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Early View

Original research article

Vitamin D Supplementation in Childhood Asthma: A Systematic Review and Meta-analysis of Randomised Controlled Trials

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Title: Vitamin D Supplementation in Childhood Asthma: A Systematic Review and Meta-analysis of Randomized Controlled Trials

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Take-Home Message

Very low to moderate certainty evidence suggests that adjuvant vitamin D supplementation might not have any protective effect in childhood asthma. Therefore, routine vitamin D supplementation in asthmatic children should be avoided.

ABSTRACT

Background: There is conflicting evidence for vitamin D supplementation in childhood asthma. We aimed to systematically synthesize the evidence on the efficacy and safety of vitamin D supplementation in childhood asthma.

Methods: We searched electronic databases (Medline, Embase, Web of Science) and register (CENTRAL) for randomized controlled trials (RCTs) published until September 30, 2021. RCTs enrolling asthmatic children (1-18 years) and comparing vitamin D against placebo/routine care were included if they met at least one of the endpoints of interest (asthma attacks, emergency visits, hospitalization). We used the Risk of Bias (RoB) 2 tool for risk of bias assessment. Random-effects meta-analysis with RevMan 5.3 software was done. The GRADE approach was used to assess the level of certainty of the evidence.

Results: Eighteen RCTs (n=1579 participants) were included. The pooled meta-analysis did not find a significant effect of vitamin D supplementation on asthma attacks requiring rescue systemic corticosteroids (6 studies, 445 participants, Risk ratio: 1.13; 95% CI: 0.86 to 1.48, I^2-0%) (Moderate-certainty evidence). In addition, there was no significant difference in the proportion of children with asthma attacks of any severity (11 trials, 1132 participants, RR:0.84; 95% CI: 0.65 to 1.09; I^2-58%) (Very-low certainty evidence). Vitamin D does not reduce the need for emergency visits (3 studies, 361 participants, RR:0.97; 95% CI: 0.89 to 1.07, I^2-0%) and hospitalization (RR:1.38; 95% CI: 0.52 to 3.66, I^2-0%) (Low certainty evidence).

Conclusion: Very low to moderate certainty evidence suggests that vitamin D supplementation might not have any protective effect in childhood asthma.

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Keywords: Asthma, Bronchodilator, Exacerbation, Pulmonary functions, Vitamin D.

INTRODUCTION

Asthma is the most common chronic disease affecting 5-30% of children [1–4]. Almost 50% of asthmatic children experience one or more acute attacks in a year, making it the third leading cause of hospitalization and the top-most reason for missing school in children [2–4]. Asthma attacks are mediated by proinflammatory cytokines such as interleukin (IL)-13,17A and Interferon-gamma [5–7]. Vitamin D has immunomodulatory properties; therefore, it might have a role in asthma control [5, 7].

Observational studies showed an association between a low 25(OH)D and an increased risk for asthma attacks in children [5]. These findings paved the way for randomized controlled trials (RCT's) to assess the therapeutic potential of vitamin D supplementation. Initial RCTs showed a favorable response with vitamin D supplementation [8–11]. Riverin et al. found low-quality evidence favoring vitamin D supplementation; however, they suggested further studies before its routine use [12]. Subsequent meta-analyses of adults and children suggested potential benefits with vitamin D supplementation in asthmatic patients [7, 13]. However, recent RCTs did not find a significant advantage in children [14–17]. Because of these conflicting results, there is a need to review and update the existing evidence systematically.

We aimed to evaluate the benefits and risks of vitamin D supplementation as adjunct therapy on acute asthma attacks requiring rescue systemic corticosteroids, emergency visits, hospitalization, pulmonary functions, and adverse effects of vitamin D supplementation in asthmatic children and adolescents (up to 18 years).

METHODS

Search strategy and Selection Criteria

This review was done following the guidance from the Cochrane Handbook for Systematic Reviews of Interventions [18] and is reported in compliance with Preferred Reporting Items for Systematic Reviews and Meta-analyses 2020 guidelines [19]. The review was prospectively registered with PROSPERO (CRD42021229450). We included RCTs meeting all the following criteria: (i) Population: Children aged 1-18 years diagnosed with bronchial asthma, (ii) Intervention: Vitamin D supplementation as an adjunct to asthma-specific therapy, (iii) Comparison: Either placebo or control group. The control group should not receive vitamin D above the maintenance dose (400 IU/day) recommended for healthy children [20, 21]. We allowed maintenance of 400 IU/day in the control group because some authors consider it unethical to withhold maintenance vitamin D in children with known vitamin D deficiency or whose vitamin D status is not known at enrolment. As vitamin D is fat-soluble and has a long half-life in tissue, a washout of at least four weeks is desirable [22, 23]. Therefore, cross-over trials with a short washout period were excluded.

Two authors (JK, JPG) developed a search strategy using database-specific index terms/subject headings and free words. The search strategy comprised of terms related to the study population (children aged 1-18 years with bronchial asthma), intervention (vitamin D), and study design (RCT). We used variable keywords, entry terms, word variations, and synonyms to improve the sensitivity (e Table 1). Two authors (JPG, JM) reviewed the search strategy using the Peer Review of Electronic Search Strategies checklist.

Two investigators (JK, JM) independently performed a literature search in Medline (by PubMed), Embase, Web of Science, and CENTRAL for RCTs published until September 30, 2021. The electronic search was supplemented by a manual search of the bibliography of relevant reports to identify additional studies. We also searched various registries (until 30

September 2021), namely ClinicalTrials.gov (https://clinicaltrials.gov/ct2/home), Clinical Trial Registry of India (http://ctri.nic.in/), Australian New Zealand clinical trials registry (http://www.anzctr.org.au/), and EU Clinical Trials Register (https://www.clinicaltrialsregister.eu/). We did not use any language restrictions or filters.

Initially, two researchers (JPG, CT) independently screened the titles and/or abstracts to identify potentially eligible reports. Later two researchers (CT, PK) thoroughly examined the full text of these reports and identified reports meeting all the inclusion criteria. If a study had more than two arms, but each component tested one drug only, we used arms comparing vitamin D and placebo/control. Whereas, for studies using a combination of active interventions (like vitamin D + Immunotherapy *vs.* Immunotherapy *vs.* placebo), we used data from the arms with similar interventions except for vitamin D (like vitamin D + Immunotherapy *vs.* Immunotherapy alone in the above example). We excluded studies with an additional active intervention (other than vitamin D and standard pharmacological management of asthma) in the treatment arm (like immunotherapy or probiotics) which is not used in the placebo arm because the effects cannot be attributed to vitamin D alone.

Outcomes

Our primary outcome was the proportion of children requiring rescue systemic (Intravenous/ oral) corticosteroids for asthma attacks. We chose this primary outcome as it is the most robust and clinically meaningful outcome, representing moderate to severe asthma attacks, and is widely used [7, 13]. Secondary outcomes included the proportion of patients with at least one asthma attack of any severity, asthma attacks requiring unscheduled/emergency visits, hospitalization, need for rescue therapy (beta-2 agonists), asthma control as assessed by scores like Childhood asthma control test (C-ACT), Asthma control test (ACT), and Global Initiative for Asthma (GINA), improvement in pulmonary functions, and adverse effects. Since there

was wide variability in defining asthma attacks (e Table 2), we used the authors' reported outcome (irrespective of definition or severity) [24].

Data analysis

Two researchers (PC, CT) independently extracted data from the eligible reports. The data comprised first author name, year of publication, study design, setting, methodology, participant characteristics, inclusion and exclusion criteria, intervention and control group details, follow-up schedule, and outcomes (as mentioned above). Disagreement was resolved through discussion with an expert (JPG). Two researchers (JK, PK) independently rechecked the accuracy and completeness of extracted data. We came across an individual participant data meta-analysis (IPD-MA) [7] with five studies [8, 11, 21, 25, 26] in common with our review. To improve the robustness, we used some of the data (not provided in original reports) from this IPD-MA.

Two researchers (JK, JPG) independently assessed the risk of bias with the *Risk of Bias 2 (RoB2) tool* and generated traffic plots and summary plots using the online robvis visualization tool [27]. Any discrepancy among them was resolved through mutual discussion.

We provided a quantitative and qualitative synthesis of primary and secondary outcomes. We did the quantitative synthesis for the outcomes reported in at least two trials in the desired format. Median (Interquartile range/ 95% CI) was converted to Mean (SD) using appropriate conversion formulas and RevMan calculator [18]. The dichotomous outcomes are reported as risk ratio (RR) with 95% CI and continuous data as mean difference (MD) with 95% CI. We used the RevMan version5.4 and STATA version 14.2 (College Station, Texas, USA) software for statistical analysis. Considering inherent heterogeneity among trials, we used a random-effects model for quantitative synthesis. Heterogeneity among studies was assessed by Chi-square test on Cochrane's Q statistics and quantified using I^2 statistics. Egger's test and Funnel plots were used to evaluate publication bias. As decided a priori, we did sensitivity analysis for

risk of bias. We also did random-effects meta-regression analysis for sample size, cumulative vitamin D dosage (which takes care of both dose and duration), active treatment use in the control group (some used maintenance dose of vitamin D), and co-treatments. We followed GRADE recommendations for assessing the level of certainty of the evidence [28].

RESULTS

We identified 974 records, of which 303 were duplicates (Figure 1). The remaining 671 records were screened through title and/or abstract, and 179 reports were considered for full-text retrieval. After reading the complete text, we excluded 161 reports. The foremost reasons for excluding full-text reports were incorrect study design (case-control, cohort, or cross-over), reviews (narrative or systematic), duplicate reports (most were conference abstracts), and study protocols (Supplementary File). We identified one additional eligible study [29] through citation searching. One study has two reports; therefore, it was considered a single study and summarized the findings under the main study [16, 30]. Finally, we included 18 trials [8–11, 14–17, 21, 25, 26, 29, 31–36] (1579 participants), of which one is published as abstract only [10]. We excluded one cross-over trial with a shorter washout period [37].

Study Characteristics

Fifteen RCTs were blinded controlled parallel-group trials, two [17, 29] were open-label, and one [10] (published as abstract only) did not provide any information. Thirteen out of 18 were done in the out-patients setting [9–11, 14–16, 21, 25, 29, 31, 32, 34, 36]. Six trials [14, 16, 17, 29, 34, 35] enrolled only vitamin D deficient (VDD)/insufficient participants. Rest 12 did not prespecify vitamin D deficiency as entry criteria though many participants were vitamin D deficient. Studies enrolling VDD children used variable cut-offs to define vitamin D deficiency/insufficiency. Recent guidelines consider a level of 20 ng/mL or more as sufficient, and <12 ng/mL (some consider <10 ng/mL) as deficient [38]. None of the trials enrolled children exclusively in the range of 25(OH)D <12 ng/mL. Therefore, we considered the

author's defined threshold for classifying deficient/insufficient. The dosing schedule, disease severity, and follow-up period varied considerably (Table 1).

Risk of Bias

We used the *ROB2 tool* for the risk of bias assessment (e Figure 1). Six trials have some bias arising from the randomization process [9, 10, 17, 29, 33, 35]. Another two have some concerns in handling missing data [8, 9]. Two were open-label and had some concerns in multiple domains; therefore, they were considered at high risk of bias [17, 29]. Yadav et al.'s trial was at risk of bias in two domains (randomization process and handling missing data); therefore, considered at high risk of bias [9]. Overall, four trials were at high risk of bias, three had some concerns in one or another domain, and the rest 11 were considered at low risk of bias in all domains. The clinical outcomes, measurement scales, and assessment time varied considerably across studies (Table 2).

Primary Outcome (Figure 2)

Nine trials reported data on corticosteroid use [9, 15, 16, 21, 25, 26, 31, 32, 36]. Seven trials (654 participants) compared the requirement of rescue systemic steroids in an asthma attack [14–16, 21, 25, 26, 32]. However, only six (445 participants) provided data for pooled analysis. Overall, 29.3% participants in vitamin D group and 29.2% in placebo/control group required rescue systemic steroids for asthma control (RR: 1.13; 95% CI: 0.86 to 1.48; I^2-0%, p-0.7) (Moderate-certainty evidence) (Table 3). As the duration of supplementation and follow-up varied across trials and can affect the primary outcome, we also assessed the impact of the duration of follow-up (Figure 2). None of the trials showed any benefit with vitamin D supplementation, and there were no significant subgroup differences (based on follow-up period, which closely mimics supplementation duration). Jat et al. did not observe any difference in the median number of courses of oral corticosteroids during the study period [14].

Sensitivity Analysis

All six trials reporting primary outcomes were at low risk of bias, therefore, precluding the need for sensitivity analysis. Also, there was no statistical heterogeneity among them; the results largely remained unchanged with fixed-effect analysis (RR: 1.09; 95% CI: 0.83 to 1.43). Only one trial exclusively enrolled vitamin D deficient (10-30 ng/mL) children, and they did not find any difference in severe asthma (requiring systemic rescue steroids) [16]. When we excluded this trial in sensitivity analysis, the results remained unchanged (5 trials, 253 participants; RR: 1.17; 95% CI: 0.80 to 1.72).

Regression Analysis

A significant overlap and variability in the disease severity, dosage, and route of vitamin D supplementation across the studies precluded the subgroup analysis on these variables (Table 2). To investigate the effect of these variables, we did a random-effects meta-regression analysis. We aimed to do meta-regression for sample size, dosage, duration, use of vitamin D (maintenance dose) in the control group, baseline vitamin D levels, disease severity, and other co-interventions. Due to significant heterogeneity in intervention dose (500 IU to 3 lac IU), duration (weeks to a year), dosing schedule (daily, weekly, combined), use of bolus (different intervals and doses), it was not possible to analyze individual covariates. Therefore, we decided to use cumulative dose as a covariate to include both dose and duration. Also, Vitamin D is a fat-soluble vitamin with a more extended washout period, so the cumulative dose is important. Due to the limited number of studies reporting baseline vitamin D, it was dropped from covariates. Therefore, the final meta-regression included sample size, cumulative dose, active intervention in the control group, and co-treatment (steroids, SCIT, etc.) as co-variates (eTable 3). We did not find any significant relationship of either of the covariates with the use of rescue systemic corticosteroids.

Secondary Outcomes

Pooled meta-analysis of eleven trials (1132 participants) did not find a significant effect of vitamin D supplementation on the proportion of children with at least one asthma attack (RR: 0.84; 95% CI: 0.65 to 1.09, I^2- 58%, p-0.007) (Very-Low certainty evidence) (e Figure 2). As the trials have different supplementation and follow-up durations and substantial heterogeneity (I^2-58%, p-0.00), we explored the relationship of asthma exacerbation with the follow-up period (e Figure 3). As the primary outcome, we did not see any significant difference in the proportion of participants with acute attacks at various follow-up time points. On meta-regression analysis (e Table 3), we did not find any significant relationship between the covariates and the asthma attacks (any severity).

Eight trials reported data on unscheduled/emergency healthcare visits for asthma attacks (Table 2). However, only three provided data for quantitative synthesis [17, 26, 32]. The pooled data (3 trials, 361 participants) suggest that vitamin D does not reduce the need for unscheduled hospital visits (RR: 0.97; 95% CI: 0.89 to 1.07; I^2- 0%, p-0.4) (low-certainty evidence). In the rest four, the vitamin D did not significantly affect emergency visits [14–16, 21]. Two trials reporting the need for hospitalization did not find significant difference (RR:1.38; 95% CI: 0.52 to 3.66, I^2-0%, p-0.8) (low-certainty evidence) [16, 26]. The proportion of participants with well-controlled asthma was similar in vitamin D (95%) and placebo (94.1%) groups (4 trials, 442 participants RR: 1.00; 95% CI: 0.97 to 1.04; I^2-0%, p-0.9) (low-certainty evidence). Only one trial (206 participants) reported data on beta-2 agonists, and they did not find any difference in rescue beta-2 agonist use (RR: 1.15; 95% CI: 0.71 to 1.85) [14].

Different scores (GINA, ACT, C-ACT, ATAQ) were used to assess asthma control. Except for two trials [9, 26], none reported a significant difference (Detailed in Table 2). Two trials (276 participants) provided C-ACT scores for quantitative synthesis. There was no significant difference in post-intervention C-ACT scores (MD: 0.22; 95% CI: -0.51 to +0.94, I^2-0%) (e

Figure 4). Twelve trials assessed pulmonary function tests (Table 2). Ten trials reported the effect of vitamin D on Forced expiratory volume in the first second (FEV1), of which nine did not show any significant impact of vitamin D. Meta-analysis of four trials (314 participants) did not observe any significant benefit with vitamin D supplementation (MD: -2.64; 95% CI: -7.04 to 1.77; I^2- 62%, p-0.05). The other pulmonary function tests (FeNO, PEFR) were similar in the two groups (Table 3, e Figure 5).

Adverse Events

Vitamin D supplementation was safe (eTable 4). There was no statistically significant difference between the two groups regarding the minor (headache, nausea, vomiting, rash, pain abdomen, rash) or serious adverse effects (RR: 1.30; 95% CI: 0.55 to 3.07; I^2-0%, p-0.9) (Table 3).

Effect in Vitamin D deficient Children

None of the trials enrolled children exclusively in the deficient range (<12 ng/mL); therefore, we included RCTs with participants having 25(OH)D levels <20ng/mL before enrolment collectively under deficient/insufficient category for subgroup analysis. Three trials enrolled children with 25(OH)D levels <20ng/mL [14, 29, 35]. However, only one study (Jat et al.) provided data on asthma exacerbation [14]. They did not observe any significant effect of vitamin D supplementation on any reported outcomes.

As a part of sensitivity analysis, we pooled the data from low risk of bias studies (e Table 5). There was no significant change in any of the outcomes. Similarly, we also did sensitivity analysis for outcomes with heterogeneity <50 % using the fixed-effect model [18]. Again, none of the results differed between the two groups (e Table 6).

Publication bias

As the primary outcome have only six studies, we could not assess publication bias for it. But we further explored this aspect for another important and generalized outcome (children with one or more asthma excarnation) reported in 11 studies. One high-risk study (Yadav et al.) [9] falls outside the pseudo 95% confidence limits (e-Figure 6), but the rest are symmetrically distributed around the log RR. There is no relationship between the study size and effect size; therefore, significant publication bias is unlikely. Considering the limitations of the funnel plot, we did a more robust Egger's linear regression test. Egger's test did not show any significant small study effect (coefficient: 0.081; 95% CI: -0.11 to 0.27, p-0.2).

DISCUSSION

This systematic review and meta-analysis did not find any protective effect of adjuvant vitamin D supplementation on reducing asthma attacks requiring rescue systemic corticosteroids in children. Also, vitamin D does not decrease any asthma exacerbations, need for emergency/unscheduled emergency visits, and hospitalization for asthma attacks. Very-low certainty evidence suggests that adjuvant vitamin D does not improve pulmonary functions either. Extremely few (0.8%) participants had severe adverse events (apart from hospitalization due to asthma attack), and none were attributed to vitamin D supplementation.

Considering the heterogeneity and high risk of bias in observational studies, we limited ourselves to RCTs. Except for four studies, the rest were of moderate to good quality. Even after limiting ourselves to high-quality trials, we did not observe any positive effect of vitamin D supplementation, reinforcing the robustness of the conclusions (Moderate-certainty evidence). An IPD-MA observed the protective effect of vitamin D supplementation in VDD adults but not among those with sufficient levels [7]. Only three trials enrolled VDD/insufficient children in our meta-analysis, and only one reported the effect on asthma attacks. Therefore, these results should not be extrapolated to VDD children.

Initial systematic review and meta-analysis showed that vitamin D might protect against moderate to severe asthma attacks (requiring rescue systemic steroids). However, the effect size and level of certainty were petite [5, 7, 12, 13, 39]. Contrary to previous reviews, we did not observe the protective efficacy of vitamin D supplementation on any of the clinical or spirometry parameters. The main reason for the contrary results is the inclusion of recent larger sample size RCTs published in the past five years, which were not part of previous systematic reviews. The earlier systematic review included 5-8 small studies (including adult studies) with an aggregate sample size of 149-573 [12, 13, 39, 40]. Our review consists of 17 trials (1572 participants) exclusively done in children and is much larger than the previous reviews. Thus, even if we restrict to low risk of bias studies, moderate certainty evidence suggests that vitamin D supplementation does not reduce asthma attacks or the need for rescue systemic steroids.

A previous systematic review concluded that the high-dose vitamin D might be useful [39]; however, we did not observe any effect of cumulative dose or duration of treatment on asthma attacks on meta-regression. Jolliffe et al. did an IPD-MA of pediatric and adult populations and observed significant effects of vitamin D supplementation [7]. They observed benefits in vitamin D deficient (<25nmol/L) individuals (3 trials, 92 participants) but not in normal levels. As 91 out of 92 VDD individuals included in that IPD-MA were adults, the findings are not applicable for children. In our meta-analysis, minimal evidence did not support vitamin D supplementation in this subpopulation; however, we are uncertain about this outcome. As many of these trials enrolled children with vitamin D levels in the deficiency range, an IPD-MA limited to VDD children shall be helpful.

Our review has several limitations. There was wide variability in the population characteristics (race, ethnicity, disease severity, vitamin D levels), intervention (dose, duration, and follow-up), and outcome (definition of attack, therapy, asthma control scores). Though we tried to address these variabilities by doing appropriate analyses, we are unsure of the impact on our

study outcomes. One may argue that the dosage of vitamin D supplementation was relatively low in some trials, and many might not have achieved "so-called" normal vitamin D levels, which might have affected the outcomes. However, it is unlikely to be accurate as trials using very high doses (up to 5 lakh IU) also did not find a beneficial effect.

This review includes four high-risk of bias studies and many small studies with wide confidence intervals. However, sensitivity analysis of the low risk of bias studies showing similar results with a better level of certainty is reassuring. Also, there was no significant difference in the effect size between the small and relatively large-sized trials. Moreover, we downgraded the level of evidence for heterogeneity, wide confidence intervals, and risk of bias. Since we do not have robust data on VDD children, these results might not apply to them.

In conclusion, this systematic review and meta-analysis did not find any protective effect of adjuvant vitamin D supplementation in preventing moderate to severe asthma exacerbations requiring rescue systemic corticosteroids in children. However, for the rest of the outcomes level of certainty is low to very low. Further, more extensive trials are needed to assess its efficacy in VDD children to improve the confidence of the evidence.

Contributors

JK, JM, PK, and JPG did the literature search. CT and PC collected the data. JC, AG, and KS supervised data collection. JK, PK, and JPG drafted the manuscript. JC, AG, and KS critically revised the manuscript. All authors designed the study, analyzed, and interpreted the data, and did the quality assessment.

All authors have seen the final manuscript and approved it for submission.

Declaration of interests

All other authors declared no competing interests regarding this manuscript.

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Consent to participate: Not required.

Consent for publication: All authors consented to publication.

Table 1: Characteristics of Included Studies (n=18)

Study			Population				Intervention (Vitamin D)				Comparison		Primary outcome	Follow-Up Time points *
Author (Year)	**RCT design**	**Setting**	**Age range (yrs)**	**Sample size**	**VDD children**	**Asthma severity**	**Baseline 25 (OH) D levels**	**Dose**	**Duration**	**Cumulative dose**	**Therapy**	**Baseline 25 (OH) D levels**		
Majak P et al. (2009)	Double-blind parallel	OPD	6-12	54	No	All severity	31.3 (3.4)	1000 IU weekly + Inhaled prednisone 20 mg + SCIT	3 months	90,000 IU	Inhaled Prednisone 20 mg + SCIT	32.0 (3.1)	ICS dose reduction	3,12
Urashima M et al. (2010)	Double-blind parallel	Multi-centric	6-15	110	No	All severity	-	1200 IU daily	4 months	144,000 IU	Placebo	-	Rate of influenza infection	4
Majak P et al. (2011)	Double-blind, parallel	OPD	5-18	48	No	Newly diagnosed	35.1 (16.9)	500 IU daily + Budesonide 800 mcg/d	6 months	90,000 IU	Budesonide 800 mcg/d	36.1 (13.9)	ATAQ score	1,2,3,4,5,6
Lewis E et al. (2012)	Double blind, parallel	Hospital	6-17	30	No	Chronic persistent asthma	-	1000 IU daily	12 months	360,000 IU	Placebo	-	ACT	6,12
Darabi B et al. (2013) Abstract only	Parallel group	OPD	6-14	63	No	Newly diagnosed	-	500 IU daily + Fluticasone 500 mug/d	6 months	90,000 IU	Fluticasone 500 mug/d	-	Asthma attacks, FEV1	6
Yadav M et al. (2014)	Double-blind, parallel	OPD	5-13	100	No	Moderate to severe	-	60000 IU monthly	6 months	360,000 IU	Placebo	-	Asthma control by GINA	1,2,3,4,5,6
Baris S et al. (2014)	Double blind parallel	OPD	5-15	50	No	Mild to moderate persistent	19 (9)	650 IU daily + SCIT	12 months	234,000 IU	SCIT alone	20 (12)	Symptom and medication score	6,12
Bar Yoseph R et al. (2015)	Double-blind, parallel	OPD	6-18	39	Yes (<30 ng/mL)	Mild	20.8 (6.5)	14000 IU weekly	6 weeks	84,000 IU	Placebo	20.0 (7.1)	FEV1	6 weeks
Jensen ME et al. (2016)	Double-blind parallel	OPD	1-5	22	No	Moderate to severe	-	1 lakh IU stat f/b 400 IU/day	6 months	172,000 IU	400 IU Vitamin D daily x 6 months. Cumulative-72,000 IU	-	Severe exacerbations	3, 6

Kerley CP et al. (2016)	Double-blind, parallel	OPD	6-16	44	No	Moderate to severe	23.2 (8.9)	2000 IU daily	15 weeks	210,000 IU	Placebo	20.4 (7.4)	Pulmonary functions	15 weeks
Tachimoto H et al. (2016)	Double-blind, parallel	Multi-centric	6-15	89	No	All severity	28.5 (7.4)	800 IU daily	2 months	32,000 IU	Placebo	29 (7.4)	Asthma control by GINA	2,6
Alansari K et al. (2017)	Open-label, parallel	Emergency	2-14	231	Yes (<25 ng/mL)	Moderate to severe	15.1 (5.4)	<5 yrs.: 3 lakhs IU stat f/b 400 IU/d >5 yrs.: 6 lakhs IU stat f/b 400 IU/d	12 months	<5 yrs.: 446,000 IU >5 yrs.: 746,000 IU	400 IU vitamin D daily x 12 months Cumulative dose-146,000 IU	15.8 (5.2)	Asthma exacerbation	3,6,9,12
Najmuddin F et al. (2017)	Open label, parallel	OPD	6-12	66	Yes (<20 ng/mL)	All severity	-	60000 IU weekly	10 weeks	600,000 IU	None	-	Pulmonary functions	10 weeks
Ducharme FM et al. (2019)	Triple blind parallel	OPD	1-5	47	No	Moderate to Severe	28.2 (5.3)	1lakh IU X 2 doses, 14 weeks apart ± daily ICS	7 months	200,000 IU	Placebo ± daily ICS	27.4 (10.4)	Asthma exacerbation	3.5,7
Swangtrakul N et al. (2019)	Double blind, parallel	Hospital	3-18	84	Yes (<20 ng/mL)	Mild to moderate	16.5 (2.2)	<30 Kg: 3 lakh IU >30kg: 6 lakhs IU	3 months	<30 kg: 420,000 IU >30kg: 840,000 IU	Placebo	16.2 (2.3)	Asthma control, FOT	1,3
Forno E et al. (2020)	Double-blind parallel	OPD	6-16	192	Yes (10-30 ng/mL)	Moderate to severe	22.5 (4.6)	4000 IU daily + Inhaled fluticasone	12 months	1440,000 IU	Placebo + Inhaled fluticasone	22.8 (4.6)	Severe asthma exacerbations	4,8,12
Jat KR et al. (2020)	Double-blind, parallel	OPD	4-12	250	Yes (<20 ng/mL)	Persistent Asthma of all severity	11.6 (4.6)	1000 IU daily	9 months	270,000 IU	Placebo	10.8 (4.4)	C-ACT score	1,3,6,9
Thakur C et al. (2021)	Double blind parallel	OPD	6-11	60	No	Moderate	15.8 (8.2)	2000 IU daily + Inhaled steroids	3 months	180,000 IU	Placebo + Inhaled steroids	16.5 (9.9)	Improvement in C-ACT Score	1,2,3

Abbreviations: ACT: Asthma control test, ATAQ: Asthma therapy assessment questionnaire, C-ACT: Childhood asthma control test, FEV1: Forced expiratory volume in one second, FOT: Forced oscillation technique, GINA: Global initiative for asthma, ICS: Inhaled Corticosteroids, IU: International Unit, OPD: Outpatient Department; SCIT: Subcutaneous Immunotherapy; VDD: Vitamin D deficient. -25 (OH)D levels are presented as mean (SD) ng/mL. Dash (-) indicates either the levels were not done at baseline, or they are not clearly presented in published paper.

*in months unless specified.

Author (Year)	Asthma exacerbations	ED visit	Steroid use	Asthma control				Pulmonary Function Tests				Post-intervention Vitamin D levels
				GINA	C-ACT /ACT	ATAQ	Other Scores	FEV1	PEFR	FeNO	FOT	
Majak P et al. (2009)	-	-	NS	-	-	-	NS*	NS	-	-	-	↑
Urashima M et al. (2010)	↓	-	-	-	-	-	-	-	-	-	-	-
Majak P et al. (2011)	↓	-	-	-	-	NS	-	NS	-	-	-	NS
Lewis E et al. (2012)	-	-	-	-	NS	-	-	NS	-	-	-	NS
Darabi B et al. (2013)	↓	-	-	-			NS**	NS	-	-	-	↑
Yadav M et al. (2014)	↓	↓	↓	↓	-	-	-	-	↑	-	-	-
Baris S et al. (2014)	NS	-	NS	-	-	-	NS***	NS	NS	-	-	↑
Bar Yoseph R et al. (2015)	-	-	-	-	-	-	-	NS	-	NS	-	↑
Jensen ME et al. (2016)	NS	NS	NS	-	-	-	-	-	-	-	-	↑
Kerley CP et al. (2016)	-	-	NS	NS	NS	-	-	NS	-	-	-	↑
Tachimoto H et al. (2016)	NS	NS	NS	↓	↓	-	-	-	NS	-	-	↑
Alansari K et al. (2017)	NS	NS	-	-	-	-	-	-	-	-	-	↑
Najmuddin F et al. (2017)	-	-	-	-	-	-	-	↑	↑	-	-	-
Ducharme FM et al. (2019)	NS	NS	NS	-	-	-	-	-	-	-	-	↑
Swangtrakul N et al. (2019)	-	-	-	-	NS	-	-	-	-	-	NS	-
Forno E et al. (2020)	NS	NS	NS	-	-	-	-	-	-	-	-	↑
Jat KR et al. (2020)	NS	NS	-	NS	NS	-	-	NS	NS	-	-	↑
Thakur C et al. (2021)	NS	NS	NS	-	NS	-	-	NS	-	NS	-	↑

Table 2: Summary of Clinical Parameters Studied Among Trials and Their Outcomes.

Abbreviations: ACT: Asthma control test, ATAQ: Asthma therapy assessment questionnaire, C-ACT: Childhood asthma control test, ED: Emergency department, FEV1: Forced expiratory volume in one second, FeNO-Fractional exhaled nitric oxide, FOT-Forced oscillation technique, GINA-Global initiative for asthma, NS: Not significant difference, PEFR: Peak expiratory flow rate

*Asthma symptoms diary, **ACQ score, ***Total asthma symptoms score

Table 3: Summary of Findings Table (Primary and Secondary Outcomes)

Outcomes	No. of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)		Certainty of the evidence (GRADE)
			Risk with Placebo	Risk with Vitamin D	
Number of children requiring systemic corticosteroids for asthma exacerbations	445 (6 RCTs)	RR 1.13 (0.86 to 1.48)	292 per 1,000	330 per 1,000 (251 to 432)	⊕⊕⊕◯ MODERATE [b]
Number of Children with one or more asthma exacerbations	1132 (11 RCTs)	RR 0.84 (0.65 to 1.09)	452 per 1,000	380 per 1,000 (294 to 493)	⊕◯◯◯ VERY LOW [a,b,d]
Number of Children requiring emergency/Unscheduled visits	361 (3 RCTs)	RR 0.97 (0.89 to 1.07)	669 per 1,000	649 per 1,000 (595 to 715)	⊕⊕◯◯ LOW [a,b]
Number of children requiring hospitalizations for asthma exacerbation	275 (2 RCTs)	RR 1.38 (0.52 to 3.66)	70 per 1,000	18 per 1,000 (22 to 124)	⊕⊕◯◯ LOW [b,c]
Number of Children with well-controlled Asthma	442 (4 RCTs)	RR 1.00 (0.97 to 1.04)	941 per 1,000	941 per 1,000 (913 to 979)	⊕⊕◯◯ LOW [a,b]
FEV1	314 (4 RCTs)	-		MD 2.64 lower (7.04 lower to 1.77 higher)	⊕⊕◯◯ LOW [b,d]
FENO	94 (2 RCTs)	-		MD 2.87 lower (24.66 lower to 18.91 higher)	⊕◯◯◯ VERY LOW [b,c,d]
Vitamin D levels post intervention	857 (8 RCTs)	-		MD 10.68 higher (6.3 higher to 15.05 higher)	⊕⊕◯◯ LOW [e]
No. of children with Serious adverse events	525 (3 RCTs)	RR 1.30 (0.55 to 3.07)	31 per 1,000	41 per 1,000 (17 to 97)	⊕⊕◯◯ LOW [b,c]

Abbreviations: CI: Confidence interval; FEV1: Forced expiratory volume in one second; FeNO-Fractional exhaled nitric oxide; MD: Mean difference; RCT: Randomized Controlled Trial; RR: Risk ratio

Explanations: [a] Includes high risk of bias trials; [b] 95% CI crosses' null line; [c] Extremely wide 95% CI; [d] I^2> 50%; [e] I^2>75%.

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Figure Legends

Figure 1: PRISMA 2020 Flow Chart

Figure 2: Forest plot showing the proportion of children with asthma exacerbations requiring rescue systemic steroids.

eFigure 1: Risk of Bias Summary a) Traffic plots and b) Summary Plots

eFigure 2: Proportion of children with one or more asthma attack of any severity

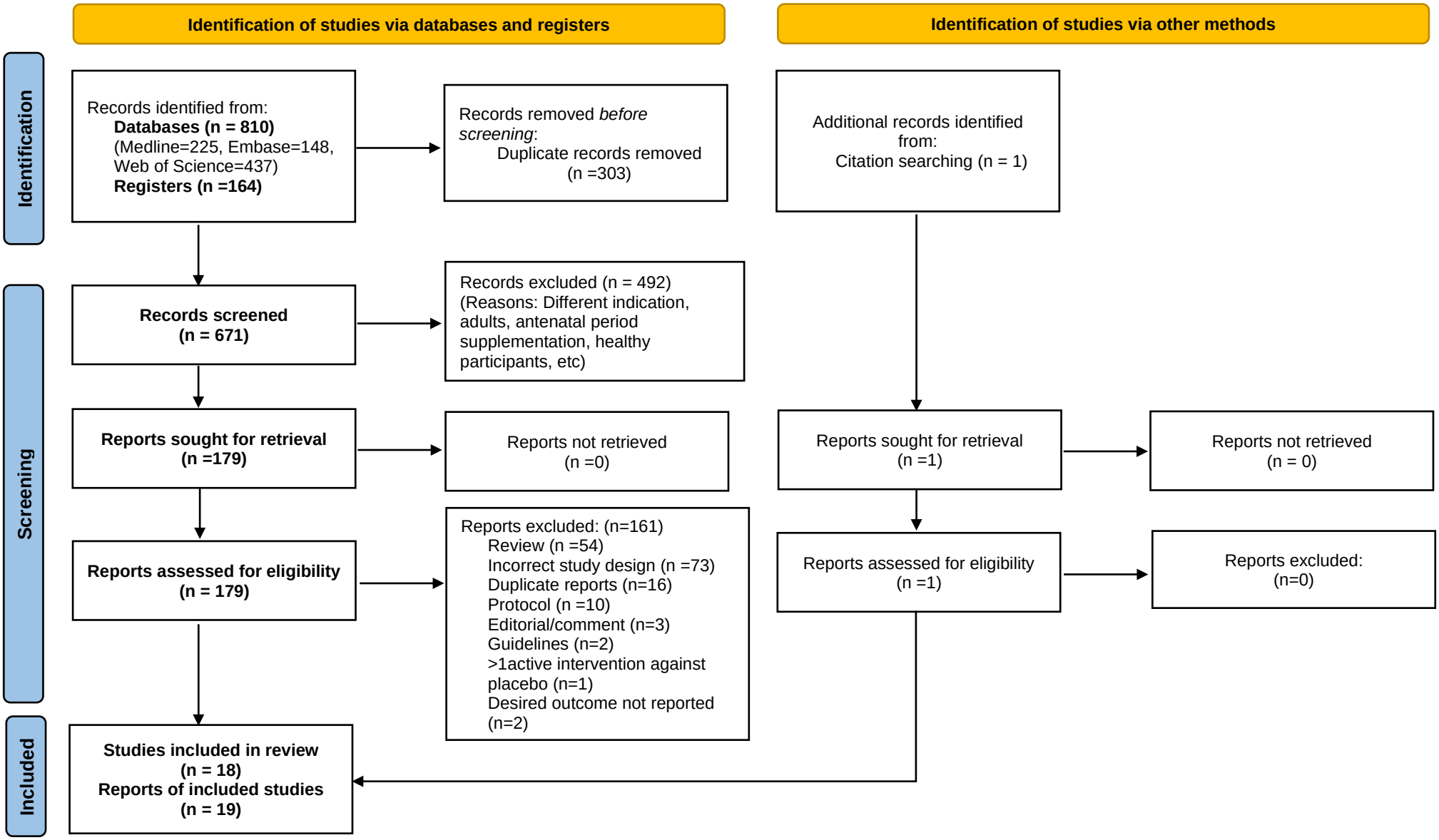
eFigure 3: Forest plot showing the relationship of the duration of vitamin D supplementation with asthma attacks

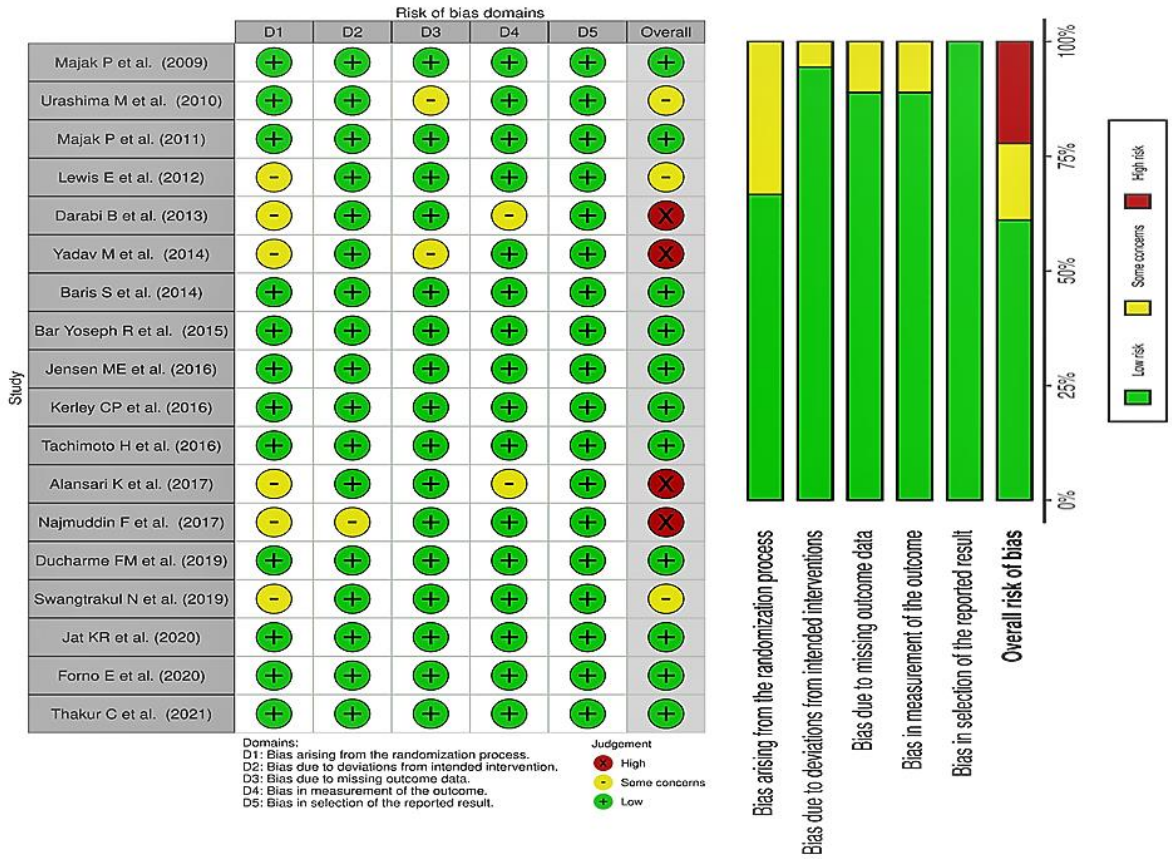
eFigure 4: Forest plot showing comparison of C-ACT Scores

eFigure 5: Forest plot showing comparison of pulmonary functions

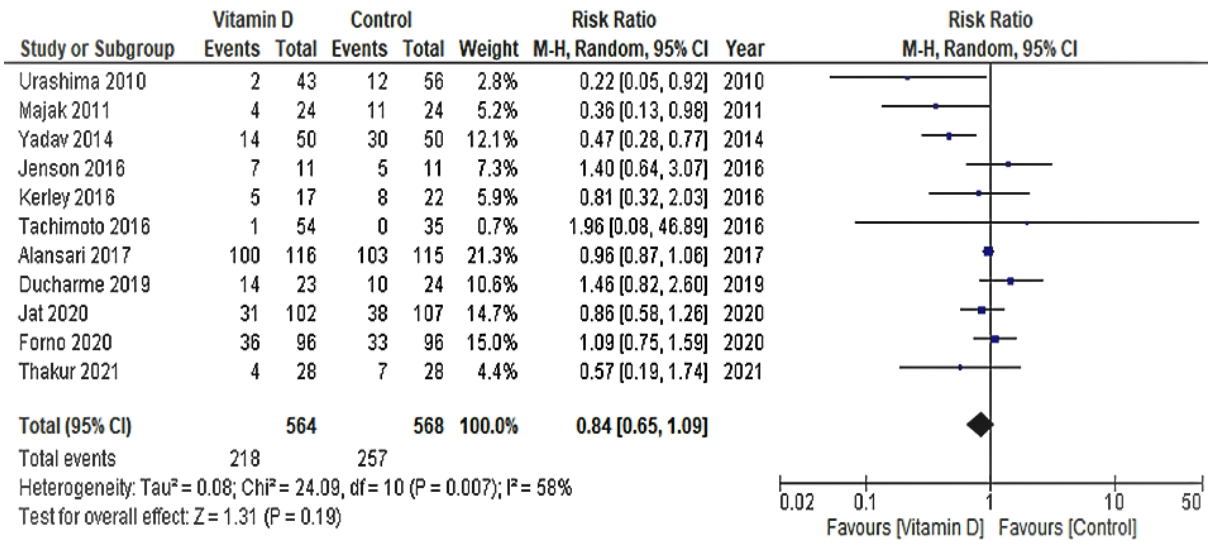
eFigure 6: Funnel plot for publication bias

Figure 1: PRISMA 2020 flow diagram

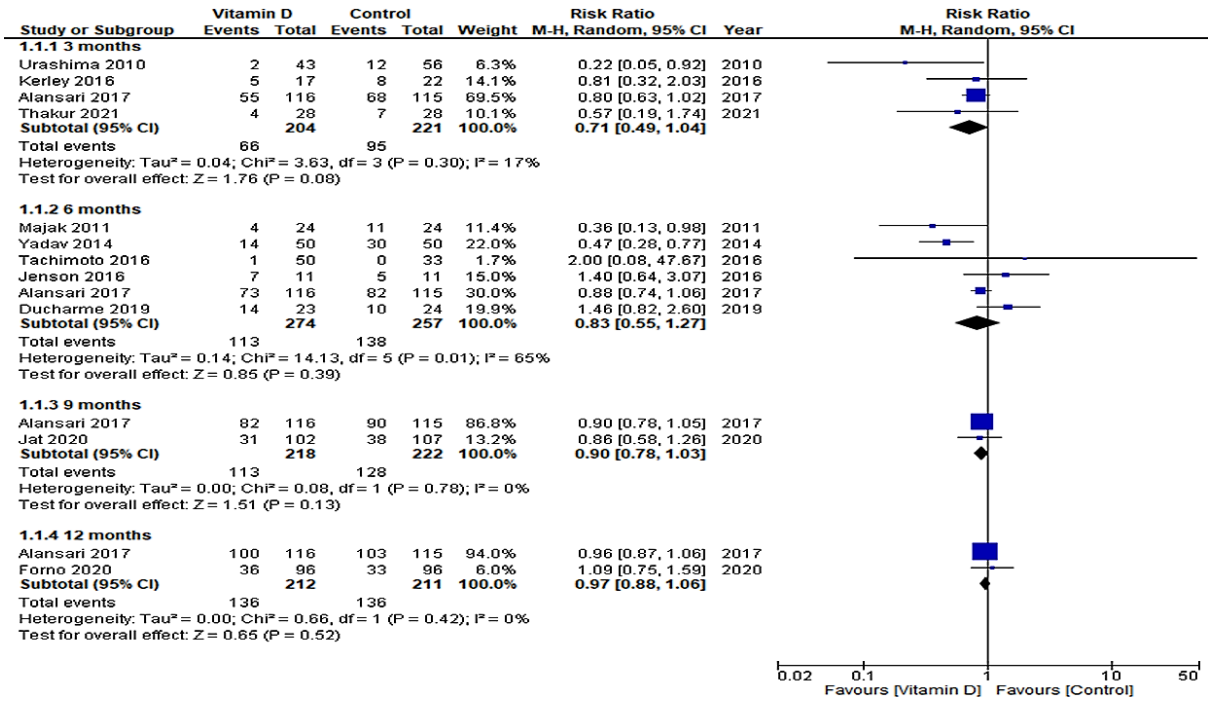




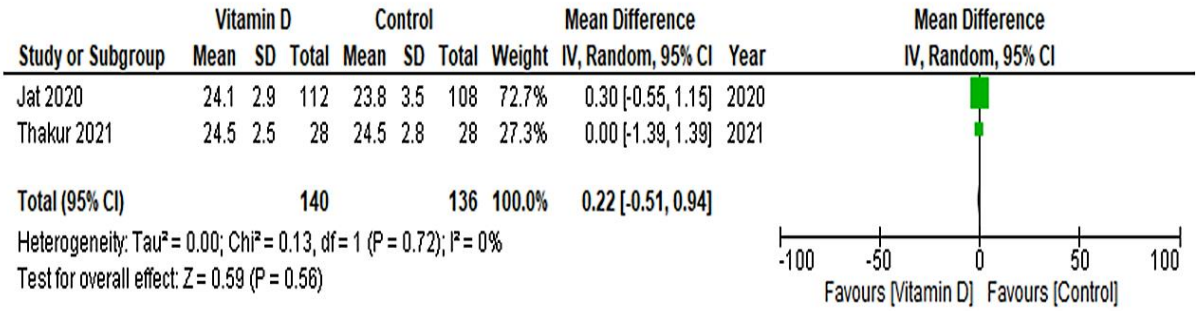
Supplementary Figure 1: Risk of Bias Summary a) Traffic plots and b) Summary Plots



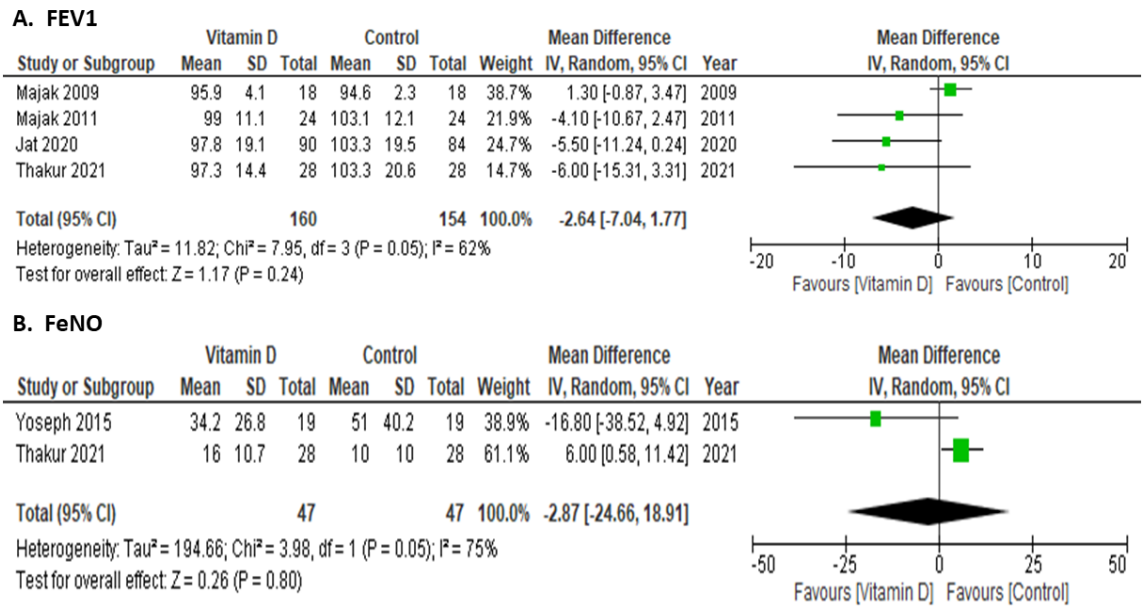
Supplementary Figure 2: Proportion of children with one or more asthma attack of any severity



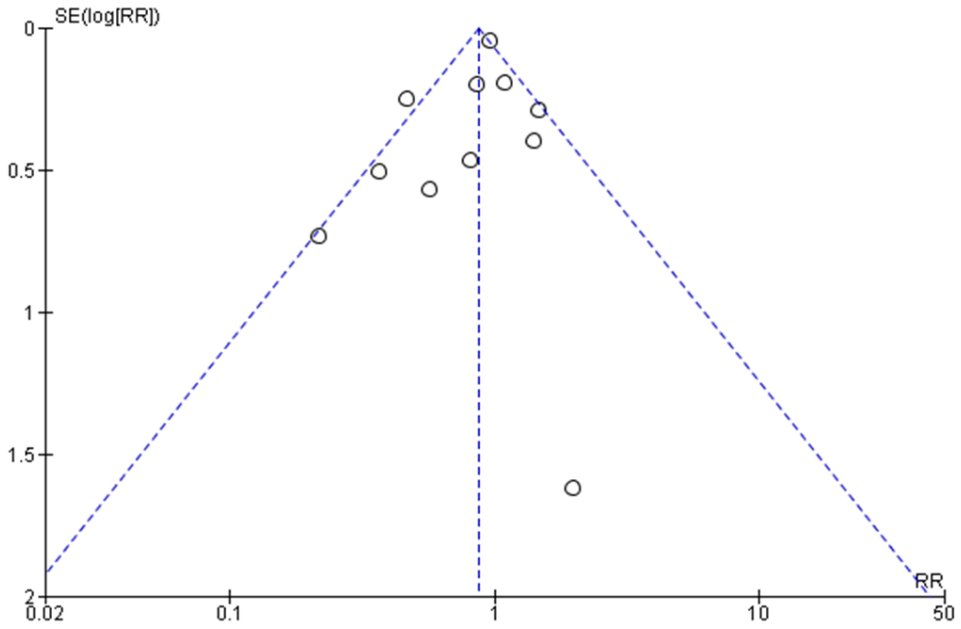
Supplementary Figure 3: Forest plot showing the relationship of the duration of vitamin D supplementation with asthma attacks



Supplementary Figure 4: Forest plot showing comparison of C-ACT Scores



Supplementary figure 5: Forest plot showing comparison of pulmonary functions



Supplementary Figure 6: Funnel plot for publication bias

Supplementary Table 1: Search strategy (30.09.2021)

Database		Query	Hits
Medline by PubMed	#1	(((((bronchial asthma[MeSH Terms]) OR (Asthma[Title/Abstract])) OR (wheeze[Title/Abstract])) OR (recurrent wheeze[MeSH Major Topic])) OR ("childhood asthma"[Text Word])) OR ("pediatric asthma"[Text Word])	186852
	#2	((((((adolescent[MeSH Terms]) OR (children[MeSH Terms])) OR (school age population[MeSH Terms])) OR (childhood[Title/Abstract])) OR (children[Title/Abstract])) OR (adolescent*[Title/Abstract])) OR (pediatric*[Title/Abstract])	3703739
	#3	(((((((((calcitriol[MeSH Terms]) OR (cholecalciferol[MeSH Terms])) OR (1,25 dihydroxy 20 epi vitamin d3[MeSH Terms])) OR (vitamin D[Title/Abstract])) OR (cholecalciferol[Title/Abstract])) OR (calcitriol[Title/Abstract])) OR (1,25 dihydroxy 20 epi vitamin d3[Title/Abstract])) OR (vitamin D[Title/Abstract])) OR (25(OH)D[Title/Abstract])) OR ("25 hydroxy D"[Title/Abstract])	84274
	#4	(randomised controlled trial [pt] OR controlled clinical trial [pt] OR randomised [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab])	5119779
	#5	**#1 AND #2 AND #3 AND #4**	**225**
Embase	#1	'vitamin d'/exp OR 'colecalciferol derivative'/exp OR 'vitamin deficiency'/exp OR 'vitamin d':ti,ab,kw OR calcitriol:ti,ab,kw OR '25 hydroxyvitamin d':ti,ab,kw OR (25:ti,ab,kw AND oh:ti,ab,kw AND d:ti,ab,kw)	238313
	#2	'child'/exp OR 'pediatric'/exp OR 'adolescent'/exp OR child:ti,ab,kw OR pediatrics:ti,ab,kw OR childhood:ti,ab,kw OR 'school age population':ti,ab,kw	4191782
	#3	'asthma'/exp OR 'recurrent wheezing'/exp OR asthma:ti,ab,kw OR 'reactive airway disease':ti,ab,kw OR wheezing:ti,ab,kw	328446
	#4	'randomized controlled trial'/exp OR 'randomized controlled trial':ti,ab,kw OR randomization:ti,ab,kw OR placebo:ti,ab,kw	917524
	#5	**#1 AND #2 AND #3 AND #4**	**148**
Web of Science	#1	TS=('vitamin D OR 'cholecalciferol derivative' OR 'vitamin D deficiency' OR 'vitamin d' OR calcitriol)	106503
	#2	TS=(child OR pediatric OR adolescent OR paediatric OR childhood OR 'school-age population' OR Child*)	1687630
	#3	TS=(asthma OR 'recurrent wheezing' OR 'reactive airway disease' OR wheezing)	194040
	#4	TS=(randomi*ed controlled trial OR controlled clinical trial OR randomized OR placebo OR randomly OR trial OR groups)	5807787
	#5	**#1 AND #2 AND #3 AND #4**	**437**
CENTRAL	#1	MeSH descriptor: [Asthma] explode all trees	11796
	#2	("asthmatic"):ti,ab,kw	8496
	#3	#1 OR #2	15698
	#4	MeSH descriptor: [Vitamin D] explode all trees	5541
	#5	("vitamin D"):ti,ab,kw	12448
	#6	("cholecalciferol"):ti,ab,kw	3009
	#7	#4 OR #5 OR #6	13544
	#8	#3 AND #7	140
	#9	MeSH descriptor: [Child] explode all trees	56872

	#10	(children):ti,ab,kw	150873
	#11	("adolescent"):ti,ab,kw	130812
	#12	("school age"):ti,ab,kw	1335
	#13	#9 OR #10 OR #11 OR #12	237337
	#14	**#8 AND #13**	**86**

Supplementary Table 2: Definition of Asthma attack used in different studies.

Author (Year)	Definition of asthma attacks
Urashima M et al. (2010)[1]	Wheezing improved by inhalation of a β stimulant in patients who already had a diagnosis of asthma
Majak P et al. (2011)[2]	Not mentioned.
Yadav M et al. (2013)[3]	Not mentioned.
Jensen ME et al. (2016)[4]	Asthma attacks require rescue oral corticosteroids (documented in medical and/or pharmacy records).
Kerley CP et al. (2016)[5]	They have not mentioned in the primary study. However, they provided data on asthma attacks requiring oral corticosteroids (mentioned in individual patient data meta-analysis by Jolliffe et al.).
Tachimoto H et al. (2016)[6]	Not mentioned. However, provided data on asthma attacks requiring systemic corticosteroids
Alansari K et al. (2017)[7]	Requiring an unplanned visit for asthma, recommended by a joint expert committee
Ducharme FM et al. (2019)[8]	Asthma attacks requiring oral corticosteroids
Forno E et al. (2020)[9]	Mentioned severe asthma attacks defined as the occurrence of either (1) use of systemic corticosteroids (tablets, suspension, or injection) for at least 3 days or (2) a hospitalization or ED visit because of asthma, requiring systemic corticosteroids.
Jat KR et al. (2021)[10]	Any asthma attack requires rescue medications (beta-agonist or corticosteroids) or an emergency visit (Personal communication).
Thakur C et al. (2021)[11]	Asthma requiring oral corticosteroids (personal communication, not mentioned in manuscript).

Supplementary Table 3: Random-effect Meta-regression Analysis for Co-Variates (Sample Size, Cumulative dose of vitamin D, Active Control, i.e., vitamin D in the control group, and co-treatment)

Log Risk Ratio	Coefficient	Standard Error (95% CI)	p-value
Use of Rescue Systemic Corticosteroids (6 studies)			
Sample Size	0.0011957	0.0194735 (- 0.2462385 to +0.2486299)	0.96
Cumulative Dose	2.82×10^{-7}	2.08×10^{-6} (-2.62×10^{-5} to $+2.68 \times 10^{-5}$)	0.91
Active Control use	-0.7138567	0.7290598 (-9.977439 to + 8.549726)	0.51
Co-treatment	0.1681983	0.5177693 (-6.410685 to + 6.747081)	0.80
Constant	-0.0289788	0.4642203 (-5.927457 to + 5.869499)	0.96
One or more asthma attacks of any severity (11 studies)			
Sample Size	0.0000952	0.0024565 (- 0.0059157 to +0.006106)	0.97
Cumulative Dose	4.65×10^{-7}	5.01×10^{-7} (-7.61×10^{-7} to $+1.69 \times 10^{-7}$)	0.39
Active Control use	-0.2410449	0.3767945 (-1.163028 to + 0.6809379)	0.55
Co-treatment	0.0103854	0.4297825 (-1.041255 to + 1.062025)	0.98
Constant	-0.2675291	0.3583356 (-1.144345 to + 0.6092866)	0.48

Supplementary Table 4: Comparison of Adverse Events

Outcome	No. of studies (Participants)	Vitamin D (n/N)	Control (n/N)	RR [95% CI]	I^2 p-value
Any Adverse Event					
Nausea	3 (503)	10/252	8/251	1.21 [0.50, 2.94]	0%, 0.8
Vomiting	1 (250)	34/125	28/125	1.21 [0.79, 1.87]	Not Applicable
Pain Abdomen	1 (250)	40/125	41/125	0.98 [0.68, 1.40]	Not Applicable
Constipation	1 (250)	12/125	11/125	1.09 [0.50, 2.38]	Not Applicable
Headache	1 (250)	25/125	25/125	1.00 [0.61, 1.64]	Not Applicable
Seizures	1 (250)	1/125	0/125	3.00 [0.12, 72.94]	Not Applicable
Altered Sensorium	1 (250)	0/125	1/125	0.33 [0.01, 8.10]	Not Applicable
Rash	1 (231)	1/116	0/115	2.97 [0.12, 72.26]	Not Applicable
Serious Adverse Events					
All*	3 (525)	11/271	8/254	1.30 [0.55, 3.07]	0%, 0.9
Hospitalization	2 (275)	9/146	6/129	1.38[0.52, 3.66]	0%, 0.8

Abbreviations: **CI:** Confidence interval; **RR:** Risk ratio

*Includes hospitalization.

n/N represents the number of events/ total number of participants.

Supplementary Table 5: Sensitivity Analysis (Low risk of Bias studies)

Outcome	No. of studies (Participants)	RR/MD [95% CI]	Heterogeneity (I^2), p-value
Participants requiring rescue systemic corticosteroids	6 (445)	1.13 [0.86, 1.48]	0%, 0.7
Participants with ≥ 1 asthma exacerbation	8 (702)	0.97 [0.75, 1.26]	19%, 0.3
Unscheduled healthcare visits	2 (130)	1.58 [0.91, 2.74]	0%, 0.9
Well-controlled asthma	3 (342)	1.01 [0.96, 1.07]	0%, 0.9
Hospitalization	2 (275)	1.05 [0.45, 2.45]	0%, 0.7
Serious Adverse events	3 (525)	1.30 [0.55, 3.07]	0%, 0.9
Serum 25(OH) D levels	7 (626)	10.77 [5.44, 16.10]	94%, 0.01
FEV1	4 (314)	-2.64 [-7.04, 1.77]	62%, 0.05
FeNO	2 (94)	-2.87 [-24.66, 18.91]	75%, 0.05

Abbreviations: CI: Confidence interval; MD: Mean difference; RR: Risk ratio

Explanations: [a] 95% CI crosses' null line; [b] Extremely wide 95% CI; [c] High heterogeneity.

Supplementary Table 6: Sensitivity Analysis (Fixed effect)

Outcome	No. of studies (Participants)	RR/MD [95% CI]	Heterogeneity (I^2), p-value
Participants with ≥ 1 asthma exacerbation requiring systematic corticosteroids	6 (445)	1.09 [0.83, 1.43]	0%, 0.7
Unscheduled healthcare visits	3 (361)	1.00 [0.90, 1.11]	0%, 0.4
Well-controlled asthma	4 (442)	1.01 [0.96, 1.06]	0%, 0.9
Hospitalization for asthma exacerbations	2 (275)	1.06 [0.46, 2.47]	0%, 0.7
Serious Adverse events	3 (525)	1.30 [0.55, 3.08]	0%, 0.9

Abbreviations: CI: Confidence interval; MD: Mean difference; RR: Risk ratio