

EDITORIAL

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Childhood asthma is a fat-soluble vitamin deficiency disease

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It has been suggested that changes in dietary habits associated with a western lifestyle, in particular, diets that are deficient in antioxidants and have a changing composition of fatty acids, may explain some of the rise in asthma and allergy prevalence [1]. Seaton, based on data that showed that there had been a decrease in fruit and vegetable intakes, which predated the rise in asthma and allergies, argued that a decrease in antioxidants in the diet increased the susceptibility of the population to these conditions [2]. The paper by Wagner et al. [3] detailing anti-inflammatory effects of γ -tocopherol, the major form of vitamin E in US diets, in the rat is directly relevant to this hypothesis. We will briefly review the human data linking vitamin E to asthma onset and prevalence.

There are multiple human studies investigating the effect of antioxidants on lung function [4–9]. Most studies have been cross-sectional and conducted in adult populations, and most have found positive associations between antioxidants and lung function. There is less evidence available in children. Cook et al. [10] assessed the effects of fruit consumption on lung function and wheeze and, although associations with fruit consumption were detected, plasma vitamin C levels in children were unrelated to forced expiratory volume in 1 s (FEV₁). The evidence for the association between antioxidants and disease, while generally showing that antioxidants are inversely associated with the risk for symptoms or disease, is less consistent than that for the positive association between antioxidants and lung function [11–13].

Rather than investigating individual antioxidants, several studies have examined intake of fruits and vegetables (the major sources of antioxidants in our diet) and their

relationship with lung function, symptoms, and disease. These studies have shown that increasing intake of fruits and vegetables are associated with greater FEV₁ values [14–16], and are inversely associated with wheeze [17] and asthma [18].

Recent studies have also shown that antioxidant intake is inversely associated with allergy. In a random sample of 2633 adults in Nottingham, UK, Fogarty et al. [19] showed that higher vitamin E intakes were associated with lower serum IgE concentrations and a lower frequency of allergen sensitization. Although vitamin E intakes were closely correlated with intakes of vitamin C, no association was found between vitamin C and either IgE concentrations or allergen sensitization. A cross-sectional analysis of serum antioxidants in NHANES III [20] showed that serum levels of vitamin E, β -cryptoxanthin, and α -carotene were inversely associated with allergic skin sensitization. Two ecological analyses using pooled data from several countries found inverse associations between intake of fruit and allergic sensitization [21], and between intake of vegetables and prevalence of symptoms of wheeze, allergic rhinoconjunctivitis, and atopic eczema [22]. Thus, there is ample cross-sectional data in adults that antioxidants are inversely associated with the prevalence of established asthma and allergies. Prospective studies and studies in children prior to disease onset, however, are sparse.

Only two published studies have investigated prenatal exposure to antioxidants and immune system outcomes in children. Devereux et al. [23] studied the T-helper cell proliferative responses of cord blood mononuclear cells from a sample of 223 neonates and found that maternal intakes of vitamin E in the highest tertile were associated with lower cord blood mononuclear proliferative responses to timothy grass and house dust mite, compared with mothers whose intakes were in the lowest tertile of vitamin E. The same group subsequently found that higher maternal vitamin E intakes were associated with

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decreased risks for wheezing in early life [24]. We have conducted a similar analysis of maternal–infant pairs who were enrolled in Project Viva [25]. We found that there was a consistent inverse association between individual maternal antioxidant intakes and cord blood lymphoproliferative responses to cockroach and dust mite. Specifically, β -carotene, folic acid, lutein+zeaxanthin, and vitamin E were significantly inversely associated with cord blood lymphoproliferative responses to Bla g 2 and Der f 1. Higher maternal antioxidant intakes were also associated with decreased risks of any wheeze and persistent wheeze in 2-year-old children [26]. These findings suggest that maternal diets rich in antioxidants may influence the fetal immune system and reduce the risk of asthma and allergies.

Given the above data, what needs to be done at this point? Clearly more animal work such as is being done by Wagner et al. [3] needs to be done to get at the basic mechanisms of disease. Their work, building on their previous studies, has shown the broad and comprehensive anti-inflammatory effects of γ -tocopherol in allergic airways. It would be interesting to see how vitamin E deficiency in the pregnant rat affects the developing immune system of the fetus. In humans, we believe that the next step would be a trial of vitamin E supplementation in pregnant women in an attempt to prevent asthma in children. Currently, we understand that such a multi-centre trial is in the process of being set up in the United Kingdom. While adult trials of vitamin E in cancer and heart disease have been unsuccessful, it is certainly possible, in the proper developmental context, that trials in asthma might be successful. While we are more enthusiastic about trials of vitamin D for asthma prevention [27, 28], because there is more data supporting an effect of vitamin D, rather than vitamin E, on the immune system, we certainly think that trials of vitamin E are indicated based on the available observational data. It is impossible to clearly separate the effects of vitamins D and E from each other based on the observational birth cohort data because their intakes are linked; this separation can only be accomplished with clinical trials that independently assess the appropriate dose of each of these fat-soluble vitamins relative to a control group. The observational data also clearly suggest that it is critical to focus on the antenatal effects of these fat-soluble vitamins rather than conducting trials to assess the postnatal effects of these vitamins on asthma and allergy occurrence. Trials of these vitamins in postnatal life will minimize any potential benefit and may risk seeing no effect at all. Population attributable risk estimates would suggest that at minimum 40% of all asthma in children is because of the deficiency of these vitamins. It certainly looks as if childhood asthma is, in part, disease of fat-soluble vitamin deficiency during pregnancy and clinical trials in pregnant mothers are the best way to test this hypothesis.

If successful, we have a potentially cheap, safe, and easy means of disease prevention.

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