-chain polyunsaturated fatty acids [36]. Breastfeeding, through its selective action on intestinal microbiota colonization and growth, can induce specific T cell responses and modulates substrates oxidation and consumption, which has a major impact on the development of immune functions and oral tolerance [37]. Other factors present in breastmilk like milk peptides may be able to down regulate neonatal immune activity, suggesting that they may promote neonatal immune competence [38].

Bottle Feeding

Artificial feedings were used since ancient times dating back to 2000 BC. However, it was not until the Industrial Revolution that a refined, hygienic feeding bottle became available [39]. Hide and Guyer et al. [40]; showed that bottle-fed infants developed asthma and bronchitis more often than their breast-fed counterparts [40]. However, with the new advancement of infant formula, the partially or extensively hydrolyzed cow's milk formula significantly decreased the incidence of wheezing than in infants fed with regular cow's milk [41]. However, there was no preventive effect of any of these formulas on the cumulative incidence of asthma at the age of 6 years [42]. More studies are needed to investigate presence of any beneficial role of the hydrolyzed formulas on the incidence of asthma in later life. Bedtime bottle feeding may be a risk factor for relapse of respiratory diseases, including asthma because of increasing the gastroesophageal reflux or microaspiration, which could aggravate the respiratory symptoms. Discontinuation of bedtime bottle feeding may alleviate respiratory symptoms in infants with chronic respiratory symptoms including asthma [43]. The effect of bottle feeding is not only related to the milk but it could be also related to the plastic products used in the feeding bottles. There is a possibility that any harmful chemicals emitted from pacifiers or feeding bottles could be the causal factor associated with asthma in children using bottle feeding [44]. Longer period of use of feeding bottles may indicate a higher risk of asthma among preschool children. However, the specific underlying mechanism of feeding bottles usage to cause asthma and other health outcomes warrants future investigation [45].

Weaning

Weaning means introduction of foods other than milk for the nursing infants with gradual transition from a milk-based diet to a diet based on solid foods. The practice of weaning had been changed over the last 50 years. The time of starting weaning had been changed from the age of 4 month on the 1960s to the age of 6 months by the late 1990s due to the recommendation of extension of exclusive breastfeeding till the age of 6 months. Nowadays; there is a rising concern that the recommended exclusive breastfeeding and delayed complementary foods till the age of 6 months may increase, rather than decrease, the risk of immune and allergic disorders including asthma. Early and regular exposure to protein during the critical early window of development which is between 4 and 6 month of live; could induce food allergen tolerance [46]. Nwaru et al. [47] showed that late introduction of solid foods was associated with increased risk of allergic sensitization to food and inhalant allergens. They reported that late introductions of oats and eggs were associated with sensitization to food allergens while late introduction of potatoes and fish was significantly associated with sensitization to any inhalant allergen. It is quite noted that breastfed babies have a delayed weaning than infants who are formula-fed [48].

Other factor that could play a protective role against allergy is the infant gut colonization. Early infant feeding has a major effect on the milieu and establishment of the gut microbiota. The intestinal microbial flora can be an important postnatal regulator of the Th1 and Th2 balance and have an essential role in the maintenance of oral immune tolerance by inhibition of potential lymphocyte reactivity [49]. Another explanation of the protective effect of early weaning is by the hypothesis which suggests that early cutaneous exposure to food protein through a disrupted skin barrier could result into allergic sensitization while early oral exposure of food allergen could induce tolerance [50]. However, early food introduction is not automatically better, since mature immune regulation may require time. Lima et al. [51] showed that early weaning was associated with wheezing

regardless of a history of asthma or atopy in the family. Complementary feeding should not be started before 17 wk and not later than 26 wk [52]. Further investigational studies are still needed before changing the established recommendation of delayed weaning.

Food Allergy

Food allergy is a potentially severe immune response to a food or food additive which may be transient or lifelong. The increased prevalence of food allergy is associated with increased prevalence of atopic conditions such as asthma. The prevalence of atopic diseases including asthma in children with food allergy is about 2-4 times more than in children without food allergy. Asthma may also present with other lower respiratory symptoms among these children. The pulmonary function tests in children with food allergy even when being normal; may be associated with significantly increased frequency of positive responses on methacholine challenge [53,54]. At the same time, there is also increased prevalence of food allergies among asthmatic children [55]. Infants with egg allergy are more liable for development of respiratory allergic symptoms and aeroallergen sensitization by the age of 4 years. However, allergy to cow's milk doesn't significantly increase the incidence of asthma [56].

Food allergy not only increases the incidence of childhood asthma, but also increases risk of asthma mortality and morbidity. Milk and peanut allergy were found to be significantly associated with increased number of asthma hospitalization. On the other hand; there is no increase in asthma morbidity in asthmatic children with associated egg or fish allergy [57]. The more the number of allergenic foods, the more is the frequency and the severity of the associated asthma and the children need for more courses of systemic steroids [58]. Wang et al. [59] found that about 45% of patients had evidence of sensitization by presence of food-specific Ig E to at least 1 food and about 19% had Ig E levels equal to or more than 50% positive predictive value for clinical reactivity to at least 1 food, with 4% of patients having levels > 95% positive predictive value for food allergy. They also found higher rate of hospitalization among asthmatic children with food sensitivity with more need for steroid medications. On the other hand, asthma is considered a risk factor for fatal or near fatal anaphylaxis to foods [60].

Obesity

Not only food allergy is associated with increased risk of asthma, but wrong feeding habits also may be another risk factor. Obese children are at increased risk for developing asthma because of the associated airway smooth muscle dysfunction from thoracic restriction, the obesity-related circulating inflammation priming the lung, and the obesity-related co-morbidities mediating asthma symptom development. Obesity in children with asthma appears to be associated with greater airflow obstruction and a mildly diminished response to inhaled corticosteroids. Abnormal feeding habits are common in obese children including feeding disinhibition, greater fast-food and saturated fat consumption, and a diet with lower nutritional content. Reduced fruits, vegetables, and fish, and increased saturated fats, burgers, and fast food appear to increase the risk for asthma [61-63].

Children Diet: Antioxidants

There are controversial data about the role of dietary antioxidants in asthma. Many studies were in favour of the beneficial role of consumption of antioxidant rich foods in prevention of asthma. Rubin et al. [64] investigated the relationship of serum vitamin E, beta-carotene, vitamin C, and selenium to childhood asthma. Serum vitamin E had little or no association with the prevalence of asthma. Both serum β-carotene and vitamin C were significantly associated with a lower risk of prevalent asthma. Selenium was inversely associated with asthma, with evidence of a stronger association among youth exposed to cigarette smoke. Kalayci et al. [65] showed that antioxidant vitamins; alpha tocopherol, beta carotene, and ascorbic acid were decreased in sera of asthmatic patients even during the asymptomatic periods of the disease, and that decrease is not totally dependent on the increased oxidative stress as reflected by lipid peroxidation products. van Oeffelen et al. [66] studied the influence of serum micronutrient concentrations on childhood asthma. They found that children with higher serum magnesium concentrations are less likely to have asthma. They found also that the associations between serum vitamin D concentrations and asthma were age-dependent. Al-Biltagi et al. [67] found that asthmatic children who received L-Carnitine supplementation showed significant statistical improvement of children Asthma Control Test (C-ACT) as well as their pulmonary functions. Flavonoids are a group of protective antioxidants participation in cell signaling pathways, and decreasing inflammation that could improve lung functions and play an antioxidant protective role against asthma. Pycnogenol (water-soluble bioflavonoids) showed to be effective as an adjunct in the management of mild-to-moderate childhood asthma [68].

Magnesium has a modulatory effect on the contractility of smooth muscles and hence has a bronchodilator effect which enable magnesium to be a rescue medication in case of asthma exacerbation emergencies. Low magnesium intake has been correlated with decreased lung function in children. Rosenlund et al. [70,71] showed inverse association between magnesium intake and asthma with protective effect of magnesium intake on childhood asthma [69]. However, other clinical trials showed that magnesium supplementation (given with vitamin C) did not show any clinical benefit on lung functions, symptoms, or on the ability to decrease steroid dose in asthmatics. However, a meta-analysis done by Gao et al. [73] showed that higher dietary intake of antioxidants was not associated with a lower risk of having asthma [72]. Also, a multicentre case-control study in Europe did not support a role for selenium in protection against asthma due to presence of two contrasting actions, one as anti oxidant decreasing the oxidant stress in asthma and another opposing action by up regulating T helper 2 responses that drive allergic asthma.

Children Diet: Vitamin D

Vitamin D is both a nutrient and a hormone that is available in foods mostly from animal sources like oily fish and fish liver oil, egg yolk, and offal. The body can form it by the effect of skin exposure to the sun. Vitamin D works as a pleiotrophic mediator that contributes to pulmonary health. It modulates the expression of many genes in bronchial smooth muscle cells, including genes previously implicated in asthma predisposition and pathogenesis. It may play an important role in pulmonary health by inhibiting inflammation, in part through maintaining regulatory T cells, and direct induction of innate antimicrobial mechanisms. It also may reverse steroid-resistance in asthmatics through induction of IL-10 secreting T-regulatory cells [74]. Vitamin D status may play a role in preventing asthma exacerbations. Vitamin D insufficiency is common in children with mild to moderate persistent asthma, and is associated with higher

incidence of severe asthma exacerbation, worse lung functions, airway inflammation, and remodelling [75]. Improving vitamin D status holds promise in primary prevention of asthma, in decreasing exacerbations of disease, and in treating steroid resistance. Circulating serum vitamin D levels (25-hydroxyvitamin D3) were measured from stored samples and subjects with higher vitamin D levels had higher Forced Expiratory Volume in 1 second (FEV1) and forced vital capacity (FVC) values.

Some studies showed that vitamin D serum levels may be used as a marker of asthma control. Chinellato et al. [76] found a significant positive correlation between FVC percent of predicted and serum 25(OH)D. However, the appropriate level of circulating vitamin D for optimal immune functioning remains unclear [77,78]. The effect of vitamin D supplement of prevention of allergic diseases may be modified by the timing of Vitamin D intake. A birth cohort Finnish study showed that regular vitamin D supplementation during the first year could marginally significantly increase the risk of asthma at age 31 yrs [79]. Another theory of "paradox of vitamin D" suggest that either an excess (resulting from supplementation) or a deficiency (due to low solar exposure and the inability to compensate with diet) of vitamin D have been associated with an increased risk of asthma and allergies in Western countries [80].

Conclusion

Asthma is a multifactorial disease. Diet plays an important role in the pathogenesis of asthma. Maternal diet during pregnancy, breastfeeding, bottle feeding, timing of weaning, and the food allergy as well as the dietary pattern could affect the possibility of developing asthma. However, the relationship between diet and asthma remains uncertain and needs further investigational studies.

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