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Dietary Factors and the Development of Asthma

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Synopsis

Asthma and allergies continue to be major public health problems in affluent westernized countries. One feature of a westernized lifestyle that may have a role in the development of asthma and allergies is the changes in dietary habits that predated the increase in asthma prevalence. Many studies have investigated the role of specific nutrients in asthma and allergies, and intervention studies with supplementation of particular nutrients have been conducted, but results have been mixed. It is likely that nutrients may exert their strongest effect early in life, when both the immune system and the lungs are not yet fully developed.

Keywords

diet; nutrition; asthma; allergies; prenatal programming

Introduction

Asthma and related allergic diseases are substantial public health problems world wide[1, 2]. Data from the US CDC indicate that the self-reported prevalence of asthma in the US increased 73.9% during 1980–1996[1]. In 2002, estimates from the National Health Interview Survey revealed that 72 people per 1,000, or 20 million people, have asthma in the US[3]. Worldwide, it is clear that more affluent Westernized countries and countries making the transition to a westernized lifestyle have higher prevalence of asthma compared with less developed countries[2]. Although recent findings suggest that the prevalence of asthma may have reached a "plateau" in most industrialized countries[4–8], there are no clear reasons for the increase in prevalence of asthma and allergies in these developed countries. It is likely a changing environment and the behaviors associated with a "westernized" lifestyle that is contributing to the problem. For example, because of improvements in hygiene and control of infectious disease, it is postulated that decreased exposure to infectious agents in early childhood may predispose to the development of asthma and allergies[9]. Thus, some studies have shown that exposure to markers associated with infectious agents such as endotoxin[10], farm animals[11] and pets[12] may decrease the risk of these disorders. Other factors associated with a western lifestyle that have been implicated in the development of these conditions and include obesity[13], and exposure to allergens[14]. Another aspect of this lifestyle is the changes in diet that have occurred over the years. This review will briefly discuss these changes, describe how diet is evaluated in epidemiologic studies, and summarize existing data relating diet with

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asthma. There have been a number of comprehensive reviews on this topic[15–17], and we will update these with recent studies, where available. Additionally, in the past 5 years, new information has surfaced regarding the association of early life diet and nutrition on subsequent asthma.[18, 19] We will review these studies, with emphasis on effects of maternal diet in pregnancy.

Dietary changes in westernized countries

In 1994, Seaton and colleagues highlighted changes in the UK diet that had preceded and paralleled the increase in asthma and atopic disease[19, 20]. They observed that there had been a decrease in vegetable consumption, particularly of potatoes and green vegetables, and suggested that a westernized diet, increasingly deficient in antioxidants had increased population susceptibility with consequent large increases in the prevalence of asthma and allergy. In the US, recent analyses have shown that fruit and vegetable consumption remains low[21, 22], despite public health efforts to improve overall diet quality[23]. It is postulated that decreased dietary antioxidant intake leads to reduced antioxidant defenses in the lung, leading to increased oxidative stress with increased susceptibility to airway inflammation and asthma[24]

Aside from antioxidants, intake of fats, particularly the changing composition of polyunsaturated fatty acids (PUFAs) in western diets, has been implicated in asthma. In 1997, Black and Sharpe[25] reviewed the changes in dietary intake of fats as a result of public health efforts to reduce the incidence of coronary heart disease, and suggested that the changing composition of PUFAs played a role in the increase in asthma and allergies. In westernized countries including the US, the reduction in intake of saturated fat was accompanied by an increase in consumption of n6 polyunsaturated fatty acids, particularly linoleic acid (LA) and arachidonic acid (AA), through increased use of margarine and vegetable oils (instead of butter and lard)[26, 27]. In addition, there has also been a decrease in consumption of oily fish, a rich source of n3 polyunsaturated fatty acids such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Thus, the hypothesis is that the increased ratio of n6:n3 PUFAs in westernized diet may have contributed to the increased asthma incidence.

The assessment of diet in epidemiological studies

Several methods are used to assess dietary exposures in epidemiological studies (Table 1)[28]. The most commonly used methods include 24-hour recall interview[29], diet record[29], food frequency questionnaires[30, 31], and measurement of nutrient biomarkers[32]. The 24-hour recall interview is administered by a trained interviewer, and subjects are asked to report everything they had to eat or drink in the past 24-hour period[29]. This method is dependent on the short-term memory of the subject. The interview may be conducted over the telephone or in person, and it is important to have skilled interviewers to probe for additional foods and to do so in a neutral manner so as to not influence the subjects' responses. Because of this, high-quality dietary information is collected with properly trained interviewers, but this makes it expensive and impractical for large-scale epidemiologic studies. Interactive, computer-based 24-hour recall software programs are being developed to circumvent these limitations[33]. The food record or food diary method is similar to the 24-hour recall, except that subjects record actual food and drink intake prospectively on one or more days[29]. Food records are quantified by asking the subject to either weigh the foods or determine volume using common household measuring tools, and assistance may be provided by the use of photographs. This prospective record minimizes reliance on memory and does not require trained interviewers. However, this method requires a reasonably high level of subject literacy and motivation, and requires some level of training in recording complete and accurate food intake. Furthermore, food records done on consecutive days may be correlated and may introduce bias in the measurement. Both the 24-hour recall and the food record methods may not capture seasonal variation of diet or may not reflect usual long-term diet. These limitations may be reduced by performing these measurements on multiple days over several months of the year.

Food frequency questionnaires are the most frequently used method for many epidemiologic studies[30, 31]. They consist of a list of foods and beverages that represent the major contributors to the diet of the population being studied and a frequency response to report how often each food is consumed. It is important that food frequency questionnaires are validated for a particular population or ethnicity, since lists of foods and beverages may be specific to a particular group (e.g. young children usually eat a more limited variety of foods compared with adults; recent immigrants will tend to find and eat foods native to their country of origin compared with non-immigrants). Food frequency questionnaires are easily administered in person or mailed to subjects. They provide information on usual intake of a large number of foods, food groups, and supplements, are substantially less expensive than other methods of dietary assessment, and can be administered repeatedly over several years to capture diet changes over time. From responses to the questionnaire, individual nutrient intake can be calculated based on the known nutrient content of foods. Alternatively, analyses based on usual intake of foods taken directly from the responses to the questionnaires (i.e. frequency of intake of fruits and vegetables) can also be performed.

Biochemical markers of dietary intake are also commonly used in epidemiologic studies[32]. In many cases, these biomarkers are used to validate information obtained from food frequency questionnaires. However, they are also used to indicate the status of the individual with regard to the nutrient of interest. In the case of some nutrients, biochemical indicators are the only reliable markers of nutrient status. For example, the selenium content of similar foods obtained from different places can vary up to 100-fold, since selenium content of soil varies from area to area. While these biomarkers can be considered as unbiased indicators of nutrient intake, many issues must be considered before using them for analyses of diet-disease associations. Biomarkers must be sensitive to nutrient intake, but this is not always the case, as genetic variation, lifestyle factors, and intake of other nutrients among many other considerations[32] may affect the level of the nutrient of interest. Additionally, knowledge of the half-life of the biomarker is necessary for interpretation of findings (i.e. short-term vs. long-term exposure).

Evidence for the association between diet and asthma

Many studies have examined the association between various nutrients or foods and asthma and asthma-related phenotypes, such as lung function, airway responsiveness, and symptoms. Most of these studies have been cross-sectional in design with a few prospective studies, and have been conducted in adults or in older children. Table 2 and Table 3 summarize selected studies that have investigated dietary factors in relation to lung function, asthma, and asthma-related symptoms. Studies that had large numbers of subjects were included, with emphasis on more recent findings, when available. Comprehensive tabular summaries are available in other recent reviews[16, 17]

Antioxidants

Oxidative stress plays a central role in asthma pathogenesis[24] and dietary antioxidants improve oxidant defenses[34] to combat free radicals. Antioxidants, namely vitamin C, vitamin E, carotenoids and flavonoids have been the most widely studied nutrients with regard to asthma and allergies, either as individual nutrients or in analyses assessing fruit and vegetable intake. Vitamin C is found in vegetables (red and green peppers, broccoli, tomato, potato, and spinach) and fruits (orange, tangerine, strawberry, cantaloupe) and fruit juices[35]. Vitamin E is also found in fruits (apples and mangos) and vegetables, vegetable oils, meat, poultry, nuts, and eggs[36]. The most abundant carotenoids in the North American diet are beta-carotene, alphacarotene, gamma-carotene, lycopene, beta-cryptoxanthin, and lutein-zeaxanthin. Food sources of carotenoids include carrots, sweet potatoes, spinach, kale, collard greens, and tomatoes[37]. Flavonoids are a large family of compounds synthesized by plants and have a wide range of biologic activities including antioxidant activities, participation in cell signaling pathways, and decreasing inflammation[38]. Flavonoids are found in fruits and vegetables, teas, soybeans and legumes. In general, observational studies have shown a protective effect of these antioxidants on either lung function asthma diagnosis or wheeze, and atopy (Table 2 and Table 3). However, results across studies were not the same, with some studies showing effects with one antioxidant and other studies showing effects with another. Most of these studies were cross-sectional and the few longitudinal studies[39–41] have also shown some protective effects of dietary antioxidants on asthma or lung function decline.

Several intervention studies with antioxidants have also been conducted. A randomized placebo-controlled trial of vitamin C and magnesium supplementation for 16 weeks in 300 asthmatics on inhaled corticosteroids did not show any benefit on lung function, methacholine airway responsiveness, peak flows, or symptom scores[42]. A second study from the same group showed that supplementation with vitamin C but not magnesium had modest steroid-sparing effects in 92 asthmatics[43]. In a randomized placebo-controlled trial of vitamin E supplementation for 6 weeks in 72 asthma patients, no evidence of clinical benefit was found[44]. Several small trials have shown protective effects of vitamin C[45, 46], β-carotene[47], and lycopene[48] on either exercise-induced bronchoconstriction or exercise-induced lung function decrements.

Antioxidants given together may work better than individual supplementation, and there is evidence to suggest that antioxidants protect against exposure to outdoor air pollution, particularly ozone exposure. In a randomized, double-blind crossover study of 47 street workers in Mexico City, supplementation of vitamin C, vitamin E, and β-carotene protected against ozone-induced decrements in lung function[49]. A study from the same group showed that supplementation with vitamin C and vitamin E attenuated the effects of ambient ozone exposure on lung function indices in Mexican children[50]. In a randomized, double-blind crossover study, 17 adult asthmatics were supplemented with both vitamin C and vitamin E, then exposed to ozone during moderate exercise, after which bronchial provocation testing with sulfur dioxide was performed[51]. Antioxidant supplementation protected against ozone-induced bronchial hyperresponsiveness.

Overall, observational studies have shown protective effects of antioxidants on asthma-related phenotypes, but large trials of antioxidant supplementation have not shown any benefit for asthma symptoms or control. Issues for these discrepancies between observation studies and intervention trials have been discussed by McKeever and Britton[16]. Some of these issues relate to accurate measurement of the dietary intakes in observational studies, confounding by other exposures that are linked with diet, lack of effectiveness of single nutrient supplements if other nutrients are important or if foods are more important than the individual nutrient. It is also possible, as the smaller intervention trials show, that antioxidant effects may be seen in only particular subsets of asthmatics (i.e. exercise-induced asthmatics) or in response to specific exposures (i.e. ozone exposures). Alternatively, since the intervention trials have been conducted in adults or children who have asthma, they do not address the issue of primary prevention of asthma. Early life programming leading to predisposition to adult diseases is a growing area of research[52], and it is possible that the effects of diet on asthma may occur much earlier in life[18]. This applies for all the nutrients and the studies of diet in early and effects on asthma incidence are reviewed in a later section.

Vitamin D

Vitamin D is both a nutrient and a hormone. However, unlike usual nutrients, vitamin D does not *naturally* occur in foods that humans eat, except in oily fish and fish liver oil, egg yolk, and offal[53]. Therefore, most of the vitamin D that we ingest comes from fortified foods (in the US, milk, some milk products such as yogurt and margarine, and breakfast cereals are fortified with vitamin D[54, 55]) and from supplements. The Institute of Medicine[54] currently recommends intakes of 200 IU/day from birth through age 50 years, 400 IU/day for those aged 51–70 years, and 600 IU/day for those over 70 years. However, there is now widespread consensus that these recommendations are woefully inadequate for overall health[56]. From an evolutionary standpoint, humans do not require vitamin D in the food supply because it is effectively produced in the skin on exposure to sunlight in the UVB range. Because people in westernized countries now spend most of their time indoors, it has been postulated that vitamin D deficiency may explain a large portion of the asthma epidemic[57]. Vitamin D may reverse steroid-resistance in asthmatics through induction of IL-10 secreting T-regulatory cells[58], and vitamin D has been shown to regulate expression of many genes in bronchial smooth muscle cells, including genes previously implicated in asthma predisposition and pathogenesis[59]. Two recent analyses have related vitamin D with lung function. The first involved 2,112 adolescents from twelve cities in the US and Canada[60], published in abstract form, found that vitamin D intake was inversely associated with lung function. The second study was a cross-sectional analysis of 14,901 adults from the NHANES study[61]. Circulating serum vitamin D levels (25-hydroxyvitamin D3) were measured from stored samples and subjects with higher vitamin D levels had higher FEV_1 and FVC values. There are no trials of vitamin D supplementation in subjects with asthma.

Minerals

Sodium—In 1987, Burney[62, 63] highlighted an association between regional table salt sales and asthma mortality, and subsequent studies have shown a positive relationship between salt intake and the presence of airway hyperresponsiveness[64, 65], but this finding has not been universal[66, 67]. Thus, it remains unclear whether salt is directly associated with asthma or is merely a marker for a diet that increases the risk for asthma. A recent study suggests that dietary salt loading enhances airway inflammation[68]. A Cochrane Database review of six randomized controlled trials did not find any significant effect of dietary salt restriction on asthma treatment or management[69]. There are no longitudinal studies that have addressed the association between salt intake and development of asthma.

Selenium—Selenium is a trace mineral that is involved in antioxidant defenses as a coenzyme of glutathione peroxidase, which recycles glutathione. Plant foods are the major dietary sources of selenium in most countries throughout the world[70]. Assessment of selenium intake is difficult because the selenium content of the same type of foods varies widely depending on where the food is obtained, owing to the variability in selenium content of soil[32]. Several case-control studies have documented lower selenium blood levels in asthmatic subjects compared to non-asthmatics[71–73]. In a small trial of 12 adult asthmatics, selenium supplementation for 14 weeks showed improvement in clinical parameters but not in objective markers of asthma[74]. A recent larger trial of 197 adult asthmatics, most of who were on inhaled steroids, did not show any clinical benefit of selenium supplementation over 24 weeks[75].

Magnesium—Magnesium is a cation with modulatory effects on smooth muscle cell contractility[76], such that hypomagnesemia induces contraction (bronchoconstriction) while hypermagnesemia induces relaxation (bronchodilatation). This potential bronchodilatory property of magnesium has led to its use in emergency department care of acute asthma exacerbations[77]. Green vegetables such as spinach are good dietary sources of magnesium[78]. Cross-sectionally, there is evidence to suggest that higher magnesium intakes are associated with decreased airway hyperreponsiveness and symptoms in adults[79] and decreased lung function in children[80]. Clinical trials of supplementation with magnesium (given with vitamin C) did not show any clinical benefit on lung function, symptoms, or on ability to decrease steroid dose in asthmatics[42, 43].

Polyunsaturated fatty acids

While there is some evidence relating diets rich in saturated fats from milk and dairy products with a reduced risk for asthma in pre-school children[81] and young adults[82], most studies have investigated intakes of n3 and n6 polyunsaturated fatty acids. The anti-inflammatory role of n3 PUFAs and the pro-inflammatory role of n6 PUFAs are well documented[83]. Briefly, n6 PUFAs (AA and LA) give rise to the eicosanoid family of mediators (prostaglandins, thromboxanes, leukotrienes, and related metabolites) which have pro-inflammatory actions and regulate the production of inflammatory cytokines, while n3 PUFAs (EPA and DHA) decrease the production of AA-derived eicosanoids, inflammatory cytokines (tumor necrosis factor, interleukin-6), and decrease the expression of adhesion molecules involved in inflammation.

Several large cross-sectional studies have found positive associations between fish intake and lung function[84, 85], and inverse associations between fish intake and asthma[86, 87]. However, Butland et al did not find any effect of fish intake on lung function in 2,512 men. McKeever et al[88] found no association between n3 PUFA intake and lung function, although there were inverse associations between some n6 PUFAs and FEV_1. Other recent studies have likewise not found associations between measured n3 PUFAs and asthma[89, 90]. Several small trials of fish oil supplementation have shown mixed results[91–94]. Results of trials of fish oil supplementation in the prenatal and early life period are presented below.

Prenatal diet and nutrition

There is growing recognition that prenatal and early life exposures, including diet and nutrition may have a role in the development of many adult diseases[52]. Research into the developmental origins of health and disease has focused mainly on obesity and the metabolic syndrome and cardiovascular disorders, but asthma and other respiratory disorders are also affected by early exposures[95, 96]. Despite the difficulty in diagnosing asthma in very young children, the available epidemiologic evidence suggests that about half of all cases of childhood asthma are diagnosed by age 3 years and 80% of all asthma cases are diagnosed by age 6[97, 98]. Thus, it is clear that early life factors play a role in the inception of the disease, however, identifying the causative early life factors remains challenging. Smoking in pregnancy, through its effects on lung development in utero, is the only definite prenatal risk factor for asthma that has been identified to date[99]. In the past few years, several studies have been published that have investigated the effects of maternal diet in pregnancy on immune outcomes and wheezing illnesses in young children (Table 4).It has been hypothesized that specific nutrients may exert their effect at the critical time period when the fetal immune system and lung development is occurring[18, 57, 100].

Devereux et al[101] studied the T helper cell proliferative responses of cord blood mononuclear cells from a sample of 223 neonates from Aberdeen, Scotland and found that higher maternal intakes of vitamin E were associated with lower cord blood mononuclear proliferative responses to timothy grass and house dust mite, compared with mothers whose intakes were in the lowest tertile of vitamin E. Follow-up of these children in the larger cohort of over 1,000 children has found that higher maternal vitamin E intakes were associated with decreased risks for wheezing and asthma in the children at 2 and 5 years of age[102 103]. Maternal vitamin E (both intake during pregnancy and plasma level of α-tocopherol at delivery) was also inversely associated with levels of exhaled nitric oxide (a marker of airway inflammation) and positively associated with post-bronchodilator FEV_1 in a subset of the 5-yr old children. Additionally, maternal zinc intake was also associated with decreased risks for several asthma-related phenotypes at 5 years. While maternal vitamin C was associated with increased risks for wheezing phenotypes at 2 years, this association disappeared when the children turned 5 years old. In a cohort from Boston, Massachusetts, USA, Litonjua et al[104] similarly found that higher maternal antioxidant intakes (vitamin E and zinc) were also associated with decreased risks of any wheeze and persistent wheeze in 1290 2-yr old children.

A subsequent study from the Scottish cohort reported that mothers who consumed more apples and fish in pregnancy had children who were less likely to wheeze[105]. A study of 631 children from Ireland also showed that higher fruit and vegetable intake in pregnancy decreased the risk for asthma by age 3[106], although it is unclear whether the FFQ was administered to the mothers during pregnancy or at recruitment when the children were 3 yrs old. That study also found that higher added fats (from butter, margarine and other spreads, salad dressings, and mayonnaise) in maternal diet in pregnancy increased the risk for asthma in the 3-yr old children. The UK ALSPAC cohort study reported low umbilical cord selenium concentrations to be associated with an increased likelihood of persistent wheeze in 2,044 children in the first 42 months of life[107]. The Scottish group also found an inverse relationship between maternal and cord blood plasma selenium and wheeze phenotypes in 2-yr old children, but this relationship disappeared when the children turned 5 years old[108]. There are no published intervention studies of prenatal antioxidant supplementation and asthma in children.

Vitamin D is both a nutrient and a hormone, and it is important for immune regulation[109]. Deficiency in vitamin D is widespread and has been postulated to contribute to the rise in asthma[110]. Two birth cohorts have assessed maternal vitamin D intake in pregnancy and wheezing symptoms in 3- to 5-yr old children. In the Boston cohort of 1194 3-yr old children, children born to mothers who had intakes of vitamin D in the highest quartile had significantly decreased risks of recurrent wheezing (OR=0.39; 95% CI: 0.25, 0.62) compared with children born to mothers in the lowest quartile of vitamin D intake[111]. In the Aberdeen[112] cohort, similar findings were obtained in 1212 children. Children born to mothers with vitamin D intakes in the highest quintile had significantly decreased risks for persistent wheeze (OR: 0.33; 95% CI: 0.11, 0.98) compared with children born to mothers with vitamin D intakes in the lowest quintile. Two other studies have suggested that vitamin D intake increases the risk for asthma. In the Northern Finland Birth Cohort, data on vitamin D supplementation in the first year of life and subsequent asthma and atopy outcomes at 31 years of age was obtained on 7,648 subjects[113]. The risk for atopy (OR=1.33, 95%CI=1.07–1.64) and allergic rhinitis (OR=1.33, 95%CI=1.12–1.58) at age 31 years was higher in subjects who had received regular vitamin D supplementation in the first year compared with other subjects. However, there was no assessment of maternal vitamin D intake and no assessment of vitamin D intake in the intervening period between the first year of life and age 31 years. A second study measured circulating vitamin D levels in pregnant women and reported that higher circulating vitamin D levels in pregnant women were associated with increased risks for eczema at 9 months and asthma at 9 years[114]. However, results were reported only in univariate models without adjustment for potential confounders, and there was significant loss to follow-up in the cohort, especially at 9 years. Thus, the question of whether vitamin D is a protective or a risk factor for asthma in children remains unresolved. Future studies will need to account for factors that affect vitamin D levels, such as use of sunscreen, time spent outdoors in the sun, season of the year, and skin color. There are no published intervention studies of vitamin D supplementation in pregnancy.

A few studies have related childhood asthma and atopic disease to maternal dietary intake of foods rich in n3-fatty acids (e.g. fish intake), but these studies were limited by retrospective recall of diet in pregnancy (e.g. mothers were asked to recall diet 5–20 years previously)[115],

[116]. Several studies have measured cord blood levels of PUFAs and related these to immune responses in CBMC. Gold et al[117] investigated cord blood PUFA levels in 192 cord blood samples and found that increased cord plasma EPA (n-3) and arachidonic acid (n-6) were both associated with decreased proliferative and IFN-γ responses, in addition to increased IL-13 responses. Several observational studies of cord blood PUFAs and atopic disease development in childhood have been conducted with variable results[118–120]. More importantly, there have been two intervention studies using fatty acids to prevent asthma or allergies. The first was conducted in the Childhood Asthma Prevention Study[121–123]. In 616 children at risk for atopic disease, the dietary intervention was 500 mg daily of n-3 PUFA rich fish oil, in addition to n-3 rich oils and spreads for the family, compared with the controls who received placebo and n-6 rich oils and spreads for the family. This study found a reduction in wheeze symptoms at 18 months[122] but minimal, if any, beneficial effect on asthma or atopic disease at 3 years[121]. The associations were null at 5 years[123]. However, this study applied the intervention post-partum. Dunstan et al[124] supplemented the diets of 40 pregnant atopic women with n-3 PUFA rich fish oil from 20 weeks gestation, and 43 control women received olive oil. Fish oil supplementation was associated with a general reduction in CBMC cytokine responses (IL-5, IL-10, IL-13, and IFNγ). In addition, maternal supplementation with fish oil was associated with borderline significant reduction in atopic sensitization to egg in 1-yr old children; no further follow-up studies on these children have been published.

Summary

Changes in diet that have predated the increases in asthma and allergy that have occurred in westernized countries are postulated to be one of the reasons for the asthma epidemic. Many observational studies in adults and children have implicated deficiencies in specific nutrients as potential causes of the asthma and allergy epidemic. However, these have not been borne out in large intervention trials of supplementation with specific nutrients in asthmatics. Smaller trials, specifically with antioxidant supplementation, suggest that the effects may be limited to subsets of asthmatics (i.e. exercise-induced asthmatics) or as modifiers of the effects of pollutants (i.e. ozone). Alternatively, because asthma and allergies have their beginnings in early life, it is likely that nutrients may exert their effects in utero and in very early life, when the immune system and the lungs are not yet fully developed. Several observational studies have shown effects of maternal diet in pregnancy, and two intervention trials on n3 PUFA supplementation have been conducted. More studies are needed to further clarify the effects of diet in early life on the inception of asthma and allergies.

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Table 1

Methods for assessment of diet/nutrition in epidemiologic studies

Method	Pro(s) and Con(s)
24-hour recall	Pro: relatively precise (recent memory), relatively low participant burden
	Con: may not reflect long-term diet, requires well-trained interviewers, nutrient analysis may be laborious
Diet record	Pro: precise record of intake over several days, recall error and bias are reduced due to prospective nature
	Con: requires high level of subject literacy and motivation, may not capture long-term diet
Food frequency questionnaire	Pro: applicable to large cohorts; assesses long-term diet; ease of administration allows for repeat measurements to capture changes in diet over time; provides information on large numbers of foods; relatively cheap to analyze and calculate nutrients
	Con: population-specific; food list needs to be validated in a particular population to ensure that main foods are captured
Biomarker	Pro: precise measure of short-term status, depending on nutrient and nutrient half-life; may be the only reliable measurement of nutrient exposure
	Con: invasive, requires collection of biological sample (blood, hair, nail)

Table 2

Selected epidemiologic studies relating dietary factors with lung function or airway hyperresponsiveness

Author	Cohort or Country	Population and Study design	Dietary assessment method	Association
Antioxidant vitamins, carotenoids, and minerals				
Schwartz & Weiss[125]	NHANES I, US	2526 adults/cross-sectional	FFQ and 24-hour recall	Positive association between dietary vitamin C intake and FEV_1; no association between vitamin C-rich vegetables and lung function
Chuwers et al[126]	CARET, US	816 adult men with asbestos exposure/cross-sectional	FFQ; serum β-carotene and retinol	Positive association between serum β-carotene and both FEV_1 and FVC; weak positive association between serum retinol and both FEV_1 and FVC; no association between intakes of these nutrients from FFQ and lung function
Hu & Cassano[127]	NHANES III, US	18,162 adults/cross-sectional	24-hour recall; Serum vitamins C, E, β-carotene and selenium	Positive associations between dietary and serum antioxidants and FEV_1
Hu et al[128]	69 counties from rural China	3085 adults/cross-sectional	3-day weighed records; plasma vitamin C from pooled samples	Positive associations between dietary vitamin C and both FEV_1 and FVC; pooled plasma vitamin C levels were positively associated with county mean FEV_1
Britton et al[129]	Nottingham, UK	2633 adults/cross-sectional	FFQ	Positive associations between vitamin C and vitamin E and both FEV_1 and FVC; intakes of vitamin C and E were correlated and there was no effect of vitamin E independent of vitamin C
Dow et al[130]	Southampton, UK	178 elderly men and women/cross-sectional	FFQ	Positive associations between vitamin E and both FEV_1 and FVC; no association for vitamin C and lung function

Author	Cohort or Country	Population and Study design	Dietary assessment method	Association
Butland et al[131]	Wales, UK	2512 men/cross-sectional	FFQ	In multivariable models, positive association between vitamin E and FEV_1; no associations between intakes of vitamin C, magnesium, and β-carotene with FEV_1; Positive association between intake of apples and FEV_1
Ness et al[132]	East Anglia	835 men & 1025 women/ cross-sectional	Plasma vitamin C	Positive associations between plasma vitamin C and both FEV_1 and FVC in men only
Grievnik et al[133]	MORGEN Study, Netherlands	6555 adults/cross-sectional	FFQ	Positive associations between dietary vitamin C & β-carotene and both FEV_1 & FVC; no associations for dietary vitamin E and lung function; Vitamin E associated with productive cough; β-carotene associated with wheeze
Tabak et al[134]	Finland, Italy, & Netherlands	middle aged men from Finland (n=1248), Italy (n=1386) and Netherlands (n=691)/cross-sectional	Diet history	Positive associations between vitamin C & β-carotene and both FEV_1 & FVC; positive association between vitamin E and FEV_1 in Finnish men only
Carey et al[39]	Health and Lifestyle Survey, UK	2171 British adults/longitudenal (7 years follow-up)	FFQ	Subjects who decreased their fruit consumption had greatest FEV_1 decline over 7 years
Britton et al[79]	Nottingham, UK	2415 adults	FFQ	Subjects with higher magnesium intake had decreased airway responsiveness
McKeever et al[41]	Nottingham, UK	2633 subjects/cross-sectional and longitudinal (follow-up on 1346 subjects after 9 yrs)	FFQ	Positive cross-sectional associations

Author	Cohort or Country	Population and Study design	Dietary assessment method	Association
				between vitamin C and magnesium intakes and FEV_1; Higher vitamin C intake was associated with slower FEV_1 decline; No associations between vitamin A or vitamin E and lung function
Cook et al[135]	England and Wales	2650 children/cross-sectional	Plasma vitamin C	No association of vitamin C levels with lung function
Vitamin D				
Black & Scragg[61]	NHANES III, US	14,091 adults aged ≥20 yrs	Serum 25(OH)D	Positive associations for 25(OH)D levels and both FEV_1 and FVC
Minerals				
Burney et al[64]	Hampshire, England	138 men/cross-sectional	24-hour urinary Na excretion	Increased odds for having PD20 ≤ 8 μmol in subjects with greater Na excretion
Pistelli et al[66]	Latium region, Italy	2593 subjects aged 9-16yrs/ cross-sectional	Dietary questionnaire; urinary sodium and potassium levels	Positive association with table salt use and symptoms but not with airway responsiveness; higher urinary potassium but not urinary sodium was associated with airway responsiveness in boys
Devereux et al[65]	Northern England	234 male shipyard workers exposed to welding fumes; 121 male rural and 111 male urban dwellers/cross-sectional	24-hour urinary Na excretion	Increased odds for methacholine airways responsiveness with greater sodium excretion among male urban dwellers only
Sparrow et al[67]	Normative Aging Study, US	273 middle aged to older men/cross-sectional	24-hour urinary Na and K excretion	Positive relationship between potassium excretion and methacholine airway responsiveness; no association of sodium excretion and airway responsiveness
Gilliland et al[80]	Children's Health Study, US	2566 children aged 11–19 yrs/cross-sectional	FFQ	Children with lower magnesium and potassium

Author	Cohort or Country	Population and Study design	Dietary assessment method	Association
				intakes had lower lung function indices; No effect of sodium intake
Fatty acids				
McKeever et al[88]	MORGEN-EPIC Study, Netherlands	13,820 adults/cross-sectional	FFQ	No association between n-3 fatty acids and FEV_1. Inverse association between some n-6 fatty acids and FEV_1
Schwartz & Weiss[84]	NHANES I, US	2526 adults/cross-sectional	24-hour diet recall	Small but significant effect of fish intake on FEV_1; effect was stronger in non-smokers; did not distinguish effects of different types of fish
Sharp et al[85]	Honolulu Heart Program, Hawaii, US	6346 men/cross-sectional	FFQ	Interaction between fish intake and smoking; lower decrements of FEV_1 due to smoking among high fish intake
Butland et al[131]	Wales, UK	2512 smen/cross-sectional	FFQ	No effect of fish intake on lung function

NHANES: National Health and Nutrition Examination Survey

CARET: Carotene and Retinol Efficacy Trial

MORGEN: Monitoring Project on Risk factors for Chronic Diseases

EPIC: European Prospective Investigation into Cancer and Nutrition Study

Table 3

Selected epidemiologic studies relating dietary factors with asthma, asthma-related symptoms, and atopy

Author	Cohort or Country	Population and Study design	Dietary assessment method	Association
Antioxidant vitamins, flavonoids, and minerals				
Schwartz & Weiss[136]	NHANES II, US	9074 adults/cross-sectional	24-hour diet recall	Serum vitamin C inversely associated with wheezing and diagnosed bronchitis
Fogarty et al[137]	Nottingham, UK	2633 subjects with allergy skin test results and 2498 subjects with total IgE/ cross-sectional	FFQ	Higher vitamin E intake was inversely associated with total IgE concentrations and was associated with decreased odds for atopy.
McKeever et al	NHANES III, US	5858 adults and 4428 children	Serum levels of several nutrients	In adults, α-carotene, β-cryptoxantine, and vitamin E were inversely associated with atopy, but lycopene was positively associated with atopy; vitamin A increased the risk of atopy in children
Troisi et al[40]	Nurses Health Study, US	77,866 nurses/longitude nal	FFQ	Positive association between vitamin C supplement users and the risk for asthma; Dietary vitamin E inversely associated with asthma; β-carotene weakly protective for asthma
Shaheen et al[138]	Greenwich, South London, UK	607 cases, 864 controls (adults)	FFQ	Consumption of apples was inversely associated with asthma; Selenium intake inversely associated with asthma; No association between intakes of vitamin C and E and asthma
Garcia et al[139]	Greenwich, South London, UK	607 cases, 864 controls (adults)	FFQ	No association between intake of three major classes of flavonoids and asthma
Okoko et al[140]	Greenwich, South London, UK	2560 children aged 5–10 yrs/cross-sectional	FFQ	Banana consumption and drinking apple juice were negatively associated with wheeze but not asthma; Fresh apple consumption was not associated with asthma or symptoms
Chatzi et al[141]	Menorca, Spain	460 children aged 6.5 yrs/ cross-sectional	FFQ	Fruity vegetable intake was inversely associated with current wheeze and atopic wheeze; fish intake was inversely associated with atopy
Chatzi et al[142]	Crete, Greece	690 children aged 7– 18/ cross-sectional	FFQ	Intake of local fruits and tomatoes was inversely associated with wheeze and allergic rhinitis but not atopy; adherence to the Mediterranean diet was inversely

Author	Cohort or Country	Population and Study design	Dietary assessment method	Association
				associated with allergic rhinitis
Sodium				
Demssie et al[143]	Montreal, Canada	187 cases and 145 controls aged 5–13 yrs	FFQ	No association of usual salt intake with asthma or exercise-induced bronchospasm; positive association with methacholine airway hyperresponsiveness
Fatty acids				
Laerum et al[86]	RHINE (Norway, Iceland, Denmark, Estonia, Sweden)	12,345 adults	FFQ	Low current fish intake was associated with greater odds of asthma and wheeze; for intake of cod oil, there was a U-shaped association with asthma
Tabak et al[87]	ISAAC-2, Netherlands	598 children aged 8–13 yrs/ cross-sectional	FFQ	Fish intake was inversely associated with current asthma and with atopic asthma with bronchial hyperresponsiveness; intake of whole grains was inversely associated with atopic asthma with bronchial hyperresponsiveness

RHINE – Respiratory Health in Northern Europe

ISAAC – International Study of Asthma and Allergies in Childhood

Table 4

Studies of the association between maternal diet and nutrient status in pregnancy and immune markers, asthma, and asthma-related outcomes in childhood

Reference	Cohort and Country	Population	Dietary assessment method	Association
Antioxidant Vitamins and Minerals				
Martindale et al[102]	SEATON, Aberdeen, Scotland	1,374 2-yr old children	Food frequency questionnaire	Maternal vitamin E intakes were negatively associated with wheeze in the absence of a cold; maternal vitamin C intakes were positively associated with ever wheeze
Devereux et al[103]	SEATON, Aberdeen, Scotland	1,253 5-yr old children; 478 5-yr old children with lung function measures	Food frequency questionnaire; maternal α-tocopherol levels in pregnancy	Maternal intakes of vitamin E and zinc were negatively associated with wheeze and asthma in 5-yr old children; maternal plasma α-tocopherol levels were positively associated with FEV_1 in the 5-yr old children
Litonjua et al[104]	Project Viva, Boston, MA US	1,290 children	Food frequency questionnaire	Maternal intakes of vitamin E and zinc were negatively associated with any wheeze and recurrent wheeze in 2-yr old children
Shaheen et al[107]	ALSPAC, UK	2,044 children for wheezing analyses; 2,173 children for eczema analyses	Cord blood levels of trace elements and minerals	Cord blood selenium was negatively associated with persistent wheeze up to 42 months of age; cord blood iron was negatively associated with late onset wheeze (wheeze occurring at 30–42 months but not before 6 months) and eczema at 18–30 months
Devereux et al[108]	SEATON, Aberdeen, Scotland	1282 2-yr old children and 1167 5-yr old children	Maternal and cord blood plasma selenium and erythrocyte glutathione peroxidase	Maternal and cord blood plasma selenium were inversely associated with wheezing in 2-yr old children. However, maternal and cord blood selenium levels were not associated with asthma or wheeze at 5 years. No associations between erythrocyte glutathione peroxidase and wheezing were found
Vitamin D				

Reference	Cohort and Country	Population	Dietary assessment method	Association
Devereux, Litonjua et al[112]	SEATON, Aberdeen, Scotland	1,253 5-yr old children	Food frequency questionnaire	Maternal intakes of vitamin D were negatively associated with ever wheeze, wheeze in the past year, and persistent wheeze in 5-yr old children
Camargo et al[111]	Project Viva, Boston, MA US	1,194 children	Food frequency questionnaire	Maternal intakes of vitamin D were negatively associated with recurrent wheeze; no association with eczema
Gale et al[114]	Southampton, UK	440 infants for eczema; 178 for asthma	Maternal 25(OH)D level	Maternal 25(OH) D levels were positively associated with eczema and asthma, although only univariate associations were presented
Fatty acids				
Yu et al[118]	Linköping, Sweden	68 infants (33 babies born to allergic mothers and 35 babies born to non-allergic mothers) followed to 6 years	Cord blood levels of fatty acids	Significant correlations between various n-6 fatty acids and between n-3 and n-6 fatty acids were found in cord blood of children who did not develop allergic disease (allergic dermatitis or asthma) by 6 yrs of age. These correlations were not found in cord blood of children who developed allergic disease by 6 yrs of age
Galli et al[119]	Rome, Italy	57 infants	Cord blood and infant levels of fatty acids	Lower AA and dihomo-gamma-linolenic acid in cord blood among infants who developed atopy (23 children, 10 eczema + 3 asthma) in the first year of life
Newson et al[120]	ALSPAC	Wheezing analyses: 1,191 and 2764 infants for cord and maternal analyses, respectively Eczema analyses: 1238 and 2945 infants for cord blood and maternal analyses, respectively	Maternal and cord blood red cell fatty acid measurements	Cord blood ratio of AA:EPA was positively associated with eczema (at 18–30 months), ratio of LA:ALA was positively associated with late-onset wheeze (wheeze occurring at 30–42 months but not before 6 months), and ratio of ALA:n3 was negatively associated with late-onset wheeze. However, after adjustment for multiple testing,

Reference	Cohort and Country	Population	Dietary assessment method	Association
				these associations were no longer significant. No associations between maternal red cell fatty acids and infant outcomes.
Dunstan et al[124]	Fish oil supplementation trial, Perth, Australia	80 pregnant women (40 with fish oil supplementation and 43 with olive oil supplementation and their 1-yr old schildren	Clinical trial of fish oil supplementation in 83 atopic pregnant women	Reductions in positive skin tests to allergens, although not statistically significant; nonsignificant reduction in risks for recurrent wheeze and asthma
Foods				
Willers et al[105]	SEATON, Aberdeen, Scotland	1,253 children	Food frequency questionnaire	Maternal intakes of apples were negatively associated with wheeze and asthma; maternal intakes of fish were negatively associated with eczema
Fitzsimon et al	Ireland	631 3-yr old children	FFQ	Maternal intakes of fruits and vegetables were inversely associated with asthma; maternal fat intake increased the risk for asthma

SEATON – Study of Eczema and Asthma To Observe the effects of Nutrition

ALSPAC – Avon Longitudinal Study of Pregnancy and Childhood