



Review

Pre- and Postnatal Vitamin D Status and Allergy Outcomes in Early Childhood

Kristina Rueter^{1,2,3,*}, Aris Siafarikas^{1,4,5,6} , Debra J. Palmer^{1,4} and Susan L. Prescott^{1,2,3,4}

¹ School of Medicine, The University of Western Australia, 35 Stirling Highway, Crawley 6009, Australia; aris.siafarikas@health.wa.gov.au (A.S.); debbie.palmer@uwa.edu.au (D.J.P.); susan.prescott@telethonkids.org.au (S.L.P.)

² Department of Immunology, Perth Children's Hospital, 15 Hospital Avenue, Nedlands 6009, Australia

³ inVIVO Planetary Health, Group of the Worldwide Universities Network (WUN), 6010 Park Ave, West New York, NJ 07093, USA

⁴ Telethon Kids Institute, The University of Western Australia, 15 Hospital Avenue, Nedlands 6009, Australia

⁵ Department of Endocrinology, Perth Children's Hospital, 15 Hospital Avenue, Nedlands 6009, Australia

⁶ Institute for Health Research, University of Notre Dame, Fremantle 6160, Australia

* Correspondence: kristina.rueter@health.wa.gov.au

Abstract: The dramatic increase in the prevalence of allergic disease in recent decades reflects environmental and behavioural changes that have altered patterns of early immune development. The very early onset of allergic diseases points to the specific vulnerability of the developing immune system to environmental changes and the development of primary intervention strategies is crucial to address this unparalleled burden. Vitamin D is known to have immunomodulatory functions. While allergic disease is multifactorial, associations with reduced sunlight exposure have led to the hypothesis that suboptimal vitamin D levels during critical early periods may be one possible explanation. Interventions to improve vitamin D status, especially in early life, may be the key to allergic disease prevention.

Keywords: vitamin D; non-communicable disease; allergic disease; pregnancy; infancy; early childhood; environmental factors; immunomodulatory functions; vitamin D observational trials; vitamin D randomized controlled trials



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1. Introduction

The prevalence of non-communicable diseases (NCDs)—including allergic disease as a very early presentation—has increased dramatically in recent decades. This trend, described as “the epidemic of the 21st century”, recognizes allergy as a major cause of morbidity in the developed world without any evidence of this crisis abating [1–3]. Although genetic risk factors influence individual susceptibility to disease, the rise in allergic diseases and other NCDs in recent decades has been far too rapid to be accounted for by changes in the population gene pool alone [4].

When looking for potential factors driving the increasing risk of allergic diseases, the dramatic environmental and lifestyle changes of the modern age are clearly implicated [5]. With economic prosperity and associated lifestyle changes, the rising propensity for inflammation is implicated in the rising burden of chronic disease including allergic diseases in all modern societies. It is therefore critically important to understand the normal processes and pathways that underpin immune development, how these are modified by adverse early environmental exposures, and how these may be favorably modified to reduce disease risk.

Whilst the impact of modern environments on the immune system is likely to be complex and multifaceted, declining microbiome biodiversity (particularly in commensal microflora), exposure to air pollution, cigarette smoke and ingested environmental contaminants [6,7], chemical allergens and irritants from cosmetic products [8], medications,

increased time spent indoors and dietary changes associated vitamin D deficiency [9] have emerged as potential causative factors influencing the development of allergic diseases. Here, timing plays a significant role. Prenatally, and during infancy, childhood and adolescence, the human body is in a constant change of development. Thus, the predefined stages of maturation display windows of accessibility, vulnerability and opportunity, where health intervention and prevention can present themselves in interactions between genes, environment, and critical developmental time periods. There is a need to intervene early to prevent disease in the first instance, by targeting the modifiable environmental risk factors that are most likely responsible [10,11], which is illustrated in Figure 1 showing potential influencing prenatal and early postnatal environmental factors.

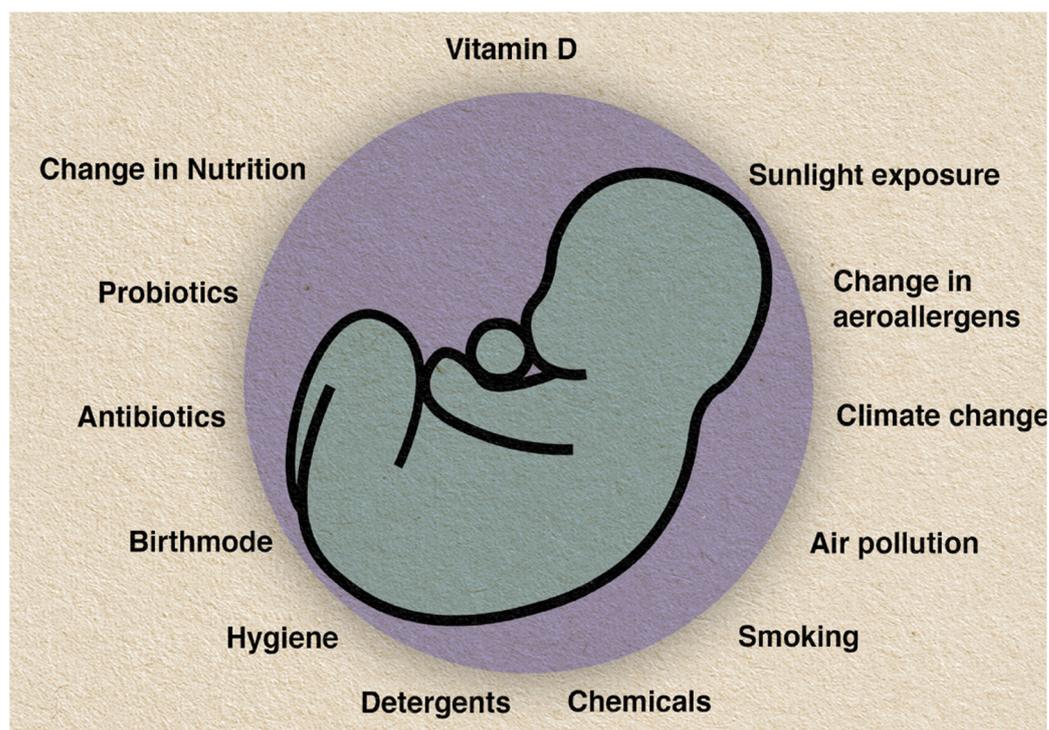


Figure 1. A number of potentially causative pre- and early postnatal environmental factors may influence the development of allergic diseases. The hygiene hypothesis suggests that increased hygiene with a lack of exposure to microbes and parasitic infections at an early age prevents the developing immune system from forming tolerance. In modern societies, increased time is spent indoors, which can lead to reduced sunlight exposure and vitamin D production. Additionally, change in nutrition and use of pro- and antibiotics, detergents and chemicals need to be considered in the context of allergy development. Furthermore, mode of delivery, smoking, air pollution, climate change and change in aeroallergens may contribute to the development of allergic diseases in early childhood.

As one key factor under consideration (Figure 1), as both a causal factor and a possible allergy prevention strategy, this review article will focus on vitamin D—important in this context because of known immunomodulatory functions, including immune pathways relevant for protecting against allergic diseases. Vitamin D deficiency and insufficiency are global phenomena afflicting more than one billion people in all age groups. As over 90% of natural vitamin D production is dependent on ultraviolet radiation (UVR), declining exposure to UVR with increasingly indoor-centered modern lifestyles is implicated in adverse vitamin D status and has been connected with the rising rates of immune and inflammatory diseases in many parts of the world. Although the physiological effects of this are likely to have a broad impact on many aspects of health, this review will focus particularly on the implications for the possible prevention of allergic diseases.

Vitamin D is known to have immunomodulatory functions and considering that immune mechanisms underly all allergic diseases, this might be a factor which beneficially modulates immune function to prevent allergies. So far, numerous observational trials and a few intervention trials have been performed, with conflicting results. In the context of reviewing further literature for vitamin D as a modifiable environmental risk factor, it is useful to first briefly describe sources of vitamin D, followed by vitamin D metabolism and immunomodulatory functions, before further exploring clinical trials on the influence of vitamin D on allergy outcomes.

2. Environmental Factors as Causes for the Global Rise of Vitamin D Deficiency and Sources of Vitamin D

Considering that up to 90 to 95% of vitamin D can be provided by cutaneous synthesis under the influence of UVB light [12], the major cause for the vitamin D deficiency pandemic is a lack of appreciation that UV light exposure is the major physiological source of vitamin D [13–15]. Increased time spent indoors due to the exponential rise of indoor employment and relaxation activities (particularly an increase in screen time) in modern times as well as sun protection behaviours [16–18] are lifestyle factors which have an influence on UV light exposure. In addition, lower UVR levels are found in high-latitude locations and winter season. Furthermore spending time outdoors exclusively in the morning or after 3 p.m. leads to reduced UV light exposure [19].

Considering physiological factors, increased skin pigmentation [20,21], aging and obesity have an influence on vitamin D status [17]. Low dietary vitamin D intakes caused by changes in nutrition from more traditional vitamin D-containing food sources to modern commercial, highly processed fast food can contribute to vitamin D deficiency by destroying the naturally contained vitamin D.

Vitamin D occurs in two forms: vitamin D2 and vitamin D3. Vitamin D2 is obtained from the UV irradiation of the yeast sterol ergosterol and is found in sun-exposed and sun-dried mushrooms. Vitamin D3 is found in oil-rich fish such as herring, salmon and mackerel, tuna, cod liver oil and egg yolk [12]. People living in the far southern or northern latitudes may also obtain vitamin D from seal blubber, whales or polar bear liver [14]. In addition, foods enriched with fortified vitamin D [12] and nutritional supplements play a role in maintaining a sufficient vitamin D status.

3. Vitamin D Metabolism and Physiology

Vitamin D is a pre-hormone which historically plays a critical role in calcium and mineral homeostasis, bone modeling and remodeling. However, the role of vitamin D goes far beyond this, as different activities of vitamin D ensure proper functioning of vital human organs including the skin [22]. Apart from functioning *on* the skin, vitamin D is also predominantly derived *from* the skin via sun exposure, which makes vitamin D unique among hormones [12,23,24].

During sun exposure, 7-dehydrocholesterol in the skin absorbs UVB radiation and undergoes chemical rearrangements to form the thermodynamically stable vitamin D3 (reviewed in [19]). Vitamin D2 and D3 act as pro-hormones and, when activated, have the same biological activity. Following ingestion or transport from the skin to the circulation, these calciferols are bound to the vitamin D-binding protein (DBP) [25]. DBP transports the calciferols to the liver, where the first step of hydroxylation to 25-hydroxyvitamin D (25(OH)D) takes place (reviewed in [26]).

While 25(OH)D is the predominant circulating metabolite, it is largely inert and displays minimal binding affinity to the vitamin D receptor (VDR) [26]. Hence, to gain biological activity in a second step, 25(OH)D must undergo further renal hydroxylation [26]. 1,25(OH)₂D (calcitriol) is the active metabolite of vitamin D which is bound to DBP while circulating in the blood and transported to the VDR. After transport to the VDR, 1,25(OH)₂D is released to dock on the VDR and induce processes in the cell nucleus [12,27]. However, 1,25(OH)₂D is not used as a measure of vitamin D status [28] due to its short circulating

half-life time (4 h), low serum concentrations and tight regulation [28]. Instead, 25(OH)D is used to evaluate vitamin D status as it has a long half-life time (2–3 weeks), provides stable serum concentrations and is present at concentrations approximately 1000-fold greater than 1,25(OH)₂D [28]. The international Endocrine Society's guidelines define vitamin D deficiency as 25(OH)D < 50 nmol/L (<20 ng/mL), and vitamin D insufficiency as <75 nmol/L (<30 ng/mL) [28].

More recent research revealed that calcitriol modulates activation, proliferation and differentiation of immune and inflammatory cells through the VDR expressed on these cells [29–33]. Apart from immune cells [33], the VDR is also present on cells of the skin [34] and cardiovascular system [35], and these functions may provide some explanation for the epidemiological associations between vitamin D status and NCDs including cardiometabolic conditions, malignancies and immune disorders [36]. Hence, the next section will further explore the role of the VDR associated with this DBP.

4. Vitamin D Receptor and Vitamin D-Binding Protein Polymorphisms and Links to Allergic Diseases

The VDR is a member of the nuclear receptor family of transcription factors and is found on most cells of the human body including skin cells (basal layer of the epidermis, keratinocytes and hair follicles) [37] and immune cells, with effects on cell differentiation, proliferation and apoptosis [38]. It is therefore quite feasible that VDR polymorphisms on interaction with environmental factors could significantly influence immune regulation by altering cell proliferation and differentiation [39]. Genetic studies have provided early evidence of a potential role of the VDR in the genesis of allergic diseases. Looking at the link to asthma specifically, the association between a number of VDR restriction fragment length polymorphisms and the risk of asthma has been described [40]. However, other studies could not confirm the role of VDR polymorphisms on allergy outcome [41,42]. In a recent review article, Tamasauskienė et al. conclude that the association of VDR gene polymorphisms and vitamin D with asthma, allergic rhinitis and atopy is variable [43]. The inconsistency between findings may be due to different study designs, but also likely reflects that allergic diseases are complex, involving multiple genetic and environmental factors [40,43].

There are numerous other genes involved in the vitamin D metabolism pathway that have been associated with the risk of allergic disease [44–46]. DBP polymorphisms and vitamin D deficiency may jointly or independently contribute to a variety of skeletal and non-skeletal adverse health outcomes including different NCDs such as osteoporosis, diabetes, thyroid autoimmunity, inflammatory bowel disease, chronic lung disease (reviewed in [47]) and allergy development [48,49]. The exact role of DBP in the pathophysiology of all these inflammatory diseases is, however, not completely understood. Additionally, as in other genetic associations, the influence of DBP on allergic diseases is likely to be affected by gene–gene and gene–environment interactions and we will have to await further studies to investigate these complex associations.

After giving an overview on vitamin D pathophysiology, metabolism and associated nuclear actions and polymorphisms, this review will now turn to some of the potential immune-modulating properties by which vitamin D may alter the course of allergic disease. An understanding of the potential immunological mechanisms is crucial as this explains clinical findings.

5. Immunoregulatory Functions of Vitamin D and the Influence on Allergic Disease Development

A link between vitamin D and the immune system was first acknowledged approximately four decades ago with the expression of the VDR in both activated T and B cells [33]. Since then, the body of evidence suggesting that vitamin D, especially its active metabolite, plays a key role in modulating the physiological activity of the immune system has grown.

5.1. The Role of Vitamin D in the Th1/Th2 Dichotomy

Early experiments showed that the active metabolite $1,25(\text{OH})_2\text{D}_3$ inhibits interleukin (IL)-2 production and T-cell proliferation [33,50]. Th (T-helper) cells are a primary target for $1,25(\text{OH})_2\text{D}_3$, suppressing Th cell proliferation through decreased Th1 cytokine production of these cells [51–53].

In the first instance, actions such as this would not seem to be beneficial for the genesis of allergic diseases. However, it needs to be considered that the immunosuppression of Th1 is not associated with an increase in pro-inflammatory Th2 cytokine production [54,55]. Indeed, an Austrian study showed that in cluster of differentiation (CD) 4^+ cord blood (CB) cells, $1,25(\text{OH})_2\text{D}_3$ suppressed Th2-driven IL-4 and IL-13 expression. Hence, $1,25(\text{OH})_2\text{D}_3$ induced a T-cell population without further predominance of Th2-related cytokines. It was concluded by the authors that predominantly naïve cells have a balanced effect on cytokine production, inhibiting both Th1 and Th2 cytokines [55].

5.2. Immunomodulatory Function of Vitamin D on T Regulatory Cells and Allergic Disease Development

Another group of T cells known to be potentially induced by $1,25(\text{OH})_2\text{D}_3$ are regulatory T cells (Treg) [56]. Allergic disease reflects a failure to develop immunotolerance and although a part of the Th family, Treg cells act to *suppress* immune responses by other T cells and are essential in controlling inflammation and promoting tolerance to allergens.

The majority of Treg arise in the thymus. These CD 4^+ FOXP 3^+ natural regulatory T cells (nTreg) mediate tolerance to self-antigens [57]. A second population of CD 4^+ FOXP 3^+ Treg develop in peripheral lymphoid tissues from naïve conventional CD 4^+ FOXP 3^+ T cells after exposure to antigens in combination with Transforming Growth Factor (TGF)-beta [58]. These cells are called induced regulatory T cells (iTreg) and are predominantly found within environmental interfaces such as lung respiratory mucosa and the intestines during chronic inflammation activities against microbial agents or importantly environmental (e.g., food and airborne) allergens [59,60]. Both subsets, nTreg and iTreg, play a key role in maintaining peripheral tolerance (reviewed in [61]).

Due to the strong associations between Treg and allergic diseases [62–65], identification of factors which may influence the number and function of Treg is crucial. Interestingly, vitamin D appears to influence Treg activity and differentiation [66], suggesting an influence on allergic disease and asthma outcome [66,67].

There is considerable evidence in animal studies that vitamin D 3 stimulates dendritic cells (DCs), which in turn may induce IL-10-producing CD 4^+ T cells and antigen-specific Treg [68]. High levels of $1,25(\text{OH})_2\text{D}_3$ have been shown to induce the lineage-specific FOXP3 transcription factor, which is essential for the development and functioning of Treg [69,70] by enhancing the number and activity of circulating CD 4^+ Treg and their anti-inflammatory functions [71–73]. A recent study by Gorman et al. found that topical application of vitamin D in mice suppressed skin swelling in response to mechanisms that may be dependent on mast cells and Treg [74].

These animal or in vitro findings are supported by different observational studies in humans showing that higher $25(\text{OH})\text{D}$ levels are associated with higher Treg/total T-cell ratios and a more immunosuppressive phenotype [75–77]. Furthermore, it was found that high doses of oral vitamin D influenced the functional capacity of Treg to suppress effector cells in patients with autoimmune or inflammatory disease [78,79].

5.3. Antigen-Presenting Cells and Dendritic Cells

Antigen-presenting cells (APCs) play a significant role in the Th1/Th2 paradigm of autoimmune and allergic disease [80] and allergic disease development [81,82]. As on many other cell types, the VDR is expressed on APCs. However, beyond this DC [83], monocytes and macrophages [84] can produce $25(\text{OH})\text{D}_3$ with subsequent local effects.

Different DC subsets have been identified on sites which are frequently involved in allergic reactions such as the skin, and the respiratory and gastrointestinal tracts. For at least

a decade, vitamin D3 has been suggested to program DCs for tolerance by reducing their capability to activate and generate T cells, while increasing their potential to upregulate Treg and altering receptor expression (reviewed in [85]). Treatment of DCs with 1,25(OH)D3 showed decreased production of pro-inflammatory cytokines (e.g., interferon (IFN)- α and IL-12) and increased production of the anti-inflammatory cytokine IL-10 [86].

In addition to being targets of vitamin D3, DCs can generate 1,25(OH)D3 locally to influence T-cell programming (reviewed in [85]). The primary function of DCs is to initiate and refine adaptive immune responses, highlighting them as a potential therapeutic tool in diseases with skewed T-cell responses, including allergic diseases. Hence, adequate 25(OH)D3 levels through preventing/correcting vitamin D deficiency may facilitate a tolerogenic, anti-inflammatory immune profile.

6. Studies of Geographical Variation and Allergy Outcome

Ecological studies were the first to report an inverse correlation between latitude (as a proxy of UV light exposure and vitamin D status) and allergic diseases when higher rates of allergic disease were observed at higher latitudes [87–89].

Camargo et al. reported that the distribution of adrenaline autoinjectors in the USA was greater in the northeast (8–12 prescriptions/1000 people) than the southwest (2–3 prescriptions/1000 people) [90]. Findings of this study regarding the strong latitude gradient [91] were reproduced and extended in a similar study in Australia, where the investigators found lower rates for anaphylaxis admissions and adrenaline autoinjector prescriptions with closer proximity to the equator [92]. This novel finding raised the possibility of an etiologic role for sunlight/vitamin D status particularly in food allergy, a major driver of adrenaline autoinjector prescriptions [93].

Two further studies located in the USA and South America directly associated anaphylaxis to latitude and showed a significant association [89,94]. Studies in South Korea [95] and Australia [96] focusing specifically on food-related anaphylaxis or allergy reported similar associations. Notably, the Australian study found an even stronger association between latitude and eczema [96]. Similarly a study in 12 European countries (the International Study of Asthma and Allergies in Childhood (ISAAC) study) identified that the prevalence of eczema symptoms increased with latitude and decreased with mean annual temperature [87].

Asthma outcome data from Brazil [97], the US and Australia [88] have also shown an association between latitude and asthma prevalence, further supporting the concept of a possible influence of an increasing geographical latitude on subsequently decreasing sun exposure and reduced vitamin D synthesis on allergic disease outcome. It can be hypothesized that this flow-on effect from eczema and food allergy in the earlier years to asthma in the later years may be related to the similar mechanistic immune effects underlying all allergic diseases, which are influenced by latitude as a proxy for sunlight exposure and vitamin D status.

The strength of these geographical studies is related to the large population-based samples and the number of risk-modifying factors that can be examined. However, allergic disease outcomes are often self- (or parent-) reported or rely on correct coding of diagnosis in the hospital, which is often performed by clerical staff with restricted medical knowledge and hence prone to misclassification. Secondly, these studies are limited by different and broad geographical classifications (continent versus state, versus country, versus city). Thirdly, although associations between latitude, UV light exposure and vitamin D status are well known, many other climatic factors could also have an influence and measures of exposure are only a proxy based on the average in the population. Living in a sunny environment of lower latitude does not necessarily lead to more sun exposure (if most time is spent indoors and other sun-protective behaviour is applied) and subsequently vitamin D production [98–100].

This initial epidemiological evidence has since driven further observational studies and interventional trials to investigate the influence of vitamin D status on allergy prevention.

Accordingly, the next sections of this literature review will explore the evidence to date from observational studies on vitamin D status and interventional randomized controlled trials (RCT).

7. In Utero Effects of Vitamin D Exposure and the Risk of Allergic Disease in Offspring

7.1. Observational Studies of Estimated Maternal Vitamin D Intake

Numerous observational prospective cohort studies have used *maternal vitamin D intake* as an indicator of in utero vitamin D exposure and associated them to allergic disease outcomes. A self-reported food frequency questionnaire (FFQ) methodology was used to estimate maternal vitamin D intake. Study results using this methodology have been very heterogeneous, which was not surprising given that corresponding UVR exposure and associated vitamin D production were not factored in.

For eczema outcomes, findings differed between an increased risk [101], no associations [102,103], or reduced risk [104] with higher estimated maternal vitamin D intakes. However, the results of these four studies were difficult to compare, as different dietary questionnaires and assessment tools were used; and, dependent on the study design, eczema was assessed in a wide range of age groups (at 16 to 24 months [104] vs. 3 years [102] vs. 5 years [103] of age) although it is known that eczema presents very early in childhood and is often fading at preschool age in most cases.

Compared to eczema, findings were more consistent regarding allergic respiratory diseases. Numerous cohorts have reported a reduced rate of asthma [103,105] or wheeze [102,104,106] in their offspring when food-derived maternal vitamin D intake or supplementation [107] was higher or beyond a certain cut off (reviewed in [108]). Again, generally, study designs differed significantly and some of the associations were very weak and even disappeared after adjustment for confounding factors [105], while others could not find any associations between maternal vitamin D intake and asthma or wheeze outcomes in offspring [109].

Two other studies performed assessments for asthma/wheeze longitudinally at two or three time points. They found a protective association with asthma but only for a limited period of time, with increasing age in the Danish study [105], but decreasing age in the study from the UK [110–112]. These differences may be explained by the dissimilar age groups when the allergic disease outcome assessments were conducted (at 18 months and 7 years in the Danish study vs. 5, 10 and 15 years in the UK-based study).

A meta-analysis [112] on this topic has found that antenatal estimated vitamin D intake may have an association with childhood asthma or wheeze in children > 5 years of age. However, this meta-analysis [112] did not find any associations when examining the pooled results of maternal 25(OH)D levels, indicating that parallel longitudinal measurements of maternal vitamin D intake and 25(OH)D levels or—more preferably—well-designed intervention studies would be required to shed clearer light on this area of uncertainty. Conflicting results were also found when associating estimated maternal vitamin D intake with allergic rhinitis (AR), with a Danish study not finding any associations at 7 years of age [105], compared to a Finnish study which found higher vitamin D intakes were associated with reduced AR in offspring at 5 years of age [103]. These varied results may have been influenced by the Finnish study design involving the FFQ being filled out retrospectively, while FFQs were completed prospectively in the Danish study.

In addition, some general weaknesses in the methodology of using FFQs need to be flagged, which challenge a direct comparison between the reviewed study results. Firstly, FFQ data were frequently collected on a single occasion, making it impossible to capture changes of dietary patterns which often occur in pregnancy. Secondly, data were collected at heterogeneous time points, ranging from first trimester, to second or third trimester. However, it is well known that particularly the timing in pregnancy could have an influence on immune development. Thirdly, different FFQs were used by the different

cohorts. Fourthly, allergic disease outcomes were assessed in a wide range of age groups and dissimilar assessment criteria were applied.

Furthermore, it is important to note that when eating a vitamin D-rich food, other nutrients with immunomodulatory properties are also being consumed. For example, a primary source of vitamin D is fatty fish, which also contains the immunomodulatory nutrient of n-3 long chain polyunsaturated fatty acids that are known to have protective effects against the development of allergic disease (reviewed in [108]). Supporting this concept, an analysis by Miyake et al. found that an inverse association between maternal vitamin D intakes and offspring eczema outcomes did not persist after adjusting for associated variations in n-3 long-chain polyunsaturated fatty acid consumption [104].

Some studies incorporated data on additional maternal vitamin D supplementation [102,103,105,106,109], while others did not [101,104], hence not including the total oral vitamin D intakes. Finally, and most importantly, as over 90% of vitamin D production can be induced by sunlight exposure, the lack of incorporation of measuring this element of vitamin D exposure in these studies is a major limitation.

In conclusion, results from the cohort studies investigating the influence of maternal vitamin D intake based on FFQs have multiple limitations, which may at least partially explain the heterogeneous findings regarding the influence of vitamin D on allergy outcomes. Measuring serum vitamin D levels to determine vitamin D status which captures both dietary (food and supplement) intakes as well as vitamin D produced from sunlight exposure is more reflective and should be used in preference to just reporting dietary intakes. A few of the following described studies in the next section have measured 25(OH)D levels both in pregnancy *and* at birth and associated them to allergic disease outcomes. Taking into account that there is a growing body of evidence regarding the timing [10] of various exposures for allergy preventative purposes [9], these studies will be reported in different sections, allowing a direct comparison with study results taken at the same time point in human development.

7.2. Observational Studies of Maternal Vitamin D Status

Measuring 25(OH)D levels in pregnancy is a better reflection of vitamin D exposure to the developing fetus than using maternally reported estimated vitamin D intake based on FFQ methodology and/or vitamin D supplementation as it reflects both vitamin D intake and vitamin D produced by sunlight exposure. Newborn infant 25(OH)D plasma levels are correlated with maternal 25(OH)D levels, indicating that fetal and newborn infant vitamin D status are dependent on maternal vitamin D status and interventions in pregnancy have an influence on the fetus and newborn [113].

Two strategies have been used in observational studies to estimate the influence of fetal 25(OH)D exposure on health outcomes: the first by measurement of maternal 25(OH)D levels in pregnancy, and the second by measuring levels in cord blood (CB) at birth. This section will focus on the former.

Similar to aforementioned publications relating allergy outcomes to maternal vitamin D intakes, studies measuring maternal vitamin D status during pregnancy have also found very heterogeneous results regarding offspring allergic outcomes. Perhaps one of the key factors explaining this may be the inconsistent stages in pregnancy at which vitamin D status was assessed. Considering the significant developmental changes a fetus faces during pregnancy, this might be a major limitation, making it difficult to compare findings. Hence, study results will be grouped in this review and compared according to when 25(OH)D levels were taken in pregnancy (1st, 2nd or 3rd trimester). This will be followed by a general discussion to elucidate why the results might be so conflicting.

No studies were strictly performed in *early pregnancy* only. A British prospective population-based study where 25(OH)D levels were measured both early but also at any other stage in pregnancy could not find any associations with child eczema (at mean age 7.5 years) [114].

However, numerous studies with conflicting results collected maternal blood samples in *mid pregnancy*. A study in Detroit included 858 mother–child pairs of different ethnic backgrounds and found that 25(OH)D levels were inversely associated with eczema outcome (via parent report) between 0 and 2 years of age (OR, 0.85; 95% CI 0.75–0.96) [115]. This was supported by another study in the USA indicating that maternal 25(OH)D levels below 25 nmol/L were associated with a higher risk of eczema in early childhood (birth to 3 years) (aOR 2.74; 95% CI 1.37–5.49) [116]. However, two other studies did not find any associations between severely deficient, deficient and sufficient vitamin D groups and eczema outcome at 2 years of age [117] and up to 4 years of age [118]. The former study also assessed the children for food allergy and aeroallergen sensitisation at 2 years and asthma at 5 years of age and could not find any associations [117].

No associations between asthma/wheeze and maternal 25(OH)D levels were found in Norwegian (current asthma at 3 years of age) and Spanish (wheeze at 1 and 4 years of age and asthma at 4 to 6 years of age) studies [119,120]. Interestingly, a Danish cohort study demonstrated a U-shaped relationship, indicating that maternal vitamin D prediction scores of ≥ 100 and < 25 – 30 nmol/L were associated with increased risks of “asthma” at 18 months of age [121], whereas an Australian study reported an increased risk of current wheeze at 6 years of age only in children born to mothers who were vitamin D deficient, but not by 14 years of age [122]. These heterogeneous results in *mid pregnancy* related to inconsistent asthma and wheeze outcome definitions across childhood.

Seven studies have conducted maternal 25(OH)D measurements in *late pregnancy* (24–42 weeks of gestation) [109,123–128]. These include a German study ($n = 378$), which found that higher maternal 25(OH)D levels at 34 weeks gestation were associated with an increased risk of food allergy and allergen sensitisation within the first 2 years of life [123]. Two recent studies from Malaysia ($n = 380$) [126] and Singapore ($n = 925$) [127] examined maternal vitamin D deficiency (< 30 and < 50 nmol/L, respectively) and could not find any associations with food allergy in infancy [126] or food sensitisation up to 5 years of age [127].

Examining eczema outcomes in these various studies also reveals conflicting results. The aforementioned German study did not find any associations between maternal 25(OH)D levels and eczema outcomes in children within the first two years of life [123]. This finding was supported by the abovementioned Malaysian [126] and Singaporean studies [127]. A small Taiwanese cohort study ($n = 164$) found that *higher* maternal 25(OH)D levels appeared to be associated with a significantly *lower risk* of eczema (OR 0.12; 95% CI 0.02–0.63; $p = 0.012$) [129]. This differed from a larger study in the UK ($n = 860$), where *higher* maternal 25(OH)D levels were associated with a *higher risk* of eczema (adjusted OR 3.26, 95% CI 1.15–9.29) [130].

Regarding asthma and wheeze, most studies did not find any consistent associations with maternal 25(OH)D levels in the third trimester [109,125–128]. The Taiwanese study revealed a *lower risk* of asthma (OR 0.22; 95% CI 0.06–0.92; $p = 0.038$) at age four when maternal 25(OH)D levels were higher [129], whereas a UK-based cohort study [124] found a *higher risk* of parent-reported asthma at 9 years of age when maternal 25(OH)D levels were higher (> 75 nmol/L compared to < 30 nmol/L) [124].

Although it was anticipated that studies based on maternal 25(OH)D *levels* rather than self-reported maternal vitamin D *intake* may have been more conclusive, results have again been heterogeneous and conflicting. This raises the critical question of why this is the case.

A limiting factor is the once-off nature of 25(OH)D measurements to assess maternal status. Given the strong seasonal influences UVR has on vitamin D production with possibly non-linear associations, measurements would have ideally been taken longitudinally at multiple time points. Additionally, studies use different assays for 25(OH)D measurement. While some investigations utilized liquid chromatography–tandem mass spectrometry (LC–MS/MS) [120,121,125], others used different immunoassays [109,122,124,128] or other methodologies [119,129]. The utilization of divergent types of assays could have an impact on 25(OH)D measurement and subsequently influence study outcomes [131]. Furthermore,

comparison of study results was limited by various assessment tools used to evaluate allergy outcomes including standardized International Study of Asthma and Allergies in Childhood (ISAAC) [132] questionnaires [109,116,129], parent report of physician diagnosis [119,127], parent report [115,128], parent report plus name of medication [120] or clinical assessment in addition to questionnaire [115,117]. Inconclusive results for wheeze and asthma may also reflect inconsistencies across studies in the definition, diagnosis and assessment of these outcomes, especially at early ages. Moreover, while some studies captured allergic outcomes in early childhood, others focused on older age groups, making a comparison of study results very difficult. Variable results may also reflect different methodologies used to assess food or aeroallergen sensitisation—some by skin prick testing (SPT) [127], while others used blood-specific IgE levels [109,126,129], or both [115].

These observational studies were also performed during varied seasons and in countries with different latitudes. Maternal UV exposure may reflect the season and region of the study, and maternal UV exposure could also have vitamin D-independent immunomodulatory effects on allergy outcome in offspring, placing major limitations on the interpretation of these findings.

7.3. Observational Studies of Cord Blood 25(OH)D Levels

Direct neonatal measures of 25(OH)D in CB at the time of birth provide a unique window and consistent time point to investigate these relationships between vitamin D status in pregnancy and allergy outcomes. Although CB 25(OH)D levels have been shown to correlate with maternal 25(OH)D levels [129,133,134], 25(OH)D levels in CB are usually lower than maternal levels [135–137]. Hence, it is important to review studies on CB 25(OH)D levels and allergy outcomes separately from studies on maternal vitamin D levels.

Examining eczema outcomes in association with CB 25(OH)D levels, studies again revealed heterogeneous results. Five studies did not find any associations between CB 25(OH)D levels and eczema [116,118,123,138,139], whereas three studies found lower CB 25(OH)D to be associated with a higher risk of eczema (Table 1) [140–142]. Here, two of the studies were located in Australia (latitude 31.9–34.9 °S) and were performed in a high-risk population (any of the parents and/or siblings diagnosed with allergic disease) [140,142]. A recent systematic review concluded that current findings revealed no robust nor consistent associations between maternal or CB 25(OH)D status on eczema outcome in infancy [143].

Table 1. Prospective birth cohort studies of 25(OH)D cord blood (CB) levels and allergy outcome in childhood.

Reference and Year Latitude	Study Population	25(OH)D Level	Main Results	Higher 25(OH)D Level
Camargo et al. (2011) Wellington and Christchurch, New Zealand Latitude 41–43 °S	922 mother–child pairs General population	CB Median = 44 nmol/L (IQR 29–78)	Lower CB 25(OH)D (<10 ng/mL) levels were at higher risk for wheezing at 15 mo, 3 and 5 years than higher CB levels (>30 ng/mL) No association with asthma at 5 years of age	W↓ A←→
Rothers et al. (2011) Tucson, Arizona Latitude 32.22 °N	219 mother–child pairs General population	CB Median = 64 nmol/L (IQR 49–81)	Lower (<50 ng/mL) and higher (≥100 ng/mL) levels of CB 25(OH)D were associated with increased total IgE and aeroallergen (sIgE) sensitization at 1, 2, 3, and 5 years of age No association with AR or asthma at 5 years	S U A←→ AR←→
Jones et al. (2012) Perth, Australia Latitude 31.95 °S	231 mother–child pairs High-risk population	CB Mean = 58 nmol/L (SD ± 24.1)	Lower CB level is associated with a higher risk for eczema at 12 months No association with wheeze, allergen sensitization or IgE-mediated food allergies	E↓ W←→ S←→ FA←→
Weisse et al. (2013) Leipzig, Germany Latitude 51.4 °N	378 mother–child pairs General population	CB median = 27 nmol/L (IQR: 17–43)	Positive association between CB 25(OH)D levels with food allergy within 2nd year of life No association with eczema and sensitization	FA↑ S←→ E←→
Baiz et al. (2014) Poitiers and Nancy, France Latitude 46–48 °N	239 mother–child pairs General population	CB Mean = 44 nmol/L (IQR: 38 nmol/L)	Inverse association between CB 25(OH)D levels with early transient wheezing and eczema by age 1, 3, and 5 years No association with asthma and AR at 5 years of age	W↓ E↓ A←→ AR←→
Stelmach et al. (2015) Lodz, Poland Latitude 51.76 °N	240 mother–child pairs General population	CB median 15.8 nmol/mL (IQR 10.4–21.3)	Inverse association between CB 25(OH)D levels wheezing in first 2 years of life No association with food allergy and eczema	W↓ E←→ FA←→
Palmer et al. (2015) Adelaide, Australia Latitude 34.92 °S	270 mother–child pairs High-risk population	CB mean 57.0 nmol/L (SD ± 24.1)	Inverse association between CB 25(OH)D and eczema to 3 years, stronger association at 1 year of age. IgE-mediated food allergies at 1 year of age in 4/260 (1.5%) children. The risk of IgE-mediated food allergies at 1 year of age (but not at 3 years of age) decreased as CB 25(OH)D concentration increased. No association with asthma, allergic rhinitis or sensitization	E↓ FA↓ A←→ AR←→

Table 1. Cont.

Reference and Year Latitude	Study Population	25(OH)D Level	Main Results	Higher 25(OH)D Level
Visness et al. (2015) Baltimore, Boston, New York and St Louis, USA Latitude 38–42 °N and Madison, Wisconsin Latitude 43.1 °N	435 mother–child pairs and 258 mother–child pairs Both high-risk populations	CB median 50.3 nmol/mL (range 10.5–109.2)	No association between CB 25(OH)D and any wheeze in first year or recurrent wheeze at 3 years No association with food allergy or food or aeroallergen sensitization to 5 years old	W←→ FA←→ S←→
Gazibara et al. (2015) Rotterdam, The Netherlands Latitude 51.91 °N	2407 mother–child pairs General population	CB median 40.2 nmol/L (range 11–144.9)	No association between CB 25(OH)D levels divided into tertiles (lowest tertile (30.5 nmol/L), middle tertile (≥30.5–49), and highest tertile (≥49.0) and wheeze within the first 6 years of age	W←→
Blomberg et al. (2017) Massachusetts, USA Latitude 42.41 °N	1418 mother–child pairs General population	CB mean or median level not given	No association between CB 25(OH)D levels of sufficiency, deficiency and insufficiency (divided into 6 categories) and eczema outcome within the first 7 to 8 years of life	E←→
Hennessy et al. (2018) Cork, Ireland Latitude 51.89 °N	1050 mother–child pairs General population	CB mean 35.5 nmol/L (SD ± 18.2)	No association between CB 25(OH)D levels and: Persistent eczema in the first 2 years Food allergy and food and aeroallergen sensitization at 2 years of age Asthma at 5 years of age	E←→ FA←→ S←→ A←→

↓: inverse association; ←→: no association; ↑: positive association; U = U-shaped association; E: eczema; FA: food allergy; W: wheeze; A: asthma; AR: allergic rhinitis; S: sensitization.

Focusing on IgE-mediated food allergies, most studies did not find any associations (Table 1) [139,140,144]. One Australian study found higher CB 25(OH)D to be associated with less IgE-mediated food allergies at 1 year of age; however, food allergy was only medically diagnosed in 1.5% of the cohort and, due to the low incidence results, should be interpreted with caution, especially as no association between CB 25(OH)D levels and IgE-mediated food allergies was found at 3 years of age [142]. A German cohort study reported an association between higher CB 25(OH)D concentrations and an increased likelihood of parent-reported food allergy by 2 years of age. It needs to be considered that this study was conducted at a higher latitude with a subsequent lower average CB concentration (median 27 nmol/L; IQR 17; 43 nmol/L). These lower average CB levels may have contributed to different findings between studies [123].

Other CB studies have focused on allergy related respiratory outcomes, with the recognized limitation that wheezing in early childhood is typically associated with viral infection and may not herald subsequent asthma [145]. Several studies revealed an inverse relationship between CB 25(OH)D levels and wheeze [139,141,146] or asthma [138], while others could not find any associations [140,144] (Table 1). The inconsistency between results in meta-analyses may be related to different eligibility criteria, searching strategies (e.g., a literature search by Song et al. [147] consisted predominantly of Chinese databases) and study selection criteria as well as inconsistency across asthma and wheeze definitions and outcomes.

None of the studies which assessed allergic rhinitis found any associations with CB 25(OH)D levels (Table 1) [138,141,142]. When looking at sensitisation to allergens, Rothers et al. described a “U-shaped association”, with increased risk of sensitisation at both high (>100 nmol/L) and low (<50 nmol/L) levels of CB 25(OH)D [148]. A similar U-shaped effect has been observed in other epidemiological studies looking at the risk of elevated IgE concentrations [149]. Numerous other studies did not find any associations between CB 25(OH)D levels and sensitisation (Table 1) [117,138,142,144] nor did a meta-analysis by Pacheco-Gonzalez et al. [150].

Overall, high heterogeneity across the reviewed observational CB studies was detected (Table 1). A major contributor for the conflicting results might have been the significant range in 25(OH)D levels (Table 1). Heterogeneous findings between studies could also be caused by inconsistencies in the definition of outcome measures, different study populations (e.g., some studies selected high-risk populations [140,142,144] while others did not), study location, sample size, duration of follow-up, assays used for vitamin D level measurement, seasonal variation, and adjustment for different covariates.

In summary, there is mixed evidence from observational studies (and associated different meta-analyses) with regard to the role of prenatal vitamin D status in the offspring's risk of allergic manifestations. Additionally, the question of causality cannot be answered by observational studies. Hence, RCTs are warranted to shed light on the possible causative and modifiable effect of fetal vitamin D status on the development of allergic disease.

7.4. Randomized Controlled Trials of Prenatal Vitamin D Supplementation

Three RCTs investigated the effects of maternal vitamin D supplementation during pregnancy on offspring allergic disease development, as summarized in Table 2, with the primary outcome being allergy related respiratory symptoms [151–153]. All three RCTs failed to find statistically significant differences between the vitamin D-supplemented and placebo groups in terms of allergy related respiratory and other allergic disease outcomes (Table 2) [151–153].

The US Vitamin D Asthma reduction Trial (VDAART) found that allergen sensitisation was lower in the higher-vitamin-D-supplemented group [153]; however, neither the Danish nor the UK study could confirm this finding [151,152]. The results may have been influenced by different methods of evaluating sensitisation with the Danish and UK studies using both SPT and allergen sIgE testing, whereas the US study only used sIgE testing. Focusing further on differences in study protocols, intervention products (ergocalciferol was used

by Goldring et al. versus cholecalciferol in the two other studies), doses of vitamin D and intervention periods were dissimilar, as were outcome measures and assessment tools (Table 2).

Two studies from Europe recruited their participants from one city only (Copenhagen [151] and London [152]), whereas Litonjua et al. included pregnant women from three different health care institutions in the US located at different latitudes. Latitude is known to have an impact on UVR and could potentially influence vitamin D levels and allergy outcomes independent of vitamin D supplementation.

In addition, the ethnicity of study populations differed (Table 2). Knowing that race and ethnicity are determinants of circulating 25(OH)D levels [154,155] and can also influence allergy outcome [156–158], this is an important factor. Although races were equally distributed between the intervention and control groups in the US- and UK-based studies, the investigators did not explore whether vitamin D supplementation had differential effects on maternal levels of 25(OH)D or on allergy outcomes in offspring according to ethnicity. Thus, to address this issue, a secondary analysis was performed by subdividing their cohort into different races (African American versus non-African American). However, this subsequent study was also unable to reveal a significant difference between both ethnic groups [159]. This is unsurprising, as even the original study design by Litonjua et al. [160] was not powered for clinical outcomes. Hence, in the sub-analysis, numbers per group were even lower and therefore most likely insufficient to find any effects. It also needs to be considered that in the secondary analysis, the “non-African American” population still consisted of different races (Hispanic, European and others).

Apart from the different study protocols, which make a comparison between these RCTs difficult, a major limitation of all three studies is a lack of power for clinical outcomes due to insufficient sample sizes.

Table 2. Randomized controlled trials of prenatal intake of vitamin D and allergic outcomes in early childhood.

Reference and Year Latitude	Study Population	Intervention Groups/Doses	Intervention Period	Duration of Intervention	Follow-Up Period/Age at Assessment	How the Outcome Was Assessed	Main Results
Goldring et al. (2013) London, UK 51.5 °N RCT, prospective	180 mothers Mixed ethnic groups: 25% Asian, 26% Middle Eastern, 25% Black, 24% White General population	Maternal: Placebo, <i>n</i> = 50 800 IU/d vitD2 <i>n</i> = 56 Single oral bolus of 200,000 IU vitD3 <i>n</i> = 52	27 weeks to birth	3 months	At 3 years of age	ISAAC questionnaire Except food allergy: physician diagnosed	800 IU/day vitD ₂ vs. placebo No difference at age 3 in: -Wheeze ever (aOR 0.56; CI 0.20–1.57; <i>p</i> = 0.27) -Eczema ever (aOR 0.61; CI 0.23–1.67; <i>p</i> = 0.34) -AR (aOR 0.63; CI 0.17–2.36; <i>p</i> = 0.49) -Food allergy (aOR 4.53; CI 0.52–39.33; <i>p</i> = 0.17) Single oral bolus of 200,000 IU vitD ₃ vs. placebo No difference at age 3 in: -Wheeze ever (aOR 1.17; CI 0.44–3.10; <i>p</i> = 0.75) -Eczema ever (aOR 0.86; CI 0.32–2.28; <i>p</i> = 0.76) -AR (aOR 0.91; CI 0.20–4.11; <i>p</i> = 0.90)
Chawes et al. (2016) Brustad et al. (2019) Denmark 55 °N RCT, prospective	623 mothers >90% European General population	Maternal: Placebo and 400 IU/d vit D3 <i>n</i> = 308 2400 IU/d and 400 IU/d vitD3 <i>n</i> = 315	24 weeks to 1 week postpartum	3.5 to 4 months	Face-to-face medical follow-up visits at 1,3,6,12,18,24,30, 36 months Sensitization tested at 6 and 18 months	Persistent wheeze/asthma diagnosed by validated quantitative algorithm Eczema: criteria of Hanifin and Rajka [161] For sensitization: Skin Prick Test (SPT): ≥2 mm than negative control; or sIgE	2800 IU/day vs. 400 IU/day vitD3 No difference in: -Persistent wheeze (HR 0.76, CI 0.52–1.12; <i>p</i> = 0.16) at 0–3 years -Asthma (OR 0.82; CI 0.50–1.36; <i>p</i> = 0.45) at 3 years -Eczema (HR 0.90; CI 0.65–1.26; <i>p</i> = 0.55) at 0–3 years -Sensitization at 6 or 18 mo by sIgE (OR 1.55; CI 0.89–2.73; <i>p</i> = 0.13) or SPT (OR 1.24; CI 0.66–2.31; <i>p</i> = 0.51)
Litonjua et al. (2016 and 2020) Boston, USA 42.3 °N Washington, USA 47.75 °N San Diego, USA 32.71 °N RCT, prospective	876 mothers Mixed ethnic groups: 49% Black, 13% White Hispanic, 20% White non-Hispanic 18% other High risk for allergies	Maternal: 400 IU/d vitD3, <i>n</i> = 436 4400 IU/d vitD3 <i>n</i> = 440	Between 10 and 18 weeks to delivery	5 to 7.5 months	Every 3 months: phone call At 1, 2, and 3 years of age: face-to-face assessment by scientific staff	Parent report of physician diagnosis sIgE levels	4400 IU/day vs. 400 IU/day vitD3 No difference within first 3 years in: -Recurrent wheeze/asthma (HR 0.8, CI 0.6–1.0; <i>p</i> = 0.51) -Eczema with rash (HR 0.9; CI 0.7–1.2; <i>p</i> = 0.56) Sensitization (IgE): lower in the 4400 IU/d group than in the 400 IU/d group: (10.7%; CI, 9.4–12.1% vs. 12.4%, CI, 11.45–13.5%, <i>p</i> = 0.02)

Table 2. Cont.

Reference and Year Latitude	Study Population	Intervention Groups/Doses	Intervention Period	Duration of Intervention	Follow-Up Period/Age at Assessment	How the Outcome Was Assessed	Main Results
Grant et al. (2016) Auckland, New Zealand 36.84 °S RCT, post hoc	260 mother–infant pairs Mixed ethnic groups: 16% European, 24% Māori, 43% Pacific, 17% Other General population	Maternal/infant pairs Placebo/placebo <i>n</i> = 87 1000 IU/400 IU/d vitD3, <i>n</i> = 87 2000 IU/800 IU/d vitD3, <i>n</i> = 86	Maternal: 27 weeks to birth Infant: birth to 6 months	Maternal: 3 months Infant: 6 months	Interviews at: 2, 4, 6 and 18 months	Primary care records for physician diagnosis For sensitization to aeroallergens: SPT (≥ 3 mm than negative control) or specific IgE levels	At 18 months of age: Sensitization Results presented for placebo, lower dose, and higher dose vitD3 - sIgE levels: Der-f1 (18% vs. 10% vs. 2%) Der-f2 (14% vs. 3% vs. 2%) Der-p1 (19% vs. 14% vs. 3%) Der-p2 (12% vs. 2% vs. 3%) For all $p < 0.05$ Grass pollen: $p = 0.74$ Cat: $p = 0.99$ -SPT: House Dust Mite (9% vs. 3% vs. 0%: $p = 0.03$) Cat: $p = 0.74$ Grass pollen: $p = 0.99$ -Asthma: (11% vs. 0% vs. 4%, $p = 0.002$)

In addition, the studies by Goldring et al. [152] and Chawes et al. [151] were conducted in the general population, where a sample size needs to be much larger than in a high-risk population to provide sufficient power for clinical outcomes [162].

Some evidence that prenatal vitamin D supplementation provided protection against wheezing was provided in the US-based study (VDAART) which was strongest for the first year of life but tended to wane between the ages of 1 and 3. However, the result did not reach significance [153]. While the authors of the Danish and US studies [151,153] argue that the non-significant trial responses observed in the individual intent-to-treat analysis of each study may be due to the lack of power, they tried to overcome the problem by combining analyses of both individual trials [163]. Compared to the Danish [151] and US-based [153] studies in isolation, the combined analysis interestingly revealed a significant effect of vitamin D supplementation on the occurrence of wheeze/asthma in offspring within the first 3 years of life particularly when 25(OH)D level was >75 nmol/L (30 ng/mL) at randomization [163]. However, it needs to be considered that combining both studies is problematic, because, as aforementioned, the study design in each individual study was different (Table 2). Firstly, vitamin D supplementation was started much earlier in the US study at 10 to 18 weeks gestation compared to 24 weeks of pregnancy in the Danish study. Secondly, the supplemented doses were different. Thirdly, the study population was dissimilar in both trials, limiting the comparison and generalizability of results. Fourthly, baseline levels of 25(OH)D vary in different geographical locations which has not been considered when combining the analyses of both studies [164]. Furthermore, the definition and assessment of outcomes (usage of heterogenous criteria and questionnaires) were varied, causing difficulties in combining and comparing the different study results (Table 2).

A meta-analysis by Garcia-Larsen et al. [165] found no overall effect on the risk of early childhood recurrent wheeze or eczema results. This meta-analysis included a fourth trial [166] conducted in Auckland, New Zealand on 260 mother–infant pairs. However, the results from this additional fourth RCT by Grant et al. were from a post hoc analysis and the primary outcome was sensitisation to aeroallergens (Table 2).

As a diagnosis of asthma is difficult to establish in early childhood, both the Danish and US groups followed their children up to 6 years of age. In these most recent publications, they also could not reveal any significant influence of high-dose vitamin D supplementation on asthma outcomes including spirometric indexes [167,168]. Asthma cases were even lower than at younger ages (high supplementation group $n = 23/274$, placebo group $n = 18/268$ children in the Danish study [167]; high supplementation group $n = 176/442$, placebo group $n = 184/439$ in the US study); hence, again, these follow-up studies were underpowered for clinical outcomes [168].

In summary, the results of these RCTs suggest that further sufficiently powered well-designed RCTs using similar study protocols are still required to determine the effect of maternal vitamin D supplementation during pregnancy as an allergy prevention strategy. There is also the question as to whether the early postnatal period may be the most critical time to ensure adequate infant vitamin D status, more so than the antenatal period. Thus, the next sections of this literature review will further explore the evidence to date in the postnatal and early childhood period.

8. Vitamin D Intake and Status during Childhood and Allergy Outcomes

Although it is unquestionable that the antenatal period has an important influence on the developing immune system [9,169–171], postnatal exposures also play a critical role [9,172–174]. Immune and organ development (e.g., lung) [175,176] continue upon exposure to environmental influences in the postnatal period. This includes exposures to foods, pollen, air pollution, climatic factors, and importantly in the context of this review, vitamin D and UV light [177].

A solid body of literature links observational studies on vitamin D status in childhood to allergic disease outcomes. To explore this in detail, this literature review will firstly describe evidence regarding postnatal vitamin D intakes, followed by vitamin D status, on allergic disease outcomes in childhood.

8.1. Observational Studies of Vitamin D Intake or Status in Relation to Allergy Outcomes

Lactating mothers with a sufficient 25(OH)D status still have comparatively low 25(OH)D levels of approximately 25 IU/L in their breastmilk [178]. These levels can be increased by more maternal UV light exposure [179] or vitamin D supplementation [180]. Studies have shown that daily supplementation of the lactating mother with 4000 to 6000 IU/day would be required to attain infant vitamin D sufficiency (≥ 50 IU/L), alternatively oral vitamin D supplementation can be given directly to the infant and/or the infant can be exposed to adequate levels of UVR [180–182].

A prospective birth cohort study in Northern Europe estimated vitamin intake from breast milk, infant formula, solid foods and vitamin D supplementation using questionnaires at 5, 7 and 10 months of age and could not find any associations with eczema at 6 years of age. However, the study results were limited by the small sample size ($n = 123$) and no serum 25(OH)D levels were measured [183]. A study in the US ($n = 389$), where vitamin D intake was determined by semi-quantitative FFQs in early childhood (median 3.2 years) found that lower vitamin D intake was associated with higher odds of persistent eczema in mid-childhood (aOR 1.37 per 100 IU decrement, 95% CI 1.01, 2.09) [116].

A Swedish study on adolescents could not find an association between vitamin D intake (reported by FFQs) and eczema or asthma at 13 years of age, and this null finding also applied for 25(OH)D levels measured at 13 years of age [184]. Another large Swedish prospective birth cohort study ($n = 4089$) investigating the use of supplements found that water-soluble vitamin D and A increased the risk of developing allergic disease (by parental questionnaires) and sensitisation to food and airborne allergens in children up to 4 years of age. Surprisingly, this effect was not seen with supplementation of the same vitamins in peanut oil. However, the study had significant limitations as the authors firstly did not specify the dose of vitamin D given, secondly no measurement of 25(OH)D levels was taken, and thirdly the possible effect of vitamin A (in isolation or in combination) on the outcome remained unclear. The mechanisms behind different results when comparing water-soluble vitamin D versus vitamin D in peanut oil remained unexplained [185].

Focusing on vitamin D blood levels taken in childhood and eczema outcomes, numerous studies could not find any associations between vitamin D status and eczema [186–189], while some found an inverse relationship [190,191] or a positive association (Table 3) [192].

Similarly, conflicting results were found for 25(OH)D levels in relation to food allergy or sensitisation with no associations [187], positive associations [193,194] or inverse associations [157,189,195]. Although both Allen et al. and Molloy et al. performed their studies in Victoria, Australia, and the major outcome was food challenge-proven food allergy, results were different. No influence of vitamin D was found in the study by Molloy et al., but this result may be related to the smaller sample size ($n = 274$) compared to the study by Allen et al. ($n = 577$). While only Allen et al. found an inverse relationship between 25(OH)D levels and food allergy outcome, it needs to be highlighted that this inverse relationship was *only* applicable for infants of Australian-born parents [157]. However, this particular relationship was not investigated in the study by Molloy et al. Furthermore, while Allen et al. took 25(OH)D levels only once (at 11–15 months) and challenges were performed at 14 to 18 months of age, 25(OH)D levels were taken earlier and twice (at birth and 6 months) by Molloy et al., who also determined outcome measures earlier (at 12 months) [187] (Table 3).

Moving to studies linking vitamin D status to allergic airway disease outcomes, results have again been heterogeneous. Some studies could not show any associations between vitamin D status and asthma, AR or aeroallergen sensitisation [188–190]. One study found a positive association with AR [196]; and opposed to this, three other studies revealed an inverse association with wheezing/asthma and AR or sensitisation to aeroallergens [189].

Whilst all of the aforementioned reviewed studies (Table 3) did not take longitudinal 25(OH)D measurements, Hollams et al. followed a birth cohort of high risk for allergy through the first 10 years of life. The *number of times* a child was found to be deficient in vitamin D was positively associated with the risk for asthma and wheeze at age 10 years, suggesting that prevention of vitamin D deficiency throughout the first few years of life may be an important determinant of asthma risk [191]. This mirrors earlier findings of the same group, where 25(OH)D levels at age 6 years were significant predictors of subsequent atopy/asthma-associated phenotypes at age 14 years [197].

In summary, consistent with prenatal observational studies on vitamin D intake or status and allergy outcome, the reviewed literature in infancy and childhood also showed variable results. Both allergy preventing and allergy promoting effects, as well as no effects, have been described. Differences in age, study population, size and risk level of allergic disease due to family history and geographical location make it difficult to compare study results. Heterogeneity in criteria used for defining allergic disease, the possibility of non-linear associations between 25(OH)D levels and outcomes, methods for measuring 25(OH)D levels (e.g., LC-MS/MS [157,187,191] versus different types of immunoassays [189,194,195]) and variables used in the statistical adjustment contribute further to these difficulties and may at least partially explain why the results of these observational studies are heterogeneous. To overcome this uncertainty, well-designed RCTs in infants and children are needed.

Table 3. Observational studies of vitamin D status in childhood and allergy outcome.

Reference Study Location Latitude	Study Design	Study Population	Assay for 25(OH)D	Time Point When 25(OH)D Level Was Taken	Data Collection/ Outcome Variable	Main Results	Higher 25(OH) D Level
Sharief et al. (2011) USA 37.09 πN	National Health and Nutrition Examination Survey (NHANES)	<i>n</i> = 3136 (1 to 21 years) Non-Hispanic White 61.9% General population	CIA	Any stage between 1 and 21 years of age (mean age 12.5 years)	NHANES 2005/2006 questionnaire [189] sIgE levels for aeroallergens and foods	25(OH)D levels of <37.5 nmol/L associated with peanut (OR 2.39; CI1.29–4.45), ragweed (OR 1.83; CI1.20–2.80) and oak (OR 4.75; CI 1.53–4.94) sensitization, (sIgE) (<i>p</i> < 0.01) 25(OH)D < 50 nmol/L and sIgE associated with dog, cockroach, Alternaria species, shrimp, ryegrass, Bermuda grass, birch, thistle (<i>p</i> < 0.05) No association with eczema and AR	S↓ E←→ AR←→
Heimbeck et al. (2013) Germany 51.2 πN	Survey	<i>n</i> = 9838 (0 to 17 years) Residence in Germany (including 1411 migrants) General population	CIA	Any stage between 1 and 17 years of age (no mean age given)	Parental questionnaire: “Did a physician ever diagnose eczema?”	25(OH)D level for eczema (<i>n</i> = 1364; mean = 50.6 nmol/L) higher than for control group (<i>n</i> = 8474; mean = 47.1 nmol/L) (<i>p</i> < 0.001) Inverse association between low 25 (OH)D levels and eczema (multivariate OR for 1st quartile vs. 2nd quartile): 0.76 (95% CI 0.61–0.94))	E↑
Wang et al. (2014) Hong Kong 22 πN	Case control study	<i>n</i> = 826 (0–18 years) Eczema: <i>n</i> = 498; No eczema: <i>n</i> = 328 (no eczema: general population) Chinese population Ethnicity not further specified	Enzyme Immuno-assay	Any stage between 0 and 18 years of age Mean age in eczema group 10.5 (SD 3.9) vs. no eczema 12.3 years (SD 4.1)	Medical assessment for eczema; Hanifin and Rajka criteria applied [161] Total IgE and sIgE for aeroallergens	Eczema cases (<i>n</i> = 498, mean age 10.5 years) more frequently 25(OH)D levels < 25 nmol/L than controls (<i>n</i> = 328, mean age 12.3 years) (mean 25(OH)D level (SD); 28.9 (15.3) vs. 34.2 nmol/L (14.5); <i>p</i> < 0.001) Total IgE and sensitization to aeroallergens (sIgE and SPT): not significant between groups	E↓ S←→

Table 3. Cont.

Reference Study Location Latitude	Study Design	Study Population	Assay for 25(OH)D	Time Point When 25(OH)D Level Was Taken	Data Collection/ Outcome Variable	Main Results	Higher 25(OH) D Level
Berents et al.(2016) Oslo, Norway 59.9 π N	Cross-sectional study	$n = 623$, <12 months of age $n = 388$ general population (mean age 6.5 months) $n = 235$ recruited from trial on acute bronchiolitis (mean age 4.3 months) 93% European ancestry	LC-MS/MS	Between 1 and 13 months (mean age 5.1 months) and at 24 months	Caregivers interviewed by a structured questionnaire: Hanifin and Rajka criteria applied [161]	Appointment at 1 to 13 months of age: ($n = 67$ eczema, $n = 529$ no eczema; mean age 5.1 months): 25(OH)D level (mean 58.2 nmol/L) no association with eczema At 2 year appointment ($n = 103$ eczema, $n = 346$ no eczema; mean age 24.7 months): 25(OH)D level (mean 66.9 nmol/L) no association with eczema	E \leftarrow →
Allen et al. (2013) Melbourne, Australia 37.81 π S	Cohort study	$n = 577$, 11 to 15 months General population 62.5% both parents born in Australia Ethnicity not provided	LC-MS/MS	11 to 15 months	Challenge-proven food allergy at 14 to 18 months ($n = 344$), sensitized but tolerant ($n = 74$) SPT (wheal size >2 mm) or sIgE to egg, sesame, peanut, cow's milk, shrimp	Infants of Australian-born parents only: if 25(OH)D ≤ 50 nmol/L at 12 months of age: More likely to have challenge-proven allergy to egg (aOR, 3.79; 95% CI, 1.19–12.08, $p = 0.025$) and peanut (aOR, 11.51; 95% CI, 2.01–65.79; $p = 0.006$) More likely to have multiple food allergies (>2) rather than a single food allergy (aOR, 10.48; 95% CI, 1.60–68.61 vs. aOR,1.82; 95% CI, 0.38–8.77, respectively) No parent-reported eczema	FA \downarrow E \leftarrow →

Table 3. Cont.

Reference Study Location Latitude	Study Design	Study Population	Assay for 25(OH)D	Time Point When 25(OH)D Level Was Taken	Data Collection/ Outcome Variable	Main Results	Higher 25(OH) D Level
Molloy et al. (2017) Barwon, Australia 38.14 π S	Birth cohort study	274 mother–infant pairs (mean age = 41 months (24; 60)) 75.2% European ancestry General population	LC–MS/MS	At birth and at 6 months	Challenge-proven food allergy at 1 year of age Questionnaire: Eczema UK working party criteria applied [198]	No association between 25(OH)D < 50 nmol/L at birth ($n = 105$; aRR 1.25, 95% CI 0.7–2.22) or at 6 months of age ($n = 55$; aRR 0.93, 95% CI 0.41–2.14) and food allergy at 1 year of age No association between 25(OH)D < 50 nmol/L at birth ($n = 105$; aRR 0.88, 95% CI 0.54–1.43) or at 6 months of age ($n = 55$; aRR 0.84, 95% CI 0.33–2.14) and eczema within first 12 months of age	FA $\leftarrow\rightarrow$ E $\leftarrow\rightarrow$
Cairncross et al. (2016) New Zealand 35–46 π S	Cross-sectional study	$n = 1329$ (2 to 3 years, mean age 41 months) General population 70% European ancestry	LC–MS/MS	Any stage from 24 to 60 months	ISAAC questionnaire	Food allergy associated with higher mean 25(OH)D levels (56 vs. 52 nmol/L, $p = 0.007$) 25(OH)D ≥ 75 nmol/L compared to 50–74.9 nmol/L ($n = 29$): increased risk of parent-reported food allergy (OR = 2.21, 1.33–3.68, $p = 0.002$) No associations between eczema (mean 25 (OH)D level 53 vs. 52 nmol/L, $p = 0.50$) AR (52 vs. 52 nmol/L, $p = 0.94$) Asthma (52 vs. 52 nmol/L, $p = 0.98$)	FA \uparrow E $\leftarrow\rightarrow$ AR $\leftarrow\rightarrow$ A $\leftarrow\rightarrow$

Table 3. Cont.

Reference Study Location Latitude	Study Design	Study Population	Assay for 25(OH)D	Time Point When 25(OH)D Level Was Taken	Data Collection/ Outcome Variable	Main Results	Higher 25(OH) D Level
Bener et al. (2014) Doha, Qatar 25.28 π N	Cross-sectional study	$n = 1833$ (5 to 16 years) General population Population from Qatar Ethnicity not further specified	RIA	Any time from 5 to 16 years	Questionnaire: Parent-reported physician diagnosed	25(OH)D < 50 nmol/L associated with risk for: wheezing (OR = 1.29; $p = 0.05$) asthma (OR = 2.31; $p = 0.001$) AR (OR 1.59; $p < 0.001$)	W↓ A↓ AR↓
Freishtat et al. (2010) Washington, USA 47.75 π N	Cross-sectional case control study	$n = 113$ African American Asthma $n = 92$ (6 to 20 years of age, mean age 11.1 (SE 0.4)) No asthma $n = 21$ (6 to 9 years, mean age 7 years (SE 0.3)) Controls younger than cases ($p < 0.001$)	Enzyme- linked immuno- absorbant assay	For cases: Any stage from 6 to 20 years For controls: Any stage from 6 to 9 years	Cases: Physician- diagnosed asthma Controls: General population	25(OH)D < 75 nmol/L associated with more asthma cases than controls (73/85 vs. 4/21, aOR = 42 (95% CI: 4.4 to 399)) 25(OH)D < 50 nmol/L associated with more asthma cases compared to controls (46/84 vs. 1/21, aOR = 20 (95% CI: 1.4 to 272))	A↓
Kutlug et al. (2017) Samsun, Turkey 41.27 π N	Case control study	$n = 200$, 6–18 years of age 100 cases with AR with seasonal symptoms for at least 2 years and positive SPT to pollen 100 controls General population	LC-MS/MS	For cases: median age 12.35 years (6; 17.8) For controls median age 11.5 years (6; 17.8)	AR diagnosis by “Allergic Rhinitis and its impact on asthma (ARIA) criteria 2008”	25(OH)D level in AR group (mean 51.95, SD 16.2) significantly higher than in control group (mean 44.8, SD 16.2), ($p = 0.002$)	AR↑

Table 3. Cont.

Reference Study Location Latitude	Study Design	Study Population	Assay for 25(OH)D	Time Point When 25(OH)D Level Was Taken	Data Collection/ Outcome Variable	Main Results	Higher 25(OH) D Level
Baeck et al. (2014) Seongnam-Si, Korea 37.44 πN	Cross-sectional study	n = 226, age 3 to 24 months High-risk population n = 168 diagnosed with eczema n = 58 suspected food allergy, no eczema	CIA	Any time from 3 to 24 months	Physician diagnosed, parent-reported questionnaire sIgE to food (milk, egg, wheat, soy)	Polysensitization group significantly lower levels of 25(OH)D than the non-sensitization (p = 0.001) and monosensitization (p = 0.023) group 25(OH)D ≤ 50 nmol/L increased the risk of sensitization to food allergens (OR 5.0; 95% CI 1.8–14.1), milk (OR10.4; 95% CI 3.3–32.7) wheat (OR 4.2; 95% CI 1.1–15.8)	S↓
Guo et al. (2020) Guangdong, China 23.38 πN	Cross-sectional study	n = 2642 (at 12 or 24 months of age) General population Chinese population, not further specified	CIA	At 12 months or 24 months of age	Total IgE Food and aeroallergen sensitization by sIgE	Positive association between 25(OH)D ≥ 75 nmol/L and sIgE to cow’s milk (<0.001), cat (p < 0.001), dog (p = 0.028) Inverse association between 25(OH)D < 75 nmol/L and sIgE to Der f (p = 0.012) No difference in total IgE	S milk↑ S cat↑ S dog↑ S Der.farinae↓ Total IgE←→
Hollams et al. (2016) Perth, Australia 31.95 πS	Cross-sectional analysis	n = 263 High-risk population	LC-MS/MS	At birth and at 0.5, 1, 2, 3, 4, 5, 10 years of age	Up to 5 years symptom diary: Clinical phenotyping Total and sIgE levels	Inverse association between 25(OH)D levels and sensitization at age 0.5, 2 and 3 years. No association for all other age groups Number of 25(OH)D-deficient levels on follow ups positively associated with risk for asthma/wheeze, eczema and sensitization at 10 years of age	S↓ at 0.5, 2, 3 years S←→ at 1, 4, 5, 10 years Number of f/u: A/W↓ E↓ S↓

↓: inverse association; ←→:no association; ↑:positive association; E: eczema; FA: food allergy; W: wheeze; A: asthma; AR: allergic rhinitis; S: sensitization.

8.2. Randomized Controlled Trials of Vitamin D Supplementation in Infancy and Allergy Outcomes

Interventional studies provide evidence for causal inference; hence, well-designed RCTs are required to shed light on the above discussed inconsistent findings.

Rosendahl et al. compared two different vitamin D supplemental doses (400 IU/day versus 1200 IU/day) given from 2 weeks to 24 months of age. However, allergy outcomes were only analysed in a secondary analysis (primary analysis investigated the effect on bone health and infection rate) [199]. The authors were unable to find an influence on food and aeroallergen sensitisation, parent-reported physician-diagnosed wheezing, food allergy or eczema at 12 months of age [200]. Cow's milk allergy was reported more frequently in the group receiving 1200 IU/day vitamin D supplementation ($n = 20/387$) compared with the 400 IU vitamin D group ($n = 9/377$) (OR, 2.23; 95% CI, 1.00–4.96). However, this finding needs to be interpreted with caution due to small case numbers, no corresponding sIgE levels for cow's milk and cow's milk allergy was based on parent report [200]. Another US-based multicenter study by Hibbs et al. found that recurrent wheezing was reduced in infants in a sustained supplementation group (400 IU/day vitamin D from 0 to 6 months of adjusted age) compared with infants in a diet-limited supplementation group (difference, -10.7% (95% CI, -27.4% to -2.9%); relative risk, 0.66 (95% CI, 0.47 to 0.94)). No differences were found for asthma, eczema, food allergy, pollen or dust allergy (parent report) or sensitisation at 12 months of age [201]. Hibbs et al. [201] primarily included preterm black infants with a low birth weight (mean gestational age 33 weeks, median birth weight 1.9 kg), including a considerable number of vitamin D-deficient or -insufficient infants. This cannot be compared to the post hoc analysis by Rosendahl et al. [200] which focused on term-born, birth weight appropriate for gestational age, White, vitamin D-sufficient infants, as it is known that ethnicity [115], prematurity and birth weight [202] can have an influence on immune development. Furthermore, any of these three infant characteristics, or the interaction between them, could lead to changes in immune function and subsequently differences in wheeze outcomes. Premature infants are also prone to developing chronic lung disease, which is known to be linked to recurrent wheeze [203], and could explain the findings in the study by Hibbs et al. Additionally, starting levels of 25(OH)D, intervention doses and intervention periods were different between both studies. No information regarding intentional or unintentional vitamin D intake (or UVR exposure) in control groups was provided. In addition to the study by Hibbs et al., the Australian Vitamin D in Allergy (VITAL) study is to date the only *primary* RCT on vitamin D supplementation in infancy and allergy outcomes in early childhood [204]. In the VITAL study, the investigators randomized term, high-risk (for allergy due to family history) infants to receive either vitamin D supplementation (400 IU/d) or a placebo until 6 months of age. The primary outcome was eczema at 6 months of age and no difference between the placebo and intervention group was found. Children were followed up until 2.5 years of age, and additional outcomes such as food allergy, wheeze/asthma, allergic rhinitis and allergen sensitisation were assessed. However, no difference between the groups regarding any of the allergy outcomes was detected [205].

9. Conclusions and Future Directions

This review indicates that there are inconsistent results in observational studies regarding associations between 25(OH)D and allergy outcomes in childhood. Furthermore, to date, no sufficiently powered intervention studies have investigated the effect of vitamin D supplementation and status in the prenatal nor early postnatal period on allergic disease development in early childhood. In addition, no single intervention study has investigated the effect of combined pre- and postnatal vitamin D supplementation and status. Moreover, only a single observational study [191] and one intervention study (the VITAL study) [131,205] analysed vitamin D status longitudinally in early childhood.

However, clear evidence exists that vitamin D has immunomodulatory properties, and reduced supply of vitamin D to immune tissues may result in an inflammatory and

allergic phenotypes [75,169,206]. In particular, vitamin D is associated with the cytokine production profiles of T cells (e.g., Th1/Th2 balance) [55], and the number or function of Treg [66,206] and DCs [85,86].

Evidence also links high latitude, and consequently reduced UV light exposure, to the increased risk of development of allergic diseases in children [96,207]. Apart from the prominent role that vitamin D production and its effects may play, sunlight *independent* of vitamin D production needs to be highlighted as a potentially critical factor in allergic disease modulation as well [96,207–209]. A recently published human study (the VITAL study) explored whether direct UV light exposure in infancy may have a vitamin D-independent effect on allergy prevention and found that exposure to direct UV light appears to be beneficial in reducing the risk of eczema development in early childhood [210]. Further research is required to expand these results and determine optimal levels of UV light exposure while balancing potential risks.

The lack of beneficial effects of vitamin D supplementation prenatally and in infancy [200,204,205] needs to be confirmed in larger trials adequately powered to detect clinical benefits and that even may extend beyond allergy. Future vitamin D studies should also help to address unanswered questions about the optimal time to start (if indicated) and the optimal duration of supplementation. Such studies may consider critical periods in developmental trajectories of organ systems, which may differentially affect outcomes, e.g., human lung development starts at approximately 3 to 4 weeks of gestation [211] and vitamin D plays an immunomodulatory role in the development of lungs and immune system [176]. However, the earliest prenatal intervention with vitamin D supplementation was in a RCT design which was started between 10 and 18 weeks of gestation [153]. This supplementation start time point was probably already too late to induce a preventative effect in the fetus. Hence, commencement of vitamin D supplementation for allergy prevention and potentially other health benefits may need to occur earlier in pregnancy or perhaps even before conception.

As previous observational studies found associations between vitamin D status and eczema [190], or asthma and allergic rhinitis outcomes [191,212,213] later in life (Table 3), long-term follow-up of trial interventions is needed. This is supported by immunological developments which can continue to expand until sexual maturity [175,214,215].

It is also likely that other benefits (such as on musculoskeletal health) [216] may not be obvious until later in childhood or adolescence. Furthermore, it is important to understand the wider implications of vitamin D status in specific risk populations (e.g., highly pigmented skin, premature delivery, and small for gestational age), where effects of vitamin D may be more pronounced and an intervention with 400 IU/day of vitamin D supplementation in early infancy might be protective for outcomes beyond allergy development.

Thus, there remains an urgent need for more studies, particularly designed as intervention trials, investigating the role of 25(OH)D supplementation and status on allergy prevention.

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