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PERSPECTIVE

Dietary fat and asthma: is there a connection?

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Dietary fat and asthma: is there a connection? P.N. Black, S. Sharpe. ©ERS Journals Ltd 1997.

ABSTRACT: The last two decades have seen an increase in the prevalence of asthma, eczema, and allergic rhinitis in developed countries. This increase has been paralleled by a fall in the consumption of saturated fat and an increase in the amount of polyunsaturated fat in the diet. This is due to a reduction in the consumption of animal fat and an increase in the use of margarine and vegetable oils containing ω-6 polyunsaturated fatty acids (PUFAs), such as linoleic acid. There is also evidence for a decrease in the consumption of oily fish which contain ω-3 PUFAs, such as eicosapentaenoic acid.

In a number of countries, there are social class and regional differences in the prevalence of allergic disease, which are associated with differences in the consumption of PUFAs. Linoleic acid is a precursor of arachidonic acid, which can be converted to prostaglandin E_2 (PGE_2), whereas eicosapentaenoic acid inhibits the formation of PGE_2. PGE_2 acts on T-lymphocytes to reduce the formation of interferon-γ (IFN-γ) without affecting the formation of interleukin-4 (IL-4). This may lead to the development of allergic sensitization, since IL-4 promotes the synthesis of immunoglobulin E (IgE), whereas IFN-γ has the opposite effect.

Changes in the diet may explain the increase in the prevalence of asthma, eczema and allergic rhinitis. The effects of diet may be mediated through an increase in the synthesis of prostaglandin E_2 which in turn can promote the formation of immunoglobulin E.

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Changes in the prevalence of asthma

Studies from the United Kingdom [1–5], Australia [6, 7], New Zealand [8, 9], Sweden [10], Finland [11], the United States [12] and Canada [13] of the same populations, years to decades apart, have provided good evidence of an increase in the prevalence of asthma in children and young adults over the last two decades. Where these studies have looked at changes in the prevalence of eczema and allergic rhinitis, they have found that these conditions have also increased. It appears that an increase in atopy, rather than just asthma, is occurring in developed countries.

Why has the prevalence of asthma changed?

A number of environmental factors, including air pollution, cigarette smoking, allergen exposure and diet, have been proposed as explanations for the changes in the prevalence of asthma. In a recent article, SEATON *et al*. [14] considered and rejected a number of these explanations. Air pollution has lessened in the UK since the 1950s with a fall in smoke and sulphur dioxide [14], and there is no clear evidence for a rise in ozone levels in the UK in the last two decades. Recent studies from Germany are of interest because they show that the prevalence of hayfever and asthma is lower in the more heavily polluted former German Democratic Republic (East Germany) [15]. Exposure to cigarette smoke *in utero* and in childhood increases the prevalence of allergic sensitization and respiratory disease [16], but there has been a steady fall over the last three decades in the proportion of the population who smoke, including women of childbearing age [17, 18]. The evidence that exposure to house dust mite and other allergens has increased is disputed [7, 19]. Attention has focused on the role of the house dust mite in the pathogenesis of asthma, but there are communities, such as Los Alamos, where the prevalence of childhood asthma is comparable to other communities in the USA despite very low levels of house dust mite [20].

SEATON *et al*. [14] argue that the fall in the consumption of fresh fruit and vegetables in the UK between 1961 and 1985 may account for the increase in asthma. The idea that antioxidant vitamins, such as vitamin C and β-carotene, could have a protective effect in asthma is plausible and the main source of these vitamins is fruit and vegetables. There are, however, problems with this hypothesis. In 1965, a cohort from the National Child Development Study in the UK was followed up at 7 yrs of age. The lowest rates of asthma were reported in Scotland and the North of England [21], but in the National Food Survey conducted in 1969 [22] these were also the two regions with the lowest consumption of green vegetables and fresh fruit. Another study from the

UK showed that the intake of vitamin C is lower in manual workers [23], whereas the prevalence of asthma is either unrelated to social class [24], or increases with higher social class [25].

In the rest of this article, we review the evidence for the hypothesis that an increase in the intake of ω-6 fatty acids, such as linoleic acid, and a decrease in the intake of ω-3 fatty acids, such as eicosapentaenoic acid, may have to led to an increase in allergic sensitization, which in turn may account for the increase in the prevalence of asthma. CHANG *et al*. [26] and HODGE *et al*. [27] have previously suggested that changes in dietary fat may explain the increase in asthma but they did not relate this to changes in allergic sensitization.

Changes in the consumption of linoleic acid

In developed countries, there has been a fall in the consumption of saturated fat and an increase in the consumption of polyunsaturated fat, particularly linoleic acid, over the last few decades. It is thought that these changes have contributed to the fall in coronary heart disease mortality. In the USA between 1935 and 1939, linoleic acid accounted for only 9% of fatty acids in the food supply [28]. By 1984, this had risen to 15%. These changes are in large part due to a decrease in the use of butter and lard and an increase in the use of margarine and vegetable oils. Figure 1 shows changes in adipose tissue linoleate in the USA, UK and Australia.

The argument for a connection between polyunsaturated fat and asthma would be more compelling if the increase in the consumption of linoleic acid antedated the rise in the prevalence of asthma. In the USA, the amount of linoleic acid (grams per capita per day) in the diet has increased over the last eight decades, with the change being most marked since the early 1960s [28]. YUNINGER *et al*. [12] found a steady increase in the incidence of asthma in children since 1964. This is what one would anticipate if the increase in the consumption of linoleic acid was contributing to the rise in the prevalence of asthma. In contrast, the increase in the consumption of linoleic acid in the UK occurred in the 1970s [29]. It is not entirely clear when the prevalence of childhood asthma began to rise in the UK but it may well have been in the early 1980s. In a review, ANDERSON [30] found little evidence for an increase in the prevalence of asthma in studies conducted prior to 1980. In contrast, BURR *et al*. [1] found an increase in the prevalence of asthma in children in Wales between 1973 and 1988, while BURNEY *et al*. [3] found an increase in children in England between 1973 and 1986. If we accept that the prevalence of childhood asthma in the UK did increase in the early 1980s, it is consistent with the rise in the consumption of linoleic acid preceding the increase in the prevalence of asthma by several years.

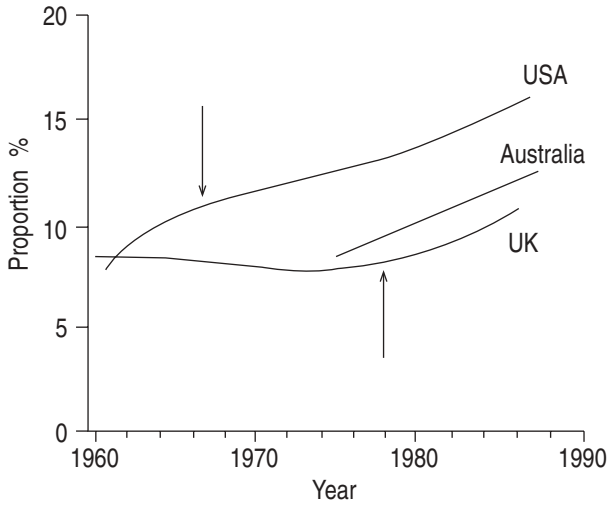

Fig. 1. – Proportion of linoleate in adipose tissue by country, 1960–1990. Arrows indicate year of down turn in coronary heart disease (CHD) death rate. (Reproduced from ROBERTS [29]).

Changes in the consumption of oily fish

The suggestion that oily fish may protect against the development of asthma stems from the observation that asthma is uncommon amongst the Eskimos, who have a high intake of fish oil [31]. SCHWARTZ and WEISS [32] analysed data from the Second National Health and Nutrition Survey in the USA, and found that dietary fish intake was protective against wheezing but, in a stepwise logistic regression, were unable to show that this was independent of other nutrients. Recently, HODGE *et al*. [33] reported a study of 584 children in Sydney, Australia. If the children included oily fish, such as salmon, tuna and sardines, in their diet the odds ratio for having current asthma was reduced to 0.26 (95% confidence interval (95% CI) 0.09–0.72). The diets of the children with current asthma did not differ from the normal children in any other regard and a protective effect was not seen with other types of fish.

Less information is available on trends in the consumption of oily fish than for changes in consumption of margarine and vegetable oils. In 1985, in the USA, the consumption of fish had increased compared with 1935–1939, but the levels of eicosapentaenoic acid in the diet were lower because of a marked decline of some oily fish in the diet [34]. HODGE *et al*. [33] speculated that the eicosapentaenoic acid, present in oily fish, may account for the protective effect which they observed. Some commentators [35] have argued that the observations by HODGE *et al*. [33] are inconsistent with studies which failed to show improvement in asthmatics treated with fish oil [36–38]. If, however, fish oil exerts its beneficial effect by reducing the risk of allergic sensitization rather than having a direct effect on asthma this conflict no longer exists.

Regional differences in asthma

Regional differences in the intake of polyunsaturated fat have been reported in a number of countries, and this provides the opportunity to compare the prevalence of asthma in these regions with the differences in diet. Studies which have looked at the prevalence of asthma and allergic rhinitis in Germany following reunification demonstrate a lower incidence of atopic disease in the former East Germany. KRAMER *et al*. [39] studied more than 4,000 preschool children in several towns in Germany, and found lower prevalences of doctor-diagnosed

asthma and rhinitis in children from the former East Germany. VON MUTIUS and co-workers [40, 41] compared 9 year old children in Leipzig in East Germany (n=1,051) and Munich in West Germany (n=5,030). The lifetime prevalence of asthma diagnosed by a doctor was 7.3% in Leipzig and 9.3% in Munich. A positive cold air challenge (defined as a 9% fall in forced expiratory volume in one second (FEV_1)) occurred in 6.4% of the children in Leipzig and 7.7% in Munich. The most striking difference was seen with the diagnosis of hayfever, which was 2.4% in Leipzig compared with 8.6% in Munich. Another study compared 7,200 subjects, aged 20–44 yrs, in Erfurt (East Germany) and Hamburg (West Germany) [42], and found higher prevalences of asthma and allergic rhinitis in Hamburg. These findings suggest that the differences between East and West Germany may be due to differences in allergic sensitization. This is supported by another study comparing 901 pupils from Leuna (East Germany) and Duisberg (West Germany) [43], which showed the prevalence of specific immunoglobulin (IgE) antibodies to house dust mite and cat was more than fivefold and threefold higher, respectively, in Duisberg.

There are fewer direct comparisons of food intakes in East and West Germany. Prior to unification, however, similar methodology was used to compare food intakes in Erfurt (East Germany) and Augsburg (West Germany) as part of the Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) project [44]. The survey involved middle-aged men keeping 3 day records of their food intake. The most striking difference was the higher intake of saturated fat in Erfurt, where the median daily intake of butter was 27 g higher than Augsburg. In contrast, margarine was consumed less frequently in Erfurt, with only 35% of men using it compared with 67% of men in Augsburg. At this time, margarine was less readily available and not as palatable in East Germany [44]. Increased consumption of margarine leads to a higher intake of linoleic acid, and we suspect that the higher incidence of asthma and other allergic diseases in West Germany at the time of reunification could be related to a higher intake of linoleic acid.

Finland has a low ratio of polyunsaturated fat to saturated fat in the diet (P:S ratio) and a high prevalence of ischaemic heart disease. The P:S ratio is lowest, and the prevalence of ischaemic heart disease is highest, in the east of the country. There are also regional differences in the prevalence of childhood asthma in Finland. In 1980, a cross-sectional study of risk factors for coronary heart disease was conducted in 3,596 Finnish children, aged 3–18 yrs, both in urban and rural areas in the south, the north and the east [45]. As part of the study, a questionnaire was sent to parents asking about chronic illnesses, including bronchial asthma, allergic rhinitis and atopic eczema [46]. The prevalence of asthma and allergic diseases was lowest in Eastern Finland (table 1). In Southern Finland, the prevalences of asthma and rhinitis (per 1,000 children) were 21 and 80, respectively, compared with values of 6 and 50, respectively, in Eastern Finland. In this study, the fatty acid composition of serum cholesterol esters was also measured in 1,348 children [47]. The levels of ω-6 fatty acids, *i.e.* linoleic acid and arachidonic acid, in the cholesterol esters were significantly lower in children from

Table 1. – Prevalence (patients per 1,000 children) of bronchial asthma, allergic rhinitis and dermatitis, in 1980 in three areas of Finland

	Patients per 1,000 children		
	Northern Finland	Southern Finland	Eastern Finland
Asthma	33*	21*	6
Rhinitis	59	80‡	50
Eczema	54#	49	31

*: p=0.003; ‡: p=0.03; #: p=0.04, significance of difference compared to Eastern Finland. (Adapted from POYSA *et al*. [46]).

Table 2. – Percentage composition of serum cholesteryl esters fatty acids in rural children from three areas in Finland

	Northern Finland (n=46)	Southern Finland (n=369)	Eastern Finland (n=275)
Linoleic acid	50.21	51.26	47.90
Arachidonic acid	5.60	5.82	5.48
EPA	1.30	1.12	1.39

EPA: Eicosapentaenoic acid. (Adapted from MOILLANEN *et al*. [47]).

Eastern Finland compared with those in the South or North. These differences are seen most clearly in the rural children (table 2). Furthermore, the levels of eicosapentaenoic acid, an ω-3 fatty acid, were significantly higher in the cholesterol esters from the children in the east of the country. These findings are consistent with the observation that the consumption of fish, which contains eicosapentaenoic acid, is higher in the East. We believe that the lower levels of ω-6 polyunsaturated fatty acid (PUFA) and higher levels of ω-3 PUFA in the cholesterol esters of children in the east of Finland explains why allergic diseases occur less frequently in this part of the country.

There is evidence that the prevalence of atopy is increasing in Japan. NAKAGOMI *et al*. [48] reported that the prevalence of one or more positive skin tests for common allergens in 13–14 year old girls increased from 21.4% in 1978 to 39.4% in 1991. In another study, middle-aged women eating a more traditional diet had a higher ω-3/ω-6 ratio in their serum phospholipids than urban women of the same age [49]. The increase in atopy in Japan could be due to a decrease in the ω-3/ω-6 ratio as more individuals eat a less traditional diet.

Socioeconomic status, dietary fat and asthma

Studies of the prevalence of coronary heart disease have shown that, in developed countries, coronary heart disease is commoner in individuals of lower socioeconomic status and those with less education [50]. These observations have been explained by differences in risk factors for coronary heart disease, such as smoking, and the intake of polyunsaturated as opposed to unsaturated fat. If the intake of dietary fat influences the prevalence of asthma one might also expect there to be socioeconomic differences in the prevalence of asthma and other

allergic diseases. Indeed, this appears to be the case, with an increased frequency of allergic diseases in higher socioeconomic groups.

A number of studies over the last few decades have reported a greater prevalence of asthma in higher socioeconomic groups [25, 51, 52]. Some of these studies have been criticised because children with asthma may have been misclassified as wheezy bronchitis. One study which avoids this problem is a recent report by LEWIS *et al*. [25]. They used information from the 1970 British Cohort Study, which included all children born in Britain during the period 5–11 April 1970. These authors included all children where there was a positive response at the age of 5 yrs to the question "Has the child ever wheezed". No distinction was made between asthma and wheezy bronchitis. Socioeconomic status was expressed as a social index, which combined information on parental occupation, education, income and housing conditions. Wheeze up to 5 yrs was greatest in the most disadvantaged group but there was no longer any independent effect of social index once other factors, such as birth weight and maternal smoking, were taken into account. In contrast, at 16 yrs, 18.3% of children in the most socially advantaged group were still wheezing compared with only 10.5% in the most disadvantaged group, and this was statistically significant.

These authors suggested that two distinct processes are involved. The associations between maternal smoking, low birth weight and wheezing in preschool children may be due to viral illnesses precipitating wheezing in children with small airways. On the other hand, wheeze persisting into adolescence occurs more frequently in higher socioeconomic groups and is more likely to represent allergic asthma. This interpretation is consistent with a study from Tucson in Arizona [53], where children who had wheezing before the age of 3 yrs, but in whom wheezing was no longer present at 6 yrs, had a reduction in tests of airway function but did not have elevated levels of IgE. In contrast, those who were still wheezing at 6 yrs had elevated levels of IgE, *i.e*. it is wheezing in later childhood that is most clearly associated with allergic sensitization.

The Nottingham group have gone on to demonstrate that there is a greater degree of allergic sensitization in those of higher socioeconomic status [54]. Skin sensitivity to five common aeroallergens was higher in social class I (33%) than in social class V (28%). Similar findings have been reported from the US with the second National Health and Nutrition Examination Survey (NHANES II) [55]. Rates of skin test reactivity to eight common allergens increased both with higher socioeconomic status and higher levels of education. Twenty five percent of white subjects with 13 or more years of education had one or more positive skin tests. In contrast, only 12.2% with 8 yrs of education or less were skin test positive. The prevalence of eczema and allergic rhinitis in children has also been reported to increase with higher socioeconomic status. WILLIAMS *et al*. [56] used information from the 1970 British National Cohort Study, and found that the point prevalences of eczema based on a physical examination at 7 yrs of age showed a similar socioeconomic gradient.

If there are socioeconomic differences in the prevalence of allergic diseases, what is the evidence for differences in the intake of dietary fat? In the Coronary Artery Risk Development in Young Adults (CARDIA) study, dietary assessments were performed in 1985–1986 on 5,111 individuals in the US aged 18–30 yrs. High school graduates (*i.e*. 12 or more years of education) had a higher P:S ratio than those with less education [57]. Two studies from Scotland have also looked at social class differences in the intake of polyunsaturated and saturated fat. FULTON *et al*. [58] studied 129 males (44–54 yrs of age) who kept detailed dietary records. In this study, nonmanual workers consumed significantly more linoleic acid than manual workers. In a larger study, BOLTON-SMITH *et al*. [59] administered a food frequency questionnaire to over 10,000 Scottish males and females aged 40–59 yrs, and found that the P:S ratio was lower in nonmanual workers, both for females (nonmanual 0.31, manual 0.28; $p<0.001$) and for males (nonmanual 0.32, manual 0.31; $p=0.025$). These findings are consistent with our hypothesis that an increase in the intake of polyunsaturated fat may contribute to the higher rates of allergic disease observed in higher socioeconomic groups. The differences in the P:S ratios between groups in these studies are relatively small, however, and other factors may also contribute to the differences observed between socioeconomic groups in the prevalence of atopic disease.

Prospective studies of diet and respiratory disease

There is a need for a prospective study of a cohort of children who have a dietary assessment and who are then followed to determine whether they develop positive skin tests and/or asthma. Studies in adults have examined the relationship between diet and respiratory disease, but none of them has addressed the issue of whether a diet high in polyunsaturated fat prediposes to allergic sensitization. In Zutphen in the Netherlands, 793 middle-aged males were followed from 1960–1985 [60]. The intake of linoleic acid was positively associated with the risk of developing chronic nonspecific lung disease but 74% were smokers, so it is likely that most had chronic obstructive pulmonary disease (COPD) rather than asthma. The relationship between diet and the onset of adult asthma was examined in 77,866 females in the Nurse's Health Study [61]. No significant association was found between the intake of polyunsaturated fat and the risk of adult onset asthma. However, in adult onset asthma many, if not most, individuals are not atopic, so these findings are probably of limited relevance to the prevalence of atopic disease in childhood.

Cytokines and PGE_2

The formation of IgE by B-lymphocytes is influenced by cytokines produced by T-helper (CD4+) lymphocytes. These CD4+ cells can be characterized by the profile of cytokines which they produce. Type 1 T-helper (Th1) cells produce interleukin-2 (IL-2) and interferon-γ (IFN-γ) while type 2 T-helper (Th2) cells produce the cytokines, interleukin-4 (IL-4) and interleukin-5 (IL-5) [62, 63]. However, the majority of CD4+ uncommited cells are T-helper (Th0) cells and produce a mixed

cytokine profile. IL-4 acts to commit B-cells to the synthesis of IgE [64], whereas IFN-γ inhibits the formation of IgE [65].

There is evidence that prostaglandin (PGE_2) can modulate the formation of cytokines by T-lymphocytes. Low concentrations of PGE_2 (10^9–10^8 M) inhibit the formation of IL-2 and IFN-γ by peripheral blood lymphocytes, whilst having no effect on the production of IL-4 and IL-5 [66, 67]. The ability of PGE_2 to inhibit the production of IFN-γ, but not IL-4, was not limited to clones of Th1 and Th2 cells but was also seen with Th0 cells. By inhibiting the formation of IFN-γ but not IL-4, PGE_2 will increase the formation of IgE. There is also evidence that PGE_2 can act directly on B-cells to stimulate the formation of IgE. ROPER and co-workers [68, 69] have reported that PGE_2 promotes the action of IL-4 to increase the number of B-lymphocytes producing IgE. If PGE_2 increases the formation of IgE we believe that dietary factors which promote the formation of PGE_2 could lead to the development of atopic disease in susceptible individuals.

Prostaglandins such as PGE_2, are formed by the action of cyclo-oxygenase on arachidonic acid. Arachidonic acid, in turn, is formed from linoleic acid. As a result, an increase in linoleic acid in the diet will promote the formation of prostaglandins [70]. Dietary ω-3 fatty acids have the opposite effect. The ω-3 fatty acids can act in two ways to modulate the formation of PGE_2 from arachidonic acid [70]. There is competitive inhibition between linoleic acid, and ω-3 fatty acids, such as linolenic acid. Increasing dietary ω-3 fatty acids results in a reduction in arachidonic acid by inhibiting its synthesis from linoleic acid. Omega-3 fatty acids also act to inhibit the action of cyclo-oxygenase. Of the ω-3 fatty acids, eicosapentaenoic acid and docosahexaenoic acid (which are found in oily fish) are the most effective at inhibiting cyclo-oxygenase.

These effects have been demonstrated *in vivo*. KNAPP and FITZGERALD [71] compared the effects of a 1 month supplementation with fish oil (containing eicosapentaenoic acid) and safflower oil (containing linoleic acid). The safflower oil diet led to a significant increase in the urinary excretion of a prostaglandin E metabolite, whereas there was a trend for a reduction in the excretion of the PGE metabolite with fish oil. However, pharmacological doses of linoleic acid were administered in this study. BLAIR *et al*. [72] addressed this issue by studying the effect of supplementation with lower doses of ω-6 PUFA, and still demonstrated an increase in the excretion of urinary PGE_2. A diet high in linoleic acid also reduced excretion of the metabolites of thromboxane-A_2, although the relevance of this to asthma or other allergic diseases is not clear.

Summary

We hypothesize that dietary polyunsaturated fatty acid influences the development of allergic sensitization by increasing the formation of prostaglandin E_2; which, in turn, promotes Th2 responses and stimulates the formation of immunoglobulin E. An increase in the amount of linoleic acid in the diet will increase the formation of prostaglandin E_2, while an increase in eicosapentaenoic acid has the opposite effect. This provides an explanation for how the changes in diet that have occurred in the last few decades may have led to the striking increases in allergic disease. It is important to recognize that the changes in lifestyle that have occurred in the developed world have not been limited to changes in the consumption of dietary fat and other factors may also be involved in the increase in the prevalence of asthma and other allergic diseases.

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