

REVIEW

Environmental and lifestyle factors may act in concert to increase the prevalence of respiratory allergy including asthma

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The prevalence of asthma and hay fever has increased over the past decades and is still increasing. Various environmental and lifestyle factors such as childhood infections [1], changed patterns of food consumption [2,3] and air pollution [4], may be partially responsible for this increase. We will outline how these three independent factors may interact with allergy-related immune responses.

Children are born with a dominant humoral responsiveness (atopic state) and generally their state is converted to a cellular immune responsiveness, possibly because of early childhood infections. In this way infections, particularly early childhood infections, may reduce the prevalence of allergy. First evidence of this notion came from studies performed soon after the reunification of Germany showing an increased prevalence of allergy in children who had experienced less childhood infections [1]. Moreover, an inverse relationship was proposed between measles [5], hepatitis [6], tuberculin responses [7] and atopic disorders, while others showed a relationship between birth order and the risk of allergic disease and atopy [8]. Viral and bacterial infections thus apparently afford protection against allergic sensitization.

In industrialized countries the progressive decrease in the consumption of fresh fruit and vegetables [3] and the increased use of polyunsaturated fatty acids (PUFAs), particularly linoleic acid [2], motivated investigators to study the putative association between diet and the increased prevalence of asthma and allergy. The rationale of such research is that consumption of fruit and vegetables containing essential cofactors like minerals, vitamins and flavonoids not only keep up the natural antioxidant capacity but may also alter the immune response [9,10]. The increased consumption of linoleic acid leads to higher levels of arachidonic acid and PGE₂ as this fatty acid is their precursor. PGE₂ inhibits interferon-gamma (IFN γ) production and induces a switch to immunoglobulin (Ig) E class antibody production [11,12].

Finally, epidemiological studies have reported an association between air pollution and an increased incidence of pulmonary and allergic diseases [4]. Perturbation of the airway epithelial layer by environmental air pollutants may elicit pulmonary inflammation and facilitate allergic disease [13].

Hypothesis

Epidemiology has shown that early childhood infections, diet and air pollution have immune regulatory actions. We hypothesize that during life time the TH1/TH2 balance may be skewed by these factors, alone or in concert, resulting in increased respiratory diseases and allergy. The establishment of the TH1/TH2 balance during early childhood and the final tuning at an age of 4–5 years [14] implies that children are especially vulnerable to environmental and lifestyle stressors affecting the TH1/TH2 balance. Older subjects, in addition, remain sensitive to a shift in the balance by such factors (see Fig. 1).

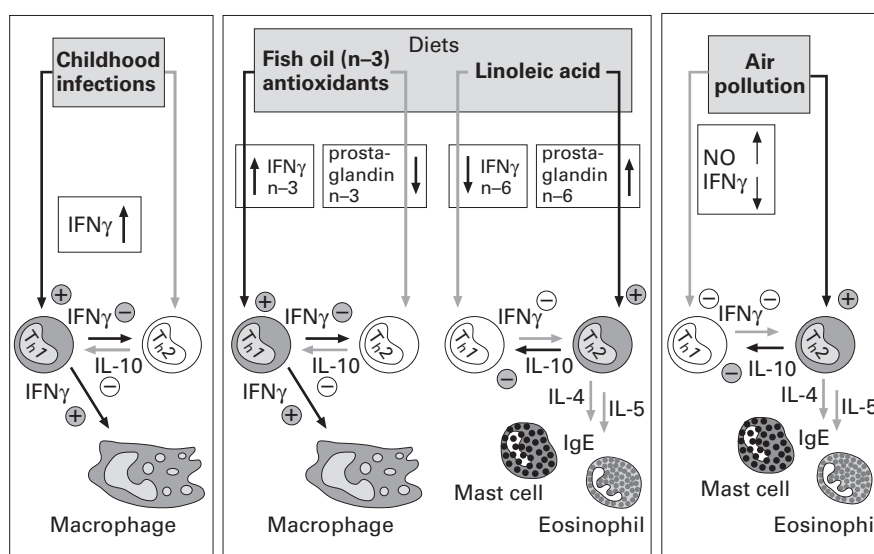
TH1/TH2 balance

The balance between the two subsets of T cells is pivotal for allergic sensitization. T-helper 1 (TH1) cells activate mononuclear phagocytes that are involved in cell-mediated immunity (contact- and delayed-type hypersensitivity and resistance to intracellular pathogens), while T-helper 2 (TH2) cells dominate parasitic infections and type I hypersensitivity [15].

Polarization of T-helper cells from T-helper 0 (TH0) cells is among others, regulated by dendritic cells, the strength of antigen stimulation and the cytokines present during priming. For instance IL-12 and IFN γ play a major role in TH1 and IL-4 in TH2 cell differentiation [16]. T-helper subsets can be distinguished by their cytokine profiles. TH1 cells produce mainly IL-2 and IFN γ and TH2 cells produce mainly IL-4, IL-5 and IL-10. The same cytokines may also induce a shift in the balance between TH1 and TH2 responses. Via the release of particular cytokines the subsets

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Fig. 1. Due to childhood infections the foetal immune response (TH2) is converted to dominant cellular immune responsiveness; consumption of fish oil (n-3) decreases the production of prostaglandin and increases the interferon- γ production; the intake of antioxidants prevents cytokine release, both activating the TH1 response. High intake of linoleic acid (n-6) increases prostaglandin production and reduces IFN γ production which activates the TH2 response; air pollution evokes production of pro-inflammatory cytokines and NO, which reduces the presence of IFN γ and results in a dominant humoral responsiveness (TH2). Thus, the factors: less childhood infections, lower intake of fruit and vegetable, high intake of linoleic acid and exposure to air pollution, in concert, may affect the TH1/TH2 balance in favour of the TH2 response.



may mutually modulate the response. For instance, release of IFN γ by TH1 cells will inhibit the TH2 response, and release of IL-10 by TH2 cells will inhibit the TH1 response.

NO (nitric monoxide) released by, e.g. epithelial cells, TH1 cells and macrophages, is another endogenous compound affecting the TH1/TH2 balance. NO inhibits TH1 cell proliferation and the production of IL-2 and IFN γ by TH1 cells but does not affect TH2 cells. As a result, NO increases antigen-driven proliferation of TH2 cells and the release of the typical TH2 cytokines IL-4, IL-5 and IL-10 [17].

Early infections

During pregnancy foetal immunity is dominated by humoral responsiveness (TH2) [18,19] which is preserved for varying periods during infancy and regulated by, e.g. PGE₂, IL-10 and IL-4. The consequence of the preferential TH2 response is increased susceptibility to allergy. However, to adequately protect the child against viral and bacterial infections the TH2 phenotype needs to be replaced by a TH1 phenotype. Accumulating evidence exists that certain early infections skew the TH2 response towards the TH1 response.

Asthma develops in early life (between 5 and 11 years of age) [20]. Infections seem to afford protection against the development of asthma and allergy [21] and children with eczema occasionally undergo temporarily spontaneous remission after severe bacterial and viral infections [22]. Young adults who experienced measles in childhood were significantly less likely to be atopic than those who had been vaccinated and/or had no measles [22,23]. Based on the

concept of the TH1/TH2 balance comprising the dichotomy in T-helper cell populations with a mutual inhibition of the TH1 and TH2 cell subset, it was recently hypothesized that infections involving a TH1 response suppress the TH2 response. Infections of the TH1-type like *Bordetella pertussis* [24], *Listeria monocytogenes* [25], *Mycobacterium bovis*, *Leishmania* [26], and many other bacteria [27] go along with increased production of IFN γ which impairs the TH2 response and thus reduce the progression of allergy/asthma. Other infections, like respiratory syncytial virus (RSV) infection, which was held responsible for paediatric asthma [28] for a long time, brucellosis, rhinovirus and *Aspergillus fumigatus* infection [29] induce TH2 responses and may thus rather increase the prevalence of allergic disorders.

In the last decade much effort was made to associate the increased prevalence of allergic disease with prior standard paediatric vaccinations [5], but results are still inconclusive [30]. Shirakawa *et al.* [7] showed that a positive tuberculin response in BCG-vaccinated schoolchildren in Japan correlated with a lower incidence of atopic disorders, but others could not confirm these findings [31].

In summary: infections stimulating the TH1 or TH2 response may suppress or stimulate, respectively, the development of allergy and asthma.

Diets

How can we explain that altered food consumption is related to allergy (other than food-allergy) via modulation of the TH1/TH2 balance?

The antioxidant system minimizes membrane damage induced by endogenous oxygen radicals. As the antioxidant status is dependent on the dietary intake of fruit and vegetables, a reduction in these food items renders the individual more susceptible to oxidative stress [3] so that reactive oxygen radicals may initiate and propagate inflammatory processes. Recently, Soutar *et al.* [32] showed that low nutritional intake of zinc, magnesium and vitamin C increased bronchial reactivity. Thus, intake below a critical level will lead to increased oxidative stress characterized by inflammatory stimulation. The increased release of pro-inflammatory cytokines such as IL-1, IL-6, IL-8, TNF α and IFN γ shift the TH1/TH2 balance in favour of the TH2 response. Generally vitamin deficiency impairs the immune function [9], which is reversed by supplementation. Supplementation of animal and human diets with vitamins E and C and beta-carotene was shown to enhance lymphocyte proliferation and to decrease prostaglandin production. Vitamin C increases IFN γ production, as well. Depending on the structure, flavonoids modulate mitogen-induced cell proliferation, inhibit prostaglandin formation and stimulate the release of IL-4, TNF α and IgE [10]. In this way, intake of micronutrients below a critical level may affect the TH1/TH2 balance and ultimately the immune response [33].

The shift in the consumption from saturated fatty acids to linoleic acid may also contribute to the increased prevalence of allergic diseases. Linoleic acid (n-6) is a precursor of prostaglandins. PGE₂ inhibits the production of IL-2 and IFN γ but not IL-4 and IL-5 [11,12] which results in inhibition of TH1 responses in favour of TH2 responses. Consumption of fish containing n-3 PUFAs has an anti-inflammatory potential because it decreases the release of PGE₂ and leukotrienes [34]. The effect of dietary factors including the n-3/n-6 ratio on the increased prevalence of allergy and asthma remain, however, to be established [34].

Air pollution

A large number of epidemiological studies has shown associations between exposure to air pollution and impaired lung function, inflammatory reactions and prevalence of allergy [4,35], but it is unclear how subjects become sensitized with allergens by air pollution. It is assumed that air pollution alone does not affect the atopics, but following combined exposure to allergens and pollutants they may have increased clinical symptoms.

Particles and irritating gases increase the production of the pro-inflammatory cytokines IL-6 and IL-8 and inducible NO-synthase (iNOS) in bronchial epithelial cells *in vitro* [36–38]. In healthy subjects and asthmatics exposed to high levels of ozone, increased levels of IL-8 and other immune mediators in nasal lavage fluid was found [39,40]. Recently it was shown that NO inhibits TH1 cells in favour of TH2

cells [17]. Increased exhaled NO levels are observed in patients with allergic asthma, airway infections, and allergic rhinitis [41]. In preliminary studies we observed that school children exposed to increased traffic emission exhaled larger amounts of NO (Steerenberg *et al.* observations submitted). The increased production of NO may predispose for a permanent respiratory disease and/or allergic state. Apparently, environmental air pollutants induce cellular damage and evoke cytokine and NO production in a similar way as infections [42] and may thus be capable of shifting the TH1/TH2 balance. One may speculate that irritation of the lung parenchyma by air pollution triggers cytokine and NO release which may not only orchestrate the detrimental actions of inflammatory cells such as eosinophils, mast cells and lymphocytes, but also affect the TH1/TH2 balance in favour of the TH2 response.

Indeed, combined exposure of animals to ovalbumin or pollen plus diesel exhaust particles (DEPs) or exposure to house dust mite and NO₂ leads to increased antigen-specific IgE titres as compared with stimulation with the allergen alone, indicating the adjuvant activity of air polluting components [43]. Studies in healthy subjects show a significant increase in total IgE, but not IgG, IgA and IgM following nasal challenge with DEPs [13]. Subjects suffering from hay fever responded with a higher pollen-specific IgE titre induced by costimulation with DEPs.

In conclusion, due to the maturation steps of the immune system during the first 5 years after birth we have to recognize a vulnerable period in which the immune system is sensitive to environmental and lifestyle stress. Infections, diet, and air pollution are likely to have a profound impact on the immune system during maturation. These factors will determine the outcome of immunological maturation individually and also in concert and have different consequences after maturation. Future epidemiological studies should therefore expand their questionnaires to include these three factors.

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