

confounders, including reduction in passive smoke or mite allergen exposure, which could explain the improvement in respiratory symptoms. These types of study are extremely difficult, expensive and time consuming, but also virtually impossible to blind. Patient reporting bias could explain the soft positive outcomes, especially in conjunction with the low follow-up rate (6 months ~55%, 12 months ~75%). Even if the study is accepted as supporting mould control, we do not know which component of mould control is effective (removal, or fungicide, or increased ventilation, or perhaps all three combined). Or perhaps improving ventilation and reducing humidity is a good thing for respiratory health whatever the mechanism?

The answer to this question has been the subject of a truly landmark study from New Zealand<sup>21</sup> which studied 1350 non-insulated homes with low income families. The houses were generally stand-alone wooden homes on piles, with heating of a living room only. Two-thirds of homes had damp and three-quarters had visible mould. The homes had at least one household member with respiratory symptoms in the last year or a history of asthma, pneumonia or chest infections. Homes were randomised to have ceiling insulation installed, draught stopping around windows and doors, and moisture impenetrable barriers fitted below the floors (cost £700/house) or to control. Over 12 months there were substantial (of the order of 50%) improvements in self-rated health, wheezing and reduced time off work and school in the intervention group, with fewer visits to GP and hospital. Visible mould was reduced by 50%. Again it is impossible to fully blind this study, but it was single blind and the size of the study and the size of improvements for a mix of

hard and soft outcomes give it great weight. Essentially, the authors have identified an important and cost effective public health intervention. Whether it works by reducing mould exposure or whether mould is a bystander of housing quality is an open question.

So there is the challenge for any society with a social conscience. The New Zealand study needs to be reproduced around the world, accounting for local housing conditions and climate, to see if the results are transferable. In New Zealand the intervention not only improves respiratory health in a vulnerable part of society, it actually saves them money. Overall heating costs went down by 20%, and that can't be bad for that other big environmental challenge—outdoor climate change!

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## Vitamin D and asthma

# Maternal diet vs lack of exposure to sunlight as the cause of the epidemic of asthma, allergies and other autoimmune diseases

Scott T Weiss, Augusto A Litonjua

## Role of vitamin D deficiency in allergic and autoimmune diseases

**A**sthma is occurring in epidemic proportions with more than 300 million affected subjects worldwide. In almost

all cases the disease has its onset in early childhood, with 80–90% of all cases initially being diagnosed before the age of 6 years.<sup>1,2</sup>

It was not always so. In the early 1970s the prevalences of asthma and allergy were roughly half of what they are today, and although the onset of the asthma epidemic started insidiously and cannot be precisely documented, it has several interesting and important features that have defied a unified explanation until now. There is clearly a North/South equatorial gradient with Western industrialised countries furthest away from the equator (New Zealand, Australia, the UK) having the highest prevalence worldwide. There is also a clear urban/rural gradient among poorer Third World countries, and a First (industrialised) World/Third World gradient with the lowest asthma prevalence occurring in rural areas in Third World societies. A very important feature of the epidemic is that it is not only asthma that has increased. A host of

other autoimmune diseases—such as multiple sclerosis, type 1 diabetes and Crohn's disease—have all increased dramatically as well.<sup>3</sup> So it is not just Th2 diseases like asthma, allergic rhinitis, eczema and food allergy that have increased, but also Th1 autoimmune diseases. Less directly connected to the epidemic is the seasonal gradient in incidence with a peak in the late winter/early spring. Finally, in the USA the asthma epidemic seems worse among the urban poor, particularly among minorities (African-Americans and Puerto Ricans).

One of the theories to explain these disparate epidemiological findings is the hygiene hypothesis, which posits that the decrease in early childhood infections leads to "missing immune deviation" from a predominantly Th2 to a more balanced Th1/Th2 immune response, eventually resulting in allergic disorders.<sup>4,5</sup> However, the hygiene hypothesis fails to explain all the features noted above, such as the parallel rise in Th1 autoimmune diseases and the fact that children most at risk for asthma are also most susceptible to respiratory infections.<sup>6</sup> A more plausible explanation is that changes in diet and lifestyle (particularly time spent indoors) have fuelled the epidemic.

Since the first paper published on the subject in 1990, a large number of studies have been performed linking diet to respiratory disease in both adults and children.<sup>7</sup> In 1997, one of us (Weiss) suggested, at a CIBA symposium meeting on the causes of the epidemic, that the key might lie in the study of maternal diet and its relationship to asthma in infants.<sup>8</sup> Now, 10 years after that symposium, a series of papers from two birth cohort studies—Project VIVA in the USA and the study by Seaton's group in Aberdeen, UK—have been published which begin to give us clues about the causes of the epidemic, but perhaps not in the ways we initially suspected.<sup>9–12</sup>

The most important finding from both studies is that a higher maternal intake of vitamin E and vitamin D has substantial effects in reducing the risk of asthma at age 3 years (VIVA) and 5 years (Aberdeen study).<sup>9–12</sup> Both vitamins are fat-soluble and their intake is correlated, since much of it (particularly of vitamin D) comes solely from dietary supplements. In fact, vitamin D normally does not come from the diet at all but, in cultures where little time is spent outdoors, dietary supplements and fortified foods may be the only source, particularly during the winter months. There is a growing body of evidence that human intake, particularly during pregnancy, may be woefully inadequate.<sup>13–15</sup>

Based on the epidemiological data to date, it is likely that deficiencies of both vitamins D and E are contributing to the epidemic and both deserve further study. However, in our view, the vitamin D story is the clearer of the two. Our interest in vitamin D devolved directly from having positionally cloned the gene for the vitamin D receptor as a gene for asthma.<sup>16</sup> We then investigated it in epidemiological studies.<sup>10,12</sup> It seems likely that a gradual decrease in exposure to sun due to sun avoidance behaviours in Western societies (sunscreen, clothing, sun avoidance, increased time spent indoors) reached a critical level in the early 1970s, such that humans were not spending enough time outdoors and vitamin D levels reached acutely low levels. Vitamin D is essential to the normal functioning of the human immune system. It is the on/off switch for CD4 positive T lymphocytes of the Th1 and Th2 variety by virtue of its control of T regulatory cell function.<sup>17–19</sup> Hence, insufficiency of vitamin D leads to dysfunctional T cell regulation and a flabby immune switch, lack of downregulation of both Th1 and Th2 inflammation via lowered levels of transforming growth factor  $\beta_1$  and interleukin-10, and the subsequent development of both Th1 and Th2 autoimmune diseases. Vitamin D deficiency is the only factor that can explain all epidemiological aspects of the allergic and autoimmune disease epidemics noted above, and now the hypothesis that urgently needs testing is whether replenishment of pregnant women with vitamin D will have a major impact on the occurrence of all autoimmune diseases, particularly if it is followed by subsequent sufficiency of vitamin D in the developing child and adult. Although there are contrary epidemiological data linking vitamin D as a cause of asthma, in our view these studies have substantial methodological flaws, most importantly the lack of assessment of vitamin D status in childhood and serious loss to follow-up, thus invalidating their conclusions.<sup>20,21</sup>

The role of vitamin E is less certain. A careful look at the data on vitamins D and E in the VIVA and Aberdeen studies suggests that vitamin E has a greater effect in Aberdeen and vitamin D has a greater effect in Boston. This is, in our view, an artifact of the very low levels and lack of variation in estimates of vitamin D intake in Aberdeen which limit the detection of the effect of vitamin D in that population. In addition, while there is a large body of data linking vitamin D deficiency to Th1 autoimmune disease, the evidence for vitamin E is weaker. In our view, the fundamental culprit for the asthma epidemic—and for the epidemic

of all autoimmune diseases (Th1 and Th2)—is vitamin D deficiency due to a decrease in sun exposure which can probably be remedied only by supplementation of pregnant women. However, in their most recent paper published in this issue of *Thorax*, Willers and coworkers<sup>22</sup> report the importance of a decline in the intake of fresh fruits and vegetables and perhaps oily fish consumption with regard to asthma, and it seems plausible that maternal dietary deficiencies of vitamin E are contributing to the epidemic of autoimmune disease as well (*see page 773*). Certainly, given the available data, randomised controlled trials of vitamin E in pregnant women are indicated.

Given these important results, what needs to be done next? First, measurement of actual vitamin D levels during pregnancy and in cord blood and determining their relationship to subsequent wheezing in birth cohort studies can easily be done. Measuring levels directly, rather than estimating intake from food frequency questionnaires, will be more reliable since levels will integrate sun exposure as well as supplement use to assess exposure accurately. Second, the two confirmatory observational birth cohort studies are enough to suggest an intervention trial of vitamin D supplements to prevent the development of immune-mediated disorders, particularly asthma. Such a trial has currently been submitted for funding and is awaiting review in the USA. While the postnatal effects of vitamin D on immune function are clear, its effects on immune development are not. More needs to be known about the mechanisms by which vitamin D, vitamin E and other nutrients influence fetal development. This is the province of epigenetics and genetic programming of the fetus and should be done in mouse models. In our view, this line of research can have major public health implications that go beyond respiratory disease and influence everything from childhood infection in the Third World to type 1 diabetes and inflammatory bowel disease in industrialised societies.

Vitamin D deficiency is the single most important dietary deficiency in the world today. It has already been linked to prostate cancer, colon cancer and breast cancer. After almost 35 years of increases in allergic and autoimmune disease, we are beginning to understand the causes of the epidemic. Much more research is needed, but the way seems clear to rapidly improve human health in a number of areas once the appropriate studies are done.

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### Air pollution and human health

# Air pollution, human health, climate change and you

George Thurston

## The “co-benefits” of reducing air pollution on climate change and human health

The study by Ko *et al*<sup>1</sup> in this issue of *Thorax* (see page 780) provides an important new contribution to the growing body of evidence that the severe adverse health effects of air pollution, so well documented in Europe and North America, are also occurring in Asia. Indeed, a recent report by the Health Effects Institute (HEI) surveyed the available published literature on this topic as part of its Public Health and Air Pollution in Asia-Science Access on the Net (PAPASAN) study. They found hundreds of published studies showing adverse health effects of air pollution in Asia and summarised the results on the web (<http://www.healtheffects.org/Asia/papasan-home.htm>). These results show that a wide range of health effects are significantly associated with air pollution

exposures in Asia, including studies of respiratory and cardiovascular morbidity and mortality in a number of cities across Asia. In fact, the HEI report identified 69 published studies of the effects of air pollution on the health of populations in Mainland China, 16 in Hong Kong, 56 in Taipei, China, 8 in Indonesia, 2 in Malaysia, 6 in Singapore, 13 in Thailand, 30 in India, 46 in Japan and 33 in South Korea. The study by Ko *et al* now adds to this knowledge by identifying a susceptible population not studied extensively before in Asia—people suffering from chronic obstructive pulmonary disease, the fifth largest cause of death in Hong Kong.

Clearly, there is a large body of studies documenting an ever widening range of adverse health effects of air pollution in

Asia. As summarised in the HEI report, the increased cardiopulmonary risks found in Asia are similar in magnitude, per amount of pollution, to the relative risks found in other parts of the world.<sup>2</sup> But the importance of these increased risks for illness, hospital admissions and mortality are much greater than in Europe or North America because the levels of air pollution in Asia are usually so much higher. For example, the populations of Hong Kong and New York City are both about 8 million, but the annual average concentration of particulates with an aerodynamic diameter <2.5  $\mu\text{m}$  (PM<sub>2.5</sub>) in Hong Kong, as reported by Ko *et al*,<sup>1</sup> is nearly triple that found in New York (36  $\mu\text{g}/\text{m}^3$  vs approximately 14  $\mu\text{g}/\text{m}^3$ ). And, as shown in fig 1, Hong Kong has among the cleanest air of Asian cities. Air pollution represents a major, and growing, public health problem in Asia. Indeed, the World Health Organisation (WHO) has estimated that urban air pollution contributes each year to approximately 800 000 deaths and 4.6 million lost life-years worldwide.<sup>4</sup> As the population and economic activity of Asia grows, and as the migration of residents from the rural countryside to the cities accelerates, the outdoor air pollution health problems will continue to worsen unless measures are taken to reduce emissions of air pollutants by industrial, motor vehicle and fossil fuel combustion sources.