

Commentary

Chronic obstructive pulmonary disease, asthma and protective effects of food intake: from hypothesis to evidence?

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(Print ISSN 1465-9921; Online ISSN 1465-993X)**Abstract**

Evidence for a role of diet in asthma and chronic obstructive pulmonary disease (COPD) has been accumulating rapidly over the past decade. Associations have been reported between the intake of fruit, fish, antioxidant vitamins, fatty acids, sodium or magnesium, and indicators of asthma and COPD. Several issues need to be addressed before causality of these associations can be established. The role of diet in the development of disease and the induction time and reversibility of the effect needs further investigation. The role of smoking habits in the relation of diet and respiratory disease also needs to be elucidated. Nevertheless, based on the available evidence, dietary guidelines could be proposed for the primary and secondary prevention of asthma and COPD that are in line with existing dietary guidelines for the prevention of coronary heart disease and cancer.

Keywords: asthma, chronic obstructive pulmonary disease, diet, epidemiology**Introduction**

Changes in patterns of dietary consumption, associated with development of a more affluent lifestyle, may have contributed to the rise in asthma over the past few decades [1,2]. Plausible mechanisms have been proposed for the influence of dietary factors such as sodium, magnesium, antioxidants, selenium and fats on respiratory symptoms and lung function (summarised in [3]). The number of observational and experimental studies supporting these mechanisms has increased rapidly over the past few years (reviewed in [3–7]). In this commentary, we shall discuss some issues that need to be addressed in future observational studies to further explore the evidence for a causal relation between dietary intake and asthma or COPD.

Current evidence from observational studies

Vitamins C, E and beta-carotene are antioxidant vitamins and may protect the lungs from oxidative damage by

smoking or air pollution. Vitamin C is a free-radical scavenger present in intracellular and extracellular lung fluids. Vitamin E is present in extracellular lung fluid and lipid membranes, where it converts oxygen radicals and lipid peroxyl radicals to less-reactive forms. Beta-carotene (provitamin A) is a free-radical scavenger present in tissue membranes.

Observational studies have shown repeatedly that the intake of vitamin C and of fruits rich in vitamin C is positively related to lung function. Effect estimates from recent studies [8–12] fit well within those of studies that were reviewed earlier [3–5]. The forced expiratory volume in 1 s (FEV₁) in subjects with a 'high' intake of fruits (once per week or more) is about 80–100 ml higher than in subjects with a low intake (less than once per week). A 100 mg increase in vitamin C intake per day is also associated with an approximately 10–50 ml increase in FEV₁ [5].

The intake of vitamin C or fruits is less consistently associated with respiratory symptoms than with lung function. The evidence for a protective effect of the antioxidant (pro)vitamins E and beta-carotene on respiratory symptoms and lung function has increased over the past few years [10–14]. The joint effect of the intake of (pro)vitamins C, E and beta-carotene was smaller than the sum of their independent effects [10]. This may be caused by their presence in the same foods and by the biological interaction of vitamins C and E [13,15].

A beneficial association between fish intake and asthma was suggested by the observation that the prevalence of asthma was low in Eskimo populations, who have a high fish intake [16]. A beneficial effect was attributed to the presence of n-3 fatty acids in fish oil, which competitively inhibits the arachidonic acid metabolism and thus reduces the production of inflammatory mediators. Although experimental studies showed that supplementation with constituents of fish oil led to increased levels in cell membranes, no improvement was observed in clinical manifestation of asthma in patients [7]. A recent systematic review of randomised controlled trials in patients with asthma concluded that there was no convincing evidence for a protective effect of fish oil supplementation or increased intake of fish oil in the improvement of asthma control [17]. A beneficial effect of fish intake on lung function was reported in several studies in the mid-1990s, but findings on the association with respiratory symptoms were conflicting [4,5,18,19]. More recent observational studies have not confirmed the earlier findings [11,12,20].

Magnesium may play a beneficial role in the prevention and treatment of asthma through relaxation of the bronchial smooth muscle [21]. A beneficial effect of magnesium on lung function, airway reactivity or wheeze was observed in two observational studies [22,23], but not confirmed in one other study [11]. Some of the experimental studies in asthma patients have shown beneficial effects of magnesium but, at present, these results are too inconsistent to draw a firm conclusion. The protective effect of the intake of flavonoids and whole wheat or bread that was recently reported also requires further confirmation [12,20,24]. Potential beneficial effects of dietary factors such as selenium, manganese, pyridoxine, copper and zinc have been suggested but need to be further investigated [4,7].

Besides these potentially protective effects of some dietary factors, adverse effects on the lungs have been suggested for other dietary factors. For example, dietary sodium may increase airway reactivity through potentiation of the electrogenic sodium pump in the membrane of the airway smooth muscle [1,25]. A high sodium intake was shown to increase bronchial hyperresponsiveness in experimental studies, especially in subjects with asthma symptoms, but the association with other respiratory end-

Table 1

Dietary factors and asthma or chronic obstructive pulmonary disease: summary of the available evidence

	Relatively consistent evidence	Further evidence needed
Potentially beneficial association	Fruits Vitamin C Vitamin E Beta-carotene	Fish oils/n-3 fatty acids Magnesium Whole wheat Flavonoids Selenium, manganese Pyridoxine Copper, zinc
Potentially harmful association	Sodium	n-6 fatty acids Trans-fatty acids

points such as medication use and lung function was not consistent [4,5,7]. There is also no consistent evidence for a harmful effect of sodium intake on bronchial hyperreactivity or other respiratory endpoints from observational studies in the general population [1,4,5]. Other dietary factors that may potentially be harmful are n-6 fatty acids and trans-fatty acids [6].

There is thus support from experimental and observational studies for an association of several dietary factors with indicators of asthma (airway reactivity, IgE, asthma symptoms) and COPD (lung function, COPD symptoms), although the consistency of the evidence is a matter of judgement (see Table 1). Because of the overlap of indicators of asthma and COPD in adults, it is often not clear from observational studies whether a specific dietary factor is associated with clinical asthma or clinical COPD. There are several other issues that need to be addressed in future studies before conclusions on causality of the associations can be drawn.

Random variation or weak association?

The findings across studies are still inconsistent for many dietary factors, which may lead to the conclusion that they result from random variation. The observed associations are, however, often weak and it is well known that small effect estimates are more susceptible to confounding bias and to misclassification of dietary intake and disease outcome [26]. Differences in methods of data collection and analysis may be another source of variability between studies. Reporting bias should be considered in reviewing the role of diet in asthma and COPD, since statistically significant findings tend to be published more frequently or more comprehensively than negative findings. True variability across populations may obviously exist in the association between diet and respiratory disease. For example, a study in three countries using the same methods of data collection and analysis showed that different dietary factors were associated with lung function in each of the countries [12].

There are thus several possible explanations for the inconsistent findings on the relation between diet and respiratory disease. A meta-analysis of the original data of some of the larger observational studies may allow a better judgement of consistency of the findings.

The role of smoking habits

Confounding by smoking is a major concern in the interpretation of the observed protective effect of diet on respiratory disease. Smoking has great impact on respiratory disease, and dietary habits of smokers are less favourable than those of nonsmokers, even more so in heavy smokers than in light smokers. Results are therefore often presented for never smokers, former smokers and current smokers separately. Residual confounding may still affect the observed associations in ever smokers, although it has been suggested that extensive control for smoking intensity and smoking duration in the statistical analysis is likely to remove most of the residual confounding by smoking [9,10].

Lungs of smokers are exposed to high levels of oxidants and other inflammatory agents, which has raised the question whether dietary factors are expected to have a similar or a larger effect in smokers compared with nonsmokers. Yet, this question remains largely unanswered because plausible biological mechanisms can be proposed for either of these effects and results from observational studies are equivocal in this respect. Some observational studies reported that associations between dietary intake and respiratory indicators were restricted to ever smokers [9,13], whereas other studies observed effects in smokers that were similar or slightly larger compared with nonsmokers (for recent examples, see [8,10,11,20,27]). One large population-based study with substantial control for smoking habits even reported effect modification by smoking status that was different in direction and magnitude for each of the antioxidant vitamins [10]. Although Hu and Cassano suggested plausible mechanisms to explain these findings, the variability in effect modification illustrates the complexity of the role of smoking in the relation between dietary intake and respiratory disease.

Nutrients, foods or a healthy diet?

The effects of diet may be due to specific nutrients, to specific foods or to a 'healthy diet'. Studying the role of individual nutrients is relevant to understand the biological mechanisms behind the observed associations. Conversely, information on a protective effect of foods or a dietary pattern (e.g. a 'healthy' diet) is more useful for the development of dietary guidelines. More information is also needed on the question whether specific nutrients or foods have an independent effect on respiratory disease or whether the net effect of different components is smaller than the sum of the independent effects, due to interaction between dietary components. For example, it was observed that a 'healthy diet' consisting of a 'realistic'

favourable intake of fruits (>180 g/day), whole grains (>45 g/day) and moderate alcohol consumption (1–3 glasses/day) was associated with a 139 ml higher FEV₁ and a 50% lower prevalence of COPD symptoms than an unfavourable intake of these foods [20]. The contribution of each of these foods to the overall beneficial effect was largely additive.

Temporal relationship

Information on the temporal relationship between dietary intake and asthma or COPD is of critical importance in the interpretation of causality. Since most of the associations between diet and respiratory disease originate from cross-sectional studies, however, there is little information on whether dietary factors are truly involved in the development of asthma or COPD. For the same reason, data on induction time or reversibility of the potential effect of diet are scarce.

Induction time

Intervention studies have shown that effects of some dietary supplements on markers of the disease process such as airway inflammation, bronchoconstriction or airway obstruction may have a short induction time (days or weeks). For example, a short-term protective effect of antioxidants on lung function was observed in two intervention studies in subjects with a high exposure to oxidative air pollution under natural conditions [28,29]. Subjects who received supplements of antioxidant vitamins C, E and beta-carotene suffered a lower loss of lung function (FEV₁) at the end of the day than the control group. Since repeated short-term loss of lung function may result in more permanent damage, this suggests that long-term lung function loss may also be prevented in subjects with high exposure to oxidants. Nevertheless, a long-term intervention study showed no beneficial effect of 6-year supplementation of alpha-tocopherol and beta-carotene intake on the 5–8-year incidence of COPD symptoms in smokers [30].

Reversibility

The reversibility of the effect of fruit intake on lung function has been addressed in two recent longitudinal studies. Carey *et al* [27] observed that a change in intake of fresh fruit over a 7-year period, but not the average intake, was beneficially associated with a change in lung function over that period. It was concluded that this supports a reversible protective effect of fruit intake. However, this conclusion was not confirmed in another prospective study showing a cross-sectional beneficial effect but no longitudinal beneficial effect of the intake of vitamin E and apples on lung function. The decline in lung function over a 5-year period was not associated with average intake or with a change in the intake of vitamin E, C or apples [11]. It is thus not clear from these longitudinal studies whether the protective effect of diet on lung function is temporal

and reversible or whether a more permanent reduction in the age-related decline in lung function exists.

The role of diet in the development of asthma in children may become clearer in a few years, when more results will become available from birth cohort studies that are currently being performed in several countries. More data on the role of diet in the development and progression of COPD are likely to become available after follow-up of several of the reported cross-sectional studies.

Conclusion

Although the interest in the association between diet and respiratory disease originates from the search for causes of the rise in asthma, sound data to confirm this hypothesis in retrospect are lacking since our living conditions have altered in many other ways than dietary habits only. The available evidence from observational studies suggests a role of diet in asthma and also in COPD, but causality of the association has not been confirmed. Looking to the future, studies among populations that have recently become exposed to a rapidly changing environment and a more affluent lifestyle, such as those in former Eastern Germany [31] or Jeddah, Saudi Arabia [32], are of particular interest. These studies will allow us to investigate the effects of diet and other environmental factors at the individual level while the environmental conditions are changing. Studies in Western countries where changes have already taken place may contribute to a better understanding of the protective role of diet in lung disease, provided they focus on the temporal effects of diet and on a careful assessment of the role of smoking and other lifestyle factors. Nevertheless, on the basis of current knowledge, it seems justified to promote a healthy diet according to existing guidelines for the prevention of coronary heart disease and cancer.

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