

SCIENCE AND SOCIETY

The increase in the prevalence of asthma and allergy: food for thought

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Abstract | Since about 1960, the prevalence of asthma and allergic disease has increased sufficiently to become a major public-health concern. Concurrently, there have been marked changes in our diet, and it has been proposed that these changes have contributed to the increase in the prevalence of asthma and allergy. In this article, these hypotheses about diet are described, together with the postulated mechanisms and the evidence for and against, leading to the most recent evidence indicating that maternal diet during pregnancy might be particularly important in the development of childhood asthma.

In westernized countries, asthma and the associated allergic diseases atopic eczema and allergic rhinitis (also known as hay fever) are now common, and are associated with considerable ill health, as well as high costs to society and in terms of health care^{1,2}. In the United Kingdom, 5.2 million people receive treatment for asthma, of which 1.1 million are children. The annual cost in the United Kingdom is estimated to be UK£2.3 billion, and the annual expenditure on asthma by the National Health Service is estimated to be £889 million¹. In the United States, it is estimated that 15 million people had active asthma in 1996 (REF. 3) and that the cost of asthma was US\$10.7 billion in 1994, with \$6.1 billion being in direct medical costs⁴. In affluent countries, atopic eczema is common, affecting up to 30% of pre-school children, 15–20% of school children and 7% of adults, with estimated economic costs similar to those for asthma^{5,6}.

Asthma and allergy are characterized by inflammatory processes, with CD4⁺ T helper (T_H)₂-cell responses of the T_H2-cell phenotype considered to be crucial for the initiation and the maintenance of asthmatic and allergic inflammation⁷. Cytokines that are secreted by T_H2 cells — such as interleukin-4 (IL-4), IL-5, IL-9 and IL-13 — are important mediators of asthmatic and allergic inflammation, which is characterized

by increased IgE concentrations, mast-cell degranulation and eosinophil-mediated inflammation⁸ (FIG. 1).

Asthma and allergy: diseases of the West

The prevalence of asthma and allergy has markedly increased in westernized countries since about 1960. As an example, this increase is reflected in cross-sectional surveys of school children aged 9–12 years in Aberdeen, United Kingdom, between 1964 and 1999 (REF. 9) (FIG. 2). Recent epidemiological studies indicate that, in some countries, the increase in asthma and allergy has reached a plateau and might even be on the decline^{10,11}.

It is generally accepted that asthma and allergy are associated with a westernized lifestyle, with their prevalence being higher in developed countries (FIG. 3). The capacity of a westernized lifestyle to induce asthma and allergy has been shown by the rapid increase in the prevalence of asthma in children who have migrated from developing countries to developed countries¹². More recently, in the former East Germany, there was a rapid increase in the prevalence of childhood hay fever and allergic sensitization within a few years of the re-unification of Germany¹³.

The increase in the prevalence of asthma and allergy has stimulated research into which factors in a westernized lifestyle might be responsible. Four features that

are associated with such a lifestyle have been suggested as possible causes of the increased prevalence of asthma and allergy. First, exposure to the house dust mite (an important perennial allergen) has increased, because modern housing, in general, favours the house dust mite and because we spend more time indoors. Second, exposure to a wide range of microorganisms has changed because of improved hygiene and cleanliness and widespread antibiotic use, as emphasized by the ‘hygiene hypothesis’. Third, the prevalence of obesity has increased, and there has been a decline in physical activity, especially in children. Fourth, the Western diet has changed. This last potentially important contributor to the increase in the prevalence of asthma and allergy is the focus of this article.

Dietary hypotheses

The modern diet in most westernized countries differs considerably from that of previous generations, in which the prevalence of asthma and allergy was considerably lower. The modern diet is dominated by food that has been processed, modified, stored and transported great distances. This is in contrast to the traditional diet, which comprised food that was produced and marketed locally and was eaten shortly after harvesting.

In addition to changes in the types of food eaten (for example, a decline in the consumption of fresh green vegetables in the United Kingdom, from 392 g per day per person in 1950 to 240 g per day per person in 2000 (REF. 14)), the nutrient content of the ‘raw materials’ from which the modern diet is composed has also changed. For example, the increased use of selenium-deficient grain in the United Kingdom is thought to underlie the decline in selenium intake in the United Kingdom since the 1970s (REF. 15). Moreover, the mineral content of vegetables, fruit and meat has also declined¹⁶. These changes in food nutrient content might have arisen because of changes in agricultural techniques and because of increased storage and transportation of ‘fresh’ food. Such dietary changes have been proposed to contribute to the increase in the prevalence of asthma and allergy^{17–19}.

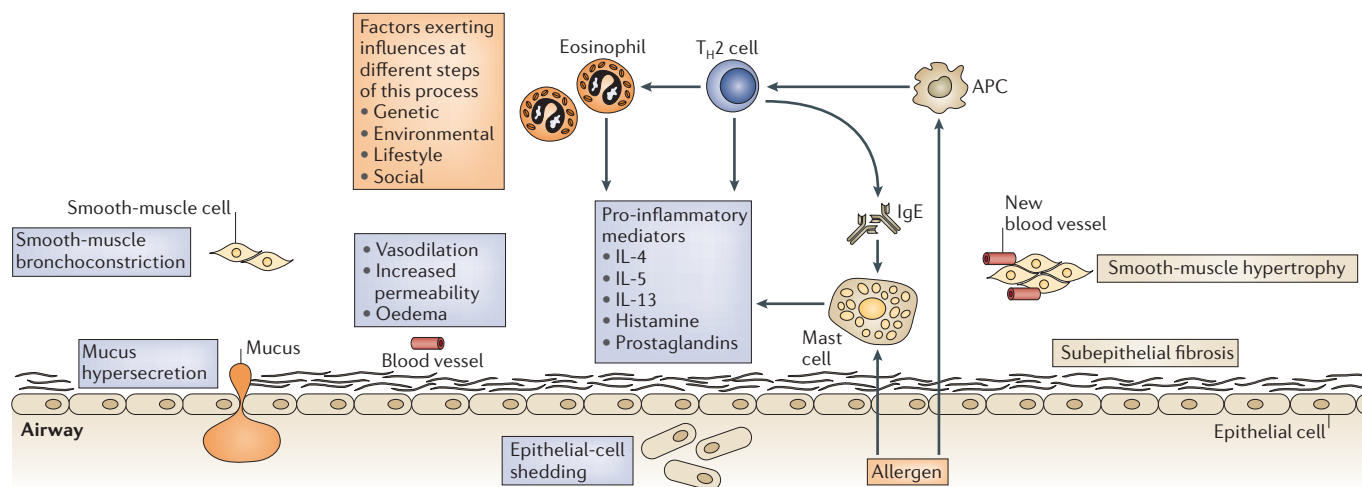


Figure 1 | Immunological pathways that result in the inflammatory changes that occur in the airways of individuals with asthma. Genetic, environmental, lifestyle, social and allergen-associated factors combine, resulting in $CD4^+$ T helper (T_H)₂-cell responses to allergens being biased towards T_H ₂-cell responses. T_H ₂ cells release the cytokines interleukin-4 (IL-4), IL-5, IL-9 and IL-13, and these cytokines induce and perpetuate inflammation mediated by eosinophils and IgE-induced mast-cell

degranulation. In the airways of individuals with asthma, this inflammatory response results in airway narrowing because of mucosal oedema, smooth-muscle constriction, mucus hypersecretion and epithelial-cell shedding into the airways. Chronic inflammation in the airways of individuals with asthma might lead to permanent structural changes, such as smooth-muscle hypertrophy and subepithelial fibrosis. APC, antigen-presenting cell.

This article focuses on the dietary intake of antioxidants and lipids, but the dietary intake of certain minerals has also been associated with asthma. Epidemiological studies have inconsistently shown adverse associations between high sodium intake and airway reactivity^{20,21}; however, it is unclear from intervention studies whether restriction of sodium intake is clinically beneficial for individuals with asthma²². Similarly, there is epidemiological evidence of a beneficial association between a higher magnesium intake and asthma²³, although intervention with magnesium supplementation for 4 months was found not to have any benefit²⁴. From other epidemiological studies, there are also inconsistent reports of associations between copper and zinc intake and asthma^{25,26}. I am unaware of any intervention studies with these minerals.

Antioxidant hypothesis. In 1994, Seaton and colleagues¹⁸ reasoned that the increase in the prevalence of asthma and allergy was not a consequence of the environment becoming more toxic but was, instead, a consequence of the population becoming more susceptible, owing to a westernized lifestyle. Over the period in which the prevalence of asthma and allergy increased, the amount of atmospheric pollution and the proportion of individuals who smoke cigarettes declined, but seasonal pollen levels were stable. Observing, however, that the increase in the prevalence of asthma and allergy had

been preceded by, and occurred in parallel with, changes in diet in the United Kingdom (particularly declining consumption of vegetables), it was suggested that a westernized diet, which was becoming progressively more deficient in antioxidants, increased the susceptibility of the population to allergens¹⁸. A proposed mechanism related reduced intake of antioxidants with reduced antioxidant-mediated defences in the lungs, together with increased susceptibility of airways to oxidant damage, increased permeability of the mucosae to allergens, increased inflammation of the airways and increased prevalence of asthma¹⁸.

Lipid hypothesis. In 1997, Black and Sharpe¹⁹ drew attention to changes in dietary fats. They proposed that the increase in the prevalence of asthma and allergy was, in part, a consequence of the following changes: increased intake of omega-6 polyunsaturated fatty acids (n-6 PUFA), which are present in margarine and vegetable oils (and which have been widely promoted to prevent coronary disease); decreased intake of long-chain n-3 PUFA, which are present in oily fish (such as herring, mackerel, trout and salmon) and oily-fish products (such as cod-liver oil); and decreased intake of saturated fats, such as those present in butter and lard. It was proposed that the increased ratio of dietary n-6 PUFA to n-3 PUFA altered the lipid composition of membranes of inflammatory cells, in particular increasing the proportion

of arachidonic-acid molecules, which are n-6 PUFA. Arachidonic acid can be metabolized by the enzyme cyclooxygenase-2 to produce prostaglandin E_2 (PGE_2). Increased synthesis of this prostaglandin is a potential mechanism by which an increase in intake of n-6 PUFA could facilitate the development of asthma and allergy, because PGE_2 suppresses differentiation into T_H ₁ cells, thereby reducing production of interferon- γ ($IFN\gamma$)²⁷, and promotes the T_H ₂-cell phenotype by increasing class switching to IgE²⁸ and indirectly promoting production of IL-4 and IL-5 (REF. 29).

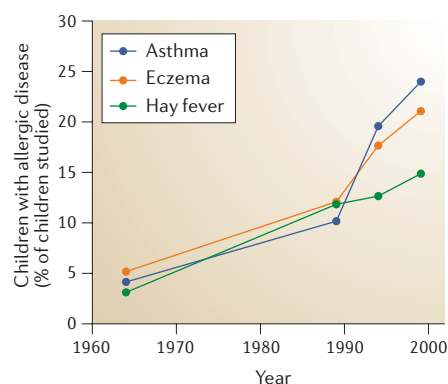


Figure 2 | The increase in the prevalence of asthma, eczema and hay fever since 1964. The results of four cross-sectional surveys of school children aged 9–12 years in Aberdeen, United Kingdom, between 1964 and 1999 are shown. Data are taken from REF. 9.

Both the antioxidant hypothesis and the lipid hypothesis have been tested in numerous epidemiological studies and in several intervention studies, some of which are discussed in the next section.

Studies of diet, asthma and allergy

Many epidemiological studies have related dietary intake of antioxidants, minerals and fats to the probability of asthma and allergy, and these studies have been reviewed in detail elsewhere³⁰. A brief overview is presented here.

Observational studies of antioxidants.

Nearly all of the epidemiological studies that relate diet to asthma and allergy have been cross-sectional surveys of adults. Although there have been several studies of older children, there have been very few studies of young children (less than 6 years of age) or longitudinal studies (that is, studies of the same group of people at more than one point in time).

Most studies have found beneficial associations between a higher intake of one, two or occasionally three nutrients (such as vitamin C, vitamin E, selenium, α -carotene, β -carotene and β -cryptoxanthin) and/or types of food (such as fresh fruit, fruit juices and vegetables) and outcomes associated with asthma and allergy (such as diagnosed asthma^{31–34}, wheezing symptoms³⁵, airway reactivity³⁶, lung function³⁷, allergic sensitization^{38,39} and IgE concentrations³⁸). The beneficial associations with a higher intake of fruit, independent of the nutrients outlined above, have led to the suggestion that the flavonoid content of fruit might be important. (Flavonoids constitute a class of plant secondary metabolites that is most commonly known for its antioxidant activity.) The beneficial associations with a higher intake of nutrients and/or food have mainly been related to improvements in asthma symptoms and respiratory outcomes. Although there are only a few reports of beneficial associations with allergic end-points, two studies do warrant consideration^{38,39}. Both studies found that sensitization to allergens, as measured by skin-prick testing, was more likely to occur in adults with a low vitamin E intake and with low blood concentrations of vitamin E, β -cryptoxanthin and α -carotene^{38,39}. These associations support the concept that dietary antioxidants can have immunomodulatory effects.

Although, as mentioned, most studies that examined nutrients or food found beneficial associations between asthma outcomes and a higher intake of up to three

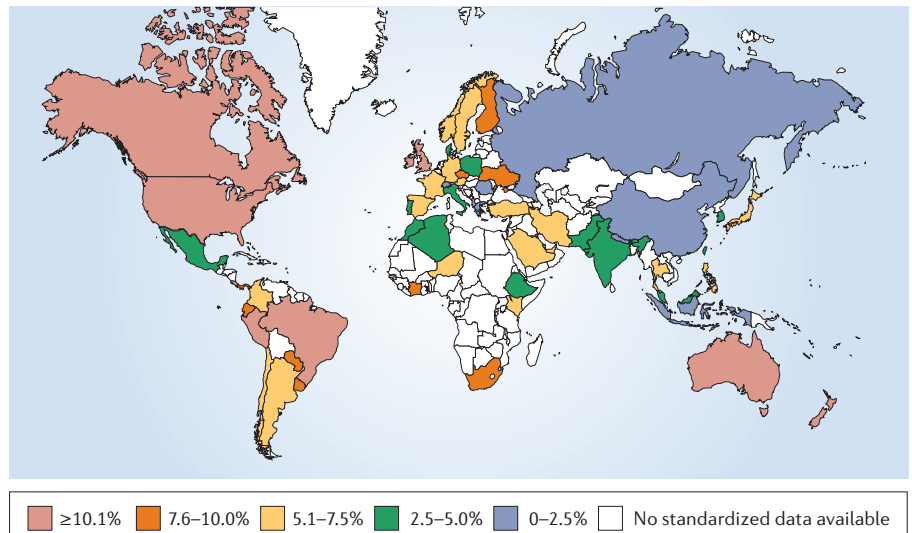


Figure 3 | **The association between a westernized lifestyle and asthma.** The variation in the global prevalence of asthma is shown, as determined using standardized methodology. Numbers indicate the percentage of individuals in each country who have asthma. This figure is modified, with permission, from REF. 72 © (2004) World Health Organization.

nutrients and/or types of food, nearly all of these studies show an absence of association with the other measured nutrients and/or types of food. Therefore, although one study might show an association with one nutrient and not another, other studies might show the converse. Although differences in design of the studies, the populations investigated and the methods of quantifying intake probably contributed to the inconsistencies between the findings of these studies, the variation might reflect the possibility that associations between diet and asthma and allergy are residual effects of diet earlier in life.

Observational studies of lipids. In general, the results of epidemiological studies of lipids and asthma and allergy are inconsistent, contradictory, inconclusive and do not support the original lipid hypothesis^{40–45} (that is, that the increasing intake of n-6 PUFA and the decreasing intake of n-3 PUFA promote the development of asthma and allergy by modulation of the production of pro-inflammatory mediators and the differentiation of T_H cells). For a detailed review, see REF. 30.

For children, fish intake has been reported to have a beneficial association⁴⁰, a harmful association⁴¹ or no association with asthma, whereas it has been reported consistently that there is no association for adults⁴². Several studies have quantified n-3 PUFA intake. For adults, most studies failed to show an association with asthma or allergy, but a higher intake of n-3 PUFA has been reported to have a beneficial association with hay fever⁴³ and a harmful association with asthma⁴⁴.

Other studies have quantified intakes of n-6 PUFA or foods rich in n-6 PUFA (such as margarine), and a few studies have measured blood concentrations of n-6 PUFA. Whereas some studies failed to show an association between n-6 PUFA intake and asthma and allergy, other studies of adults and children showed that margarine intake and/or n-6 PUFA intake have a harmful association with asthma, wheezing, hay fever and allergic disease^{42,45}. These studies are contradicted by reports that margarine use, n-6 PUFA intake and erythrocyte-membrane n-6 PUFA levels are beneficially associated with childhood wheezing and adult asthma⁴⁴. In children, there are reports that use of butter as a spread is beneficially associated with hay fever and other allergies⁴⁵, adversely associated with wheezing and not associated with asthma and allergy.

The obvious differences between these studies are inconsistent with the original lipid hypothesis. They might, however, reflect differences in study design and methodology, as well as the practical and financial difficulties of biochemical analysis. An alternative approach to the investigation of lipids and asthma and allergy has been dietary supplementation with PUFA.

Intervention studies in individuals with established disease. The results of studies that supplement the diets of individuals who have established disease weaken the case for there being an association between diet and asthma and allergy. Most of these studies use supplementation with either vitamin C or

n-3-PUFA-rich fish oil. There are few studies of vitamin E or selenium supplementation. Nearly all of these supplementation studies have shown no effect. In the few reports of benefits, the effects were small and probably clinically insignificant^{46–49}. However, there is scope for further intervention studies that are well designed and are of substantial duration, especially in children⁴⁶.

The generally negative results that have been obtained from dietary-intervention studies in adults with established disease raise the possibility that the reported epidemiological associations between diet and asthma and allergy might be spurious. However, recent work indicates that maternal diet during pregnancy might have an important influence on the development of childhood asthma and allergy.

Maternal diet during pregnancy

There is increasing evidence that many factors that influence susceptibility to asthma and allergy exert their main influence on disease pathogenesis during fetal life. Factors that are influential during fetal life have the potential to exert disproportionately potent

effects, because small perturbations in organogenesis can be exaggerated by rapid growth during fetal life⁵⁰. The importance of antenatal factors on the immunopathogenesis of asthma and allergy has been highlighted by work showing that the proliferation of neonatal cord-blood mononuclear cells and the production of cytokines (IFN γ , IL-4, IL-6, IL-10 and IL-13) after stimulation with allergens *in vitro* are associated with subsequent asthma and allergy⁵¹. Furthermore, these responses are associated with maternal diet and smoking⁵².

The concept that diet influences the development of asthma and allergy during a crucial period, mainly during fetal life, might explain the ineffectiveness of dietary supplementation of asthmatic adults and the inconsistent associations that have been reported for cross-sectional studies of older children and adults. Such a model does not preclude the possibility of minor effects later in life: for example, on airway reactivity. Several considerations indicate that maternal diet during pregnancy has the potential to influence the development of childhood asthma and allergy.

Possible mechanisms of modulation. The development of the airways mainly occurs during fetal life. And, in fetal rats, antioxidant deficiency has adverse effects on airway number, growth and complexity⁵³. Longitudinal studies of lung function from infancy into childhood indicate that children who have reduced lung function in early life and develop allergic sensitization are particularly likely to develop asthma. Therefore, there is the potential for maternal diet during pregnancy to influence fetal airway development and to influence the probability that asthma will develop, especially if the child develops T_H2-cell-biased immune responses to allergens.

As mentioned earlier, T_H2-cell-biased immune responses greatly increase the probability that asthma will develop, especially in the presence of abnormal airway development. In addition to effects on fetal airway development, antenatal intake of certain antioxidant nutrients also has the potential to influence the differentiation of T_H cells^{54,55}, with suboptimal nutrient status being associated with T_H2-cell-biased immune responses^{56–61}. In animal models and human studies, vitamin E, selenium and the flavonoid quercetin have been reported to promote differentiation into T_H1 cells by increasing secretion of the T_H1 cytokine IFN γ ^{57,59} and/or by inhibiting secretion of the T_H2 cytokines IL-4 and IL-5 (REFS 56,57,61) and reducing secretion of IgE⁵⁶. The mechanism by which vitamin E can influence the differentiation of T_H cells has been clarified: vitamin E downregulates expression of *IL4* mRNA in human T_H cells by inhibiting the binding of the transcription factors nuclear factor- κ B and activator protein 1 to the *IL4* gene promoter region⁶¹.

This evidence indicates that maternal diet during pregnancy has the potential to modulate the risk of childhood asthma and allergy by influencing fetal airway development and T_H-cell differentiation (FIG. 4). The association between maternal diet during pregnancy and childhood asthma and allergy has recently been clarified by several cohort studies.

Studies of antenatal diet and asthma and allergy

The Avon Longitudinal Study of Parents and Children, a population-based study in the United Kingdom, found that higher selenium concentrations in the umbilical cord at birth were negatively associated with persistent childhood wheezing at 0–6 months and 30–42 months⁶².

In a Scottish population-based birth cohort, lower maternal vitamin E intake during pregnancy was reported to be

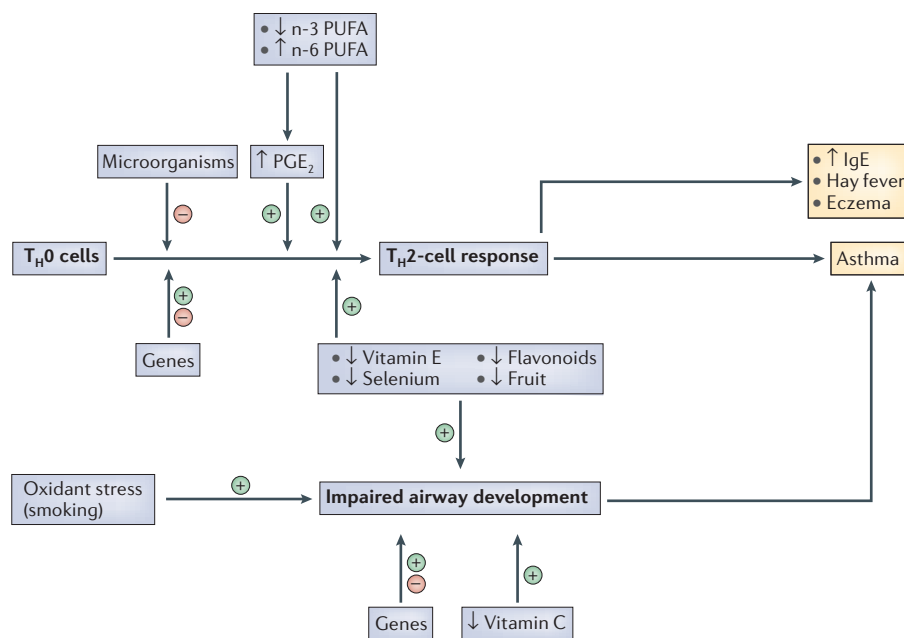


Figure 4 | Potential mechanisms by which maternal diet during pregnancy can influence the development of childhood asthma and allergy. Maternal nutrient status during pregnancy, as well as genetic and other environmental factors, has the potential to promote neonatal CD4⁺ T helper (T_H) cell responses to allergens being biased towards T_H2-cell responses. This bias increases the probability of developing asthma, eczema and hay fever in childhood. Nutrient intake by mothers during pregnancy also has the potential to impair the development of the fetal airways, increasing the risk of development of asthma in childhood. For example, reduced maternal intake of vitamin E might affect the development of asthma in childhood by influencing both T_H-cell responses and airway development. The ineffectiveness of dietary supplementation to treat established disease later in life is compatible with this model. n-3 PUFA, omega-3 polyunsaturated fatty acids; n-6 PUFA, omega-6 polyunsaturated fatty acids; PGE₂, prostaglandin E₂.

associated with increased proliferation of cord-blood mononuclear cells in response to stimulation with allergens at birth⁵², as well as with increased wheezing and eczema when these infants reached 2 years of age⁶³. More recently, this study showed that a low intake of vitamin E by mothers during pregnancy is associated with increased prevalence of wheezing, asthma and allergic sensitization, as well as reduced lung function and increased exhaled nitric oxide (a marker of asthmatic airway inflammation), when these children were 5 years of age⁶⁴. The magnitude of some of these associations was substantial, showing a fivefold difference in the probability of developing asthma between children who were born to mothers in the top 20% and the bottom 20% of vitamin E intake.

Similarly, the Project Viva birth-cohort study, in the United States, has found similar associations between lower vitamin E intake by mothers during pregnancy and increased proliferative responses of cord-blood mononuclear cells at birth and recurrent wheezing during the first 2 years of life⁶⁵.

An extrapolation of the results from the Scottish study indicates that the decline in the average vitamin E intake in the United Kingdom, from ~15 mg per day in 1950 to ~9 mg per day in 2000 (REFS 14,66), was associated with a doubling of the probability of children developing asthma by 5 years of age. Therefore, focusing on maternal diet during pregnancy seems particularly promising, with similar results from two other birth cohorts highlighting beneficial associations with a higher maternal vitamin E intake during pregnancy.

Two studies have related the PUFA composition of cord blood to the subsequent development of atopic disease^{67,68}, although the largest of these studies found no association between cord-blood PUFA composition and subsequent childhood eczema and wheezing⁶⁷. However, an intervention study that used supplementation with n-3-PUFA-rich fish oil during pregnancy found an association between cord-blood mononuclear-cell responses to allergens and supplementation, but this study was not designed to investigate clinical outcomes⁶⁹.

Implications

The evidence is steadily growing in support of large, well-designed dietary-intervention studies of pregnant women, with follow-up of the birth cohorts, to ascertain whether dietary modification during pregnancy reduces the probability of children developing asthma and allergic disease. It would

seem that a fairly moderate (50%) increase in vitamin E intake by mothers during pregnancy (to an amount similar to that of 1950, ~15 mg per day) could halve the risk of developing childhood asthma by 5 years of age⁶⁴. Such an increase in vitamin E intake could be achieved by vitamin E supplementation (5–10 mg per day) or by dietary modification. Although more difficult to carry out than a supplementation study, a dietary-intervention study to increase moderately the maternal intake of foods that contain vitamin E would offer several advantages. First, such a healthy diet would be widely perceived as natural. Second, supplementation with high doses of vitamin E during pregnancy is controversial at present⁷⁰. And, last, vitamin E is found in several types of food that contain other potentially important combinations of micronutrients that could have synergistic effects.

The cellular mechanism(s) by which nutrients, particularly vitamin E, could influence the development of asthma and allergy need to be clarified, particularly the molecular and genetic pathways by which nutrients influence immune function and airway development and structure. The identification of cellular mechanisms could add a further dimension to observational and intervention studies: that is, the investigation of gene–nutrient interactions, and the identification of individuals for whom nutrients are particularly important for modifying the risk of developing asthma and allergy in childhood. Clarification of the cellular mechanisms could direct investigators to other nutrients that might influence the development of asthma and allergy: for example, vitamin D⁷¹. The justification for further research into the role of diet in the development of asthma and allergy is based on the genuine prospect of a practical, safe and acceptable public-health intervention in the form of dietary modification to reduce the burden of asthma and allergic disease.

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Competing interests statement

The author declares no competing financial interests.

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