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Vitamin D status, aeroallergen sensitization, and allergic rhinitis: A systematic review and meta-analysis

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ABSTRACT

Purpose: The role of vitamin D status in the etiology of allergic diseases is uncertain. The aim of this study was to investigate the association of vitamin D status with risk of two main outcomes: aeroallergen sensitization and allergic rhinitis (AR).

Methods: We performed a systematic review of Medline, Scopus, Science Citation Index, and Google Scholar databases. Studies were included if they reported on prevalent or incident cases of aeroallergen sensitization or AR according to vitamin D status. Quality assessment, data extraction and meta-analysis were performed.

Results: A total of 21 observational studies were included. Children with serum 25(OH)D ≥ 75 nmol/L had significantly reduced odds of aeroallergen sensitization, but neither vitamin D intake in pregnancy nor vitamin D supplementation in infancy were associated with risk of AR. Individuals with serum 25(OH)D ≥ 75 nmol/L had lower prevalence of AR compared to those with serum 25(OH)D < 50 nmol/L (OR: 0.71, 95%CI: (0.56–0.89), $p = 0.04$). This association was mainly observed in adult men; prevalence of AR was lower in men with serum 25(OH)D ≥ 75 nmol/L compared to men with serum 25(OH)D < 50 nmol/L, while this association was not observed in women.

Conclusions: The current literature suggests significant age- and sex-specific relations of vitamin D status to risk of aeroallergen sensitization and AR.

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Aeroallergen; allergic rhinitis; atopy; diet; vitamin D

Introduction

Allergic rhinitis (AR) is a chronic inflammatory disease of upper airways characterized by rhinorrhea, sneezing, itching, and commonly allergic conjunctivitis [1]. AR has been estimated to affect approximately 40% of children and 10 to 30% of adults; it tends to begin at young ages since 80% of adults with AR had symptoms prior to 20 years of age [2]. About 400 million people worldwide suffer from AR with higher prevalence in developed and industrialized countries [3]. Early phase and late phase type 1 hypersensitivity responses to aeroallergens constitute the main pathophysiology of AR similar to allergic asthma [1]. At present, the main risk factors for AR include atopy (aeroallergen sensitization), genetic factors, high socioeconomic status, environmental exposure to air pollutants, cigarette smoking, and certain respiratory tract infections [1]. The etiology of AR remains poorly understood and it is an active area of research.

Vitamin D deficiency is increasingly recognized as a potential etiologic or disease-modifying factor in several allergic diseases, including eczema [4], food allergy [5], and asthma [6]. Less research has focused on the relation of vitamin D status to aeroallergen sensitization and AR, a situation that motivated the current systematic review and meta-analysis. Interest in the health effects of vitamin D has grown because of evidence from national population surveys that find a high prevalence of vitamin D deficiency that is growing year by year, possibly due to spread of the westernized life style [7]. The U.S. National Health and Nutritional Examination Survey (NHANES) revealed that mean serum 25-hydroxyvitamin D (25(OH)D) decreased from 30 ng/mL in 1988–1994 to 24 ng/mL in 2001–2004 [7]. This epidemiologic pattern for vitamin D is coupled with the growing epidemic of allergic diseases in western countries and thereby raises the possibility of a link between these two variables.

There is, however, controversy about the relation between vitamin D status and allergic diseases. Indeed, national surveys and large population studies have led to disparate conclusions about the association of serum 25(OH)D with AR. Wjst et al found that those with the highest quartile of serum 25(OH)D were at increased risk of AR (OR, 1.20; 95%CI, 1.12-1.28), while Mai et al found the opposite (OR, 0.57; 95%CI 0.39-0.84) [8, 9]. The controversy also exists with regard to latitude, which is a proxy for ultraviolet-B exposure, the major determinant of vitamin D status in humans [10]. Although anaphylaxis admissions and epinephrine auto-injectors are positively associated with latitude, consistent with more anaphylaxis in populations with less ultraviolet-B exposure and presumably lower vitamin D status [11, 12], this tidy pattern may not hold for aeroallergen and AR [13]. Hughes et al found that greater sunshine exposure in winters between the ages of 6 to 15 years was associated with increased odds of having AR [13]. Curiously, this finding was not related to ultraviolet-B exposure, perhaps suggesting that even sunlight may have complex associations with allergy development [13]. Given these disparate findings in the current scientific literature, we performed a systematic review and meta-analysis to investigate the association of vitamin D status with aeroallergen sensitization and AR.

Materials and methods

This study was conducted and reported according to recommendations of reporting Meta-analysis Of Observational Studies in Epidemiology (MOOSE) [14]. Serum 25-hydroxyvitamin D, or 25(OH)D, is the primary exposure of interest. Serum 25-hydroxyvitamin D, or 25(OH)D, is the best available measure of vitamin D status in the body because 1,25(OH)₂D, the active form of vitamin D, has much shorter half-life compared to 25(OH)D and serum 1,25(OH)₂D level is under tight regulation by parathyroid hormone [10]. While serum 25(OH)D $\geq$ 75 nmol/L is generally considered sufficient, while values $<$ 50 nmol/L are generally considered as vitamin D deficiency. Values between these two extremes are often categorized as vitamin D insufficiency. Although most vitamin D in the body is synthesized via the ultraviolet-B stimulation during sunlight exposure, a smaller portion is derived by dietary intake [10]. Thus, the secondary exposure of interest is estimated daily intake of vitamin D in food or supplements.

The primary outcome measures are prevalence and incidence of aeroallergen sensitization and AR, according to the serum 25(OH)D level. Secondary outcomes of interest include: the relations of dietary intake of vitamin D with prevalence and incidence of aeroallergen sensitization and AR; and the mean difference of serum

25(OH)D between patients with AR and healthy controls. Aeroallergen sensitization was defined as presence of a aeroallergen-specific IgE in serum with values of $\geq$ 0.35 KU/l. AR was either reported as physician-diagnosed or identified using the International Study of Allergies and Asthma in Childhood (ISAAC) criteria [15].

Eligibility criteria

Observational studies (cross-sectional, case-control, and cohort) were included if they reported the prevalence or incidence of aeroallergen sensitization or AR in separate quartiles/categories of serum 25(OH)D. Case-control studies were included if they met aforementioned eligibility criteria or reported the mean differences of 25(OH)D between patients with AR and healthy controls. We excluded case series, reviews, commentaries or editorials and duplicate articles retrieved via searching different databases. Cohorts that investigated the association of maternal or childhood dietary intake of vitamin D with incidence of aeroallergen sensitization or AR were also included. Although we wanted to include interventional studies in this meta-analysis, we identified only one randomized controlled trial (RCT) comparing the effect of vitamin D supplementation (compared to placebo) on the incidence of aeroallergen sensitization or AR [16]. We used findings of this study in the discussion because all other identified studies were all observational.

Search strategy

To find relevant studies, both electronic searches and manual reference retrievals were performed. The Medical Subject Heading (MeSH) terms of “allergy” and “vitamin D” were used to provide a more sensitive search strategy. In addition, combined text words of (allergic rhinitis text word AND vitamin D text word) OR (Hay fever text word AND vitamin D text word) OR (food allergy text word AND vitamin D text word) OR (asthma text word AND vitamin D text word) were used to find potentially relevant studies. We searched databases of Medline (Pubmed, Embase, and Ovid), Scopus (sciedirect), and Science Citation Index (ISI Web of Knowledge). To find relevant gray literature, Google was searched with the same strategy and 600 first retrieved links were reviewed. Whenever the results of an eligible study were inaccessible, we contacted the first or corresponding authors. The bibliographies of eligible studies were also screened to identify additional relevant publications. No language or time limitations were applied. The initial search of literature was conducted in 2014 and updated in January, 2015.

Data extraction

Those studies that met eligibility criteria were selected for data extraction. The agreement value (kappa) of investigators to select articles for data extraction was 0.85, which is considered high. In cases of disagreement, a faculty member was asked to review and decide. Quality assessment was done for all included studies according to Critical Appraisal Skill Program (Figure S1). We extracted data on the characteristics of each study including study design, study population, follow up (for cohort studies), geographical area where study conducted (including latitude), measure of vitamin D status, and primary outcome measures (i.e., aeroallergen sensitization or AR). For studies that used narrower cut points, we merged the data to calculate the results selected cut points of 25(OH)D ≥ 75 nmol/L compared to serum 25(OH)D of <50 . For instance, Wjst et al [9] results were merged prior to meta-analysis.

Statistical analysis

The statistical analysis was performed using EXCEL software (Microsoft, USA) and Comprehensive Meta-Analysis version 2 (CMA, Biostat, Inc, USA). We estimated the pooled odds ratio (OR), relative risk (RR) and 95% confidence intervals (95%CI) of aeroallergen sensitization and AR with respect to different categories of serum 25(OH)D or vitamin D intake. We reported the age and sex-specific pooled estimates as applicable due to the reported interactions of age and sex with association of vitamin D status with allergic outcomes [8, 17].

Cochrane's Q statistics was used to estimate the heterogeneity of included studies. When $I^2 \geq 60\%$ or $p \leq 0.10$, the random effect model was applied for meta-analysis; when $I^2 < 60\%$ and $p > 0.10$, we used the fixed effect model. Forest plots of pooled estimates, as well as a funnel plot of primary outcome measures, were drawn. Visual inspection of the funnel plots, coupled with Begg's rank correlation and Egger's linear regression test, was used to assess publication bias. Relative weights are expressed as percentages. The analyses were two-tailed and $p < 0.05$ was considered statistically significant.

Results

Study characteristics

Figure 1 shows the flow diagram of identification of studies for this meta-analysis. Among 11 studies investigating the association between serum 25(OH)D and aeroallergen sensitization, 7 reported overall sensitization to aeroallergens [18–24] and 4 provided the odds

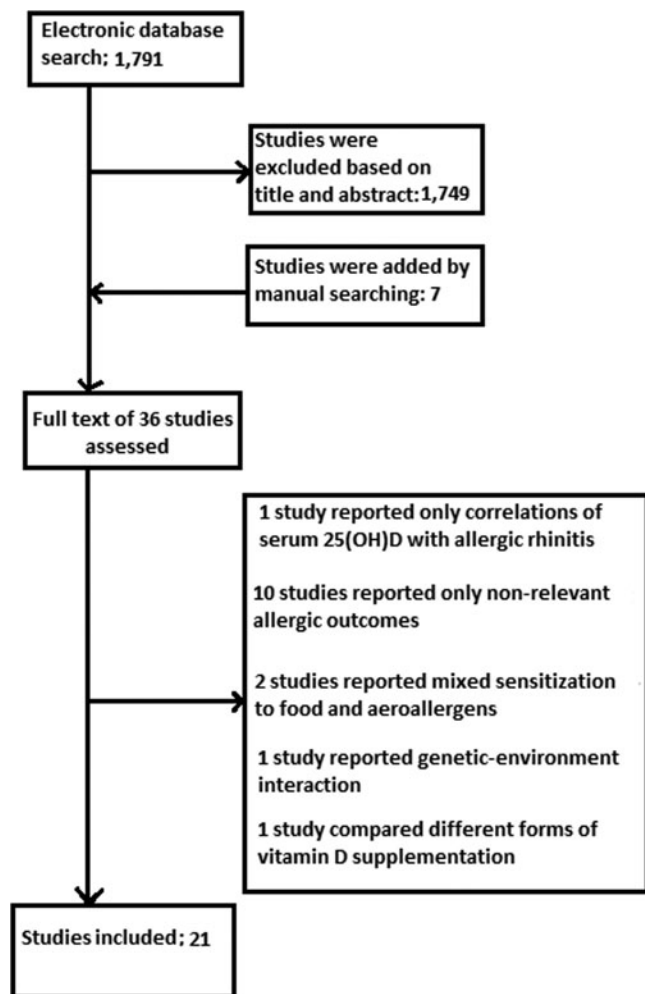


Figure 1. Flow diagram of all studies included in this meta-analysis; of 1,791 studies identified via electronic and hand searching, a total of 21 studies were included.

of sensitization to specific aeroallergens [24–27]. A total of 7 studies reported prevalence of AR in quintiles of serum 25(OH)D [9, 13, 20, 23, 24, 28, 29] while 5 studies [8, 21, 27, 30, 31] reported prevalence of AR in categories of serum 25(OH)D level. Only 2 studies reported risk of AR incidence in offspring according to maternal categories of vitamin D intake during pregnancy [32, 33]. Among 3 studies [34–36] that reported allergen sensitization in mother–child pairs with known maternal dietary intake of vitamin D during pregnancy, 2 reported mixed aeroallergen and food-allergen sensitization [34, 36] and 1 study reported aeroallergen sensitization separately [35]. Regarding early life intake of vitamin D and risk of aeroallergen sensitization or AR, 2 studies were included [37, 38]. Only 3 studies [24, 30, 39] investigated the mean difference of serum 25(OH)D between patients with AR and healthy controls. Detailed characteristics of the included studies are summarized in Table 1. The funnel plot of included studies with primary outcome showed a low possibility of publication bias (Figure S2). The Begg's

Table 1. Characteristics of 21 studies included in the meta-analysis.

Study	Risk of Bias*	Design (follow up)	Participants (female %)	Geographic area (latitude)	Vitamin D status in study population	Exposure measure	Outcome measure	Main findings and conclusions
Hypponen et al 2004 [38]	L	Cohort (31 years)	5,007 (50%)	Finland (64° N)	NA	Vitamin D intake in infancy	AR was defined as self-reported rhinitis after exposure to aeroallergens, asthma as wheezing during the past 12 months or by current use of asthma medication	Regular use of vitamin D supplementation with dose of 2000 IU/day or more was associated with increased risk of atopy and AR
Wjst et al 2007 [9], NHANES III study 1988-1994	H	Cross-section	18,224 (NA)	United States (40° N)	NA	Serum 25(OH)D in a national survey including both children and adults	AR was defined by the question "Did a doctor ever tell you had hay fever?"	Positive association of serum 25(OH)D with prevalence of AR
Hypponen et al 2009 [19]	M	Cross-section	7,288 (50%)	England (52.4° N)	23.4% had sufficient, 35.8% insufficient and 41.8% had deficient serum 25(OH)D levels	Serum 25(OH)D was measured among adult British participants with mean age of 45 years (ranged from 44 to 46)	Aeroallergen sensitization was investigated considering specific IgE	A U-shaped non-linear relation between serum 25(OH)D and aeroallergen sensitization; those with serum 25(OH)D more than 135 nmol/L or less than 25 nmol/L were at increased risk of sensitization
Back et al 2009 [37]	H	Cohort (6 years)	123 (NA)	Sweden (61.3° N)	NA	Vitamin D intake during infancy was measured	AD, AR and asthma were investigated using ISAAC questionnaire	Prevalence of AD was higher among infants received higher dose of vitamin D during infancy but not AR nor asthma
Erkkola et al 2009 [32]	L	Cohort (5 years)	1669 (47%)	Finland (64° N)	Maternal total intake of vitamin D during pregnancy was 5.8 ± 3.8 µg/day	Vitamin D intake during pregnancy was measured	AD, AR and asthma were investigated using ISAAC questionnaire at 5 years of age in offspring	Maternal vitamin D intake was inversely associated with risk of AR and asthma incidence in offspring
Hughes et al 2010 [12]	H	Cross-section	480 (77.7%)	Australia (27–43° S)	NA	Latitude, UVB exposure and serum 25(OH)D among control group of Ausimmune Study aged 18-61 years	AR was defined by the modified ISAAC questionnaire "a problem with sneezing, runny or blocked nose without a cold or flu, sometimes accompanied by watery, itchy eyes", AD, asthma	No significant association between, UVB exposure or serum 25(OH)D with AR, asthma and AD, by each 10° increase of latitude prevalence of asthma decreased (OR, 0.91, 95%CI, (0.84–0.98))
Hollams et al 2011 [29], Raine Study	L	Cohort ¹ (8 years)	693 (45.1%)	Australia (32° S)	59.3% had sufficient, 36.3% insufficient and 4.4% had deficient serum 25(OH)D levels	Serum 25(OH)D at 6 years and 14 years	AR was defined by ISAAC questionnaire "runny, blocked or itchy nose in the presence of runny or itchy eyes over the preceding 12 months" HDM, sensitization, BHR and asthma investigated at 14 years	Significant inverse association between each 1 unit increase in log-transformed serum 25(OH)D and AR (OR 0.17, 95%CI (0.05–0.59)), HDM sensitization (OR 0.18 95%CI, (0.05–0.60), BHR (OR, 0.28 95%CI (0.06–1.37)), asthma (OR, 0.11 95%CI (0.02–0.84))
Li et al 2011 [20]	H	Cross-section	435 (61.6%)	China (35° N)	2.8% had sufficient, 8.2% insufficient and 89.0% had deficient serum 25(OH)D levels	Serum 25(OH)D measured among adults with asthma (mean age of 42.65 ± 1.2 years)	FEV1, FEV/FVC, FEV% predicted, AR was defined using ISAAC questionnaire	Significant Positive but weak correlation between serum 5(OH)D and FEV1, FEV/FVC, and FEV% predicted, But no association with prevalence AR observed (OR, 0.910, 95%CI, (0.495–1.672).



Rothers et al 2011 [21]	L	Cohort (5 years)	219 (51.1%)	Boston, United states (42.3° N)	32.5% had sufficient, 41.1% insufficient and 26.5% had deficient serum 25(OH)D levels median cord blood 25(OH)D level was 64 nmol/L (IQR, 49-81 nmol/L).	Cord blood 25(OH)D measured at delivery	AR was defined as doctor-diagnosed rhinitis at 3 or 5 years plus symptoms since the age of 4 years, Asthma Sensitization to Alternaria species, Dermatophagoides farinae, Bermuda grass, careless weed, olive, and mulberry	Those with the lowest (<50 nmol/L) and highest (>100 nmol/L) cord blood 25(OH) were at increased risk of aeroallergen sensitization (OR, 2.4 95%CI (1.1-5.5) and OR, 4.0 95%CI (1.4-11.6), respectively) but no significant association was found regarding AR and asthma
Sharief et al 2011 [27], NHANES 2005-2006	M	Cross- section	6590 (50.1%)	United states (40° N)	13.3% had sufficient, 61.6% insufficient and 25.1% had deficient serum 25(OH)D levels	Serum 25(OH)D measured among 3336 children and 3454 adults with mean age of 12.5 ± 0.2 years	AR was defined using ISAAC questionnaire, asthma, eczema and aeroallergen sensitization	Children but not adults with vitamin D deficiency were at increased risk of pollen sensitization. By contrast, AR was fewer among those with vitamin D deficiency, however total prevalence of asthma, AR and Ad were significantly higher among vitamin D deficient individuals
Jung et al 2011 [30], Korean NHANES IV2009	M	Cross- section	8012 (50.3%)	Korea (36° N)	13.7% had sufficient, 44.2% insufficient and 42.1% had deficient serum 25(OH)D Levels. Mean serum 25(OH)D was 17.55 ± 0.24 ng/mL	Serum 25(OH)D measured among adult population with mean age of 44.41 ± 0.37 years	AR was defined according to ISAAC questionnaire	Those with sufficient level had significantly lower prevalence of AR
Van Oeffelen et al 2011, [22] PIAMA study	L	Cohort (4 years)	328 (46%)	Netherland (52.3° N)	NA	Serum 25(OH)D, zinc, magnesium, and selenium were measured among 4 year old children 4 and reinvestigated in 8 years of age	Asthma, atopy and BHR by age of 4 and 8 years	Serum 25(OH)D measured at 4 years was inversely associated with asthma (OR, 0.49, 95%CI (0.25-0.95)
Brehm et al 2012 [18]	H	Cross- section	560 (46.0%)	Puerto Rica (18.2° N)	45.5% of participants had serum 25(OH)D below 30 ng/mL	Serum 25(OH)D measured among children with mean age of 10.2 years (ranged from 6 to 14)	Asthma severity, FEV1, FEV1/FVC and aeroallergen sensitization	Vitamin D insufficiency was associated with higher asthma exacerbations (OR, 2.6, 95%CI (1.5-4.9)
Arshi et al 2012 [39]	H	Case-control	5379 (55%)	Iran (32° N)	5.1% of normal population and 30% of patients with AR had severe vitamin D deficiency	Serum 25(OH)D was measured among adult population	AR was defined according to ISAAC questionnaire	Patients with AR had significantly lower serum 25(OH)D compared to healthy individuals

(Continued on next page)

Table 1. (Continued).

Study	Risk of Bias*	Design (follow up)	Participants (female %)	Geographic area (latitude)	Vitamin D status in study population	Exposure measure	Outcome measure	Main findings and conclusions
Montero-Arias 2013 [31]	H	Cross-section	121 (83.5%)	Costa-Rica (9.95° N)	9.9% had sufficient, 60.3% insufficient and 29.8% had deficient serum 25(OH)D levels	Serum 25(OH)D measured among adults with asthma with mean age of 48.1 ± 15.7 years	AR was defined according to ISAAC questionnaire, FEV1, FVC, FEV1/FVC	No significant association between serum 25(OH)D and AR was observed, while, serum 25(OH)D was significantly correlated with FEV1 and those with vitamin D efficiency had significantly severe asthma
Cheng et al 2013 [50], Korean NHANES II, III, IV and V (2008-2010)	M	Cross-section	15212 (49.4%)	Korea (36° N)	NA	Serum 25(OH)D was measured among adult Korean population with mean age of 44 ± 15.1 years	AR was defined according to physician diagnosis, Asthma, AD and allergic sensitization	Patients with AD or AR had significantly lower serum 25(OH)D compared to healthy individuals. On the other hand, those with vitamin D deficiency had an increased likelihood of atopic dermatitis, but not asthma, allergic rhinitis, or IgE sensitization
Baiz et al 2013 [28], EDEN study	M	Cohort (5 years)	239 (41.8%)	France (47° N)	Mean cord serum 25(OH)D was 17.8 ng/mL and IQR of 15.1 ng/mL	Cord serum 25(OH)D was measured at the time of delivery	AR was diagnosed according to ISAAC questionnaire, AD asthma	significant inverse association was observed between cord serum 25(OH)D levels and risk of transient early wheezing but not asthma nor AR
Maslova et al 2013 [33]	L	Cohort (7 years)	44,825 (49%)	Denmark (55.7° N)	Median total intake of vitamin D was 11.73.0-19.4) µg/day	Vitamin D intake during pregnancy was measured	AD, AR and asthma were investigated using ISAAC questionnaire at 5 years of age in offspring	Mothers with the highest intake of vitamin D had children in whom prevalence of asthma was fewer comparing to those with the least intake
Mai et al 2014 [8], HUNT study 1995-97 2006-2008	L	Cohort (11 years)	1351 (57.8%)	Norway (61° N)	23.4% had sufficient, 39.3% insufficient and 37.0% had deficient serum 25(OH)D Levels	Serum 25(OH)D was measured among adult population	AR was defined according to answer to following question "Do you have allergic rhinitis or hay fever?"	There existed a gender difference in association of serum 25(OH)D and AR incidence each 25 nmol/L reduction of 25(OH)D level was associated with AOR, 1.84 95% CI 1.18-2.87 in men and 0.83 95% CI (0.66-1.05) in women
Keet et al 2014 [26]	M	Cohort(3 years)	82 (57%)	united states (42.3° N)	Median serum 25(OH)D was 24.7 ng/ml	Serum 25(OH)D and folate were measured among employee of Jackson laboratory with median age of 30.7 years	Sensitization to mouse was investigated	Higher serum folate concentrations but not 25(OH)D was associated with increased risk of sensitization
Wawro et al 2014 [23]	M	Cross-sectional	2815 (48.8%)	Germany (52.5° N)	NA	Serum 25(OH)D was measured at 10 years of age	Sensitization to aeroallergens and prevalence of AR were investigated	Higher serum 25(OH)D was associated with increased aeroallergen sensitization but not AR

Abbreviations: NHANES: National Health and Nutrition Examination Survey, HUNT: Nord-Trøndelag Health Study, PLAMA: Prevention and Incidence of Asthma and Mite Allergy, NA: Not Available, AR: Allergic Rhinitis, AD: Atopic Dermatitis, FA: Food Allergy, UVB: Ultra-Violet B, ISAAC: International Study of Asthma and Allergies in Childhood, BHR: Bronchial Hyper-Responsiveness, FEV1: Forced Expiratory Volume in 1 second, FVC: Forced Vital Capacity, IQR: Inter-Quartile Range * results of quality assessment of each study.

- Hollams et al (reference number 28 in the main text) only evaluated allergic rhinitis at 14 years of age.
- The study by Jung et al (reference number 29 in the main text) and Cheng et al (reference number 23 in the main text) overlapped but their results were quite different; it was not possible to separate them so we considered both in the analysis.

rank correlation test (Z score = 1.56, p -value = 0.12) and Egger linear regression test (T score = 1.42, p -value = 0.18) indicated no significant publication bias regarding studies on AR.

Children

The prevalence of specific sensitization to aeroallergens were significantly lower among children with serum 25(OH)D ≥ 75 nmol/L compared to children with serum 25(OH)D < 50 nmol/L (OR, 0.54, 95%CI 0.43-0.68, $p < 0.001$, Figure 2-A). However, overall sensitization was not associated with serum 25(OH)D (Figure S3). We identified only one study [35] that reported the association between maternal intake of vitamin D during pregnancy and aeroallergen sensitization in offspring. Nwaru and colleagues [35] found that energy-adjusted intake of vitamin D was inversely associated with food allergy sensitization (OR, 0.56, 95%CI, 0.37-0.86), while it did not have a statistically significant association with aeroallergen sensitization (OR, 0.72, 95%CI, 0.50-1.05).

While the prevalence of AR was lower in those with serum 25(OH)D ≥ 75 nmol/L compared to those with serum 25(OH)D < 50 nmol/L, this association did not reach the significant level (OR, 0.91, 95%CI, 0.81-1.01, $p = 0.051$, Figure 3-A). Two cohorts [37, 38] investigated dietary intake of vitamin D during infancy. Their results did not support an association between low dietary intake of vitamin D in early childhood and incidence of AR (RR, 1.58, 95%CI, 0.90-2.76, $p = 0.11$, Figure 4-A). Two cohorts compared the incidence of AR in offspring of mothers in the highest quartile of dietary intake of vitamin D during pregnancy compared to the lowest quartile; (> 40.54 versus < 0.31 mg/MJ in study by Erkkola and colleagues [32] and > 16.5 versus < 5.5 μ g/day in study by Maslova et al [33]). Erkkola et al [32] found a significant “protective” association of high intake of vitamin D during pregnancy, while Maslova et al [33] did not find a statistically significant association between dietary intake of vitamin D and incidence of AR. The pooled estimate showed a possible “protective” trend regarding maternal intake of vitamin D and incidence of AR but it was not statistically significant (RR, 0.86, 95%CI, 0.67-1.11, $p = 0.24$, Figure 4-B).

Adults

Adults with serum 25(OH)D ≥ 75 nmol/L had higher prevalence of aeroallergen specific IgE sensitization compared to those with serum 25(OH)D < 50 nmol/L (OR, 1.26, 95%CI 1.12-1.42, $p < 0.001$, Figure 2-B). Prevalence of AR was lower in those with serum 25(OH)D

≥ 75 nmol/L compared to those with serum 25(OH)D < 50 nmol/L (OR, 0.64; 95%CI, 0.51-0.81, $p < 0.001$, Figure 3-B). This association remained significant after pooling the results of children and adults (OR; 0.71, 95%CI; (0.56-0.89), $p = 0.04$). In addition, pooling the results of studies used the same method (i.e., ISAAC questionnaire) to identify AR did not change the results; serum 25(OH)D ≥ 75 nmol/L was associated with the reduced odds of AR in both children and adults (OR, 0.71, 95%CI 0.53-0.95, $p < 0.001$, Figure S4). Only 2 studies reported sex-specific prevalence of AR in categories of vitamin D status [8, 30]. Interestingly, a sex difference was found regarding association of serum 25(OH)D and AR; men with serum 25(OH)D ≥ 75 nmol/L had lower prevalence of AR compared to men with serum 25(OH)D < 50 nmol/L (OR, 0.53, 95%CI, 0.34-0.83, $p = 0.006$), while such an association was not found in women (OR, 1.17, 95%CI, 0.83-1.65, $p = 0.36$, Figure 5). Finally we estimated the mean difference of serum 25(OH)D between patients with AR and healthy controls. Patients with AR had significantly lower serum 25(OH)D level compared to controls (mean difference, -3.30 , 95%CI, -4.97 to -1.63 nmol/L, $p < 0.001$, Figure S5).

Discussion

This systematic review and meta-analysis revealed that serum 25(OH)D is inversely associated with prevalence of aeroallergen-specific IgE sensitization in children and adolescents. Prevalence of AR is lower in adults with serum 25(OH)D ≥ 75 nmol/L compared to serum < 50 nmol/L. We also found sex-differences in association of serum 25(OH)D with AR; serum 25(OH)D ≥ 75 nmol/L is associated with lower prevalence of AR in men, while no significant association is observed in women. The present study summarizes a growing literature and sheds light into significant age- and sex-specific relations of vitamin D status to risk of aeroallergen sensitization and AR.

Aeroallergen sensitization

This meta-analysis suggested that, generally speaking, serum 25(OH)D is inversely associated with aeroallergen sensitization. However, the results are conflicting in children and adults. Prevalence of aeroallergen sensitization in children with serum 25(OH)D ≥ 75 nmol/L is lower than their peers with serum 25(OH)D < 50 nmol/L (OR, 0.54, 95%CI 0.43-0.68), while the opposite is seen in adults (OR, 1.26, 95%CI 1.12-1.42). These results were drawn mostly from the study by Sharief et al [27] that showed an inverse association between serum 25(OH)D

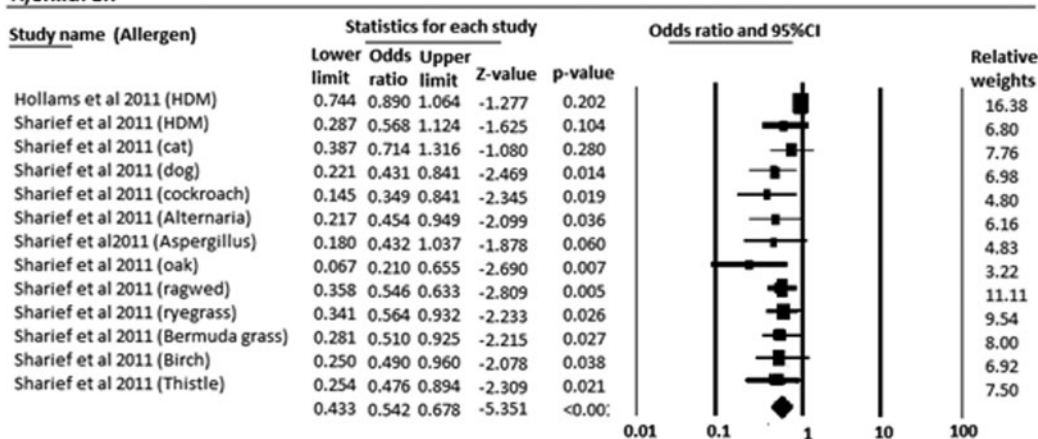
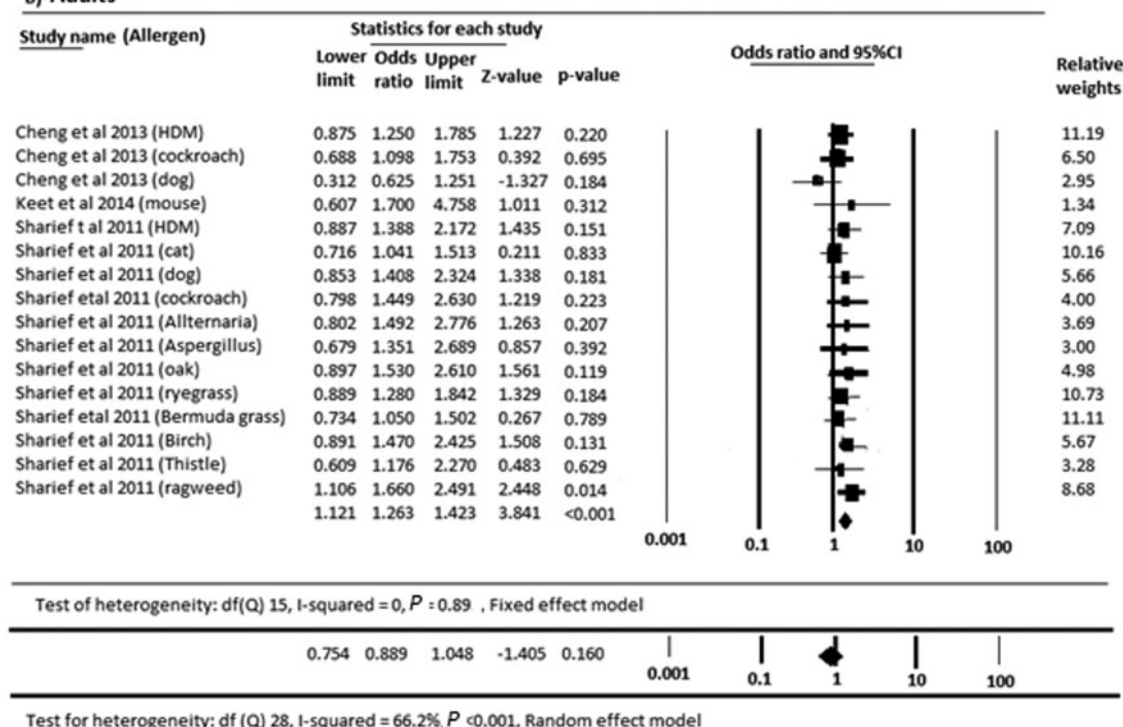
A) Children**B) Adults**

Figure 2. Association between serum 25(OH)D level and aeroallergen-specific IgE sensitization among: (A) children and (B) adults. Serum 25(OH)D $\geq$ 75 nmol/L favors protection against aeroallergen-specific IgE sensitization in children, while it favors increased prevalence of aeroallergen-specific IgE sensitization in adults.

and aeroallergen sensitization in children but not adults. However, other studies that focused only on adults or children showed a similar pattern [24, 26, 29]. Goleva et al also reported that serum 25(OH)D was negatively associated with serum IgE only in asthmatic children but not in asthmatic adults [40]. In line with these findings, Grant et al randomized pregnant women and then their infants from birth to 6 months age to placebo/placebo, 1000 IU/400 IU, or 2000 IU/800 IU of oral vitamin D, daily [16]. They found that incidence of sensitization to mites as measured by Der-p1 and 2 and Der-f1 and 2 specific

IgE at 18 months of age was lower in the active arm supporting the hypothesis that vitamin D supplementation during pregnancy and infancy reduces the risk of aeroallergen sensitization in infants [16].

Our meta-analytic finding for increased specific IgE against aeroallergens among adults with serum 25(OH)D $\geq$ 75 nmol/L merits further comment. This pooled estimate has been derived from data of three studies in Korean and American population [24, 26, 27]. Although the raw data from each study were borderline significant and did not support any association between serum

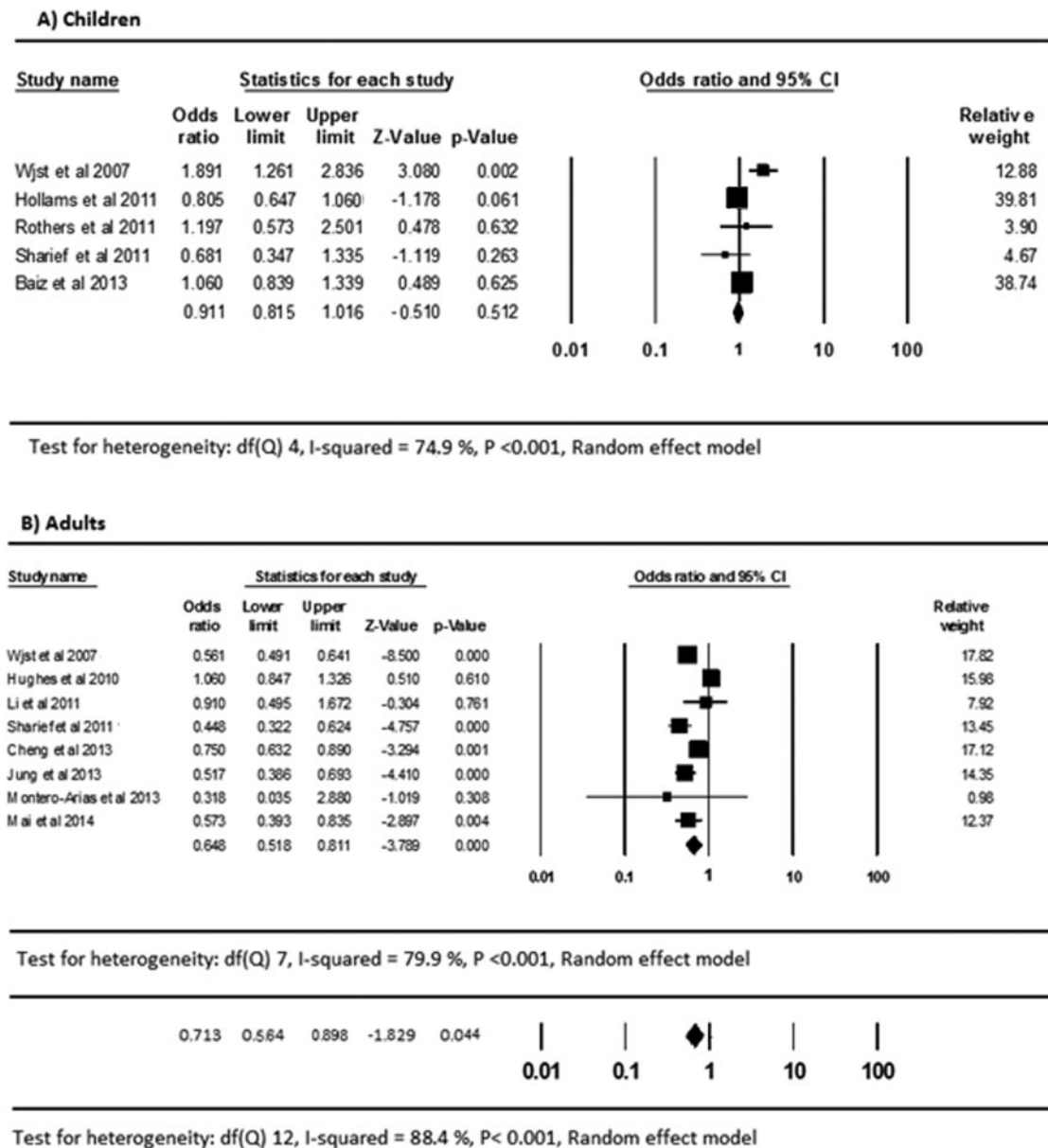
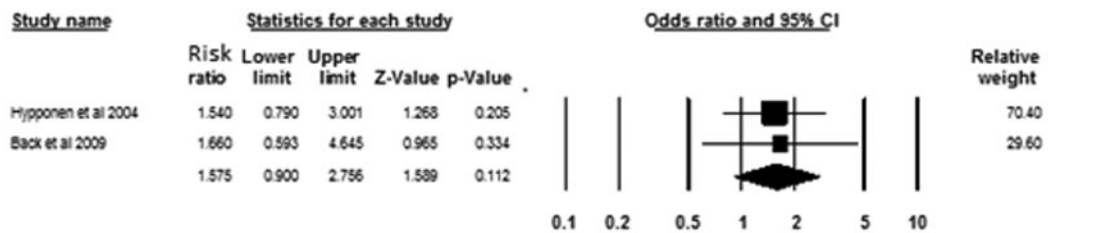


Figure 3. Association between serum 25(OH)D level and allergic rhinitis among: (A) children, and (B) adults. Serum 25(OH)D ≥ 75 nmol/L is associated with reduced risk of AR in both children and adults.

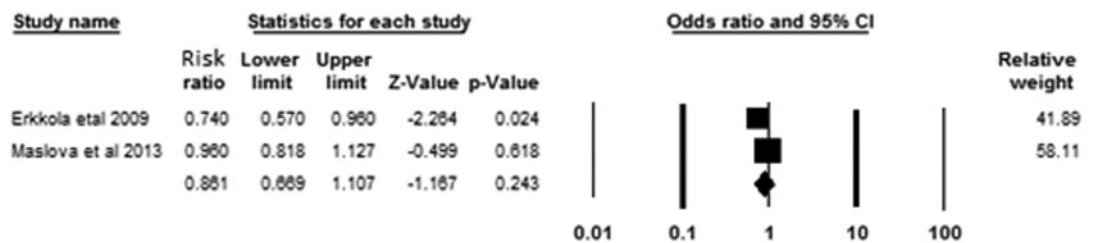
25(OH)D and aeroallergen sensitization [24, 26, 27], after pooling a weak but statistically significant positive association was observed between serum 25(OH)D and aeroallergen sensitization. This result does not fit with the larger literature and merits further study.

To date, the nature of age-specific effects of vitamin D and allergic sensitization is unclear [10]. Previous studies suggested that aeroallergen sensitization begins at early age and low vitamin D status past this age may be detrimental [27, 40]. The immune system is evolving and the immune responses shape in response to environment. Interestingly, expression of some major immune system factors in the scenario of aeroallergen sensitization has been shown to be age-dependent. Contribution of CD14

to airway hyper-responsiveness is age-specific and it is also under influence of gene-environment interactions [41, 42]. CD14 expression is the highest in the first years of life and will be reduced by gene methylation throughout the life [42]. On the other hand, 25(OH)D regulates expression of pattern recognition receptors (PRRs) including Toll like receptor (TLR)-2, TLR4 and CD14, and it inhibits NF κ B activity and thereby inflammatory responses [43, 44]. Vitamin D plays an important role in immune responses and synthesis of specific IgE. It enhances the ability of regulatory cells as well as steroids to suppress Th2 and inflammatory responses [40]. Perhaps expression of vitamin D receptors, as well as enzymes involving in vitamin D pathway, are age-specific,

A) Vitamin D supplementation in infancy and risk of incidence of allergic rhinitis

Test for heterogeneity : $df(Q) 1$, I^2 -squared = 0.00, $P = 0.90$, Fixed effect model

B)Vitamin D intake during pregnancy and risk of allergic rhinitis in offspring

Test for heterogeneity : $df(Q) 1$, I^2 -squared = 64.0%, $P = 0.09$, Random effect model

Figure 4. (A) vitamin D supplementation in infancy does not increase nor decrease the risk of allergic rhinitis, and (B) vitamin D intake during pregnancy does not increase nor decrease the risk of allergic rhinitis in offspring.

a possibility that has not yet been studied to our knowledge. Our findings encourage this new line of research.

Allergic rhinitis (AR)

The association of vitamin D status with AR appears to be age- and sex specific. Children with serum 25(OH)D ≥ 75 nmol/L had lower odds of having AR which did not attain significance (OR, 0.91, 95%CI, 0.81-1.01, $p = 0.051$), while this figure was significant in adults (OR, 0.64; 95%CI, 0.51-0.81). Previously, Keet et al reported that association of serum 25(OH)D with wheezing is age- and atopy-dependent [45]. They found a strong inverse association between serum 25(OH)D and current wheezing in older participants. In addition, this association was stronger in nonatopic subjects with lower serum IgE [45]. It seems that vitamin D may protect from AR but not via lowering of serum IgE. Vitamin D may inhibit acute respiratory infections, such as those caused by respiratory syncytial virus and human rhinovirus, and thereby lower the chance developing allergic airway diseases later in childhood [46, 47].

Our meta-analysis also revealed a significant negative association between serum 25(OH)D and prevalence of AR in adult population which was observed only in men. Men with serum 25(OH)D ≥ 75 nmol/L are at

reduced risk of AR (OR, 0.53, 95%CI, 0.34-0.83). In line with this meta-analytic findings, Sharief et al reported significant interaction between serum 25(OH)D values and sex for sensitization to birch [27]. But neither Sharief et al, nor other included studies, reported their results of aeroallergen sensitization stratified by sex. Previous studies suggest that women may have a greater ability to use the same bioavailable amounts of 25(OH)D; women have fewer *CYP24A1* transcripts encoding the 1,25-dihydroxyvitamin D3-inactivating enzyme, as well as greater vitamin D3-binding protein affinity comparing to males [48]. In addition, 17- β estradiol and 25(OH)D act synergistically through the estrogen receptor α [48] and progesterone up-regulates vitamin D receptors in target cells [49]. So it is possible that women may do better at lower values of serum 25(OH)D compared to men. Differences in sex hormones may explain part of these findings but not completely. Hollams et al investigated the association of serum 25(OH)D with allergic outcomes in children prior to puberty and found that a negative association of serum 25(OH)D with allergic phenotypes that was restricted to boys [29]. It is possible that daily requirements of vitamin D intake differ in men and women. In addition, children with vitamin D deficiency require particular attention not only to prevent rickets but perhaps also to prevent aeroallergen sensitization.

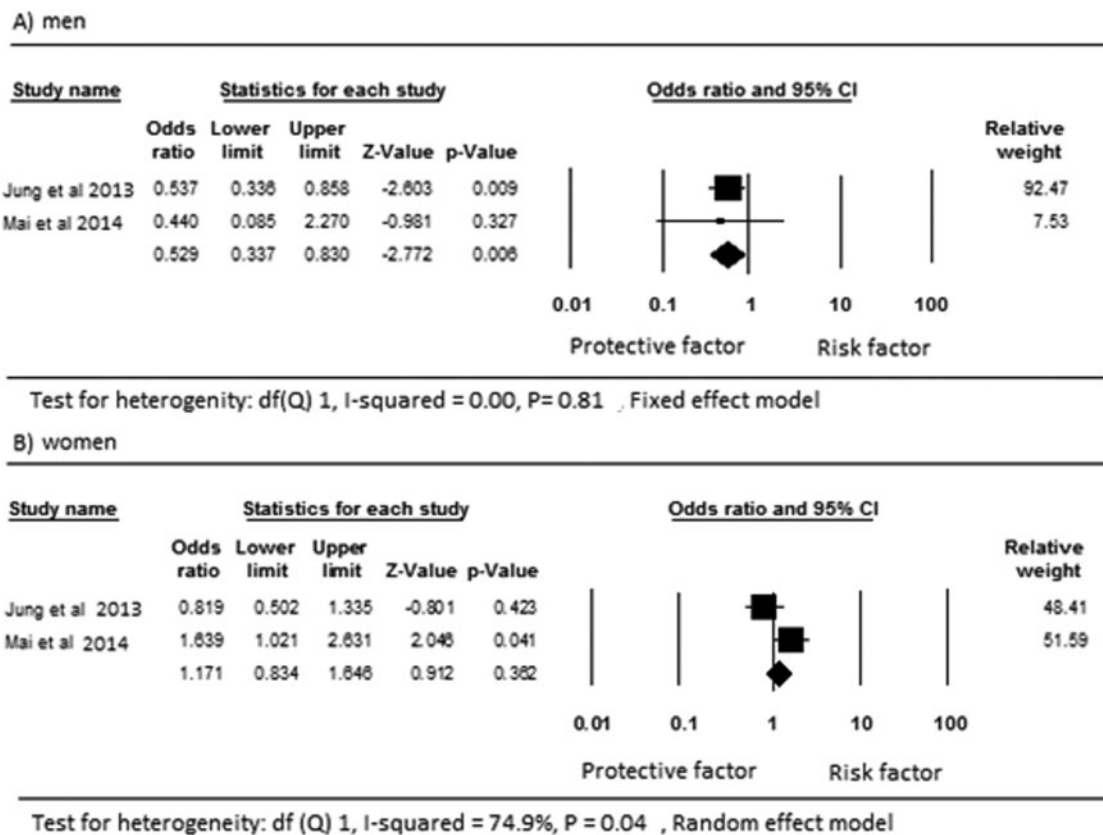


Figure 5. Sex differences in the association between serum 25(OH)D and allergic rhinitis (AR). Men with serum 25(OH)D ≥ 75 nmol/L are at lower risk of AR compared to men with serum 25(OH)D < 50 nmol/L; by contrast, no association was observed in women. (A) Odds of having AR for those with the serum 25(OH)D > 75 nmol/L to those with values < 50 nmol/L in men., (B) Odds of having AR for those with the serum 25(OH)D ≥ 75 nmol/L to those with values < 50 nmol/L in women.

Future epidemiologic studies should present their results stratified by the age and sex of participants.

U-shaped hypothesis

Extremes of serum 25(OH)D—either very low or very high—are associated with increased prevalence of allergic diseases. For example, Rothers et al described serum levels of < 50 nmol/L or ≥ 100 nmol/L as levels associated with increased risk of allergic sensitization [21], while Hypponen et al used different cut points of 25 nmol/L and 135 nmol/L, respectively [19]. Investigators' use of different cut points did not allow us to pool the data and thereby draw a quantitative conclusion; however, these articles do support a possible U-shaped association between serum 25(OH)D and AR. The U-shaped hypothesis implies that both low and high serum 25(OH)D may increase the risk of aeroallergen sensitization and AR [21]. A limitation of our meta-analysis is that we are unable to compare the odds of aeroallergen sensitization and AR by each 10 nmol/L increase in serum 25(OH)D as this level of details was not reported by most of the identified studies. If we could analyze the data in that way, we would be able to test the hypothesis of U-shaped association of serum

25(OH)D with aeroallergen sensitization and AR. Going forward, we encourage data pooling with the use of consistent cutpoints or even sharing of individual participant data. The latter approach would maximize the ability of the collaborative team to explore non-linear associations and the impact of likely effect modifiers, such as age and sex.

Strengths and limitations

To our knowledge, this is the first systematic review and meta-analysis on the association of vitamin D status with aeroallergen sensitization and AR. We estimated the pooled OR using data from 21 large-scale studies which suggests low type 2 error. Several of the included studies were nationally representative and we included studies from different racial/ethnic groups. Hence, the results should have good external validity.

The most important limitation of present study is that we performed meta-analysis on observational studies and thereby we cannot draw a causal link between vitamin D status and the study outcomes. The lack of RCT data is striking but should improve in coming years as a few large ongoing trials come to a close. With respect to

the significant age- and sex-specific associations of vitamin D with aeroallergen sensitization and AR, and the heterogeneity of the included observational studies, an individual participant data meta-analysis probably would help us to draw more accurate conclusions. Regardless, we encourage the presentation of age- and sex-stratified results in all future studies on the association of vitamin D with allergy-related outcomes.

Conclusions

This systematic review and meta-analysis found that children with serum 25(OH)D < 50 nmol/L were at increased risk of aeroallergen sensitization compared to those who have values ≥ 75 nmol/L. The findings point to the potential importance of correcting vitamin D deficiency in children in order to prevent them from further sensitization. Another important finding of this paper is the sex-disparity in the association of serum 25(OH)D and AR development; vitamin D deficient men, but not women, are at increased risk of AR. Accordingly, vitamin D deficiency may be considered as a modifiable risk factor for aeroallergen sensitization and AR development in boys but not girls. If true, these data have important implications for research on the pathogenesis of allergy. Whether taking a vitamin D supplement will alter this risk remains to be studied in large, well-designed RCTs.

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Declaration of interest

The authors declare no conflict of interest. The authors alone are responsible for the content and writing of the article.

Author contribution

ZA did the literature review, assessed the quality of included studies, performed the meta-analysis, and wrote the primary draft of manuscript. NR did the literature review, assessed the quality of included studies, and revised the manuscript critically. CC had the concept, did the literature review, and revised the manuscript critically. All of the authors read and approved the final draft.

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