

# Vitamin D and food allergies in children: A systematic review and meta-analysis

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## ABSTRACT

**Background:** Vitamin D insufficiency has been associated with immune dysfunction and linked to the epidemic of atopic diseases in the Western hemisphere, yet there are studies with conflicting results, and the risk has not been quantified uniformly across studies.

**Objective:** To perform a systematic review and meta-analysis to evaluate and quantify if vitamin D deficiency is associated with the presence and persistence of food allergy.

**Methods:** A systematic review was undertaken to assess for the association between food allergy and vitamin D status in children.

**Results:** A total of 368 citations relevant to this systematic review were identified. In the whole review, 5105 children were included. We did not find a significant association between 25 hydroxy vitamin D (25(OH)D) status and risk of food allergy in children (odds ratio [OR] 1.35 [95% confidence interval [CI], 0.79–2.29];  $p = 0.27$ ,  $I^2 = 58.3\%$ ). We conducted subgroup analyses based on different cutoffs of the 25(OH)D status (20 versus 30 ng/mL). Only one study used 30 ng/mL and found that children with <30 ng/mL were more likely to report food allergy than children with a 25(OH)D status of  $\geq 30$  ng/mL (OR 2.04 [95% CI, 1.02–4.04];  $p = 0.04$ ). Four studies compared children with a 25(OH)D status of <20 ng/mL to children with a 25(OH)D status of  $\geq 20$  ng/mL and found no significant differences (OR 1.18 [95% CI, 0.62–2.27];  $p = 0.62$ ,  $I^2 = 62.7\%$ ).

**Conclusion:** Based on the studies analyzed, this systematic review did not identify a significant association between vitamin D status and food allergy. Interpretation of the included studies was limited by a lack of a standard definition for vitamin D deficiency and insufficient knowledge regarding the optimal vitamin D status needed to impact immune function. Longitudinal studies are warranted to assess if vitamin D might contribute to the development of food allergy.

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Over the past 50 years, many studies have shown an increase in the prevalence of atopic diseases. This trend is especially pronounced in the United States and Europe as well as other countries that adopt similar Western lifestyles.<sup>1</sup> The increased predominance of atopic diseases was first recognized in asthma and later confirmed with additional studies to have a positive association between vitamin D deficiency and the prevalence of hay fever, allergies, and eczema.<sup>2</sup> More recently, within the past decade, food allergies have followed this same trend, indicated by rising inci-

dence and prevalence.<sup>3,4</sup> The general increase of allergic diseases is poorly understood, but most researchers agree that the cause is multifactorial. Changes in lifestyle, including more time spent indoors for both work and play, modifications in dietary habits, and advancements in sanitation, which lead to fewer infections, are all thought to play a significant role in this increase. Children today seem to be more sedentary and have less exposure to sunlight, which likely contributes to the extremely high prevalence of low 25 hydroxy vitamin D (25(OH)D) levels in children in the most recent National Health and Nutrition Examination Survey (NHANES) study.<sup>5</sup> These factors have given rise to the theory that a lower vitamin D status could be a contributing factor in the increased incidence of allergic diseases.

Vitamin D is a fat soluble vitamin that plays a critical role in calcium metabolism and bone health. In addition to its role in calcium metabolism, vitamin D is thought to have a variety of functions in other organ systems, including involvement in muscle strength, mood issues (e.g., depression),<sup>6</sup> cardiovascular health and diseases (e.g., hypertension),<sup>7</sup> and metabolic syndrome and/or diabetes.<sup>8</sup> Vitamin D is known to play a

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role in a variety of immune processes and atopic diseases. Proposed immune involvement of vitamin D includes the induction of tolerance by promoting the development of T-regulatory cells,<sup>9</sup> upregulation of interleukin 10 production,<sup>10</sup> and suppression of immunoglobulin E (IgE) production from B cells.<sup>11</sup> *In vitro* addition of vitamin D<sub>3</sub> to CD4<sup>+</sup> T cells from patients with steroid-resistant asthma increased the secretion of interleukin 10 to a status comparable with cells from nonsteroid resistant counterparts.<sup>12</sup>

A subsequent cross-sectional study found that patients with steroid-resistant asthma had lower numbers of forkhead box P3 (Foxp3)<sup>+</sup> T regulatory cells and this correlated with vitamin D deficiency.<sup>9</sup> Furthermore, patients with asthma and with vitamin D insufficiency seem to have decreased forced expiratory volume in the first second of expiration compared with their counterparts who have sufficient vitamin D levels,<sup>13–16</sup> and a correlation between low vitamin D status and an increased number of severe exacerbations has been described.<sup>17</sup> A direct cause and effect relationship has not been established for these correlations, however, and studies that linked vitamin D deficiency and asthma continue to be considered controversial.<sup>18</sup>

There is a growing body of literature that investigated the correlation between vitamin D deficiency and food allergy. There are studies that showed that anaphylaxis rates increase with distance from the equator. For example, in a U.S. study, the rate of prescriptions for epinephrine autoinjectors was higher in New England (Connecticut, Rhode Island, Massachusetts, Vermont, New Hampshire, and Maine) than in the more southern states.<sup>20</sup> Two studies, one in the United States<sup>21</sup> and another in Australia,<sup>22</sup> also show that patients diagnosed with food allergy are more likely to have been born in the winter months. In fact, food allergies were nearly threefold higher in children born in the winter compared with those born in the summer.

The idea that insufficient vitamin D status contributes to the development of food allergy is intriguing because it is a modifiable risk factor. The current American Academy of Pediatric guidelines recommend supplementing 400 IU of vitamin D daily for all infants who are breast fed and for infants who are formula fed and who consume <34 ounces of formula per day.<sup>23</sup> Despite these recommendations, it is unclear if this degree of supplementation is adequate to prevent vitamin D deficiency in all cases, especially for infants are high risk, including those born in the winter months and who live at higher latitudes. In addition, the optimal status of vitamin D required to potentially decrease the risk of developing a food allergy is unknown. In addition to clinical studies, there have been prospective and retrospective attempts to study this question more objectively by measuring vitamin D

status and by confirming type-1 hypersensitivity to food. However, a randomized controlled trial has not been performed. Therefore, to better understand if there is a relationship between low vitamin D status and an increased risk for food allergy, a systematic review of the literature was undertaken. Only studies that confirmed food allergy *via* positive clinical history and positive testing (specific IgE in the blood, skin-prick testing, and/or positive food challenge) and studies that obtained measurement of 25 (OH)D status in the blood were included.

## METHODS

In this systematic review, a study protocol that defined inclusion and exclusion criteria, a search strategy, outcomes of interest, and an analysis plan were developed and followed. The reporting of this study was in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement.<sup>24</sup>

### Literature Search and Study Selection

A comprehensive search of three data bases, including PubMed, Ovid MEDLINE, and Ovid Embase, was conducted to find relevant articles from the very inception of said data bases until week 41, 2015 (October 5, 2015). Subject headings, keywords, and related variations were searched for the terms “vitamin D” and “food allergy.” These search terms were broad, without language and country restrictions. An experienced reference librarian (P.E.) developed the search strategy with the help of the senior author (A.J.). Relevant systematic reviews and meta-analyses for additional citation were also searched.

To be eligible, the studies had to be clinical trials or observational studies that evaluated the association between the vitamin D status and food allergy in children < 18 years old, regardless of sex, ethnicity, or study locations. The outcome of interest was any type of food allergy defined by the practice parameters.<sup>25</sup> Studies that only reported food sensitization were excluded. For vitamin D status, the search was restricted to studies that reported the total 25(OH)D value or as calculated as sum of 25(OH)D<sub>2</sub> and 25(OH)D<sub>3</sub> levels as potential reasons of food allergy, although publication language was not restricted. Editorials, letters, *errata*, notes, or commentaries of studies were excluded. Conference abstracts were also excluded because these are typically not peer reviewed. Two pairs of independent reviewers, who worked independently ([M.M., B.P.] and [J.J., E.W.]) and in duplicate, screened the titles and abstracts of potentially eligible studies. Studies deemed relevant by either pair of reviewers were further screened by using full-text articles by the same

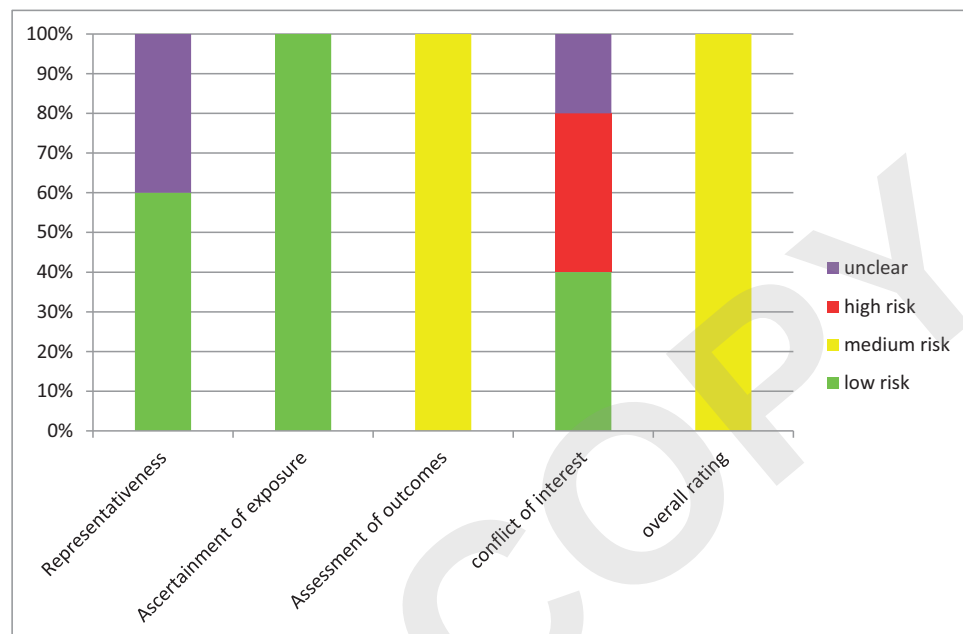


**Figure 1.** Quality of studies and risk of bias.

pairs of the reviewers. Discrepancies among all the reviewers were resolved through discussions and consensus between the reviewers and the senior author (A.J.).

### Data Extraction

The same pairs of reviewers, working independently and in duplicate, extracted study details by using a standardized pilot-tested form. Discrepancies were resolved by discussion and consensus. The following data were extracted from each study: the geographic location of the study; the design of the study; the age, sex, weight, body mass index of the patients; 25(OH) status; and the type of food allergy of the patients. The primary outcome (the number patients with food allergy) was also extracted from each study.

### Quality Assessment

To assess the risk of bias of the included studies, the modified Newcastle-Ottawa quality<sup>26</sup> assessment scale was used. The following quality items were used: representativeness of the patients, ascertainment of exposure, assessment of outcome, conflict of interest, and overall rating.

### Statistical Analysis

By using the primary outcome of the included studies, the odds ratio (OR) was calculated. The log-transformed ORs were then combined by using the DerSimonian and Laird random effects method,<sup>27</sup> with the estimate of heterogeneity from the Mantel-Haenszel model.<sup>28</sup> The original study's definition<sup>27</sup> of vitamin D insufficiency was adopted; however, a

subgroup analysis based on different vitamin D cut-offs (20 versus 30 ng/mL) was also conducted. Heterogeneity across the included studies was measured by  $I^2$  in which >50% indicated substantial heterogeneity. Potential publication bias was unable to be evaluated due to the small number of studies included in the analysis.<sup>29</sup> Two-sided  $p$  values of <0.05 were considered statistically significance. All statistical analyses were conducted by using Stata version 14.1 (StataCorp, LLP, College Station, TX).

### Risk of Bias

The quality of the studies was variable and is described in Fig. 1. Vitamin D statuses were all confirmed by laboratory tests; however, all of the included studies used self-reported outcomes on food allergy. Overall, the studies indicated a moderate risk of bias.

## RESULTS

A total of 368 citations relevant to this systematic review were identified: 366 from data base searches and 2 from previous systematic reviews. After an abstract screening and a full-text screen, five observational studies met the inclusion criteria and were included in the analysis (Fig. 2).<sup>30–34</sup> The characteristics of these studies are summarized in Table 1. In the whole review, 5105 children were included. The average age of each patient was 86 months (range, 13–159 months). Forty-seven percent of the patients were girls. Of the five studies, two were case-control studies, two were cross-sectional studies, and one was a prospective cohort study, with an average follow-up of 3.2 years. Geographically, two studies were conducted in the

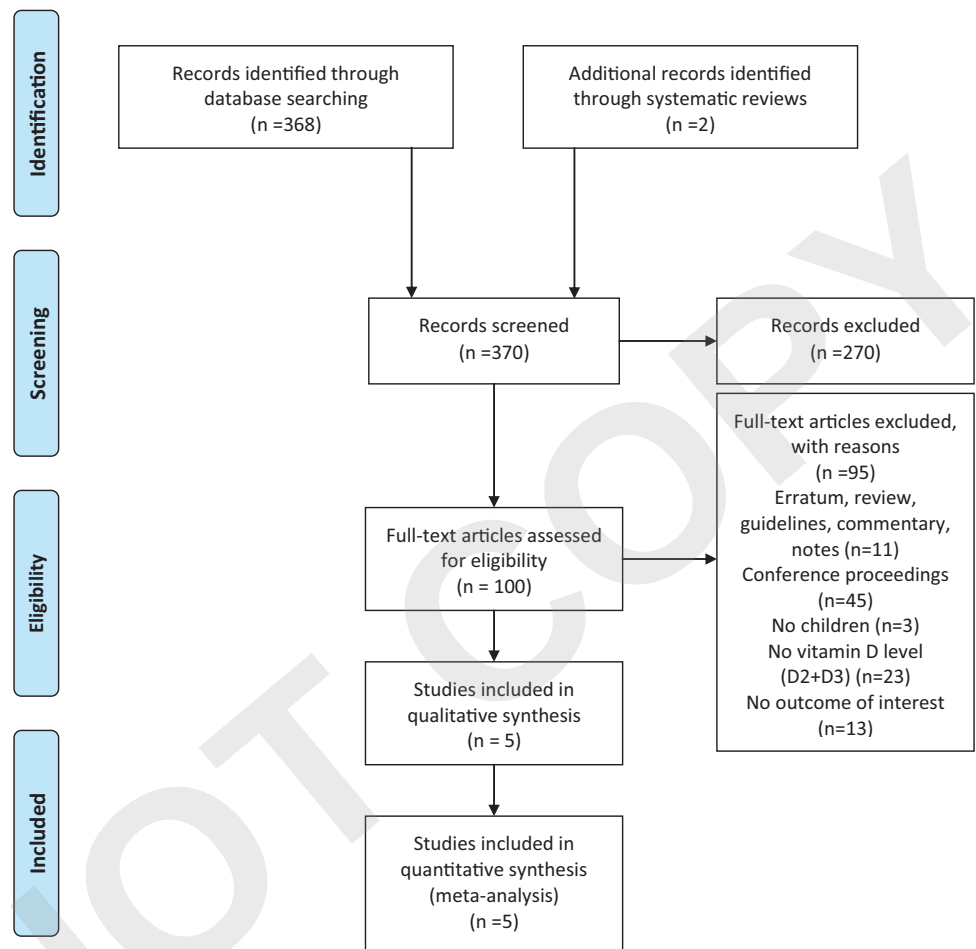


Figure 2. Flowchart.

United States and in west Europe, respectively, and one was in the Middle East.

We did not find a significant association between 25(OH)D levels or vitamin D status and a risk of food allergy in children (OR 1.35 [95% confidence interval {CI}, 0.79–2.29];  $p = 0.27$ ,  $I^2 = 58.3\%$ ). We conducted subgroup analyses based on different cutoffs of 25(OH)D levels (20 versus 30 ng/mL). Only one study<sup>34</sup> used 30 ng/mL and found that children with <30 ng/mL were more likely to report food allergy than children with a 25(OH)D level of  $\geq 30$  ng/mL (OR 2.04 [95% CI, 1.02–4.04];  $p = 0.04$ )(ref). Four studies<sup>30–33</sup> compared children with 25(OH)D levels of <20 ng/mL to children with 25(OH)D levels of  $\geq 20$  ng/mL and found no significant differences (OR 1.18 [95% CI, 0.62–2.27];  $p = 0.62$ ,  $I^2 = 62.7\%$ )(ref). Based on the studies analyzed, this systematic review did not identify a significant association between vitamin D status and food allergy.

## DISCUSSION

Based on the studies analyzed, this systematic review did not identify a significant association between vitamin D status and established food allergy. It should

be noted, however, that, after selecting only those studies that defined food allergy as a suggestive clinical history with corresponding positive skin-prick test results, blood IgE status, or oral food challenge, only 5 of the original 338 studies met the predefined criteria. Of these studies included in the review, only studies identifying a significant difference in the risk of developing food allergies based on Vitamin D status were included<sup>30–34</sup> (Fig. 3). This outcome highlighted the need for more large scale, well-designed, prospective studies with clinically accepted definitions of food allergy to examine this question. This can be difficult to accomplish, and studies that aimed to define the prevalence of food allergy have faced many of the same challenges. However, as the understanding of food allergy increases, the potential involvement of vitamin D status in the development and persistence of food allergy warrants continued investigation.

Current studies are also limited by a lack of consensus of what constitutes as vitamin D insufficiency or deficiency.<sup>35,36</sup> This was reflected in the reviewed studies and presented another challenge in evaluating the literature. For instance, in the five studies<sup>30–34</sup> included

Table 1 Description of the studies included in the systematic review and meta-analysis

| Study ID | Study, y                                                                                                                             | Design             | Total Sample Size | Age, mo         | Girls, % | Ethnicity, %                                       | BMI, kg/m <sup>2</sup> | Weight, kg     | Geographic Location | Definition of Food Allergies, IgE-mediated Reaction                                                                                                                                                             |
|----------|--------------------------------------------------------------------------------------------------------------------------------------|--------------------|-------------------|-----------------|----------|----------------------------------------------------|------------------------|----------------|---------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 60       | Liu <i>et al.</i> , <sup>34</sup> 2013                                                                                               | Prospective cohort | 460               | Infants         | 47       | NA                                                 | NA                     | NA             | United States       | Defined as cases as children who had allergen-specific IgE levels of $\geq 0.35$ kUA/L to any of eight common food allergens ( <i>i.e.</i> , egg white, milk, peanut, walnut, soy, shrimp, cod fish, and wheat) |
| 68       | Allen <i>et al.</i> , <sup>30</sup> 2013;<br>Koplin <i>et al.</i> , <sup>43</sup> 2016;<br>Peters <i>et al.</i> , <sup>44</sup> 2014 | Cross-sectional    | 712               | 11–15           | 47       | NA                                                 | NA                     | NA             | Australia           | IgE-mediated reaction: + IgE or SPT and positive oral challenge                                                                                                                                                 |
| 70       | Persson <i>et al.</i> , <sup>32</sup> 2013                                                                                           | Case control       | 62                | 159.2 $\pm$ 0.6 | 48.4     | NA                                                 | 19.9 $\pm$ 1.1         | 51.9 $\pm$ 4.1 | Sweden              | IgE-mediated reaction: based on clinical history, analysis of specific IgE to the offending foods, and oral food challenges                                                                                     |
| 96       | Ehlayel <i>et al.</i> , <sup>31</sup> 2011                                                                                           | Case control       | 966               | 92.4 $\pm$ 8.4  | 46.9     | NA                                                 | NA                     | NA             | Middle East         | Physician diagnosis, survey (other specific information not given)                                                                                                                                              |
| 101      | Sharief <i>et al.</i> , <sup>33</sup> 2011                                                                                           | Cross-sectional    | 3136              | 150 $\pm$ 2.4   | 47.6     | Non-Hispanic white, 61.9; non-Hispanic black, 14.1 | NA                     | NA             | United States       | No specific information given on definition of food allergy except that serum-specific IgE levels to food allergens were assessed                                                                               |

BMI = Body mass index; IgE = immunoglobulin E; NA = not available; SPT = skin-prick test.

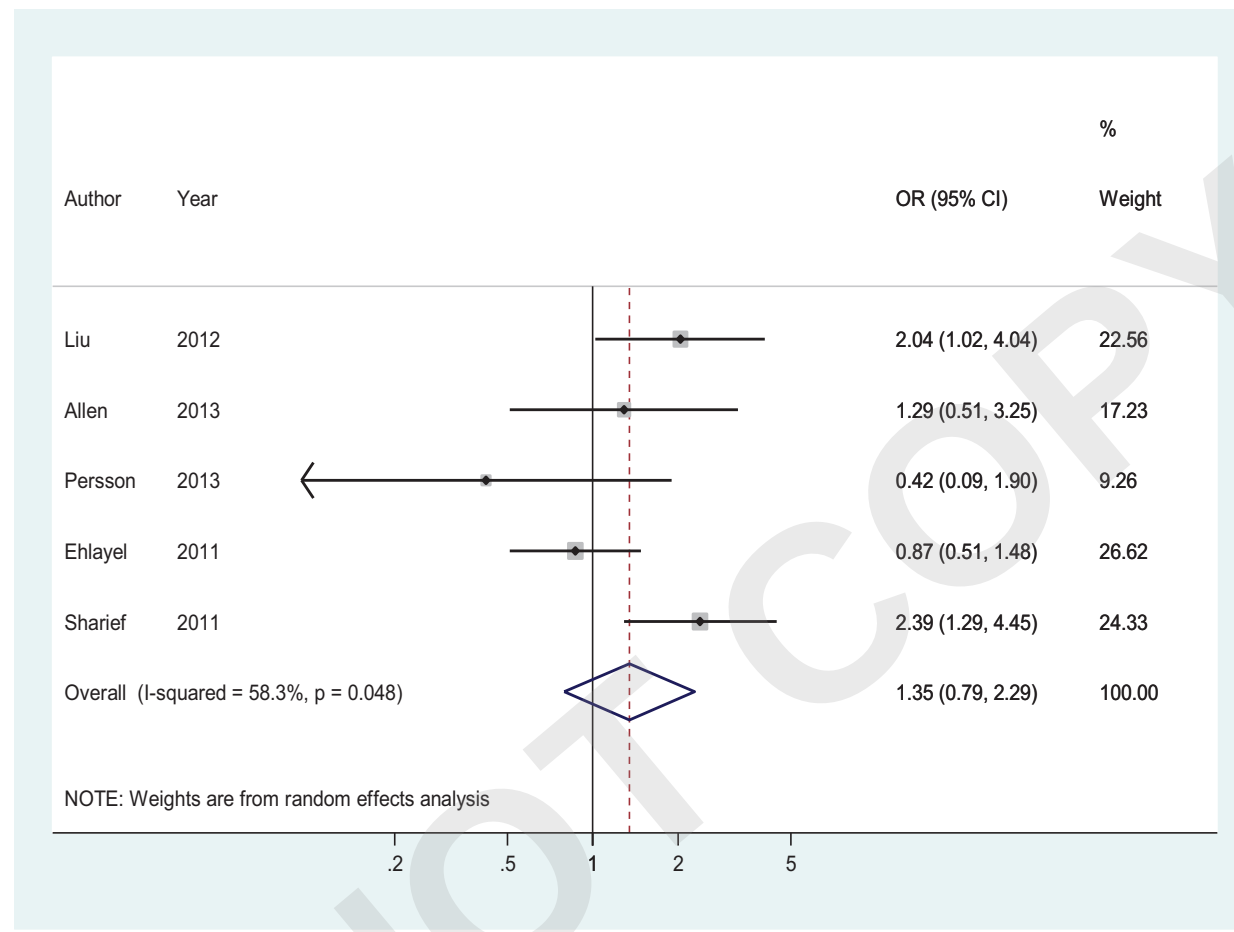


Figure 3. Pooled odds ratios (OR) from the included studies.

for analysis, one of the studies<sup>30</sup> used a cutoff of <30 ng/mL for vitamin D deficiency, whereas the other studies used a cutoff of <20 ng/mL. This is an example<sup>30</sup> of the discrepancies in the current literature because a patient with a vitamin D level of 25 ng/mL would be considered “insufficient or deficient” in one study, and vitamin D “sufficient” in another. The assigned terms are likely less meaningful than the assigned cutoff; however, to risk stratify patients, a consensus of what constitutes optimal status of vitamin D in children must be defined.

The ideal status of 25(OH) vitamin D has not been identified.<sup>37,38</sup> Current supplementation guidelines for all ages are based on levels needed to maximize bone health and muscle function, and are based on studies that investigated the amount of vitamin D required to efficiently absorb calcium from the gut. The Endocrine Society guidelines for vitamin D deficiency state that the amount of supplementation needed for nonskeletal health benefits is unknown<sup>30</sup>; therefore, it is possible that the optimal status of vitamin D needed to prevent adverse bone outcomes differs from the optimal status needed to maintain

immune function and to protect the body from atopic disease.<sup>39</sup>

Another layer of complexity to these studies involves the best time to measure vitamin D. It is unclear if a low vitamin D status in cord blood is a risk factor for developing allergy. It is possible that the vitamin D status during pregnancy is less important than the vitamin D status throughout infancy.<sup>40,41</sup> In addition, vitamin D status varies with the time of year and is usually higher in summer than in winter months.<sup>42</sup> Therefore, multiple measurements throughout the year would help define the overall vitamin D status of an individual instead of basing the individual’s status on a one time measurement. Future studies should measure vitamin D status at multiple times during life to help answer this question as well as use consistent assays for measuring 25(OH)D levels.<sup>41</sup> Polymorphisms in the vitamin D binding protein may alter the bioavailability of vitamin D, which further defines the complexity of vitamin D activity in the body,<sup>43</sup> hence, documenting 25(OH)D levels in individuals with food allergy may be only one part of a more-complex picture.

## CONCLUSION

If vitamin D is a contributing factor to the development of atopic diseases<sup>40</sup> and food allergy, then it could have a large impact on the current epidemic of food allergies. Larger studies are needed to determine what, if any, role vitamin D plays in the development of food allergy. Further studies are also needed to identify cutoff values for sufficiency, insufficiency, and deficiency, along with studies that investigate the vitamin D status needed to achieve optimal immune function. Until those studies are completed, we have insufficient evidence to support the role of vitamin D deficiency or insufficiency in subjects with established food allergy.

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