

REVIEW

The role of diet in the aetiology of asthma

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Asthma is a respiratory disease characterized by increased airway responsiveness, inflammation and variable airflow obstruction. The prevalence of asthma and associated atopy has increased substantially over the past 30 years in most developed countries [1–4] and appears to have risen in developing countries in relation to the degree of affluence of the population [5–11]. These observations suggest that the prevalence of asthma and atopy is strongly dependent on environmental factors associated with an affluent lifestyle, and have initiated a search for cultural influences that may be implicated.

Although the explanation for the rise in asthma prevalence in developed countries is not known, it has coincided with a marked change in the diet of these nations, with decreased intake of fresh fruit, green vegetables, potatoes, meat, fish and milk, as seen in the United Kingdom [12], a trend that is also seen elsewhere in the developed world. Diet is an environmental factor that changes rapidly with the shift from a rural subsistence to an urban lifestyle, and from a controlled to a free market economy. The hypothesis that an alteration in the diet of nations may be causing the changes in the prevalence of asthma was initially proposed by Burney [13] and later developed by Seaton [14], and has since attracted a great deal of interest. Available evidence falls into two broad categories: epidemiological studies examining the role of differences in dietary intake of specific nutrients in explaining the distribution and incidence of asthma; and intervention studies utilizing dietary or parenteral supplementation to modify the disease. Identification of a food constituent that influences the development or severity of asthma permits the possibility of dietary manipulation as a therapeutic intervention.

This review will consider the published evidence for the effects of individual nutrients on asthma and the possibilities for treatment, concentrating particularly on sodium, magnesium, antioxidants including vitamins C and E, and fatty acids. The evidence reviewed is derived from various sources, including some large epidemiological datasets

which have been used by several independent investigators to explore effects from different nutrients. For convenience, these datasets are summarized now. Four, large, cross-sectional studies explored the role of nutrient intake in asthma by using dietary questionnaires to measure intake of food constituents, and different methods of measuring diseases and outcomes in different populations. The First National Health and Nutrition Examination Study (NHANES I) measured forced expiratory flow rate in 1 s (FEV₁) in 2526 randomly sampled adults aged 30–70 years from the USA [15], and the Second National Health and Nutrition Examination Survey (NHANES II) assessed the relationship between dietary intake and respiratory symptoms in 9074 adults aged 30 years or older [16]. The MORGEN Study measured FEV₁ and forced vital capacity (FVC) in 6555 subjects aged 20–59 years from the Netherlands [17], and we assessed bronchial reactivity and spirometry in 2633 subjects in an adult population aged 18–70 years from Nottingham in the UK [18–20]. There are two large prospective studies of the effect of diet on lung disease. The Nurses' Health Study from The United States contains dietary questionnaire data on 77866 women aged 34–68 years followed since 1980 [21], and is the only prospective study to use diagnosed asthma as an endpoint. The Zutphen Study followed 793 middle aged men in the town of Zutphen in the Netherlands from 1960 to 1985, using an interview with a dietician to assess diet and having an endpoint of chronic non-specific lung disease, a diagnosis based on episodes of respiratory symptoms lasting more than 3 months, or a diagnosis of asthma, chronic bronchitis or emphysema [22]. All of these datasets have been used to address dietary and other hypotheses relating to asthma, and different investigators analysing individual nutrient effects have not always adjusted for effects of other nutrients shown to be related to the outcome in question in other studies. It is therefore sometimes unclear whether effects seen in these analyses are truly independent, although effects seen consistently in different datasets are perhaps more likely to be valid. The effects of different nutrients seen in these and other studies are as follows.

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Sodium

The suggestion that sodium may play a role in the aetiology of asthma was first advanced by Burney, with the observation that regional differences in asthma mortality in men and children (but not women) in England and Wales correlated with table salt purchases [13]. This hypothesis is physiologically plausible in view of the key role of sodium in maintaining nerve and muscle function, and a parallel can be drawn with the emergence of dietary sodium as a significant factor in the aetiology of hypertension, another disease involving smooth muscle dysfunction [23]. In a study of adult men with recent respiratory symptoms, bronchial reactivity was seen to be related to 24 h urinary sodium excretion, with a 10-fold difference in reactivity over the 95% range of sodium excretion in 138 men [24]. A similar association has since been reported in a sample of men of whom approximately half had symptoms suggestive of asthma [25]. In children with asthma, dietary salt intake has been shown to be associated with increased airway reactivity to methacholine, but not with the diagnosis of asthma or the presence of exercise-induced bronchospasm [26]. In a study of 2593 children, a high sodium intake was found to be related to the presence of wheeze in boys, although no association was seen either in girls or with sodium excretion in either gender [27]. Other epidemiological studies have found no evidence in support of this hypothesis, however, with two large cross-sectional population surveys showing no relationship between high urinary sodium excretion and bronchial reactivity in 2020 children [27] or 1702 adults [19], and negative findings in two smaller cross-sectional studies [28,29] and also in a study of 205 adults assessing sodium intake by dietary questionnaire [30].

The first of the clinical intervention studies carried out to date was a small open study that showed a rise in airway responsiveness to histamine in men and women when dietary sodium was increased [31]. Three randomized double-blinded clinical trials have since produced objective evidence of an improvement in several clinical parameters of asthma following a period of sodium restriction compared with sodium supplementation for up to five weeks, although not all of the observed effects were conclusive. Improvements were seen in bronchial reactivity in 14 men but not in 22 women in one study [32], in bronchial reactivity, FEV₁, peak flow, symptom scores and bronchodilator use in 27 men [33] in another study, and in FEV₁ and symptoms but not bronchial reactivity in 14 adults of both sexes [34] in a third study. One similar study found no effect on peak flow or β -agonist usage in 17 subjects [35]. Direct comparison of these studies is difficult because they all used different degrees of sodium restriction and supplementation, with daily sodium supplements varying from replacement [32] to supraphysiological levels [33].

On balance, however, these trials suggest that although dietary sodium does not have a consistent association with bronchial reactivity in the general population, an increase in sodium intake does seem to increase bronchial reactivity and other relevant clinical parameters of asthma, particularly in men. A potential mediator for this effect has been noted in the serum of young men with hyperresponsive airways, which, when incubated with leucocytes from non-atopic subjects, leads to increased intracellular sodium [25]. The important question of the extent to which simple reduction of sodium intake in the normal diet of patients with asthma can contribute to an improvement in asthma control in usual clinical practice remains uncertain, but in view of the simplicity and widespread applicability of this intervention, it merits further investigation.

Magnesium

Magnesium is a predominantly intracellular cation that plays a part in the maintenance of the resting potential across cell membranes; it is also an essential co-factor for enzymes that require adenosine triphosphate, has an anti-inflammatory effect [36], and is involved in the synthesis and replication of RNA and DNA [37]. It is obtained principally from cereals, nuts, green vegetables and dairy produce, although cooking or processing of food leads to depletion of magnesium [38].

We reported epidemiological evidence of a relation between dietary magnesium intake and airway reactivity in a random cross-sectional sample of 2633 adults from a Local Authority Area in Nottingham, UK [20]. The effect of dietary magnesium on bronchial reactivity was identified while exploring potential confounders of a failure to detect an association with sodium [19]. Dietary magnesium intake was measured by semi-quantitative questionnaire and assessed in relation to lung function and allergen skin prick test data. Airway reactivity was measured in 2415 of these individuals by methacholine challenge. After adjusting for the effects of age, sex, height, atopy and smoking, a 100 mg/day higher magnesium intake was associated with a reduction in the relative odds of hyper-reactivity by a ratio of 0.82 and a 27.7 mL higher FEV₁. However, the difference in FEV₁ rose to 68 mL per 100 mg/day higher magnesium intake after adjustment for total kJ intake to allow for confounding by other general nutrient effects. The same incremental difference in daily magnesium intake was also associated with a reduction in the odds of self-reported wheeze in the past 12 months by a ratio of 0.85 adjusted for age, sex, smoking, atopy and kJ intake. Similarly, an association between bronchial reactivity and dietary magnesium was shown in a more recent case-control study from Scotland of 52 subjects reporting respiratory, ocular and nasal symptoms, demonstrating a

dose-effect relationship with a fivefold difference in the risks of bronchial reactivity between the lowest and the highest tertile of magnesium consumption [39]. Comparison of intracellular magnesium levels in asthmatic subjects in relation to healthy controls has produced conflicting results [40–42], although two recent studies have shown an association between decreased bronchial reactivity and intracellular erythrocyte magnesium levels [43,44].

The developing epidemiological evidence that dietary magnesium may be of relevance in the aetiology of asthma has coincided with an increasing consideration of the benefits of intravenous magnesium in the treatment of other diseases, such as myocardial infarction [45] and eclampsia [46], and the realization that magnesium supplementation may have a role in the management of bronchial asthma [47]. Studies on the effect of magnesium supplementation on asthma have been carried out in both stable asthma and during episodes of exacerbation. There is some evidence that in stable asthma, magnesium supplementation may have an effect on asthma control. In a study of 18 stable subjects with asthma, oral magnesium supplementation of 300 mg/day in an open label study over approximately 30 days [48] decreased bronchial reactivity as measured by methacholine challenge, although a randomized placebo cross-over study of 17 stable asthmatic subjects exposed to 400 mg magnesium for three weeks while on a low magnesium diet was only associated with a significant improvement in symptom scores, with no evidence of improvement in objective measures of airflow or airway reactivity [49]. Single dose parenteral administration of magnesium sulphate in a double-blind, placebo-controlled, cross-over study in stable asthma resulted in a bronchodilating effect (approximately 130 mL increase in FEV₁ maximal at 20 min) but with no associated change in bronchial reactivity in this study [50]. Although this is consistent with earlier reports of bronchodilatation with similar doses of intravenous magnesium [47,51], a beneficial effect has not always been observed [52]. Similarly, some studies of parenteral magnesium supplementation in acute asthma have shown evidence of benefit but overall, the results of these studies have been inconclusive [53–57].

In summary, the current evidence suggests that a high dietary magnesium intake may be associated with higher levels of lung function and reduced bronchial reactivity, while magnesium administered systematically has a mild bronchodilator effect, which may be more easily demonstrable in acute exacerbations than in stable disease. Definitive trials of the role of dietary magnesium on asthma are required, and we are presently investigating the effect of magnesium supplements on the control of asthma over 4 months with a placebo-controlled trial.

Potassium

Potassium is the main intracellular cation and has a role in maintaining the trans-membrane potential difference that influences nerve conduction and muscle tone. Morning urinary potassium concentration was shown to be associated with higher levels of bronchial reactivity in a cross-sectional study of 916 boys [27], but results in adults have been conflicting. One study suggested an association between methacholine-induced bronchoconstriction and 24 h urinary potassium excretion [28], while another did not show a relationship in 138 men with respiratory symptoms as assessed by histamine challenge [24]. No association was noted between potassium intake and wheezing or bronchitis in the NHANES II survey [16]. At present, therefore, there is no consistent evidence for the involvement of potassium in the aetiology of asthma.

Antioxidants

Oxidizing free radicals are thought to play a significant role in mediating the pathogenesis of both asthma and COPD, and this has given rise to the hypothesis that relative deficiencies of dietary antioxidants such as vitamin C, vitamin E and selenium may increase susceptibility to these diseases [58]. It is also possible that a diet containing increasing amounts of polyunsaturated fat susceptible to lipid peroxidation has led to a greater requirement for dietary antioxidants compared with 30 years ago [59]. The roles of individual antioxidant nutrients will be considered together with studies of the effects of fruit intake, since this food is a major source of antioxidant vitamins.

Fruit and vitamin C

Epidemiological studies have consistently demonstrated lower levels of pulmonary function in individuals who consume lower levels of vitamin C or foods containing this vitamin. Cross-sectional studies of randomly selected populations have shown positive associations between fresh fruit consumption and lung function in national surveys of 9003 adults [60] and 2650 children [61], with a larger effect on FEV₁ in a subset of subjects who reported wheeze in the latter study. Similarly, evidence supporting the hypothesis that vitamin C influences lung function is available from large cross-sectional studies, although the effect was relatively weak. Data from the NHANES I population from the United States [15] demonstrated a 40 mL difference in FEV₁ between the highest and lowest tertiles of vitamin C intake, although not for vitamin C-rich vegetables. Our study in Nottingham, UK [18], provided consistent results, with a 25 mL higher FEV₁ for each standard deviation or 40 mg in vitamin C intake. A similar effect was seen in the MORGEN

study [17], with a 53 mL increase in FEV₁ between the 10th and 90th percentiles of vitamin C intake, and to a lesser extent in a study of 3085 adults from China, in which an increase of 100 mg vitamin C/day was associated with a rise of 22 mL in FEV₁ [62]. However, no relation between vitamin C and lung function was seen in a smaller study of an older population from England [63]. In terms of symptoms, vitamin C consumption was inversely related to cough but not wheeze in the MORGEN study from The Netherlands [17]. An association between bronchial reactivity and vitamin C intake was shown in a case-control study from Scotland of people with seasonal asthma symptoms, with a sevenfold increase in the risk of bronchial reactivity in the lowest tertile of vitamin C consumption compared with the highest [39].

Plasma vitamin C levels have also been used as a marker of dietary intake, although this needs to be interpreted with caution as plasma levels are reduced in smokers [64] and tend not to vary in relation to higher levels of intake. Plasma vitamin C levels in asthmatic subjects have been found consistently to be lower in both adults [65] and children [66]; raised levels of serum vitamin C appear to be associated with higher lung function [67], lower frequencies of self-reported wheezing and bronchitis in NHANES II [16], and protection against adult onset wheeze in Scotland [68]. Thus, the cross-sectional data on the effect on asthma of dietary fruit and vitamin C intake, and serum vitamin C levels as a marker of intake, consistently show a benefit of higher levels of consumption of fruit and food containing vitamin C.

However, data from prospective longitudinal studies of the development of asthma and pulmonary disease show different effects of the consumption of fruit and vitamin C. The Zutphen study suggested that fruit, but not specifically vitamin C intake was inversely related to the subsequent development of chronic non-specific lung disease [22], and a prospective study of 2171 adults without a history of chronic respiratory disease over a 7-year period showed a more marked fall in FEV₁ in subjects who reduced their fresh fruit consumption the most, compared with those who did not change their dietary fruit intake after adjustment for region, social class and smoking [69]. However, The Nurses' Health Study demonstrated no relationship between dietary vitamin C intake and the subsequent incidence of asthma in a cohort of 77 866 women [21]. The discrepancy between the Zutphen Study and the Nurses' Health Study may possibly be explained by the difference in the gender of the subjects and the different outcome measures used, the chronic non-specific lung disease outcome used in the Zutphen Study encompassing a wider range of diseases, particularly in a group consisting of a large proportion of smokers. Alternatively, a protective effect of fruit may be attributable to fruit constituents other than vitamin C.

Several studies of vitamin C supplementation on bronchial reactivity in asthmatic subjects have shown evidence of improvement and we will concentrate on some of the larger of these. Beneficial effects of vitamin C supplementation in short-term studies (involving less than three days of supplementation) were observed, leading to a reduction in exercise-induced bronchospasm in one double-blind trial [70], and decreased bronchial reactivity to methacholine in others [71,72]. Not all studies support these findings, however, with no beneficial effect of vitamin C supplementation seen in asthmatics as assessed by spirometry [73], in two double-blind studies using histamine challenge 1 h after vitamin C supplementation [74], or in spirometry, airway conduction and antigen-induced bronchospasm after 7 days supplemental vitamin C [75]. The protective effect of vitamin C on methacholine-induced bronchoconstriction has been shown to be attenuated by indomethacin, suggesting that the mechanism of action involves prostaglandin metabolism [71]. In subjects without asthma, a three-day course of vitamin C was shown to confer a protective effect on airway hyper-responsiveness to methacholine induced by nitrogen dioxide exposure [76], while vitamin C and vitamin E together attenuate ozone-induced bronchoconstriction [77]. Similarly, vitamin C, vitamin E and β -carotene over 18 days prevented bronchoconstriction in Mexican street workers exposed to high levels of ozone in a double-blind cross-over trial [78], and the same combination of antioxidants for three months conferred protection against bronchoconstriction after exercise by cyclists during exposure to ozone [79]. The only clinical double-blinded study of longer term supplementation with vitamin C in subjects with asthma demonstrated a reduction in the severity and frequency of asthma attacks during 14 weeks in the Nigerian rainy season in patients receiving vitamin C, compared with a control group [80]. A further double-blind controlled trial of other measures of atopy showed no change in skin testing to antigen or nasal airway resistance after vitamin C supplementation in adults with seasonal allergic rhinitis [81].

Thus, the evidence suggests that consumption of higher quantities of either fruit or vitamin C from all dietary sources is associated with a small, but consistently higher level of FEV₁, that vitamin C in combination with vitamin E and β -carotene confers protection against bronchoconstriction associated with ozone exposure both in the presence and absence of exercise, and that vitamin C supplementation alone may reduce bronchial reactivity. The majority of supplementation studies to date have involved single dose or short-term administration in small numbers of adults. Questions that remain to be answered relate to the identification of the factor or factors responsible for the beneficial effect of fruit consumption on lung function, clarification of the benefit of vitamin C supplementation to subjects with

stable asthma over a longer period of time, and the role, if any, of vitamin C supplementation in acute asthma exacerbations.

Vitamin E

Vitamin E is a fat-soluble micronutrient that is a constituent of the cell membrane and, in conjunction with vitamin C, is thought to contribute to the antioxidant defences against membrane injury [82,83]. Thus, it may also have a protective role in asthma. Vitamin E may also modulate other functions of the cell through effects on membrane stability and permeability, eicosanoid production, suppression of neutrophil migration [82] and inhibition of IgE production [84].

Cross-sectional and case-control studies of the relation between dietary vitamin E and lung function in the general population are conflicting. Two of the larger studies, from England [18] and the Netherlands [17], showed no independent effect of vitamin E after allowing for the effect of vitamin C. Nonetheless, a smaller cross-sectional trial of 178 elderly individuals demonstrated that vitamin E intake was positively associated with lung function, independent of vitamin C intake, in an elderly population [63], and a larger cross-sectional investigation of 29 133 smokers from the Alpha-Tocopherol Beta-Carotene Cancer Prevention study demonstrated that the symptoms of dyspnoea and wheeze were less frequent in relation to increased serum levels or dietary intake of vitamin E [85]. Although no effect of vitamin E intake on bronchial reactivity has been demonstrated in two case-control studies [39,86], a recent nested case-control study from Scotland demonstrated that higher intakes of vitamin E and a raised serum α -tocopherol:triglyceride ratio (adjusting for postprandial variation) were inversely related to adult onset wheeze [68]. A case-control study has also demonstrated lower vitamin E intake in subjects with brittle asthma, as opposed to those with non-brittle asthma or non asthma [87].

In the prospective Nurses' Health Study, the subjects in the highest quintile of vitamin E intake were found to be at reduced prospective risk, compared with the lowest quintile, of incident asthma over 10 years by a factor of about 50% [21]. However, intervention with 5–8 years supplementation to a subset of the Alpha-Tocopherol Beta-Carotene Cancer Prevention study using vitamin E in male smokers had no effect on the subsequent development of symptoms associated with chronic bronchitis, such as cough, dyspnoea and phlegm production [85], although no data have been presented from that study on lung function. Vitamin E with vitamin C and β -carotene in randomized trials protected both Mexican street workers [78] and cyclists [79] against bronchoconstriction after exposure to ozone.

The role or potential of vitamin E in the aetiology of

asthma is therefore still relatively unclear, appearing to be important in the incidence of asthma but not lung function. Further studies of the role of vitamin E in preventing bronchoconstriction, with and without vitamin C and β -carotene, are warranted.

Niacin

Dietary intake of niacin, which acts as a co-factor for a variety of enzymes involved in cellular respiration, was inversely related to the risk of wheezing but not bronchitis in the NHANES II study [16]. No other data are available on the role of this vitamin in asthma.

Selenium

Selenium is essential to the activity of the glutathione peroxidase enzymes, which are involved in lung antioxidant defences [88]. Several investigators have shown lower blood levels of selenium in subjects with asthma [89–94], with conflicting observations on glutathione peroxidase activity [89,90,95,96] which appears to be particularly low in aspirin-induced asthma [97,98]. It is unclear whether these observed low selenium levels are contributing to the development of asthma or are a secondary effect of increased antioxidant consumption. However, independent verification of this relation has not been found, either in a cross-sectional study of selenium levels and bronchial reactivity in a case-control study from Scotland [39], or prospectively in the development of chronic respiratory disease in the Zutphen study [22]. The only intervention study available is a randomized placebo-controlled trial lasting 14 weeks in 24 subjects with asthma which demonstrated a clinical improvement with selenium as assessed by a composite measure of clinical parameters, lung function and pulmonary reactivity, although not for individual components [99]. On current evidence, it is uncertain whether selenium is involved in the pathogenesis, or is of potential value in the treatment of asthma. At an ecological level, there are areas, such as Tibet, China, Siberia and North Korea, where selenium deficiency is reported to be endemic [100] but to date, there is no evidence of increased prevalence of asthma in these countries [101] relative to those with abundant selenium in the diet. The effect of dietary selenium in the aetiology of asthma therefore remains uncertain.

Manganese

Manganese is an essential trace element that is a co-factor in many cellular enzymes including those with antioxidant activity. Only one case-control study to date has investigated the role of manganese in asthma, and this concluded

that manganese dietary intake is inversely related to bronchial reactivity, with an odds ratio of 8 for having increased bronchial reactivity for those in the lowest tertile of dietary consumption compared with those in the highest tertile [39]. Further work is needed to clarify the role of this element and its status in the asthmatic subject.

Vitamin A and β -carotene

β -carotene acts as a dietary precursor for vitamin A, conversion occurring in the small intestine [82]. It is also absorbed intact and has some intrinsic biological activity with antioxidant properties. Most studies have examined these substances individually, but it should be borne in mind that levels of vitamin A and β -carotene are interdependent.

β -carotene

Two, large, cross-sectional studies have suggested that higher levels of dietary β -carotene consumption are associated with higher levels of pulmonary function and reduced respiratory symptoms. The MORGEN study showed that subjects with the highest quintile of intake of β -carotene had a 60 mL higher FEV₁ and 75 mL higher FVC than those with the lowest quintile of intake [17]. The Alpha-Tocopherol Beta-Carotene Cancer Prevention study of 29 133 smokers demonstrated that dyspnoea and wheeze were lower with increased serum levels and dietary intake of β -carotene [85]. Similarly, the Carotene and Retinol Efficacy trial showed that higher serum β -carotene levels were associated with greater baseline FEV₁ in an asbestos-exposed cohort [102]. However, two case-control studies found no evidence of association between β -carotene consumption and bronchial reactivity [39] or adult onset wheeze [68], and two longitudinal prospective studies have found no relationship between dietary β -carotene consumption and the subsequent development of either chronic non-specific lung disease [22] or asthma [21].

Intervention with β -carotene supplements had no effect on decline either of lung function when given with vitamin A for an 11-year period in the Carotene and Retinol Efficacy trial (CARET) [103], or on the development of symptoms in the Alpha-Tocopherol Beta-Carotene Cancer Prevention study when 5–8 years of supplementation was given [85]. However, there may be a benefit when given in combination with other antioxidants [78,79]. Evidence to date suggests, therefore, that dietary β -carotene intake is related cross-sectionally to lung function, but not to the prospective development of asthma. Its role in preventing bronchoconstriction requires further consideration, particularly to tease out its relative contribution in studies with vitamin C and vitamin E.

Vitamin A

Few investigators have explored the role of dietary vitamin

A alone in the pathogenesis of asthma, although studies of the relation between dietary vitamin A and lung function are more numerous. A case-control study demonstrated a decreased intake of vitamin A in subjects with brittle asthma compared with those with non-brittle asthma or controls [87], while data from the NHANES I study from the United States showed that low levels of vitamin A and milk consumption were associated with an increased risk of airway obstruction, particularly in heavy smokers [104]. However, this relationship was not seen in a larger study using data from the Atherosclerosis Risk in Community (ARIC) study [105]. Raised serum retinol in an asbestos-exposed cohort of current and former smokers was associated with a higher FVC but not FEV₁ [102], while elevated serum retinol was a marker of a lower risk of subsequent airway obstruction 5 years later in white males [86].

However, in the prospective Nurses' Health study there was no relationship between vitamin A intake and subsequent development of asthma over a 10 year follow-up period [21] and similarly, the Zutphen study and the CARET study demonstrated no relationship between dietary vitamin A and the risk of subsequent development of disease [22,103]. One very small study (of six subjects with air flow limitation) demonstrated a reversible bronchodilator effect at 30 days [106]. At present, the evidence for an independent role of vitamin A in the development of asthma or chronic airflow obstruction is inconsistent.

Pyridoxine

Observations of altered tryptophan metabolism in subjects with asthma led to the consideration of substances that may account for these changes, particularly pyridoxine, in the pathogenesis of asthma [107,108]. Cross-sectional studies in adult asthmatics demonstrating low levels of serum pyridoxal phosphate have been noted [109], although in children with asthma, levels of a marker of pyridoxine status, erythrocyte aspartate amino transferase, were similar to controls without asthma [110].

The effect of administration of pyridoxine in asthma has been tested in two trials in children. In one open study of 20 cases, pyridoxine was associated with a decrease in the occurrence and severity of exacerbations [108], while in a double-blind study in 76 children with asthma, pyridoxine reduced the number of asthma attacks, symptoms and medication usage compared with the placebo [107]. However, in a similar study in 31 adults who required oral or inhaled steroids for their asthma, there was no improvement in spirometry, symptoms scores or skin test reactivity to histamine [111]. The mechanism of any beneficial effect of pyridoxine in asthma is unclear, and changes in the haemoglobin binding of oxygen [109] or tryptophan metabolism

have been suggested to be important [107]. An alternative explanation may be an effect involving magnesium metabolism, since pyridoxine elevates red blood cell magnesium levels [112], and pyridoxine depletion leads to an increase in magnesium excretion that is reversed with pyridoxine supplementation [113]. One factor complicating the cross-sectional studies of pyridoxine levels in asthmatics is that theophylline can reduce serum pyridoxal phosphate levels [114] and thus distort any observations between those with and without asthma. It is paradoxical that a known bronchodilator, such as theophylline, should decrease pyridoxine levels in the blood yet improve asthma control, thus suggesting that the role of pyridoxine in asthma, if one exists, may be complex.

Copper

Copper may theoretically influence lung function, possibly by its presence in superoxide dismutase, influencing antioxidant status [115]. Few studies have specifically addressed this question. In the NHANES II study, the serum zinc:copper ratio was noted to be inversely related to lung function [16], while in a subgroup of males from the Normative Ageing study who had never smoked, the copper concentration in drinking water was associated with higher measures of lung function [116]. A similar study in Nigerian children demonstrated lower plasma levels of copper in those with asthma [117].

Zinc

There are few studies on the role of zinc in asthma, but a case-control study from Scotland showed an increased risk of seasonal allergic symptoms in the lowest tertile of dietary zinc [39], while, as noted above, the zinc:copper ratio was inversely related to lung function in NHANES II [16].

Fatty acids

The hypothesis that the consumption of dietary fatty acids can influence the development and activity of an inflammatory disease such as asthma is attractive in view of the complex metabolic role that fatty acids play in cell metabolism and structure. During the period of increasing asthma prevalence in England and Wales, dietary consumption of fatty acids has also changed, with a marked increase in the intake of omega-6 polyunsaturated fats and a decrease in saturated fatty acids [59]. Support for the hypothesis that fat intake may be important is available from a case-control study showing an association of higher fat intake with adult onset wheeze in Scotland [68], and a cohort study from

Malmö in which men with asthma had a higher intake of dietary fat [118].

At present, the role of fatty acids on cell function and disease is poorly understood, and, as many of the studies available have utilized *in vitro* or animal models, the relevance to humans remains unclear. However these merit more detailed review as many observations may be pertinent to the pathogenesis of asthma. Fatty acids are classified as saturated or unsaturated depending on the presence of carbon double bonds that alter molecular shape and are susceptible to peroxidation. The metabolically influential polyunsaturated fatty acids can be divided into two broad groups based on the position of carbon double bonds: the *n*-6 fatty acids, which are precursors for arachidonic acid and inflammatory mediators produced by lipo-oxygenase and cyclo-oxygenase such as prostaglandins and leukotrienes [119]; the *n*-3 fatty acids, which competitively inhibit the metabolism of arachidonic acid and also result in the production of less active prostanoids [120]. These latter, therefore, have the potential to reduce airway inflammation and prevent bronchoconstriction. Fatty acids also have a structural role in the cell membrane, influencing membrane properties including beta-adrenergic receptor function [121] and membrane-bound enzymes such as Na⁺K⁺ ATPase responsible for membrane electrolyte transport [122], all of which are thought to play a role in the pathogenesis of asthma. Fatty acids also have effects on the immune system which may be influential in the pathogenesis of asthma. Polyunsaturated lipids decrease the synthesis of cytokines (IL-2 and γ -interferon) associated with the development of non-atopic Th1 lymphocyte lines [123,124], and may therefore contribute to the shift from Th1 to Th2 lymphocyte phenotype that is implicated in the pathogenesis of asthma and atopy [125]. Higher concentrations of unsaturated fatty acids enhance the production of IgE and inhibit that of IgM, IgG and IgA, and the observation that this effect may be replicated by the oxidizing agent, hydrogen peroxide, and diminished by vitamin E suggest that this may be due to increased lipid peroxidation [84]. The end result, again, is likely to be a more atopic phenotype. Polyunsaturated fatty acids also influence lymphocyte activity by their effects on cellular adhesion [126–128], eosinophil chemotaxis [129], and the ability to present and recognize antigen that underpins the immune response [128,130]. More detailed consideration of these potential effects on lymphocyte function is beyond the scope of this article, but they have been recently reviewed by Calder [123]. It is possible to construct a hypothesis that an imbalance of the inflammatory mediators found in the airways of asthmatic subjects and of the atopic/non-atopic lymphocytes that mediate the disease, and changes in the tone and reactivity of the airways, are influenced by changes in the dietary fats, leading to an increase in asthma prevalence.

n-6 Polyunsaturated fatty acids

Relative and absolute consumption of polyunsaturated fatty acids has increased over recent decades, the ratio of polyunsaturated to saturated fatty acids in the diet in the UK increasing from 0.22 in 1970 to 0.40 in 1990 [12]. The enhanced use of foods such as margarine that are rich in polyunsaturated fatty acids has been noted to be greater in genetically similar populations with higher incidences of atopic disease in both Germany and Finland [59]. Data from the former East Germany suggest that hay fever is positively related to the pattern of polyunsaturated fat consumption from margarine in a dose-related manner, and changes in the consumption of butter showed an inverse association with hay fever and atopic sensitization as assessed by skin prick tests [131]. The NHANES II study did not show any relationship between linoleic acid consumption and respiratory symptoms [16], but the prospective Zutphen Study demonstrated a positive association between consumption of the *n-6* fatty acid linoleic acid and the development of chronic non-specific lung disease [22]. However, the Nurses' Health Study showed no relation between linoleic acid consumption and development of asthma [21]. The only two double-blind intervention studies with an *n-6* polyunsaturated fatty acid used evening primrose seed oil and demonstrated no benefits [132].

n-3 Polyunsaturated fatty acids

Epidemiological studies of the effects of *n-3* fatty acids have predominantly measured the effect of diet on lung function, and much of the available evidence therefore pertains to chronic obstructive airways disease rather than asthma. A large survey of 3450 individuals in Norway using a postal questionnaire found no clear correlation between fish intake and respiratory symptoms [133], although a smaller study of Australian children did suggest an inverse relationship between weekly oily fish intake and asthma [134]. At present, this is the only study specifically providing evidence of a link between fatty fish consumption and asthma. Dietary fish intake was associated with higher spirometry readings in the NHANES I study [135], and two large cross-sectional surveys from the United States found that a higher dietary intake of *n-3* fatty acids was inversely associated in a dose-related manner to the risk of chronic pulmonary disease in both current smokers and ex-smokers from the ARIC study [136], and that lung function was higher among those with a high fish intake in a population of current smokers from the Honolulu Heart Program [137]. Data from the second National Health and Nutrition Examination survey suggested a protective effect of fish consumption, the main dietary source of *n-3* fatty acids, against symptoms of bronchitis and wheezing in an initial single factor

analysis, although this effect disappeared after consideration of the effects of other nutrients and socio-economic factors [16]. The Nurses' Health study, the only prospective study of the relationship between fatty acid consumption and development of asthma, found no association with any fatty acid intake over 10 years [21], while the Zutphen study demonstrated no relation between *n-3* polyunsaturated fatty acid and the development of chronic non-specific lung disease [22].

Intervention studies of eicosapentaenoic acid (EPA), an *n-3* fatty acid and the active ingredient in fish oils, in asthma have generally been disappointing, and have not demonstrated the marked anti-inflammatory effect expected from a competitive inhibitor of arachidonic acid metabolism. Placebo-controlled, randomized, short-term trials in severe asthmatics showed no clinical effect, despite suppressing mediator generation and neutrophil chemotaxis [138]. Similarly, EPA given to milder asthmatics showed no effect as assessed by clinical symptoms or bronchial reactivity in adults, despite attenuation of neutrophil function [139]. Fish oil supplements also had no effect on lung function and symptoms in a study of asthmatic children aged 8–12 years [140]. Supplementation with EPA for 6 months similarly showed no clinical benefit in patients with pollen-induced asthma and seasonal hay fever [141]. In aspirin-intolerant subject, EPA led to a deterioration of asthma, possibly due to an additional effect of cyclooxygenase inhibition resulting in increased levels of bronchoconstricting leukotrienes [142]. The only positive studies demonstrating an effect of intervention with EPA on measurements of asthma suggested a 23% significant improvement in FEV₁ at 9 months of a 12-months course of double-blind supplementation in 12 subjects [143], and the less clinically relevant attenuation of the airway late response to allergen in 17 atopic individuals [144]. Adjustment of the *n-3:n-6* polyunsaturated fatty acid ratio by fish oil supplementation identified a group of nine responders out of 19 asthmatic subjects as assessed by improvement in methacholine challenge, distinguished from non-responders by the rise in 5-series leukotriene excretion and suggesting a heterogeneity of those studied [145].

Thus, the role of dietary polyunsaturated fatty acids in the pathogenesis of asthma remains largely undefined, but the present epidemiological evidence suggests that *n-3* polyunsaturated fatty acids may have a protective effect on lung function, particularly in smokers. However, it may be that the absolute and relative quantities of other polyunsaturated and saturated fatty acids are equally important, as suggested by Chang [146], and that an excess of other polyunsaturated fatty acids such as the *n-6* subset may be influential. This remains an area of debate, however [147]. A recent ecological study has demonstrated an association between symptoms of atopy and consumption of the *trans* fatty acids that

are found in industrially hydrogenated vegetable fats and dairy products, and no relationship with national monounsaturated or polyunsaturated *cis* fatty acids [148], thus suggesting a new line of enquiry. Certainly, further work remains to be done in this area, particularly focusing on appropriate cross-sectional studies and intervention trials of longer duration.

Summary

On the basis of the current knowledge, we would argue that there is relatively persuasive evidence that reduced magnesium and vitamin C intake, and increased sodium consumption, may be involved in the aetiology of asthma, though these hypotheses remain unproven. The status of other nutrients, such as vitamin E, pyridoxine, manganese, copper, potassium, selenium and fatty acids, is even less clear but merit further investigation. Overall, there is a general consistency in the evidence that an unhealthy diet seems to be associated with an increased risk of asthma and/or chronic obstructive pulmonary disease, but the mechanisms and importance of these associations in therapeutic and public health terms remains to be resolved.

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