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Vitamin D levels in allergic rhinitis: a systematic review and meta-analysis

Yoon Hee Kim¹, Kyung Won Kim¹, Min Jung Kim¹, In Suk Sol¹, Seo Hee Yoon¹, Hyeong Sik Ahn², Hyun Jung Kim², Myung Hyun Sohn¹ & Kyu-Earn Kim¹

¹Department of Pediatrics, Severance Hospital, Institute of Allergy, Brain Korea 21 PLUS Project for Medical Science, Yonsei University College of Medicine, Seoul, South Korea

²Department of Preventive Medicine, College of Medicine, Korea University, Seoul, South Korea

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Correspondence

Myung Hyun Sohn, Department of Pediatrics, Severance Hospital, Yonsei University College of Medicine, 50-1, Yonsei-ro, Seodaemun-gu, Seoul 120-752, South Korea.

Tel: 82-2-2228-050, Fax: 82-2-393-9118, E-mail: mhsohn@yuhs.ac

Hyun Jung Kim, Department of Preventive Medicine, College of Medicine, Korea University, 126-1, Anam Dong 5-ga, Seongbuk-gu, Seoul, 136-705, South Korea

Tel: 82-2-2286-1341, Fax: 82-2-2286-1342, E-mail: moole02@naver.com

Myung Hyun Sohn and Hyun Jung Kim contributed equally to this study as a corresponding author.

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Vitamin D levels in allergic rhinitis: a systematic review and meta-analysis

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Abstract

Background: We aimed to systematically review observational studies investigating the relationship between vitamin D levels and allergic rhinitis (AR).

Methods: Studies were selected if they evaluated the relationship between vitamin D levels and AR, and included studies that evaluated other allergic conditions if those studies also contained data on AR. We assessed the incidence and prevalence of AR according to vitamin D levels and compared vitamin D levels in AR patients to levels in controls.

Results: Nineteen studies were selected. Of these, only 7 focused solely on AR; 10 studies evaluated the other allergic diseases as well as AR; and 2 studies evaluated asthma primarily, but also included data on patients with AR. The pooled odds ratios (ORs) for the incidence of AR according to vitamin D levels were not statistically significant for either children or adults. Lower vitamin D levels were associated with a higher AR prevalence only in children (pooled OR [95% confidence interval (CI)], 0.75 [0.58, 0.98]). The pooled mean vitamin D level in AR patients was lower than that of controls only in children (pooled means difference [95% CI], -7.63 [-13.08, -2.18]).

Conclusions: Prior vitamin D levels were not related to developing AR, but lower vitamin D levels were associated with a higher AR prevalence only in children. There is insufficient evidence to support vitamin D supplementation for AR prevention. However, physicians should consider evaluating patients for vitamin D deficiency during AR management, especially in children.

Keywords: allergic rhinitis; children; incidence; prevalence; vitamin D.

Requests for reprints should be addressed to Myung Hyun Sohn, M.D., Department of Pediatrics, Severance Hospital, Yonsei University College of Medicine, 50-1, Yonsei-ro, Seodaemun-gu, Seoul 120-752, South Korea.

Tel: 82-2-2228-050, Fax: 82-2-393-9118, E-mail: mhsohn@yuhs.ac

Introduction

With the increasing interest in vitamin D as an immune modulator, many studies in the past 50 years have suggested a relationship between the increasing incidence of allergic diseases and vitamin D deficiency (1). The underlying mechanisms of this relationship have been studied to understand the important roles of vitamin D in the immune system, including regulatory T cell activation, cytokine production, and B-lymphocyte inhibition, the last of which leads to decreased IgE production (2-4). Of all the allergic diseases, asthma appears to be the one whose association with vitamin D deficiency has been most investigated including animal models and large clinical studies (5, 6). Vitamin D synthesis occurs through an ultraviolet B photochemical reaction in the skin. Given this relationship, many studies have explored the relationship between atopic dermatitis (AD) with chronic skin inflammation and vitamin D deficiency (7). Although the studies on asthma and AD have yielded conflicting results, most studies suggest that vitamin D deficiency may be related to asthma and AD (8, 9).

Allergic rhinitis (AR), one of the most common allergic diseases, has an incidence rate that has been increasing constantly and a worldwide prevalence rate that is quite high, which make the social burden of AR substantial (10-12). Because the diagnosis of AR is usually based on patients' subjective perceptions rather than on physicians' objective tests, unlike in the diagnosis of asthma and AD, there are fewer studies about AR aside from those investigating allergic diseases in general (13). Conversely, AR can be considered as part of

one airway disease along with asthma and a comorbidity of other allergic diseases; indeed, many studies about other allergic diseases have collected data about AR as well (14).

This study aimed to perform a systematic review and meta-analysis of all studies examining the relationship between vitamin D levels and AR, including studies that also evaluated other allergic conditions such as asthma, AD, and allergic sensitization.

Methods

The methods used in this study were based on the Cochrane Review Methods (15).

Data source & Study selection criteria

We searched MEDLINE (January 1, 1976 to April 30, 2015), EMBASE (January 1, 1985 to April 30, 2015), and the Cochrane Central Register of Controlled Trials (January 1, 1987 to April 30, 2015). We put no restrictions on language or year of publication or type of publication in our search. The following keywords and controlled vocabulary (MeSH, Emtree), among others, were used in searching each database: rhinitis, allergy, asthma, and vitamin. See Table S1 for the comprehensive list of search terms.

Studies were selected if they evaluated the relationship of vitamin D level and allergic conditions, including AD or asthma, as long as one of the diseases evaluated in the study was AR. Studies were excluded if they were about only animal research, cytokines, or genetic data. Studies were also excluded if they evaluated the serum vitamin D level in only special populations, such as intensive care unit patients, or chronic or infectious disease patients (e.g., autoimmune disease, tuberculosis, hypertension, and cancer). Studies were also excluded if more than one study investigated the same data (16-19).

Assessment of methodological quality

The methodological qualities for each study were assessed using the Quality In Prognosis Studies (QUIPS) tool (20). The QUIPS tool consists of six bias domains (study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, and statistical analysis and reporting), which can be graded as high, moderate, or low risk of bias. The domains that could not be applied to our selected studies were omitted from analysis.

Publication bias was not assessable in these trials. Tests for funnel plot asymmetry are generally performed only when at least 10 studies are included in the meta-analysis. As our analysis included less than 10 studies, tests for asymmetry would be ineffective because they would be unable to differentiate chance from asymmetry.

Statistical analysis

The primary outcomes of our meta-analysis were the incidence and prevalence rates of AR according to the vitamin D-level categories, and the secondary outcomes were the vitamin D levels of participants with or without AR. The vitamin D categories varied among studies; therefore, we compared the top and bottom categories of vitamin D levels in each study. For evaluating the incidence rate, the independent risk factor used was the baseline vitamin D category of the subject's mother during pregnancy, or cord blood, and the outcome was the presence of AR in those subjects. For evaluating the prevalence rate, the independent risk factor was vitamin D category of the subject, and the outcome was the presence of AR evaluated during the same period in which the vitamin D level was measured. Subgroup analysis was also performed according to the age of the participant.

The most appropriate statistic to use for meta-analyses is the odds ratio (OR), using a method for assessing the impact of multiple variables (covariates and factors) in the same

model. If provided in the study, the reported OR was used in our meta-analysis. Otherwise, the incidence and prevalence were extracted from the data reported, and OR was calculated from the total number of participants and the observed number of patients with AR in all groups. For the dichotomous outcomes (incidence and prevalence of AR), the results were expressed as ORs with 95% confidence intervals (CI). Data were pooled using the generic inverse variance method with the random-effects model. For the continuous outcome (vitamin D level), the results were expressed as the mean differences and their 95% CIs using the inverse variance method with the random-effects model.

To estimate heterogeneity, we estimated the proportion of between-study inconsistency using the I^2 statistic, with values of 25%, 50%, and 75% considered low, moderate, and high, respectively. We used RevMan version 5.2 for these analyses.

Results

Identification of studies

The flow diagram describing the selection process is shown in Fig. 1. The one identified study containing incidence data, in which the baseline vitamin D levels were obtained from adults, was excluded (21). After we screened the studies and applied our inclusion and exclusion criteria, 19 studies remained. Of these, only 7 focused solely on AR; 10 studies evaluated the other allergic diseases, as well as AR; 2 studies evaluated asthma primarily, but also included data on patients with AR.

We extracted three categories of data from the studies, which are summarized in Table 1: (1) the incidence of AR according to vitamin D levels; (2) the prevalence of AR according to vitamin D levels; and (3) comparisons of vitamin D levels in AR patients and controls. Two studies (17, 22) contained data that fell into two of the above three categories. Thus, from the 19 studies, we were able to extract 5 sets of data on AR incidence, 10 sets of

data on AR prevalence, and 6 sets of data comparing vitamin D levels in AR patients versus controls.

The relationship between the incidence of AR and vitamin D levels

We extracted data about the incidence of AR from 5 studies, as shown in Table 1. In a comparison between the top category (over 30 ng/ml) of vitamin D levels and the bottom one (reference group, below 20 ng/ml), the pooled OR (95% CI) for the incidence of childhood AR was 0.91 (0.41, 2.03), and the pooled OR (95% CI) for the incidence of adulthood AR was 1.06 (0.63, 1.77), as shown in Fig. 2A.

When considering the confounding factors summarized in Table 2, 4 studies assessed the adjusted OR for the incidence of AR using the median vitamin D category (over 20 ng/ml and below 30 ng/ml) as a reference category. In our meta-analysis, the pooled adjusted OR (95% CI) in comparing the median vitamin D category with the bottom category (reference group, below 10-20 ng/ml) was performed, and we found no significant relationship between vitamin D levels and the incidence of AR, as shown in Fig. 2B.

The relationship between the prevalence of AR and serum vitamin D levels

We extracted data related to prevalence from the 10 studies shown in Table 1: 5 of these studies were only about children below 16 years old, 3 studies were about children and young adults below 21 years old, and 4 studies were about adults over 18 years old. In children, the pooled OR (95% CI) for the prevalence of AR in a comparison between the top vitamin D category with the bottom one (reference group) was 0.75 (0.58, 0.98); in children and young adults, the pooled OR (95% CI) was 1.20 (0.58, 2.50); and in adults, the pooled OR (95% CI) was 1.19 (0.70, 2.01), as shown in Fig. 3A. When adjusting for the confounding factors listed

in Table 2 across the three different age groups, we found no significant relationship between vitamin D levels and the prevalence of AR, as shown in Fig. 3B.

The comparison of serum vitamin D levels between AR patients and controls

We extracted data analyzed in six studies comparing vitamin D levels in AR patients with vitamin D levels in controls, as shown in Table 1. Four of these studies were about children, and two studies were about adults. The pooled mean of vitamin D levels in AR patients was lower than that in the controls, with a pooled mean difference of -7.63 (-13.08, -2.18) in children. However, we found no such statistically significant difference in adults, as shown in Fig. 4.

Discussion

The relationship between vitamin D levels and the incidence and prevalence of AR was investigated in this meta-analysis of 21 data sets extracted from 19 studies. We found no significant relationship between the incidence of AR and vitamin D levels, as measured from cord blood or maternal blood during pregnancy, which is considered reflective of the subject's vitamin D levels during infancy. In children, the current vitamin D levels were associated negatively with the prevalence of AR and were lower in AR patients than in controls; however, the same associations were not found in adults.

The results of our meta-analysis suggest that low vitamin D levels were caused by AR or existed together with AR, but were not one of the predisposing factors of AR. One explanation for this relationship may be the lifestyle adjustments patients with AR make to avoid symptoms. Patients with AR may refrain from engaging in outdoor activities to avoid allergens that trigger or aggravate AR symptoms (23). These lifestyle adjustments may occur

more frequently in children, whose access to the outdoors may be controlled effectively by their parents, than in adults, who may not be able to avoid outdoor exposure depending on their social and economic obligations. Because the synthesis of vitamin D in the skin requires sun exposure, reduced outdoor activity can lead to lower vitamin D levels (24).

Another explanation for the negative relationship between vitamin D levels and AR prevalence may be related to treatment. As discussed in the introduction, AR can co-exist with other conditions, such as asthma and AD, which may require repeated treatment with oral steroids for exacerbations or failure to respond to other therapies (14, 25). The use of oral steroids can lead to vitamin D deficiency (26). The use of inhaled steroids, which are often included in asthma treatment regimens, has been reported to be inversely correlated with serum vitamin D levels (27). The mechanism of vitamin D deficiency in patients on corticosteroids is not yet clear; however, some studies have suggested that steroids increase the renal metabolism of vitamin D or upregulate vitamin D enzymatic activity via glucocorticoid and vitamin D receptors (28, 29). Children with allergic diseases who experience an acute exacerbation, such as eczema caused by a food allergen or wheezing caused by repeated respiratory infections, might be given steroids more often than adults under the same circumstances (25, 30).

For evaluating the AR incidence according to vitamin D levels, all selected studies were birth cohort studies. Because birth cohort studies have the advantage of investigating all possible factors that can influence disease development from as early as the in utero period, these studies are used widely for investigating allergic diseases that usually develop early in life (31). In our selection process for this study, we excluded one study (20) investigating whether vitamin D levels in adults were associated with the incidence of AR 11 years later, because the influencing factors for the development of allergic disease are quite different in infant periods as compared to factors in the adult period (17).

In the forest plot of the incidence of AR shown in Fig. 2A, the “Chawes 2014” (32) study greatly deviated to the right, as compared to the other studies. The subjects in this study were children of mothers diagnosed with asthma, while those in the other studies were from the general population. The possibility that imprudent use of vitamin D could negatively influence people who are more susceptible to developing allergic disease has been debated in the literature (33). The mechanisms by which vitamin D contributes to the development of allergic disease seem to conflict and have been debated in several studies, which show that immune responses vary based on vitamin D dosing differences (34, 35). The selected longitudinal cohort studies on the incidence of AR used about 20 to 30 ng/ml as the reference vitamin D range. This reflects awareness about the U-shaped association between vitamin D levels and allergic diseases, in which both overly low and overly high levels of vitamin D may play a role in allergic disease development (34).

In the simple comparisons of vitamin D levels between AR patients and controls, vitamin D levels of AR patients were significantly lower only in children, but not in adults, which was consistent with the results of our investigation of AR prevalence according to vitamin D levels. Because most studies comparing vitamin D levels in the two groups used hospital-based cross-sectional data, stricter standards for AR diagnosis were applied than would have been used in an outpatient setting, such as a confirming allergen sensitization or a detailed medical examination. “San 2013” (36) was heavily weighted toward a lower level of vitamin D in the AR group as shown in Fig. 4. Notably, the subjects in that study were very young with a median age of 5 years old. These findings are consistent with the significant negative association we found between vitamin D levels and the AR prevalence in children.

A limitation in our calculation of the pooled, adjusted ORs was the difference and variety of confounding factors and categories of vitamin D levels used in each study. Another limitation of this review stems from the various time periods and differing methods of AR diagnosis utilized in the underlying studies, as well as the differing time points of vitamin D measurements. In-depth meta-analysis for subgroups according to sex, BMI, regions, and ethnicity could not be performed because not all studies considered these factors.

Nevertheless, this meta-analysis is significant in that it reviewed not only studies specifically about AR, but also those about other allergic diseases that included data on AR as a comorbidity. Moreover, the results of this meta-analysis are consistent with the differences between characteristics of children with AR and those of adults with AR.

In conclusion, prior vitamin D levels were not associated with developing AR; however, lower current vitamin D levels were associated with AR prevalence rate, but only in children. There is insufficient evidence to support vitamin D supplementation for the prevention of AR in either children or adults. However, physicians should consider evaluating for vitamin D deficiency during management of AR, especially in children.

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FIGURE LEGENDS

Figure 1 Flowchart for identification of studies selected.

Figure 2 Forest plots of (A) the pooled odds ratios (ORs) with 95% confidence intervals (CI)

comparing the incidence rate of allergic rhinitis between the top category (over 30 ng/ml) of vitamin D levels and the bottom one (reference group, below 20 ng/ml), and (B) the pooled ORs adjusted for confounding factors with 95% CI between the top category (over 30 ng/ml) of vitamin D levels and the median one (reference group, over 20 ng/ml and below 30 ng/ml) in children and adults.

Figure 3 Forest plots of (A) the pooled odds ratios (ORs) with 95% confidence intervals (CI) and (B) the pooled ORs adjusted for confounding factors with 95% CI comparing the prevalence rate of allergic rhinitis between the top category of vitamin D levels and the bottom one (reference group) in children below 16, children and young adults below 21, and adults over 18 years old.

Figure 4 Forest plots of the pooled mean differences with 95% confidence intervals between vitamin D levels in AR patients and those of controls in children and adults.

Table 1 Main characteristics of studies included in the meta-analysis

Studies for the analysis of AR incidence according to vitamin D levels								
Study name	Original study type	Study location	Age (years)	Measured samples	Vitamin D range (ng/ml)		Sample size	
					Bottom	Top	Total	AR
Chawes 2014(32)	Hospital-based birth cohort	Denmark	7	cord blood	< 20	> 30	191	23
Chiu 2015(22)	Population-based birth cohort	Taiwan	4	maternal blood before delivery	< 20	≥ 30	164	60
Maslova 2014(37)	Population-based birth cohort	Denmark	7	mid-pregnancy blood	< 20	≥ 32	483	21
Rothers 2011(38)	Population-based birth cohort	United States	5	cord blood at birth	< 20	≥ 30	192	38
Hansen 2015(39)	Population-based birth cohort	Denmark	25	maternal blood in 3 rd trimester	< 20	≥ 30	632	100
Studies for the analysis of AR prevalence according to vitamin D levels								
Study name	Original study type	Study location	Age (years)	Vitamin D range (ng/ml)		Sample size		
				Bottom category	Top category	Total	AR	
Bener 2014(40)	School-based cross-sectional	Qatar	< 16	< 10	30 ≤ range ≤ 80	1833	276	
Chiu 2015(22)	Population-based birth cohort	Taiwan	4	< 20	≥ 30	102	60	
Hollams 2011(41)	Pregnancy cohort	Perth, Australia	14	≤ 30	> 30	1336	527	
Ito 2013(42)	School-based cross-sectional	Japan	9-10	< 20	≥ 30	1115	216	
Kemp 2013(23)	Population-based birth cohort	Tasmania, Australia	16	5 < range < 17	27 < range < 67	1492	300	
Sharief 2011(43)	Population-based cross-sectional	United States	≤ 21	< 15	≥ 30	3121	365	
			> 21			3517	1393	
Wjst 2007(44)	Population-based cross-sectional	United States	≤ 20	0 ≤ range < 25	≥ 160	2985	218	

			> 20			15239	1399
Yao 2014(45)	School-based cohort	Taiwan	< 20	< 20	≥ 30	1277	378
Cheng 2014(17)	Population-based cross-sectional	Korea	37.9 ± 12.5	< 20	≥ 30	15212	1791
Li 2011(46)	Hospital-based cross-sectional	China	> 18	median 6.5	median 19.8	217	164

Studies for the analysis of the association between vitamin D levels and AR

Study name	Original study type	Study location	Age (years)	Method for recruiting the control	Sample size	
					Control	AR
Baumann 2015(47)	Population-based cross-sectional	Peru	13~15	Population-based NAR	1180	261
Bonanno 2014(48)	Hospital-based cross-sectional	Italy	10.3 ± 2.1	Not explained in the original study	28	11
San 2013(36)	Hospital-based cross-sectional	Turkey	5.0 (2.0/11.0)	Outpatient clinic for other than AR	30	30
Yoon 2015 (49)	Hospital-based cross-sectional	Korea	9.0 ± 3.2	Health screening clinic	57	72
Cheng 2014(17)	Population-based cross-sectional	Korea	37.9 ± 12.5	Population-based NAR	13421	1791
Tural Onur 2015(50)	Hospital-based cross-sectional	Turkey	41 ± 9.3	Age- and sex-matched without specific diseases*	25	47

AR, allergic rhinitis; NAR, non-allergic rhinitis.

Study name expressed as first author's last name and year of publication.

Data expressed as mean $\pm$ standard deviation, median (min/max), or number.

* The controls were selected from the same outpatient clinic and had no autoimmune disorder or allergic disease and no history of atopic, cardiac, liver, renal, or pulmonary disease.

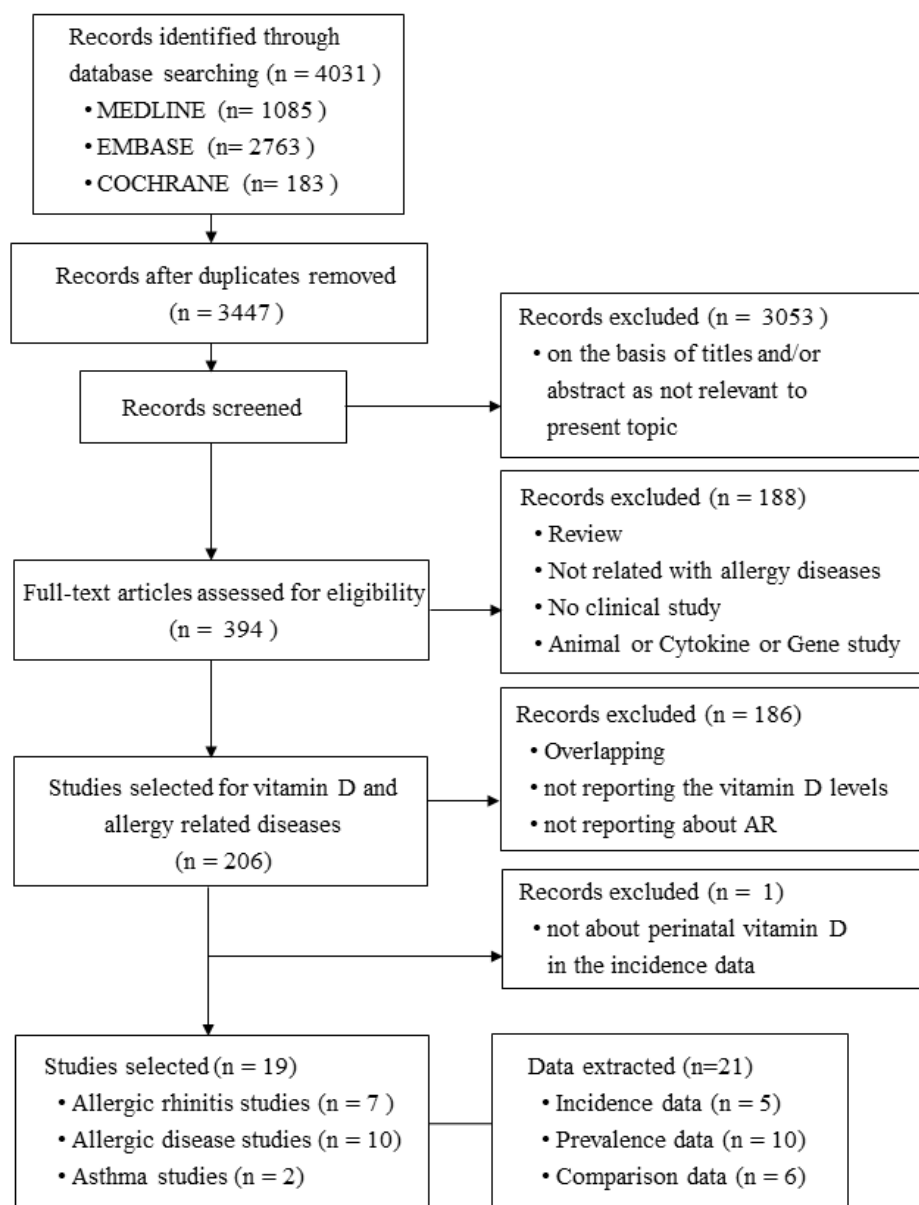
Table 2 Study quality assessment

Study name	Meta-analysis	Main disease*	Confounders	QUIPS tool: low(L), medium(M), high(H) risk of bias					
				Study Participation	Study Attrition	Prognostic Factor Measurement	Outcome Measurement	Study Confounding	Statistical Analysis, Reporting
Baumann 2015(47)	C	AR	NA	L	NA	L	L	H	M
Bener 2014(40)	P	AR	NA	L	NA	L	M	H	M
Bonanno 2014(48)	C	AR	NA	L	NA	L	L	H	M
Chawes 2014(32)	I	allergy	mother's age at birth, season blood sample was taken, older siblings, hair nicotine level at age 1 yr	L	L	L	L	M	L
Cheng 2014(17)	P, C	allergy	age, sex, region of residence, income, education, smoking, BMI	L	NA	L	L	M	L
Chiu 2015(22)	P, I	allergy	season of birth, maternal age, breastfeeding over 6 months	L	H	L	L	L	L
Hansen 2015(39)	I	allergy	maternal age, parity, sex, smoking during pregnancy, prepregnancy BMI, education	L	L	L	L	M	L
Hollams 2011(41)	P	asthma	NA	L	NA	L	L	H	M
Ito 2013(42)	P	allergy	sex, parental smoking, pet owning, obesity (BMI $\geq$ 95 th percentile), kindergarten (before 1 yr)	L	NA	L	L	M	L
Kemp 2013(23)	P	allergy	age at adolescent questionnaire completion, sex, family history of asthma, perinatal score, month of blood collection for vitamin D	L	NA	L	L	L	L
Li 2011(46)	P	asthma	NA	L	NA	L	M	L	L
Maslova 2014(37)	I	allergy	maternal age, socioeconomic position, parity, prepregnancy BMI, smoking during pregnancy, secondary smoking exposure during pregnancy, partner's smoking during pregnancy, maternal paracetamol use during pregnancy, maternal and paternal history of asthma and allergies, month of last menstrual period, breastfeeding duration, child sex	L	H	L	L	L	L
Rothers 2011(38)	I	allergy	maternal ethnicity, household smoking, and birth season	L	L	L	L	M	L
San 2013(36)	C	AR	NA	M	NA	L	L	H	M

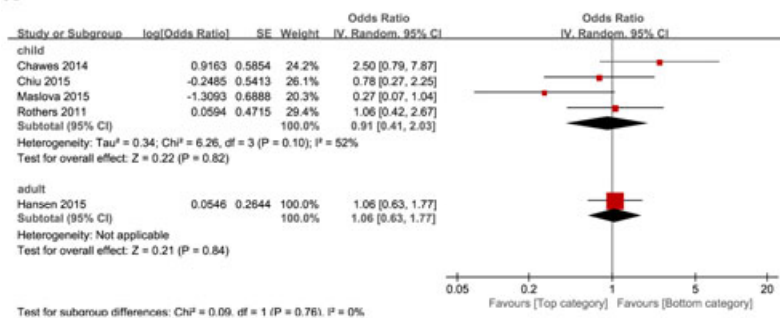
Sharief 2011(43)	P	allergy	Age, sex, race/ethnicity, obesity, low SES, milk intake, television and videogame and computer use, serum cotinine levels, vitamin D supplement use	L	NA	L	M	L	L
Tural Onur 2015(50)	C	AR	NA	M	NA	L	M	H	M
Wjst 2007(44)	P	AR	sex, geographical region, month of examination	L	NA	M	L	H	L
Yao 2014(45)	P	allergy	age, gender, BMI, season of sampling, passive smoking	L	NA	L	L	M	L
Yoon 2015(49)	C	AR	NA	M	NA	L	L	H	M

AR, allergic rhinitis; BMI, body mass index; C, comparison of vitamin D levels between AR patients and controls; I, incidence of AR according to vitamin D levels; NA, not applicable; P, prevalence of AR according to vitamin D levels; QUIPS, Quality in prognosis studies; SES, socioeconomic status.

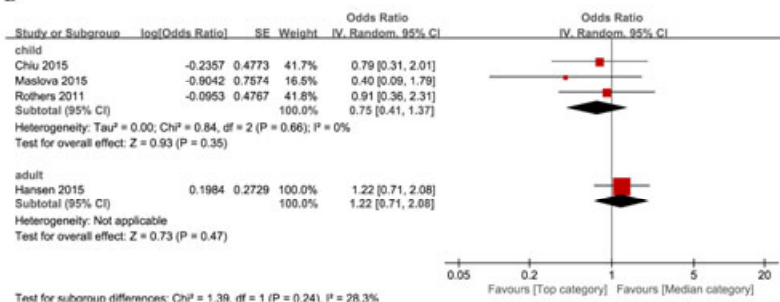
*The main disease evaluated in the original study.



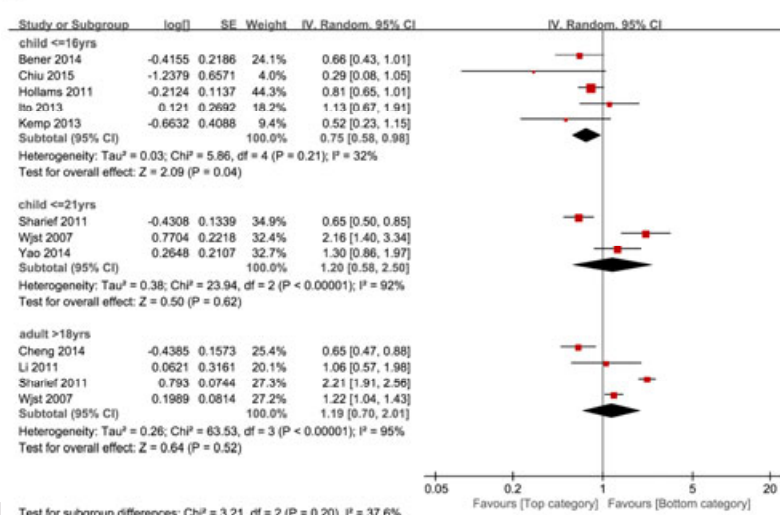
A



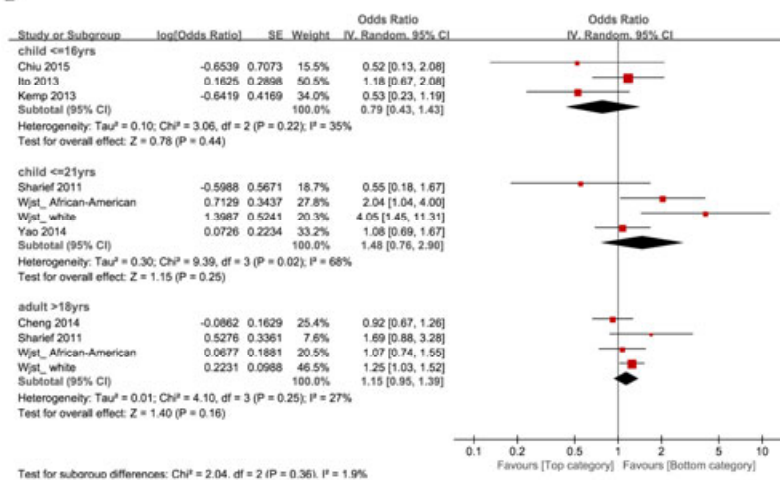
B



A



B



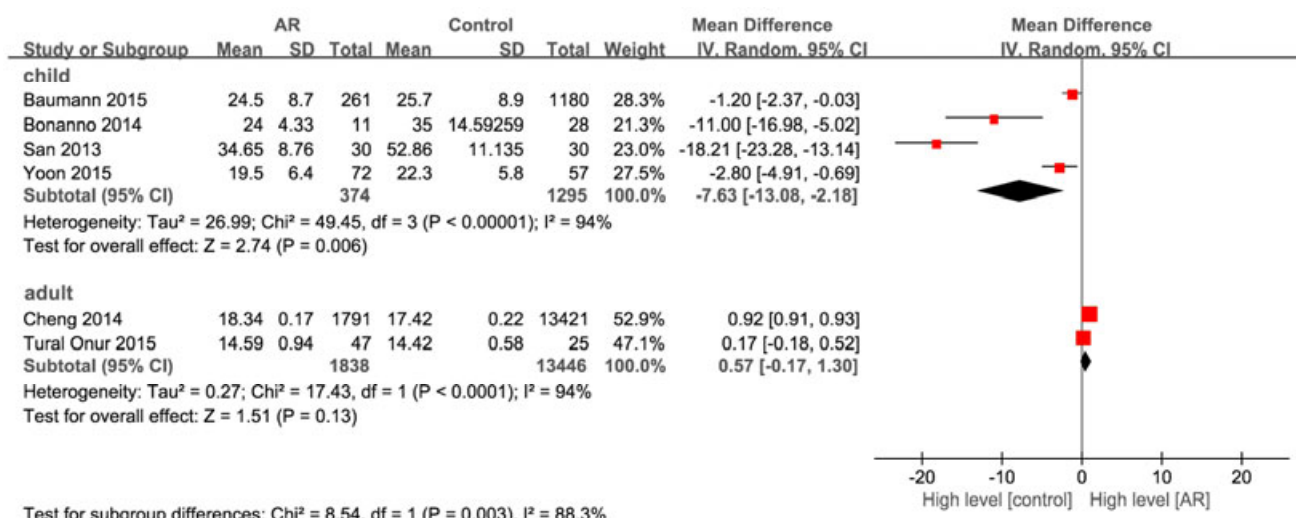


Table S1 Search Strategy

MEDLINE

1. Rhinitis[tiab] OR Rhinitides[tiab] 20662
 2. "Rhinitis"[Mesh] 27387
 3. 1 OR 2 34825
 4. asthma* OR antiasthma* OR anti-asthma* OR Wheez* OR bronchospas* 158690
 5. ((bronchi OR bronchial) AND spasm*) OR bronchoconstrict*) 14323
 6. ((bronchi OR bronchial) AND constrict*) OR ((bronchial OR respiratory OR airway* OR lung) AND 7. (hypersensitiv* OR hyperreactiv* OR allergy OR allergi* OR insufficiency)) 142650
 7. ((dust or mite*) AND (allergi* OR hypersensitiv*)) 8900
 8. "Asthma"[Mesh] OR "Bronchial Spasm"[Mesh] OR "Bronchoconstriction"[Mesh] OR "Bronchial Hyperreactivity"[Mesh] OR "Respiratory Hypersensitivity"[Mesh:NoExp] 119387
 9. 4-8/OR 233756
 10. 3 OR 9 251497
 11. ("Vitamins"[Mesh:NoExp]) OR "Vitamin D"[Mesh] 61121
 12. Cholecalciferol[tiab] OR Vitamins[tiab] OR Vitamin[tiab] OR calciferol[tiab] OR Ergocalciferols[tiab] 159345
 13. 11 OR 12 181791
 14. 10 AND 13 1409
 15. "review"[Publication Type] OR "review literature as topic"[MeSH Terms] 1950902
 16. 14 NOT 15 1084
-

EMBASE

- 1.asthma*:ab,ti OR antiasthma*:ab,ti OR (anti:ab,ti AND asthma*:ab,ti) OR Wheez*:ab,ti OR bronchospas*:ab,ti 176003
 2. ('bronchi'/exp OR bronchi:ab,ti OR bronchial:ab,ti) AND (spasm*:ab,ti OR constrict*:ab,ti) 1625
 3. bronchoconstrict* OR ((bronchial OR respiratory OR airway* OR 'lung'/exp OR lung) AND (hypersensitiv* OR hyperreactiv* OR allergy OR 'allergy'/exp OR allergi* OR insufficiency)) 149053
 4. ('dust'/exp OR dust OR mite*) AND (allergi* OR hypersensitiv*) 12403
 5. bronchoconstrict* 10246
 6. 'asthma'/exp OR 'bronchospasm'/exp OR 'bronchoconstriction'/exp OR 'bronchus hyperreactivity'/exp OR 'respiratory tract allergy'/de 218888
 7. 1-6/OR 325882
 8. Rhinitis:ab,ti OR Rhinitides:ab,ti 28998
 9. "Rhinitis"/exp 66437
 10. 8 OR 9 70539
 11. 7 OR 10 363675
 12. 'vitamin supplementation'/exp 21794
 13. 'vitamin'/de OR 'vitamin d'/de OR '25 hydroxyvitamin d'/exp OR 'colecalciferol derivative'/exp OR 'ergocalciferol derivative'/exp OR 'vitamin d derivative'/exp 127633
 14. Cholecalciferol:ab,ti OR Vitamins:ab,ti OR Vitamin:ab,ti OR calciferol:ab,ti OR Ergocalciferols:ab,ti 196954
 15. 12-14/OR 258648
 16. 15 AND 11 4453
 17. 16 NOT 'review'/it 3257
 18. 17 AND 'human'/de 2768
-

COCHRANE

1. MeSH descriptor: [Rhinitis] explode all trees 3101
 2. Rhinitis or Rhinitides:ti,ab,kw (Word variations have been searched) 6677
 3. #1 or #2 6677
 4. asthma* or antiasthma* or anti-asthma* or Wheez* or bronchospas*:ti,ab,kw (Word variations have been searched) 23980
 5. ((bronchi or bronchial) and spasm*) or bronchoconstrict*) 2563
 6. bronchi or bronchial) and constrict* 235
 7. bronchial or respiratory or airway* or lung:ti,ab,kw (Word variations have been searched) 61804
 8. hypersensitiv* or hyperreactiv* or allergy or allergi* or insufficiency:ti,ab,kw (Word variations have been searched) 22587
 9. #7 and #8 5007
 10. #6 or #9 5205
-

11. dust or mite*:ti,ab,kw (Word variations have been searched) 1508
 12. allergi* or hypersensitiv*:ti,ab,kw (Word variations have been searched) 13848
 13. #11 and #12 785
 14. MeSH descriptor: [Asthma] explode all trees 9404
 15. MeSH descriptor: [Bronchial Spasm] explode all trees 354
 16. MeSH descriptor: [Bronchoconstriction] explode all trees 528
 17. MeSH descriptor: [Bronchial Hyperreactivity] explode all trees 554
 18. MeSH descriptor: [Respiratory Hypersensitivity] this term only 205
 19. #14-18/or 9902
 20. #4 or #5 or #10 or #13 or #19 27160
 21. #3 or #20 31873
 22. MeSH descriptor: [Vitamins] this term only 1253
 23. MeSH descriptor: [Vitamin D] explode all trees 2388
 24. Cholecalciferol or Vitamins or Vitamin or calciferol or Ergocalciferols:ti,ab,kw (Word variations have been searched) 14090
 25. #22-24/or 14578
 26. #21 and #25 198
 27. #26/Trials 183
-

Table S2 Vitamin D measuring and AR diagnosis methods in the selected studies

Study name	Vitamin D measuring methods	AR diagnosis methods
Baumann 2015	LIAISON 25OH vitamin D total assay (DiaSorin Inc., Stillwater, MN)	Self-report in the past 12 months or a physician diagnosis
Bener 2014	ELISA kit (DiaSorin Corporate Headquarter, Saluggia, Italy)	Questionnaire about AR symptoms
Bonanno 2014	ELISA kit (Immunodiagnostic system Ltd.)	ARIA guidelines
Chawes 2014	LC-MS/MS(Aarhus University Hospital, Denmark)	Self-report in the past 12 months
Cheng 2014	Radioimmunoassay kit (DiaSorin Corporate Headquarter, Saluggia, Italy)	Questionnaire about physician-diagnosed AR
Chiu 2015	Electrochemiluminescence-based assay (Roche Diagnostics, Mannheim, Germany)	Questionnaire about AR symptoms in the past 12 months or current use of medication
Hansen 2015	LC-MS/MS kit (PerkinElmer, Waltham, Mass)	Questionnaire about physician-diagnosed AR
Hollams 2011	Radioimmunoassay kit (DiaSorin, Stillwater, MN, USA)	Questionnaire about AR symptoms in the past 12 months
Ito 2013	Radioimmunoassay	Japanese version of the ISAAC questionnaire
Kemp 2013	Radioimmunoassay kit (DiaSorin, Stillwater, MN, USA)	ISAAC question and an ImmunoCAP (Pharmacia Diagnostics AB, Uppsala)
Li 2011	ELISA kits (Immunodiagnostic system Limited, Bolden, UK)	Physician-diagnosed AR in the single center
Maslova 2014	MSMS vitamin D kit from Perkin Elmer (Waltham MA)	Questionnaire about physician-diagnosed AR
Rothers 2011	LC-MS/MS	Questionnaire about physician-diagnosed AR
San 2013	Radioimmunoassay (ICN ISO DATA Gamma Counter, Belgium) (Louvain-La-Neuve, Belgium)	Physician-diagnosed AR in the single center
Sharief 2011	2-step procedure with the DiaSorin, Inc. (Stillwater, Minn; formerly INCSTAR)	Questionnaire about AR symptoms in the past 12 months
Tural Onur 2015	Radioimmunoassay (Cobra Quantum, Packard, MN)	Physician-diagnosed AR in the single center
Wjst 2007	Not shown	Questionnaire about physician-diagnosed AR
Yao 2014	Electrochemiluminescence-based (Roche Diagnostics, Mannheim, assay Germany)	Questionnaire about AR symptoms in the past 12 months or current use of medication

Yoon 2015

Radioimmunoassay methods with a using a Packard Cobra Gamma Counter

ARIA guidelines with an ImmunoCAP (Pharmacia Diagnostics AB, Uppsala)

AR, allergic rhinitis; ARIA, allergic rhinitis and its impact on asthma; BMI, body mass index; LC-MS/MS, liquid chromatography-tandem mass spectrometry.

Study name expressed as first author's last name and year of publication.