

Maternal diet during pregnancy: an emerging risk factor for childhood asthma

Expert Rev. Clin. Immunol. 4(6), 663–668 (2008)

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Evaluation of: Willers SM, Wijga AH, Brunekreef B *et al.* Maternal food consumption during pregnancy and the longitudinal development of childhood asthma. *Am. J. Respir. Crit. Care Med.* 178, 124–131 (2008).

It has been hypothesized that the recent marked increase in the prevalence of asthma may, in part, be a consequence of changing diet. There is increasing interest in the possibility that childhood asthma may be influenced by maternal diet during pregnancy and an increasing number of studies have highlighted associations between childhood asthma and maternal intake of certain foods (e.g., fish, fruits and vegetables) and nutrients (e.g., vitamin E, vitamin D, zinc and polyunsaturated fatty acids) during pregnancy. Maternal diet during pregnancy has the potential to influence fetal immune and airway development during a critical period of life with long-term irreversible consequences, such as childhood asthma. Further research, particularly intervention studies, needs to be carried out to establish whether dietary intervention during pregnancy can be used as a healthy, low-cost, public-health measure to reduce the prevalence of childhood asthma.

KEYWORDS: childhood asthma • diet • polyunsaturated fatty acid • pregnancy • vitamin D • vitamin E

In Westernized countries, the prevalence of asthma and atopic disease has increased markedly since the early 1960s. Asthma is now a public-health concern because of its high prevalence, associated ill health and high societal and healthcare costs. The current clinical approach to asthma is long-term treatment with bronchodilating and anti-inflammatory medications to reverse airway inflammation and its sequelae. At the present time, asthma cannot be cured and treatment is usually lifelong and expensive. It is for these reasons that there is increasing interest in the primary prevention of asthma. Although genetic susceptibility is important in the etiology of asthma, population-scale gene therapy to prevent asthma is extremely unlikely. The identification of environmental factors that influence the development of asthma is now a priority so that interventions can be developed and implemented to prevent asthma and atopic disease. Maternal diet during pregnancy has emerged as a possible factor that influences the development of asthma. The study of Willers *et al.* is one of an increasing number demonstrating associations between maternal diet during pregnancy and childhood asthma [1].

Summary of methods & results

This study is part of the Dutch Prevention and Incidence of Asthma and Mite Allergy birth-cohort study. The aim of this study was to investigate longitudinally the influence of maternal diet during pregnancy on the prevalence of symptoms of childhood asthma from 1 to 8 years of age. The study population comprised 3963 pregnant mothers recruited in late pregnancy who completed a questionnaire that included questions on their diet during pregnancy. The women provided information on the frequency with which they had consumed the following food groups in the previous month: vegetables, fresh fruit, fish, eggs, milk, milk products, nuts and nut products, such as peanut butter. The children born to this cohort of women were followed up annually by postal questionnaire, with response rates in excess of 80% for each period of follow up. The outcome variables of interest were wheeze, dyspnea, the use of prescribed inhaled corticosteroids for respiratory problems and a composite variable, 'asthma symptoms', in the previous year. Instead of performing cross-sectional analyses of each

year of childhood respiratory outcomes, general estimating equations (GEEs) were used to simultaneously model associations between maternal diet during pregnancy and childhood respiratory symptoms during the first 8 years of life. GEEs are able to account for repeated measures in the same individual and enable adjustment for potentially confounding influences.

After suitable adjustment, there were no associations between maternal consumption of vegetables, fresh fruit, fish, eggs, milk, milk products and nuts and childhood wheeze, dyspnea, corticosteroid use and asthma symptoms. The daily consumption of peanut products during pregnancy was significantly associated with childhood wheeze, dyspnea, corticosteroid use and asthma symptoms, with odds ratios between 1.42 and 1.62. The regular consumption of peanut products by pregnant women (one to more than four-times in a week) was not associated with any childhood outcomes and there was no evidence of a dose response between regular, daily and rare consumption of peanut products. Although maternal diet during pregnancy and the child's diet at 2 years were strongly associated, inclusion of the child's diet in the models did not alter the associations with maternal diet.

Discussion

This large study with an excellent follow-up rate is the first to have used longitudinal statistical techniques to investigate the associations between maternal diet during pregnancy and childhood respiratory outcomes over a period of time. Previous studies have effectively performed cross-sectional analyses between maternal diet and childhood outcomes at a specific age. Information about maternal dietary intake during pregnancy was limited to eight major food groups and no information on portion size was obtained, thus it was not possible to investigate associations with specific foods (e.g., apples and oily vs non-oily fish) or nutrients (e.g., vitamin E and vitamin D). This study adds to a growing body of evidence suggesting that maternal diet during pregnancy is associated with childhood asthma, raising the tantalizing possibility of reducing the likelihood of childhood asthma by modification of maternal diet during pregnancy.

A number of studies (mostly prospective) have reported beneficial associations between maternal intake of foods (e.g., fish, apples, fruit, vegetables, spreads and a Mediterranean diet) [2–6], nutrients (e.g., vitamin E, vitamin D, zinc and selenium) [9–15] and childhood wheeze, asthma and atopic disease. An adverse association has been reported between maternal vitamin D status and childhood asthma [16] and between maternal vitamin C intake and childhood wheeze and eczema at 2 but not 5 years of age [9,10].

Some of the foods adversely associated with childhood wheeze, asthma and eczema are recognized food allergens and in the study of Willers *et al.*, the significant association was with nut products (predominantly peanut butter in The Netherlands) and not nuts (e.g., brazil, cashews, macadamia and pistachios) [1]. Sausenthaler *et al.* reported that maternal intake of allergenic foods during pregnancy (celery, citrus fruit and raw sweet peppers) was associated with an increased likelihood of atopic sensitization (inhalant and food) [6]. Concerns have been raised that maternal allergen exposure during pregnancy increases the likelihood of childhood

atopic disease because of fetal immunological sensitization to maternally derived allergens. These concerns are largely based on the observation that allergens can traverse the placenta [17,18], that cord blood mononuclear cells (CBMCs) respond after *in vitro* stimulation by food allergens [19] and that these responses are associated with the subsequent development of atopic disease [20]. In the UK and New Zealand, pregnant women are advised to avoid peanut products if they, their partner or their children are atopic [21–23].

Subsequent studies suggest that *in utero* exposure to food allergens does not increase the likelihood of childhood asthma and atopic disease; indeed, in the study of Willers *et al.*, maternal intake of nut products was associated with childhood asthma but not atopic sensitization or doctor-diagnosed peanut allergy [1]. Recent studies of CBMC responses demonstrate no association between maternal allergen exposure and CBMC responses [24,25]. After a detailed investigation of CBMC responses, Thornton *et al.* concluded that responding neonatal cells are naive immature thymic emigrants that interact nonspecifically with protein antigens, providing short-lived cellular immunity that does not generate conventional T-cell memory [26]. Subsequent work from this group concluded that stable IgE-associated Th2-cell memory to peanut occurs entirely postnatally and appears after 6 months of age [27]. Recent consensus reports from the USA and Australia conclude that current evidence does not support a major role for maternal dietary restrictions during pregnancy [28,29].

Willers *et al.* suggest that the association between maternal nut product consumption during pregnancy and childhood asthma could be a consequence of increased maternal intake of the n-6 polyunsaturated fatty acid (PUFA) linoleic acid [1]. Several studies have reported associations between maternal dietary intake of foods rich in n-3 and n-6 PUFAs during pregnancy and childhood respiratory and atopic outcomes [2–8]. Increased maternal dietary intake of fish during pregnancy has been associated with reduced likelihood of childhood eczema [2,5,6], asthma [4] and wheeze [7], with the study of Fitzsimon *et al.* highlighting associations with oily fish [4]. Increased maternal dietary intake of margarine [4,6] and vegetable oils [6] has been associated with an increased likelihood of childhood asthma and eczema. It has been hypothesized that changes in dietary lipids, specifically increasing n-6 (margarine, vegetable oils) and decreasing n-3 (oily fish) PUFA intake has contributed to the recent increase in atopic disease and asthma. A proposed mechanism relates an increased ratio of dietary n-6: n-3 PUFAs to increased inflammatory-cell membrane arachidonic acid levels and consequent increased synthesis of prostaglandin (PG) E₂ by the action of COX-2 on arachidonic acid [30]. *In vitro*, PGE₂ suppresses Th1 differentiation (reduces IFN- γ secretion) [31,32] and promotes the Th2 phenotype, associated with asthma and atopic disease, by enhancing IgE-isotype switching and indirectly promoting IL-4 and IL-5 secretion [33,34]. In addition, n-3 and n-6 PUFAs can modulate T-cell function directly through effects on cell membrane fluidity, cell signaling and gene transcription, and n-3 PUFAs have also been reported to

affect the ability of antigen-presenting cells to present antigen to T cells [35,36]. Maternal lipid intake during pregnancy has the potential to modulate the initial interactions between the immune system of the child and allergens towards or away from the Th2 phenotype associated with asthma and atopy.

In a case-control intervention study, supplementation of the diets of pregnant atopic women with n-3 PUFA-rich fish oil from 20 weeks gestation was associated with a general reduction in CBMC cytokine responses; however, only the reduction in the IL-10 response after stimulation with cat allergen was statistically significant [37]. Although clinical outcomes were reported, this study was only powered to detect changes in CBMC responses. Maternal fish-oil supplementation was associated with borderline significant reductions in atopic sensitization to egg in 1-year-old children. These observations suggest that while n-3 PUFAs in pregnancy may influence neonatal immune responses to allergens, it remains to be seen whether these immunological associations can be translated into clinical effects.

Two birth-cohort studies have reported associations between maternal nutrient intake and childhood respiratory outcomes. Low maternal dietary intake of vitamin E-containing foods during pregnancy has been associated with increased wheezing outcomes in 2-year-old children and with increased wheeze, asthma and exhaled nitric oxide, and reduced ventilatory function in 5-year-old children [9–11].

Reports demonstrating associations between maternal vitamin E intake during pregnancy and CBMC responses suggest that vitamin E influences the first interactions between the immune system and allergens, with a low vitamin E status promoting the Th2 phenotype [38,39]. In animal models and humans, reduced vitamin E status is associated with the Th2 phenotype, either by reducing T-helper cell secretion of IFN- γ and/or increasing secretion of IL-4 or IL-5 [40–45]. Vitamin E appears to influence T-cell activity by two mechanisms. First, reduced vitamin E status is associated with increased COX-2 activity and increased production of PGE₂ by macrophages [45]. Second, vitamin E has direct effects on T cells, downregulating IL-4 mRNA expression in human T-helper cells by inhibiting binding of the transcription factors NF- κ B and AP-1 to the IL-4 promoter region [40]. Vitamin E may influence the development of the Th2 phenotype by inducing Treg cells [46].

There are somewhat contradictory associations between maternal vitamin D status and childhood respiratory disease. Two cohort studies have reported reduced maternal dietary intake of vitamin D during pregnancy to be associated with increased likelihood of childhood wheeze at 2 and 5 years of age [12,13]. In a third cohort, elevated maternal blood 25-hydroxyvitamin D in the third trimester of pregnancy was associated with an increased likelihood of childhood eczema at 9 months and asthma at 9 years of age; however, the follow-up rate at 9 years was 30% [16]. Evidence suggests that vitamin D can influence T-helper cell differentiation by promoting the development of IL-10-secreting Treg cells that can inhibit both Th1 and Th2 cytokine secretion. In adults, Treg cells secrete high levels of IL-10 when stimulated in the presence of corticosteroid and vitamin D3; furthermore, these

IL-10-secreting Treg cells inhibit cytokine secretion by allergen-specific Th2 cells [47]. In cord blood cells, vitamin D inhibits not only IL-12-generated IFN- γ production, but also suppresses Th2-related IL-4 and IL-4-induced expression of IL-13 [48].

Expert commentary & five-year view

The study of Willers *et al.* contributes to a growing body of evidence that maternal diet during pregnancy influences the development of childhood asthma and atopic disease. CBMC data support the notion that maternal diet influences the first key interactions between the child's immune system and allergens [38,39]. Although not discussed here, it is possible that maternal diet may also be influencing fetal airway development [50].

While this review has concentrated on the role of maternal diet, it is unlikely that dietary changes alone are responsible for the recent increase in asthma incidence. The hygiene hypothesis postulates that the increase in atopic disease in Westernized societies is a consequence of altered exposure to microbial constituents. Although usually considered separately, it is likely that dietary and hygiene factors are not exclusive. The development of asthma probably requires multiple exposures and, in genetically predisposed individuals, dietary and microbial exposures may interact, resulting in the more-severe and persistent asthma phenotypes.

The ultimate aim of this research is to ascertain whether maternal dietary modification during pregnancy is a viable public-health intervention to prevent childhood asthma and atopic disease. The concept of modifying the nutrient intake of pregnant women to prevent long-term disease in their children is not new; the use of folic-acid supplements by pregnant women to reduce the likelihood of spina bifida in their children is widely recommended. However, the current level of evidence is insufficient to make recommendations to pregnant women regarding asthma.

In the next 5 years, it is likely that this field of investigation will develop along four lines. First, more observational epidemiological studies are required to verify (or refute) the associations reported above, and these studies will provide ideal opportunities to identify gene-nutrient interactions. Second, the mechanisms by which nutrients such as vitamin E and D influence the immune system and the developing fetal airways need to be elucidated; this will require studies of Th cells, Treg cells, airway epithelial cells and epigenetics. Third, there is a need to replicate epidemiological observations in animal models. Of particular relevance will be the manipulation of the diets of pregnant animals to observe the effects on their offspring. Fourth, trials of dietary intervention in pregnant women are required and, by necessity, these trials will last more than 5 years.

Several important considerations need to be addressed in the design of any interventional trial. The nutritional intervention needs careful consideration. At the present time, my personal opinion is that vitamin E holds the most promise; similar associations have been reported in two cohort studies with differing dietary and socioeconomic profiles; furthermore, maternal vitamin E intake has been associated consistently with subjective (e.g., wheeze and diagnosed asthma) and objective (e.g., CBMC

responses, ventilatory function, exhaled nitric oxide and atopic sensitization) outcomes in children [9–11,38,39]. By contrast, maternal vitamin D intake has only been associated with childhood wheezing and not asthma or objective outcomes [12,13]. Furthermore, high maternal blood vitamin D levels during pregnancy have been adversely associated with childhood asthma [16]. The magnitude of any nutritional intervention will be critical; low-dose physiological supplementation would seem more logical than high-dose supplementation. Ideally, any nutritional intervention should aim to normalize intake and replicate intakes that were present 50–60 years ago, and supraphysiological doses are likely to be inappropriate, especially since concerns have been raised regarding adverse effects of high-dose vitamin supplementation [51].

Nutritional supplementation of pregnant women is relatively straightforward; women are willing to take vitamin supplements during pregnancy and this form of supplement can be administered in a double-blind, placebo-controlled manner. However, nutrients are seldom eaten in isolation and it is possible that for optimal effects a single nutrient supplement may require other nutrients. This problem is probably mostly easily addressed by providing the nutrient in its natural form – food. Food also addresses the issue of the identified nutrient being a marker

for other nutrients or combinations of nutrients. Dietary intervention to optimize nutrient intake is an attractive option that is likely to be viewed by women as being ‘more natural’ and lacking the potential side effects of pills. Dietary intervention is likely to be a challenge and will require more than simple dietary advice.

The demonstration that childhood asthma can be reduced by short-term, fairly simple, low-cost dietary interventions during pregnancy will represent a major advance in the understanding and prevention of asthma. It will be at least 5 years before any recommendations can be made; many hurdles still need to be cleared and it is possible that these hurdles may not be overcome.

Financial & competing interests disclosure

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Key issues

- In Westernized countries, the prevalence of asthma and atopic disease has increased dramatically since the 1960s.
- Epidemiological studies have demonstrated associations between maternal diet during pregnancy and childhood asthma and atopic disease.
- It is likely that maternal dietary nutrients influence the first interactions between the child's immune system and allergens.
- It is possible that maternal dietary nutrients influence fetal airway development.
- The dietary components most consistently associated with childhood outcomes are vitamin E, vitamin D, zinc and fish.
- No advice should be given to pregnant women at the present time.
- Further epidemiological, immunological and interventional studies are required.
- In the future, manipulation of maternal diet during pregnancy may be implemented as a public-health measure to prevent asthma.

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