Proceedings of the Nutrition Society (2010), **69**, 1–10 doi:10.1017/S0029665109991753
 First published online 8 December 2009

A Meeting of the Nutrition Society, hosted by the Irish Section, was held at Queen's University Belfast on 17–19 June 2009

Symposium on 'Dietary management of disease'

Session 1: Allergic disease
Nutrition as a potential determinant of asthma

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Asthma is characterised by chronic lung airway inflammation, increased airway responsiveness and variable airflow obstruction. In Westernised countries asthma is a public health concern because of its prevalence, associated ill health and high societal and healthcare costs. In recent decades there has been a marked increase in asthma prevalence, particularly in Westernised countries. It has been proposed that changing diet has contributed to the increase in asthma. Several dietary hypotheses exist; the first relates the increase in asthma to declining dietary antioxidant intake, the second to decreased intake of long-chain *n*-3 PUFA and increasing intake of *n*-6 PUFA. Vitamin D supplementation and deficiency have also been hypothesised to have contributed to the increase in asthma. Observational studies have reported associations between asthma and dietary antioxidants (vitamin E, vitamin C, carotenoids, Se, flavonoids, fruit), lipids (PUFA, butter, margarine, fish) and vitamin D. However, supplementing the diets of adults with asthma with antioxidants and lipids has minimal, if any, clinical benefit. There is growing interest in the possibility that childhood asthma is influenced by maternal diet during pregnancy, with studies highlighting associations between childhood asthma and maternal intake of some nutrients (vitamin E, vitamin D, Se, PUFA) during pregnancy. It has been suggested that maternal diet during pregnancy influences fetal airway and/or immune development. Further intervention studies are needed to establish whether modification of maternal nutrient intake during pregnancy can be used as a healthy low-cost public health measure to reduce the prevalence of childhood asthma.

Asthma: Diet: Antioxidants: PUFA: Vitamin D

Asthma is a chronic inflammatory disorder of the lung airways associated with increased airway responsiveness and variable airflow obstruction. Typical symptoms include periodic wheezing, breathlessness, paroxysmal cough and chest tightness, and severity ranges from occasional minor symptoms to disabling persistent severe symptoms and/or frequent life-threatening exacerbations. Asthma is a public health concern in Westernised countries because of its prevalence, associated ill health and high societal and healthcare costs[1–3]. In the UK 5·2 million individuals receive treatment for asthma, 1·1 million of whom are children. Asthma is responsible annually in the UK for an estimated 12·7 million lost working days, 4·1 million general practitioner consultations and about 70 000 hospital admissions[1,2]. It has been estimated that asthma costs the UK economy about £$2{\cdot}3 \times 10^9$ annually in lost productivity, benefits and National Health Service costs[1,2].

Asthma and the allergic diseases of atopic eczema and allergic rhinitis (hayfever) are characterised by inflammatory processes, with T-helper (Th)-cell responses of the Th2 phenotype being considered crucial for the initiation and maintenance of asthmatic and allergic inflammation[4]. Cytokines such as IL-4, IL-5 and IL-13 secreted by Th2 cells are important mediators of asthmatic and allergic inflammation that is characterised by elevated IgE, mast-cell degranulation and eosinophilic inflammation[4,5]. There is increasing interest in the role of regulatory T-cells in the pathogenesis of asthma and allergic disease because of their ability to directly inhibit both Th1 and Th2 responses[6]. Although immunologically-mediated

Abbreviations: CBMC, cord blood mononuclear cell; IFN-γ, interferon-γ; Th, T-helper.

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inflammation plays a central role in asthma, it appears that the airway epithelium contributes to the airway inflammatory response[7,8]. The airway epithelium of individuals with asthma appears to be intrinsically abnormal, with increased susceptibility to injury and impaired ability to repair resulting in a chronic pro-inflammatory milieu and airway remodelling[7,8].

The recent increase in asthma prevalence

Since the 1960s there has been a marked increase in asthma prevalence throughout the world, particularly in Westernised countries[3,9]. For example, in the UK the lifetime prevalence of parentally-reported asthma in schoolchildren living in Aberdeen was approximately 4% in 1964, whereas by 2004 it had increased to approximately 26%[10,11]. Although recent studies suggest that asthma prevalence has reached a plateau and might even be declining, asthma remains the most common chronic disease of childhood requiring medication in the developed world[9,12]. The recent trends in asthma are most likely to be a consequence of changing environmental exposures rather than changing genetic susceptibility, and current research into the environmental aetiology of asthma is driven by four hypotheses. It has been hypothesised that the increase in asthma is a consequence of increasing exposure to major perennial allergens such as house-dust mite (*Dermatophagoides pteronyssinus*), because modern housing in general favours the mite and more time is being spent indoors[13]. The 'hygiene hypothesis' emphasises altered exposure to micro-organisms because of improved hygiene, cleanliness and widespread antibiotic usage[14]. Recently, it has been suggested that the increase in asthma has resulted from increasing obesity and declining physical activity, especially in children[13]. In the past decade, changing diet has emerged as a somewhat surprising contributory environmental factor to the increase in asthma.

Asthma: dietary hypotheses

Antioxidants

Four hypotheses relate increasing asthma prevalence to changing diet. In 1994 it was hypothesised that the increase in asthma is a consequence of declining dietary intake of antioxidants[15]. This hypothesis was based on the observed increase in asthma at the same time as the decline in dietary intakes of antioxidant-rich foods. European Se intake and blood Se concentrations have declined, probably because of increased use of European grain and changes in bread-making technology[16]. In the UK average Se intake has fallen from 60 µg/d in 1975 to 30–40 µg/d currently[16,17]. In the UK vitamin C intake remained relatively stable between 1980 and 2000[18]. The limited data on UK vitamin E intake suggest little change from 10·8 mg/d in 1994 to 10·7 mg/d in 2004–5[19]. However, extrapolation of the 2000–1 National Diet and Nutrition Survey using the UK National Food Surveys suggests that vitamin E intake in the early 1950s was probably higher at approximately 13–15 mg/d, perhaps because of increased consumption of green vegetables and bread and cereals[18,20]. The mechanism proposed in the original antioxidant hypothesis relates declining lung antioxidant defences to increased oxidant-induced airway damage, airway inflammation and asthma[15]. Whilst plausible, the evidence now suggests that this oxidant–antioxidant model is most probably a minor mechanism and that biological effects independent of antioxidant properties are more plausible.

PUFA

In 1997 changes in dietary fat intake were highlighted and it was suggested that changes in dietary fat intake may have contributed to the increase in asthma[21]. Dietary intake of saturated fats (butter and lard) has decreased and consumption of *n*-6 PUFA present in margarine and vegetable oils has increased, probably in response to public health measures to reduce CHD[21]. Also highlighted was the decreasing dietary intake of oily fish rich in long-chain *n*-3 PUFA, and it was proposed that increasing intake of *n*-6 PUFA and decreasing intake of *n*-3 PUFA, particularly those derived from oily fish, had contributed to the increase in asthma. A suggested mechanism relates the increased dietary *n*-6:*n*-3 PUFA to increased arachidonic acid levels in inflammatory cell membranes and consequent increased synthesis of PGE_2 by the action of cyclooxygenase-2 on arachidonic acid[21]. *In vitro*, PGE_2 suppresses Th1 differentiation and promotes the Th2 phenotype associated with asthma and allergic disease. Although elegant, this proposed mechanism is probably an oversimplification because the immunological consequences of changing PUFA intake are far more complex than the hypothesis suggests. PGE_2 has been reported to have other actions, e.g. suppressing dendritic cell leukotriene B_4 secretion by an IL-10-dependent mechanism[22]. The enzyme pathways that metabolise arachidonic acid also metabolise *n*-3 PUFA such as EPA to 3-series PG and 5-series leukotrienes that possess biological activity, albeit less potent than arachidonic acid metabolites. Furthermore, both *n*-3 and *n*-6 PUFA can modulate T-cell function directly through effects on cell membrane fluidity, cell signalling and gene transcription[23] and *n*-3 PUFA influence the ability of antigen-presenting cells to present antigen to T-cells[24].

Vitamin D

Two contradictory hypotheses relate vitamin D to asthma and allergy. In 1999 it was hypothesised that the increase in asthma and allergy is a consequence of widespread rickets prophylaxis with vitamin D supplements in Westernised countries[25], highlighting the effects of vitamin D in promoting Th-cell differentiation towards the Th2 phenotype[26,27]. In contrast, in 2007 the widespread vitamin D insufficiency in Westernised countries was highlighted and it was hypothesised that the increase in asthma is a consequence of widespread vitamin D insufficiency[28]. The increasing tendency to stay indoors and the promotion of sunshine avoidance to prevent skin cancer and the inability to compensate by diet-sourced vitamin D are the most

likely reasons for inadequate vitamin D status. The effects of vitamin D on promoting regulatory T-cell populations were also highlighted[29,30] and it was suggested that vitamin D insufficiency promotes the development of asthma and allergy by reducing the inhibitory effect of regulatory T-cells on Th2 immune differentiation[28].

Observational studies of antioxidants

Many observational epidemiological studies have related dietary antioxidants to asthma and allergic outcomes[31]. Most studies have been of cross-sectional or case–control design and studies in adults predominate. These observational studies are beset with the usual problems of quantifying dietary intake, but in addition individuals with asthma and allergies may alter their diet because of their disease. Furthermore, reduced blood antioxidant levels may be a consequence of the systematic oxidant stress associated with the inflammatory processes of asthma[32].

Several studies have reported associations between asthma and reduced vitamin E status[31]. The Nurses' Health Study has reported low vitamin E intake to be associated with an increased incidence of asthma over a 10-year period[33] and in Saudia Arabia a case–control study has reported childhood asthma to be associated with reduced dietary vitamin E intake[34]. Reduced dietary and blood vitamin C has been associated with reduced lung function in adults[35] and an increased likelihood of asthma in adults[36] and children and adolescents[37,38]. Asthma has also been reported to be associated with reduced blood carotenoid concentrations in adults[39,40] and children[37,38]. Asthma has been associated with reduced Se status in case–control studies. Dietary Se intake has been reported to be reduced in adults with asthma[41] and blood Se levels and glutathione peroxidase activity has been reported to be reduced in adults[42,43] and children[44] with asthma. Several studies reporting associations between foods and asthma have highlighted the flavonoid content of the foods as possible antioxidants of interest. In adults apple consumption has been associated with a reduced likelihood of asthma[41] and in children daily consumption of bananas and apple juice from concentrate have been independently associated with a reduced likelihood of wheezing symptoms[45]. A high intake of 'fruity vegetables', citrus fruit and kiwi fruit has been reported to be associated with a reduced likelihood of wheezing outcomes in children[46–48]. The Mediterranean diet has been associated with a reduced likelihood of asthma and wheezing in children[46,49].

Antioxidant intervention in established asthma

The epidemiological data suggest that asthma is associated with reduced blood levels and/or reduced dietary intake of the antioxidants vitamin C, vitamin E, some carotenoids, Se, flavonoids and antioxidant-rich fruits[50–52]. However, these studies cannot differentiate between the possible roles of antioxidants in the aetiology of asthma and the effects of asthma on antioxidant intake and metabolism. Whilst these issues have been partly addressed by studies of antioxidant supplementation in adults with asthma, there remains the need for intervention studies investigating the potential for antioxidant supplementation to primarily prevent asthma.

A Cochrane review of vitamin C supplementation in asthma has concluded that there is insufficient evidence to recommend vitamin C in asthma treatment[50]. A randomised controlled trial of Se supplementation in subjects with mild asthma has reported no beneficial effects on any of the variables measured[51] and vitamin E supplementation was not found to improve any variable of asthma control in a randomised controlled trial conducted in subjects with mild to moderate asthma[52]. Whilst these studies do not support the use of single antioxidant supplements as adjuncts to conventional therapy for asthma, there is still scope for studies of antioxidant combinations and studies in children.

Observational studies of PUFA

Many observational epidemiological studies have related lipid status to asthma and allergic outcomes. The majority of studies have investigated children, perhaps reflecting the focus of the original lipid hypothesis on the effects of PUFA on the first interactions between Th-cells and allergens. Several studies have reported beneficial associations between fish intake and reduced risk of asthma in adults[53,54] and children[55,56]. The risk of current asthma is markedly reduced in children who eat fresh oily fish[55] and in adults wheeze and asthma are more likely if they infrequently consume fish[53]. Fish intake has been associated with an increased risk of asthma in children; however, the reported association was not adjusted for potential confounding by socio-economic factors[57].

In addition to fish, surrogate markers for PUFA intake that have been studied include oils, butter and margarine. Although an increased dietary intake of margarine has been associated with an increased likelihood of allergic outcomes[58], several studies have reported associations between asthma outcomes and margarine and butter intake[59–61]. In adults high margarine intake has been associated with an increased likelihood of adult-onset asthma[60] and in children regular margarine consumption has been associated with an increased likelihood of wheezing symptoms[61]. The use of PUFA in spreads and cooking oils has been linked to recent asthma in children[62], and polyunsaturated oil intake has been associated with an increased risk of childhood wheezing symptoms[56].

Associations have been reported between asthma outcomes and dietary intakes and blood concentrations of individual PUFA[63–66]; however, many of these studies are characterised by numerous comparisons and a relative paucity of significant associations. A study that has quantified the dietary intake of individual PUFA by children has reported childhood wheezing to be more likely with increasing intakes of total PUFA, total *n*-3, total *n*-6 and linoleic acid[63]. Current asthma in children has been reported to be more likely with higher *n*-6 PUFA:*n*-3 PUFA[64]. Blood PUFA concentrations in adults and children have similarly been related to asthma and wheeze,

with increasing serum levels of linoleic acid being associated with reduced childhood wheeze and asthma, whereas increasing arachidonic acid levels have been associated with an increased risk of childhood wheeze and asthma[65]. The same study has shown increasing linolenic acid levels and linolenic acid:linoleic acid to be associated with increased wheeze and asthma outcomes[65]. In adults no consistent associations between plasma *n*-3 PUFA levels and asthma outcomes have been found, but current asthma have been shown to be associated with increasing plasma dihomo-γ-linolenic acid levels[66].

The observational data consistently report beneficial associations between fish intake and asthma; however, the studies of individual PUFA suggest that both *n*-3 and *n*-6 PUFA appear to be adversely and beneficially associated with asthma outcomes. Whilst these studies support an association between lipids and asthma, they provide little evidence to support the original lipid hypothesis.

PUFA intervention in established asthma

Whilst the observational studies suggest an association between PUFA and asthma they cannot elaborate on the temporal associations between diet and asthma and whether the associations observed have contributed to the aetiology of asthma or are a consequence of disease. These issues have been addressed to some extent by intervention studies that have investigated the therapeutic potential of *n*-3 PUFA supplements (usually in the form of fish oil capsules) in established asthma and in the primarily prevention of childhood asthma.

A Cochrane Review of marine *n*-3 PUFA supplementation in asthma has concluded that there is no convincing evidence that marine *n*-3 PUFA supplementation leads to an improvement in asthma control[67]. The review highlights two exemplary randomised controlled trials of *n*-3 PUFA supplementation that are nevertheless excluded from the review. In elite athletes with exercise-induced bronchoconstriction *n*-3 PUFA supplementation reduces exercise-induced bronchoconstriction and urinary and blood inflammatory markers[68]. It is unlikely that these observations can be translated to non-elite non-athletic individuals with asthma who are not exercising to volitional exhaustion. In a subsequent study subjects with asthma with exercise-induced bronchoconstriction were supplemented with *n*-3 PUFA, which was found to reduce rescue bronchodilator use, exercise-induced bronchoconstriction and sputum inflammatory markers[69]. The clinical applicability of the latter study is limited by the cessation of all asthma maintenance therapies during the study.

Studies of *n*-3 PUFA supplementation conducted since the Cochrane review[67] have reported conflicting results. *n*-3 PUFA supplementation has been reported to reduce markers of bronchial inflammation but to have no clinical benefit in subjects with house-dust mite-sensitised asthma[70]. In another small study *n*-3 PUFA supplementation of women with asthma was not found to be associated with any improvement in inflammatory markers, asthma control or lung function[71].

Most studies of *n*-3 PUFA (and antioxidant) supplementation have been conducted in adults and there is a need for well-conducted studies in children. Recently, it has been reported that *n*-3 PUFA, vitamin C and Zn supplementation of children with asthma, either individually or in combination, improves asthma control, lung function and inflammatory markers[72]. At the present time, however, there is little evidence to support the use of *n*-3 PUFA as adjuncts to conventional therapy in asthma.

Early-life influences in the aetiology of asthma

Although the current evidence suggests that antioxidant and/or *n*-3 PUFA supplementation have little clinical beneficial effect, there is increasing interest in the notion that early-life diet influences the development of asthma. It is now evident that early-life factors play a critical role in the development of asthma and allergy[73]. Anthropometric and lung function measurements at birth are associated with the development of asthma and allergic disease during childhood and adulthood[74,75] and maternal smoking during pregnancy increases the risk of childhood asthma[76]. In addition, neonatal *in vitro* cord blood mononuclear cell (CBMC) responses after stimulation with allergens have been shown to be associated with recognised risk factors for asthma[77] and the subsequent development of childhood asthma and allergic disease[78].

Maternal intakes of some antioxidants, PUFA and vitamin D during pregnancy have been highlighted as potential determinants of childhood asthma. The concept that diet primarily influences asthma aetiology during fetal development might explain the ineffectiveness of dietary supplementation in adults with asthma discussed earlier. It has also been suggested that the associations reported between antioxidants and asthma in older children and adults are indirect reflections of associations with maternal diet during pregnancy[79]. Habitual dietary patterns are established in early childhood and are influenced by parental dietary habits such that there are correlations between the diets of parents and their children, and within individuals between adult and childhood diet[80,81].

The postulated mechanisms by which maternal diet during pregnancy could influence the development of asthma in children have focused on fetal airway and immune development because of the potential for small changes in nutrient status to exert disproportionately potent irreversible long-term influences on the development of childhood asthma. Airway development occurs predominantly antenatally and is nearly complete by birth; subsequent development is limited to increases in length and diameter[82]. Disturbances of respiratory epithelial and mesenchymal development, particularly branching morphogenesis, have been implicated in the pathogenesis of asthma[7,8] and it is possible that suboptimal fetal nutrient status adversely affects respiratory epithelial and mesenchymal development resulting in suboptimal early-life airway function. Such an adverse effect on fetal airway development will be associated with an increased risk of developing asthma because reduced neonatal lung function

is associated with an increased risk of wheezing and asthma in later childhood[74,83].

Early-life dietary influences on the initial interactions between the Th-cells and allergens have the potential for long-term irreversible effects. Any suboptimal nutritional deviation of initial encounters between allergen and Th-cells towards the Th2 phenotype are likely to be disproportionately exaggerated by the natural immunoregulatory mechanisms that promote further Th-cell differentiation towards the Th2 phenotype and inhibit development of the reciprocal Th1 phenotype[5]. Whilst it seems highly likely that neonates are exposed to allergen fairly soon after delivery, there is debate as to whether the fetus is exposed to allergens and, if so, whether such exposure influences the immune development, asthma and allergic disease[84]. The concept that PUFA influence the earliest interactions between the immune system and allergens is inherent to the original lipid hypothesis and may be the reason why most studies in this field have focused on the early-life influences of PUFA. There are relatively few studies of early-life influences of antioxidants and vitamin D.

Early-life lipid status and asthma

Maternal and infant dietary intakes of foods pertinent to the lipid hypothesis during pregnancy have been associated with childhood asthma and allergic disease. In the Children's Health Study maternal intake of oily fish during pregnancy was found to be associated with a reduced likelihood of asthma in children at age 5 years; however, this association was limited to mothers with asthma and maternal diet was assessed >10 years after the pregnancy[85]. In the prospective Dutch Prevention and Incidence of Asthma and Mite Allergy birth cohort study the daily intake of foods containing milk fat (butter, full cream milk, milk products) at age 2 years was shown to be associated with reduced likelihood of asthma and/or wheeze at the age of 3 years[86].

PUFA concentrations of umbilical cord blood have been related to the subsequent development of childhood asthma and allergic disease with complex and somewhat contradictory results. The UK Avon Longitudinal Study of Parents and Children Study is the largest study relating wheeze and eczema in the first 42 months of life to erythrocyte-membrane PUFA composition of cord blood and maternal blood at 20 weeks of gestation[87]. Although no associations were demonstrated with maternal PUFA concentrations, several associations with cord blood PUFA concentrations were demonstrated; however, because of the large number of statistical comparisons performed, the authors conclude that it seems unlikely that fetal exposure to *n*-3 and *n*-6 PUFA is an important determinant of early-childhood wheezing and allergic disease[87]. The potential for PUFA to influence the first interactions between the immune system and allergens has been investigated in the US Project Viva birth cohort, which has reported increased cord plasma EPA and arachidonic acid concentrations to be associated with reduced CBMC proliferative and interferon-γ (IFN-γ) responses[88]. In addition, higher cord plasma linoleic acid was shown to be associated with increased IL-13 responses[88]. The similarity of the associations with *n*-3 and *n*-6 PUFA, whilst consistent with some of the observational studies outlined earlier[63] are at variance with the lipid hypothesis. The findings are however consistent with the observation that IFN-γ responses of murine splenic lymphocytes are reduced by both *n*-3 and (less potently) *n*-6 PUFA supplementation[89]. Possible explanations for the observations could be the direct effects of *n*-3 and *n*-6 PUFA on Th-cells and/or non-PGE_2 metabolites. Alternatively, *n*-3 and *n*-6 PUFA may be influencing regulatory T-cells[6].

Although further observational work is required, a number of early-life intervention studies based on the original lipid hypothesis have been conducted. As a follow-up to a Danish intervention study investigating the effects of fish oil supplementation on pregnancy outcomes, registry data were used to ascertain the asthma status of children born to women who had supplemented their diets from 30 weeks of gestation with fish oil or olive oil and a further group of women who had been randomised to take no capsules. When compared with the children whose mothers received olive oil, the children of women receiving the fish oil supplement were less likely to develop asthma[90]. Unfortunately, it cannot be concluded from this study that fish oil supplementation during pregnancy reduces the likelihood of childhood asthma because the children of women nominally taking no capsules during pregnancy had asthma outcomes remarkably similar to those of the fish oil-supplemented group[90]. This surprising association may have been a consequence of cross-contamination of study groups, with women allocated to 'no capsules' choosing to take commercially-available fish oil capsules.

The potential for PUFA to influence the first interactions between the immune system and allergens has also been investigated by an intervention study in which the CBMC responses of children of women supplemented with *n*-3 PUFA-rich fish oil from 20 weeks of gestation were compared with those of women who had received control olive oil capsules[91]. Maternal fish oil supplementation was found to be associated with a general reduction in CBMC cytokine responses; however, only the reduction in IL-10 response after stimulation with cat allergen was found to be significant ($P = 0{\cdot}046$). These observations suggest that *n*-3 PUFA in pregnancy may influence neonatal immune responses to allergens; however, it remains to be seen whether the immunological associations are translated into clinical effects.

The Childhood Asthma Prevention Study is a randomised controlled trial that has investigated the potential for preventing asthma by supplementing the diets of infants with *n*-3 PUFA[92]. Infants were supplemented with *n*-3 PUFA-rich fish oil at the commencement of formula feed or at 6 months if breast-fed. Although *n*-3 PUFA supplementation was found to be associated with reductions in wheeze outcomes in the first 18 months of life, at follow-up at 3 and 5 years minimal, if any, beneficial effect was found to be indicated and it was concluded that *n*-3 PUFA-rich fish oil supplementation reduces the likelihood of early-childhood wheeze but has no effect on the likelihood of asthma, wheeze and allergic disease in later

childhood[92]. Although a negative trial, the study highlights a number of issues relating to PUFA supplementation trials. It is possible that *n*-3 PUFA intervention commenced 'too late', and given the evidence that *n*-3 and *n*-6 PUFA may have similar effects on Th-cells[63,88,89] the use of *n*-6 PUFA supplementation in the control group may have masked any beneficial effect of *n*-3 PUFA supplementation.

Maternal antioxidant intake during pregnancy and childhood asthma

The potential for maternal antioxidant intake during pregnancy to modify the risk of childhood asthma has been highlighted by several birth cohort studies. The reported associations also support the notion that biological properties of antioxidants independent of antioxidant activity influence fetal airway and immune development. The UK Avon Longitudinal Study of Parents and Children Study has reported low umbilical cord Se concentrations to be associated with an increased likelihood of persistent wheeze in children up to 42 months[93]. A subsequent Scottish birth cohort study has similarly reported that low maternal plasma Se concentrations in pregnant women and neonates are associated with an increased likelihood of wheezing at 2 years[94]. However, by age 5 years there is an absence of associations between maternal and/or neonatal Se status and asthma outcomes, perhaps reflecting a short-term effect of maternal Se intake during pregnancy on early-life immune responses to viral infection[94].

The Project Viva cohort study has reported associations that suggest that maternal diet during pregnancy influences neonatal immune responses to allergens and childhood wheezing symptoms. Low maternal intake of vitamin E and some carotenoids (β-carotene, leutein + zeaxanthin) during pregnancy is associated with increased CBMC proliferative responses[95]. The study also reports that low maternal vitamin E intake during pregnancy is associated with an increased likelihood of wheeze outcomes in children at age 2 years[96]. A Scottish birth cohort study has also reported that low maternal vitamin E intake during pregnancy is associated with increased neonatal CBMC proliferative responses[97] and an increased likelihood of wheezing and asthma outcomes in 5-year-old children, together with increased exhaled breath NO (a marker of asthmatic airway inflammation)[98]. In addition, low maternal plasma α-tocopherol levels during pregnancy are associated with reduced lung function at age 5 years[98]. Furthermore, there is an association between reduced maternal apple intake during pregnancy and an increased likelihood of wheeze and asthma outcomes in children at 5 years. However, there are no associations with other fruits, suggesting an apple-specific effect, possibly because of their phytochemical content, such as flavonoids[99]. The Irish Life-ways Cross-Generation Cohort Study has reported that high maternal fruit and vegetable intake during pregnancy are associated with a reduced likelihood of asthma in children at age 3 years[100]. A Menorcan birth cohort study has reported that wheeze in children aged 6–7 years is less frequent if mothers consume a Mediterranean diet during pregnancy[101]. The Menorcan and the Scottish studies quantified the diets of the children and it was found that whilst maternal and child diets are correlated there are no associations with children's diets[98,101].

The associations reported by these studies suggest that maternal nutrient intake during pregnancy (particularly vitamin E and probably flavonoids) influences the development of childhood asthma, possibly by influencing fetal airway development and the first interactions between the neonatal immune system and allergens[95,97]. The absence of a general association with antioxidants such as vitamin C and carotenoids and the associations with immune and lung function suggest that biological properties of vitamin E independent of antioxidant activity may be relevant[102]. Vitamin E and flavonoids have been reported to have complex effects on immunological and inflammatory pathways that may be relevant to the development of asthma and allergic disease[102–104]. The anti-inflammatory effects of vitamin E are believed to be mediated by the inhibition of protein kinase B and C activity, which may inhibit the activation and DNA binding of the transcription factor NF-κB, with consequent effects on the regulation of inflammatory cytokines, adhesion molecules and other pro-inflammatory molecules.

Vitamin E has many effects on the immune system, with reduced vitamin E status promoting the Th2 phenotype either by reducing IFN-γ secretion and/or increasing IL-4 or IL-5 secretion by Th-cells[105–109]. Several mechanisms have been proposed for these immunomodulatory effects. Vitamin E influences PGE_2 secretion by macrophages[108], with reduced vitamin E status being associated with increased cyclooxygenase-2 activity and increased production of PGE_2, which has been shown to promote the Th2 phenotype. Vitamin E has also been reported to inhibit the binding of NF-κB and activator protein-1 to the IL-4 promoter region, down regulating IL-4 mRNA expression in human Th-cells[106]. Vitamin E may also influence the development of regulatory T-cells[110]. The effects of vitamin E on the immune system appear to be age related, enhancing the IFN-γ responses of young but not old mice[111], and in human subjects naïve Th-cells are more responsive than memory Th-cells to vitamin E[105,107–109]. These age-dependent associations may explain the ineffectiveness of vitamin E supplementation in adults with asthma; conversely, any putative effects of vitamin E on asthma may be most potent in early infancy during initial encounters with allergens rather than after disease has been established.

Although flavonoids are best known for their powerful antioxidant properties, they also have anti-inflammatory and immunomodulatory properties that appear analogous to those of vitamin E. Flavonoids have been reported to inhibit protein kinase B and C and the activation and DNA binding of the transcription factor NF-κB with consequent effects on the regulation of inflammatory cytokines, adhesion molecules and other pro-inflammatory molecules. Flavonoids have also been reported to inhibit the synthesis of eicosanoid metabolites by inhibiting cyclooxygenase-2 and 5-lipoxygenase activity[104,112]. In animal models flavonoid supplementation inhibits Th2 differentiation and allergic responses by enhancing the

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Th-cell IFN-γ responses and inhibiting the IL-4 and IL-5 secretion[113]. Supplementation of human peripheral mononuclear cells with the flavonoid quercetin has been reported to increase gene and protein expression of IFN-γ and inhibit the expression of IL-4[114].

The reported association between low maternal plasma α-tocopherol levels at 12 weeks of gestation and reduced lung function in children at age 5 years[98] is consistent with the notion that vitamin E influences fetal airway development. In rat models maternal vitamin E supplementation accelerates growth in hypoplastic lungs, increasing lung complexity, surface area and bud count[115]. Vitamin E also modulates the expression of some genes implicated in cell signalling, cell-cycle regulation and extracellular matrix proteins that could be potentially relevant to fetal airway development[116,117].

Vitamin D

The investigation of associations between vitamin D and asthma has focused on possible associations with early-life exposure, probably reflecting the proposed influences of vitamin D on early-life interactions between the immune system and allergens. The few observational studies have reported conflicting results. Two birth cohort studies have reported potentially beneficial associations between maternal dietary vitamin D intake during pregnancy and childhood wheeze; however, no account was made of sunlight-derived vitamin D. In Project Viva low maternal vitamin D intake during pregnancy was found to be associated with an increased risk of recurrent wheeze at age 3 years[118] and in a Scottish study low maternal vitamin D intake was reported to be associated with an increase in wheezing outcomes in children at age 5 years[119]. Two cohort studies have reported potentially adverse associations. In a large Northern Finnish study regular high-dose (≥50 μg/d) vitamin D supplementation during infancy has been associated with an increased likelihood of allergic outcomes at 31 years[120]. However, many of the characteristics predictive of reduced compliance with vitamin D supplementation were shown to be associated with reduced risk of asthma and allergies and after adjustment for these factors no association between vitamin D supplementation and asthma was found. A UK birth cohort has reported that elevated maternal blood 25-hydroxyvitamin D in the third trimester is associated with an increased likelihood of childhood asthma at 9 years; however, the study response rate was low (30%) and there was no adjustment for potential confounding[121].

Conclusions

There is now evidence of an association between nutrition and asthma; however, the clinical and public health relevance of the associations remains unclear. At the present time there is insufficient evidence to advise individuals with asthma, pregnant women, parents and children to change or supplement their diet in order to treat or reduce the risk of developing asthma. There is also little evidence that antioxidant or PUFA supplementation can be used as an adjunct to conventional therapy for asthma, although there is still a need to conduct well-designed randomised controlled trials of nutrient intervention in children with asthma and for trials of combinations of nutrients. The emerging associations between maternal intake of vitamin E, vitamin D and PUFA during pregnancy and childhood asthma provides tantalising evidence that perhaps nutritional supplementation in the developmental context of pregnancy may have a role in the primary prevention of asthma in children. This concept is already established for folic acid supplementation during pregnancy for the prevention of neural-tube defects[122]. Before pregnant women can be advised to modify their diet, further work is needed. Particularly important will be well-designed intervention studies, and at the present time trials of vitamin E, vitamin D and PUFA supplementation seem the most promising. Whilst nutritional supplementation of pregnant women in a double-blind placebo-controlled manner is relatively straightforward, nutrients are seldom eaten in isolation and it is possible that for optimal effects a single-nutrient supplement may require other nutrients, this problem is probably mostly easily addressed by providing the nutrient in its natural form, food. Food also addresses the issue of the identified nutrient being a marker for other nutrients or combinations of nutrients. Even if dietary modification can be shown to reduce the risk of asthma, it is extremely unlikely that dietary modifications will reduce the prevalence of asthma by >30–40%, because asthma is a multifactoral disease requiring multiple exposures in genetically-predisposed individuals and dietary exposures are likely to be only one of many risk factors within an individual.

Acknowledgements

The author declares no conflicts of interest.

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