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Vitamin D supplementation during pregnancy and the risk of wheezing in offspring: a systematic review and dose-response meta-analysis

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ABSTRACT

Background: In the past few years, growing evidence supports a preventive role of vitamin D supplementation during pregnancy for wheezing or asthma in offspring. However, the optimal dose of vitamin D intake is unclear. We conducted a meta-analysis to examine the linear and nonlinear dose-response pattern of vitamin D intake during pregnancy and asthma or wheezing in offspring. **Questions/purposes:** The purpose of this study was to answer the following question: Which dose of vitamin D is more effective in preventing wheezing in offspring? **Method:** We identified relevant studies by searching PubMed, EMBASE and CENTRAL up to December 2017 and by hand-searching reference lists. Meta-analysis and subgroup analysis were performed. Fixed or random effects model linear trends analyses were conducted based on the heterogeneity test. Then, if the data did not show linear trends, we considered a nonlinear trend analysis instead. **Results:** A total of 6068 participants were included in the study. Our analysis showed an inverse relationship between the intake of vitamin D during pregnancy and the occurrence of wheezing in offspring (pooled OR = 0.68, 95% CI = 0.55–0.83, $I^2 = 24\%$, Z statistic = 3.64, $p < 0.01$). We found a nonlinear U-shaped association between vitamin D supplementation during pregnancy and asthma or wheezing in offspring, with the lowest risk at approximately 800 IU/d. Publication bias was shown in a funnel plot without Egger's test. **Conclusions:** Vitamin D intake during pregnancy is inversely related to wheezing or asthma in offspring. Furthermore, the trend analysis indicates that offspring may benefit from approximately 800 IU/d vitamin D intake during pregnancy.

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Asthma; dose-response meta-analysis; pregnancy; vitamin D; wheezing

Introduction

Wheezing illnesses begin as early as in the first few weeks of life [1]. In early childhood, asthma, wheezing and respiratory tract infections (RTIs) are difficult to distinguish [2], and are closely related to atopic eczema and allergic rhinitis. Wheezing illnesses are common causes of morbidity and mortality among children [3]. To improve the clinical outcomes of asthma or recurrent wheezing, it is essential to identify strategies to decrease the exacerbations.

Traditionally, vitamin D has been regulated as a nutrient and its effects on bone-related diseases are well known [4–6]. Currently, vitamin D is considered both a nutrient and a hormone, and plasma concentrations of vitamin D are dependent on dietary intake and exposure to sunlight [7]. Vitamin D deficiency is widespread [8], and it is reported that lower levels of

vitamin D in the blood are associated with worse lung function, greater exacerbation frequencies and higher respiratory infection rate in patients with asthma [9], especially during pregnancy [10]. In addition, growing evidence from high-quality randomized controlled trials (RCTs) [1,11,12], cohort studies [13–16] and systematic reviews [17,18] supports a preventive role of vitamin D supplementation during pregnancy against wheezing or asthma in offspring.

In the past few years, although the number of studies on this topic has increased rapidly, the optimal dose of vitamin D is still unclear. We hope to answer the following question of which dose of vitamin D is more effective in preventing wheezing in offspring. Findings from such a study may help determine how much vitamin D could be beneficial for the prevention of wheezing or asthma, with the aim of reducing the health burden on children.

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Table 1. Characteristics of eligible prospective cohorts.

First author (Year)	Country	Design	Participants	Dose Group (IU/d)	Adjusted odds ratio	Outcomes	Statistical methods
Devereux (2007)	United Kingdom	Prospective cohort	1212	77	1	Wheeze and asthma at 2 and 5 years of age Atopic sensitization, spirometry and FENO at 5 years of age	Logistic regression
				104	0.86 (0.51-1.47)		
				128	0.70 (0.41-1.20)		
				157	0.57 (0.32-1.01)		
				275	0.48 (0.25-0.91)		
Camargo (2007)	United States	Prospective cohort	1194	356	1	Recurrent wheeze and eczema at 6, 12, 24 and 36 months after birth	Logistic regression
				513	0.47 (0.28-0.77)		
				603	0.54 (0.33-0.89)		
				724	0.38 (0.22-0.65)		
Miyake (2010)	Japan	Prospective cohort	763	140	1	Wheeze and eczema at 16–24 months after birth	Logistic regression
				204	0.48 (0.28-0.80)		
				256	0.80 (0.49-1.31)		
				364	0.69 (0.42-1.14)		
Miyake (2014)	Japan	Prospective cohort	1354	128	1	Wheeze and eczema at 16–24 months after birth	Logistic regression
				184	0.69 (0.33-1.44)		
				236	0.49 (0.22-1.07)		
				344	0.60 (0.27-1.27)		

Table 2. Characteristics of RCTs.

First author (Year)	Country	Design	Participants	Intervention	Result (OR with 95%CI)	Outcomes
Goldring (2013)	United Kingdom	RCT	158	800 IU/d from 27 weeks gestation until delivery vs. no treatment	0.63 (0.26–1.55)	Wheeze ever before 3 years old
Litonjua (2016)	United States	RCT	806	4000 + 400 IU/d from 10-18 weeks gestation until delivery vs. placebo +400 IU/d	0.75 (0.55–1.01)	Asthma or recurrent wheeze before 3 years old
Chawes (2016)	Denmark	RCT	581	2400 + 400 IU/d from 24 weeks gestation until 1 week postpartum vs. placebo +400 IU/d	0.77 (0.50–1.17)	Persistent wheeze before 3 years old

Methods

Protocol and registration

The protocol was registered with the PROSPERO International Prospective Register of Systematic Reviews (www.crd.york.ac.uk/PROSPERO/). The protocol ID is 42017065634. This meta-analysis was reported in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

Search strategy

We conducted an online search for articles published up to December 2017, in PubMed (<https://www.ncbi.nlm.nih.gov/pubmed>), Embase (<http://www.embase.com>), and the Cochrane Central Register of Controlled Trials (CENTRAL) (<http://onlinelibrary.wiley.com/cochranelibrary/>) with the search terms '(vitamin D OR nutrition OR nutrient) AND (asthma OR asthmas OR wheeze OR wheezing OR respiratory tract infections OR bronchiolitis OR allergy OR atopic dermatitis OR atopic eczema OR allergic rhinitis) AND (prenatal OR antenatal OR pregnant OR pregnancy OR pregnancies OR gestation OR maternal)'. In

addition, we performed hand-searches of the references of all identified articles and relevant reviews (JG).

Inclusion and exclusion criteria

Eligible clinical trials were defined based on the following criteria: (1) Prospective cohort study or RCT with at least two dose groups. (2) Records of the diet questionnaire during pregnancy. (3) Outcome with wheezing or asthma. (4) Provided risk estimates of RRs, HRs, or ORs and CIs.

Exclusion criteria: (1) Animal research. (2) Not prospective cohort studies or RCT. (3) Reviews, letters or case reports.

Two authors reviewed the titles and abstracts (WL and YC) to determine the eligibility of each clinical trial. If there were discrepancies between the reviewers, then another author (ZQ) was consulted to reach a consensus.

Data extraction

We collected data from each eligible study, including the name of the first author, publication year, geographical location, study design, cases, participants, doses, adjusted odds ratios with 95% CIs, outcomes and statistical methods. We followed the recommendations for reporting the

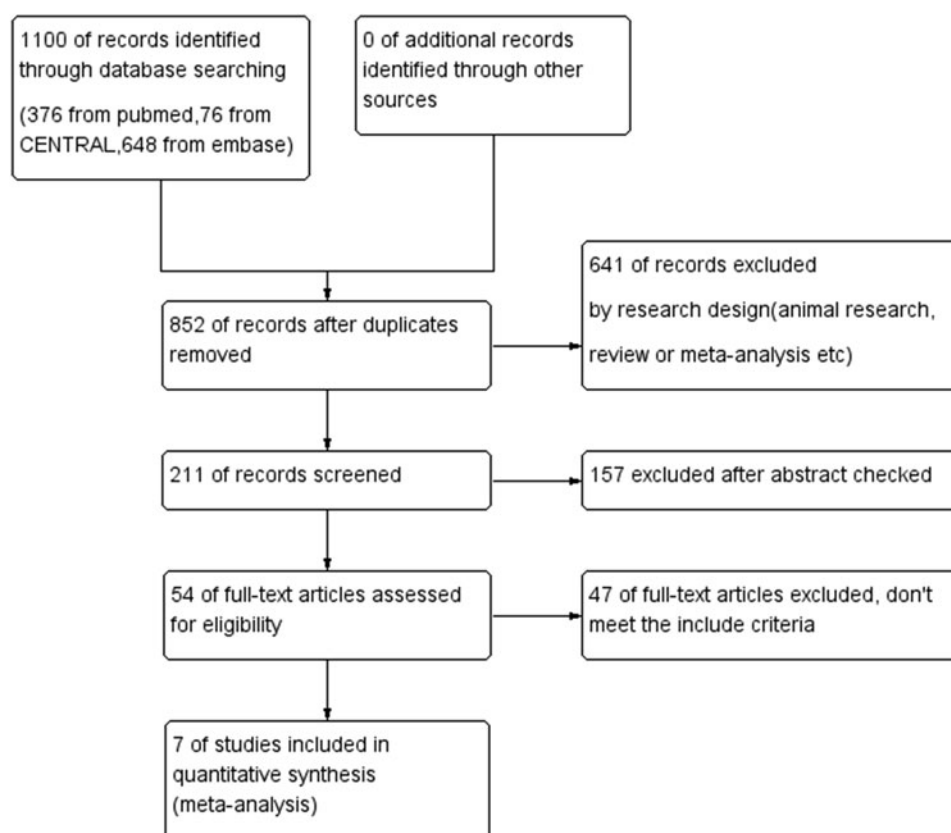


Figure 1. Study flow diagram.

PRISMA guidelines. We evaluated the quality of individual records according to the Newcastle-Ottawa Scale (NOS) [19,20] for prospective cohorts and the Cochrane handbook for RCTs. The characteristics of the trials are shown in [Tables 1](#) and [2](#).

Statistical analysis

Data analysis and statistical software (STATA version 14.0, StataCorp LLC, Texas, USA) and the generalized least squares estimation (GLST) packages were used for statistical analysis [21].

I^2 and chi-square tests were used for heterogeneity estimation. If $p > 0.1$ or $I^2 < 40\%$, the fixed effects model analysis was used. When there was a high degree of heterogeneity, a random effects analysis and subgroup analysis were performed. For each group, a high level of consumption of vitamin D was compared with a low level of consumption. Chi-squared tests were used for the heterogeneity estimates for the linear association analysis. If there was no significant heterogeneity, then we conducted a fixed effects model analysis to examine the linear trends. If there was significant heterogeneity, then a random effects model linear trends analysis was conducted. Then, if

the data did not show linear trends, we considered a nonlinear trend analysis.

Results

Study description

Using the search strategy mentioned above, a total of 1100 records were identified, after duplicates have been removed. After screening the title and the abstracts, we retrieved the full texts of 54 records, of which seven were ultimately included in our analysis. The details of the exclusions are shown in [Figure 1](#). In total, 6068 participants were included in the study.

Risk of bias

For the four prospective cohorts, the risk of bias was assessed according to the NOS ([Table 3](#)). All prospective cohorts showed a low risk of bias. The Cochrane handbook was used to evaluate the risk of bias for RCTs, and we found a low risk of bias for two RCTs and an intermediate risk for one RCT ([Table 4](#)).

Table 3. Risk of bias of included cohort studies.

[illegible]

Table 4. Risk of bias of included randomized controlled trials.

[illegible]

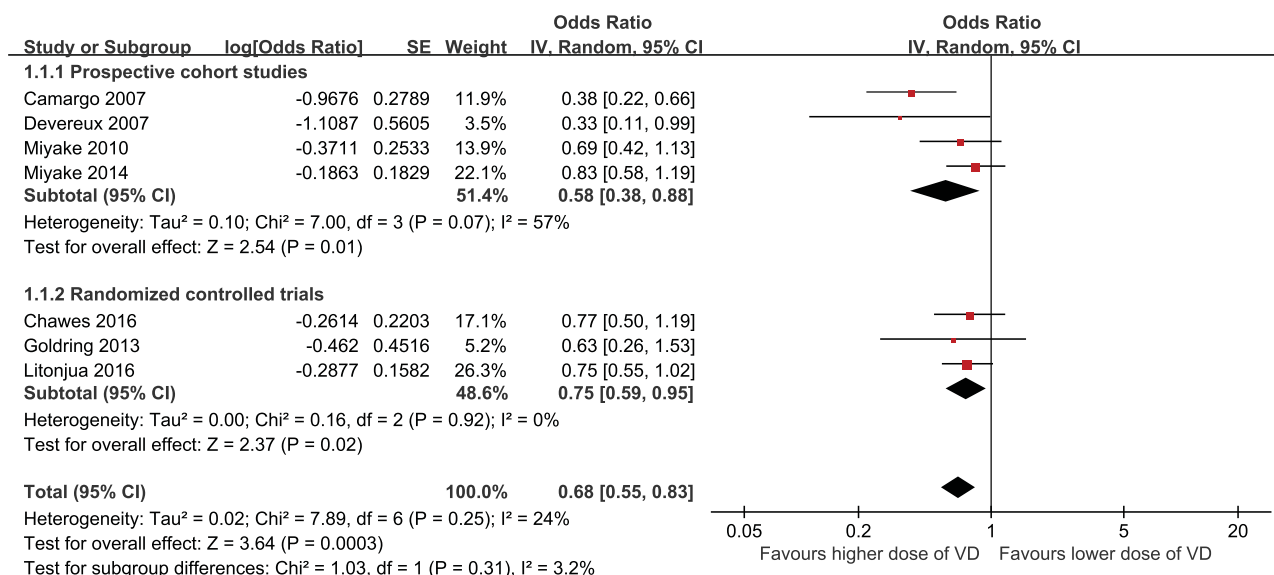


Figure 2. Pooled effect of vitamin D intake during pregnancy and wheezing in offspring.

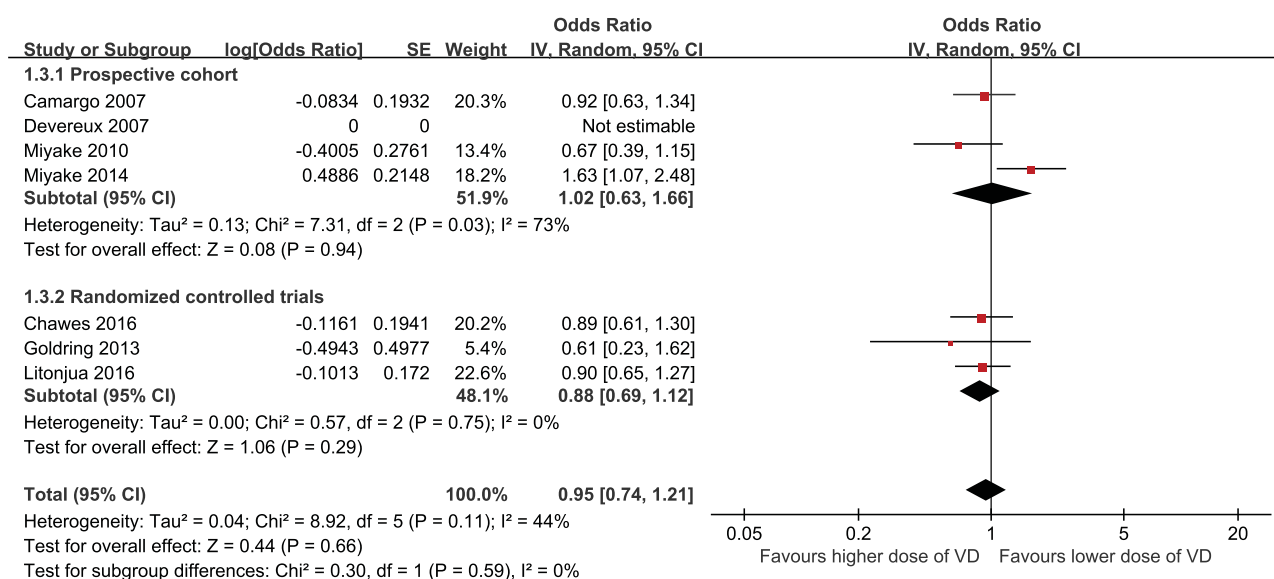


Figure 3. Pooled effect of vitamin D intake during pregnancy and eczema in offspring.

Meta-analysis and subgroup analysis

Primary outcome

Our analysis showed an inverse relationship between the intake of vitamin D during pregnancy and the occurrence of wheezing in offspring [1,11–16] (pooled OR = 0.68, 95% CI = 0.55–0.83, $I^2 = 24\%$, Z -statistic = 3.64, $p < 0.01$, Figure 2). A subgroup analysis by research design showed that both demonstrated the preventive effect of maternal vitamin D intake on wheezing in offspring (prospective cohorts: pooled OR = 0.58, 95% CI = 0.38–0.88, $I^2 = 57\%$, Z -statistic =

2.54, $p = 0.01$. RCTs: pooled OR = 0.75, 95% CI = 0.59–0.95, $I^2 = 0\%$, Z -statistic = 2.37, $p = 0.02$).

Secondary outcome

Eczema is a kind of allergic disease that is always positively correlated with wheezing or asthma. Our analysis showed an inverse relationship between the intake of vitamin D during pregnancy and the occurrence of eczema in offspring but was not significant (pooled OR = 0.95, 95% CI = 0.74–1.21, $I^2 = 44\%$, Z -statistic = 0.44, $p = 0.66$, Figure 3). IgE was also

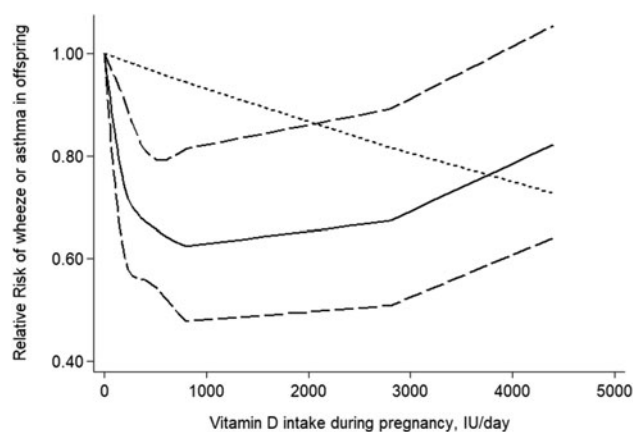


Figure 4. Dose-response analysis of vitamin D intake during pregnancy and wheezing in offspring.

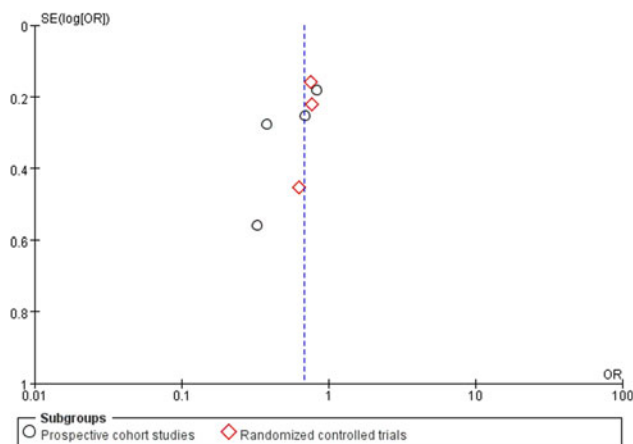


Figure 5. Publication bias of included trials.

evaluated with no positive result (pooled $OR = 0.88$, 95% $CI = 0.77-1.01$, $I^2 = 76\%$, Z -statistic = 1.88, $p = 0.06$).

Dose-response analysis

We found a nonlinear association between vitamin D supplementation during pregnancy and asthma or wheezing in offspring (p for likelihood ratio test = 0.001). A U-shaped dose-response relationship was found between maternal vitamin D intake and the risk of wheezing in offspring (Figure 4), with the lowest risk of wheezing at approximately 800 IU/d vitamin D (the dashed line indicates the 95% CI of the effect size).

Publication bias

The funnel plot for the number of patients with wheezing appeared to be slightly asymmetrical (Figure 5).

However, seven studies with 6068 participants were enrolled in this meta-analysis, which may be insufficient for the assessment by Egger's test.

Discussion

At the earliest, vitamin D was thought to be the vitamin that controls the metabolism of calcium and phosphorus [22]. In recent years, it has been recognized that vitamin D modulates a variety of processes [23] and regulatory systems, including host defense [24], inflammation, immunity [25,26], and repair. Vitamin D has known effects on the immune system and asthma, although the mechanisms by which how vitamin D modulates the pathogenesis of asthma are not entirely clear. Deficiency of vitamin D may partly explain the increases in asthma and allergic diseases [27], and lower cord blood 25(OH)D at birth (<31 ng/mL) was associated with a higher risk of recurrent wheezing in the first year of life [28]. Growing evidence from included high quality RCTs [1,11,12], cohort studies [13–16] and systematic reviews [17,18] supports a preventive role of vitamin D supplementation during pregnancy against wheezing or asthma in offspring.

However, high dosages of vitamin D intake pose potential risks [29]. High dosages of vitamin D supplementation increased risk of fractures [30] and kidney stone [31]. Children whose mothers had high vitamin D levels during pregnancy had an increased risk of asthma [32]. A systematic review found that approximately 70 nmol/L of maternal 25-hydroxyvitamin D (25(OH)D) has the lowest risk of childhood asthma [33].

We focused on the dose-response relationship between vitamin D intake and wheezing in offspring. A reasonable dose of vitamin D intake benefits most pregnant people and their children. Eight-hundred IU/d may be a reasonable dose for vitamin D supplementation during pregnancy, as the benefits decrease at higher doses. The dose-response analysis showed that there is a U-shaped association between vitamin D serum status during pregnancy and wheezing in offspring [33]. Our research showed a similar trend. This trend may suggest that a multicenter RCT is needed to compare the benefit of an intermediate dose (800 IU/d) and a high dose of vitamin D intake in pregnant women.

Several potential limitations of this meta-analysis should be mentioned. First, only seven trials were included, making it difficult to evaluate the publication bias with Egger's or Begg's tests. Additional high-

quality RCTs and larger sample sizes may lead to more reliable results. Second, our main finding of the potential effect of vitamin D supplementation during pregnancy for offspring may be biased because the evidence came from both observational studies and RCTs, which are known to confer inherent shortcomings. There were relatively large differences in the doses of vitamin D used in the included studies. In the literature, there was a lack of observational studies that used high doses of vitamin D (>2000 IU/d), forcing us to consider RCTs as two-group dose cohort studies and include them in our study, even though they are not particularly well suited for the analysis of dose-response. Third, childhood asthma and wheezing risks are associated with many important factors, most notably maternal asthma, maternal smoking during pregnancy and parental smoking in childhood. However, our meta-analysis did not adjust for these factors because they were not recorded in the original manuscripts. Fourth, in early childhood, respiratory infections may present with wheezing, which is why asthma, respiratory infections and persistent wheezing are difficult to distinguish [18] in children of 5 years of age or younger. The included articles have heterogeneous outcomes; some used asthma [13] with clear diagnosis, while others used wheezing [16] as a symptom without spirometry, and this may induce the heterogeneity. The last point is that we found high heterogeneity between the two subgroups. Interestingly, a lower dose of vitamin D existed in the prospective cohort subgroup, and a higher dose existed in the RCT subgroup; this made it difficult to determine whether the heterogeneity stemmed from the different doses or the trial designs.

Conclusions

Evidence from the studies included in this meta-analysis suggests that vitamin D intake during pregnancy is inversely related to wheezing or asthma in offspring. Furthermore, the trend analysis indicates that offspring may benefit from approximately 800 IU/d vitamin D intake during pregnancy.

Declaration of interest

No potential conflict of interest was reported by the authors.

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