

CORRESPONDENCE

Vitamin D in early life: good or bad for food allergies?

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There is controversial evidence for an influence of 25-Hydroxyvitamin D₃ (25-OHD) levels and nutritional vitamin D supplementation, respectively, on the development of allergic diseases during childhood. We have read with great interest the paper by Weisse et al. who analyzed data of a subgroup of the prospective German LINA cohort study, including 378 mother–child pairs (1). The authors describe a positive association of 25-OH-D₃ levels, in both maternal and cord blood, with parent-reported doctor diagnosis of food allergy in the second year of life, but not in the first year. In addition, maternal 25-OH-D₃ levels were positively associated with the child's serum level of IgE specific for food allergens (but not inhalant allergens) at the age of two. We believe that unfortunately, this study suffers from some major limitations that do not allow the drawing of the published conclusions.

Most importantly, food allergy was diagnosed by parental report of a doctor diagnosis and not by an oral food challenge test. Although the authors have mentioned this limitation, we would like to point out that the prevalence of parent- or self-reported food allergy differs markedly when compared with objective measures. This has been shown in a meta analysis by Rona et al. and a systematic review by Zuidmeer et al. (2, 3). Therefore, a number of expert panels from various organizations have published consensus documents on the appropriate diagnosis of food allergies highlighting the importance of oral food challenges for diagnosing food allergy (4, 5). Thus, the authors used an outcome definition for food allergy that has not been validated. It does not allow the conclusion to be drawn that high vitamin D levels increase the risk of food allergy.

Furthermore, the authors had not prioritized their primary outcome and secondary outcomes. Multiple testing of 30

outcomes increases the finding of statistically significant associations by chance. This is acceptable if the results are clearly interpreted as explorative and are used as the basis for planning future studies. It is not acceptable for advice in favor of or against vitamin D supplements. Also, vitamin D deficiency is strongly associated with low birth weight (6). By not regarding birth weight as an important clinical parameter in this setting, the authors have missed the chance to clarify a potential association of birth weight and atopic disease.

Finally, the authors falsely concluded that cord blood vitamin D levels are correlated with regulatory T cells. This does not correspond to the scatter plot (Fig. 4) or the correlation coefficient of $r = -0.17$. It is a misinterpretation of their results based on only interpreting the *P*-value but ignoring the low correlation coefficient, which is close to zero (equal to no correlation) and far away from 1 (equal to best correlation). Therefore, the last sentence of the Results section in the abstract as well as the last two sentences of the Results in the main text could mislead the readers. Thus, the suggestion that Treg numbers in cord blood might mediate the effect of vitamin D levels on atopic outcomes remains hypothetical.

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We read with interest the article by Weisse et al. (1) who observed that higher 25-hydroxyvitamin D (25[OH]D) levels in maternal (34th week of gestation) and cord blood were associated with an increased risk of food allergy within the first 2 years of life. They hypothesized that this finding might be explained by an inhibition of regulatory T cells (Tregs) because they observed an inverse correlation between cord blood 25 (OH)D and numbers of Tregs (1). Weisse and colleagues finally concluded that their results would argue against vitamin D supplementation (1). This work is definitely of high interest but the conclusion may also cause confusion among physicians and parents on how to apply vitamin D supplementation during pregnancy and early life. We therefore wish to put the article of Weisse et al. into the perspective of existing information relating to vitamin D and food allergies (1, 2).

We want to guide particular attention to the work by Allen et al. who reported that in 1-year-old infants of Australian-born parents, vitamin D insufficiency, that is, 25(OH) D concentrations ≤ 20 ng/ml (50 nmol/l), was associated with significantly increased risk of peanut and egg allergies (3). In addition, these vitamin D insufficient infants were more likely to have multiple rather than single food allergies (3). These data were derived from a population-based sample and are based on the use of gold standard methods for food allergy status (3). By contrast, Weisse et al. (1) acknowledged as limitations of their study the potential bias by high rates of participating atopic parents and the lack of provocation tests. Another point to discuss is the inverse association between Tregs and 25(OH)D in the work by Weisse et al. (1). This stands in contrast to a recent pilot trial and a randomized controlled trial (RCT) showing that vitamin D supplementation significantly increases the numbers of Tregs in apparently healthy adults (4, 5). Taken together, the data by Weisse et al. on associations of 25(OH)D levels with food allergies and Tregs are thus contradictory to studies later in life (1–5). Is the relationship between vitamin D status and the immune system therefore completely different throughout the lifespan? To answer this question, we recommend further

studies to address the relationship between vitamin D status and food allergies by measuring 25(OH)D repeatedly during different periods of life.

At present, we can only conclude that the existing evidence is insufficient to argue for or against vitamin D supplementation in pregnancy with regard to prevention of food allergies. This conclusion is also supported by the fact that Allen et al. (3) reported on no significant association between vitamin D supplement intake during pregnancy and food allergies. However, we also want to underline that according to data from available RCTs, vitamin D supplementation during pregnancy can significantly increase 25(OH)D levels and can be considered to be safe and probably beneficial with regard to maternal comorbidities of pregnancy, while other long-term health outcomes of vitamin D supplementation in pregnant women need to be addressed in further studies (6).

Author contributions

Stefan Pilz and Winfried März contributed equally to the conception, drafting, and revising the manuscript.

Conflicts of interest

None.

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REPLY

We appreciate the discussion on the role of vitamin D in allergy development and read with interest the letters by Pilz et al. and Querfeld et al., which give us the opportunity to further clarify some aspects of our study (1).

As highlighted by Pilz et al., a recently published Australian study (2) showed an association between vitamin D insufficiency and multiple food allergies based on data from one-year-old children. At first glance, the result of this study seems to be contradictory to our data. However, the Australian data were derived from one-year-old children, whereas we focused on maternal vitamin D during pregnancy and cord blood vitamin D at birth. The different result obtained from different time points could give evidence that in fact the relationship between the vitamin D status and the immune system might be different in the pre- and postnatal period. Furthermore, the result 'low vitamin D – high risk of food allergies' was only seen in infants whose both parents were born in Australia. Among all 481 participants as well as in infants with one or both parents born overseas, this result could not be confirmed, which even more is pointing out the heterogeneous results on vitamin D and allergy development.

We are aware of the limitation (as critically discussed in the article) that our food allergy outcome relies solely on the parental report of a doctor's diagnosis with the uncertainty that this might not have been verified by oral food challenge. However, it is general practice in epidemiological studies that food allergy is based on questionnaire information and not necessarily on additional provocation tests (3).

When we have studied the association between the vitamin D status during pregnancy and at birth with later atopic outcomes, we have also tested for a potential confounding effect of the birthweight. Comparing mothers having low vitamin D levels with mothers having the high vitamin D levels, we saw no differences regarding the birthweight of their children (3355 g and 3387 g for the 1st vs. 4th vitamin D quartile ($P = 0.629$), respectively). Moreover, including birthweight as a confounding factor in the regression model did not change the obtained results.

Regarding the comments on our Treg data, studies cited by Pilz et al. (4) showing that vitamin D supplementation increases %Treg were performed in healthy adults who are completely different in their immunological pathways compared with newborns. Within our LINA study, we also observed a positive association in the mothers: increasing maternal Treg numbers with higher maternal vitamin D levels (Spearman correlation, $R = 0.157$, $P = 0.043$). The inverse relationship we have found for cord blood Treg and cord blood vitamin D confirmed data from earlier studies (5) and may give further evidence that the vitamin D impact on immune regulation differs through life.

We agree that the observed correlation coefficient is rather low. However, this is not surprising because it was already shown that besides vitamin D, several factors may have an impact on Treg numbers including the maternal immune status, parental atopy history and maternal tobacco smoke exposure (6).

We are highly aware of the potential difficulties of presenting conflicting data on vitamin D. However, we saw these results in our study that do not support earlier data showing vitamin D as allergy preventive. We believe that it is our responsibility to communicate that vitamin D might also have – under special circumstances – inverse effects regarding allergy development, and this should be taken into account when recommendations for supplementations are drawn. Vitamin D undoubtedly has many beneficial effects but presumably acts via different mechanisms throughout the lifespan.

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