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Diet and Asthma: Nutrition Implications from Prevention to Treatment

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ABSTRACT

Asthma is characterized by lung airway inflammation initiated and perpetuated by an inappropriate immune response, increased airway responsiveness, and variable airflow obstruction. In Western countries there has been a marked increase in asthma prevalence such that it has become a public health concern. It has been hypothesized that the increase may be due to changing antioxidant intake, increasing dietary ratio of n-6:n-3 polyunsaturated fatty acids (PUFA), and vitamin D deficiency (and supplementation). Observational studies have reported associations between asthma and dietary antioxidants (vitamin E, vitamin C, carotenoids, selenium, polyphenols, and fruit), PUFA, and vitamin D. However, supplementing the diets of adults with asthma with antioxidants and n-3 PUFA has minimal, if any, clinical benefit. Currently there is insufficient evidence to support the use of nutrient supplements to complement conventional treatment; however, results of ongoing studies are awaited, and additional research is required, particularly in children. Interest in the potential of dietary intervention during pregnancy to reduce the likelihood of childhood asthma has increased. A small number of cohort studies have highlighted associations between childhood asthma and reduced maternal intake of some nutrients (vitamin E, vitamin D, selenium, zinc, and PUFA) during pregnancy. Although vitamin D intervention studies during pregnancy are ongoing and two intervention studies suggest that dietary PUFA manipulation during pregnancy may be advantageous, further trials are needed to establish if modification of maternal nutrient intake during pregnancy can be used as a healthy, low cost, public health measure to reduce the prevalence of childhood asthma.

J Am Diet Assoc. 2011;111:258-268.

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Manuscript accepted: April 19, 2010.

0002-8223/$36.00

doi: 10.1016/j.jada.2010.10.048

Asthma is a chronic disorder of the lung airways associated with increased airway responsiveness and variable airflow obstruction. Typical symptoms include periodic wheezing, breathlessness, paroxysmal cough, and chest tightness, and severity ranges from occasional symptoms to disabling persistent symptoms and/or frequent life-threatening exacerbations. Asthma and the allergic diseases of atopic dermatitis (eczema), allergic rhinitis (hayfever), and immunoglobulin E–mediated food allergy are closely associated, the likelihood of developing asthma being increased by a personal or family history of allergic disease. Asthma and allergic diseases are characterized by inflammatory processes with T-helper (Th) cell responses of the Th2 phenotype being considered crucial for the initiation and perpetuation of the inflammatory responses (1). Cytokines such as interleukin (IL)-4, IL-5, and IL-13 secreted by Th2 cells are important mediators of asthmatic and allergic inflammation that is characterized by elevated immunoglobulin E, mast-cell degranulation, and eosinophilic inflammation (1,2). There is increasing interest in the role of regulatory T (Treg)-cells in the pathogenesis of asthma and allergic disease because of their ability to directly inhibit both Th1 and Th2 responses (3).

Asthma is one of the world's most common chronic diseases, with a conservative estimate of 300 million people being affected by it. It is associated with Western urban communities, and it is estimated that by 2025 there could be an additional 100 million people with the disease. Asthma is a common and costly disease globally, accounting for the loss of approximately 15 million disability-adjusted life years, being the 25th greatest cause of disability-adjusted life years lost in 2001 (4). North America (the United States and Canada) has a high prev-

alence of asthma at 11.2%, representing 35.5 million people with asthma in a population of 316.9 million, with the United States having a prevalence rate of 10.9%, which in 1994 cost the economy an estimated $12 billion (4). Between 2001 and 2003 there were an average of 20 million people with asthma living in the United States each year, with 6.2 million of them being children (5). Access to drugs essential to control the condition tends to be good, with more than 95% of people able to acquire them. This may be reflected in the relatively low fatality rate of 5.2 per 100,000 people with asthma (4). In the absence of curative treatments, clinical management of asthma aims to control symptoms using bronchodilator and anti-inflammatory therapies. Given the high prevalence of asthma and its affect on individuals and society there is a need to identify interventions that can be used to complement conventional asthma therapy and more importantly, interventions to reduce the likelihood of children developing asthma.

INCREASING PREVALENCE OF ASTHMA

The prevalence of asthma has been rapidly increasing within Westernized countries, with increases of between 25% and 75% per decade being observed since 1960 (4). A recent survey by Moorman and colleagues (5) reported that the prevalence of self-reported asthma in the United States increased from 3.1% in 1980 to 5.6% in 1995, being more marked in children (an increase from 3.5% to 7.5%) than adults (an increase from 2.9% to 5.0%). The increase in asthma has probably been greater in the United Kingdom; for example, serial cross-sectional surveys of Aberdeen schoolchildren aged 9 to 12 years have demonstrated that the prevalence of asthma increased from 4.1% in 1964 to 28.4% in 2004 (6). The rate of increase in asthma prevalence appears to have slowed, with studies from some Westernized countries reporting that asthma prevalence may have plateaued; for example, in the United States the prevalence of asthma did not significantly change between 2001 and 2004 (5).

The rapid increase in asthma is most likely to be a consequence of changing environmental/lifestyle rather than genetic influences. In the past 15 years, several dietary hypotheses have been proposed and, somewhat surprisingly, changing diet has emerged as a promising candidate as a contributory environmental factor to the increase in asthma. In this narrative review, the rationale for investigating associations between diet and asthma is outlined, the potential for dietary intervention to complement conventional asthma treatment is then discussed, and finally the recent data suggesting that diet may influence the development of asthma are summarized. In each section, to reflect the focus of recent studies, nutrients are discussed in three groups: antioxidants (vitamins A, C, E, selenium, and antioxidant-rich foods), polyunsaturated fatty acids (PUFA), and vitamin D. To identify relevant articles, a set of 117 search terms relevant to asthma and diet were developed. These included symptoms of asthma (eg, wheeze), physiological parameters (Forced expiratory volume in 1 second), broad dietary terms, and specific nutrients (eg, vitamin E and PUFA). Included studies were all those relevant to adults and children (ie, mothers during pregnancy, infants, and children) that investigated the association between nutrients and foods and asthma (ie, cohort, case-controlled, cross-sectional, and all intervention studies). Three international databases were searched: Cochrane Library, MEDLINE, and EMBASE. The literature search encompassed studies from 1950 to December 2009. All references of published studies were hand searched. Of the 1,457 identified studies, 329 were considered to be directly relevant and were categorized into systematic reviews, intervention, and observational studies. While this review emphasizes published systematic reviews and clinical trials, such studies are relatively few, limited to adults, and focus on a few specific nutrients (eg, vitamin C). In the absence of systematic reviews and interventional study data, illustrative examples of the best available observational studies are presented.

Antioxidants

Two hypotheses relate the increase in asthma to changing dietary antioxidant intake.

The first proposes that the increase is a consequence of declining dietary antioxidant intake (7). This was based on the observation that in the United Kingdom asthma had increased concurrently with marked changes in the diet. The changes highlighted were those associated with the transition from a traditional diet comprising foods produced and marketed locally and eaten shortly after harvesting to the modern diet dominated by foods that have been processed, stored, and transported great distances. There is some evidence that the nutrient content of food may also have changed; for example, in the United Kingdom it has been suggested that the mineral content of vegetables, fruit, and meat has declined (8). Temporal changes in dietary habits and food nutrient content appear to have resulted in changes in antioxidant intake. Unfortunately, longitudinal data are very limited for antioxidants highlighted in studies of asthma. European selenium intake and blood selenium concentrations have declined, probably because of declining use of North American grain and changes in bread-making technology (9). In the United Kingdom, average selenium intake has fallen from 60 mg/day in 1975 to 30 to 40 mg/day currently (9-11). The limited data on United Kingdom vitamin E intake suggest little change from 10.82 mg/day in 1994 to 10.66 mg/day in 2004-2005 (12). However, extrapolation of the 2000-2001 UK National Diet and Nutrition Survey using the UK National Food Surveys suggests that vitamin E intake in the early 1950s was probably higher, at about 13 to 15 mg/day, perhaps because of increased consumption of green vegetables and bread/whole grains/cereals (13,14).

The second antioxidant hypothesis proposes that the increase in asthma and allergic disease is a consequence of increased antioxidant intake because of the increased availability of functional and antioxidant-enriched foods (15). This hypothesis was based on in vitro observations that some antioxidant rich foods and extracts of traditional Vietnamese and Chinese herbal medicines suppress secretion of the Th1 cytokine interferon-γ (15). It is postulated that increased antioxidant intake by suppressing Th1 differentiation promotes Th2 differentiation because of inherent cross-regulatory mechanisms. Whilst this hypothesis is primarily based on in vitro immunological observations, there is some evidence that the intake

of some antioxidant-rich (principally vitamin C) food groups has increased, for example in the United Kingdom fruit juice consumption increased from 7 mL/person/week in 1950 to 303 mL/person/week in 2000 (13).

Many observational studies have related dietary antioxidants to asthma outcomes (16); typical of these are those that have reported associations between reduced dietary and blood vitamin C and reduced lung function in adults (17), and an increased likelihood of asthma in adults (18) and children (19,20). The prospective Nurses Health Study reported low vitamin E intake to be associated with an increased incidence of asthma over a 10-year period (21) and in Saudi Arabia a case-control study reported childhood asthma to be associated with reduced dietary vitamin E intake (22). Asthma has also been reported to be associated with reduced blood carotenoid concentrations in adults (23,24) and children (19,20). Asthma has been associated with reduced selenium status in case-control studies: Dietary selenium intake has been reported to be reduced in adults with asthma (25) and blood selenium levels and glutathione peroxidase activity have been reported to be reduced in adults (26,27) and children (28) with asthma. A recent systematic review and meta-analysis of 40 studies relating vitamins A, C, and E to asthma concluded that dietary vitamin A and C intakes and blood vitamin C levels were significantly lower in adults and children with asthma, especially in those with severe asthma. Vitamin E intake was significantly lower in people with severe asthma but was unrelated to asthma status (29). Overall the body of observational evidence is inherently weak because of the biases and limitations of the cross-sectional and case-control studies that predominate. These limitations include the difficulties in quantifying dietary intake, reverse causation (people with asthma and allergic disease may change their diet) and lack a temporal element. Even studies of blood antioxidant biomarkers are limited by the systemic oxidant stress associated with the asthma that reduces the concentration of blood antioxidants (30).

Based on these observational data, a small number of intervention studies have clarified whether antioxidant (predominantly vitamin C) supplementation has a therapeutic role complementing conventional therapy in people with asthma. A Cochrane review (31) of vitamin C supplementation in asthma concluded that there is insufficient evidence to recommend vitamin C supplementation in the treatment of asthma. Randomized controlled trials (RCTs) of selenium (32) and vitamin E (33) supplementation in adults with mild to moderate asthma reported no beneficial effects on any of the parameters measured. While these studies do not support the use of vitamin C, vitamin E, or selenium supplements to complement conventional therapy for asthma, there is still a need to conduct for studies in children and of combinations of antioxidants and antioxidant-rich foods.

There appear to be no intervention studies or systematic reviews investigating the associations between asthma and polyphenols and antioxidant-rich foods such as fruit. Several studies reporting associations between foods and asthma have highlighted polyphenolic compounds such as flavonoids as possible antioxidants of interest. In adults, apple consumption has been associated with a reduced likelihood of asthma (25), and in children, daily consumption of bananas and apple juice from concentrate were independently associated with a reduced likelihood of wheezing symptoms (34). A high intake of so-called fruity vegetables, citrus fruit, and kiwifruit has been reported to be associated with a reduced likelihood of wheezing outcomes in children (35-37). A Mediterranean-style diet has been associated with a reduced likelihood of asthma and wheezing in children (35,38). There is minimal evidence supporting the hypothesis of an adverse association between antioxidants and asthma.

PUFA

In Westernized countries, the change from traditional to modern diet has been associated with changes in dietary fat intake, principally increasing intake of n-6 PUFA present in spreads (eg, margarine) and oils sourced from vegetables, and decreasing intakes of saturated fats (butter, lard) and long-chain n-3 PUFA such as eicosapentaenoic acid and docosahexaenoic acid that are present in fresh oily fish (eg, fresh tuna, herring, mackerel, trout, and salmon) or derived fish oil products (cod liver oil). It is likely that public health advice on healthy eating to prevent coronary heart disease has contributed to this change (39). It has been hypothesized that the combination of decreasing n-3 and increasing n-6 PUFA intakes has contributed to the increase in allergic disease and consequently asthma (39). A suggested mechanism relates increased dietary n-6:n-3 PUFA ratio to increased inflammatory-cell membrane arachidonic acid levels and consequent increased synthesis of prostaglandin E_2 by the action of cyclooxygenase-2 (39). In vitro, prostaglandin E_2 suppresses Th1 and promotes Th2 differentiation. Although elegant, this proposed mechanism is almost certainly an oversimplification because the immunological consequences of changing PUFA are very complex. For example, prostaglandin E_2 has been reported to have other actions, n-3 PUFA are metabolized to biologically active three-series prostaglandins, and both n-3 and n-6 PUFA can modulate T-cell function directly through effects on cell signalling and gene transcription (40-42).

Many observational studies have related PUFA status to asthma and allergic outcomes, with studies of PUFA-containing foods in relation to childhood allergy predominating over asthma. Fish intake has been reported to be associated with a reduced risk of asthma in adults (43,44) and children (45,46). Fish intake has also been associated with an increased risk of asthma in children; however, the reported association had not been adjusted for potential confounding by socioeconomic factors (47). In adults, high margarine intake (a source of n-6 PUFA) has been associated with an increased likelihood of adult-onset asthma (48) and in children regular margarine consumption has been associated with an increased likelihood of wheezing symptoms (49). The use of PUFA in spreads and cooking oils has been linked to recent asthma in children (50), and polyunsaturated oil intake has been associated with an increased risk of childhood wheezing symptoms (46). Associations have been reported between asthma and dietary intakes and blood concentrations of individual PUFAs (51-54); however, these studies are characterised by numerous comparisons, a relative paucity of significant associations, and no clear pattern of

association (43,44,53,54). Overall, the body of observational evidence relating PUFA to asthma is weak, with a predominance of cross-sectional and case-control studies, lack of consistent association, adverse associations, and very few studies have actually quantified individual PUFA. A recent comprehensive review concluded that the published data do not support the hypothesis that allergy and asthma are associated with increased n-6 PUFA intake nor increased tissue levels. It was also concluded that reports of associations with reduced n-3 PUFA intake were inconsistent (55). The review suggested that the observational data are more in keeping with reduced levels of n-6 PUFA being associated with allergy and asthma.

Most intervention studies of n-3 PUFA supplementation in established asthma have used fish oil capsules and these have been systematically reviewed with the conclusion with that there is no convincing evidence that marine n-3 PUFA supplementation leads to an improvement in asthma control (56). The review highlighted two exemplary RCTs that were nevertheless excluded from the review. n-3 PUFA supplementation of elite athletes with exercise-induced bronchoconstriction reduced exercise-induced bronchoconstriction and urinary, sputum, and blood inflammatory markers (57,58); however, it is unlikely that these observations can be translated into everyday clinical practice because of the subjects studied and/or the withdrawal of asthma medication. Studies of n-3 PUFA supplementation conducted since the systematic review have reported conflicting results (59,60). Most studies of n-3 PUFA (and antioxidant) supplementation have been conducted in adults and there is a need for well-conducted studies in children. Recently, Biltagi and colleagues (61) reported n-3 PUFA, vitamin C, and zinc supplementation of asthmatic children, either individually or in combination, improved asthma control, lung function, and inflammatory markers. Currently there is little evidence to support the use of n-3 PUFA as an adjunct to conventional therapy in asthma; however, in light of the conclusion that asthma and allergy are associated with reduced n-6 and n-3 PUFA there may be scope for the use of combinations of these PUFA in the future. Before such recommendations can be made intervention studies need to be conducted to test this new systematic interpretation of the observational data.

Vitamin D

Two contradictory hypotheses relate vitamin D to the increase in allergy and asthma. The first proposes the increase in allergy and asthma to be a consequence of widespread early life vitamin D supplementation for rickets prophylaxis in Westernized countries (62) citing immunologic studies of high dose in vitro vitamin D supplementation promoting Th2 differentiation (63,64).

The second hypothesis highlights the widespread vitamin D insufficiency reported in Westernized countries, reflecting the increasing tendency to stay indoors, concerns about melanoma, and the inability to compensate by diet-sourced vitamin D. It was proposed that at the increase in allergy and asthma is a consequence of widespread vitamin D insufficiency (65) and cited immunological reports of vitamin D promoting regulatory T-cell function and consequent inhibition of Th2 differentiation (66,67).

There are no intervention studies or systematic reviews relating vitamin D with asthma. There are a few observational studies of vitamin D status in relation to asthma and allergic outcomes. Low serum 25-hydroxyvitamin D (25[OH]D) levels have been reported to be associated with reduced lung function adults participating in the third National Health and Nutrition Examination Survey in the United States (68) Recently, Brehm and colleagues (69) reported that in Costa Rican children with asthma, low serum 25(OH)D levels were associated with increased parameters of asthma severity (increased hospital admissions, use of anti-inflammatory asthma medication, airway responsiveness) and allergy (immunoglobulin E, eosinophilia). The association between asthma and vitamin D has been investigated in a United Kingdom-based case-control study of adults living in the north and south of the country. Serum 25(OH)D levels were identical in adults with and without asthma; furthermore, in the adults with asthma there were no associations between serum 25(OH)D and asthma severity (70). These few data do not support the hypothesis that asthma is directly associated with vitamin D; however, in children low serum 25(OH)D levels may be associated with more severe asthma. The therapeutic potential of vitamin D in established asthma is likely to be clarified by the results of several ongoing trials of vitamin D supplementation in people with asthma.

EARLY LIFE INFLUENCES IN THE ETIOLOGY OF ASTHMA

Although antioxidant and/or n-3 PUFA supplementation currently appear to have minimal, if any, clinical benefit in established asthma, there is increasing interest in the potential of dietary modification (particularly during pregnancy) in the primary prevention of childhood asthma. Early life factors play a critical role in the development of asthma (71): measurements of length, head circumference, and lung function at birth are associated with the subsequent development of childhood asthma (72,73); maternal smoking during pregnancy increases the risk of childhood asthma (74); and neonatal in vitro cord blood mononuclear cell (CBMC) responses are associated with recognized risk factors for asthma (75) and the subsequent development of childhood asthma and allergic disease (76).

The concept that diet primarily influences the development of childhood asthma during fetal development may explain the ineffectiveness of dietary supplementation in adults with asthma. Furthermore, because childhood dietary patterns are influenced by parental dietary habits and correlated with dietary patterns later in life (77,78) it is possible that the associations reported between diet and asthma in older children and adults may indirectly reflect associations with maternal diet during pregnancy (79).

Antioxidants

The potential for maternal antioxidant intake during pregnancy to modify the risk of childhood asthma has been highlighted by several birth cohort studies. The UK Avon Longitudinal Study of parents and Children reported low umbilical-cord selenium concentrations to be

Table 1. Observational studies relating maternal/fetal selenium measurements to subsequent childhood asthma/wheeze

Study author(s)	Design	Nutrient assessment	Outcomes	Association
Shaheen and colleagues (80)	Birth cohort (N=2,044)	Umbilical cord selenium	Wheeze 0-6 30-42 mo	OR[a] (95% CI[b]) highest vs lowest quintile of cord selenium 0.58 (0.36-0.91); P=0.019
Devereux and colleague (81)	Birth cohort (N=1282)	Maternal plasma selenium at 12 wks gestation, cord blood	Wheeze 2 and 5 y, diagnosed asthma 5 y, lung function at 5 y, exhaled nitric oxide at 5 y	OR (95% CI)/10 mg/kg maternal plasma selenium 2-y current wheeze 0.86 (0.76-0.97) P=0.011 OR (95% CI)/10 mg/kg cord plasma selenium 2-y current wheeze 0.67 (0.47-0.96) P=0.030 No associations with 5-y wheeze, asthma outcomes

[a]OR=odds ratio.
[b]CI=confidence interval.

Table 2. Observational studies relating maternal/fetal vitamin E measurements to subsequent childhood asthma/wheeze

Study author(s)	Design	Nutrient assessment	Outcomes	Association
Devereux and colleagues (85)	Birth cohort (N=1,253)	Maternal intake assessed at 32 wks by food frequency questionnaire Maternal plasma tocopherol measured at 12 wks gestation	At age 5 y: wheeze diagnosed asthma lung function exhaled nitric oxide	OR[a] (95% CI[b]) highest vs lowest quintiles of maternal vitamin E intake Ever asthma, 0.47 (0.24-0.92) P for trend=0.04 Doctor diagnosed asthma, 0.45 (0.23-0.89) P for trend=0.02 Ever wheeze 0.75 (0.44-1.28) P for trend=0.07 Current wheeze 0.46 (0.24-0.90) P for trend=0.01 Lung function of children born to mothers with the lowest tertile of plasma α-tocopherol was reduced by 77 mL (95% CI, 26-128; $P<$ 0.01)
Litonjua and colleagues (82)	Birth cohort (N=1,290)	Maternal intake assessed at 10 and 26-28 wks gestation by food frequency questionnaire	Wheeze at age 1 and 2 y	OR (95% CI) highest vs lowest quartile of maternal vitamin E intake Ever wheeze 0.70 (0.48-1.03) P for trend=0.06 Recurrent wheeze 0.49 (0.27-0.90) P for trend=0.05
Miyake and colleagues (83)	Birth cohort (N=763)	Maternal intake assessed 5-39 wks gestation by dietary history questionnaire	Wheeze 16-24 mo	OR (95% CI) highest vs lowest quartile of maternal vitamin E intake Wheeze 0.54 (0.32-0.90) P for trend=0.04

[a]OR=odds ratio.
[b]CI=confidence interval.

associated with an increased likelihood of persistent wheeze in children up to age 42 months (80) (Table 1). A Scottish birth cohort study similarly reported low plasma selenium concentrations in pregnant women and neonates to be associated with an increased likelihood of wheezing at age 2 years (81). However, by age 5 years there were no associations between maternal/neonatal selenium status and asthma outcomes, perhaps reflecting a short-term effect of maternal selenium intake during pregnancy on early life immune responses to viral infection.

The Project Viva cohort study in the United States has reported low maternal vitamin E intake during pregnancy to be associated with an increased likelihood of wheeze outcomes in children at age 2 years (82) (Table 2). In Japan, the prospective Osaka Maternal and Child Health Study has reported low maternal vitamin E intake during pregnancy to be associated with an increased likelihood of wheezing in children aged 16 to 24 months (83). A Scottish birth cohort study has reported associations suggesting that maternal diet during pregnancy influences fetal lung growth and neonatal immune responses. Reduced first trimester maternal plasma α-tocopherol was associated with reduced fetal growth (84) and, at age 5 years, with reduced lung function and an increased risk of asthma (85). Furthermore, reduced maternal vitamin E intake during pregnancy was associated with increased neonatal CBMC proliferative responses after in vitro stimulation with allergens (86) and an increased likelihood of wheezing and asthma outcomes in 5-year-old children (85). Although zinc is not considered to be an antioxidant, Project Viva and the Scottish study reported reduced maternal zinc intake during pregnancy to be associated with an increased likelihood of childhood

Table 3. Observational studies relating maternal/fetal zinc measurements to subsequent childhood asthma/wheeze

Study author(s)	Design	Nutrient assessments	Outcomes	Association
Shaheen and colleagues (80)	Birth cohort (N=2,044)	Umbilical cord zinc	Wheeze 0-6 30-42 mo	Wheeze and zinc not significantly associated
Litonjua and colleagues (82)	Birth cohort (N=1,290)	Maternal intake assessed at 10 and 26-28 wks gestation by food frequency questionnaire	Wheeze at age 1 and 2 y	OR[a] (95% CI[b]) highest vs lowest quartile of maternal zinc intake Ever wheeze 0.59 (0.41-0.88), *P* for trend=0.01 Recurrent wheeze 0.49 (0.27-0.87) *P* for trend=0.06
Devereux and colleagues (85)	Birth cohort (N=1,253)	Maternal intake assessed at 32 wks by food frequency questionnaire Maternal plasma zinc measured at 12 wks gestation	At age 5 y: wheeze diagnosed asthma lung function exhaled nitric oxide	OR (95% CI) highest vs lowest quintiles of maternal zinc Ever asthma, 0.51 (0.27-0.97) *P* for trend=0.04 Active asthma in previous year 0.28 (0.12-0.67) *P* for trend=0.003 No associations with lung function or plasma zinc

[a]OR=odds ratio.
[b]CI=confidence interval.

wheezing and asthma (82,85) (Table 3). The Irish Life-Ways Cross-Generation Cohort Study reported high maternal fruit and vegetable intake during pregnancy to be associated with a reduced likelihood of asthma in children at age 3 years (87). A Menorcan birth cohort study has reported wheeze in children aged 6 to 7 years to be less frequent if mothers consumed a Mediterranean-style diet during pregnancy (88). The Menorcan and the Scottish study quantified the diets of the children and whilst maternal and child diets were correlated there were no associations with children's diets (85,88).

The biological mechanisms by which antioxidants could influence the development of childhood asthma are probably independent of their antioxidant properties because the associations appear limited to certain nutrients (with and without antioxidant properties) and not with all antioxidants. The birth cohort studies are consistent with the hypothesis that maternal intake of certain nutrients influences fetal lung development and the first critical interactions between the immune system and allergens. Vitamin E has been reported to have complex effects on immunological and inflammatory pathways that may be relevant to the development of asthma and allergic disease (89-94). It would also appear that the effects of vitamin E on the immune system are age dependent, becoming less potent as the immune system ages and matures (95-98).

PUFA

Several studies have related dietary PUFA intake by women during pregnancy and infants to childhood asthma and allergic disease. In the Japanese Osaka Maternal and Child Health Study high maternal intake of the n-3 PUFA docosahexaenoic acid and α-linolenic acid were associated with a reduced likelihood of childhood wheezing at ages 16 to 24 months; in addition, higher maternal intakes of the n-6 PUFA linoleic acid were associated with an increased risk of childhood eczema (99). In the prospective Dutch Prevention and Incidence of Asthma and Mite Allergy birth cohort study (100), the daily intake of foods containing milk fat (butter, full cream milk, and milk products) at age 2 years was associated with reduced likelihood of asthma and/or wheeze at age 3 years.

Umbilical cord blood PUFA concentrations have been related to subsequent childhood asthma, and in general the reported associations have been inconsistent and fail to conform to a consistent pattern (55). The largest such study utilized the Avon Longitudinal Study of parents and Children birth cohort and although several associations were reported between wheeze outcomes at age 42 months and cord blood erythrocyte n-3 and n-6 PUFA composition, because of the large number of statistical comparisons performed, the authors concluded that it seemed unlikely that fetal exposure to n-3 and n-6 PUFA is an important determinant of early childhood wheezing and allergic disease (101). The potential for PUFA to influence the first interactions between the immune system and allergens has been investigated in the Project Viva birth cohort, which reported that high umbilical cord plasma n-3 and n-6 PUFA concentrations were associated with reduced CBMC proliferative and interferon-γ responses (102).

Several intervention studies have investigated the potential for early life n-3 PUFA supplementation to prevent childhood asthma and allergic disease. A Danish RCT investigating pregnancy outcomes supplemented the diets of pregnant women from 30 weeks gestation with fish oil or olive oil. Unfortunately the study was not placebo controlled and the women randomized to nothing were given no capsules (103). When compared with children of olive oil supplemented mothers, the children of fish oil supplemented women were less likely to develop asthma. However, the study was unable to conclude that

Table 4. Observational studies relating maternal/fetal vitamin D measurements to subsequent childhood asthma/wheeze

Study author(s)	Design	Nutrient assessment	Outcomes	Association
Camargo and colleagues (107)	Birth cohort (N=1,194)	Maternal intake assessed at 10 and 26-28 wks gestation by food frequency questionnaire	Wheeze at age 3 y	OR[a] (95% CI[b]) highest vs lowest quartile of maternal vitamin D intake 0.38 (0.22-0.65) *P* for trend<0.001
Devereux and colleagues (108)	Birth cohort (N=1,253)	Maternal intake assessed at 32 wks by food frequency questionnaire Maternal plasma zinc measured at 12 wks gestation	At age 5 y: wheeze diagnosed asthma lung function exhaled nitric oxide	OR (95% CI) highest vs lowest quintile of maternal vitamin D intake Ever wheeze 0.48 (0.25-0.91) *P* for trend=0.01 Current wheeze 0.35 (0.15-0.83) *P* for trend=0.009 Persistent wheeze 2 and 5 y 0.33 (0.11-0.98) *P* for trend=0.01
Erkkola and colleagues (109)	Birth cohort (N=1,669)	Maternal dietary intake assessed by food frequency questionnaire after delivery	At age 5 y Diagnosed asthma	Hazard ratio (95% CI) maternal vitamin D intake from food 0.80 (0.64-0.99) *P*<0.05
Miyake and colleagues (106)	Birth cohort (N=763)	Maternal intake assessed 5-39 wks gestation by dietary history questionnaire	Wheeze 16-24 mo	OR (95% CI) highest quartile vs lower 3 quartiles maternal vitamin D intake 0.64 (0.43-0.97) *P*<0.05 No association across the quartiles
Gale and colleagues (110)	Birth cohort (N=178)	Maternal blood vitamin D at 33 wks gestation	Diagnosed asthma at 9 y (response rate 38%)	OR (95% CI) highest vs lowest quartiles of maternal blood vitamin D 5.40 (1.09-26.7) *P*=0.038

[a]OR=odds ratio.
[b]CI=confidence interval.

fish oil supplementation during pregnancy reduces the risk of childhood asthma because the children of women randomized to receive no capsules also had a reduced risk of asthma, comparable to fish oil supplementation, possibly because women allocated to no capsules chose to take commercially available fish oil capsules. An Australian RCT of fish oil supplementation from 20 weeks' gestation reported that maternal fish oil supplementation was associated with a general reduction in neonatal CBMC cytokine responses; however, only the reduction in IL-10 response after stimulation with cat allergen was statistically significant (104). These two studies suggest that antenatal n-3 PUFA supplementation has the potential to influence neonatal immune responses to allergens and reduce the likelihood of children developing asthma and allergic disease; however, further work, especially a randomized placebo controlled trial of n-3 PUFA/fish oil supplementation during pregnancy, is required. Postnatal infant n-3 PUFA supplementation appears to confer minimal benefit. The Childhood Asthma Prevention Study concluded that whilst n-3 PUFA rich fish oil supplementation during infancy reduced the likelihood of early childhood wheeze (age 18 months) it had no effect on the likelihood of asthma, wheeze, and allergic disease in later childhood (age 3 and 5 years) (105).

Vitamin D

The small number of studies relating early life vitamin D exposure to asthma have reported conflicting results (Table 4). Three birth cohort studies have now reported low maternal vitamin D intake during pregnancy to be associated with an increased risk of wheeze outcomes at age 16 to 24 months (106), 3 years (107), and 5 years (108). The associations between maternal vitamin D intake and childhood asthma are conflicting with one study reporting no association with asthma at age 5 years (108), while another reported low maternal vitamin D intake to be associated with an increased risk of asthma at age 5 years (109). None of these studies assessed total vitamin D status as reflected by serum 25(OH)D. A UK birth cohort that quantified maternal blood 25(OH)D in the third trimester reported that elevated 25(OH)D was associated with an increased likelihood of childhood asthma at 9 years; however, the study response rate was low (30%) and there was no adjustment for potential confounding (110). Vitamin D has also been adversely associated with asthma by a large Northern Finnish study whereby regular high dose (2,000 IU/day) vitamin D supplementation during infancy was associated with an increased likelihood of asthma and allergic outcomes at age 31 years (111).

CONCLUSIONS

The generally weak observational and very limited intervention data suggest that while there are associations between diet and asthma, the nature of the associations (with PUFA, antioxidants, nutrients, and food), the timing (antenatal, infancy, childhood, and adulthood) and the therapeutic potential of the associations are far from clear; indeed, it remains a distinct possibility that the observed associations are a consequence of confounding by complex social and behavioral factors. From the available intervention data it appears fairly clear that the supplementation of the diets of adults with vitamin C,

vitamin E, selenium, and n-3 PUFA-rich fish oil has minimal, if any, clinical benefit in established asthma. This may change when ongoing vitamin D supplementation studies are completed. Further work, particularly in children, is required to establish if dietary intervention with individual nutrients, nutrient combinations, or food has a role in complementing conventional asthma treatment. Further investigation is also required to ascertain whether dietary intervention could be targeted at genetically susceptible individuals with asthma.

The manipulation of maternal diet during pregnancy to reduce the risk of childhood asthma remains a tantalizing possibility worthy of further investigation because of the potential benefits for individuals and society. Ultimately the role of dietary intervention to prevent childhood asthma will only be elucidated by intervention studies; however, the nature of any diet-based intervention needs careful consideration. Currently, the limited intervention data suggest that manipulation of PUFA intake during pregnancy may reduce the likelihood of childhood asthma and allergy. Most research in the field to date, driven by the original PUFA hypothesis, has aimed to increase n-3 PUFA intake; however, a recent detailed review of the available evidence concluded that this may not be the ideal strategy and that "a combination of fish oil with some longer chain n-6 PUFAs may be more efficacious" (55). Perhaps future intervention studies of PUFA should be of combinations of n-3 and n-6 PUFA, either as supplements or food, an intervention likely to be considered safer and more acceptable by pregnant women.

Currently several cohort studies from populations with differing socioeconomic, genetic, smoking, and dietary profiles have reported low maternal dietary vitamin E, vitamin D, and zinc intakes during pregnancy to be associated with an increased likelihood of childhood wheezing and asthma (82,83,85,106-109). Currently, there are at least two intervention studies underway investigating the effects of supplementing women during pregnancy on childhood asthma and allergy. The results of these studies will clarify the role of vitamin D in the primary prevention of asthma and allergy. The scientific justification for the obvious simple vitamin E intervention study during pregnancy is weakened by the negative results of RCTs investigating the effects of antioxidant supplementation on cardiovascular disease, cancer, and all-cause mortality despite a wealth of data from observational studies suggesting beneficial associations (112). Published results from a vitamin E intervention study during pregnancy evaluating effects on pre-eclampsia, suggest that high-dose vitamin E supplementation during pregnancy (albeit in a highly selected maternal population) was not associated with a reduction in childhood wheeze and asthma (113). The disparity between observational studies and RCTs has been attributed to a failure to appreciate the complex and important differences between adults with high and low antioxidant intakes (112). An obvious oversimplification is to assume that vitamin E, in isolation, is exerting a beneficial effect on childhood asthma. Traditionally, we have always consumed vitamin E in the form of foods that also contain other nutrients, and it is likely that any putative effect on childhood asthma is mediated by a complex mixture of nutrients characterized by a high vitamin E content. Indeed, it may be these nutrients and not vitamin E that is exerting beneficial effect. Future studies should consider the use of dietary intervention to increase the intake of nutrients highlighted by birth cohorts (vitamin E, PUFA, vitamin D, and zinc) to capture the complexity of dietary nutrient intake. If shown to be efficacious such a dietary intervention could be the basis for a low-cost, safe public health intervention to rapidly reduce the prevalence of asthma in children and ultimately adults, with obvious beneficial consequences for the well-being of individuals and society as a whole.

Until the results of ongoing and planned trials are available, the practical consequences of research linking diet with asthma are minimal, and based on the available evidence, people with asthma, pregnant women, parents, and children should not be advised to change or supplement their diet to treat or reduce the risk of developing asthma.

STATEMENT OF POTENTIAL CONFLICT OF INTEREST: No potential conflict of interest was reported by the authors.

FUNDING/SUPPORT: Keith Allan is supported by an MRC Capacity Building PhD Studentship.

References

1. Georas SN, Guo J, De Fanis U, Casolaro V. T-helper cell type-2 regulation in allergic disease. *Eur Respir J*. 2005;26:1119-1137.
2. Abbas AK, Murphy KM, Sher A. Functional diversity of helper T lymphocytes. *Nature*. 1996;383:787-793.
3. Robinson DS. Regulation: The art of control? Regulatory T cells and asthma and allergy. *Thorax*. 2004;59:640-643.
4. Masoli M, Fabian D, Holt S, Beasley R, Medical Research Institute of New Zealand, Wellington New Zealand, University of Southhampton, United Kingdom. Global burden of asthma developed for the Global Initiative for Asthma. http://www.ginasthma.org/GuidelinesResources.asp?l1=2&l2=0. Posted May 2004. Accessed December 9, 2010.
5. Moorman JE, Rudd RA, Johnson CA, King M, Minor P, Bailey C, Scalia MR, Akinbami LJ. National surveillance for asthma—United States, 1980-2004. *MMWR Surveill Summ.* 2007;56:1-54.
6. McNeill G, Tagiyeva N, Aucott L, Russell G, Helms PJ. Changes in the prevalence of asthma, eczema and hay fever in pre-pubertal children: A 40-year perspective. *Paediatr Perinatal Epidemiol*. 2009; 23:506-512.
7. Seaton A, Godden DJ, Brown K. Increase in asthma: A more toxic environment or a more susceptible population? *Thorax.* 1994;49:171-174.
8. Thomas D. A study on the mineral depletion of the foods available to us as a nation over the period 1940 to 1991. *Nutrition Health.* 2003;17:85-115.
9. Rayman MP. Dietary selenium: Time to act. *Br Med J*. 1997;314:387-388.
10. MacPherson A, Barclay MNI, Dixon J, Groden BM, Scott R, Kesson E. Decline in dietary selenium intake in Scotland and effect on plasma concentrations. In: Anke M, Meissner D, Mills CF, eds. *Proceedings of the Eighth International symposium on Trace Elements in Man and Animals 1993.* Jena, Germany: Verlag Media Touristik; 1993:269-270.
11. Shortt CT, Duthie GG, Robertson JD, Morrice PC, Nicol F, Arthur JR. Selenium status of a group of Scottish adults. *Eur J Clin Nutrition.* 1997;51:400-404.
12. Family food in 2005-06. UK Department of Environmental Farming and Rural Affairs Web site. http://www.defra.gov.uk/evidence/statistics/foodfarm/food/familyfood/documents/familyfood-200506/pdf. Posted 2007. Accessed December 9, 2010.
13. National Food Survey datasets. UK Department of Environmental Farming and Rural Affairs Web site. http://www.defra.gov.uk/evidence/statistics/foodfarm/food/familyfood/nationalfoodsurvey/index.htm. Updated March 2010. Accessed December 9, 2010.
14. Henderson L, Irving K, Gregory J, Bates CJ, Prentice A, Perks J, Swan G, Farron M. The National Diet and Nutrition Survey: Adults

aged 19 to 64 years. http://www.food.gov.uk/multimedia/pdfs/ndnsv3.pdf. Posted 2003. Accessed December 9, 2010.
15. Murr C, Schroecksnadel K, Winkler C, Ledochowski M, Fuchs D. Antioxidants may increase the probability of developing allergic diseases and asthma. *Med Hypotheses*. 2005;64:973-977.
16. Tricon S, Willers S, Smit HA, Burney PG, Devereux G, Frew AJ, Halken S, Høst A, Nelson M, Shaheen S, Warner JO, Calder PC. Nutrition and allergic disease. *Clin Exp Allergy Rev*. 2006;6:117-188.
17. Hu G, Cassano P. Antioxidants and pulmonary function: The third National Health and Nutrition Examination Survey (NHANES III). *Am J Epidemiol.* 2000;151:975-981.
18. Huang S-L, Pan W-H. Dietary fats and asthma in teenagers: Analyses of the first Nutrition and Health Survey in Taiwan (NAHSIT). *Clin Exp Allergy*. 2001;31:1875-1880.
19. Harik-Khan RI, Muller DC, Wise RA. Serum vitamin levels and the risk of asthma in children. *Am J Epidemiol*. 2004;159:351-357.
20. Rubin RN, Navon L, Cassano PA. Relationship of serum antioxidants to asthma prevalence in youth. *Am J Respir Crit Care Med.* 2004;169:393-398.
21. Troisi RJ, Willett WC, Weiss ST, Trichopoulos D, Rosner B, Speizer FE. A prospective study of diet and adult-onset asthma. *Am J Respir Crit Care Med.* 1995;151:1401-1408.
22. Hijazi N, Abalkhail B, Seaton A. Diet and childhood asthma in a society in transition: A study in urban and rural Saudi Arabia. *Thorax.* 2000;55:775-779.
23. Riccioni G, Bucciarelli T, Mancini B, Di Ilio C, Della Vecchia R, D'Orazio N Plasma Lycopene and antioxidant vitamins in asthma: The PLAVA Study. *J Asthma.* 2007;44:429-432.
24. Wood LG, Garg ML, Blake RJ, Garcia-Caraballo S, Gibson PG. Airway and circulating levels of carotenoids in asthma and healthy controls. *J Am Coll Nutr.* 2005;24:448-455.
25. Shaheen SO, Sterne JAC, Thompson RL, Songhurst CE, Margetts BM, Burney PG. Dietary antioxidants and asthma in adults: Population-based case-control study. *Am J Respir Crit Care Med.* 2001; 164:1823-1828.
26. Omland Ø, Deguchi Y, Sigsgaard T, Hansen JC. Selenium serum and urine is associated with mild asthma and atopy. The SUS study. *J Trace Elem Med Biol.* 2002;16:123-127.
27. Qujeq D, Hidari B, Bijani K, Shirdel H. Glutathione peroxidase activity and serum selenium concentration in intrinsic asthmatic patients. *Clin Chem Lab Med*. 2003;41:200-202.
28. Kocyigit A, Armutcu F, Gurel A, Ermis B. Alterations in plasma essential trace elements selenium, manganese, zinc, copper, and iron concentrations and the possible role of these elements on oxidative status in patients with childhood asthma. *Biol Trace Elem Res.* 2004;97:31-41.
29. Allen S, Britton J, Leonardi-Bee J. Association between antioxidant vitamins and asthma outcomes: Systematic review and meta-analysis. *Thorax*. 2009;64:610-619.
30. Katsoulis K, Kontakiotis T, Leonardopoulos I, Kotsovili A, Legakis IN, Patakas D. Serum total antioxidant status in severe exacerbation of asthma: Correlation with the severity of the disease. *J Asthma.* 2003;40:847-854.
31. Kaur B, Rowe BH, Arnold E. Vitamin C supplementation for asthma. *Cochrane Database Syst Rev*. 2009;1:CD000993.
32. Shaheen SO, Newson RB, Rayman MP, Wong AP, Tumilty MK, Phillips JM, Potts JF, Kelly FJ, White PT, Burney PGJ. Randomised, double blind, placebo-controlled trial of selenium supplementation in adult asthma. *Thorax.* 2007;62:483-490.
33. Pearson PJK, Lewis SA, Britton J, Fogarty A. Vitamin E supplements in asthma: A parallel group randomised placebo controlled trial. *Thorax.* 2004;59:652-656.
34. Okoko BJ, Burney PG, Newson RB, Potts JF, Shaheen SO. Childhood asthma and fruit consumption. *Eur Respir J.* 2007;29:1161-1168.
35. Chatzi L, Torrent M, Romieu I, Garcia-Esteban R, Ferrer C, Vioque J, Kogevinas M, Sunyer J. Diet, wheeze, and atopy in school children in Menorca, Spain. *Pediatr Allergy Immunol.* 2007;18:480-485.
36. Chatzi L, Apostolaki G, Bibakis I, Skypala I, Bibaki-Liakou V, Tzanakis N, Kogevinas M, Cullinan P. Protective effect of fruits, vegetables and the Mediterranean diet on asthma and allergies among children in Crete. *Thorax.* 2007;62:677-683.
37. Forastière F, Pistelli R, Sestini P, Fortes C, Renzoni E, Rusconi F, Dell'Orco V, Ciccone G, Bisanti L, the SIDRIA Collaborative Group, Italy (Italian Studies on Repiratory Disorders in Children and the Environment). Consumption of fresh fruit rich in vitamin C and wheezing symptoms in children. *Thorax*. 2000;55:283-288.
38. De Batlle J, Garcia-Aymerich J, Barraza-Villarreal A, Antó JM, Romieu I. Mediterranean diet is associated with reduced asthma and rhinitis in Mexican children. *Allergy.* 2008;63:1310-1316.
39. Black PN, Sharpe S. Dietary fat and asthma: Is there a connection? *Eur Respir J.* 1997;10:6-12.
40. Harizi H, Juzan M, Moreau JF, Gualde N. prostaglandins inhibit 5-lipoxygenase-activating protein expression and leukotriene B_4 production from dendritic cells via an IL-10 dependent mechanism. *J Immunol.* 1997;159:28-35.
41. Calder PC, Yaqoob P, Thies F, Wallace FA, Miles EA. Fatty acids and lymphocyte functions. *Br J Nutr.* 2002;87(suppl 1):S31-S48.
42. Sanderson P, MacPherson GG, Jenkins CH, Calder PC. Dietary fish oil diminishes the antigen presentation activity of rat dendritic cells. *J Leukocyte Biol.* 1997;62:771-777.
43. Laerum BN, Wentzel-Larsen T, Gulsvik A, Omenaas E, Gislason T, Janson C, Svanes C. Relationship of fish and cod oil intake with adult asthma. *Clin Exp Allergy.* 2007;37:1616-1623.
44. Miyamoto S, Miyake Y, Sasaki S, Tanaka K, Ohya Y, Matsunga I, Yoshida T, Oda H, Ishiko O, Hirota Y, Osaka Maternal and Child Health Study Group. Fat and fish intake and asthma in Japanese women: Baseline data from the Osaka Maternal and Child Health Study. *Int J Tuberc Lung Dis*. 2007;11:103-109.
45. Hodge L, Salome CM, Peat JK, Haby MM, Xuan W, Woolcock AJ. Consumption of oily fish and childhood asthma risk. *Med J Aust*. 1996;164:137-140.
46. Kim JL, Elfman L, Mi Y, Johansson M, Smedje G, Norb D. Current asthma and respiratory symptoms among pupils in relation to dietary factors and allergens in the school environment. *Indoor Air*. 2005;15:170-182.
47. Takemura Y, Sakurai Y, Honjo S, Tokimatsu A, Gibo M, Hara T, Kusakari A, Kugai N. The relationship between fish intake and the prevalence of asthma: The Tokorozawa Childhood Asthma and Pollinosis Study. *Prev Med*. 2002;34:221-225.
48. Nagel G, Linseisen J. Dietary intake of fatty acids, antioxidants and selected food groups and asthma in adults. *Eur J Clin Nutr.* 2005; 59:8-15.
49. Foliaki S, Annesi-Maesano I, Tuuau-Potoi N, Waqatakirewa L, Cheng S, Douwes J, Pearce N. Risk factors for symptoms of childhood asthma, allergic rhinoconjunctivitis and eczema in the Pacific: An ISAAC Phase III study. *Int J Tuberc Lung Dis*. 2008;12:799-806.
50. Haby MM, Peat JK, Marks GB, Woolcock AJ, Leeder SR. Asthma in pre-school children: Prevalence and risk factors. *Thorax.* 2001;56: 589-595.
51. Miyake Y, Sasaki S, Arakawa M, Tanaka K, Murakami K, Ohya Y. Fatty acid intake and asthma symptoms in Japanese children: The Ryukyus Child Health Study. *Clin Exp Allergy.* 2008;38:1644-1650.
52. Oddy WH, de Klerk NH, Kendall GE, Mihrshani S, Peat JK. Ratio of omega-6 to omega-3 fatty acids and childhood asthma. *J Asthma.* 2005;41:319-326.
53. Bolte G, Kompauer I, Fobker M, Cullen P, Keil U, von Mutius E, Weiland SK. Fatty acids in serum cholesterol esters in relation to asthma and lung function in children. *Clin Exp Allergy.* 2006;36:293-302.
54. Woods RK, Raven JM, Walters EH, Abramson MJ, Thien FCK. Fatty acid levels and risk of asthma in young adults. *Thorax.* 2004;59;105-110
55. Sala-Vila A, Miles EA, Calder PC. Fatty acid composition abnormalities in atopic disease: Evidence explored and role in the disease process examined. *Clin Exp Allergy.* 2008;38:1432-1450.
56. Thien FCK, De Luca S, Woods R, Abramson MJ. Dietary marine fatty acids (fish oil) for asthma in adults and children. *Cochrane Database Syst Rev.* 2002; 2:CD001283.
57. Mickleborough TD, Murray RL, Ionescu AA, Lindley MR. Fish oil supplementation reduces severity of exercise-induced bronchoconstriction in elite athletes. *Am J Respir Crit Care Med.* 2003;168: 1181-1189.
58. Mickleborough TD, Lindley MR, Ionescu AA, Fly AD. Protective effect of fish oil supplementation. *Chest.* 2006;129:39-49.
59. Schubert R, Kitz R, Beerman C, Rose MA, Lieb A, Sommerer PC, Moskovits J, Alberternst H, Böhles HJ, Schulze J, Zielen S. Effect of n-3 polyunsaturated fatty acids in asthma after low dose allergen challenge. *Int Arch Allergy Immunol.* 2009;148:321-329.
60. Moreira A, Moreira P, Delgado L, Fonseca J, Teixeira V, Padrao P, Castel-Branco G. Pilot study of the effects of n-3 polyunsaturated fatty acids on exhaled nitric oxide in patients with stable asthma. *J Investig Allergol Clin Immunol.* 2007;17:309-313.
61. Biltagi MA, Baset AA, Bassiouny M, Kasrawi MA, Attia M. Omega-3 fatty acids, vitamin C and Zn supplementation in asthmatic children: A randomized self-controlled study. *Acta Paediatrica.* 2009;98: 737-742.

62. Wjst M, Dold S. Genes, factor X, and allergens: What causes allergic diseases? *Allergy*. 1999;54:757-759.
63. Lemire JM, Archer DC, Beck L, Spiegelberg HL. Immunosuppressive actions of 1,25-dihydroxy vitamin D_3: preferential inhibition of Th1 functions. *J Nutr*. 1995;125(suppl):1704S-1708S.
64. Jirapongsananuruk O, Melamed I, Leung DY. Additive immunosuppressive effects of 1,25-dihydroxyvitamin D3 and corticosteroids on TH1, but not TH2, responses. *J Allergy Clin Immunol*. 2000;106:981-985.
65. Litonjua AA, Weiss ST. Is vitamin D deficiency to blame for the asthma epidemic? *J Allergy Clin Immunol*. 2007;120:1031-1035.
66. Xystrakis E, Kusumakar S, Boswell S, Peek E, Urry Z, Richards DF, Adikibi T, Pridgeon C, Dallman M, loke T-K, Robinson DS, Barrat FJ, O'Garra A, Lavender P, Lee TH, Corrigan C, Hawrylowicz CM. Reversing the defective induction of IL-10-secreting regulatory T cells in glucocorticoid-resistant asthma patients. *J Clin Invest*. 2006; 116:146-155.
67. Penna G, Roncari A, Amuchastegui S, Daniel KC, Berti E, Colonna M, Adorini L. Expression of the inhibitory receptor ILT3 on dendritic cells is dispensable for induction of CD4+Foxp3+ regulatory T cells by 1,25-dihydroxyvitamin D3. *Blood*. 2005;106:3490-3497.
68. Black PN, Scragg R. Relationship between serum 25-hydroxyvitamin D and pulmonary function in the third national health and nutrition examination survey. *Chest*. 2005;128:3792-3798.
69. Brehm J, Celedón JC, Soto-Quiros ME, Avila L, Hunninghake GM, Forno E, Lasky D, Fylvia JS, Hollis BW, Weiss ST, Litonjua AA. Serum Vitamin D levels and markers of severity of childhood asthma in Costa Rica. *Am J Respir Crit Care Med*. 2009;179;765-771.
70. Devereux G, Wilson A, Avenell A, McNeill G, Fraser WD. A case control study of vitamin D status and asthma in adults. *Allergy*. 2010;65:666-667.
71. Holt PG, Devereux G, Sly P. Early life origins of allergy and asthma. In: Holgate ST, Church MK, Lichenstein LM, eds. *Allergy*. 3rd ed. Philadelphia, PA: Mosby Elsevier; 2006:223-232.
72. Haland G, Carlsen KC, Sandvik L, Devulapalli CS, Munthe-Kaas MC, Pettersen M, Carlsen KH. Reduced lung function at birth and the risk of asthma at 10 years of age. *N Engl J Med*. 2006;355:1682-1689.
73. Katz KA, Pocock SJ, Strachan DP. Neonatal head circumference, neonatal weight, and risk of hayfever, asthma and eczema in a large cohort of adolescents from Sheffield, England. *Clin Exp Allergy*. 2003;33:737-745.
74. Gilliland FD, Li YF, Peters JM. Effects of maternal smoking during pregnancy and environmental tobacco smoke on asthma and wheezing in children. *Am J Respir Crit Care Med*. 2001;163: 429-436.
75. Devereux G, Barker R. Studies of Cord Blood Mononuclear Cell responses and allergy: Still in their infancy? *Clin Exp Allergy*. 2002; 32:331-334.
76. Prescott SL. Early origins of allergic disease: a review of processes and influences during early immune development. *Curr Opin Allergy Clin Immunol*. 2003;3:125-132.
77. Lynch JW, Kaplan GA, Salonen JT. Why do poor people behave poorly? Variation in adult health behaviours and psychosocial characteristics by stages of the socioeconomic lifecourse. *Soc Sci Med*. 1997;44:809-819.
78. Talvia S, Räsänen L, Lagstrm̈ H, Pahkala K, Viikari J, Rönnemaa T, Arffman M, Simell O. Longitudinal trends in consumption of vegetables and fruit in Finnish children in an atherosclerosis prevention study (STRIP). *Eur J Clin Nutr*. 2006;60:172-180.
79. Devereux G, Seaton A. Why don't we give chest patients dietary advice? *Thorax*. 2001;56(suppl 2):S15-S22.
80. Shaheen SO, Newson RB, Henderson AJ, Emmett PM, Sherriff A, Cooke M. Umbilical cord trace elements and minerals and risk of early childhood wheezing and eczema. *Eur Respir J*. 2004;24:292-297.
81. Devereux G, McNeill G, Newman G, Turner S, Craig LCA, Martindale S, Helms PJ, Seaton A. Early childhood wheezing symptoms in relation to plasma selenium in pregnant mothers and neonates. *Clin Exp Allergy*. 2007;37:1000-1008.
82. Litonjua AA, Rifas-Shiman S, Ly NP, Tantisira KG, Rich-Edwards JW, Weiss ST, Gillman MW, Gold DR. Maternal antioxidant intake in pregnancy and wheezing illnesses in children at 2 y of age. *Am J Clinical Nutr*. 2006;84:903-911.
83. Miyake Y, Sasaki S, Tanaka K, Hirota Y. Consumption of vegetables, fruit, and antioxidants during pregnancy and wheeze and eczema in infants. *Allergy*. 2010;65:758-765.
84. Turner SW, Campbell D, Smith N, Craig LCA, McNeill G, Forbes SH, Harbour PJ, Seaton A, Helms PJ, Devereux GS. Associations between fetal size, maternal alpha-tocopherol and childhood asthma. *Thorax*. 2010;65:391-397.
85. Devereux G, Turner SW, Craig LCA, McNeill G, Martindale S, Harbour PJ, Helms PJ, Seaton A. Reduced maternal vitamin E intake during pregnancy is associated with asthma in 5-year-old children. *Am J Respir Crit Care Med*. 2006;174;499-507.
86. Devereux G, Barker RN, Seaton A. Ante-natal determinants of neonatal immune responses to allergens. *Clin Exp Allergy*. 2002; 32:43-50.
87. Fitzsimon N, Fallon UB, O'Mahony D, Loftus BG, Bury G, Murphy AW, Kelleher CC. Mothers' dietary patterns during pregnancy and the risk of asthma symptoms in children at 3 years. *Irish Med J*. 2007;100:27-32.
88. Chatzi L, Torrent M, Romieu I, Garcia-Esteban R, Ferrer C, Vioque J, Kogevinas M, Sunyer J. Mediterranean diet in pregnancy is protective for wheeze and atopy in childhood. *Thorax*. 2008;63:507-513.
89. Azzi A, Gysin R, Kempna P, Ricciarelli R, Villacorta L, Visarius T, Zingg JM. The role of α-tocopherol in preventing disease: From epidemiology to molecular events. *Molec Aspects Dis*. 2003;24:325-336.
90. Reiter E, Jiang Q, Christen S. Anti-inflammatory properties of α- and γ-tocopherol. *Molec Aspects Med*. 2007;28:668-691.
91. Manthey JA. Biological properties of flavonoids pertaining to inflammation. *Microcirculation*. 2000;7(suppl):S29-S34.
92. Li-Weber M, Giasisi M, Trieber MK, Krammer PH. Vitamin E inhibits IL-4 gene expression in peripheral blood T-cells. *Eur J Immunol*. 2002;32:2401-2408.
93. Wakikawa A, Utsuyama M, Wakabayashi A, Kitagawa M, Hirokawa K. Vitamin E enhances the immune functions of young but not old mice under restraint stress. *Exp Gerontology*. 1999;34:853-862.
94. Tan PH, Sagoo P, Chan C, Yates JB, Campbell J, Beutelspacher SC, Foxwell BMJ, Lombardi G, George AJT. Inhibition of NF-KB and oxidative pathways in human dendritic cells by antioxidative vitamins generates regulatory T cells. *J Immunol*. 2005;174:7633-7644.
95. Okamoto N, Murata T, Tamai H, Tanaka H, Nagai H. Effects of alpha tocopherol and probucol supplements on allergen-induced airway inflammation and hyperresponsiveness in a mouse model of allergic asthma. *Int Arch Allergy Immunol*. 2006;141:172-180.
96. Malmberg KJ, Lenkei R, Petersson M, Ohlum T, Ichihara F, Glimelius B, Frödin J-E, Masucci G, Kiessling R. R. A short-term dietary supplementation of high doses of vitamin E increases T helper 1 cytokine production in patients with advanced colorectal cancer. *Clin Cancer Res*. 2002;8:1772-1778.
97. Wang Y, Huang DS, Eskelson CD, Watson RR. Long term dietary vitamin E retards development of retrovirus induced disregulation in cytokine production. *Clin Immunol*. 1994;72:70-75.
98. Meydani SN, Han SN, Wu D. Vitamin E and immune response in the aged: Molecular mechanisms and clinical implications. *Imm Rev*. 2005;205:269-281.
99. Miyake Y, Sasaki S, Tanaka K, Ohfuji S, Hirota Y. Maternal fat consumption during pregnancy and risk of wheeze and eczema in Japanese infants aged 16-24 months: The Osaka Maternal and Child Health Study. *Thorax*. 2009;64:815-821.
100. Wijga AH, Smit HA, Kerkhof M, de Jongste JC, Gerritsen J, Neijens HJ, Boshuizen HC, Brunekreef B. Association of consumption of products containing milk fat with reduced asthma risk in pre-school children: The PIAMA birth cohort study. *Thorax*. 2003;58:567-572.
101. Newson RB, Shaheen SO, Henderson AJ, Emmett PM, Sherriff A, Calder PC, the ALSPAC Study Team. Umbilical cord and maternal blood red cell fatty acids and early childhood wheezing and eczema. *J Allergy Clin Immunol*. 2004;114:531-537.
102. Gold DR, Willwerth BM, Tantisira KG, Finn PW, Schaub B, Perkins DL, Tzianabos A, Ly NP, Schroeter C, Gibbons F, Campos H, Oken E, Gillman MW, Palmer LJ, Ryan LM, Weiss ST. Associations of cord blood fatty acids with lymphocyte proliferation, IL-13 and IFN-γ. *J Allergy Clin Immunol*. 2006;117:931-938.
103. Olsen SF, Osterdal ML, Salvig JD, Mortensen LM, Rytter D, Secher NJ, Henriksen TB. Fish oil intake compared with olive oil intake in late pregnancy and asthma in the offspring: 16 y of registry-based follow-up from a randomized controlled trial. *Am J Clin Nutr*. 2008; 88:167-175.
104. Dunstan JA, Mori TA, Barden A, Beilin LJ, Taylor AL, Holt PG, Prescott SL. Fish oil supplementation in pregnancy modifies neonatal allergen-specific immune responses and clinical outcomes in in-

fants at high risk of atopy: A randomized, controlled trial. *J Allergy Clin Immunol.* 2003;112:1178-1184.
105. Marks GB, Mihrshahi S, Kemp AS, Tovey ER, Webb K, Almqvist C, Ampon RD, Crisafulli D, Belousova EG, Mellis CM, Peat JK, Leeder SR, for the Childhood Asthma Prevention Study team. Prevention of asthma during the first 5 years of life: A randomized controlled trial. *J Allergy Clin Immunol*. 2006;118:53-61.
106. Miyake Y, Sasaki S, Tanaka K, Hirota Y. Dairy food, calcium, and vitamin D intake in pregnancy and wheeze and eczema in infants. *Eur Respir J*. 2010;35:1228-1234.
107. Camargo CA, Rifas-Shiman SL, Litonjua AA, Rich-Edwards JW, Weiss ST, Gold DR, Kleinman K, Gillman MW. Maternal intake of Vitamin D during pregnancy and reports of recurrent wheezing in children at 3 y of age. *Am J Clin Nutr*. 2007;85:788-795.
108. Devereux G, Litonjua AA, Turner SW, Craig LCA, McNeill G, Martindale S, Hems PJ, Seaton A, Weiss ST. Maternal vitamin D intake during pregnancy and early childhood wheeze. *Am J Clin Nutr*. 2007;85:853-859.
109. Erkkola M, Kaila M, Nwaru BI, Kronberg-Kippila C, Ahonen S, Nevalainen J, Veijola R, Pekkanen J, Ilonen J, Simell O, Knip M, Virtanen SM. Maternal vitamin D intake during pregnancy is inversely associated with asthma and allergic rhinitis in 5-year-old children. *Clin Exp Allergy*. 2009;39:875-882.
110. Gale CR, Robinson SM, Harvey NC, Javaid MK, Jiang B, Martyn CN, Godfrey KM, Cooper C, Princess Anne Hospital Study Group. Maternal vitamin D status during pregnancy and childhood outcomes. *Eur J Clin Nutr*. 2008;62;68-77.
111. Hypponen E, Sovio U, Wjst M, Patel S, Pekkanen J, Hartikainen AL, Jarvelinb MR. Infant vitamin D supplementation and allergic conditions in adulthood: Northern Finland birth cohort. 1966. *Ann N Y Acad Sci*. 2004;1037:84-95.
112. Lawlor DA. Davey Smith G. Kundu D. Bruckdorfer KR. Ebrahim S. Those confounded vitamins: What can we learn from the differences between observational versus randomised trial evidence? *Lancet.* 2004;363:1724-1727.
113. Greenough A, Shaheen SO, Shennan A, Seed PT, Poston L. Respiratory outcomes in early childhood following antenatal vitamin C and E supplementation. *Thorax.* 2010;65:998-1003.