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Diet in respiratory disease
Diet as a protective factor

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Educational aims

- To introduce dietary factors and nutrients linked to lung function and diseases.
- To describe host and environmental factors affecting pulmonary and systemic nutritional status.
- To present epidemiological evidence of the association between nutrition and respiratory health.
- To discuss nutritional counselling and vitamin supplementation.

Summary

Several lung diseases have been associated with oxidative stress. Consequently, dietary factors and nutrients with a potentially protective role in the oxidative process and inflammatory response have been implicated in the genesis or evolution of these diseases. Antioxidant vitamins and other nutrients have also been related to several components of the immune response. This paper briefly reviews the epidemiological evidence of an association between diet and lung health, focusing on the nutrients most frequently studied.

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Oxidative stress occurs when there is an imbalance between the antioxidant defence system of the body and oxidant insults, such as cigarette smoke, air pollution and infections. Oxidative stress has been implicated in a number of lung diseases, including asthma, emphysema and chronic obstructive pulmonary disease (COPD), cystic fibrosis, pneumonia, idiopathic pulmonary fibrosis, adult acute respiratory distress syndrome and tuberculosis (TB). Therefore, a number of antioxidant vitamins have been suggested as beneficial to lung health, including vitamins A, C and E, carotenoids and selenium. Examples of some of the dietary sources of the various antioxidant vitamins are shown in table 1.

Other nutrients that have been shown to be beneficial to lung health include magnesium and omega-3 fatty acids. Magnesium is beneficial as it acts as a cofactor for enzyme activity, it is a bronchodilator for airway smooth muscle, it is involved in the inhibition of cholinergic neuromuscular transmission, and it stabilises mast cells and T-lymphocytes.

The dietary sources of magnesium include nuts, legumes, cereals, whole grains and seeds, carrots, spinach and seafood.

Omega-3 fatty acids are involved in decreasing leukotrienes synthesis, the inhibition of prostaglandin E_2 synthesis and the growth regulation of malignant cells. However, it is not the amount of omega-3 fatty acid intake that is the most important, but more that the ratio of omega-6 to omega-3 fatty acids should range 4/1 to 10/1. Omega-3 fatty acids can be found in fish oils, fish and shellfish, soy, flaxseed oil and leafy vegetables. Omega-6 fatty acids are found in vegetable oil, margarine, mayonnaise and processed food with oil.

Lung cancer

Lung cancer is a leading cause of cancer-related death worldwide. Evidence from multiple observational retrospective and prospective studies strongly suggests that high consumption of fruit or vegetables or both reduces the risk of lung cancer by ~25%, with a similar magnitude in current smokers, ex-smokers and never-smokers [1]. However, vitamin supplementation has not been shown to decrease lung cancer risk.

The results from two major primary randomised chemoprevention trials, which used vitamin supplementation as an intervention, reported an increase in lung cancer incidence in the group receiving high doses of β-carotene. After 5–8 years of supplementation with 20 mg β-carotene, either alone or with α-tocopherol, there was an 8% increase in overall mortality and an 18% increase in lung cancer. Such changes were not seen in the vitamin E group [2]. In the β-CArotene and Retinol Efficacy Trial (CARET), which was conducted in the USA [3], the supplementation group experienced 28% more lung cancer and 17% more deaths than participants not taking the supplements. In addition, the Physician Health Study showed no positive or negative effects of β-carotene supplementation [4].

It has been suggested that high doses of β-carotene could downregulate tumour suppressor genes and upregulate genes of cell proliferation, particularly among smokers [5]. It might also be possible that the supplementation needed a longer time in order to have an impact on a disease with such long latency.

Very recently, a re-analysis of CARET showed that a high intake of fruit and vegetables decreased the risk of lung cancer in the placebo arm by ~78% (when comparing lowest with highest quintiles) after 12 years of follow-up [6]. Similarly, in the Alpha-Tocopherol Beta-Carotene (ATBC) trial, after 14 years of follow-up, dietary intake and serum levels of carotenoids, including β-carotene, were found to be related to a decreased risk in lung cancer (37% decrease for fruit and vegetable intake, comparing highest with lowest quintile intake) [7]. These findings suggest that other dietary factors associated with fruit and vegetable intake may be protective and are not present when supplements are given (*e.g.* fibre, other carotenoids or nutrients, other protective chemicals such as non-provitamin A carotenoids).

Obstructive lung diseases

Most of the evidence on nutritional determinants of the major obstructive airways diseases (COPD

Table 1 Dietary sources of antioxidant vitamins

Vitamins and nutrients	*Dietary source*
Vitamin C	*Citrus fruits and juices, kiwi fruit, broccoli, green pepper*
β-Carotene	*Apricot, cantaloupe melon, mango, carrot, kale, pepper, spinach, sweet potato*
Vitamin E	*Wheat germ, grains, vegetable oil, margarine, almond, peanut*
Selenium	*Grains (depending on soil content), animal products, seafood*

and asthma) is consistent with an association between high intake of dietary antioxidants and some minerals, and a reduced risk of these disorders. However, most of this evidence comes from cross-sectional studies, which cannot provide information on the temporal relationship between dietary intake and lung diseases.

Dietary agents might plausibly act at different stages of the disease process, and the effect of diet on lung development might be an important factor for obstructive lung diseases in adulthood. In addition, the complexity of reconstructing past dietary intake and the potential confounding effect of other lifestyle factors render the interpretation of cross-sectional data difficult.

COPD

Antioxidants

Cross-sectional and longitudinal studies strongly suggest that long-term vitamin C intake is significantly associated with better lung function. Flavonoids are effective antioxidants because of their free-radical scavenging properties and because they are chelators of metal ions [8]. Flavonoids are a large family of polyphenolic compounds synthesised by plants (catechins *i.e.* apples, berries, red grapes, red wine, teas, chocolate; flavanones *i.e.* citrus fruits and juices; flavones *i.e.* parsley, thyme, celery, hot peppers). A higher intake of flavonoides (flavonol, among which catechin and flavone) has been found to be positively associated with forced expiratory volume in one second and inversely associated with chronic cough [9]. Although the amplitude of the effect varies from study to study, the consistency of the results suggests a real association between fresh fruit consumption and lung function. However, fresh fruit intake may be a marker of a healthier lifestyle, and other nutrients that have not been accounted for may have a beneficial effect on lung function. In addition, since cigarette smoking is a strong predictor of lung function and smokers generally have a poorer diet, the observed effect of diet on lung function could be due to residual confounding.

Few nutritional randomised controlled trials have been carried out in chronic obstructive lung disease. The impact of supplementation with β-carotene and α-tocopherol has been studied in a subgroup of participants in the ATBC study. During a median follow-up period of 6 years, there was no evidence of a reduced incidence of COPD symptoms in males receiving β-carotene or α-tocopherol supplements [10]. Data from CARET also indicate that vitamin A supplementation has

no effect on the rate of decline of lung function in smokers and former smokers [11]. However, subjects recruited in these trials were either subjects with extensive past exposure to asbestos (CARET) or heavy smokers (ATBC), thus impairing the generalisability of the results.

Omega-3 fatty acids

Cross-sectional data suggest that omega-3 fatty acids may have a protective effect against COPD and lung function decrement; however, study results were inconsistent in identifying the subgroups in whom fish oil appears to have the greatest effect [12]. None of these studies controlled for the intake of other nutrients, such as antioxidant vitamins, which may be correlated with omega-3 fatty acid intake. More recent observational studies did not confirm the earlier findings of a protective effect [13]. The only prospective study observed no protective effect of omega-3 fatty acids after adjusting for other nutrients; however, in this study, intake of solid fruits had a strong protective effect against chronic non-specific lung diseases [14].

Airway hyperresponsivenes, wheezing and asthma

A deficiency in dietary antioxidants and other nutrients, such as omega-3 fatty acids, might be one of the factors that contribute to asthma, as a consequence of the marked changes in diet with a decrease in intake of fresh fruit and vegetables in the USA and other countries [15]. Several recent reviews have addressed the role of diet in the aetiology of asthma [16, 17].

Antioxidants

Vitamins and foods rich in antioxidants are the most strongly implicated in asthma aetiology.

1. Vitamin C

Asthma patients have been reported to have lower than normal concentrations of vitamin C in their plasma and blood leukocytes [16], which suggests that asthma could be associated with chronically lower concentrations of vitamin C. Vitamin C has been shown in several cross-sectional and case-controlled studies to be associated with a reduced risk of asthma. Studies among children and young adults have consistently shown a beneficial impact of the consumption of fresh fruit and of some vegetables, although the type of beneficial foods varies across studies. The variability in protective foods across studies might be linked to different dietary patterns across the populations studied, given that enough variability is necessary within the population studied to evaluate the impact of specific foods or nutrients. However, a large intervention study on vitamin C and magnesium (1 g per day vitamin C, 450 µg per day magnesium) among asthmatic adults does not support the protective effect of vitamin C [18].

2. Vitamin E and other antioxidants

A few cross-sectional studies have linked vitamin E to asthma [17]. Higher concentrations of vitamin E intake have been associated with a lower prevalence of allergen skin sensitisation and lower total serum IgE levels in adults [19, 20]. In a recent supplementation study of patients with adult-onset asthma, using 500 mg of vitamin E for 6 weeks, the authors did not observe any benefit from the supplementation of vitamin E in adults with mild-to-moderate asthma [21]. While antioxidant nutrients have been shown to reduce the prevalence of wheezing and respiratory symptoms, there is no evidence that such nutrients have an effect on the incidence of asthma. The only prospective study conducted in a large cohort of adult females did not find an association between the intake of vitamin C or other antioxidants and onset of asthma [22].

Omega-3 fatty acids

The hypothesis that high dietary fish intake may reduce people's susceptibility to chronic airway diseases originated from the observation that the Inuit population had a very low prevalence of asthma, whereas, in most other populations, asthma rates have been shown to rise with the increase in dietary intake of polyunsaturated fats, particularly linoleic acid (omega-6). Data from cross-sectional studies have suggested that a high intake of oily fish is related to a lower prevalence of wheezing among children. The risk of current wheezing among children eating oily fish was 3.8 times lower than among children who did not eat oily fish [23]. No study in adults has observed such an effect. A recent study from Norway suggested that fish intake early in life could protect against allergic rhinitis later in life [24].

Omega-3 fatty acids, atopy and asthma

Experimental studies of omega-3 fatty acids have shown a decrease in airway hyperresponsiveness and inflammatory markers (tumour necrosis factor-α, leukotrienes), but little or no effect on symptoms in children and young adults. As events initiating allergic immune responses are likely to occur before birth [25], and immunity is influenced by nutrients, supplementation with n-3 fatty acids in pregnancy could provide a non-invasive method to modulate immune development before allergic responses are established. There is now evidence to suggest that the *in utero* period and the first 2 years of life are key periods in the development of the adult pattern of immune response [26], and that the increase in allergic disease might be the result of failure of normal immune regulation in early life, rather than simple "T-helper (Th)2 skewing" of the immune response [27]. Both epidemiological studies and experimental data provide a plausible link between low consumption of n-3 fatty acids and allergic diseases and asthma [28]. Although trials with n-3 fatty acids supplementation in adults with established asthma have been disappointing [29], this might indicate that once allergic immune responses are established, this kind of intervention could be too late.

Two recent reports in infants suggest that dietary omega-3 polyunsaturated fatty acid (n-3 PUFA) supplements in pregnancy or in the early post-natal period could have immunomodulatory properties and associated clinical effects. In one study, fish oil supplementation (3.7 g per day) or placebo was randomly assigned from 20 weeks of pregnancy until delivery to 83 atopic mothers. Results suggest that n-3 PUFA supplementation decreases the level of Th2 cytokines (interleukin-13) in the umbilical cord and expression of Th2 cytokines by neonatal mononuclear cells [28]. Infants in the fish oil group were consistently less likely to develop clinical features, including food allergy, recurrent wheeze, persistent cough, diagnosed asthma and anaphylaxis, compared with the control group [28]. However because of the small sample size, the author could not firmly conclude that there was a benefit of n-3 PUFA. In another study, the role of post-natal fish oil supplementation was examined in children at a high risk of allergic disease in a parallel-group, randomised controlled trial of 616 pregnant females. Fish oil supplementation given to the child from 6 months to 18 months reduced the risk of wheezing; however, it had no effect on IgE concentrations or sensitisation to food or atopic dermatitis [30].

Nutritional protection of the effect of air pollution on respiratory health

The effects of nutrient supplementation at levels above those that are physiologically required on air pollutant toxicity have been studied in both animal and humans. Results suggest that increased intake of antioxidants modulates the pulmonary response to the photo-oxidants ozone and nitrogen dioxide. Controlled human studies of healthy subjects and asthmatics have suggested that antioxidant supplementation may protect against the acute effects of ozone on lung function. Supplementation ranged from 250 mg to 1 g per day of vitamin C and from 500–800 IU per day of vitamin E. Randomised trials in the open population have also suggested that vitamin C and α-tocopherol might have a protective effect on the lungs [31, 32].

Summary

Cross-sectional studies suggest that the impact of nutrition on obstructive lung disease (COPD and asthma) is mostly related to antioxidant intake, particularly vitamin C and to a lesser extent vitamin E. Fruit intake also appears to be beneficial, and nutrients such as flavonoids, which are strong antioxidants, might also play a role. Longitudinal data suggest that higher intakes of vitamin C and fruits are related to lower declines in lung function overtime. Cross-sectionally, omega-3 PUFA intake has been associated with lower asthma symptoms; however, data are still sparse at this stage and the impact of omega-3 intake could be on atopy rather than asthma.

Intervention studies have not confirmed the impact of antioxidant supplementation on lung function decline. However, the study populations in the ATBC and CARET trials had heavy past and present exposure to asbestos and smoking, and supplementation might have been given too late in the process to have a beneficial effect. Intervention studies in asthmatic adults with vitamin C, vitamin E and magnesium have also been negative. The use of antioxidant vitamin supplementation appears to inhibit short-term effects of ozone on the airways, although the long-term relevance of this effect is not established. The variability of effect among various studies might be due to the baseline antioxidant status of the participants, as well as the intensity of the oxidant exposure.

Fruit intake and, to some extent, vegetable intake have a beneficial effect on lung health, as with other chronic diseases. The dietary guidelines from the National Institute of Health, presented in the report Healthy People 2000–2010 "five a day for better health", recommend the consumption of two to four portions of fruit per day and three to five vegetable portions per day, an amount that should cover the recommended dietary allowances (RDA) for important micronutrients. The RDA is defined as the amount of nutrients that most individuals must ingest to achieve an optimal body function and to minimise the risk of disease [33]. However, in some circumstances, metabolic, environmental and genetic factors can lead to an individual requirement that differs from the estimated RDA and justify supplementation. There are two major reasons for using dietary supplements: 1) to optimise cellular function linked to nutrient deficiency; and 2) to cover an increased requirement linked to genetic susceptibility or special conditions, *i.e.* subjects exposed to oxidants or with chronic infection [33]. Figure 1 presents an approach to dietary supplementation.

As chest physicians, it is important to incorporate dietary assessment and nutritional counselling in everyday practice, particularly in high-risk subjects with pre-existing diseases, such as asthma or COPD and TB. Recommendations to increase fresh fruit and vegetable intakes should be provided, and in circumstances where intake cannot cover the needs, supplementation of vitamins C and E could be proposed in high-risk patients.

Latest developments
People with an inactive form of the GSTM1 gene (involved in elimination of potent anti-cancer compounds) were found to be 33% less likely to get lung cancer if they ate cruciferous vegetables on a weekly basis, as reported in a recent study in the Lancet. Brennan P, Hsu CC, Moullan N, et al. Effect of cruciferous vegetables on lung cancer in patients stratified by genetic status: a mendelian randomisation approach. Lancet 2005; 361: 1558–1560.

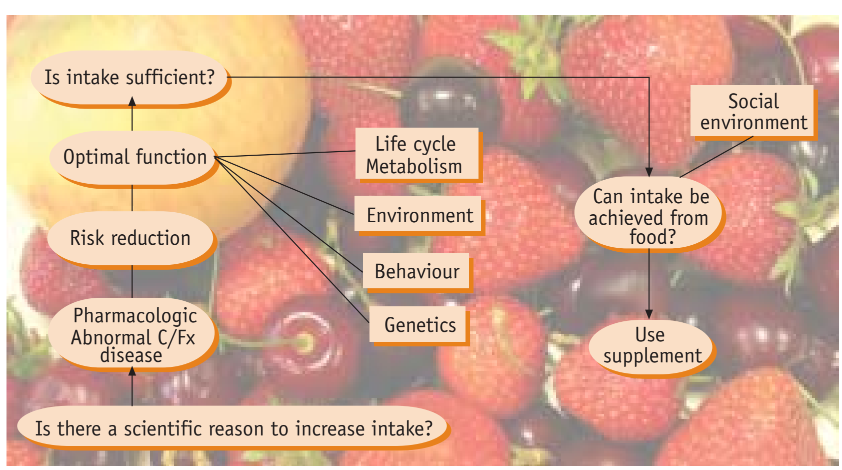

Figure 1
Dietary supplementation. Modified from [31].

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Diet as a risk factor in respiratory diseases

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There are less data available on the deleterious effects of diet and respiratory disease than on the beneficial effects of diet on respiratory diseases. Dietary factors that increase the risk of other diseases may also be harmful for respiratory health, and these include high salt intake, increased n-6 and trans-fatty acids, increased body mass index (BMI), and possibly food additives.

Salt

The recommended daily allowance for salt is 5–6 g per day. Currently, in the UK, the consumption is 9–12 g per day.

Proposed mechanisms

- Increased smooth muscle contraction.
- Increased circulating blood volume, thereby reducing lung function *via* lung microcirculation.
- Sodium influx could impact airway reactivity.

Summary

Most population-based, cross-sectional studies have shown no association between salt intake and asthma. However, early randomised, controlled trials have indicated that high salt diets increase the risk of asthma or exacerbations in adults with asthma. Current evidence from clinical trails have been summarised in a Cochrane review and the overview results were inconclusive. A decrease in salt intake is associated with an improvement in lung function and airway hyperresponsiveness, particularly in males; however, these results have been inconsistent. Trials of reduction of salt in exercise-induced asthma have shown more promising results. Larger trials with longer duration of intervention and a longer washout period between interventions are needed to fully understand the effects of salt on lung health.

Fatty acids

Over the last 15 years, there have been changes in the dietary fats consumed in "developed countries". In particular, the intake of dietary n-6 fatty acids and trans-fatty acids has increased, while concomitant decreases in the intake of butter, lard and n-3 fatty acids have been observed over the same period.

Proposed mechanisms

- Generalised increase in cellular susceptibility to inflammatory insults.
- Increase in inflammatory mediators, including prostaglandins and leukotrienes.

Summary

Current research can be divided into early-life evidence and research that has been conducted in adults. Currently, there is a greater body of evidence investigating exposure to fatty acids early in life. Exposure to fatty acids has been determined through the fatty acid composition of breast milk or through composition in the umbilical cord, and these have been investigated in relation to a child's risk/incidence of allergic disease. The current evidence suggests that allergic children are exposed to higher levels of n-6 fatty acids and lower levels of n-3 fatty acids. However, results are not yet consistent, so no clear message can be obtained from the literature at present.

The majority of evidence in adults has been

Suggested further reading

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from case–control studies. However, there is no clear and consistent evidence emerging from this research.

There is only very limited evidence concerning the effect of trans-fatty acids on asthma. One ecological study showed that countries with higher levels of trans-fatty acid intake had a higher prevalence of asthma. In addition, a cross-sectional study found that higher levels of margarine consumption increased the risk of asthma, although others have not found this effect.

Obesity

Levels of obesity are rising in both the developed and developing world.

Proposed mechanisms

- Mechanical effects.
- Immune modification.
- Genetics.
- Environment.

Summary

There has been increasing research activity in this area over the last 5 years as levels of obesity have been increasing. Current evidence suggests that higher levels of obesity increase the incidence of asthma and airway hyperresponsiveness. In addition, obese individuals have decreased lung function. There is controversy regarding whether these effects are limited to females or are seen in both sexes. To date, there is limited evidence available on the effect of weight loss on respiratory health. Evidence from morbidly obese subjects suggests that weight reduction could improve symptoms, airway hyperresponsiveness and lung function. There is also some research suggesting a shared genetic component for asthma and obesity.

Food additives

Some common food additives have been suggested as risk factors for exacerbations of asthma, and they include tartarzine, monosodium glutamate (MSG) and sulphites. Tartarzine is a common food additive, which is also used in many medications, and current research suggests it may increase asthma severity only in a few susceptible individuals. While initial evidence suggested that MSG may exacerbate asthma, more rigorously designed trials demonstrate no association.

Sulphites have been mainly investigated as the cause of wine-induced asthma and, again, there is still only very limited research into these associations.

Conclusions

- Reduce salt intake.
- Control n-6 fatty acid and total fat intake.
- Maintain a normal body mass index.

For more detailed further reading and references related to each topic in this section please go to www.breathe-cme.org.