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Diet as a risk factor for atopy and asthma

Graham Devereux, MA, MD, PhD, FRCP, and Anthony Seaton, MD, FRCP, FMedSci

Aberdeen, United Kingdom

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It has been hypothesized that decreasing antioxidant (fruit and vegetables), increased n-6 polyunsaturated fatty acid (PUFA; (margarine, vegetable oil), and decreased n-3 PUFA (oily fish) intakes have contributed to the recent increases in asthma and atopic disease. Epidemiologic studies in adults and children have reported beneficial associations between dietary antioxidants and lipids and parameters of asthma and atopic disease. The associations with n-6 and n-3 PUFA appear to be very complex and might differ between asthma and atopic dermatitis. Dietary antioxidants are probably exerting antioxidant and nonantioxidant immunomodulatory effects. Dietary lipids exert numerous complex effects on proinflammatory and immunologic pathways. It has also been suggested that atopic dermatitis is associated with an enzyme defect in lipid metabolism. In spite of this, the results of interventional supplementation studies in established disease have been disappointing, and there is now increasing interest in the possibility that dietary antioxidant and lipid intakes might be important in determining expression of disease during pregnancy and early childhood and that dietary interventions should be targeted at these groups. It also seems likely that there is individual variation in the responses of individuals to lipid, and probably antioxidant, supplementation. Further research to determine whether dietary intervention can reduce the risk of asthma and atopic disease is justified. (*J Allergy Clin Immunol* 2005;115:1109-17.)

Key words: *Asthma, atopic dermatitis, antioxidants, n-3 polyunsaturated fatty acid, n-6 polyunsaturated fatty acid*

During the latter half of the 20th century, throughout prosperous industrialized countries, there were well-documented increases in the prevalence of asthma and the atopic diseases hay fever, eczema, and food allergy.¹⁻³

Abbreviations used

DHA: Docosahexaenoic acid

EPA: Eicosapentaenoic acid

NHANES: National Health and Nutrition Examination Survey

PGE₂: Prostaglandin E₂

PUFA: Polyunsaturated fatty acid

The reasons for the increase in these diseases to important economic and public health concerns have stimulated much speculation and research. Although asthma and atopy have genetic determinants, these alone cannot account for recent time trends. Instead, these rapid increases are most likely to be a result of changes in environmental influences, with consequent changes in gene-environment interactions that increase the expression of genetic susceptibility. An increasingly western lifestyle is associated with complex changes in behavior and the environment, and in this review we discuss studies investigating the possibility that dietary change has contributed to the recent increase in asthma and atopy.

THE ANTIOXIDANT AND LIPID HYPOTHESES

In 1994, we argued that the increases in asthma and atopic diseases were unlikely to be a consequence of the air we breathe becoming increasingly toxic.⁴ There had been well-documented decreases in atmospheric pollution and cigarette smoking, and there was little evidence for increased exposure to aeroallergens. Instead, we hypothesized that the increase in asthma and atopy had resulted from increasing population susceptibility. We noted that the increase in asthma and atopy had been preceded and paralleled by changes in the UK diet. There had been a decrease in vegetable consumption, particularly of potatoes and green vegetables (Fig 1).⁵ We therefore suggested that a westernized diet increasingly deficient in antioxidants has increased population susceptibility, with consequent large increases in disease prevalence.⁴ In support of this, we showed that hay fever had increased in spite of no increase in pollen levels.⁶ A proposed mechanism related changes in dietary antioxidant intake to

From the Department of Environmental and Occupational Medicine, University of Aberdeen.

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Reprint requests: Graham Devereux, MD, Clinic C, Aberdeen Royal Infirmary, Foresterhill, Aberdeen AB25 2ZN, United Kingdom. E-mail: Graham.Devereux@nhs.net.

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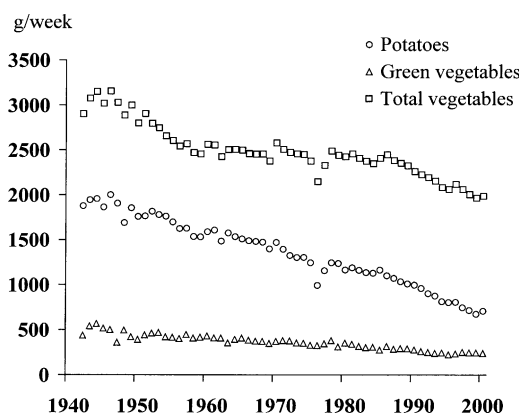


FIG 1. Trends in UK consumption of total vegetables, fresh green vegetables, and potatoes since 1942. Adapted from "Consumption of selected household foods (GB) 1942 to 2000."⁵

reduced lung antioxidant defenses, with increased airway susceptibility to oxidant damage resulting in airway inflammation and asthma.

In 1997, Black and Sharpe⁷ pointed to recent changes in dietary fat intake that had preceded and then paralleled the increase in asthma and atopic disease. In industrialized countries, as a consequence of public health measures to reduce coronary heart disease, dietary intake of saturated fats (butter and lard) has decreased, and consumption of n-6 polyunsaturated fat present in margarine and vegetable oils has increased (Fig 2).⁵ Black and Sharpe⁷ also suggested that decreasing dietary intake of oily fish (fresh tuna, herring, mackerel, trout, and salmon) or derived fish oil products (cod liver oil) rich in the n-3 polyunsaturated fatty acids (PUFAs) eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) might have contributed to the increase in asthma and atopic disease.

An attractive feature of this hypothesis is the proposed mechanism by which atopic sensitization and inflammation could be promoted by increasing dietary intakes of n-6 PUFAs from margarine and vegetable oils and decreasing intake of n-3 PUFAs from oily fish.⁷ The most common dietary PUFAs are linoleic acid (n-6) and α -linolenic acid (n-3), both of which can be converted to longer-chain PUFAs by a single desaturation and elongation enzyme pathway (Fig 3). Linoleic acid is converted to arachidonic acid that can be metabolized by COX and lipoxygenase enzymes ultimately to produce 2-series prostaglandins, thromboxanes, and 4-series leukotrienes, lipoxins that are of particular pertinence to asthma and atopic disease. Four-series leukotrienes have proinflammatory activity,⁸ and the 2-series prostaglandin E_2 (PGE₂) is known to have immunomodulatory properties, promoting the T_H2 phenotype associated with asthma and atopic disease.⁹ Black and Sharpe⁷ argued that increasing dietary intake of n-6 linoleic acid has resulted in increased arachidonic acid and PGE₂ production, with a consequent increase in the likelihood of atopic T_H2 sensitization, asthma, and atopic disease. Conversely, the postulated

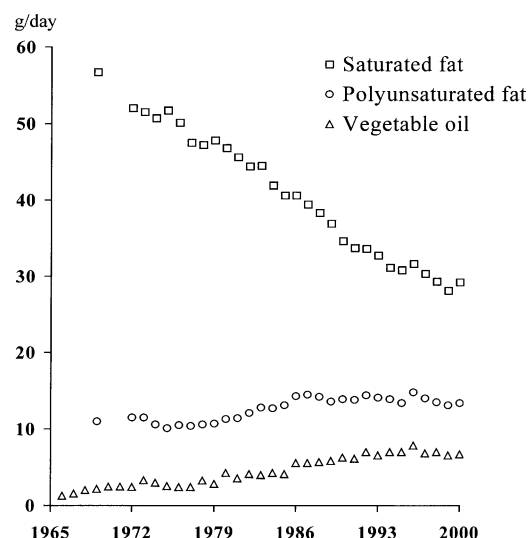


FIG 2. Trends in UK consumption of saturated fats, polyunsaturated fats, and vegetable oils since 1966. Adapted from "Consumption of selected household foods (GB) 1942 to 2000."⁵

beneficial effects of increasing dietary intake of the n-3 α -linolenic acids EPA and DHA stem from reduced arachidonic acid and PGE₂ production because α -linolenic acid competitively inhibits linoleic acid metabolism by the single enzyme cascade, and EPA-DHA reduces COX-2 gene expression and inhibits COX-2 activity.¹⁰ However, the consequences of increasing n-6 and decreasing n-3 PUFA intakes are undoubtedly more complex than outlined by Black and Sharpe.⁷ The lipoxygenase-COX pathways can metabolize dihomo- γ -linolenic acid and EPA to produce prostaglandins and leukotrienes (Fig 3) with biologic activity, albeit less potent than arachidonic acid metabolites. Many 2-series prostaglandin metabolites of arachidonic acid oppose the actions of PGE₂.⁸ Furthermore, both n-3 and n-6 PUFAs can modulate T-cell function directly through effects on cell membrane fluidity, cell signaling, and gene transcription.¹¹

OBSERVATIONAL STUDIES OF ANTIOXIDANTS

Vitamin C

Water-soluble vitamin C provides intracellular and extracellular aqueous-phase antioxidant capacity primarily by scavenging oxygen free radicals and suppressing macrophage secretion of superoxide anions. In general, most studies of dietary vitamin C have reported beneficial associations with ventilatory function, a smaller number have reported associations with asthma, and very few, if any, have shown associations with atopic disease.

Many epidemiologic studies have demonstrated that dietary vitamin C intake or serum ascorbate is positively associated with ventilatory function in children and adults.¹²⁻¹⁵ In the First National Health and Nutrition Examination Survey (NHANES I) dietary vitamin C

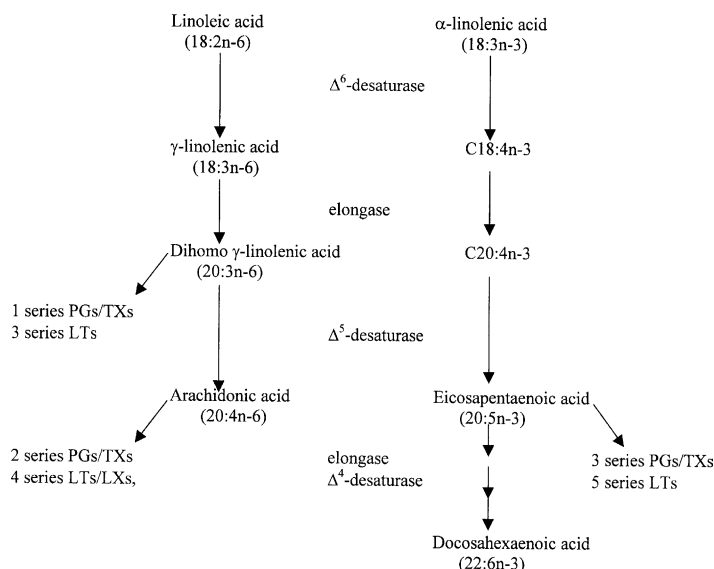


FIG 3. Schematic outline of n-6 and n-3 PUFA metabolism. PGs, Prostaglandins; TXs, thromboxanes; LTs, leukotrienes; LXs, lipoxins.

intake was positively associated with FEV₁ in adults, with a mean 40-mL FEV₁ difference between subjects with the highest and lowest tertiles of vitamin C intake.¹³ In NHANES III serum, but not dietary, vitamin C was positively associated with FEV₁ in a cross-sectional adult study, with an SD increase in serum vitamin C being associated with an average 17-mL increase in FEV₁.¹⁴ Dietary vitamin C has been less frequently associated with asthma and wheezing symptoms in children and adults.¹⁶⁻¹⁹ In NHANES III a negative association between serum ascorbate and asthma was reported in children aged 4 to 16 years, with an SD increase in serum ascorbate being associated with a 19% reduction in asthma prevalence.¹⁶ In a nested case-control study of adults, serum ascorbate was negatively associated with adult-onset wheeze, with an SD increase in serum ascorbate being associated with a 40% reduction in adult onset wheeze.¹⁸ In a case-control study dietary vitamin C intake was negatively associated with the likelihood of methacholine airway reactivity in adults.¹⁹

Vitamin E

Lipid-soluble vitamin E is the principal defense against oxidant-induced membrane injury. In contrast to vitamin C, it also has nonantioxidant effects on immune function that might account for differences in its epidemiologic associations. Studies have consistently demonstrated beneficial associations between dietary vitamin E and ventilatory function,^{12,14,20,21} and a few have demonstrated beneficial associations with asthma and atopy.^{18,22-24}

In a cross-sectional study of children aged 11 to 19 years, dietary vitamin E intake was positively associated with ventilatory function.¹² These associations were more marked in boys, with dietary vitamin E intakes in the lowest decile being associated with reduced FEV₂₅₋₇₅ (8.9%), FEV₁/forced vital capacity ratio (2.3%), and peak

expiratory flow rate (5.1%) when compared with intakes greater than the lowest decile. The Caerphilly heart disease study reported that dietary vitamin E intake was positively associated with FEV₁ in a cross-sectional analysis. A 5-year longitudinal analysis indicated that the protective effect of vitamin E was not reversible because there was no significant association between change in FEV₁ over a 5-year period and change in dietary vitamin E intake or averaged dietary vitamin E intake.²¹ Dietary vitamin E intake was negatively associated with asthma and wheezing in a case-control study of 12-year-old Saudi Arabian children.²² Dietary and serum vitamin E have been negatively associated with adult-onset wheeze.¹⁸ The US Nurses' Health Study reported that the incidence of physician-diagnosed asthma over a 10-year period was negatively associated with dietary intake of vitamin E.²³ The highest quintile of intake was associated with a 47% reduction in the likelihood of asthma development when compared with the lowest quintile. In adults a negative association has been demonstrated between dietary vitamin E intake and serum IgE levels and the likelihood of atopic sensitization.²⁴

Vitamin A

Vitamin A comprises retinol and more than 600 carotenoids, many of which (β-carotene, β-cryptoxanthin, lutein-zeaxanthin, and lycopene) have strong antioxidant activity. Although retinol is not usually considered to be an antioxidant, it has been implicated in normal respiratory epithelial development and lung development. Beneficial associations have been demonstrated between dietary carotenoids and ventilatory function, diagnosed asthma, and respiratory symptoms.^{12,14,16,17,20} Two analyses of NHANES III data from children aged 4 to 17 years demonstrated negative associations between asthma

SUMMARY**Hypothesis: Dietary changes have contributed to the increase in asthma and atopic disease.**

Reduced consumption of foods rich in antioxidants (fruit, vegetables), increased n-6 PUFA (margarine, vegetable oils) intake, and reduced n-3 PUFA (oily fish) intake have been implicated.

In epidemiologic studies beneficial associations have been reported between vitamins C and E, selenium, carotenoids, fruit, and asthma, wheezing, and ventilatory function.

Dietary antioxidant deficiency might influence disease pathogenesis through both immunomodulatory and reduced antioxidant mechanisms.

In epidemiologic studies associations have been demonstrated between margarine, fish, n-6 PUFA, and n-3 PUFA and asthma and atopic dermatitis.

The suggestion that increased n-6 PUFA and reduced n-3 PUFA intakes increase proinflammatory eicosanoid metabolites, and PGE₂-induced T_H2 differentiation is almost certainly an oversimplification.

In atopic dermatitis a mild enzyme deficiency has been proposed, resulting in altered PUFA metabolism that compromises epithelial structure and function.

With the possible exception of n-6 PUFA supplementation for atopic dermatitis, antioxidant and lipid intervention studies in established disease have been disappointing.

Dietary antioxidant and lipid intakes might be particularly important during pregnancy and early childhood: this is an area of active investigation.

Further research is required to establish the feasibility and efficacy of dietary manipulation as a public health measure to reduce the risk of asthma and atopic disease.

and serum levels of α -carotene¹⁷ and β -carotene.¹⁶ SD increases in serum α -carotene and β -carotene levels were associated with 13% and 20% reductions in asthma prevalence, respectively. Dietary and serum β -carotene levels were positively associated with FEV₁ in adults participating in NHANES III.¹⁴

Selenium

The trace element selenium enters the food chain through plants, but there is geographic variation in soil selenium content. Selenium is an important antioxidant, principally because of its incorporation into glutathione peroxidase, an enzyme that plays a key role in protecting cells against oxidative damage. Selenium status has been negatively associated with asthma, respiratory symptoms, and ventilatory function.^{14,16,25,26} A negative association between asthma and serum selenium content in children aged 4 to 16 years has been demonstrated in NHANES III, with an SD increase in serum selenium being associated with a 10% reduction in asthma prevalence.¹⁶ A borderline significant negative association between serum selenium and wheeze 8 years later was reported in a New Zealand study of children aged 8 to 13 years.²⁵ Serum selenium was positively associated with FEV₁ among adults participating in NHANES III, with an SD increase in serum selenium being associated with a 25-mL increase in FEV₁.¹⁴ Dietary selenium intake was negatively associated with asthma (odds ratio, 0.84/quintile increase) in a case-control study of adults.²⁶

Fruit

Potential advantages of investigating dietary fruit are that intake tends to be easily remembered, portion size is obvious, and fruits contain many potentially important

antioxidants that cannot be currently quantified. Furthermore, by demonstrating associations with fruit, the nature of potential intervention studies and public health measures are obvious and more acceptable. Beneficial associations have been reported between fruit intake and asthma,²⁶ ventilatory function,^{21,27,28} and respiratory symptoms²⁹ in children and adults.

The Health and Lifestyles Study demonstrated that FEV₁ was positively associated with winter consumption of fresh fruit or fruit juice in adults.²⁷ A second study of the same subjects 7 years later also reported positive associations between fruit consumption and FEV₁.²⁸ Change in ventilatory function between the 2 surveys was related to changes in dietary fruit intake rather than the mean fruit intake over the 7-year interval. The authors suggested that the cross-sectional effects of fruit consumption on ventilatory function appeared to be reversible and not progressive, with consistently low levels of fruit intake appearing not to increase the rate of ventilatory decrease. The Caerphilly heart disease study demonstrated a positive association between apple consumption and FEV₁ in adults.²¹ However, in contrast to the Health and Lifestyles Study,²⁸ longitudinal analysis indicated that the rate of FEV₁ decrease was not associated with average or change in apple consumption, suggesting that the protective effect of apples was not reversible. Apple consumption was negatively associated with asthma in a case-control study of adults, with frequent apple consumption being associated with a 30% decrease in risk when compared with infrequent apple consumption.²⁶ It was suggested that the beneficial effects of apples could be a consequence of certain types of flavonoids (eg, anthocyanins and phloridzin) because of beneficial associations with red wine consumption and lack of associations with carotene and vitamins C and E intakes.

ANTIOXIDANT INTERVENTION STUDIES

The epidemiologic studies discussed above suggest that there are beneficial associations between asthma and atopic disease and dietary antioxidants, such as vitamin C, vitamin E, some carotenoids, selenium, and antioxidant-rich fruits. There have been many intervention studies, the majority of which have supplemented with vitamin C. Studies of vitamin E and selenium supplementation are few in number. In general, the results of these supplementation studies have been disappointing, with many reporting insignificant effects, and in the few studies reporting beneficial effects, the effects are small and probably clinically insignificant.³⁰⁻³³

ANTIOXIDANTS, ASTHMA, AND ATOPIC DISEASE: POSSIBLE MECHANISMS

The respiratory airways are particularly vulnerable to oxidative damage, and to counteract this, numerous enzymatic and nonenzymatic antioxidant defense mechanisms are present.³⁴ In experimental models oxidants induce many features of asthma by inducing release of proinflammatory mediators, including cytokines, chemokines, and eicosanoid metabolites.³⁵ Oxidant stress also activates gene expression of 2 pivotal inflammatory regulators, nuclear factor κ B and activator protein 1.³⁵

There is an obvious disparity between the consistent beneficial associations reported from epidemiologic studies of antioxidants and the generally disappointing results of supplementation studies in established asthma. One postulated reason for the ineffectiveness of intervention is that antioxidant supplementation is only effective when there is an antioxidant deficiency, but subgroup analyses of supplementation studies make this unlikely.^{31,32} The criticism that supplementation studies have been of short duration has been partly addressed by several recent well-designed studies.^{31,32} It is possible that the observed epidemiologic associations are a consequence of other nutrients closely associated with antioxidants or the result of residual confounding by factors associated with socioeconomic status, lifestyle, or both. What is clear, however, is that the beneficial associations between dietary antioxidants and ventilatory function, asthma, and respiratory symptoms cannot be simply explained by antioxidants reducing oxidant damage and the rate of decrease of ventilatory function.

An alternative proposal is that dietary antioxidants are particularly important during childhood, when airways are growing. Suboptimal antioxidant status during this critical period might result in oxidative airway damage, with long-term effects on airway caliber, airway compliance, or both. Studies of pulmonary function in early life suggest that children with reduced pulmonary function in early life are more likely to wheeze, have asthma, and have reduced ventilatory function later in life, particularly if they become atopic.³⁶ A model with a critical period of suscep-

tibility in early childhood during which antioxidant intake is important is consistent with reported associations between antioxidants and ventilatory function and symptoms in children and adults because habitual dietary patterns are, to a large extent, established very early in life, such that adult and early childhood dietary patterns are significantly associated.³⁷ Thus the epidemiologic associations with adult antioxidant status might be an indirect association with childhood diet. Furthermore, if antioxidants exert their beneficial influences early in life, intervention during adulthood would be highly unlikely to be effective; there is thus a need for intervention studies during early childhood.

As suggested in our original hypothesis,⁴ maternal dietary antioxidant intake during pregnancy might also be particularly important. In fetal rat models *in vivo* and *in vitro* antioxidant supplementation corrects hypoplastic lung growth.³⁸ It therefore seems plausible that reduced maternal dietary antioxidant intake during pregnancy might be associated with the impaired lung development that is associated with wheeze, asthma, and reduced lung function later in life. This model predicts that increased fetal oxidant stress should be associated with reduced lung function and asthma. Such associations have been demonstrated with maternal cigarette smoking (an oxidant stress) during pregnancy.³⁹

The antioxidant properties of vitamin E, selenium, and fruit fail to explain associations with IgE and atopic sensitization. Of particular relevance to these associations is the recognition that some antioxidants have nonantioxidant properties, and it has even been suggested that vitamin E acts principally as a nonantioxidant.⁴⁰ The nonantioxidant properties of vitamin E, selenium, and flavonoids pertinent to asthma and atopic disease are those exerted on T_H cells that play pivotal roles in the initiation and perpetuation of the chronic inflammatory process associated with asthma and atopic disease. In animal models and human subjects, vitamin E, selenium, and quercetin (a flavonoid) have been reported to promote T_H1 differentiation by increasing T_H1 cytokine secretion, inhibiting T_H2 cytokine secretion, or both.⁴¹⁻⁴⁶ Human T_H cells supplemented with physiologic quantities of vitamin E demonstrate reduced IL-4 secretion in a dose-dependent manner.⁴⁷ Vitamin E appears to act by down-regulating IL-4 mRNA expression in human T_H cells by inhibiting binding of the transcription factors nuclear factor κ B and activator protein 1 to the IL-4 promoter region.⁴⁷ Immunologic considerations of T_H cell differentiation suggest that antioxidants should probably exert their most potent influences on T_H cell polarization during the earliest exposures of the immune system to allergens (ie, fetal and early life [0-5 years]). It is possible that reduced antioxidant status during fetal and early life increases the likelihood that the initial critical encounters between T_H cells and allergens result in T_H2-biased responses.

Reduced dietary intake of vitamin E, selenium, flavonoids, and fruit by mothers during pregnancy and by young children has the potential to predispose toward

asthma not only by affecting airway development but also by promoting T_H2 differentiation and atopic sensitization. This model is consistent with the general ineffectiveness of intervention studies in adults and, because of the concordance between infant and adult diet, is also consistent with the results of epidemiologic studies of children and adults. At the present time, there are few studies investigating the effects of maternal diet during pregnancy and early (0-5 years) childhood diet. Umbilical cord selenium concentrations have been reported to be negatively associated with persistent wheeze in children up to 3½ years.⁴⁸ We have found maternal dietary vitamin E intake during pregnancy to be negatively associated with cord blood mononuclear cell responses and, in the second year of life, with “wheeze in the absence of a cold” and with eczema in children born to atopic mothers.^{49,50}

OBSERVATIONAL STUDIES OF LIPIDS

Several cross-sectional studies have reported beneficial associations between dietary fish intake, asthma, and atopic disease.^{51,52} Hodge et al⁵¹ reported that in children aged 8 to 11 years the risk of current asthma was significantly reduced in those who included fresh oily fish in their diet. A number of studies of adult populations have reported no association between dietary fish intake and asthma, respiratory symptoms, and ventilatory function.⁵³ and Takemura et al⁵⁴ reported an adverse positive association between fish consumption and asthma in 6- to 15-year-old children; however, this association had not been adjusted for the potentially confounding factors associated with socioeconomic status.

Margarine contains up to 20 times more n-6 linoleic acid than butter, and an increased dietary intake of margarine has been associated with an increased likelihood of atopic sensitization and atopic disease.^{52,55,56} Dunder et al⁵² reported the results of a case-control study of 3- to 18-year-old children recruited in 1980 and re-examined in 1986 and 1989. Children with atopic disease consumed more margarine and less butter than nonatopic control subjects. In a longitudinal analysis of dietary data in 1980 related to the development of atopic disease by 1989, children who had atopic disease consumed less butter and fish than those who remained nonatopic.⁵² In addition, in 1980 and 1986, children with atopic dermatitis had reduced serum levels of EPA and DHA. Haby et al⁵⁷ reported an adverse association between the high use of PUFA in spreads and cooking oils and recent asthma in 3- to 5-year-old children. Total dietary fat intake has been reported to be positively associated with bronchial hyper-responsiveness¹⁹ and, in women, atopic sensitization and hay fever.⁵⁶ Dietary saturated fat intake has been reported to be positively associated with bronchial hyperresponsiveness,¹⁹ asthma,⁵⁸ and, in women, atopic sensitization and hay fever.⁵⁶

There is an extensive literature relating the concentration of PUFA in serum, erythrocytes, and adipose tissue to atopic disease, particularly atopic dermatitis. Much of the

work originated from observations in the 1930s that rats fed a diet deficient in unsaturated fats experienced a scaly dermatitis similar to atopic dermatitis. It has been suggested that in addition to possible effects on inflammatory mediators and T_H cell differentiation, PUFAs are also necessary for normal epidermal structure and function, and that atopic dermatitis might be a consequence of a minor inherited abnormality of PUFA metabolism (Δ 6-desaturase).⁵⁹ The complex effects of dietary PUFA intake on inflammatory mediators, T_H cell differentiation, and epidermal integrity and the possibility that these effects might differ between atopic diseases make it likely that epidemiologic and interventional studies will produce complex and conflicting results. This seems to be the case.

Studies of adipose tissue, serum, erythrocyte, and leukocyte PUFA levels in children, young adults, and adults support the notion that atopic dermatitis is associated with reduced activity of the Δ 6-desaturase enzyme that converts linoleic acid to γ -linolenic acid and α -linolenic acid to stearidonic acid.⁶⁰⁻⁶³ Manku et al^{60,61} reported that levels of plasma linoleic acid were significantly increased in adults with atopic dermatitis, whereas the levels of its metabolites, γ -linolenic, dihomo- γ -linolenic, and arachidonic acids, were reduced. In addition, there was a nonsignificant increase in the major n-3 PUFA α -linolenic acid, with significant reductions in all of its metabolites. A small number of epidemiologic studies are consistent with the Black and Sharpe hypothesis.^{64,65} In children aged 12 to 15 years, atopic disease and atopic sensitization were associated with reduced DHA and n-3 PUFA and an increase in n-6/n-3 PUFA ratio.⁶⁴ In addition, serum IgE levels were positively associated with n-6 PUFAs and negatively associated with serum EPAs. In contrast, Griese et al⁶⁶ reported that plasma and mononuclear cell phospholipid EPA levels were positively associated with atopic asthma and serum IgE in children.

Several studies have related cord blood PUFA composition to the subsequent development of atopic disease,^{67,68} with the largest study to date finding no association between cord blood PUFA intake and subsequent childhood eczema and wheezing.⁶⁷ Galli et al⁶⁸ reported significant reductions in cord blood plasma dihomo- γ -linolenic acid and arachidonic acid concentrations in neonates who subsequently had atopic dermatitis. A modest but insignificant increase in linoleic acid was also reported. These findings were interpreted as evidence of reduced Δ 6-desaturase activity predating the development of atopic dermatitis.

LIPID INTERVENTION STUDIES

As outlined above, investigation of asthma and dietary lipids has pursued the suggestion that asthma and atopy are a consequence of increasing n-6 PUFA intake and decreasing n-3 PUFA consumption and effects on inflammatory mediators and T_H cell differentiation. Studies of atopic dermatitis have focused on reduced activity of

$\Delta 6$ -desaturase enzyme and consequent effects on epidermal structure-function and T_H cell differentiation. This is probably why there has been an emphasis on increasing intake of n-3 PUFA derived from oily fish in asthma, whereas in atopic dermatitis the aim has been to increase intake of linoleic acid, γ -linolenic acid, or both.

Systematic review of the clinical effects of n-3 PUFA fish oil supplementation in established asthma has concluded that it is not consistently associated with beneficial effects and that there is little evidence to recommend such supplementation or dietary modification to improve asthma control.⁶⁹ Supplementation with evening primrose oil (approximately 72% linoleic acid, 9% γ -linolenic acid) has not been associated with beneficial effects on asthma control.⁷⁰ A potentially important observation from 2 supplementation studies is that individuals with asthma differ considerably in their response to lipid supplementation. This variation appears to be closely associated with the ability of n-3 PUFA supplementation to modify the leukotriene profile and is probably genetic in origin.^{71,72} Okamoto et al⁷¹ reported that only a subgroup of asthmatic patients benefited from supplementation with perilla oil (a vegetable source of n-3 PUFA) and that the leukocytes of these individuals characteristically reduced leukotriene C_4 secretion after such supplementation. If variation in susceptibility to the beneficial effects of PUFAs can be confirmed and characterized, future studies and possible treatment with PUFAs could be targeted at susceptible individuals.

Horrobin⁵⁹ has reviewed the results of n-6 PUFA intervention studies for atopic dermatitis. Studies from the 1930s and 1960s demonstrated that supplementation with very high doses of linoleic acid resulted in clinical improvement. More recently, 2 interventional studies with linoleic-rich corn or soybean oil reported sustained improvements in atopic dermatitis.^{73,74} Many studies have supplemented the diet of subjects with atopic dermatitis with γ -linolenic acid, usually as evening primrose oil. Horrobin⁵⁹ concluded that, on the balance of the evidence, supplementation with modest doses of n-6 PUFA γ -linolenic acid was associated with clinical improvement, reduced use of antibiotics, oral corticosteroids, and potent topical corticosteroids. There have been relatively few studies of n-3 PUFA supplementation for atopic dermatitis. Although fish oil supplementation has been reported to have no clinical effect on atopic dermatitis,⁷⁵ a number of studies have reported beneficial effects.^{73,74} In 2 studies supplementation with fish oil n-3 PUFA was as effective in improving atopic dermatitis as n-6 PUFA supplementation.^{73,74} At present, there is little evidence to recommend dietary supplementation with n-3 or n-6 PUFA for established asthma; however, there might be individuals who would benefit from such supplementation if identified, and more research is required. In contrast, there is a more substantial body of evidence suggesting that supplementation with n-6 PUFA and possibly n-3 PUFA have beneficial effects on established atopic dermatitis; this might relate to the role of PUFAs in maintaining epidermal structure and function.

There is increasing interest in the use of dietary PUFA supplementation to prevent the development of atopic disease.⁷⁶⁻⁷⁸ Although 2 studies of postnatal dietary modification-supplementation have been disappointing, a single antenatal supplementation study has hinted at possible beneficial effects. Postnatal fish oil supplementation and dietary modification to reduce n-6 PUFA intake in genetically susceptible infants was associated with a significant reduction in wheeze at 18 months, but this was not evident at 3 years.⁷³ Postnatal dietary supplementation of genetically susceptible infants for 6 months with γ -linolenic acid (borage oil) was not associated with reduction in the prevalence of atopic dermatitis or serum IgE at 1 year.⁷⁷

Fish oil n-3 PUFA supplementation in a small group of atopic women ($n=40$) during pregnancy has been reported to be associated with nonsignificant reductions in cord blood mononuclear cell proliferative and cytokine responses. However, there was a significant reduction in IL-10 responses after stimulation with cat allergen, and at 1 year, fish oil supplementation was associated with nonsignificant reductions in asthma and atopic sensitization and a nonsignificant increase in atopic dermatitis in the children.⁷⁵ Further follow-up of this cohort and a larger intervention study are required. At present, there are too few studies and insufficient evidence to recommend or refute the role of dietary PUFA supplementation during pregnancy, early life, or both to prevent the development of asthma and atopic disease.

CONCLUSION

Epidemiologic studies have reported associations between dietary antioxidant and lipid intakes and asthma and atopic disease. With the possible exception of n-6 PUFA supplementation for atopic dermatitis, a major criticism of the dietary hypotheses is the generally disappointing results of intervention studies. However, the realization that dietary habits are established early in life and that fetal and early life factors influence the development of asthma and atopic disease has moved the focus of the dietary hypotheses to pregnancy and early childhood. In addition to exerting antioxidant effects, several antioxidants appear to have immunomodulatory properties that are probably relevant. There are 2 proposed mechanisms by which lipids can influence the development of asthma and atopic dermatitis; however, epidemiologic and immunologic studies suggest that the actual effects of lipids are far more complex and unpredictable. It is clear that further research in this field is justified and required, in particular the role of diet during fetal and early life and the issue of individual susceptibility. The ultimate aim of dietary modification or supplementation to reduce the likelihood of asthma and atopic disease appears to be far from a remote possibility.

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