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EDITORIAL

Vitamin D in asthma and allergy: what next?

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Much of the original work on vitamin D and asthma incidence focused on birth cohort studies. These studies examined the effect of maternal intake of vitamin D during pregnancy and its impact on asthma/wheeze in the first few years of life [1–3]. In all three of these methodologically well-performed birth cohort studies, higher maternal intake of vitamin D was associated with a lower incidence of asthma and wheeze in the child. However, one cohort study with very a small sample size and high loss to follow-up may have obtained spurious negative results as a consequence of these significant methodological flaws [4]. Another relevant concern is that the positive studies did not measure vitamin D directly but simply looked at maternal vitamin D intake, mostly from supplements, as a proxy for vitamin D levels.

This brings us to the study by HOLLAMS *et al.* [5] in this issue of the *European Respiratory Journal*, which looked at 989 6-yr-olds and 1,380 14-yr-olds from an unselected birth cohort in Perth, Australia. Of the Raine cohort participants, 689 subjects were seen longitudinally at both ages 6 and 14 yrs, and the predictive value of vitamin D levels at age 6 yrs could be used to assess clinical outcomes at age 14 yrs. Loss to follow-up, the major validity threat in a study such as this, was demonstrated not to influence their results. Vitamin D levels at ages 6 and 14 yrs were predictive of allergy/asthma outcomes at that age. But more importantly, vitamin D levels at age 6 yrs were predictive of subsequent atopy/asthma-associated phenotypes at age 14 yrs. The significant results were restricted to males. This study is the first to demonstrate such an association, as seen in the early-life birth cohort studies, in older children and is one of the first using vitamin D levels as a biomarker of vitamin D exposure.

What about serum Vitamin D levels as a biomarker, particularly as it pertains to asthma? This question needs to be broken up into several parts. First, what is an adequate serum level of vitamin D? There is a great deal of controversy as to what represents adequate levels of vitamin D in the blood for human health generally, let alone for asthma specifically [6–8]. There is a greater number of studies in the medical literature in which vitamin D levels have been measured in prevalent asthma cases rather than in population samples of predominantly normal subjects [9–12]. That having been noted, we would agree that >75 nmol·L^{-1} (>30 ng·mL^{-1}) is sufficient while 50–75 nmol·L^{-1} (20–30 ng·mL^{-1}) is insufficient and <50 nmol·L^{-1} or <20 ng·mL^{-1} is deficient. Using these criteria, 41.4% of the children in the Raine cohort had sufficient vitamin D levels at age 14 yrs during the winter months. This is actually substantially higher than many other populations, and may relate to the greater time spent outdoors in the temperate climate of Western Australia. In many western populations, the prevalence of insufficiency is >70% [13, 14] and varies by season of the year, making it impossible to perform such a study as that of HOLLAMS *et al.* [5].

The second part of the question is methodological. How good a biomarker is serum vitamin D? The Raine investigators took advantage of two methodological features of their data and their data analysis. First, they utilised vitamin D as a continuous variable to obtain maximal power and secondly, they had an unusually high correlation between the age 6 yrs and the age 14 yrs serum vitamin D levels (r=0.93). In most investigations of serial vitamin D levels, the r-value (correlation) between two subsequent serum vitamin D values taken about 3 months to 1 yr apart is ~0.4, similar to what one might find for low-density lipoprotein cholesterol. This is reflective of the high degree of variability in vitamin D measurements due to environmental, metabolic and genetic factors. Environmental factors influencing vitamin D levels include sun exposure, sun screen use, time spent outdoors, diet and season of the year. Only season of the year was actually measured by HOLLAMS *et al.* [5], but 95% of all subjects were Caucasian (controlling for skin colour) and perhaps controlling for season was critical. Alternatively, the other potential environmental variables must not have changed over the 8 yrs of the study. This is a most remarkable finding since in most studies, a biomarker such as vitamin D will be only weakly predictive over such a long period of time due to the low correlation on repeat measurement and subsequent misclassification of exposure.

As noted by HOLLAMS *et al.* [5], the authors had no information on children at birth or in the first few years of life in the time frame of the early birth cohort studies noted above [1–3]. Fortunately, there are some observational data that can be brought to bear on this age group. CAMARGO JR *et al.* [15] noted that 27% of New Zealand infants would be in the range of sufficiency (*e.g.* levels >75 nmol·L^{-1}) based on cord blood vitamin D levels. Those authors then found that lower cord blood levels of vitamin D were predictive of respiratory illness at age 3 months and of wheezing at 15 months, 3 yrs and 5 yrs of age. While CAMARGO JR *et al.* [16] make a point of emphasising a lack of association of cord blood levels with asthma at age 5 yrs, this seems less relevant given the low predictive power of a single measure of vitamin D as a biomarker and the

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small number of sufficient subjects at birth in this study. This work would tend to confirm the paper by HOLLAMS *et al.* [5] for an early life birth cohort.

Mechanistically, vitamin D exerts its effects in asthma through both immune and structural effects in the developing fetal and perhaps post-natal lung. These effects are extensively reviewed elsewhere [17–19]. Recently, the role of vitamin D as a modulator of the infant intestinal microbiome has also been suggested as another potential mechanism involved in asthma and other autoimmune disease pathogenesis [20]. All of this mechanistic work is strengthened by the epidemiology presented by HOLLAMS *et al.* [5] and CAMARGO JR *et al.* [16].

Another interesting aspect of the study by HOLLAMS *et al.* [5] is the finding that their results pertained to males but not females. They note that there is a functional synergy between 1,25-hydroxyvitamin D_3 and 17-β-oestradiol, mediated through oestrogen receptor α, to enhance vitamin D receptor expression, inactivate vitamin D catabolism (CYP24A1) and increase vitamin D_3-binding protein. We would note that for a given height and age, females have more body fat than men and that vitamin D is a fat-soluble vitamin, so these compensatory mechanisms may be evolutionarily important given the important role of vitamin D in fertility and conception [21–24]. Whether these biological mechanisms explain the results or whether they are due to small sample size, further exploration of the evolutionary adaptions to low vitamin D exposure in pregnancy is a worthwhile scientific endeavour. It is worth noting that, consistent with the animal data and basic research, different observational human studies have shown effects of vitamin D on allergy phenotypes, asthma/wheeze, lung function, airway responsiveness and bronchodilator response but never have these effects been present in every study. Vitamin D levels, length of follow-up, age, sample size and myriad other factors influence which of these phenotypes are most significant in an individual investigation.

At the end of the day, all of the studies cited here are observational and hence are subject to multiple potential biases, such as loss to follow-up, small sample size [4] or recall and information bias [25]. Given our lack of knowledge about the optimal dose of vitamin D for immune system functioning, the variability of vitamin D as a biomarker, and the very high prevalence of vitamin D insufficiency in western industrial populations, clinical trial results are needed to make definitive recommendations for both asthma prevention and for the use of vitamin D with inhaled corticosteroids to prevent steroid resistance. Fortunately, such trials for asthma prevention (www.clinicaltrials.gov identifiers NCT00920621 and NCT00856947), for enhancing steroid effectiveness in established disease (NCT01248065) or for prevention of exacerbations (NCT00978315) are under way. One of the debates that will occur, should the prevention trials show positive benefit, is the relative role of the protective effect of vitamin D with maternal pregnancy *versus* post-natal supplementation. It seems highly unlikely that maternal supplementation to sufficiency during pregnancy alone will, by itself, prevent asthma and allergic phenotypes; some degree of post-natal supplementation will also probably be necessary to maintain normal immune function in the long term.

STATEMENT OF INTEREST

None declared.

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