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Original Article

Association between vitamin D deficiency and insufficiency and the risk of childhood asthma: evidence from a meta-analysis

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Abstract: Objective: Whether vitamin D deficiency and insufficiency are associated with childhood asthma remains unclear. Thus, we conducted a meta-analysis to summarize the evidence from epidemiological studies of vitamin D deficiency and insufficiency and the risk of childhood asthma. Methods: Pertinent studies were identified by searching of PubMed and Web of Knowledge. The random effect model was used to combine the results. Meta-regression and subgroups analyses were used to explore potential sources of between-study heterogeneity. Publication bias was estimated using Egger's regression asymmetry test. Results: Finally, 14 articles with 15 studies including 3424 cases for vitamin D deficiency and 9 articles with 10 studies including 2756 cases for vitamin D insufficiency were included in this meta-analysis. The relative risk (95% confidence interval) of childhood asthma risk for vitamin D deficiency was 1.684 (1.321-2.148), and the associations were significant in America and Europe. Significant association of childhood asthma between vitamin D insufficiency and childhood asthma risk was found overall [1.577 (1.230-2.023)] and the subgroups of America, Europe and Asia. No evidence of significant publication bias between vitamin D deficiency and insufficiency and childhood asthma risk were found. Conclusions: Results from this meta-analysis suggested that vitamin D deficiency and insufficiency might increase the risk of childhood asthma.

Keywords: Vitamin D deficiency, vitamin D insufficiency, childhood asthma, meta-analysis

Introduction

Asthma is a highly prevalent respiratory condition in childhood [1]. Development of asthma is associated with many immunological markers [2]. Hypovitaminosis is prevalent worldwide, and an increasing body of evidence supports pleotropic effects of vitamin D on various chronic disorders including those associated with immune regulatory function [3, 4]. This includes associations with a number of childhood disorders [5], such as type I diabetes mellitus [6, 7], celiac disease, and asthma [8].

The hypothesis is that vitamin D has immunoregulatory properties [9] that protect from asthma [10]. Up to now, a number of epidemiologic studies have been published to explore the relationship of vitamin D deficiency and insufficiency and the risk of childhood asthma. However, the results are not consistent. Therefore, we conducted a meta-analysis to assess the childhood asthma risk for vitamin D deficiency and vitamin D insufficiency. We also assess the heterogeneity among studies and publication bias.

Methods

Search strategy

Studies were identified by a literature search of PubMed and Web of Knowledge up to January 2015 and by hand-searching the reference lists of the computer retrieved articles. The following search terms were used: vitamin D deficiency or vitamin D insufficiency and childhood asthma or pediatric asthma without restrictions. Moreover, we reviewed the reference lists from retrieved articles to search for further relevant studies. Two investigators searched articles and reviewed of all retrieved studies indepen-

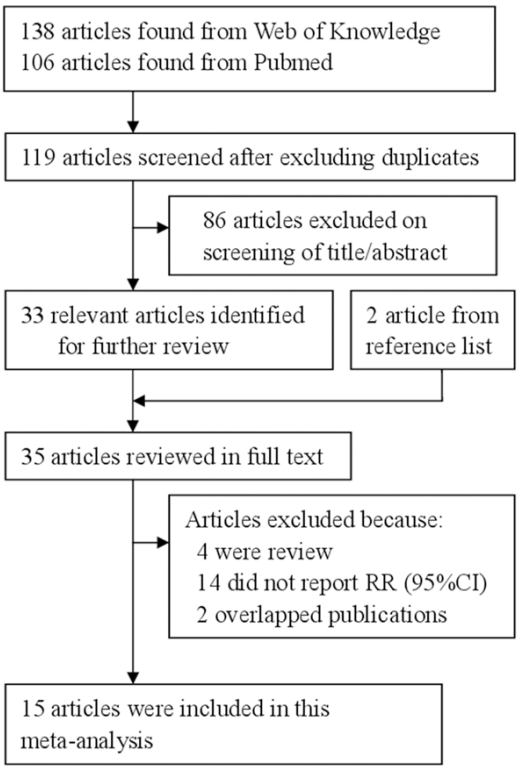

Figure 1. The detailed steps of our literature search.

dently. Disagreements between the two investigators were resolved by consensus with a third reviewer.

Inclusion criteria

For inclusion, studies had to fulfill the following criteria: (1) the exposure of interest was vitamin D deficiency or vitamin D insufficiency; (2) the outcome of interest was childhood asthma or pediatric asthma; (3) the design type were case-control study, cohort study, cross-sectional study or randomized controlled trials and (4) multivariate-adjusted relative risk (RR) with 95% confidence interval (CI) was provided (or data can calculate them). Accordingly, the following exclusion criteria were also used: (1) reviews and (2) repeated or overlapped publications.

Data extraction

The following data were collected from all studies independently by two investigators: the design type (case-control study, cohort study, cross-sectional study or randomized controlled trials), the first author's last name, publication year, location where the study was performed, sample size and number of cases, variables adjusted for in the analysis, RR (OR) estimates with corresponding 95% CI for vitamin D deficiency or insufficiency and the risk of childhood asthma, respectively. For studies that reported results from various covariate analyses, we abstracted the estimates based on the model that included the most potential confounders. If there was disagreement between the two investigators about eligibility of the data, it was resolved by consensus with a third reviewer.

Statistical analysis

The pooled measure was calculated as the inverse variance-weighted mean of the natural logarithm of multivariate adjusted RR with 95% CI for vitamin D deficiency and insufficiency and childhood asthma risk. Random-effects model was used to combine study-specific RR (95% CI), which considers both within-study and between-study variation [11]. The Q test and I^2 of Higgins & Thompson [12] were used to assess heterogeneity among included studies. I^2 describes the proportion of total variation attributable to between-study heterogeneity as opposed to random error or chance, and I^2 values of 0, 25, 50 and 75% represent no, low, moderate and high heterogeneity, respectively [13]. Meta-regression with restricted maximum likelihood estimation was performed to assess the potentially important covariate exerting substantial impact on between-study heterogeneity [14]. Publication bias was estimated using Egger's regression asymmetry test [15]. A study of influence analysis [16] was conducted to describe how robust the pooled estimator is to removal of individual studies. An individual study is suspected of excessive influence, if the point estimate of its omitted analysis lies outside the 95% CI of the combined analysis. All the statistical analyses were performed with STATA version 10.0 (Stata Corporation, College Station, TX, USA). Two-tailed $P \leq 0.05$ was accepted as statistically significant.

Results

The search strategy identified 106 articles from PubMed and 138 articles from the Web of Knowledge. Fifteen articles [17-31] were used in this meta-analysis. The detailed steps of our literature search are shown in **Figure 1**. For vitamin D deficiency and childhood asthma risk, data from 14 articles with 15 studies (4 prospective studies, 8 case-control studies and

Table 1. Characteristics of studies on vitamin D deficiency and insufficiency and childhood asthma risk

First author, year	Country	Study design	Cases, age	RR (95% CI)
Bener et al., 2012	Qatar	Case-control	483, <16	Vitamin D deficiency 4.82 (2.41-8.63)
Brehm et al., 2009	Costa Rica	Cross-sectional	616, 6-14	Vitamin D deficiency 2.30 (0.65-4.00)
Brehm et al., 2012	Puerto Rico	Cross-sectional	287, 6-14	Vitamin D insufficiency 2.70 (1.50-4.90)
Camargo Jr et al., 2007	United States	Prospective	298, <12	Vitamin D deficiency 1.78 (1.08-2.94)
Chawes et al., 2014	Denmark	Prospective	132, 0-7	Vitamin D deficiency 1.63 (0.47-5.61)
Checkley et al., 2014	Peruvian	Case-control	308, 14.86	Vitamin D deficiency 1.97 (0.58-6.71) for Lima 1.23 (0.14-10.83) for Tumbes Vitamin D insufficiency 1.52 (0.44-5.25) for Lima 1.98 (0.69-5.69) for Tumbes
Ehlayel et al., 2011	Qatar	Case-control	323, <15	Vitamin D deficiency 1.22 (0.78-1.93) Vitamin D insufficiency 1.54 (0.94-2.52)
Freishtat et al., 2010	United States	Case-control	85, 6-20	Vitamin D deficiency 20.00 (1.40-272)
Goleva et al., 2012	United States	Case-control	53, <18	Vitamin D deficiency 1.25 (0.57-2.73) Vitamin D insufficiency 1.07 (0.48-2.35)
Hughes et al., 2011	Australia	Case-control	32, 6-15	Vitamin D deficiency 1.20 (0.89-1.61)
Ito et al., 2013	Japan	Cross-sectional	109, 9-10	Vitamin D deficiency 1.06 (0.51-2.21) Vitamin D insufficiency 1.22 (0.80-1.88)
Maalmi et al., 2012	Tunisia	Case-control	39, 6-16	Vitamin D deficiency 6.80 (3.49-61.75) Vitamin D insufficiency 5.67 (1.92-10.98)
Magnus et al., 2013	Norwegian	Prospective	489, 1-3	Vitamin D deficiency 1.49 (1.05-2.08) Vitamin D insufficiency 1.25 (0.89-1.61)
Uysalol et al., 2013	Turkey	Cross-sectional	85, 2-14	Vitamin D deficiency 1.59 (0.81-3.53) Vitamin D insufficiency 1.77 (0.76-4.14)
Van Oeffelen et al., 2011	Netherlands	Prospective	372, 5-8	Vitamin D deficiency 1.54 (0.86-2.78) Vitamin D insufficiency 1.25 (0.87-1.63)

Abbreviations: RR = relative risk; CI = confidence interval.

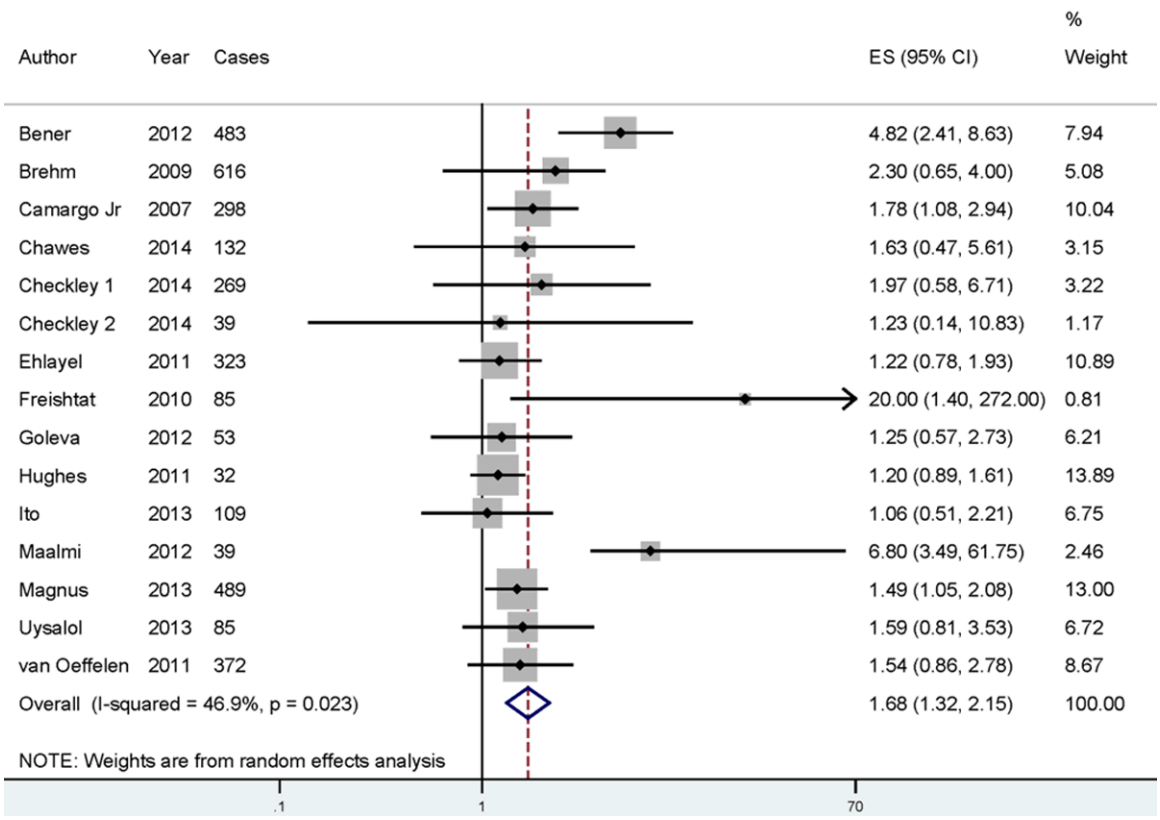

Figure 2. The forest plot between vitamin D deficiency and the risk of childhood asthma.

3 cross-sectional studies) were used including 3424 cases. Six studies were carried out in America, 4 in Asia, 3 in Europe, 1 in Australia and 1 in Tunisia. Five studies reported that vitamin D deficiency can increase the risk of childhood asthma, while no significant associations were reported in 10 studies. For vitamin D insufficiency and childhood asthma risk, data from 9 articles with 10 studies (2 prospective studies, 5 case-control studies and 3 cross-sectional studies) were used including 2756 cases. Four studies were carried out in America, 3 in Asia, 2 in Europe and 1 in Tunisia. Two studies reported that vitamin D insufficiency can increase the risk of childhood asthma, while no significant associations were reported in 8 studies. The detailed characteristics of the 15 articles are shown in **Table 1**.

Vitamin D deficiency and childhood asthma risk

In our meta-analysis, the significant association between vitamin D deficiency and childhood asthma risk was found [summary RR=1.684, 95% CI=1.321-2.148, I^2=46.9%] (**Figure 2**). For the subgroup analyses by study design, the associations were also significant in the prospective studies [RR=1.572, 95% CI=1.225-2.017] and case-control studies [RR=2.061, 95% CI=1.220-3.481], but not in the cross-sectional studies for the vitamin D deficiency and the risk of childhood asthma. In subgroup analyses of geographic locations, when we restricted the analysis to America, Europe and Asia, significant associations were found in America [RR=1.796, 95% CI=1.257-2.567] and Europe [RR=1.509, 95% CI =1.132-2.011], but not in the Asia. The detailed results are shown in **Table 2**.

Vitamin D insufficiency and childhood asthma risk

Vitamin D insufficiency was significantly associated with the risk of childhood asthma [RR=1.577, 95% CI=1.230-2.023, I^2=47.8%] (**Figure 3**). For the subgroup analyses by study design, the associations were both significant in the prospective studies [RR=1.250, 95% CI=1.008-1.551], case-control studies [RR= 1.914, 95% CI=1.098-3.337] and cross-sec-

Table 2. Summary risk estimates of the association between vitamin D deficiency and insufficiency and the risk of childhood asthma

Sub-groups	Cases	Studies	RR (95% CI)	I^2 (%)	$P_{heterogeneity}$
Vitamin D deficiency	3424	15	1.684 (1.321-2.148)	46.9	0.023
Study design					
Prospective	1291	4	1.572 (1.225-2.017)	0.0	0.953
Case-control	1323	8	2.061 (1.220-3.481)	71.1	0.001
Cross-sectional	810	3	1.494 (0.952-2.345)	0.0	0.420
Geographic locations					
America	1360	6	1.796 (1.257-2.567)	0.0	0.485
Europe	993	3	1.509 (1.132-2.011)	0.0	0.988
Asia	1000	4	1.772 (0.901-3.486)	78.5	0.003
Vitamin D insufficiency	2756	10	1.577 (1.230-2.023)	47.8	0.045
Study design					
Prospective	861	2	1.250 (1.008-1.551)	0.0	1.000
Case-control	960	5	1.914 (1.098-3.337)	54.5	0.067
Cross-sectional	935	3	1.742 (1.030-2.946)	56.5	0.100
Geographic locations					
America	894	4	1.853 (1.177-2.918)	14.1	0.322
Europe	861	2	1.250 (1.008-1.551)	0.0	1.000
Asia	962	3	1.395 (1.032-1.887)	0.0	0.658

tional studies [RR=1.742, 95% CI=1.030-2.946]. Subgroup analysis by geographic locations suggested that significant associations were found in America, Europe and Asia. The detailed results are shown in **Table 2**.

Influence analysis and publication bias

Influence analysis showed that no individual study had excessive influence on the above-mentioned pooled effect. Egger's test showed no evidence of significant publication bias between childhood asthma risk and vitamin D deficiency (P=0.153) and insufficiency (P=0.191).

Discussion

The findings from this meta-analysis indicate that vitamin D deficiency and vitamin D insufficiency were associated with an increased risk of childhood asthma. We also found significant associations in America and Europe.

Vitamin D deficiency (defined as 25(OH)D <20 ng/mL [<50 nmol/L]) vitamin D insufficiency (defined as 25(OH)D <30 ng/mL [<75 nmol/L]) [32] are currently associated with asthma. The protective effects of vitamin D in asthma could be attributable to its immunomodulatory properties [33]. Beyond a central role in calcium and bone physiology, vitamin D metabolism, specifically the conversion of 25(OH)D to the active form of vitamin D (1,25[OH]2D), has effects on epithelial cell, T-cell, B-cell, and dendritic cell functions, which are important for innate and adaptive immunity [3, 34]. Our results also showed that vitamin D deficiency and insufficiency can increase the risk of childhood asthma.

As seen in **Figures 2** and **3**, moderate of heterogeneities were found in the pooled results. Between-study heterogeneity is common in meta-analysis [35], and exploring the potential sources of between-study heterogeneity is the essential component of meta-analysis. For vitamin D deficiency and insufficiency with the risk of childhood asthma, evidence of heterogeneity were found in the pooled results. The between-study heterogeneity might arise from publication year, study region, study design and number of cases. Thus, we used meta-regression to explore the causes of heterogeneity for covariates. However, no covariate having a significant impact on between-study heterogeneity for vitamin D deficiency and childhood asthma risk. For the analysis between vitamin D insufficiency and childhood asthma risk, geographic locations was found contributing sig-

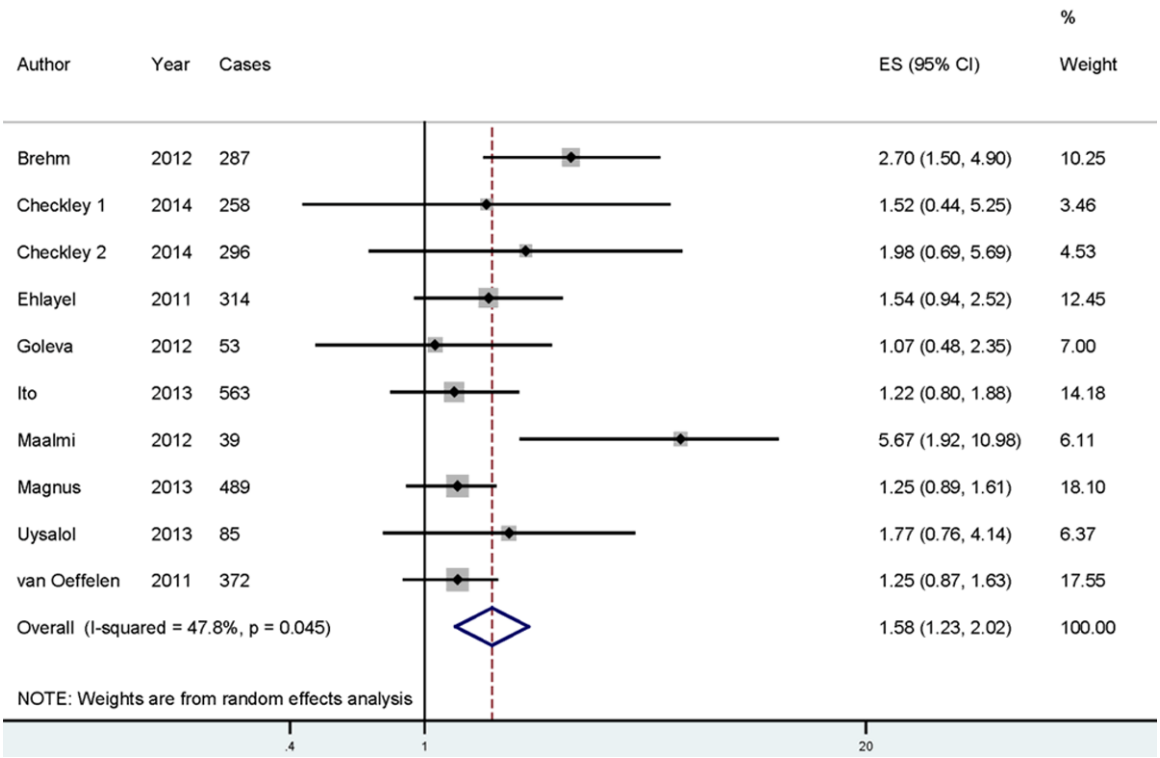

Figure 3. The forest plot between vitamin D insufficiency and the risk of childhood asthma.

nificantly to the between-study heterogeneity overall (P=0.02). When we conducted the subgroup analysis by geographic locations, the between-study heterogeneity was very low in the subgroups of America, Europe and Asia.

As a meta-analysis of published studies, our findings showed some advantages. First, this is the first comprehensive meta-analysis conducted to assess the association between vitamin D deficiency and insufficiency and the risk of childhood asthma. Second, large number of cases and participants were included, allowing a much greater possibility of reaching reasonable conclusions between vitamin D deficiency and insufficiency and childhood asthma risk. Third, no significant publication bias was found, indicating that our results are stable. However, there were some limitations in this meta-analysis. First, as a meta-analysis of observational studies, we cannot rule out that individual studies may have failed to control for potential confounders, which may introduce bias in an unpredictable direction. Second, measurement errors are important in the assessment of dietary intake, which can lead to overestimation of the range of intake and underestimation of the magnitude of the relationship between dietary intake and childhood asthma risk [36]. Third, many case-control studies were included in this meta-analysis. Overstated association may be expected from the case-control studies because of recall or selection bias, and early symptoms in patients may have resulted in a change in dietary habits. However, the associations were both significant in the case-control studies and prospective studies. Considering the little studies conducted in prospective design, further studies with prospective design are wanted to confirm this association between vitamin D deficiency and insufficiency and childhood asthma risk. Fourth, we found significant associations between vitamin D deficiency and childhood asthma risk in the America and Europe. Only 4 studies came from Asia, 1 from Australia and 1 from Tunisia, in which we found no significant association, probably due to the little number of studies included. Due to this limitation, the results are applicable to the America and Europe for vitamin D deficiency and childhood asthma risk, but cannot be extended to European populations. More studies originating in other countries are required to investigate the association between vitamin D

deficiency and childhood asthma risk. Finally, between-study heterogeneity was found in some analysis in this meta-analysis, but the between-study heterogeneity was not successfully explained by the subgroup analysis and meta-regression for vitamin D deficiency and childhood asthma risk. However, other genetic and environment variables, as well as their possible interaction may be potential contributors to this disease-effect unconformity.

In summary, results from this meta-analysis suggested that vitamin D deficiency and insufficiency might increase the risk of childhood asthma. Since the potential biases and confounders could not be ruled out completely in this meta-analysis, further studies are warranted to confirm this result.

Disclosure of conflict of interest

None.

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