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Association between vitamin D status and asthma control: a meta-analysis of randomized trials

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Abstract

Background: There is a controversy in terms of the efficacy of vitamin D supplementation in improving asthma symptom control. Moreover, whether there is a difference in the treatment effect with respect to baseline vitamin D status remains unknown. This meta-analysis was to assess the correlations of vitamin D status with asthma-related respiratory outcomes.

Methods: PubMed, EMBASE, and Cochrane Library were searched for randomized controlled trials of vitamin D supplementation in patients with asthma. Primary outcomes were the rate of asthma exacerbation and predicted percentage of forced expiratory volume in first second (FEV_1%). Secondary outcomes were asthma control test (ACT) scores, fractional exhaled nitric oxide (FeNO), interleukin-10 (IL-10) and adverse events.

Results: A total of 14 randomized controlled trials (1421 participants) fulfilled the inclusion. Vitamin D supplementation was associated with a significant reduction in the rate of asthma exacerbation by 27% (RR: 0.73 95%Cl (0.58-0.92)). In subgroup analysis, the protective effect of exacerbation was restricted in patients with vitamin D insufficiency (vitamin D < 30ng/ml) (RR: 0.76, 95%Cl (0.61-0.95)). An improvement of FEV_1% was demonstrated in patients with vitamin D insufficiency and air limitation (FEV_1% < 80%) (MD: 8.3, 95%Cl (5.95-10.64). No significant difference was observed in ACT scores, FeNO, IL-10 and adverse events.

Conclusions: Vitamin D supplementation reduced the rate of asthma exacerbation, especially in patients with vitamin D insufficiency. Additionally, the benefit of vitamin D had a positive effect on pulmonary function in patients with air limitation and vitamin D insufficiency.

Keywords: Asthma; Vitamin D; Treatment; Meta-analysis; RCTs.

Abbreviations: FEV_1% = predicted percentage of forced expiratory volume in first second, ACT = asthma control test, IL-10 = interleukin-10, FeNO = fractional exhaled nitric oxide, 25(OH)D = 25-hydroxyvitamin D, CI = confidence interval, MD = mean differences, SMD = standardized mean differences, RR = risk ratios.

1. Introduction

Asthma is a heterogeneous disease and characterized by chronic airway inflammation, which can be control [1]. However, current asthma management remains imperfect that substantial proportion of patients do not achieve optimal asthma control despite high-dose treatment [2]. Recently, multiple epidemiological studies have identified strong associations between vitamin D insufficiency (25-hydroxyvitamin D (25(OH)D) < 30ng/ml) and increased asthma incidence, especially in patients with severe and uncontrolled asthma [3-5]. This may explain by that, vitamin D plays a key role in modulating the immune response and showing anti-inflammatory effects [3,6-9]. Thus, there has been enormous interest in the use of vitamin D as a potential therapeutic option.

The evidence-base increasingly supports vitamin D supplementation being a safe, practical and beneficial part of the comprehensive management of asthma [10]. Nevertheless，a recent review by Hall et al. [11] indicated that the positive effect of vitamin D in asthma control remained controversial. Moreover, randomized controlled trials (RCTs) published recently have examined the potential contribution caused by vitamin D supplementation to asthma susceptibility. One study [12] indicated that 4-month vitamin D supplementation was associated with an improvement in pulmonary function regardless of vitamin D status, whereas other studies [13,14] showed a negative effect on it. In addition, Musharraf et al. [15] reported that vitamin D supplementation was efficacious in the prevention of asthma exacerbation, while two studies [16-17]

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reported the inconsistent results. Therefore, the effect of vitamin D supplementation on patients with bronchial asthma is still controversial.

To date, a total of six aggregate data meta-analyses [18-23] have been conducted with inconsistent results. However, few systematic reviews have examined the role of vitamin D on pulmonary function, and the question of whether vitamin D insufficiency is a risk factor for asthma needs to be clarified. Additional five RCTs [12-15,17] have been published since the most recent meta-analysis. In consequence, the main goal of our meta-analysis was to synthesize the evidence to justify whether the recently published RCTs would alter previous conclusions and to sort out causal relationships between baseline vitamin D status and asthma-related outcomes.

2. Material and methods

2.1. Search Strategies

The recommendations on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) were regarded as a guideline to perform our meta-analysis [24]. Our protocol was registered in PROSPERO website in April 2018 (CRD42018094893). We performed a comprehensive search in the databases PubMed, EMBASE, Cochrane Library and Clinical Studies.gov using following medical subject heading (MeSH) and free-text terms: “Vitamin D” or “25-hydroxyvitamin D (25(OH)D)” or “Vitamin D-3” or “25-hydroxyvitamin D” or “Cholecalciferol” and “Asthma” or “Bronchial Asthma”. Publication type was limited in RCTs. The databases were searched from the inception to the end of March 2018. In addition, a manual search was conducted by searching reference of former meta-analyses and relevant studies, which were not identified in our electronic search. There was no limitation to language.

2.2. Study selection

Two reviewers screened the records independently. Inclusion criteria were listed as following: (1) RCTs; (2) participants with diagnosed asthma; (3) intervention was vitamin D, regardless of the drug names, doses, and administration routines, or as an adjunct to other forms of asthma treatment; (4) outcomes were reported in predicted percentage of forced expiratory volume in first second (FEV_1%), the rate of asthma exacerbation, fractional exhaled nitric oxide (FeNO), asthma control test (ACT) scores, interleukin-10 (IL-10) and the rate of adverse events. Exclusion criteria were: (1) non-RCTs; (2) population of studies was pregnant; (3) the dosing regimen included the fixed administration of another drug or vitamin D without an appropriate control arm; (4) studies only with abstract. The final inclusion was obtained by discussion.

2.3. Data extraction

The following information was screened closely and extracted by two investigators (MMW and CRW) independently to a standardized collection form which we had been made before. A third (YX) reviewer made the final decision when disagreements occurred. Data were collected from the included studies as follows: name of the first author, publication year, country of origin, number of the participants in each trial, details of the intervention treatment, basic characteristics of included patients. Outcomes extracted included FEV_1%, the rate of asthma exacerbation, FeNO, ACT scores, IL-10 and the rate of adverse events. When essential data were not reported, we communicated with the original author of the study to get the desired data. Besides, missing data were also collected in ClinicalStudies.gov when we got the NCT number.

2.4. Outcomes

Primary outcomes were FEV_1% and the rate of asthma exacerbation. FEV_1% was calculated as a change from baseline. Definition of asthma exacerbation differed among studies. Thus, our group utilized the variable definitions reported in primary publications in our meta-analysis. It was defined as an increase in symptoms of shortness of breath, cough, wheezing or chest tightness and progressive decrease in pulmonary function, or require a change in treatment (including short-acting β2-agonists, antibiotics or oral corticosteroids). Acute-care visit was reported in

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one trial [16] which was also considered asthma exacerbation.

Second outcomes were FeNO, ACT scores, IL-10 and the rate of adverse events. The outcomes of FeNO, ACT scores, and IL-10 were also calculated as the change from baseline. ACT scores was defined by GINA [1], and consisted of day-time and night-time symptom control, rescue use of relievers and activity limitations. The following factors were considered as adverse events: hypercalcemic, nephrolithiasis, or urine calcium after vitamin D supplementation.

2.5. Quality assessment

Two reviewers independently evaluated the quality of each selected study using the Cochrane collaboration tools in following seven aspects: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other forms of bias. Moreover, the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) was used to assess the quality of each endpoint.

2.6. Statistical Analysis

The statistical analysis was performed with the RevMan software [Review Manager (RevMan). Version 5.2, The Cochrane Collaboration, Copenhagen, Denmark] and the Stata 12.0 software (Statacorp LP, College Station, Texas, USA). Due to studies differed in the mixes of interventions and participants, a random-effect model was conducted to perform the statistical analysis. When data from 3 or more studies were available, outcomes were pooled using mean differences (MD) and standardized mean differences (SMD) (inverse variance method) for continuous variable or risk ratios (RR) (Mantel–Haenszel method) for dichotomous variables. Besides, change between baseline and the longest follow-up duration was conducted to avoid the disturbance of baseline's unbalance for continuous outcomes. Mann–Whitney U-tests was used to conduct statistical analyses, and a two-sided P-value of < 0.05 was considered statistically significant. Heterogeneity among the studies was assessed by Cochran's Q-test, and $P < 0.10$ was considered statistically significant. Furthermore, the I^2 statistic was used to calculate the degree of heterogeneity between included studies. I^2 values of 25%, 50%, and 75% were considered low, moderate, and high heterogeneity [25]. Moreover, prespecified subgroup analyses were stratified by baseline of FEV_1%, 25(OH)D level, co-medication, age (children or adults), dose and duration of vitamin D treatment. And these were conducted to explore the influence and heterogeneity in each outcome. Potential publication bias was failed to perform using funnel plot as each outcome did not reach ten studies. Sensitivity analyses were performed to examine robustness of our results by omitting one study and analyzing the remainders in each turn.

3. Results

3.1. Study Selection

We identified 501 studies using our search strategy. A total of 129 duplicate studies were removed. After titles and abstracts screening, 58 potentially relevant studies were identified. And after reviewing the full-text, 14 studies [12-17,26–33] met our inclusion criteria. A flow chart showing the study selection is presented in Fig. 1.

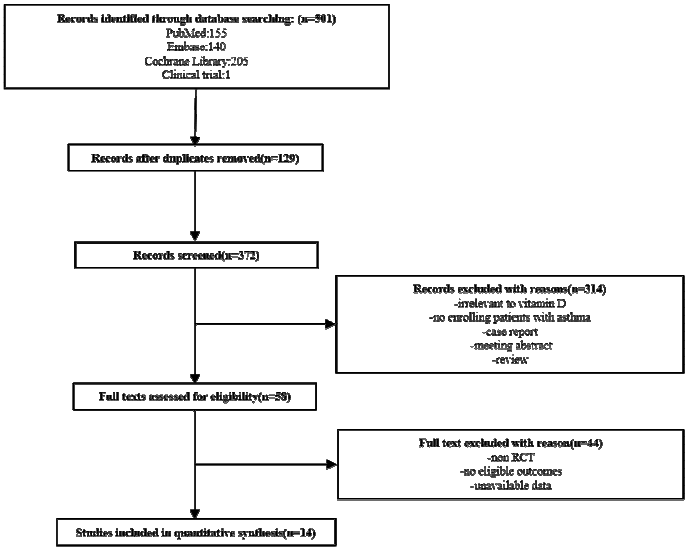

Figure 1 Flowchart for identification of studies used.

3.2. Study Characteristics

The characteristics of the included studies and participants are listed in Table 1 and 2. A total of 1421 participants (711 intervention group and 710 control group) were enrolled. Among fourteen included studies, clinical features of patients were reported in eleven studies of which eight studies [12,14,17,26,29,30-32] described as stable asthma, one [16] as viral-induced asthma, one [28] as nonatopic asthma and one [33] as IgE-dependent asthma. Nine studies [12,14,15,17,26-28,30,32] were conducted in adults, while five [13,16,29,31,33] studies were in children. Regarding the intervention method, four studies [16,17,27,29] compared vitamin D to placebo as a treatment individually, while other studies received vitamin D as an adjunct treatment. With respect to the baseline 25(OH)D level, eleven studies were vitamin D insufficiency [12,13,15-17,26-29,30,32], while two studies were vitamin D sufficiency (25(OH)D > 30ng/ml) [31,33].

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Author Year	Country	N	participants	Intervention			Duration (mo)	Follow-up (mo)	Outcomes
				Drug	Dose	Co-intervention			
Ali2017[12]	Egypt	60	Intermittent to severe persistent asthma	ALF	1mg/d	Intermittent: inhaler 100μg salbutamol Moderate: 12 mg formoterol/ 400 mg theophylline, twice daily severe asthma (>50%): high dose beclomethasone	4	1, 2, 3, 4	FEV_1%, AdE
Musharraf 2017[15]	Pakistan	80	Asthma Diagnosed for≥1 year with VD < 30 ng/ml.	VD	50,000IU/2w	ICS (Salmeterol/fluticasone 25/250μg twice daily) + Montelukast 10mg	3	3	AE
ABBAS2017[26]	Iraq	44	Asthma	VD	2000IU/d	Conventional therapy (no description)	3	3	FEV_1%, IL-10
Rubén2017[17]	Spain	106	Asthma with VD < 30 ng/ml.	CAL	16,000IU/w	None	6	6	AE, ACT
Jensen2016[16]	Canada	22	Viral-induced asthma	VD	100,000 IU	Vitamin D_3 400IU/d	6	0.3, 3, 6	AE, AdE,
Kerley2016[13]	Ireland	39	Uncontrolled asthma	VD	2000IU/d	Conventional therapy (no description)	3.75	3.75	FEV_1%, ACT, IL-10, AdE
Martineau2015[27]	UK	250	Asthma treated with ICS	VD	120000 IU/2mo	None	12	2, 6, 12	FEV_1%, ACT, FeNO, AE
de Groot2015[28]	Netherlands	44	Nonatopic asthma	VD	400,000 IU	Conventional therapy (no description)	1.5	0.25, 1.5	FEV_1%, FeNO, AdE
Nageswari2015 [14]	India	141	Severe persistent asthma	VD	1000 IU/d	ICS (budesonide 800μg + formoterol 24μg) /d	6	1, 2, 3, 4, 5, 6	AdE
Castro2014[32]	US	408	Asthma with VD < 30 ng/ml	VD	100000 IU once then 4000 IU/d	Inhaled ciclesonide 320μg/d + levalbuterol	7	7	AE, AdE
Yoseph2014[29]	Israel	38	Mild asthma with VD < 30	VD	14,000 IU/w	None	1.5	1.5	IL-10, FeNO

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			ng/ml						
Arshi2014[30]	Iran	130	Mild to moderate persistent asthma	VD	100000IU once then 50000IU/w	ICS (budesonide/budesonide+ formoterol)	6	2, 6	FEV_1%, AE,
Majak2011[31]	Poland	48	Newly diagnosed asthma and sensitive only to house dust mites	VD	500 IU/d	Inhaled budesonide 800μg/d	6	2 ,4, 6	FEV_1%, AE,
Majak2009[33]	Poland	36	IgE - dependent asthma with regular symptoms requiring long - term treatment with ICSs, and a disease duration of at least 2 years.	VD	1000IU/d	prednisone 20mg	3,12	3, 12	FEV_1%, IL-10

N = number; mo = month; ALF = alfacalcidol; FEV_1% = predicted percentage of forced expiratory volume in first second; AdE = adverse events; w = week; VD = vitamin D; ICS = inhaled corticosteroids; AE = asthma exacerbation; IL-10 = interleukin-10; CAL= calcifediol; ACT = asthma control test; FeNO = fractional exhaled nitric oxide.

Table 1 Details of included studies.

Author Year	Age (years) Mean (SD)		Sex (Female%)	FEV_1% Mean (SD)		FeNO (ppb) Mean (SD)		ACT Scores Mean (SD)		IL-10 (pg/ml) Mean (SD)		25(OH)D (ng/ml) Mean (SD)	
	I	C		I	C	I	C	I	C	I	C	I	C
Ali2017[12]	43(10.25)	48(11.25)	68.3	57(20.25)	57(20.25)	NM	NM	NM	NM	NM	NM	18(10.33)	18.5(12.8)
Musharraf2017 [15]	29.70(7.74)	29.43(8.47)	42.5	NM	NM	NM	NM	NM	NM	NM	NM	<30	<30
ABBAS2017[26]	41.4 (13.6)	40.75(17.31)	75.0	43.92(20.36)	50.90(16.04)	NM	NM	NM	NM	37.0(8.64)	29.5(5.17)	8.90(6.82)	6.33(4.64)

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Rubén2017[17]	54.57(15.83)	56.61(15.00)	77.7	NM	NM	NM	NM	17.71(4.54)	19.02(4.59)	NM	NM	<30	<30
Jensen2016[16]	2.2 (1.19)	3.1 (1.33)	63.6	NM	NM	NM	NM	NM	NM	NM	NM	24.86 (2.51)	27.27 (2.51)
Kerley2016[13]	10(4.44)	7(2.22)	38.5	105(16.3)	96 (10.37)	NM	NM	19(2.96)	17(3.48)	111 (27.41)	110 (47.41)	20.45 (7.43)	20.45 (8.92)
Martineau2015[27]	49.4(14.8)	46.4 (13.8)	56.4	82.0 (18.7)	81.0 (20.4)	38.1(29.1)	37.0(26.0)	19.2(3.9)	18.9 (3.9)	NM	NM	19.97 (10.1)	19.81 (9.7)
de Groot2015[28]	59(9.7)	53.6(16.7)	40.9	99.1(15.7)	97.6(18.1)	24(12.59)	33(38.52)	NM	NM	NM	NM	24.06 (9.27)	22.85 (8.91)
Nageswari2015 [14]	58.46(8.6)	57.18(9.2)	52.1	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Castro2014[32]	39.9(13.1)	39.5(12.7)	68.1	80.7(13.8)	80.5 (14.2)	NM	NM	NM	NM	NM	NM	19 (10.37)	18.8 (11.85)
Yoseph2014[29]	13.5(3.6)	12.4(3.6)	36.8	NM	NM	36.6(39.1)	58.6(54.7)	NM	NM	0.95(0.19)	0.96(0.19)	20.8(6.5)	20.0(7.1)
Arshi2014[30]	24.40(9.63)	28.64(9.78)	60.8	69.1(9.39)	71.2(7.46)	NM	NM	NM	NM	NM	NM	23.82 (16.33)	24.02 (16.45)
Majak2011[31]	10.8 (3.2)	11.1 (3.3)	33.3	94.4(13)	98.7(12)	NM	NM	NM	NM	NM	NM	36.1 (13.9)	35.1 (16.9)
Majak2009[33]	6-12	6-12	38.9	95.2(4.8)	93.4(3.2)	NM	NM	NM	NM	80.0(20.0)	75.3(25.9)	32.0(3.1)	31.3(3.4)

FEV_1% = predicted percentage of forced expiratory volume in first second; FeNO = fraction of exhaled nitric oxide; ACT = asthma control test; IL-10 = interleukin-10; 25(OH)D = 25-hydroxyvitamin D; SD = standard derivation; NM = not mentioned.

Table 2 Baseline characteristics of patients in the 14 studies included.

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3.3. *Quality assessment*

The risk-of-bias assessment results are shown in Fig.2. Eight studies [12,14-16, 27, 31-33] described the random sequence generation (e.g., a computer-generated random list, randomization table, random allocation software, a computer-generated allocation schedule) and were regarded as a low risk of bias. However, six [13,17,26,28-30] studies were deemed to have an unclear risk of bias for this domain because there was no description in these studies. Three studies [14,16,28] stated the allocation concealment process and eleven study [12,13,15,17,26,27,29-33] was considered as unclear risk of bias, because we were unclear whether the envelopes were concealed. For blinding of participants and personnel and outcome assessment, two studies [26,30] were open-label and there was no description in five studies [13,15,26,29,31]. However, we thought the endpoints were not affected by a lack of blinding. Thus, these seven studies were defined as a low risk of bias. In the domain of incomplete outcome data, one [13] had an unclear risk of bias because of a high rate of loss. Meanwhile, in the domain of other biases, all the studies were deemed to have a low risk except for three studies [15,29,30]. In the domain of selective reporting, all the studies were deemed to have a low risk of bias. The evidence classification results, summarized from the GRADE evidence profile assessed by the GRADEpro software, are presented in Table 3. The associated quality of evidence was rated as very low or low due to risk of bias, heterogeneity and imprecision. Consequently, the results should be interpreted cautiously.

Figure 2 Risk of bias graph for included studies.

Outcome	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Quality of evidence
FEV_1%	RCT	Serious[1]	Very serious[2]	No serious	Serious[3]	Serious[4]	Very Low
Subgroups:							
A	RCT	Serious[1]	No serious	No serious	Serious[3]	No Serious	Low
B	RCT	Serious[1]	Serious[2]	No serious	Serious[3]	No Serious	Low
C	RCT	Serious[1]	No serious	No serious	Serious[3]	No Serious	Low
Adults	RCT	Serious[1]	Serious[2]	No serious	serious[3]	No Serious	Low
Children	RCT	Serious[1]	Serious[2]	No serious	Very serious[3]	Serious	Very Low
Exacerbation	RCT	Serious[1]	No serious	No serious	Serious[3]	Serious[4]	Very Low
Subgroups:							
D	RCT	Serious[1]	No serious	No serious	Serious[3]	No Serious	Low
E	RCT	Serious[1]	No serious	No serious	Serious[3]	Serious[4]	Very Low
Adults	RCT	Serious[1]	No serious	No serious	Serious[3]	No Serious	Low
Children	RCT	Serious[1]	Serious[2]	No serious	Very serious[3]	Serious[4]	Very Low
ACT scores	RCT	Serious[1]	Very serious[2]	No serious	Very serious[3]	No Serious	Very Low
FeNO	RCT	Serious[1]	No serious	No serious	Very serious[3]	No Serious	Very Low
IL-10	RCT	Serious[1]	Very serious[2]	No serious	Very serious[3]	No Serious	Very Low
Adverse events	RCT	Serious[1]	No serious	No serious	Very serious[3]	No Serious	Very Low

FEV_1% = predicted percentage of forced expiratory volume in first second; RCT = randomized controlled trials; VD = vitamin D; ACT = asthma control test; FeNO = fractional exhaled nitric oxide; IL-10 = interleukin-10; A = subgroup of patients with air limitation and vitamin D insufficiency; B = subgroup of patients without air limitation and vitamin D insufficiency; C = subgroup of patients without air limitation and vitamin D sufficiency; D = subgroup of patients with vitamin D insufficiency; E = subgroup of patients with vitamin D sufficiency.

[1] blinding method and selective reporting and other types of some included trials were not offered.

[2] Inconsistency were reported by moderate to high heterogeneity.

[3] The total sample size is much less than OIS and the overall number of events was less than 300.

[4] Publication bias were reported by incomplete outcome data.

Table 3 GRADE assessment of the quality of evidence for endpoints.

3.4. Clinical results

3.4.1. Pulmonary function

Of fourteen studies, eight studies [12,13,26-28,30,31,33] provided data on respiratory function. We demonstrated that there was no significant difference between vitamin D supplementation and placebo (MD: 0.67 95%CI (-3.83, 5.16)), but with a high heterogeneity (P <0.00001 I^2 = 86%) (Fig. 3A).

Pre-specified subgroup analyses were conducted to identify the influence of outcomes and possible sources of heterogeneity. Vitamin D supplementation was associated with a significant improvement of FEV_1% in patients with vitamin D insufficiency and airflow limitation (baseline FEV_1% < 80%) (MD: 8.30 95%CI (5.95, 10.64), without heterogeneity (P = 0.40, I^2 = 0)) (Fig. 3A). No such protective effect was observed among patients without airflow limitation (Fig. 3). Vitamin D supplementation was associated with the FEV_1% improvement in adults (MD: 4.65 95%CI (0.02, 9.28)) but with a high heterogeneity (P=0.006 I^2 = 72%), no such protective effect was seen in children. There was no significant association within subgroups based on different doses or treatment duration of vitamin D, but with a high heterogeneity in the subgroups

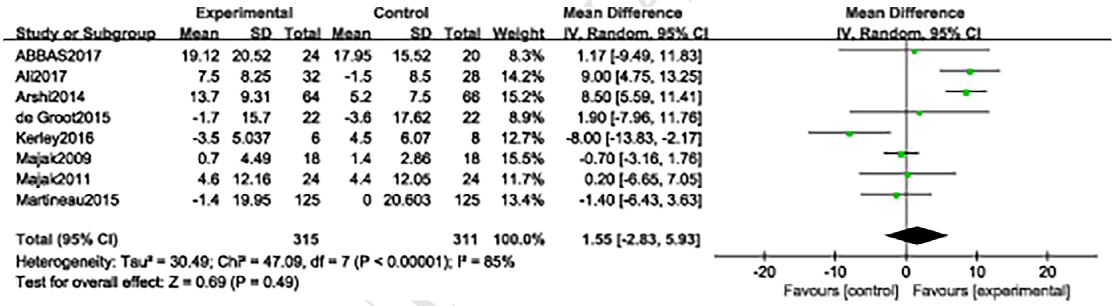

Figure 3 Pooled mean difference for the FEV_1% with 95% confidence intervals of eligible studies comparing vitamin D supplement vs placebo.

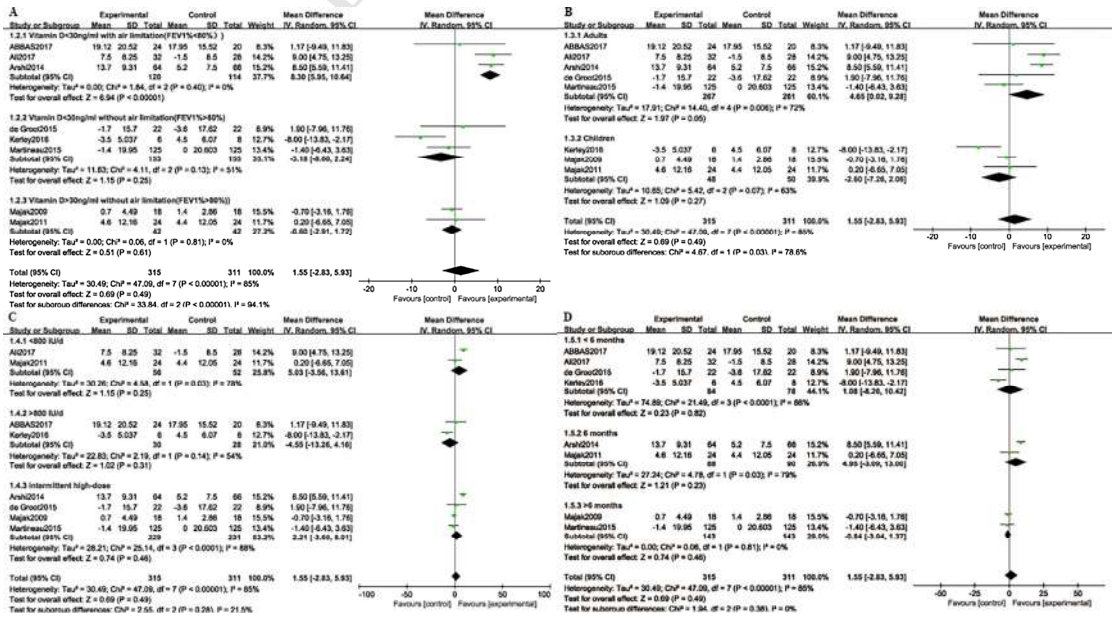

Figure 4 Pooled mean difference for the subgroup analyses of FEV_1% (Panel A: subgroup analysis by baseline status of FEV_1 % and vitamin D; Panel B: subgroup analysis by different ages; Panel C: subgroup analysis by doses of vitamin D; Panel D: subgroup analysis by durations of vitamin D).

3.4.2. Asthma exacerbation

Seven studies [15-17,27,30-32] provided data on asthma exacerbation. Except for one study [31], others included patients with vitamin D insufficiency. Pooled evidence indicated that vitamin D supplementation was associated with a reduction in the rate of exacerbation compared with placebo ((RR:0.73 95%Cl (0.58, 0.92), with low heterogeneity (P = 0.39, I^2 = 5%)) (Fig. 4A).

Evaluations of the influence of prespecified subgroup analyses on exacerbation were conducted. Vitamin D supplementation was associated with a lower rate of asthma exacerbation among those with vitamin D insufficiency ((RR:0.76 95%Cl (0.61, 0.95), with no heterogeneity (P = 0.52, I^2 = 0%)). However, there was only one study in the subgroup of vitamin D sufficiency, and showed a consistent effect on exacerbation. With respect to different ages, we obtained a significant reduction in the rate of exacerbation in adults ((RR:0.75 95%Cl (0.59, 0.95), with no heterogeneity (P = 0.41, I^2 = 0%)), but no such protective effect in children. Besides, it may be associated with a lower rate of exacerbation in the subgroup of less than six months of vitamin D treatment, which only contained one trial (RR: 0.43 95%Cl (0.22, 0.82)). Nevertheless, there was no significant association of other treatment durations and different doses of vitamin D with asthma exacerbation.

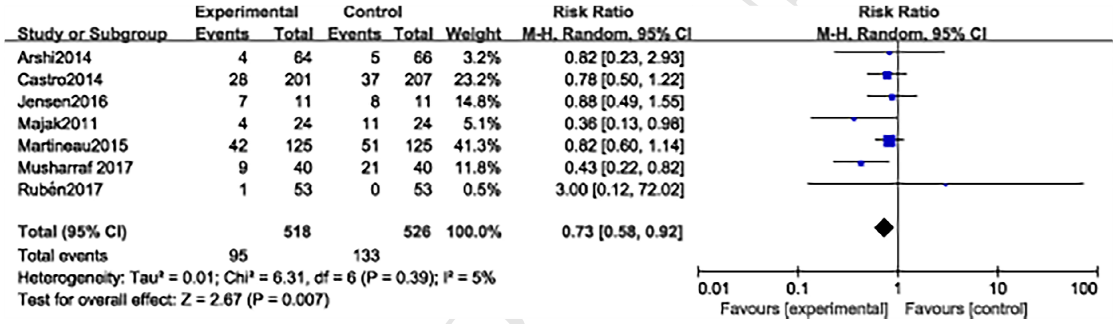

Figure 5 Pooled relative risk for asthma exacerbation with 95% confidence intervals of eligible studies comparing vitamin D versus placebo.

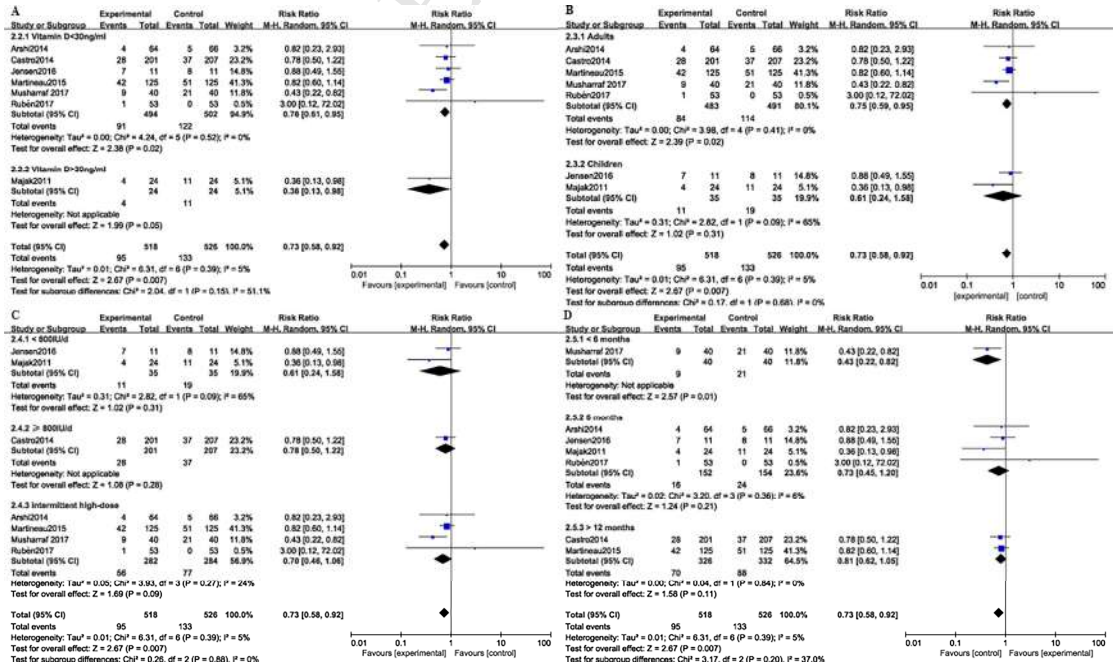

Figure 6 Pooled relative risk for the subgroup analyses of asthma exacerbation (Panel A: subgroup analysis by baseline status of vitamin D; Panel B: subgroup analysis by different ages; Panel C: subgroup analysis by doses of vitamin D; Panel D: subgroup analysis by durations of vitamin D).

3.4.3. Asthma control test (ACT) scores

Three studies [13,17,27] provided data on ACT scores. The pooled data indicated there was no significant difference between vitamin D and placebo groups (MD: 0.80,95%Cl (-2.61, 4.22), with high heterogeneity (P = 0.0006, I^2 = 86%)) (Table.4).

3.4.4. Fractional exhaled nitric oxide (FeNO)

Data on FeNO were available in three studies [27-29]. There was no significant difference between the two groups in terms of the effect on FeNO (MD: 1.86 ,95%Cl (-4.59, 8.32), without heterogeneity (P = 0.88, I^2 = 0)) (Table 4).

3.4.5. Interleukin-10(IL-10)

Four studies [13,26,29,33] provided data on IL-10. Because of the considerable differences in means among included trials, we chose the SMD with 95% CI as the pooled statistic. No difference was found between vitamin D and placebo groups regarding the effect on IL-10 (SMD: 0.46, 95%Cl (-0.44, 1.36), with high heterogeneity (P < 0.0001, I^2 = 86%)) (Table 4).

3.4.6. Safety

Six studies [12-14,16,28,32] investigated the incidence of adverse events. The pooled analysis showed no significant difference between groups regarding the rate of any serious adverse events (RR 0.87, 95% CI (0.41,1.81), without heterogeneity (P = 0.61, I^2 = 0)) (Table 4).

Outcome	Studies	N	Estimate	Effect(95%CI)	I^2%(P)
ACT scores	13,17,28	395	MD	0.16 (-2.62, 2.30)	81% (0.005)
FeNO	28-30	331	MD	1.86 (-4.59, 8.32)	0% (0.88)
IL-10	13,27,30,35	157	SMD	0.46 (-0.44, 1.36)	86% (0.0001)
Adverse event	12-14,16,29,34	714	RR	0.87 (0.41,1.81)	0% (0.61)

CI = confidence interval; ACT = asthma control test; IL-10 = interleukin-10; FeNO = fractional exhaled nitric oxide; MD = mean difference; SMD = Standardized mean difference; RR = risk ratio; N = number of subjects.

Table 4 Effect of vitamin D supplementation vs placebo on different asthma outcomes.

3.4.7. Sensitivity Analysis

Sensitive analysis of primary outcomes was conducted by STATA (12.0) software, the findings showed that our results were consistent with the full analysis for all endpoints after excluding each individual study (Table 5).

Outcome	Imputing coefficient	Effect estimate (95% CI)
FEV_1%	-0.639	(-5.414, 4.136)
	2.013	(-2.409, 6.435)
Exacerbation	0.671	(0.489, 0.919)

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	0.790	(0.629, 0.993)
ACT scores	-1.549	(-5.168, 2.070)
	0.970	(-1.222, 3.163)
FeNO	1.284	(-5.739, 8.307)
	5.054	(-8.926,19.034)
IL-10	0.054	(-0.571, 0.680)
	0.820	(-0.060, 1.699)
Adverse events	0.738	(0.343， 1.590)
	1.084	(0.104,11.260)

CI = confidence interval; FEV_1% = predicted percentage of forced expiratory volume in first second; ACT = asthma control test; IL-10 = interleukin-10; FeNO = fraction of exhaled nitric oxide

Table 5 Sensitivity analysis with highest and lowest correlation coefficients.

4. Discussion:

In this meta-analysis, fourteen studies demonstrated that vitamin D supplementation for the management of asthma was associated with a lower rate of exacerbation. It had no association with FEV_1%, ACT scores, FeNO, IL-10 and adverse events. In addition, the subgroup analyses of primary outcomes suggested that vitamin D supplementation would not be of help in all patients with bronchial asthma but in a certain group of patients those with vitamin D insufficiency at baseline.

Subgroup analysis of different baseline status of vitamin D was performed according to the Endocrine Society that defined vitamin D deficiency and insufficiency as a 25(OH)D < 30ng/ml [34]. It revealed that vitamin D supplementation was associated with a protective effect of exacerbation in participants with vitamin D insufficiency. However, there was only one study in the subgroup of patients with vitamin D sufficiency, and it suggested that there was a significant improvement of vitamin D supplementation upon asthma exacerbation. Nevertheless, it was considered insufficient to judge the positive effect of vitamin D supplementation for patients with vitamin D sufficiency. It was also associated with FEV_1% improvement in patients with air limitations and vitamin D insufficiency. With regards to different ages, we found that vitamin D supplementation might be associated with a lower rate of exacerbation and an improved pulmonary function in adults, but it did not have such positive effect on children. The small number of trials included children have a lower statistical power to extend the findings to all children. The probable explanation for the negative effect on children may be that, pulmonary function related outcomes were reported by three studies [13,31,33] in children. Its baseline status of FEV_1% was much greater than the patients in studies with adults. As a result, it left little room for improvement in pulmonary function. Another possible explanation may be that negative results were driven by varied baseline of vitamin D status among patients in the studies with children. Inversely, patients were all vitamin D insufficiency in the studies with adults. In a recently concluded nationwide study, it was found a consistent result that vitamin D insufficiency was associated with current asthma and wheeze in children as well as current asthma in adults [35]. Moreover, our subgroup analyses did not provide evidence about optimum doses and duration of vitamin D supplementation. The subgroup analysis of co-medicines was not performed due to unavailability of suitably disaggregated data.

There is plenty of evidence to support our results that vitamin D acts on the cells of the innate and adaptive immune systems as well as on structural cells in the airways, with its deficiency promoting inflammation and its supplementation alleviating these effects [3.4.6]. Our results are consistent with what many [36-39] have suggested that vitamin D supplementation had the capacity to reduce asthma exacerbations and improve asthma control, especially in patients with severe asthma and low vitamin D status. It is more readily explicable, based on the principle that people who are the most deficient in a micronutrient will be the most likely to respond to its replacement. However, our results may be inconsistent with other studies entirely. A recently cross-sectional study [40] found no association between vitamin D status and markers of asthma severity or control in adults. The potential explanation of inconsistent results was that the majority of including participants were adults with generally better symptom control. It also confirmed by another cross-sectional study [41] that the incidence of severe vitamin D insufficiency was high.

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So far, six meta-analyses incorporating data from trials of vitamin D for the management of asthma have been done. Compared with them, our meta-analysis has several strengths. First, additional five studies were included in the current meta-analysis. Thus, the merging effect measures were more meaningful for our outcomes. Five studies were excluded, which were included in prior meta-analyses [20-22], one [42] was to detect steroid-induced bone loss in adult patients with asthma, another [43] was a randomized, two-period crossover trial with run-in and washout periods, which recruited different populations. In addition, three studies [44-46] did not meet our inclusion criteria for solely patients with asthma. Second, former meta-analysis failed to detect the source of heterogeneity and influence factors owing to the small number of remaining studies within each subcategory. In present meta-analysis, subgroup analyses were stratified by baseline of FEV_1%, 25(OH)D level, ages, different doses and durations of vitamin D supplementation. High heterogeneity of outcome in pulmonary function was resolved by subgroup analyses as well. These analyses make the results more meaningful for clinical decisions of asthma treatment. In view of the small number of patients in the second outcomes, sampling error was probably the main reason for the heterogeneity. Third, a sensitivity analysis on outcomes generated similar results, which indicated that results of the present meta-analysis were robustness.

Our meta-analysis also has several limitations. First, there is considerable variation in the definition of exacerbation. Except two studies [17, 30], all of studies presented the definition of asthma exacerbation. However, there was no significant heterogeneity in the outcome of exacerbation. Second, our meta-analysis included studies varied in relation to the study population, control medicines of asthma, duration of treatment, which might contribute to potential confounders for accurate inclusions. Consequently, we conducted subgroup analyses according to these factors and performed analysis using a random-effect model to avoid type □ error. Confidence intervals for the average intervention effect would be wider and corresponding claims of statistical significance would be more conservative. Equally, the uncertainty is greater. Third, it was limited for our study to permit the funnel plot or meta-regression to assess the publication bias and potential influencing factors. Fourthly, our meta-analysis incorporated evidence from a relatively small number of studies and the finding was based primarily on results of trials conducted in patients with stable asthma. Therefore, it should not be generalized to patients with acute asthma. Finally, small sample sizes, clinical heterogeneity, or a combination of above factors' controversy have emerged among results of numerous studies, besides, optimal dosage and duration of vitamin D necessary for good control of asthma symptoms are yet unknown. All these aspects reinforce the need to perform larger, well designed randomized controlled trials to clarify causality for treatment of asthma and vitamin D supplementation.

In conclusion, our meta-analysis elucidated that vitamin D supplementation played a role in reducing the rate of asthma exacerbation, particularly in patients with vitamin D insufficiency. Additionally, it also had an improvement on FEV_1% in patients with air limitation and vitamin D insufficiency. Through the assessment for ACT scores, FeNO and IL-10, vitamin D supplementation was non-inferior to placebo. As a potential therapeutic option, vitamin D supplementation represents a low-cost, low-risk method to treat and control asthma. Therefore, larger and well-designed RCTs are required to evaluate the role of vitamin D in identical medication dose and administration duration of asthma.

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Conflicts of interest

None

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Role of authors:

Mingming Wang and Gang Cheng were engaged in design, interpretation of data, statistical analyses and drafting of the manuscript.

Cairu Wang and Yue Xiao were responsible for data extraction, statistical analyses, interpretation of data and administrative and technical support.

Meicen Liu and Meijuan Zou were responsible for conception and critical revision of the manuscript.

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Author Year	Country	N	participants	Intervention			Duration (mo)	Follow-up (mo)	Outcomes
				Drug	Dose	Co-intervention			
Ali2017[12]	Egypt	60	Intermittent to severe persistent asthma	ALF	1mg/d	Intermittent: inhaler 100μg salbutamol Moderate: 12 mg formoterol/ 400 mg theophylline, twice daily severe asthma (>50%): high dose beclomethasone	4	1, 2, 3, 4	FEV_1%, AdE
Musharraf 2017[15]	Pakistan	80	Asthma Diagnosed for≥1 year with VD < 30 ng/ml.	VD	50,000IU/2w	ICS (Salmeterol/fluticasone 25/250μg twice daily) + Montelukast 10mg	3	3	AE
ABBAS2017[26]	Iraq	44	Asthma	VD	2000IU/d	Conventional therapy (no description)	3	3	FEV_1%, IL-10
Rubén2017[17]	Spain	106	Asthma with VD < 30 ng/ml.	CAL	16,000IU/w	None	6	6	AE, ACT
Jensen2016[16]	Canada	22	Viral-induced asthma	VD	100,000 IU	Vitamin D_3 400IU/d	6	0.3, 3, 6	AE, AdE,
Kerley2016[13]	Ireland	39	Uncontrolled asthma	VD	2000IU/d	Conventional therapy (no description)	3.75	3.75	FEV_1%, ACT, IL-10, AdE
Martineau2015[27]	UK	250	Asthma treated with ICS	VD	120000 IU/2mo	None	12	2, 6, 12	FEV_1%, ACT, FeNO, AE
de Groot2015[28]	Netherlands	44	Nonatopic asthma	VD	400,000 IU	Conventional therapy (no description)	1.5	0.25, 1.5	FEV_1%, FeNO, AdE
Nageswari2015 [14]	India	141	Severe persistent asthma	VD	1000 IU/d	ICS (budesonide 800μg + formoterol 24μg) /d	6	1, 2, 3, 4, 5, 6	AdE
Castro2014[32]	US	408	Asthma with VD < 30 ng/ml	VD	100000 IU once then 4000 IU/d	Inhaled ciclesonide 320μg/d + levalbuterol	7	7	AE, AdE
Yoseph2014[29]	Israel	38	Mild asthma with VD < 30	VD	14,000 IU/w	None	1.5	1.5	IL-10, FeNO

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			ng/ml						
Arshi2014[30]	Iran	130	Mild to moderate persistent asthma	VD	100000IU once then 50000IU/w	ICS (budesonide/budesonide+ formoterol)	6	2, 6	FEV_1%, AE,
Majak2011[31]	Poland	48	Newly diagnosed asthma and sensitive only to house dust mites	VD	500 IU/d	Inhaled budesonide 800μg/d	6	2 ,4, 6	FEV_1%, AE,
Majak2009[33]	Poland	36	IgE - dependent asthma with regular symptoms requiring long - term treatment with ICSs, and a disease duration of at least 2 years.	VD	1000IU/d	prednisone 20mg	3,12	3, 12	FEV_1%, IL-10

N = number; mo = month; ALF = alfacalcidol; FEV_1% = predicted percentage of forced expiratory volume in first second; AdE = adverse events; w = week; VD = vitamin D; ICS = inhaled corticosteroids; AE = asthma exacerbation; IL-10 = interleukin-10; CAL= calcifediol; ACT = asthma control test; FeNO = fractional exhaled nitric oxide.

Table 1 Details of included studies.

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Author Year	Age (years) Mean (SD)		Sex (Female%)	FEV_1% Mean (SD)		FeNO (ppb) Mean (SD)		ACT Scores Mean (SD)		IL-10 (pg/ml) Mean (SD)		25(OH)D (ng/ml) Mean (SD)	
	I	C		I	C	I	C	I	C	I	C	I	C
Ali2017[12]	43(10.25)	48(11.25)	68.3	57(20.25)	57(20.25)	NM	NM	NM	NM	NM	NM	18(10.33)	18.5(12.8)
Musharraf2017 [15]	29.70(7.74)	29.43(8.47)	42.5	NM	NM	NM	NM	NM	NM	NM	NM	<30	<30
ABBAS2017[26]	41.4 (13.6)	40.75(17.31)	75.0	43.92(20.36)	50.90(16.04)	NM	NM	NM	NM	37.0(8.64)	29.5(5.17)	8.90(6.82)	6.33(4.64)
Rubén2017[17]	54.57(15.83)	56.61(15.00)	77.7	NM	NM	NM	NM	17.71(4.54)	19.02(4.59)	NM	NM	<30	<30
Jensen2016[16]	2.2 (1.19)	3.1 (1.33)	63.6	NM	NM	NM	NM	NM	NM	NM	NM	24.86 (2.51)	27.27 (2.51)
Kerley2016[13]	10(4.44)	7(2.22)	38.5	105(16.3)	96 (10.37)	NM	NM	19(2.96)	17(3.48)	111 (27.41)	110 (47.41)	20.45 (7.43)	20.45 (8.92)
Martineau2015[27]	49.4(14.8)	46.4 (13.8)	56.4	82.0 (18.7)	81.0 (20.4)	38.1(29.1)	37.0(26.0)	19.2(3.9)	18.9 (3.9)	NM	NM	19.97 (10.1)	19.81 (9.7)
de Groot2015[28]	59(9.7)	53.6(16.7)	40.9	99.1(15.7)	97.6(18.1)	24(12.59)	33(38.52)	NM	NM	NM	NM	24.06 (9.27)	22.85 (8.91)
Nageswari2015 [14]	58.46(8.6)	57.18(9.2)	52.1	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Castro2014[32]	39.9(13.1)	39.5(12.7)	68.1	80.7(13.8)	80.5 (14.2)	NM	NM	NM	NM	NM	NM	19 (10.37)	18.8 (11.85)
Yoseph2014[29]	13.5(3.6)	12.4(3.6)	36.8	NM	NM	36.6(39.1)	58.6(54.7)	NM	NM	0.95(0.19)	0.96(0.19)	20.8(6.5)	20.0(7.1)

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Arshi2014[30]	24.40(9.63)	28.64(9.78)	60.8	69.1(9.39)	71.2(7.46)	NM	NM	NM	NM	NM	NM	23.82 (16.33)	24.02 (16.45)
Majak2011[31]	10.8 (3.2)	11.1 (3.3)	33.3	94.4(13)	98.7(12)	NM	NM	NM	NM	NM	NM	36.1 (13.9)	35.1 (16.9)
Majak2009[33]	6-12	6-12	38.9	95.2(4.8)	93.4(3.2)	NM	NM	NM	NM	80.0(20.0)	75.3(25.9)	32.0(3.1)	31.3(3.4)

FEV_1% = predicted percentage of forced expiratory volume in first second; FeNO = fraction of exhaled nitric oxide; ACT = asthma control test; IL-10 = interleukin-10; 25(OH)D = 25-hydroxyvitamin D; SD = standard derivation; NM = not mentioned.

Table 2 Baseline characteristics of patients in the 14 studies included.

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Outcome	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Quality of evidence
FEV_1%	RCT	Serious[1]	Very serious[2]	No serious	Serious[3]	Serious[4]	Very Low
Subgroups:							
A	RCT	Serious[1]	No serious	No serious	Serious[3]	No Serious	Low
B	RCT	Serious[1]	Serious[2]	No serious	Serious[3]	No Serious	Low
C	RCT	Serious[1]	No serious	No serious	Serious[3]	No Serious	Low
Adults	RCT	Serious[1]	Serious[2]	No serious	serious[3]	No Serious	Low
Children	RCT	Serious[1]	Serious[2]	No serious	Very serious[3]	Serious	Very Low
Exacerbation	RCT	Serious[1]	No serious	No serious	Serious[3]	Serious[4]	Very Low
Subgroups:							
D	RCT	Serious[1]	No serious	No serious	Serious[3]	No Serious	Low
E	RCT	Serious[1]	No serious	No serious	Serious[3]	Serious[4]	Very Low
Adults	RCT	Serious[1]	No serious	No serious	Serious[3]	No Serious	Low
Children	RCT	Serious[1]	Serious[2]	No serious	Very serious[3]	Serious[4]	Very Low
ACT scores	RCT	Serious[1]	Very serious[2]	No serious	Very serious[3]	No Serious	Very Low
FeNO	RCT	Serious[1]	No serious	No serious	Very serious[3]	No Serious	Very Low
IL-10	RCT	Serious[1]	Very serious[2]	No serious	Very serious[3]	No Serious	Very Low
Adverse events	RCT	Serious[1]	No serious	No serious	Very serious[3]	No Serious	Very Low

FEV_1% = predicted percentage of forced expiratory volume in first second; RCT = randomized controlled trials; VD = vitamin D; ACT = asthma control test; FeNO = fractional exhaled nitric oxide; IL-10 = interleukin-10; A = subgroup of patients with air limitation and vitamin D insufficiency; B = subgroup of patients without air limitation and vitamin D insufficiency; C = subgroup of patients without air limitation and vitamin D sufficiency; D = subgroup of patients with vitamin D insufficiency; E = subgroup of patients with vitamin D sufficiency.

[1] blinding method and selective reporting and other types of some included trials were not offered.

[2] Inconsistency were reported by moderate to high heterogeneity.

[3] The total sample size is much less than OIS and the overall number of events was less than 300.

[4] Publication bias were reported by incomplete outcome data.

Table 3 GRADE assessment of the quality of evidence for endpoints.

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Outcome	Studies	N	Estimate	Effect(95%CI)	I^2%(P)
ACT scores	13,17,28	395	MD	0.16 (-2.62, 2.30)	81% (0.005)
FeNO	28-30	331	MD	1.86 (-4.59, 8.32)	0% (0.88)
IL-10	13,27,30,35	157	SMD	0.46 (-0.44, 1.36)	86% (0.0001)
Adverse event	12-14,16,29,34	714	RR	0.87 (0.41,1.81)	0% (0.61)

CI = confidence interval; ACT = asthma control test; IL-10 = interleukin-10; FeNO = fractional exhaled nitric oxide; MD = mean difference; SMD = Standardized mean difference; RR = risk ratio; N = number of subjects.

Table 4 Effect of vitamin D supplementation vs placebo on different asthma outcomes.

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Outcome	Imputing coefficient	Effect estimate (95% CI)
FEV_1%	-0.639	(-5.414, 4.136)
	2.013	(-2.409, 6.435)
Exacerbation	0.671	(0.489, 0.919)
	0.790	(0.629, 0.993)
ACT scores	-1.549	(-5.168, 2.070)
	0.970	(-1.222, 3.163)
FeNO	1.284	(-5.739, 8.307)
	5.054	(-8.926,19.034)
IL-10	0.054	(-0.571, 0.680)
	0.820	(-0.060, 1.699)
Adverse events	0.738	(0.343，1.590)
	1.084	(0.104,11.260)

CI = confidence interval; FEV_1% = predicted percentage of forced expiratory volume in first second; ACT = asthma control test; IL-10 = interleukin-10; FeNO = fraction of exhaled nitric oxide

Table 5 Sensitivity analysis with highest and lowest correlation coefficients.

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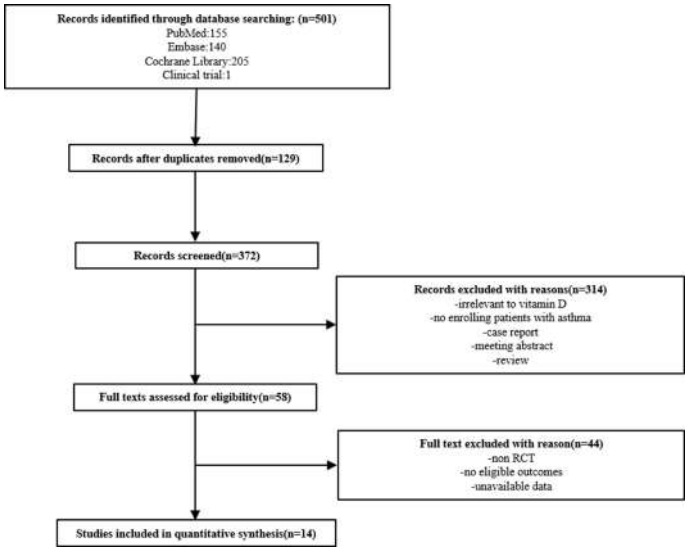

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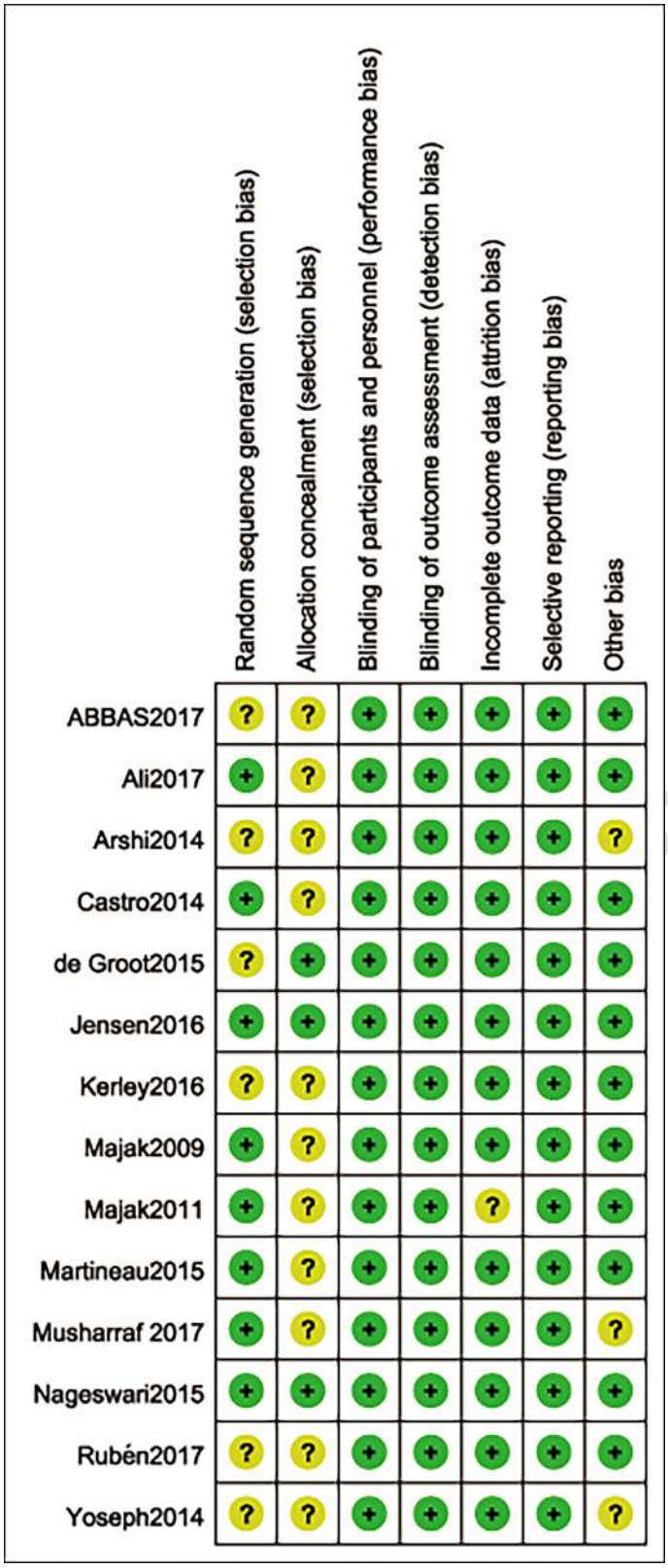

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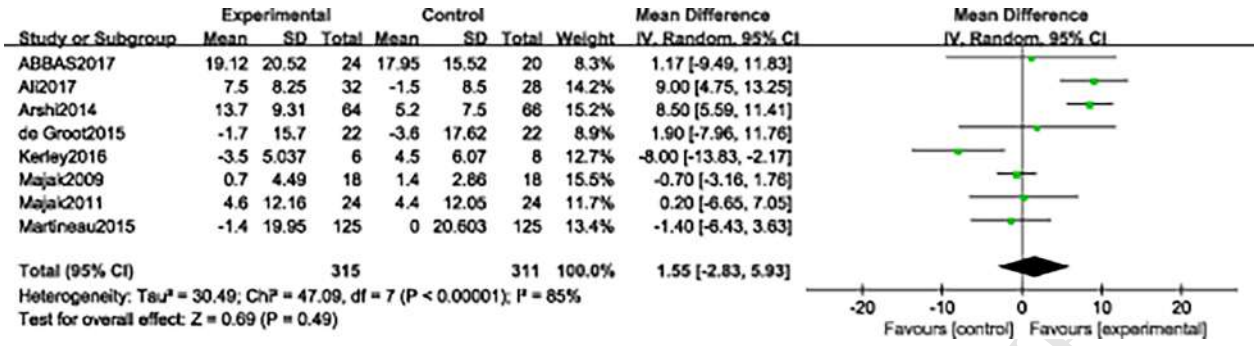

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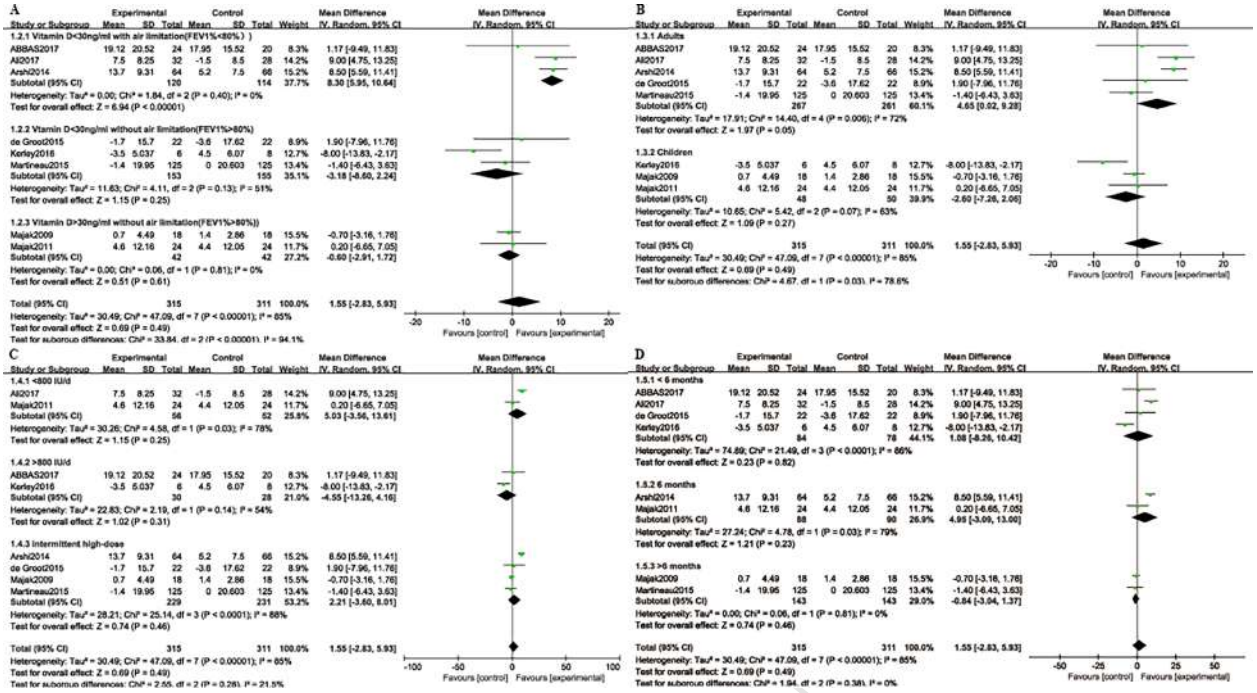

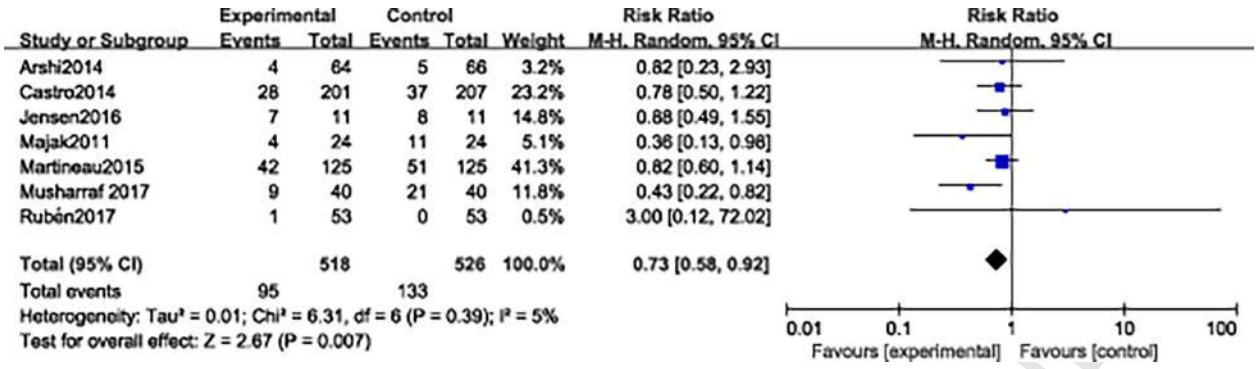

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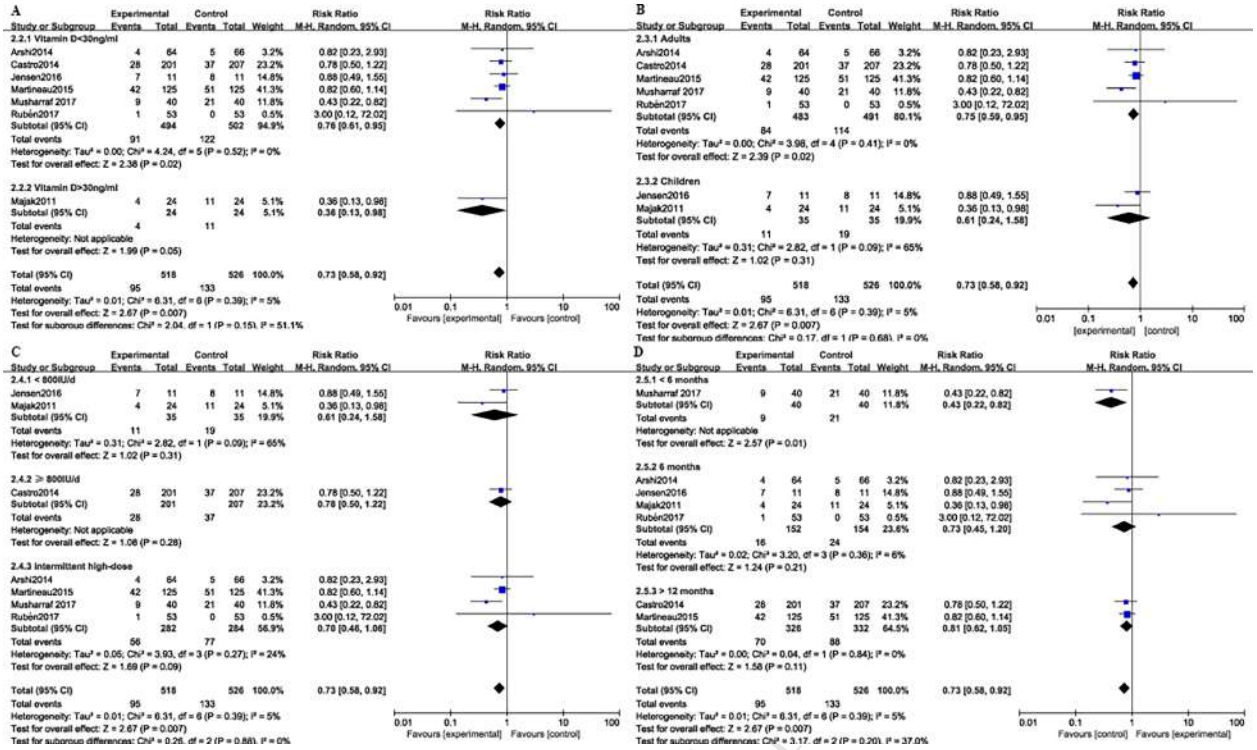

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Highlights

Vitamin D may be an adjunct therapy for a certain group of patients with asthma.

We evaluated the influence of baseline vitamin D status on asthma-related outcomes.

Treatment effect was found in patients with air limitation and vitamin D insufficiency.

More RCTs are required to evaluate the identical dose and duration of vitamin D.

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Conflict of interest statement

We declare that we have no financial and personal relationships with other people or organizations that can inappropriately influence the work submitted, there is no professional or other personal interest of any nature or kind in any product, service and/or company that could be construed as influencing the position presented in, or the review of, the manuscript entitled, “ Association between vitamin D status and asthma control: a meta-analysis of randomized trials ”.

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