

***In utero* exposure to 25-hydroxyvitamin D and risk of childhood asthma, wheeze, and respiratory tract infections: A meta-analysis of birth cohort studies**

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Background: Studies of the associations between *in utero* 25-hydroxyvitamin D (25[OH]D) exposure and risk of childhood asthma, wheeze, and respiratory tract infections are inconsistent and inconclusive.

Objectives: We sought to assess associations between 25(OH)D levels in cord blood or maternal venous blood and risk of offspring's asthma, wheeze, and respiratory tract infections.

Methods: Data were derived from PubMed, Embase, Google Scholar, references from relevant articles, and *de novo* results from published studies until December 2015. A random-effects meta-analysis was conducted among 16 birth cohort studies.

Results: Comparing the highest with the lowest category of 25(OH)D levels, the pooled odds ratios were 0.84 (95% CI, 0.70-1.01; $P = .064$) for asthma, 0.77 (95% CI, 0.58-1.03; $P = .083$) for wheeze, and 0.85 (95% CI, 0.66-1.09; $P = .187$) for respiratory tract infections. The observed inverse association for wheeze was more pronounced and became statistically significant in the studies that measured 25(OH)D levels in cord blood (0.43; 95% CI, 0.29-0.62; $P < .001$).

Conclusions: Accumulated evidence generated from this meta-analysis suggests that increased *in utero* exposure to 25(OH)D is inversely associated with the risk of asthma and wheeze during childhood. These findings are in keeping with the results of 2 recently published randomized clinical trials of vitamin D supplementation during pregnancy. (J Allergy Clin Immunol 2016;■■■:■■■-■■■.)

Key words: 25(OH)D, asthma, wheeze, respiratory tract infections, meta-analysis, birth cohort studies

Asthma, which is characterized by variable airway obstruction, wheeze, bronchial hyperresponsiveness, and airway inflammation,¹ is very common worldwide and usually starts in childhood.² Although allergic constitution, sensitization to allergens,³⁻⁵ and/or familial history of allergic disease⁶ are recognized risk factors for asthma, studies also suggest that maternal vitamin D status during pregnancy can be associated with the risk of asthma in childhood.^{7,8} To date, some birth cohort studies have shown that vitamin D status might play an important role in the development of fetal lungs.⁹⁻¹¹ Also, epidemiologic studies have suggested that maternal vitamin D intake,^{12,13} as well as vitamin D levels in blood,¹⁴⁻¹⁶ were inversely associated with respiratory tract infections and other wheezing illnesses, presumably because of its multiple immune effects, including induction of antibacterial responses and modulation of T lymphocytes to suppress inflammation.^{17,18} Data from randomized clinical trials are sparse, but 2 recently published trials reported a nonsignificant more than 20% reduced risk of persistent wheeze/asthma at age 0 to 3 years from prenatal vitamin D supplementation.^{19,20} In addition to the relatively short follow-up period, the investigators acknowledged that the studies might be underpowered.

A systematic review of 3 cohort studies qualitatively summarized the evidence suggesting a potential link between serum levels of vitamin D and the diagnosis of asthma in childhood.²¹ Another systematic review of 23 published articles, including 9 cross-sectional, 2 case-control, and 12 cohort studies in both children and adults, suggested that higher serum levels of 25-hydroxyvitamin D (25[OH]D) were associated with lower risk of asthma exacerbations but provided little evidence on whether lower *in utero* exposure to 25(OH)D has a programming effect on development of asthma in childhood.²² Notably, neither of these reviews considered wheeze and respiratory tract infections as outcomes.

Because placental transfer of 25(OH)D is the major source of vitamin D in the developing fetus, we conducted this meta-analysis to quantitatively summarize the up-to-date literature to examine the overall associations between 25(OH)D levels of cord

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Supported by the Abbott Fund Institute of Nutrition Sciences (AFINS-2013-06); the Key Laboratory of Pediatric Gastroenterology and Nutrition, Shanghai (11DZ2260-500); and the National Natural Science Foundation of China (81573140).

Disclosure of potential conflict of interest: H. Feng and Y. Wan have received a grant from the Abbott Fund Institute of Nutrition Sciences (AFINS-2013-06). K. Pike has received a grant from the Food Standards Agency. H. Bisgaard has received grants from the Danish Ministry of Health, the Lundbeck Foundation, the Danish Strategic Research Foundation, the Danish Advanced Technology Foundation, and the National Institutes of Health (NIH) and has consultant arrangements with Chiesi Pharmaceuticals and Boehringer Ingelheim. W. Cai has received grants from Abbott Fund Institute of Nutrition Sciences (AFINS-2013-06) and the Key Laboratory of Pediatric Gastroenterology and Nutrition, Shanghai (11DZ2260-500). K. He has received a grant from the NIH (R01ES021735). The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication February 9, 2016; revised May 19, 2016; accepted for publication June 3, 2016.

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0091-6749/\$36.00

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<http://dx.doi.org/10.1016/j.jaci.2016.06.056>

Abbreviations used

25(OH)D: 25-Hydroxyvitamin D
 NOS: Newcastle-Ottawa Scale
 OR: Odds ratio
 RR: Relative risk

blood or maternal venous blood and risk of childhood asthma, wheeze, and respiratory tract infections.

METHODS**Search strategy and selection criteria**

Two investigators (H.F. and P.X.) scrutinized publications independently based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.²³ The complete search process is outlined in Fig 1. First, PubMed (1966-) and Embase (1974-) were searched from inception to December 31, 2015, by using the terms “vitamin D,” “lung disease or asthma or respiratory tract diseases,” “epidemiological studies,” and “cohort/prospective or follow-up or longitudinal studies.” Second, Google Scholar was used to search for any other studies that were not identified from the aforementioned literature review. Third, references from the retrieved articles were manually searched for possible additional studies. Conference abstracts and unpublished studies were not included. Finally, to get additional information, we requested *de novo* data specifically for this meta-analysis from some primary studies.²⁴⁻²⁶

The following inclusion criteria were used in this meta-analysis: (1) English article; (2) prospective birth cohort design; (3) cord blood or maternal venous blood 25(OH)D measurement as exposure; (4) offspring's asthma, wheeze, or respiratory tract infections, which were diagnosed by physicians or met international guidelines or were reported as outcomes by parents; and (5) available data on the relevant odds ratio (OR), relative risk (RR), or hazard ratio and the corresponding 95% CIs.

Quality assessment and data extraction

Two investigators (H.F. and P.X.) independently evaluated the quality of each primary study based on the criteria derived from the Newcastle-Ottawa Scale (NOS) for quality assessment with a maximum score of 9 points.²⁷ Any discrepancy was adjudicated by a third reviewer (K.H.). The NOS score for cohort studies was divided into 3 groups: selection of cohort (4 points), comparability of cohort (2 points), and assessment of outcome (3 points). The quality of the study was considered high or moderate if the sum score was 8 points or greater or between 5 and 7 points, respectively. We limited our meta-analysis to those studies that were rated as high or moderate quality. One study was excluded from the main analysis because of low quality.²⁸ Table E1 in this article's Online Repository at www.jacionline.org shows the details of study quality assessment.

Data were extracted from all eligible studies by 2 independent researchers (H.F. and P.X.) based on a standardized form, and any controversy was resolved through consensus by discussion with a third researcher (K.H.). From each included study, we extracted the following information: name of the first author, year of publication, country of origin, study name, proportion of boys, duration of follow-up, numbers of participants/events, exposure assessment and categorization, outcome definition and assessment, adjusted covariates in the final model, and OR/RR/hazard ratio estimates with corresponding 95% CIs for all categories, continuous exposure of interest, or both.

Linear associations were standardized per 10 nmol/L increment in blood 25(OH)D levels to examine the dose-response relationship. If the linear association was not reported in the primary study, we estimated it by using Greenland and Longnecker's generalized least-squares method if the participants and events in each category were available or by using variance-weighted least-squares estimation if this information was unavailable.^{29,30} If the highest exposure category was open ended (eg, >89 nmol/L), its upper limit was determined by assuming its range was the same interval as

that of the adjacent category. Twelve of 16 included studies reported ORs (95% CIs). In addition, we obtained *de novo* data for ORs (95% CIs) from 2 studies,^{25,26} and converted RRs (95% CIs) to ORs (95% CIs) in the other 2 studies^{31,32} by using the following formula:

$$OR = [(1 - P_0) * RR / (1 - RR * P_0)],$$

where P_0 indicated the incidence of the outcome of interest in the nonexposed/reference group.³³

Statistical analysis

The ORs and corresponding 95% CIs extracted from individual studies were transformed to natural logarithms to normalize their distribution, stabilize variances, and facilitate calculation of SEs. The pooled ORs and corresponding 95% CIs for each outcome of interest were computed by using a random-effects model by weighting the inverse of variance. To determine the pooled association for risk of asthma and wheeze, we pooled the 2 outcomes within each study first using a random-effects model if the study reported both of the 2 outcomes. The heterogeneity among studies was tested by using the Cochran Q test with a significance level of .10 and quantified by using the I^2 statistic. An I^2 value of 0% to 25%, 26% to 50%, 51% to 75%, or greater than 75% represents very low, low, moderate, or high heterogeneity, respectively. Publication bias was determined by using the Egger regression asymmetry test also with a significance level of .1. The Duval and Tweedie nonparametric “trim and fill” method was used to adjust for publication bias, if applicable.³⁴

Stratified analyses were performed to determine modification effects by a few prespecified factors, including blood source (cord blood vs maternal venous blood), outcome diagnosis (clinician diagnosis vs parental report), and seasonal variation consideration (yes vs no). A random-effects meta-regression model was used to obtain the P value for interaction between each of these factors and the exposure.³⁵ Sensitivity analyses were conducted to evaluate the influence of replacing a random-effects model with a fixed-effects model and the influence of a single study on the associations by omitting 1 primary study each time in the meta-analysis.

All analyses were performed with STATA statistical software (version 13.0; StataCorp, College Station, Tex). A 2-sided P value of .05 or less was considered statistically significant, if not otherwise specified.

RESULTS**Literature search**

Fig 1 shows the flow of the study selection process. A total of 130 articles in PubMed and 356 in Embase were identified initially. Of them, 8 in PubMed (5 reviews and 3 case reports) and 102 in Embase (28 reviews and 74 case reports) were excluded. Also, 111 articles in PubMed and 249 in Embase were excluded after reviewing the title and abstract. Of the 11 studies in PubMed and 5 in Embase, 3 were excluded after full-text review because of substantial overlap with other studies. In addition, 4 studies were found by using Google Scholar. Thus, by systematically searching the literature, 17 studies^{10,11,24-26,28,31,32,36-44} were identified. After quality assessment, 1 study was excluded.²⁸ Finally, 16 birth cohort studies were included in this meta-analysis.

Study characteristics

Characteristics of the 16 included studies are summarized in Table E2 in this article's Online Repository at www.jacionline.org. These primary studies were conducted in Asia,^{38,40,43} Europe,^{10,24-26,31,32,36,41,44} North America,⁴² and Australia.^{11,37,39} Of the 16 studies, 10 focused on asthma, including 8871 participants (1494 incident cases) with an average 5.9-year follow-up; 10 studies reported results on wheeze, including

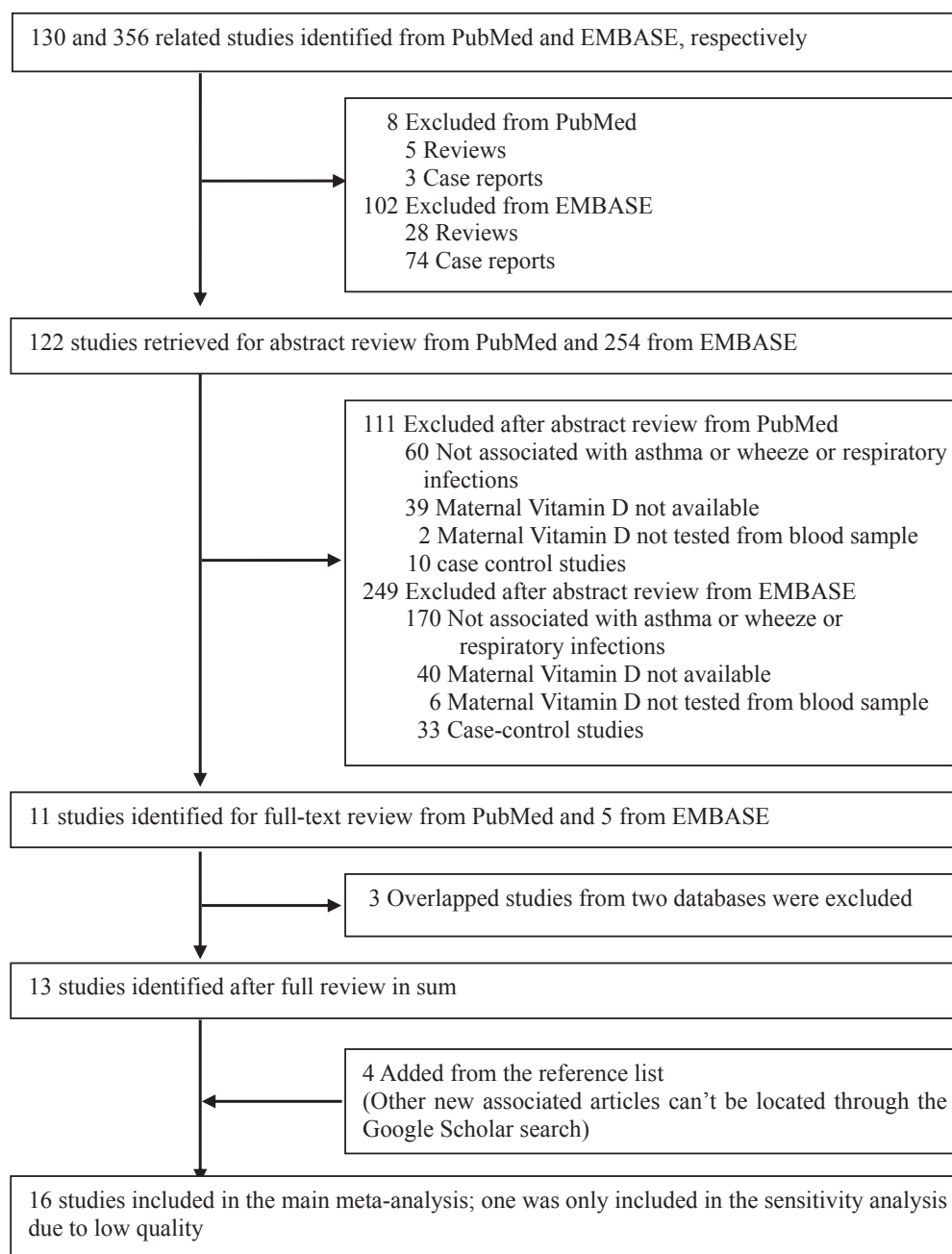


FIG 1. Flowchart of study selection.

9072 subjects (2277 incident cases) with an average 5.5-year follow-up; and 10 studies presented findings on respiratory tract infections, including 8359 subjects (2562 incident cases) with an average 1.4-year follow-up. Blood 25(OH)D levels were measured with various methods, including chemiluminescence immunoassay, electrochemiluminescence, enzyme immunoassay, HPLC, liquid chromatography–tandem mass spectrometry, HPLC–tandem mass spectrometry, and RIA. Blood samples were of either cord blood or maternal venous blood during pregnancy in different stages. Seven studies were evaluated as high quality,^{24-26,36,37,40,44} whereas the other 9 studies were evaluated as moderate quality.^{10,11,31,32,38,39,41-43}

Primary analyses

Asthma. According to available data from 8 studies,^{10,11,24-26,37,38,41} a borderline significant inverse association between *in utero* exposure to vitamin D and risk of asthma in offspring was found. The pooled OR for offspring's asthma was 0.84 (95% CI, 0.70-1.01; $P = .064$), comparing the highest with the lowest category of 25(OH)D levels (Fig 2). No evidence of heterogeneity ($I^2 = 10.4\%$, $P = .349$) and publication bias ($P = .308$, Egger test) was found.

No statistically significant linear association was observed based on available data derived from 8 studies.^{10,24-26,36,37,41,42} The pooled OR for offspring's asthma was 0.99 (95% CI,

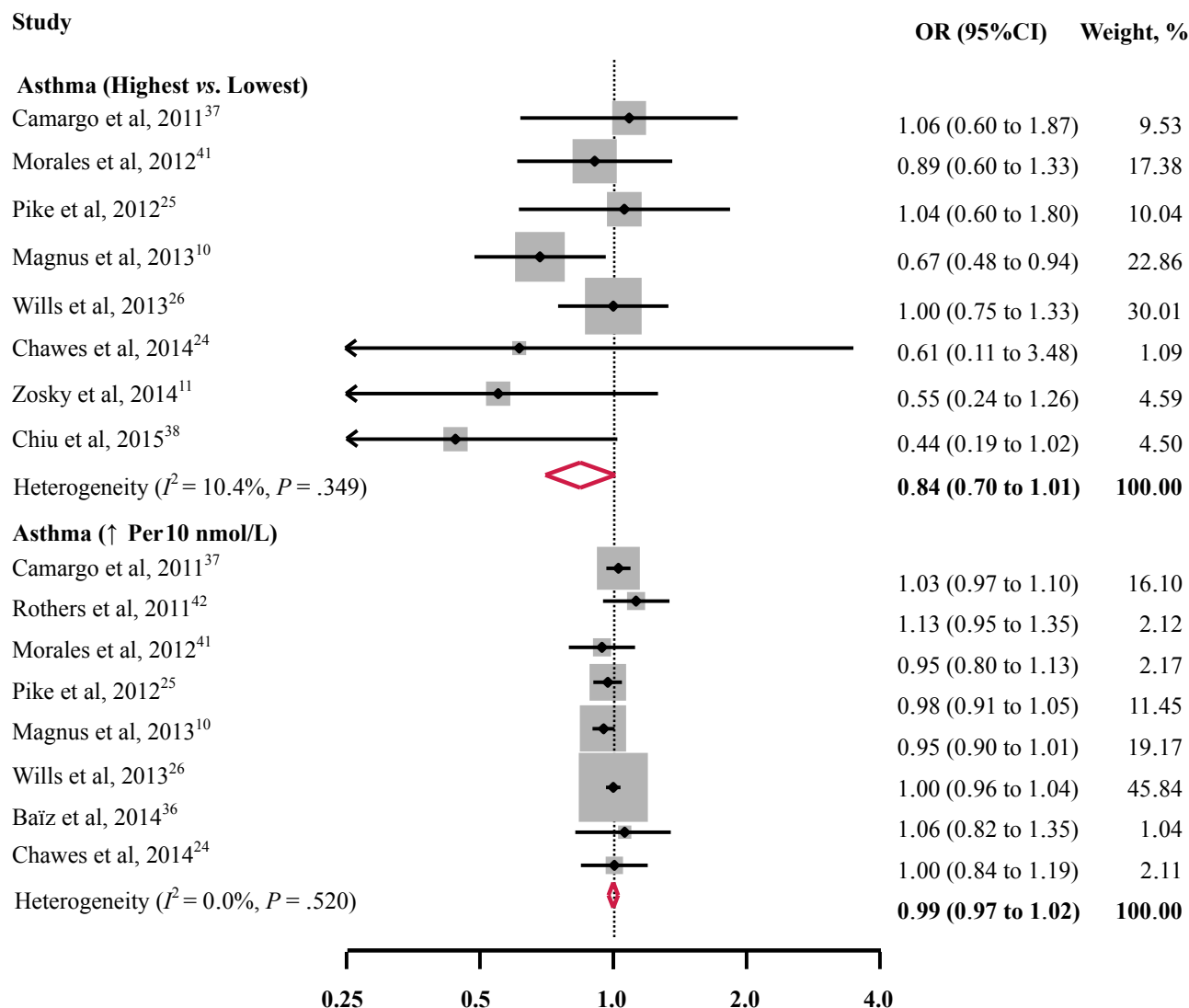


FIG 2. Multivariable-adjusted ORs and 95% CIs (horizontal lines) of asthma. The summary estimates (diamond data markers) were obtained by using a random-effects model. Dots indicate adjusted ORs comparing the highest with the lowest category of or per 10 nmol/L increment in 25(OH)D levels. The size of the shaded square is proportional to the weight of each study.

0.97-1.02; $P = .691$), with a 10 nmol/L increment in 25(OH)D levels. Neither heterogeneity ($I^2 = 0.0\%$, $P = .520$) nor publication bias ($P = .570$, Egger test) was evidenced.

Wheeze. Similar to asthma, a borderline significant inverse association was observed between *in utero* exposure to vitamin D and risk of wheeze in offspring when combining data from 8 eligible studies.^{11,24-26,31,37,41,44} The pooled OR for wheeze was 0.77 (95% CI, 0.58-1.03; $P = .083$), comparing the highest with the lowest category of 25(OH)D levels (Fig 3). A moderate heterogeneity exists across included studies ($I^2 = 62.1\%$, $P = .010$). No publication bias was evident ($P = .122$, Egger test).

No statistically significant linear association was determined by using available data from 9 studies.^{24-26,31,36,37,39,41,44} The pooled OR for offspring's wheeze was 0.98 (95% CI, 0.96-1.004; $P = .114$) with every 10 nmol/L increment in 25(OH)D levels. No heterogeneity ($I^2 = 5.3\%$, $P = .391$) or publication bias ($P = .286$, Egger test) exists.

Respiratory tract infections. Ten studies examined cord blood or maternal venous blood 25(OH)D levels in relation to offspring's respiratory tract infections.^{10,24,25,31,32,37,40,41,43,44} The combined results did not reveal a significant inverse association. The pooled OR was 0.85 (95% CI, 0.66-1.09; $P = .187$), comparing the highest with the lowest category of 25(OH)D levels (Fig 4). There was no evidence on publication bias ($P = .486$, Egger test), but a moderate heterogeneity existed across included studies ($I^2 = 66.1\%$, $P = .003$).

A nonsignificant linear association was found. The pooled OR was 0.97 (95% CI, 0.94-1.01; $P = .156$), with a 10 nmol/L increment in 25(OH)D levels. Neither heterogeneity ($I^2 = 0.0\%$, $P = .495$) nor publication bias ($P = .798$, Egger test) existed.

Stratified analysis

We examined potential effect modifications of a few prespecified factors (Table I). The association with risk of wheeze was

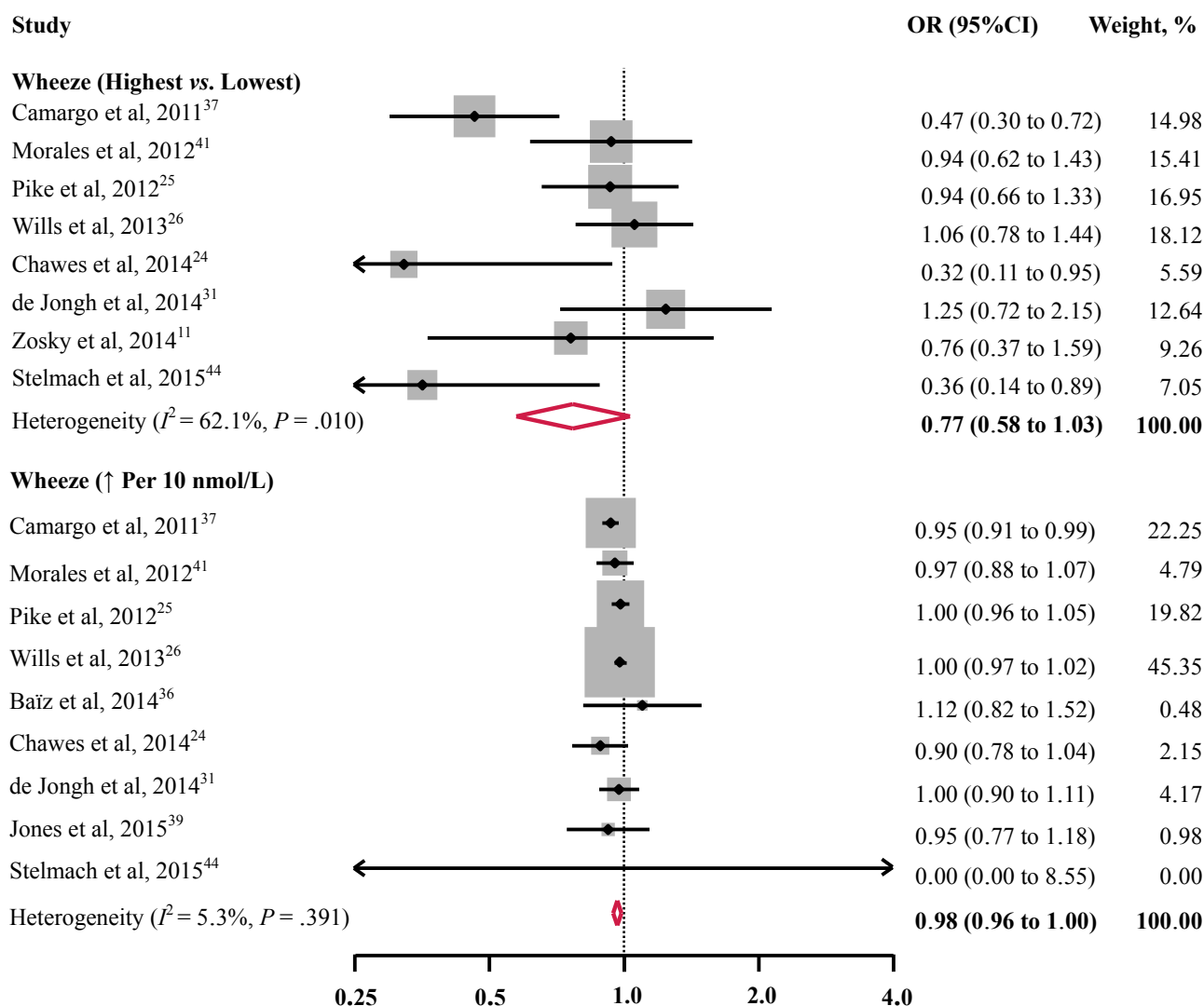


FIG 3. Multivariable-adjusted ORs and 95% CIs (horizontal lines) of wheeze. The summary estimates (diamond data markers) were obtained by using a random-effects model. Dots indicate adjusted ORs comparing the highest with the lowest category of or per 10 nmol/L increment in 25(OH)D levels. The size of the shaded square is proportional to the weight of each study.

modified by the source of 25(OH)D (P for interaction = .007). A statistically significant inverse association was documented when combining data from studies with 25(OH)D levels measured in cord blood. The pooled OR was 0.43 (95% CI, 0.29-0.62; $P < .001$), comparing the highest with the lowest category of cord blood 25(OH)D levels. The risk of offspring's wheeze was decreased by 5% with every 10 nmol/L increment in cord blood 25(OH)D levels (0.95; 95% CI, 0.91-0.99; $P = .009$). By contrast, no significant association was found when combining studies with 25(OH)D levels measured in maternal venous blood. Other factors, including outcome diagnosis and seasonal variation consideration, did not appreciably modify the associations of interest. Of note, 1 primary study¹¹ reported a sex difference. Hence we requested *de novo* data on sex differences and received data from 3 primary studies.²⁴⁻²⁶ After combining data from these 4 available studies, no significant sex difference was found (data not shown).

Sensitivity analysis

When replacing a random-effects model with a fixed-effects model, the results were generally consistent, except that the association between *in utero* exposure to 25(OH)D (highest vs lowest) and risk of respiratory tract infection became statistically significant (0.93; 95% CI, 0.91-0.95; $P < .001$; see Table E3 in this article's Online Repository at www.jacionline.org). Because the most common cause of recurrent wheezing is asthma attacks, we combined these 2 endpoints with available data from 10 studies.^{10,11,24-26,31,37,38,41,44} The pooled OR was 0.80 (95% CI, 0.66-0.98; $P = .028$), comparing the highest with the lowest category of 25(OH)D levels.

A few studies substantially affect the pooled results (see Table E4 in this article's Online Repository at www.jacionline.org). The overall association between 25(OH)D levels and asthma was strengthened and became statistically significant when the study by Camargo et al³⁷ (categorical analysis: 0.82; 95% CI, 0.67-0.999; $P = .049$) or the study by Wills et al²⁶ (categorical

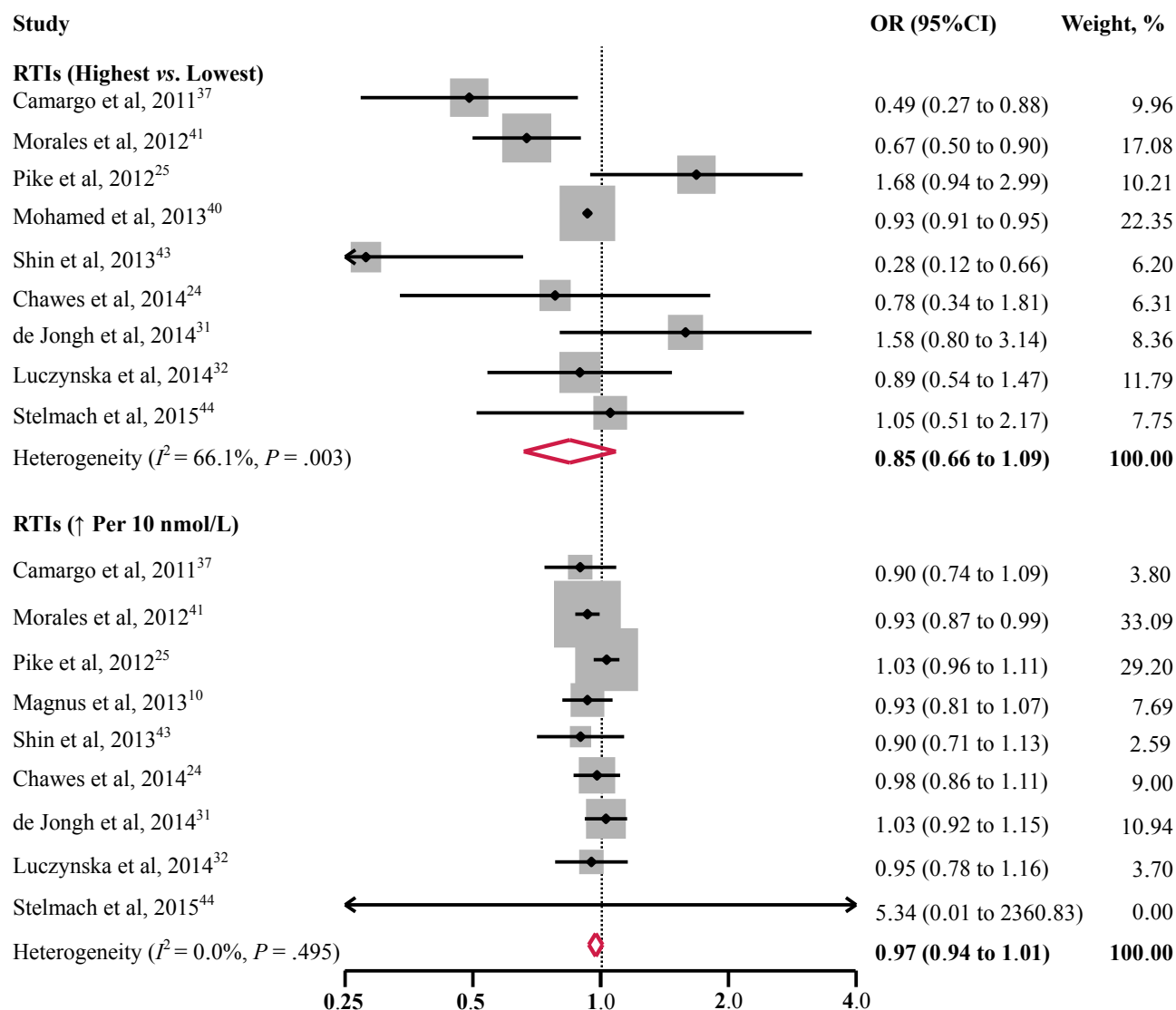


FIG 4. Multivariable-adjusted ORs and 95% CIs (horizontal lines) of respiratory tract infections. The summary estimates (diamond data markers) were obtained by using a random-effects model. Dots indicate adjusted ORs comparing the highest with the lowest category of or per 10 nmol/L increment in 25(OH)D levels. The size of the shaded square is proportional to the weight of each study. RTI, Respiratory tract infection.

analysis: 0.78; 95% CI, 0.64-0.96; $P = .017$) was omitted. Similarly, the overall association between 25(OH)D levels and wheeze was strengthened and became statistically significant by omitting the study by de Jongh et al³¹ (categorical association: 0.72; 95% CI, 0.53-0.99; $P = .041$) or by omitting the study by Wills et al²⁶ (linear association: 0.97; 95% CI, 0.95-0.9996; $P = .047$).

DISCUSSION

In this meta-analysis we found that increased *in utero* exposure to 25(OH)D was inversely associated with risk of offspring's wheeze and asthma in childhood, which is in adherence with the findings from 2 recent randomized clinical trials of vitamin D supplementation during pregnancy. The evidence was strengthened when 25(OH)D levels were measured in cord blood. The observed associations were not appreciably modified by sex, outcome diagnosis methods, and seasonal variation consideration in primary studies.

Strengths and limitations

One unique strength of this meta-analysis is that we obtained *de novo* data from a few primary studies,²⁴⁻²⁶ which provide more accurate and/or additional information specifically for this meta-analysis. Another main strength of this study is that *in utero* exposure to vitamin D is measured by objective biomarkers (ie, cord blood or maternal venous blood) that are a reflection of the current circulating vitamin D levels obtained from diet and sun exposure. However, we realize that serum 25(OH)D levels might not be the best biomarker; alternative vitamin D biomarkers (eg, tissues and intracellular fluid) are definitely needed in future studies depending on the scale of the study and the budget and ethical considerations.

Despite the above merits, results should be interpreted with caution because of some limitations. First, moderate heterogeneity existed in some pooled analyses. The variations in several factors might generate this heterogeneity. For example, different study population, study location, sample size, duration

TABLE I. Stratified analyses of the associations between *in utero* exposure to 25(OH)D and risk of childhood asthma, wheeze, and respiratory tract infections

Outcome	25(OH)D	Potential modifiers	No. of cohorts	No. of participants/events	Heterogeneity test	OR (95% CI)	P value for interaction		
Asthma	Highest vs lowest	Overall	8	8438/1 446	$I^2 = 10.4\%, P = .349$	0.84 (0.70-1.01)	—		
		Blood source	Cord blood	3	1208/238	$I^2 = 33.3\%, P = .223$	0.73 (0.39-1.37)	.760	
			Maternal venous blood	5	7230/1 208	$I^2 = 15.2\%, P = .318$	0.85 (0.70-1.04)		
		Outcome assessment	Doctor diagnosed	4	1533/144	$I^2 = 13.3\%, P = .326$	0.71 (0.46-1.09)	.435	
			Parental report	4	6905/1 302	$I^2 = 17.8\%, P = .302$	0.88 (0.71-1.08)		
		Season considered*	Yes	4	5870/1080	$I^2 = 21.1\%, P = .284$	0.87 (0.67-1.11)	.684	
	No		4	2567/366	$I^2 = 22.1\%, P = .278$	0.78 (0.56-1.10)			
	↑ Per 10 nmol/L	Overall	8	8397/1468	$I^2 = 0.0\%, P = .520$	0.99 (0.97-1.02)	—		
		Blood source	Cord blood	4	1455/260	$I^2 = 0.0\%, P = .736$	1.04 (0.98-1.10)	.137	
			Maternal venous blood	4	6942/1208	$I^2 = 0.0\%, P = .582$	0.98 (0.96-1.01)		
		Outcome assessment	Doctor diagnosed	3	1253/147	$I^2 = 15.8\%, P = .305$	1.01 (0.93-1.09)	.810	
			Parental report	5	7144/1321	$I^2 = 0.0\%, P = .439$	0.99 (0.97-1.01)		
		Season considered*	Yes	6	6304/1128	$I^2 = 11.1\%, P = .345$	1.00 (0.97-1.03)	.532	
	No		2	2093/340	$I^2 = 0.0\%, P = .757$	0.97 (0.91-1.04)			
	Wheeze†	Highest vs lowest	Overall	8	8694/2150	$I^2 = 62.1\%, P = .010$	0.77 (0.58-1.03)	—	
Blood source			Cord blood	3	1240/612	$I^2 = 0.0\%, P = .757$	0.43 (0.29-0.62)	.007	
			Maternal venous blood	5	7454/1538	$I^2 = 0.0\%, P = .825$	1.00 (0.83-1.20)		
Season considered†*			Yes	3	4263/920	$I^2 = 83.2\%, P = .003$	0.60 (0.29-1.23)	.427	
			No	5	4431/1230	$I^2 = 28.8\%, P = .230$	0.89 (0.67-1.18)		
↑ Per 10 nmol/L			Overall	9	8784/2277	$I^2 = 5.3\%, P = .391$	0.98 (0.96-1.004)	—	
		Blood source	Cord blood	5	1618/665	$I^2 = 0.0\%, P = .438$	0.95 (0.91-0.99)	.074	
			Maternal venous blood	4	7166/1538	$I^2 = 0.0\%, P = .962$	1.00 (0.97-1.02)		
		Season considered*	Yes	5	4641/973	$I^2 = 28.0\%, P = .235$	0.97 (0.94-1.01)	.512	
			No	4	4143/1230	$I^2 = 0.0\%, P = .485$	1.00 (0.96-1.03)		
		RTIs	Highest vs lowest	Overall	9	7129/2365	$I^2 = 66.1\%, P = .003$	0.85 (0.66-1.09)	—
Blood source				Cord blood	6	2753/1250	$I^2 = 59.8\%, P = .029$	0.74 (0.53-1.02)	.227
				Maternal venous blood	3	4426/1115	$I^2 = 81.8\%, P = .004$	1.16 (0.58-2.30)	
Outcome assessment				Doctor diagnosed	6	5280/1644	$I^2 = 66.4\%, P = .011$	0.81 (0.61-1.07)	.653
				Parental report	3	1899/721	$I^2 = 77.0\%, P = .013$	0.95 (0.45-2.03)	
Season considered*	Yes			5	3246/1232	$I^2 = 73.4\%, P = .005$	0.72 (0.41-1.27)	.471	
	No	4	3933/1133	$I^2 = 58.5\%, P = .065$	0.91 (0.70-1.17)				
	↑ Per 10 nmol/L	Overall	9	8153/2500	$I^2 = 0.0\%, P = .495$	0.97 (0.94-1.01)	—		
		Blood source	Cord blood	5	2547/1188	$I^2 = 0.0\%, P = .892$	0.95 (0.87-1.03)	.515	
			Maternal venous blood	4	5606/1312	$I^2 = 48.0\%, P = .123$	0.98 (0.92-1.04)		
		Outcome assessment	Doctor diagnosed	4	3199/1200	$I^2 = 0.0\%, P = .878$	0.94 (0.89-0.99)	.120	
			Parental report	5	4954/1300	$I^2 = 0.0\%, P = .466$	1.01 (0.95-1.06)		
		Season considered*	Yes	6	4426/1429	$I^2 = 0.0\%, P = .541$	0.99 (0.94-1.04)	.811	
	No		3	3727/1071	$I^2 = 20.3\%, P = .285$	0.96 (0.89-1.04)			

RTI, Lower respiratory tract infection.

*Season of measurement of the exposure was adjusted in the model, or season-standardized exposure was used.

†Wheeze, as a symptom, was reported by parents in all the included studies, except the Copenhagen Prospective Studies on Asthma in Childhood study, in which wheeze was diagnosed at acute visits to the research clinic and based on a daily diary of respiratory symptoms.

of follow-up, source of blood samples for measuring vitamin D status, outcome diagnosis, seasonal variation consideration, and adjustment for different covariates in primary studies. In the analyses a random-effects model was used in concordance with the heterogeneity. In addition, stratified analyses were conducted to explore any potential effect modifier.

Second, asthma and respiratory tract infections in some primary studies and wheeze in all studies were reported by parents, except the Copenhagen Prospective Studies on Asthma in Childhood study,²⁴ in which wheeze was diagnosed at acute visits to the research clinic and by using a daily diary of respiratory symptoms. Although the signs of these health conditions might be clearly visible, the likelihood of misclassification could not be completely ruled out; for example, parents might report wheeze as a respiratory tract infection. Nevertheless, the potential misclassification should not substantially affect our results because the great majority of parental reports were based on a clinician's diagnosis.

Third, maternal 25(OH)D levels in some studies were measured in venous blood during pregnancy at different time points. This inconsistency in the measurement time window might introduce errors in exposure assessment, but this would presumably lead to a bias toward the null. However, most of the studies (12/16) measured 25(OH)D levels in the later stage of pregnancy (ie, 2 studies at 34-week gestation^{25,31}) or at birth (10 studies^{24,32,36-40,42-44}). Thus the different measurement timing in a few studies should not substantially bias our findings.

Fourth, most of the primary studies measured 25(OH)D levels only once, which might not adequately reflect long-term exposure and might attenuate any possible associations of interest because of random variation. Our findings are more likely to suggest a beneficial effect of higher levels of vitamin D in late pregnancy. Further longitudinal studies with repeat measurements of 25(OH)D levels at different stages of pregnancy are warranted.

Fifth, baseline vitamin D levels varied across studies, but we were not able to adjust for this variation in the meta-analysis because of the lack of original data.

Sixth, we were not able to pool the data comparing subjects with vitamin D levels of 75 nmol/L or greater with that of all other subjects because of data insufficiency.

Finally, although the pooled analyses were based on fully adjusted models in individual studies, our results might be biased by the inherent limitations in the primary studies, such as residual confounding or confounding from unknown or unmeasured factors.

Comparison with previous studies

In light of the considerable complexity of the pathogenesis of these respiratory outcomes, it is not surprising to see the inconsistency in the available data on vitamin D status and offspring's asthma, wheeze, and respiratory tract infections. One meta-analysis nested in a systematic review based on only 3 birth cohort studies suggested a possible association between low serum vitamin D levels and risk of asthma in children.²¹ Another review, which summarized data from 9 cross-sectional, 2 case-control, and 12 cohort studies in both children and adults, suggested that higher serum levels of 25(OH)D were related to lower risk of asthma exacerbations. However, the study did not provide information on the association of *in utero* exposure to 25(OH)D with the development of asthma in childhood.²²

Notably, neither of these 2 reviews considered wheeze and respiratory tract infections as outcomes. In addition, 1 recent meta-analysis that combined data from 4 cohort studies found that maternal dietary intake of vitamin D was associated with lower odds of offspring's wheeze during childhood.⁴⁵ However, dietary intake only accounts for 10% of circulating 25(OH)D.

Findings from the present meta-analysis are generally consistent with those of the previous reviews and provide important additional information on *in utero* exposure to 25(OH)D and risk of the offspring's wheeze and respiratory tract infections in childhood. Furthermore, the findings are in line with those of 2 recently published randomized clinical trials of vitamin D supplementation during pregnancy, showing a nonsignificant more than 20% reduced risk of persistent wheeze/asthma at age 0 to 3 years.^{19,20} Of note, a recent randomized clinical trial found that maternal or cord blood vitamin D levels should be at least 75 nmol/L to result in reversal or protection of autoimmune effects,²⁰ but the optimal level during pregnancy for lung and immune maturation is still unknown. In our meta-analysis the distribution of 25(OH)D levels varied across the primary studies, but overall, approximately 28% of participants had 25(OH)D levels of 75 nmol/L or greater (see Table E5 in this article's Online Repository at www.jacionline.org). Thus the pooled results are biologically in concordance with findings from the randomized clinical trials.

Possible explanations

Vitamin D is an immune regulator involved in both cellular and humoral immunity.⁴⁶ There are several explanations for the potential beneficial effect of vitamin D on the development of asthma and wheeze, including the following: (1) 25(OH)D can modify T-cell differentiation and dendritic cell activation,¹⁷ which plays an important role in the inflammatory response; (2) 25(OH)D can induce a shift in the profile of cytokine secretion during an immune response to an anti-inflammatory phenotype, with regulatory T lymphocytes predominating in the cell population⁴⁷; and (3) in macrophages vitamin D can promote antimicrobial responses through induction of antibacterial proteins¹⁸ and stimulation of autophagy and autophagosome activity.

One study demonstrated a very high correlation between maternal and umbilical cord blood vitamin D levels (Spearman correlation = 0.91),⁴⁸ which supports a common belief that 25(OH)D levels measured in maternal venous blood should be parallel to measures in cord blood. However, we found that the association was more pronounced in the studies in which 25(OH)D levels were measured in cord blood. Notably, the heterogeneity of the time window for measuring 25(OH)D levels in maternal venous blood during pregnancy might attenuate any possible associations.

Studies suggest that early lung development differs between boys and girls,^{49,50} which might explain the higher prevalence of asthma in boys than in girls before puberty.⁵¹ Although the present meta-analysis did not observe a sex difference, a potential effect modification of sex cannot be completely ruled out because the available data were derived from a limited number of studies.^{11,24-26}

Because of seasonal variations in UV radiation exposure, seasonal variation in vitamin D status is recognized.⁵² One study found that vitamin D deficiency was marginally associated with

an increased risk of lower respiratory tract infections in children born in the fall but not in children born in the other 3 seasons.³² Some but not all primary studies considered vitamin D seasonal variation in the analysis. This inconsistency might affect the pooled results, contribute to the heterogeneity, or both. Nevertheless, seasonal variation consideration did not materially modify the associations of interest in this meta-analysis.

Conclusion

This meta-analysis of birth cohort studies accumulates evidence supporting that increased *in utero* exposure to 25(OH) D is inversely associated with the risk of asthma and wheeze during childhood. These findings are in keeping with the results of 2 recently published randomized clinical trials of vitamin D supplementation during pregnancy, showing a more than 20% reduced risk of persistent wheeze/asthma at age 3 years.

Key messages

- Two recent randomized clinical trials suggest a nonsignificant protective effect of prenatal vitamin D supplementation on the risk of persistent wheeze/asthma in early childhood. However, the trials might be underpowered.
- After meta-analyzing data from 16 birth cohorts, we show that increased *in utero* exposure to 25(OH)D is inversely related to risk of offspring's asthma and wheeze but not respiratory tract infections.

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E Table 1. Quality assessment using Newcastle-Ottawa quality assessment scale for the studies included in the meta-analysis

Source	Selection [*]	Comparability [†]	Outcome [‡]	Quality
Gale et al., 2008, the UK ²⁸	★★★	zero	★	low
Camargo et al., The New Zealand Asthma and Allergy Cohort Study, 2011, New Zealand ³⁷	★★★★	★★	★★	high
Rothers et al., The Tucson Infant Immune Study, 2011, USA ⁴²	★★★	★★	★	moderate
Morales et al., The INMA Study, 2012, Spain ⁴¹	★★★★	★★	★	moderate
Pike et al, The Southampton Women's Study, 2012, the UK ²⁵	★★★★	★★	★	High
Magnus et al, The Norwegian Mother and Child Cohort Study, 2013, Norway ¹⁰	★★★	★★	★	Moderate
Mohamed et al., 2013, Saudi Arabia ⁴⁰	★★★★	★★	★★	High
Shin et al., the COCOA Study, 2013, Korea ⁴³	★★★	★★	★★	Moderate
Wills et al., The Avon Longitudinal Study of Parents and Children, 2013, the UK ²⁶	★★★★	★★	★★	High
Baiz et al., The EDEN Cohort Study, 2014, France ³⁶	★★★★	★★	★★	High
Chawes et al., The COPSAC2000 Birth Cohort Study, 2014, Denmark ²⁴	★★★	★★	★★★	High
de Jongh et al., The Southampton Women's Survey, 2014, the UK ³¹	★★★	★★	★★	Moderate
Luczynska et al., 2014, Germany ³²	★★★	★★	★★	Moderate
Zosky et al., The Western Australian Pregnancy Cohort Study, 2014, Australia ¹¹	★★★	★★	★	Moderate
Chiu et al., The PATCH study, 2015, Taiwan ³⁸	★★	★★	★★	Moderate
Jones et al., 2015, Australia ³⁹	★★★	★	★★	Moderate
Stelmach et al., The Polish Mother and Child Cohort Study, 2015, Poland ⁴⁴	★★★★	★★	★★	High

25(OH) D, 25-Hydroxyvitamin D; COCOA, the COhort for Childhood Origin Asthma and allergic disease; COPSAC, Copenhagen Prospective Study on Asthma in Childhood; EDEN, Étude sur les Déterminants pré-et postnatals précoces du développement psychomoteur et de la santé de l'ENfant (Pre- and postnatal determinants of child growth, development and health); INMA, the INFancia y Medio Ambiente (Environment and Childhood); PATCH, birth cohort in the Prediction of Allergies in Taiwanese Children; UK, United Kingdom; USA, the United States of America.

*Stars awarded for representativeness of the birth cohort, selection of the normal birth cohort, the accuracy of vitamin D test and the ascertainment of the diagnostic of the asthma. A maximum of 4 stars is to be awarded.

†Stars awarded for adjustment of related confounders. A maximum of 2 stars is to be awarded.

‡Stars awarded for assessment of asthma, length of follow-up, and adequacy of follow-up cohorts. A maximum of 3 stars is to be awarded.

E Table 2. Characteristics of 16 included studies in this meta-analysis

Source	Proportion of boys, %	Follow-up time	No. of individuals /events	Exposure categories	Exposure assessment	Outcome and its assessment	Adjusted variables	Main results
Camargo et al., The New Zealand Asthma and Allergy Cohort Study, 2011, New Zealand ³⁷	50.5	Asthma: 5 years Wheeze: 5 years Respiratory infection: 3 months	Asthma: 823/181 Wheeze: 823/533 Respiratory infection: 882/553	Categories of 25(OH) D (nmol/L): <25; 25-74; ≥75.	Time: at birth. Method: The Diasorin (Stillwater, MN) LIAISON automated CLIA. Blood sample: the newborn's cord blood.	Asthma was defined as parent report of doctor- diagnosed asthma by the time the child was 5 years old and reported inhaler use or wheezing since the age of 4 years old. Parent report wheeze status was cumulatively assessed at age 15 months, 3 years and 5 years by using the same question across all visits: "Has he/she ever had wheezing or whistling in the chest at any time? " Respiratory infection was defined as a parents' positive response to a series of questions ("Has [child's name] had any of the	Asthma: Season of birth plus 13 potential confounders (study site, maternal age at birth, New Zealand deprivation index, maternal history of asthma, paternal history of asthma, gestational age, child's sex, child's ethnicity, any smoking during pregnancy, any passive smoke exposure at 3 months of age, number of children younger than 16 years in household at the time the child was 3 months old, endotoxin on bedroom floor at the time the child was 3 months old, and duration of exclusive breastfeeding). Wheeze: The confounders above.	Incident asthma by age 5 [OR(95%CI)*#: 0.94 (0.53 to 1.64); 1.19 (0.78 to 1.83); 1.00 (reference). Per 10 nmol/L increment [OR(95%CI)]: 1.03 (0.97 to 1.10). Wheeze by age 5 [OR(95%CI)*: 2.15 (1.39 to 3.33); 1.63 (1.17 to 2.26); 1.00 (reference). Per 10 nmol/L increment [OR(95%CI)]: 0.95 (0.91 to 0.99). Respiratory infection by age 3 months [OR(95%CI): 2.04 (1.13 to 3.67); 1.35 (0.88 to 2.08); 1.00 (reference).

						following?”) about colds, cough, whooping cough, chest infections, and ear infections during the first 3 months of life.	Respiratory infection: The confounders above plus damp musty smell in any room of home at the time the child was 3 months old.	
Rothers et al., The Tucson Infant Immune Study, 2011, USA ⁴²	48.9	Asthma: 5 years	194/29	Categories of 25(OH) D (nmol/L) < 50; 50-74.9; 75-99.9; ≥ 100.	Time: at birth. Method: LC-MS. Blood sample: the newborn’s cord blood.	Doctor diagnosed asthma at 1, 2, 3, or 5 years plus either asthma symptoms or medication use since 4 y of age.	Maternal ethnicity, household smoking, and birth season.	Prevalent asthma at year 5 [OR(95%CI)]: 0.5 (0.2 to 1.6); 1.0 (reference); 1.1 (0.4 to 3.1); 1.4 (0.4 to 5.4).
Morales et al., The INMA Study, 2012, Spain ⁴¹	51.0	Asthma: 4-6 years Wheeze: 4 years LRTI: 1 year	Asthma: 1 233/253 Wheeze: 1 223/220 LRTI: 1 693/627	Quartiles of 25(OH) D (ng/ml): <21.9; 21.9-29.1; 29.2-37.0; ≥37.1.	Time: 77% were done during the second trimester of pregnancy, with 22% during the 1 st trimester and 1% late in pregnancy. Method: HPLC. Blood sample: the mother’s plasma.	Asthma was defined as parental report of doctor- diagnosed asthma or receiving treatment at the age of 4-6 years or wheezing since the age of 4 years. Wheezing was defined as parent reported history of wheezing at the age of 1 year and annually thereafter. Diagnosis of LRTI was physician confirmed.	Asthma/wheeze/ LRTI: Child’s sex, maternal education, siblings at birth, breastfeeding duration, maternal smoking in pregnancy, day-care attendance, maternal asthma, and maternal pre-pregnancy BMI.	Asthma at age 4-6 [OR(95%CI)]: Q1:1.00 (reference); Q2:0.88 (0.59 to 1.29); Q3:0.81 (0.54 to 1.20); Q4:0.89 (0.59 to 1.32). Wheezing at age 4 [OR(95%CI)]: Q1:1.00 (reference); Q2:0.89 (0.59 to 1.34); Q3:0.82 (0.54 to 1.25); Q4:0.94 (0.62 to 1.43). LRTI at age 1 [OR (95%CI)]: Q1:1.00 (reference); Q2:0.89 (0.67 to 1.19); Q3:0.92 (0.70 to 1.23); Q4:0.67 (0.50 to 0.90).

Pike et al., The Southampton Women's Study, 2012, the UK ^{25†}	51.7	Asthma: 6 years	Asthma: 860/87	Tertiles of 25(OH) D (nmol/L): 10.4~46; 46.1~74; 74~203.	Time: at 34 weeks' gestation. Method: RIA (DiaSorin, Stillwater, Minnesota, USA, coefficient of variability<10%). Blood sample: the mother's serum.	Asthma was diagnosed by doctor and defined as current based upon symptoms or asthma treatment present within the last 12 months. Wheeze: Mothers were asked at each visit whether their child had experienced 'episodes of chestiness associated with wheezing or whistling in his/her chest since they were last seen in the study'. LRTI was defined as parent answering yes to either 'chest infection or bronchitis', or 'bronchiolitis or pneumonia' in first 6 months.	Asthma: Maternal education, maternal asthma, and paternal rhinitis. Wheeze: Maternal BMI, child's sex, maternal education, maternal asthma, paternal asthma, and maternal rhinitis. LRTI: Parity, maternal smoking in pregnancy, year of birth, and season of birth.	Asthma at age 6 [OR(95%CI)]: All: T1:1.00 (reference); T2:0.70 (0.39 to 1.28); T3:1.04 (0.60 to 1.80). Boys: T1:1.00 (reference); T2:1.09 (0.51 to 2.34); T3:1.24 (0.58 to 2.67). Girls: T1:1.00 (reference); T2:0.30 (0.10 to 0.88); T3:0.88 (0.39 to 1.97). Per 10 nmol/L increment [OR(95%CI)]: All: 0.98 (0.92 to 1.04). Boys: 1.00 (0.90 to 1.10). Girls: 0.96 (0.86 to 1.08). Any wheeze at or before 6 years old [OR(95%CI)]: All : T1:1.00 (reference); T2:0.85 (0.60 to 1.21); T3:0.94 (0.66 to 1.33). Boys: T1:1.00 (reference); T2:1.22 (0.71 to 1.83); T3:1.04 (0.63 to 1.71). Girls: T1:1.00 (reference); T2:0.59 (0.36 to 0.97); T3:0.79 (0.48 to 1.31). Per 10 nmol/L increment [OR(95%CI)]:
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								All: 1.00 (0.96 to 1.05). Boys: 1.01 (0.95 to 1.08). Girls: 0.98 (0.92 to 1.05). LRTI before 6 months old [OR(95%CI)]: All: T1:1.00 (reference); T2:1.05 (0.57 to 1.93); T3:1.68 (0.95 to 2.99). Boys: T1:1.00 (reference); T2:0.90 (0.42 to 1.96); T3:1.35 (0.65 to 2.81). Girls: T1:1.00 (reference); T2:1.63 (0.56 to 4.69); T3:3.33 (1.17 to 9.26). Per 10 nmol/L increment [OR(95%CI)]: All: 1.03 (0.96 to 1.11). Boys: 1.01 (0.93 to 1.11). Girls: 1.08(0.97 to 1.21).
Magnus et al., The Norwegian Mother and Child Cohort Study, 2013, Norway ¹⁰	NA	Asthma: 3 years LRTI: 3 years	Asthma: 1 672/489 LRTI: 1 180/297	Categories of 25(OH) D (nmol/L): ≤50; 51-75; >75.	Time: median gestational week of sample collection was 18 weeks (range: 9, 35). Method: HPLC-MS. Blood sample: the mother's plasma.	The definition of asthma is based on meeting both criteria: (i) the mother responding yes, has now to whether the child had asthma on the 36-month questionnaire, and (ii) the mother reporting names of	Asthma and LRTI: Maternal age at delivery, maternal education, maternal parity, region of delivery, maternal pre-pregnancy BMI, maternal smoking during pregnancy, maternal midpregnancy plasma folate level, maternal	Asthma at age 5 [OR(95%CI)]: 1.00 (reference); 0.84 (0.61 to 1.17); 0.67 (0.48 to 0.95). Per 20 nmol/L increment [OR(95%CI)]: 0.91 (0.81 to 1.02). Per 20 nmol/L increment in 25(OH) D with frequency of LRTIs at age

						inhaled asthma medications.	history of asthma, maternal multivitamin use during pregnancy, maternal frequency of leisure time physical activity during pregnancy, gestational week of sample and season of sample collection.	3 [OR(95%CI): None: 1.00 (reference); 1 or 2: 0.98 (0.87 to 1.12); ≥3: 0.74 (0.58 to 0.93).
						LRTI: Mother reported.		
Mohamed et al., 2013, Saudi Arabia ⁴⁰	59.2	Acute LRTI: 2 years	Acute LRTI: 206/62	Categories of 25(OH) D (nmol/L): ≤50; >50.	Time: At birth. Method: RIA (Immunodiagnostic systems Inc., Fountain Hills, AZ, USA).	LRTI: clinical diagnostic of bronchiolitis or pneumonia based on medical record review.	Birth weight, maternal age, maternal asthma, and skin color.	Acute LRTI at age 2 [OR(95%CI)]: 1.08 (1.05 to 1.10); 1.00 (reference).
					Blood sample: the newborn's cord blood.			
Shin et al., the COCOA Study, 2013, Korea ⁴³	54.1	Respiratory tract infection: 6 months.	Respiratory tract infection: 525/172	Categories of 25(OH) D (nmol/L): <25; 25-74.9; ≥75.	Time: At birth Method: CLIA (Roche, Indianapolis, IN, USA) Blood sample: the newborn's cord blood.	Respiratory tract infection was diagnosed by pediatricians and pediatric allergy and pulmonology specialists.	Multivitamin use during pregnancy, season of birth, and exposure to passive smoking during pregnancy.	Respiratory tract infection: at age 6 months [OR(95%CI)]: 3.56 (1.52 to 8.34); 2.06 (0.91 to 4.64); 1.00 (reference).
Wills et al., The Avon Longitudinal Study of Parents and Children, 2013, the UK ^{26†}	52.0	Asthma: 7.5 years. Wheeze: 7.5 years.	Asthma: 3 177/379 Wheeze: 3 211/330	Quintiles of 25(OH) D (nmol/L): <38; 38- 52; 52 -67;	Time: any stage in pregnancy and the majority samples taken in the final trimester (52%).	Children were defined as having current doctor-diagnosed asthma if mothers responded	Asthma and wheeze: Smoking, infections, anxiety score, antibiotic use, paracetamol use, BMI, alcohol intake,	Asthma at age 7.5 [OR(95%CI)]: Q1:1.00 (reference); O2:0.94 (0.71 to 1.26); Q3:0.86 (0.64 to 1.14); Q4:0.86 (0.64 to 1.15);

				67- 89; ≥89.	Method: HPLC-MS. Blood sample: the mother's serum.	positively to the question: "Has a doctor ever actually said that your study child has asthma?" and positively to one or both of the questions on wheezing and asthma in the past 12 months. Wheezing was defined as parents reported wheeze.	educational level, housing tenure, financial difficulties, ethnicity, age, parity, history of asthma, eczema, rhino conjunctivitis, migraine, breastfeeding, daycare, pets, exposure to damp/mould in home, environmental tobacco smoke exposure, number of younger siblings, gestational age, birth weight, head circumference, birth length, BMI at age 7 years and offspring serum 25(OH)D, sex and offspring age, and season of measurement.	Q5:1.00 (0.75 to 1.33). Wheeze at age 7.5 [OR(95%CI)]: Q1:1.00 (reference); Q2:0.94 (0.69 to 1.27); Q3:0.84 (0.62 to 1.14); Q4:0.84 (0.61 to 1.15); Q5:1.06 (0.78 to 1.43).
Baiz et al., The EDEN Prospective Birth Cohort Study, 2014, France ³⁶	58.2	Asthma: 5 years Wheeze: 5 years	Asthma: 239/19 Wheeze: 239/93	25(OH) D (nmol/L): continuous	Time: At birth. Method: CLIA performed on the LIAISON platform (DiaSorin, Sallugia, Italy). Blood sample: the newborn's cord blood.	Asthma was defined as parental report of a doctor's diagnosis of asthma plus either 1 or more attacks of wheeze or use of asthma medication in the last 12 months. Wheeze was	Asthma and wheeze: City, mother's age, maternal history of allergy, pre- pregnancy BMI, any smoking during pregnancy, any passive smoke exposure during the first 3 years of life, number of siblings, household income,	Per 12.5 nmol/L increment: Asthma at age 5 [OR(95%CI)]: 1.07 (0.78 to 1.45). Different wheezing patterns [OR(95%CI)]: Early transient 0.67 (0.54 to 0.81).

						defined as present if the parents answered yes to the following question: Has your child had wheezing or whistling in the chest in the preceding 12 months?"	newborn's sex and weight, season of birth, and exclusive breast-feeding for 4 months or longer.	Late onset 0.86 (0.67 to 1.11). Persistent 1.15 (0.79 to 1.691).
Chawes et al., The COPSAC ₂₀₀₀ Birth Cohort Study, 2014, Denmark ^{24†}	48.2	Asthma: 7 years Wheeze: 7 years LRTI: 3 years	Asthma: 199/31 Wheeze: 229/57 LRTI: 204/116	Categories of 25(OH) D (nmol/L): <50; 50-75; >75.	Time: at birth. Method: LC-MS [Calibrators traceable to NIST SRM 972 Chromsystems, DE]. Blood sample: the newborn's cord blood.	Asthma is diagnosed according to international guidelines and was based on recurrent wheeze, including diary verified troublesome lung symptoms, symptoms judged by the COPSAC pediatricians to be typical of asthma; in need of intermittent rescue use of inhaled β_2 agonist; responding to a 3- month trial of inhaled corticosteroids and relapsing when stopping treatment. Wheeze: recurrent wheeze was	Asthma, wheeze and LRTI: Mother's age at newborn's birth, blood sampling season, older siblings, and hair nicotine level at age 1.	Asthma at age 7 [OR(95%CI)]: All: 1.63 (0.47 to 5.61); 1.20 (0.30 to 4.77); 1.00 (reference). Boys: 3.97 (0.38 to 42.06); 4.63 (0.38 to 56.62); 1.00 (reference). Girls: 1.05 (0.22 to 4.97); 1.64 (0.10 to 3.99); 1.00 (reference). Per 10 nmol/L decrement [OR(95%CI)]: All: 1.01 (0.84 to 1.19). Boys: 0.98 (0.72 to 1.34). Girls: 1.01 (0.82 to 1.25). Wheeze at age 7 [OR(95%CI)]: All: 3.09 (1.06 to 9.04); 2.00 (0.64 to 6.24);

	defined as troublesome lung symptoms ≥4weeks or ≥5 episodes of ≥3 consecutive days within 6 months.	1.00 (reference). Boys: 8.60 (1.40 to 53.05); 10.39 (1.49 to 72.34); 1.00 (reference). Girls: 1.91 (0.46 to 7.93); 0.88 (0.18 to 4.31); 1.00 (reference).
	LRTI: The diagnoses were established at the acute visits to the clinic by the research pediatricians based on clinical appearance regardless of identified pathogen(s) in accordance with predefined standard procedures or if the child had been hospitalized.	Per 10 nmol/L decrement [OR(95%CI)]: All: 0.90 (0.78 to 1.04). Boys: 0.86 (0.68 to 1.09). Girls: 0.93 (0.76 to 1.13). LRTI at age 7 [OR(95%CI)]: All: 1.28 (0.55 to 2.96); 1.01 (0.42 to 2.43); 1.00 (reference). Boys: 2.21 (0.62 to 7.93); 1.42 (0.38 to 5.37); 1.00 (reference). Girls: 0.96 (0.29 to 3.17); 0.84 (0.24 to 2.92); 1.00 (reference). Per 10 nmol/L decrement [OR(95%CI)]: All: 0.90 (0.73 to 1.12). Boys: 0.86 (0.68 to 1.09). Girls: 1.01 (0.85 to 1.19).

de Jongh et al., The Southampton Women's Surve ³¹	NA	Wheeze and LRTI: 2 years	Wheeze: 1 876/484 LRTI: 1 875/382	Categories of 25(OH) D (nmol/L): <25; 25-49; 50-74; ≥75.	Time: 34 week gestation. Method: RIA (Diasorin, Stillwater, MN, USA). Blood sample: the mother's serum.	Parents reported wheeze and LRTI. Chest infection, bronchitis, bronchiolitis and pneumonia were combined into one variable labelled "LRTI".	Wheeze and LRTI: Child's sex, birth weight and gestational age, and for maternal age at childbirth, educational level, pre- pregnancy BMI, parity, ethnicity, smoking in pregnancy, and duration of breastfeeding.	Wheeze at age 2 [RR(95%CI)]: 0.85 (0.58 to 1.25); 1.01 (0.84 to 1.22); 0.92 (0.75 to 1.12); 1.00 (reference). Diagnosed LRTI at age 2 [RR(95%CI)]: 0.69 (0.41 to 1.14); 0.98 (0.79 to 1.22); 0.92 (0.73 to 1.16); 1.00 (reference).
Luczynska et al., 2014, Germany ³²	51.2	LRTI: 1 year	LRTI: 777/285	Quartiles of 25(OH) D (nmol/L) based on the season of blood collection standardized values: <22.1; 22.1-<29.5; 29.5-<40.2; ≥40.2.	Time: At birth. Method: EIA (IDS, Immunodiagnostic systems Ltd, Boldon, UK). Blood sample: the newborn's cord blood.	Incidence of LRTI during the child's first year of life was determined using a self- administered ques- tionnaire completed by the child's physician during the 1 year follow- up period.	Sex, whether the child had a sibling under 5 years of age, premature delivery, and breastfeeding duration.	LRTI at age 1 [RR(95%CI)]: Q1:1.06 (0.82 to 1.37); Q2:1.04 (0.79 to 1.36); Q3:1.15 (0.89 to 1.48); Q4:1.00 (reference).
Zosky et al., The Western Australian Pregnancy Cohort Study, 2014, Australia ¹¹	46.6	Asthma and wheeze: 14 years	Asthma and wheeze: 288/NA	Two level of 25(OH) D (nmol/L): ≤50; >50.	Time:16~20 week gestation; mean:18week. Method: EIA (Immunodiagnostic Systems; Scottsdale, AZ) Blood sample: the mother's serum	Current asthma was defined as a doctor diagnosis of asthma at any time, with wheeze and use of any asthma medication in the past 12 months. Current wheeze was defined by questionnaire at	Asthma and wheeze: Maternal asthma, parental education, maternal age, birth order, maternal smoking, maternal alcohol consumption, breastfeeding, and femur length Z-score at 16 to 20 weeks' gestation.	Current asthma at age 14 [OR(95%CI)]: All: 1.82 (0.79 to 4.17); 1.00 (reference). Boys: 1.53 (0.31 to 7.54); 1.00 (reference). Girls: 0.21 (0.01 to 3.51); 1.00 (reference).

						each age (yes/no).	Sex analysis: Factors above, Plus Tanner score.	Current wheeze at age 14 [OR(95%CI)]: All: 1.31 (0.63 to 2.75); 1.00 (reference). Boys: 1.54 (0.69 to 5.97); 1.00 (reference). Girls: 1.11 (0.42 to 2.94); 1.00 (reference).
Chiu et al., The PATCH study, 2015, Taiwan ³⁸	55.9	Asthma: 4 years	Asthma: 186/26	Two level of 25(OH) D (nmol/L): <50; ≥50.	Time: At birth. Method: ECL (Roche Diagnostics, Mannheim, Germany). Blood sample: the newborn's cord blood.	Asthma was diagnosed as ever having asthma with the occurrence of wheeze or current use of asthma medication.	Maternal age at delivery, maternal history of atopy, paternal history of atopy, any passive smoke exposure during pregnancy, any older siblings, household income, gestational age, sex, and exclusive breast- feeding for 6 months or longer.	Asthma at age 4 [OR(95%CI)]: 2.27(0.98 to 5.28); 1.00(reference).
Jones et al., 2015, Australia ³⁹	55.6	Wheeze: 2.5 years	Wheeze: 139/34	25(OH) D (nmol/L): continuous	Time: At birth. Method: LC-MS (RDDT, Melbourne, Vic., Australia). Blood sample: the newborn's cord blood and peripheral blood at 6 months.	Parents reported wheeze. Questions regarding wheeze were based on the international study of asthma and allergies in childhood phase on questionnaire.	Sex and season of birth.	Wheeze at age 2.5 [OR(95%CI)]: Per 10 nmol/L increment in cord 25(OH) D level: 0.95 (0.77 to 1.18). Per 10 nmol/L increment in peripheral blood 25(OH) D level: 0.83 (0.67 to 1.02).

Stelmach et al., The Polish Mother and Child Cohort Study, 2015, Poland ⁴⁴	NA	Multi- triggered wheezing and respiratory infection: 2 years	Multi- triggered wheezing: 188/22 respiratory infection: 159/62	Two levels of 25(OH) D (nmol/L): <10.4; ≥10.4.	Time: At birth. Method: HPLC (produced by ChromosystemsR). Blood sample: the newborn's cord blood.	Multi-triggered wheezing was defined as wheezing triggered by two or more factors (e.g., viral infection, weather, and activity). Respiratory infections were defined as episodes of cold without wheezing.	Wheeze and respiratory infection: number of infections and paternal smoking.	Multi-triggered wheezing at age 2 [OR(95%CI)]: 2.81 (1.13 to 7.00); 1.00 (reference). Per 2.5 nmol/L increment [OR(95%CI)]: 0.20 (0.02 to 1.71). Respiratory infections at age 2 [OR(95%CI)]: 0.95 (0.46 to 1.96); 1.00 (reference). Per 2.5 nmol/L increment [OR(95%CI)]: 1.52 (0.33 to 6.94).
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25(OH) D, 25-Hydroxyvitamin D; AZ, Arizona; BMI, body mass index; CI, confidence interval; CLIA, chemiluminescence immunoassay; COCOA, The COhort for Childhood Origin Asthma and allergic disease; COPSAC, COpenhagen Prospective Study on Asthma in Childhood; ECL, electrochemiluminescence; EDEN, Étude sur les Déterminants pré- et postnatals précoces du développement psychomoteur et de la santé de l'Enfant (Pre- and postnatal determinants of child growth, development and health); EIA, enzyme immunoassay; HPLC, high-performance liquid chromatography; HPLC-MS, high-performance liquid chromatography-tandem mass spectrometry; IDS Ltd, immunodiagnostic systems limited; INMA, the INfancia y Medio Ambiente (Environment and Childhood); LC-MS, liquid chromatography-tandem mass spectrometry; LRTI, lower respiratory tract infection; MN, Minnesota; NA, not available; OR, odds ratio; PATCH, birth cohort in the Prediction of Allergies in Taiwanese CHildren; Q, quartile/quintile; RIA, radioimmunoassay; RR, relative risk; T, tertile; UK, United Kingdom; USA, the United States of America.

*Only season was adjusted.

[†]We got *de novo* results for these studies.

E Table 3. Multivariable adjusted association of 25 (OH) D with risk of asthma, wheeze, and respiratory tract infection using a fixed-effects model: a sensitivity analysis

Outcome	Odds Ratio (95%CI)	
	Highest vs. lowest	Per 10 nmol / L increment
Asthma	0.85 (0.72 to 1.001)	0.99 (0.97 to 1.02)
Wheeze	0.85 (0.72 to 0.996)	0.98 (0.97 to 1.003)
Respiratory tract infection	0.93 (0.91 to 0.95)	0.97 (0.94 to 1.01)

25(OH) D, 25-Hydroxyvitamin D; CI, confidence interval; OR, odds ratio.

E Table 4. Influence of a single study on the pooled association of 25 (OH) D with risk of asthma, wheeze, and respiratory tract infection using a random-effects model: a sensitivity analysis

Outcome	Study omitted	Odds Ratio (95%CI)	
		Highest vs. lowest	Per 10 nmol / L increment
Asthma	None	0.84 (0.70 to 1.01)	0.99 (0.97 to 1.02)
	Camargo et al, 2011 ³⁷	0.82 (0.67 to 0.999)	0.99 (0.97 to 1.02)
	Rothers et al, 2011 ⁴²	--	0.99 (0.97 to 1.02)
	Morales et al, 2012 ⁴¹	0.82 (0.66 to 1.03)	0.996 (0.97 to 1.02)
	Pike et al, 2012 ²⁵	0.82 (0.67 to 1.002)	0.997 (0.97 to 1.02)
	Magnus et al, 2013 ¹⁰	0.91 (0.75 to 1.10)	1.00 (0.98 to 1.03)
	Wills et al, 2013 ²⁶	0.78 (0.64 to 0.96)	0.99 (0.96 to 1.03)
	Baiz et al, 2014 ³⁶	--	0.99 (0.97 to 1.02)
	Chawes et al, 2014 ²⁴	0.84 (0.69 to 1.03)	0.99 (0.97 to 1.02)
	Zosky et al, 2014 ¹¹	0.86 (0.71 to 1.03)	--
	Chiu et al, 2015 ³⁸	0.87 (0.74 to 1.03)	--
Wheeze	None	0.77 (0.58 to 1.03)	0.98 (0.96 to 1.004)
	Camargo et al, 2011 ³⁷	0.88 (0.68 to 1.13)	0.99 (0.97 to 1.02)
	Morales, 2012 ⁴¹	0.73 (0.52 to 1.04)	0.98 (0.96 to 1.01)
	Pike et al, 2012 ²⁵	0.73 (0.51 to 1.04)	0.98 (0.95 to 1.003)
	Wills et al, 2013 ²⁶	0.72 (0.51 to 1.005)	0.97 (0.95 to 0.9996)
	Baiz et al, 2014 ³⁶	--	0.98 (0.96 to 1.004)
	Chawes et al, 2014 ²⁴	0.82 (0.61 to 1.09)	0.99 (0.97 to 1.01)
	de Jongh et al, 2014 ³¹	0.72 (0.53 to 0.99)	0.98 (0.96 to 1.01)
	Zosky et al, 2014 ¹¹	0.77 (0.56 to 1.06)	--
	Jones et al, 2015 ³⁹	--	0.98 (0.96 to 1.01)
	Stelmach et al, 2015 ⁴⁴	0.82 (0.62 to 1.10)	0.98 (0.97 to 1.01)
Respiratory tract infection	None	0.85 (0.66 to 1.09)	0.97 (0.94 to 1.01)
	Camargo et al, 2011 ³⁷	0.90 (0.70 to 1.15)	0.98 (0.94 to 1.01)
	Morales et al, 2012 ⁴¹	0.88 (0.66 to 1.18)	0.99 (0.95 to 1.04)
	Pike et al, 2012 ²⁵	0.78 (0.61 to 1.01)	0.95 (0.91 to 0.99)
	Magnus et al, 2013 ¹⁰	--	0.98 (0.94 to 1.02)
	Mohamed et al, 2013 ⁴⁰	0.82 (0.58 to 1.18)	--
	Shin et al, 2013 ⁴³	0.90 (0.72 to 1.13)	0.98 (0.94 to 1.01)
	Chawes et al, 2014 ²⁴	0.85 (0.65 to 1.11)	0.97 (0.93 to 1.01)
	de Jongh et al, 2014 ³¹	0.80 (0.62 to 1.04)	0.97 (0.93 to 1.01)
	Luczynska et al, 2014 ³²	0.84 (0.63 to 1.11)	0.97 (0.93 to 1.01)
	Stelmach et al, 2015 ⁴⁴	0.83 (0.63 to 1.09)	0.97 (0.94 to 1.01)

25(OH) D, 25-Hydroxyvitamin D; CI, confidence interval; OR, odds ratio.

E Table 5 Summary of levels of 25(OH)D in the included studies in this meta-analysis

Source	Average (range) of 25(OH)D, nmol/L	Lowest category of 25(OH)D		Highest category of 25(OH)D	
		Levels (nmol/L)	% of participants	Levels (nmol/L)	% of participants
Camargo et al., 2011 ³⁷	44 (~5 to ~290)	<25	19.5	≥75	27.2
Rothers et al., 2011 ⁴²	~68 (13 to 172.5)*	<50	26.5	≥75 (≥100)	32.5 (11.0)
Morales et al., 2012 ⁴¹	75.75 (14.25 to 227.5)	<54.75	~25.0	≥92.75	24.8
Pike et al., 2012 ²⁵	59 (10.4 to 203)*	<46	33.3	≥74	33.3
Magnus et al., 2013 ¹⁰	73.3 (NA)	≤50	18.9	>75	46.1
Mohamed et al., 2013 ⁴⁰	60.1 (17.4 to 80.4)	≤30	12.1	≥75	43.7
Shin et al., 2013 ⁴³	38.2 (11.9 to 1200)	<25	34.3	≥75	10.1
Wills et al., 2013 ²⁶	61.5 (8.5 to 240.5)*	<38	16.5	≥89	21.3
Baiz et al., 2014 ³⁶	44.5 (6 to 120)	<25	~23.5*	≥75	~15.0*
Chawes et al., 2014 ²⁴	47.6 (10 to 145)	<50	53.0	≥75	15.0
de Jongh et al., 2014 ³¹	59.0 (43 to 88)	<25	5.1	≥75	34.3
Luczynska et al., 2014 ³²	29.5 (up to ~100)	<25	46.1	≥50	17.4
Zosky et al., 2014 ¹¹	58.0 (NA)	<50	34.9	≥75	18.8
Chiu et al., 2015 ³⁸	59.5 (up to ~135)	<50	58.0	≥50(≥75*)	42.0 (~20.0*)
Jones et al., 2015 ³⁹	57.9 (20 to ~120)*	<50	NA	≥75	>50.0
Stelmach et al., 2015 ⁴⁴	15.8 (up to ~70)*	<10.4	25.0	≥75	0.0

25(OH) D, 25-Hydroxyvitamin D; NA, not available.

* *de novo* results.