

Vitamin D deficiency and the asthma epidemic

The enthusiastic editorial by Weiss and Litonjua (*Thorax* 2007;**62**:745–6) may have left some readers with the impression that a single cause of the rise in asthma, multiple sclerosis, inflammatory bowel disease and type 1 diabetes in the West has now been discovered, namely vitamin D deficiency, and that primary prevention of asthma and autoimmune disease is just around the corner. Indeed, their bold conclusion portrays vitamin D supplementation as a likely panacea for many ills worldwide.

Weiss and Litonjua argue that the epidemiological evidence to implicate prenatal vitamin D and vitamin E deficiency in the aetiology of asthma and atopy is sufficiently compelling to justify urgent prenatal supplementation trials. They cite their own observational data linking a higher maternal intake of vitamin E and vitamin D to a lower risk of early wheezing, but dismiss contrary evidence which suggests that a higher vitamin D status in utero and infancy may increase the risk of atopic conditions in later life.^{1,2} However, these latter findings, and recent data in adults,³ are in keeping with the original “vitamin D hypothesis” of Wjst and Dold, not cited in the editorial, which proposed that increasing intake of vitamin D, as a result of fortification of foods such as margarine, may have contributed to the rise in atopy in the West.⁴ I would argue therefore that the vitamin D story is, at present, rather more confused than Weiss and Litonjua suggest, and that before rushing into prenatal nutrient supplementation trials, we need more convincing data to support their hypothesis, and greater confidence that such an intervention would be safe.

Given the failure to translate observational associations between antioxidant deficiency and asthma into beneficial interventions in adults, we need to be more sure that observational links with prenatal nutrition are not confounded, and that longer term follow-up of birth cohorts does not reveal a positive relation between prenatal vitamin D status and atopy. Demonstration of interactions between prenatal vitamin D status and vitamin D receptor polymorphisms on asthma and atopic outcomes would strengthen causal inference. As the authors themselves point out, we know very little about the effects of vitamin D and E on fetal and immune development, and it would be prudent to heed a recent lesson from a trial of prenatal vitamin C and E supplementation in which, compared with placebo, vitamin supplementation increased the risk of low birth weight.⁵

S O Shaheen

Correspondence to: Dr S O Shaheen, Respiratory Epidemiology and Public Health Group, National Heart and Lung Institute, Imperial College London, Emmanuel Kaye

Building, Manresa Road, London SW3 6LR, UK; s.shaheen@imperial.ac.uk

Funding: SOS is an Asthma UK Senior Research Fellow.

Competing interests: None.

Thorax 2008;**63**:293. doi:10.1136/thx.2007.091728

REFERENCES

1. Gale CR, Robinson SM, Harvey NC, *et al*. Maternal vitamin D status during pregnancy and child outcomes. *Eur J Clin Nutr* 2008;**62**:68–77.
2. Hyponen E, Sovio U, Wjst M, *et al*. Infant vitamin D supplementation and allergic conditions in adulthood: Northern Finland Birth Cohort 1966. *Ann N Y Acad Sci* 2004;**1037**:84–95.
3. Wjst M, Hyponen E. Vitamin D serum levels and allergic rhinitis. *Allergy* 2007;**62**:1085–6.
4. Wjst M, Dold S. Genes, factor X, and allergens: What causes allergic diseases? *Allergy* 1999;**54**:757–9.
5. Poston L, Briley AL, Seed PT, *et al*. Vitamins in Pre-eclampsia (VIP) Trial Consortium. Vitamin C and vitamin E in pregnant women at risk for pre-eclampsia (VIP trial): randomised placebo-controlled trial. *Lancet* 2006;**367**:1145–54.

Author's reply

We would like to thank Dr Shaheen for his interest in our recent editorial (*Thorax* 2007;**62**:745–6). Shaheen brings up several important points, which we were unable to discuss because of the space limitations. Many of these points have been discussed in our recently published commentary in another journal.¹ We agree with one of the points that Shaheen makes—namely, we certainly acknowledge that there is some evidence for a contrary hypothesis that Wjst and Dold put forth, as we have discussed.¹ However, there are other points where we disagree.

Firstly, Shaheen states that the Wjst–Dold vitamin D hypothesis was a “result of fortification of foods such as margarine, which may have contributed to the rise in atopy in the West”. Despite food fortification, multiple studies have now shown that vitamin D deficiency is highly prevalent² even in sun-replete areas of the world³ and that vitamin D supplementation and fortification of foods in current doses are inadequate to prevent deficiency.⁴ This suggests to us that behaviours that have led to decreased sun exposure have had a larger effect than diet on vitamin D status of human populations.

The two greatest sources of vitamin D are sun exposure and supplements, not diet, except in rare circumstances. Therefore, we would argue that fortification of foods may have improved the vitamin D status of populations just enough to prevent widespread rickets (although not entirely eradicated in Western society⁵) but did not have sufficient impact on the development of asthma and allergic disorders. Secondly, he suggests that before clinical trials of supplementation are performed, “we need more convincing data to support their hypothesis, and greater confidence that such an intervention would be safe”. A query of the US clinical trials database

(www.clinicaltrials.gov) shows that there are at least 218 registered vitamin D studies for various diseases, with at least seven trials investigating vitamin D supplementation in pregnancy, lactation and low birth weight infants.

These studies are ongoing and preliminary data have shown no adverse effects of vitamin D supplementation in pregnancy with doses up to 6000 IU/day.⁶

Thirdly, Shaheen suggests that we need more observational epidemiology to assess whether the effect observed in the Project Viva and SEATON cohort studies are real. We disagree. More observational epidemiology will never answer this question definitively; what is needed is a randomised controlled trial of vitamin D supplementation during pregnancy, the time period where we observed the large beneficial effect on asthma outcomes in two separate and independent birth cohorts with widely different exposure levels.

Finally, Shaheen suggests that study of vitamin D receptor polymorphisms would strengthen causal inference. While it is not entirely clear how it would do this, we do agree that this is of some relevance. However, genetic polymorphisms in VDR and its binding protein will only explain a small percentage of phenotypic variation in vitamin D levels and will be much less important than environmental factors such as dietary supplements and sun exposure behaviours in determining vitamin D levels, which are primarily a measure of recent rather than chronic exposure.

We regret that the limits of the editorial did not allow a complete review of this interesting and important topic.

S T Weiss, A A Litonjua

Channing Laboratory, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA

Correspondence to: Dr S Weiss, Channing Laboratory, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02115, USA; scott.weiss@channing.harvard.edu

Competing interests: None.

Thorax 2008;**63**:293. doi:10.1136/thx.2007.092569

REFERENCES

1. Litonjua AA, Weiss ST. Is vitamin D deficiency to blame for the asthma epidemic? *J Allergy Clin Immunol* 2007;**120**:1031–5.
2. Holick MF. Vitamin D deficiency. *N Engl J Med* 2007;**357**:266–81.
3. Binkley N, Novotny R, Krueger D, *et al*. Low vitamin D status despite abundant sun exposure. *J Clin Endocrinol Metab* 2007;**92**:2130–5.
4. Bischoff-Ferrari HA, Giovannucci E, Willett WC, *et al*. Estimation of optimal serum concentrations of 25-hydroxyvitamin D for multiple health outcomes. *Am J Clin Nutr* 2006;**84**:18–28.
5. Allgrove J. Is nutritional rickets returning? *Arch Dis Child* 2004;**89**:699–701.
6. Wagner CL, Hulseley TC, Fanning D, *et al*. High-dose vitamin D3 supplementation in a cohort of breastfeeding mothers and their infants: a 6-month follow-up pilot study. *Breastfeeding Med* 2006;**1**:57–68.