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Effect of vitamin D supplementation on the immune response to respiratory tract infections and inflammatory conditions: A systematic review and meta-analysis

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ABSTRACT

Context: Vitamin D acts as an immune modulator, by downregulating the production of inflammatory immune markers and upregulating the production of anti-microbial peptides and anti-inflammatory markers. Hence, vitamin D may be useful in improving the immune response against respiratory tract diseases.
Objective: A systematic review (following PRISMA guidelines) and meta-analysis were performed to study the effect of vitamin D supplementation on the immune response to respiratory tract diseases irrespective of population type.
Data sources: Electronic search engines Pubmed, Pubmed Central, Google Scholar, Clinicaltrials.gov, Clinical Trial Registry India, ScienceDirect, and Web of Science were searched for relevant articles.
Data extraction: Sixteen RCTs were eligible for inclusion. Jadad scale was used to assess the quality of studies. Methods of the selected studies were assessed using the Cochrane Risk of Bias assessment. Using the random-effects model meta-analysis was performed if at least three articles studied similar immune markers. Thus, IL-6, cathelicidin, CRP, TNF alpha, and IFN gamma, were included in the analysis. In all 16 articles were included for qualitative assessment, and 14 articles for meta-analysis.
Data analysis: There was a significant decrease in CRP levels after intervention with an overall effect of $Z = 3.37$ ($P < 0.00$). The observed increase in IL-10 levels was not significant with an overall effect of $Z = 0.84$ ($p = 0.40$). There was no significant decrease in IL6 [$Z = 0.59$ ($P = 0.56$)], and interferon-gamma levels [$Z = 1.70$ ($p = 0.09$)]. Secondary outcomes including mortality, and length of hospital stay did not show a significant difference in the intervention group.
Conclusion: Among the biomarkers studied CRP significantly decreased, with no significant changes in the others. Our findings suggest that vitamin D supplementation modestly affects the immune response. Pooling infectious and non-infectious respiratory diseases could have underestimated our findings. More RCTs are warranted to obtain substantial results.

1. Introduction

The multiple burdens of diseases are a global public health concern. Respiratory tract diseases, infectious and non-infectious are the leading cause of morbidity and mortality worldwide. Predominant respiratory tract diseases that affect populations are tuberculosis, chronic obstructive pulmonary disease (COPD), asthma, and pneumonia. According to the Global Burden of Disease (GBD) 2019 estimates lower respiratory tract infections rank 4th among the top 10 causes of DALYs across ages [1]. In East and Southeast Asia, although the deaths due to lower respiratory tract infections declined, the burden of infections is reportedly high in China and India. A substantial increase in prevalence was also observed in high-income countries [2–4]. Emerging infections add to the burden of existing diseases. The COVID-19 pandemic was a devastating public health challenge worldwide, with 771 M confirmed cases and 6.9 M deaths [3].

Associations between undernutrition and infections have been well established. In developing countries, macro and micronutrient

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deficiencies add to the multiple burdens of diseases. Vitamin D among micronutrients has gained global attention not just for its function in bone homeostasis and maintaining skeletal health, but also for its role as an effective immunomodulator. In respiratory tract diseases, it is known to modulate both innate and adaptive immune responses [5–8]. Populations with a high prevalence of vitamin D are likely to be at risk of severe infections. The global prevalence of vitamin D deficiency accounts for about 1 billion [9]. The Endocrine Society for Clinical Practice guidelines define sufficiency of vitamin D levels between 75 and 250 nmol/L, 50–75 nmol/L as insufficient, and below 50 nmol/L as deficient. It also states that vitamin D above 75 nmol/L can have additional benefits for reducing the risk of infections [10]. Literature evidence suggests that more than 80 % of adults in Pakistan, India, and Bangladesh are vitamin D deficient. These are the regions where infections are highly prevalent. Low vitamin D status in temperate regions has been associated with higher skin melanin content, and extensive skin coverage, particularly in Middle Eastern countries [11]. Despite adequate sunlight, and the availability of supplements and fortified food, vitamin D deficiency is widely prevalent.

Several observational studies report that serum vitamin D concentration is inversely associated with the outcome of respiratory tract diseases [12,13]. Adding to the evidence, in-vitro and in-vivo studies suggest that vitamin D potentially exerts a positive effect in reducing the levels of proinflammatory and increasing anti-inflammatory cytokine levels impacting the overall improvement in the outcomes of diseases [8, 14,15]. Furthermore, the peak of respiratory tract infections (RTI) in winter, strengthens the association between lack of sunshine, low vitamin D, and RTI [12,16]. Low serum vitamin D resulting from intake of pharmaceutical drugs including antihypertensives, antineoplastics, antiepileptics, antibiotics, anti-inflammatory agents, antiretrovirals, endocrine drugs, and a few herbal medicines, has been linked to increased mortality during COVID-19 infection [12].

Evidence from randomized controlled trials (RCT) possibly asserts the effectiveness of vitamin D in preventing respiratory diseases. To date, few RCTs have tested the effect of vitamin D supplementation and immune marker levels on respiratory tract disease outcomes. Although the effects of vitamin D supplementation in respiratory tract diseases are heterogeneous, a pooled effect on immune markers would provide directions for programs and policies. This systematic review aims to detail the published literature and estimate the pooled effect of supplemented vitamin D on immune markers and respiratory disease outcomes.

1.1. Preliminary research and idea validation

To avoid duplication of work and ensure the validity of the chosen topic of vitamin D supplementation on the immune response in respiratory tract disease outcomes, we performed a preliminary search in PubMed with search terms viz. vitamin D supplementation, respiratory tract infections and diseases, COVID-19, and allergic response. In the absence of published systematic reviews and meta-analyses specifically on immune markers levels, we chose to perform this research. We also found substantial articles with these search terms that enabled us to progress with this research.

2. Methods

2.1. Search and screening strategy

Two researchers independently conducted a literature search on databases that included http://Clinicaltrials.gov, Clinical Trial Registry India, Pubmed, Google Scholar, Science Direct, Web of Science, and Pubmed Central, with the following keywords for primary search:‘vitamin D supplementation and respiratory tract infections, vitamin D and respiratory tract diseases, vitamin D and respiratory tract infections and immune response’. A secondary search was done for specific diseases with keywords - vitamin D and TB, vitamin D and COVID-19, vitamin D and asthma, vitamin D and COPD’. The search syntax for the alternate terms was as follows: ((“vitamin d" [MeSH Terms] OR “vitamin d" [All Fields] OR “ergocalciferols" [MeSH Terms] OR “ergocalciferols" [All Fields]) AND (“respiratory tract infections" [MeSH Terms] OR (“respiratory" [All Fields] AND “tract" [All Fields] AND “infections" [All Fields]) OR “respiratory tract infections" [All Fields]) AND (“immunity" [MeSH Terms] OR “immunity" [All Fields] OR (“immune" [All Fields] AND “response" [All Fields]) OR “immune response" [All Fields])) AND (“2011/01/17" [PDat]: “2021/01/13" [PDat]). We further hand-searched references listed in the identified articles for additional relevant literature. Duplicate articles were removed by EndNote X8 software.

2.2. Study selection

For the present systematic review and meta-analysis, RCTs that tested vitamin D supplementation in participants with respiratory tract diseases and healthy individuals were included. Studies were selected according to Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) 2009 guidelines.

The criteria defined for selecting studies included - RCTs, full-text articles, and published manuscripts during the last 10 years in the English language. Under respiratory tract diseases, considering both infectious and non-infectious diseases, literature on COVID-19, pneumonia, tuberculosis, other bacterial infections, and chronic diseases such as asthma and chronic obstructive pulmonary disease (COPD). Studies among individuals of any age group with respiratory symptoms that measured immune markers were selected. Among biomarkers of interest, those that estimated IL-6, cathelicidin, CRP, TNF alpha, IFN gamma, IL-10, IgG, IgA, IgE, eosinophils count, and studies with ex-vivo antigen stimulation were included. Studies among participants who were immunocompromised, or with genetic conditions like cystic fibrosis, pregnant women, interventions that tested vaccine efficacy for respiratory tract infections RTI with vitamin D, or vitamin D with other nutrients, and in vitro studies were excluded. Fig. 1 gives the protocol for the selection of studies using PRISMA guidelines.

2.3. Data extraction

Two researchers independently extracted the data from the selected articles in Microsoft Excel. Data regarding author’s name, year of publication, study setting, population, design, form and dosage of vitamin D supplemented, duration, demographic characteristics, vitamin D levels, pre and post-supplementation, immune markers, and other outcomes reported for prevention or improvement in diseases after the intervention, and the number of missing participants were extracted for each study. To obtain missing information, the corresponding authors were contacted by email. Articles that presented data as median were converted into mean and standard deviation [17,18].

2.4. Assessment of study quality

The studies were assessed for their methodological quality using the validated Jadad scale [19]. The scale comprised eight criteria that included-i) Description of randomization, ii) Appropriateness of randomization, iii) Description of blinding procedure, iv) Appropriateness of blinding procedure, v) Description of withdrawals and dropouts, vi) Description of inclusion and exclusion criteria, vii) Description of methods used to assess adverse effects, and viii) Description of statistical methods employed. Every criterion in the scale was allocated a numerical score of ‘1’ for the strongest reporting quality, and ‘0’ for the weakest and in case of missing information marked as ‘unclear’. For assessment of the appropriateness of randomization and blindness of RCTs, we used The Cochrane Risk of Bias (RoB) Tool for Randomized Controlled Trials [20]. Per the criteria, low risk was scored 1 and high risk was scored 0. Every selected study was assessed by the above

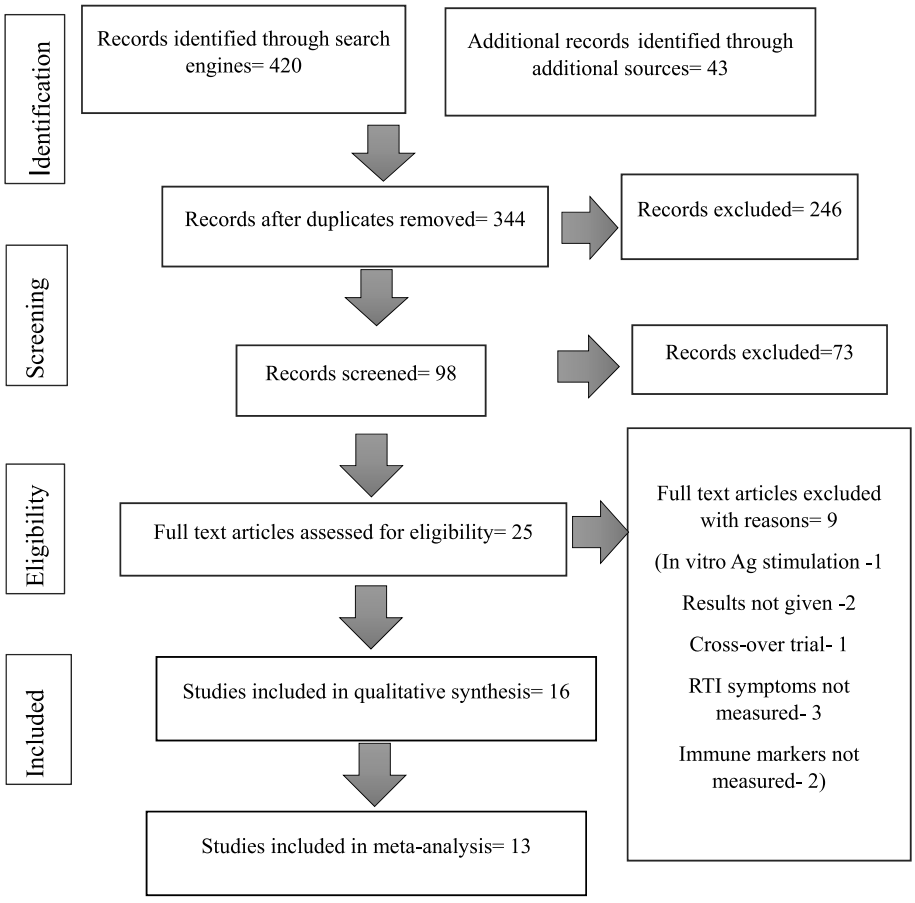

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analysis flow diagram.

criteria and the sum of the individual scores ranged from 0 to 8 points. Scores 1–3 were categorized as low quality, 4–8 signified high quality (Table 1).

2.5. Statistical analysis

Meta-analysis was performed by using a random-effects model due to the inherent variations among the selected studies. The SPSS version 29 was used to derive a forest plot and to demonstrate the degree of heterogeneity among the selected articles [21]Immune markers and vitamin D levels being continuous outcomes, we used standard mean difference as a statistical method for analysis [22]. $Chi^{2,}$ $I^{2,}$ df, and Tau^2 were computed to study heterogeneity. The overall effect was given by the Z and P-values. We derived separate forest plots for immune markers that were common across the studies post-intervention. CRP, IL-6, IFN gamma, IL-10, and vitamin D levels were thus extracted and a meta-analysis was performed. A funnel plot was generated to assess publication bias. A minimum of 10 studies is required to generate a funnel plot, we thus generated only for vitamin D levels after the intervention which met this criteria. Variations in the immune markers studied limited such derivation. Sensitivity tests for the meta-analysis were performed by comparing the Z and P values of random and fixed effects models and by eliminating the outliers.

3. Results

3.1. Results of the search

Our search identified 420 articles from electronic search engines and 43 articles from other sources. After removing duplicates, we screened 344 articles for eligibility and excluded 319. Full texts were further screened leading to the exclusion of nine studies. In all thirteen studies were selected for the meta-analyses [16,23–32] [33,34] with a total of 1749 participants randomly assigned to intervention and control or placebo groups. Fig. 1 depicts the PRISMA chart for the study section.

3.2. Study characteristics

All the selected studies used parallel-group randomized controlled trials as the study design. Double-blinded (N = 13) [16,23–27,29,31] [32,34–37]. Multi-centric design was employed in one trial [25]. Study settings were hospitals, health service trusts, or clinics from both developed and developing countries. The majority of the studies were conducted among participants 19–64 years old, with a few exceptions that were among children [30,36]. Tables 1 and 2 provide the summary of included studies on the effect of vitamin D supplementation on the immune response to respiratory tract infections and allergic conditions.

Respiratory tract conditions in the selected studies included COVID-19, pneumonia, tuberculosis, upper respiratory tract infections, asthma, and chronic obstructive pulmonary disease.

Vitamin D3 was the form used for intervention in the included studies. A single mega dose that ranged from 1,00,000 IU to 4,00,000 IU [24,25,29,32,34,36], or a daily dose between 650IU–60,000IU [16,27, 30,33,35], or weekly or monthly dosage between 60,000IU and 3 mg [23,26,28,31,37] were tested. The duration of interventions ranged from 7 days–12 months.

The studies varied in their immune markers measured for the outcomes. A majority of studies measured CRP [29,31–34] IL-6 [26,28,29, 32], followed by IFN gamma [23,26,27], IL17 [24,25], IL10 [24,26,27] cathelicidin [27,35–37], lactoferrin [16], Ig A [16,36], Ig M [36], Ig G [30,36], Ig E [25,27] and cxcl [37], WBCs-eosinophil count [25–27], IL5 [27], IL17A [24], and IL8 [29].

Table 1
Summary of included studies on the effect of vitamin D supplementation on the immune response to respiratory non infectious diseases.

Study	Country	Study Setting	Study design	Study population	Age	Clinical condition	Dosage of Vitamin D	Duration of intervention	Immune Markers Measured and outcomes	Other Outcomes
Martineau et al., 2014 [26]	UK, London	Clinic based	Double-blind randomized placebo-controlled trial	250	Vitamin D 49.4 (14.8) Placebo 46.4 (13.8)	Asthma	2-monthly oral doses of 3 mg vitamin D3	12 months	Eosinophil count, IL10, INF G No significant change in any of the immune markers	Time to first severe asthma exacerbation, or time to first URI, asthma control test and St George's Respiratory Questionnaire scores, fractional exhaled nitric oxide and concentrations of inflammatory markers in induced sputum
Ramos-Martinez et al. [27]	Mexico	Hospital based	Randomized, double-blind, placebo-controlled trial	86	Vitamin D 41 ± 11 Placebo 42 ± 15	Asthma	Vitamin D (0.25 μg calcitriol) (1,25-(OH)2D3) per day orally	6 months	Eosinophil count, IL10, IFN gamma, IgE, IL5, IL9, IL13, LL37 IFN gamma increased. IL5, IL9, IL13 decreased in the intervention group	Pathogenic bacterial growth
Shabana et al., 2019 [24]	Egypt	Clinic based	Double-blinded randomized controlled interventional study	79	Vitamin D 34.00 ± 7.40 Placebo 35.50 ± 7.00	Asthma	Asingle dose of 300,000 IU of cholecalciferol, intramuscular	3 months	IL10, IL17 Significant decrease in IL17A, and increase in IL10.	Improvement of pulmonary function, improvement of FEV1, IL17/IL10 ratio
Dodamani et al., 2018 [28]	India	Clinic based	A prospective, open-label, parallel-group randomized controlled trial	30	Vitamin D 33 (12.5) Placebo 32 (12.2)	Acute -stage allergic bronchopulmonary aspergillosis complicating Asthma	Vitamin D supplementation (oral capsule of cholecalciferol 60,000 IU) once weekly for eight weeks	6 months	IL4, IL 17L10, IL6,IL10, IgE Ig E No change after intervention	Exacerbation of bronchial asthma
Dastan et al., 2019 [29]	Iran	Hospital-based	Randomized, double-blind placebo-controlled trial	70	Vitamin D 64.42 ± 7.58 Placebo 63.24 ± 8.41	Acute Exacerbation of Chronic Obstructive Pulmonary Disease	300,000 IU of vitamin D (25-hydroxycholecalciferol) or placebo as a single intramuscular injection	6 days	IL6, IL 8, CRP Significant decrease in all three markers	Changes in dyspnea severity scale (mMRC) Length of Hospital Stay, Mortality rate
Baris et al., 2013 [30]	Turkey	Clinic based	A prospective, randomized, controlled trial	55	Vitamin D 9.2 ± 2.6 Placebo 8.8 ± 2.4	Asthma	Vitamin D supplementation (650 IU/day)	12 months	IgE, IL10, Ig G4 IgE decreased, IL10 no significant difference	Total asthma symptom score (TASS), total symptom score (TSS), discontinuation of inhaled corticosteroid (ICS)
de Groot et al., 2015 [25]	Netherlands	Hospital-based	A randomized, double-blind, placebo-controlled single-center study	44	Vitamin D 59.0 ± 9.7 Placebo 53.6 ± 16.7	Non-atopic Asthma	A single high dose of oral vitamin D3 preparation (400,000 IU cholecalciferol)	9 weeks	Eosinophil count IgE No significant difference in blood eosinophils, IgE	Effect on Sputum neutrophils and eosinophils, asthma control questionnaire score, QOL score, sino nasal outcome test score, FEV_1/FVC ratio

Table 2
Summary of included studies on the effect of vitamin D supplementation on the immune response to respiratory tract infections.

Study	Country	Study setting	Study design	Study Population	Age	Clinical condition	Vitamin D form and dosage	Duration of intervention	Immune markers measured and outcomes	Other outcomes
Murai et al., 2020 [34]	Brazil	Hospital-based	Double-blind, parallel-group, randomized placebo-controlled trial	240	Vit D- 56.8 (14.2)yrs Placebo 55.8 (15.0) yrs	COVID 19	D3 single oral dose of 200,000 IU	7 days	CRP Significant decrease in CRP in vitamin D supplemented group.	Hospital length of stay, admission to ICU Mortality, mechanical ventilation requirement
Rastogi et al., 2020 [33]	India	Hospital-based	Randomized, placebo-controlled, study	40	Vit D- 50.0 (36–51) yrs Placebo 47.5 (39.3–49.2) yrs	COVID19	D3 daily 60,000 IU of cholecalciferol, 7 days, if deficient continued for another 7 days	7days+ 7days	CRP No significant difference in between intervention and control group.	Change in D-dimer, fibrinogen, ferritin and procalcitonin, SARS-CoV-2 negativity
Gupta et al., 2016 [36]	India	Hospital-based	Randomized, double-blind placebo-controlled trial	324	Vit D- 16·4 (12·9) mo Placebo 16·9 (13·4) mo	Severe pneumonia	D3 single Mega dose of 1,00,000 IU	6 months	Cathelicidin, IgA, IgG No significant difference between the intervention and control group.	Time taken for resolution of severe pneumonia, recurrence of pneumonia, Duration of hospitalization, Time to complete recovery, mortality
Miroliaee et al., 2017 [32]	Iran	Hospital-based	Double-blind, randomized, placebo-controlled trial	51	Vit D- 57.83 ± 18.84yrs Placebo 56.45 ± 20.70yrs	Ventilator-Associated Pneumonia	D3 intramuscular vitamin D (3,00,000 Units) injection	7days	CRP, IL6 IL6 reduced, no significant change in CRP	Mortality, scores for assessment of organ functions, infections
Ganmaa et al., 2017 [31]	Mongolia	TB clinic-based	Two-arm parallel double-blind randomized placebo-controlled trial	390	Vit D31 (23–44) yrs Placebo 35 (25–47) yrs	Pulmonary Tuberculosis	D3 four biweekly oral doses of 3.5 mg (1,40,000 IU) vitamin D	8weeks	CRP Significant decrease in CRP	Time to sputum culture conversion, sputum smear conversion
Salahuddin et al., 2013 [23]	Pakistan	Hospital-based	Randomized double-blinded, multi-center, placebo-controlled clinical trial	259	Vit D- 27.8 ± 13.2 yrs Placebo 28.3 ± 14.1 yrs	Active pulmonary tuberculosis	D3 600,000 IU of intramuscular vitamin D3 (cholecalciferol) for 2 doses one month apart	12 weeks	IFN gamma (unstimulated) Signifcant increase among those deficient in vitamin D	Sputum smear Conversion, mean weight gain, number of zones involved, reduction in cavity size
Coussens et al., 2012 [37]	United Kingdom	Hospital based	Double-blind randomized placebo-controlled trial	95	Vit D- 30·7 (24·5–41·5) yrs Placebo 30·5 (24·8–38·4) yrs	Tuberculosis	D3 four doses of 2.5 mg vitamin D3 or placebo by 1-week gap	8weeks	CXCL9, CXCL10, cathelicidin, IL1RA, IL6, IL12, TNF, IL10, CRP Significant reduction in IL6 and increase in INF gamma.	Immunomodulatory actions of vitamin D to individuals with tt, Tt, TT genotype
Bergman et al., 2012 [35]	Sweden	Hospital-based	Randomized, double-blind placebo-controlled study	140	Vit D- 55.4 yrs Placebo 50.8 yrs	RTIs	D3 vitamin D3 (Vigantol, 4000 IU/day,	12 months	Cathelicidin, and HNP1-3 No statistical difference between intervention and control groups.	Respiratory tract symptoms score, Number of positive samples, SNP variants and treatment effect,
Jung et al., 2018 [16]	USA		Randomized, double-blinded, and placebo-controlled	26	Vit D and placebo 19.9 yrs	URTIs	D3 daily orally vitamin D3 (5000 IU)	4 weeks	SIgA, salivary lactoferrin level Signifcant increase in SIgA	URTI symptom (score/day), QOL score, change in body composition

Quality Assessment using Jadad scale score.

Table 3 describes the study quality employing the Jadad Scale. As per the criteria 'Low risk' of bias was given a score of 1 and the high risk was scored 0. Out of sixteen studies, fourteen studies [16,23,25–32,34–37] scored 4–8 which signified high quality. Two studies [24,33] scored 3 which signified low quality.

3.3. Primary outcome

3.3.1. Meta-analysis: effect of vitamin D supplementation on immune markers

We undertook a statistical pooling of estimates across 13 studies, to quantify the difference in the levels of various immunological markers (CRP, IL-6, IL-10, INF gamma) and vitamin D levels after vitamin D supplementation in the intervention group as compared to the control group, through a meta-analysis. At least three studies with common immune markers were subjected to meta-analysis.

Five studies (n = 788) were included to assess the difference in CRP levels after vitamin D supplementation. The standard mean difference of −0.25 with low heterogeneity among studies (I^2 = 0.0 %). There was a significant decrease in CRP levels after intervention with an overall effect of Z = 3.47 (P < 0.00) (Fig. 2).

The standard mean difference of studies that measured the difference in IL-6 levels after intervention (N = 4; sample n = 398) was −0.35 with high heterogeneity among the studies (I2 = 95 %). There was no significant decrease in IL6 levels after intervention with an overall effect of Z = 0.59 (P = 0.56) (Fig. 3).

The meta-analysis of the studies (N = 3, sample n = 415) [24,26,27] that measured the difference in IL-10 levels after the intervention showed a high standard mean difference of 11.89 indicating high heterogeneity between the studies (I^2 = 100 %). The observed increase in IL-10 levels after the intervention was not significant with an overall effect of Z = 0.93 (p = 0.35) (Fig. 4).

Three studies (n = 592) [23,26,27] were included to test the difference in INF gamma levels after the intervention. The standard mean difference was 3.95, with high heterogeneity among the studies (I^2 = 100 %). There was no significant reduction in the INF gamma levels after the intervention, with an overall effect of Z = 1.67 (p = 0.09) (Fig. 5).

3.3.2. Description of other immune markers

Among the different immune markers studied, IL-17 showed contradictory results [31]. Dodamani and colleagues reported a reduction in IL-17 after vitamin D supplementation [24], while Marwa's work showed a significant increase in IL-17 in the control arm. Among the four studies that measured immunoglobulins [16,25,27,36] two showed significant differences [16,27] while the others did not [25,36]. Eosinophil count too did not show reduction post-intervention [25–27]. Positive observations were reported in studies that measured a few other immune markers such as CXCL10, IL 1 RA, IL6, IL12, and TNF alpha. Similar was the observation with IL5, IL9, IL13, and Der p 1-specific IgG4.

3.3.3. Secondary outcome

3.3.3.1. Effect of vitamin D supplementation on vitamin D levels after intervention. The standard mean difference of vitamin D status before and after intervention (N = 10, sample n = 1194) was 5.52 with high heterogeneity between studies (I^2 100 %) [16,24–26,28–31,33,36]. There was a significant increase in vitamin D levels after intervention as compared to the control group with an overall effect of Z = 2.7 (P = <0.01) (Fig. 6).

A funnel plot was created using SPSS version 29, for a visual assessment of the presence of a possible publication bias among studies of each outcome. The asymmetry observed in the funnel plot could be due to the direction of the results i.e., an increase in vitamin D levels post

Table 3
Description of study quality employing the Jadad Scale.

Corresponding Authors	Was the study described as randomized?	Was the method of randomization appropriate?	Was the study described as blinding?	Was the method of blinding appropriate?	Was there a description of withdrawals and dropouts?	Was there a clear description of the inclusion/ exclusion criteria?	Was the method used to assess adverse effects described?	Was the method of statistical analysis described?	Total Score
Igor et al., 2020	1	1	1	1	1	1	0	1	**7**
Rastogi et al., 2020	1	unclear	0	0	1	unclear	0	1	**3**
Gupta et al., 2016	1	1	1	1	1	1	1	1	**8**
Miroliaee et al., 2017	1	1	1	unclear	1	0	0	1	**5**
Ganmaa et al., 2017	1	1	1	1	1	unclear	1	1	**7**
Salahuddin et al., 2013	1	1	1	1	0	1	0	1	**6**
Coussens et al., 2012	1	unclear	1	1	0	1	0	1	**5**
Bergman et al., 2012	1	1	1	1	1	1	1	1	**8**
Jung et al., 2018	1	0	1	unclear	1	1	unclear	1	**5**
Martineau et al., 2014	1	1	1	1	1	1	1	1	**8**
Ramos-Martínez et al., 2017	1	1	1	1	1	1	unclear	1	**7**
Marwa et al., 2019	1	unclear	1	unclear	0	0	unclear	1	**3**
Dodamani et al., 2018	1	1	0	0	0	1	1	1	**5**
Dastan et al., 2019	1	1	1	1	1	1	0	1	**7**
Baris et al., 2013	1	1	1	1	1	1	1	1	**8**
Degroot et al., 2014	1	unclear	1	1	1	1	1	1	**7**

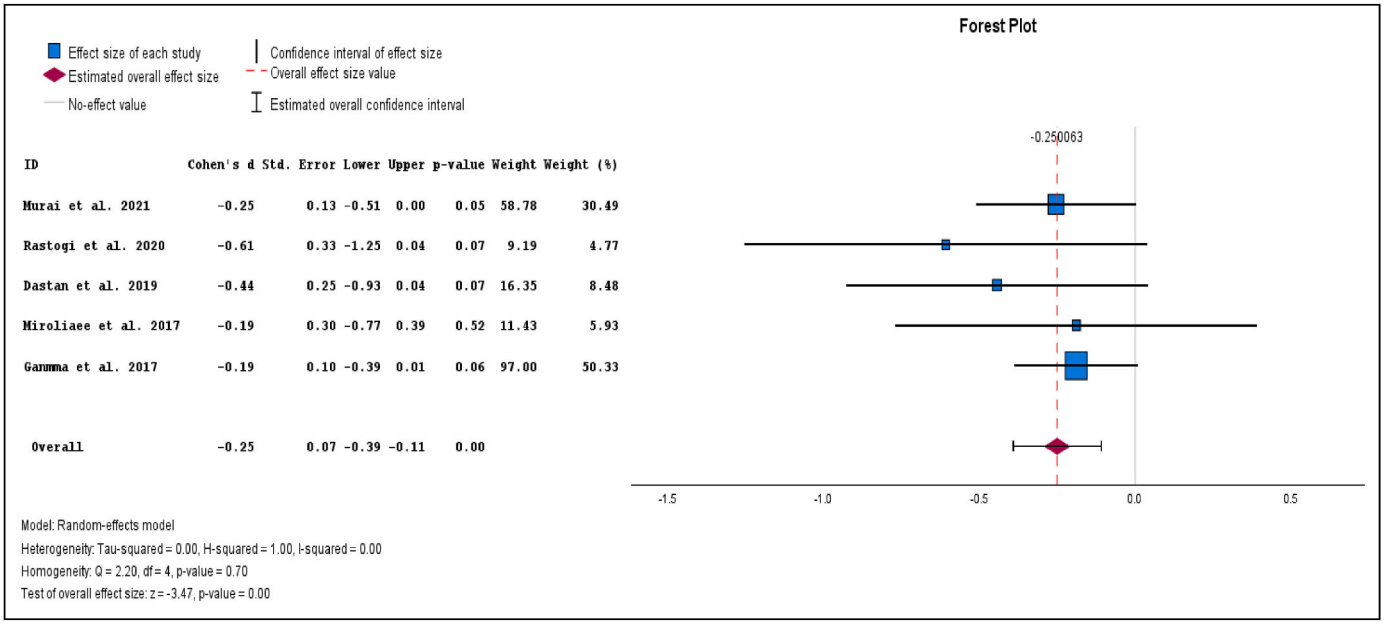

Fig. 2. Forest plot for the difference in CRP levels after the intervention.

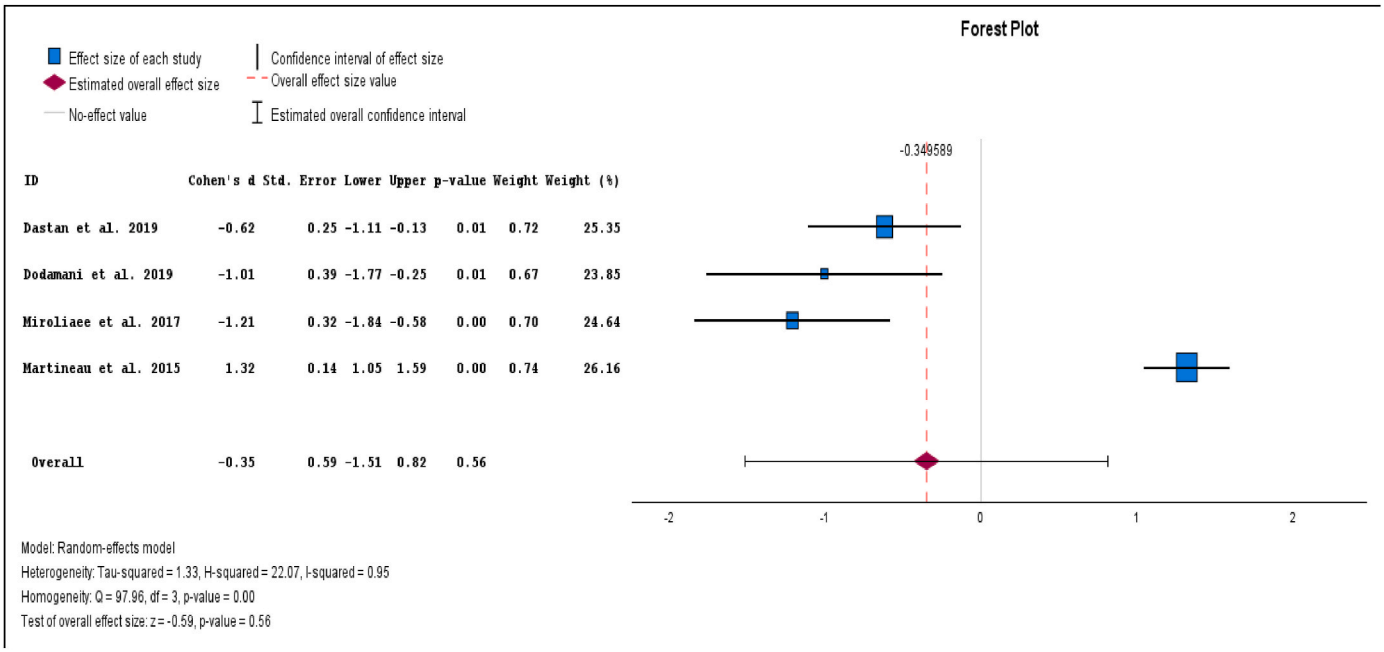

Fig. 3. Forest plot for the difference in IL6 levels after intervention.

supplementation (Fig. 7). The Egger's test confirmed publication bias with a SEi = 1.02 ($p < 0.001$) (Supp Table 1). Despite the significance, publication bias cannot be ascertained due to the inherent bias of the test toward small studies.

A summary of our findings per the REM, showed a significant decrease in the CRP status after vitamin D supplementation. The increase in IL-10 status observed in the results was not statistically significant. Likewise, the changes in the other two biomarkers studied viz. IL-6 and INF Gamma were not statistically significant.

As the heterogeneity was greater than zero ($I^2 > 0$), according to the REM, the results were predominantly influenced by the effect of small studies on all the biomarkers. We therefore performed a sensitivity test by comparing the overall effect (Z) and its significance (P) between random and fixed effects models. The analysis was repeated excluding the study with the lowest and highest weights to observe changes in the results. The results of the sensitivity test revealed no change in the overall effect (z) of CRP and its significance following the comparisons or exclusion. However, IL6 showed a significant increase when the outlier study was removed. The excluded study (outlier) that gave contradictory results from the rest of the pooled studies focused on asthma, while the retained studies were infectious respiratory tract diseases. Studies with lower weight when removed did not alter the results. INF Gamma [Z = 9.25, P = 0.00] and Il-10 [−9.04, P = 0.00] showed a significant decrease according to the fixed effects model. The increase in INF Gamma was observed in participants who had vitamin D deficiency typical of tuberculosis. Due to the effect of non-infectious diseases pooled in the analysis, this was not significant (Table 4). Thus, excluding the non-infectious diseases is likely to provide a true

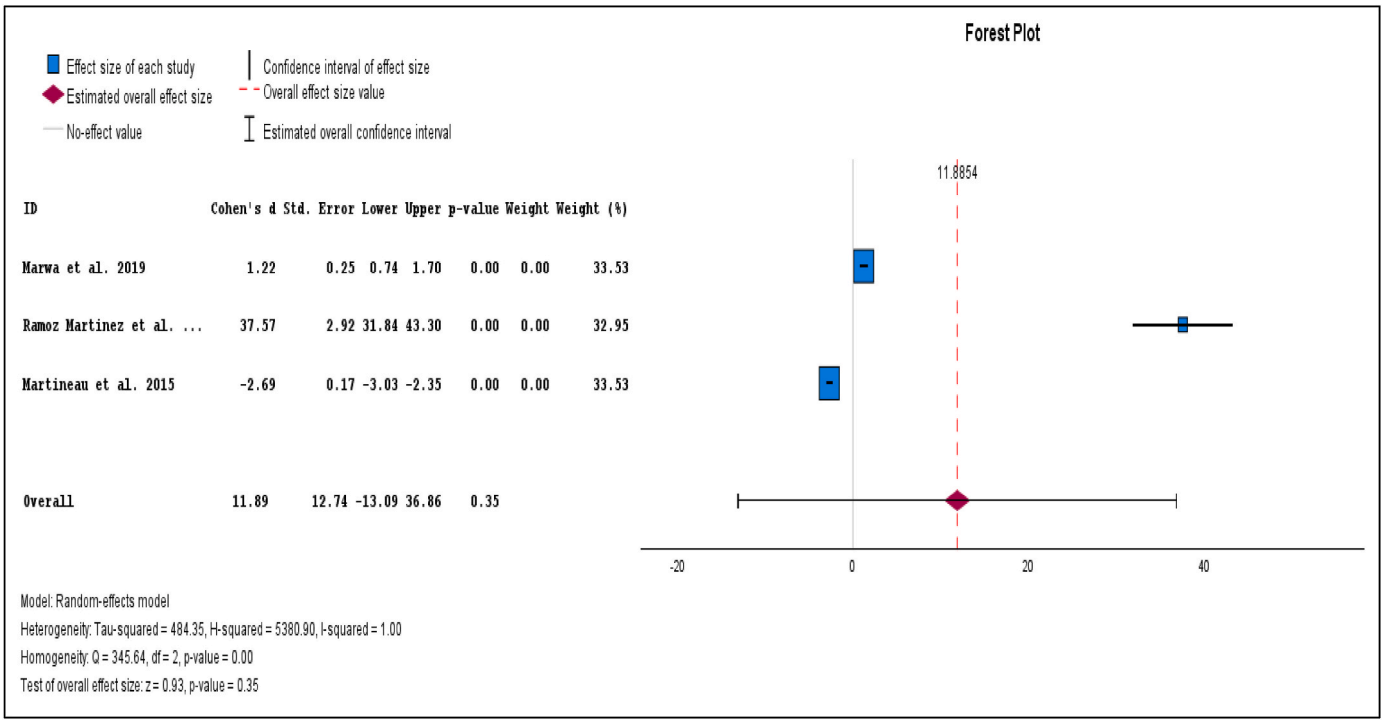

Fig. 4. Forest plot for the difference in IL10 levels after intervention.

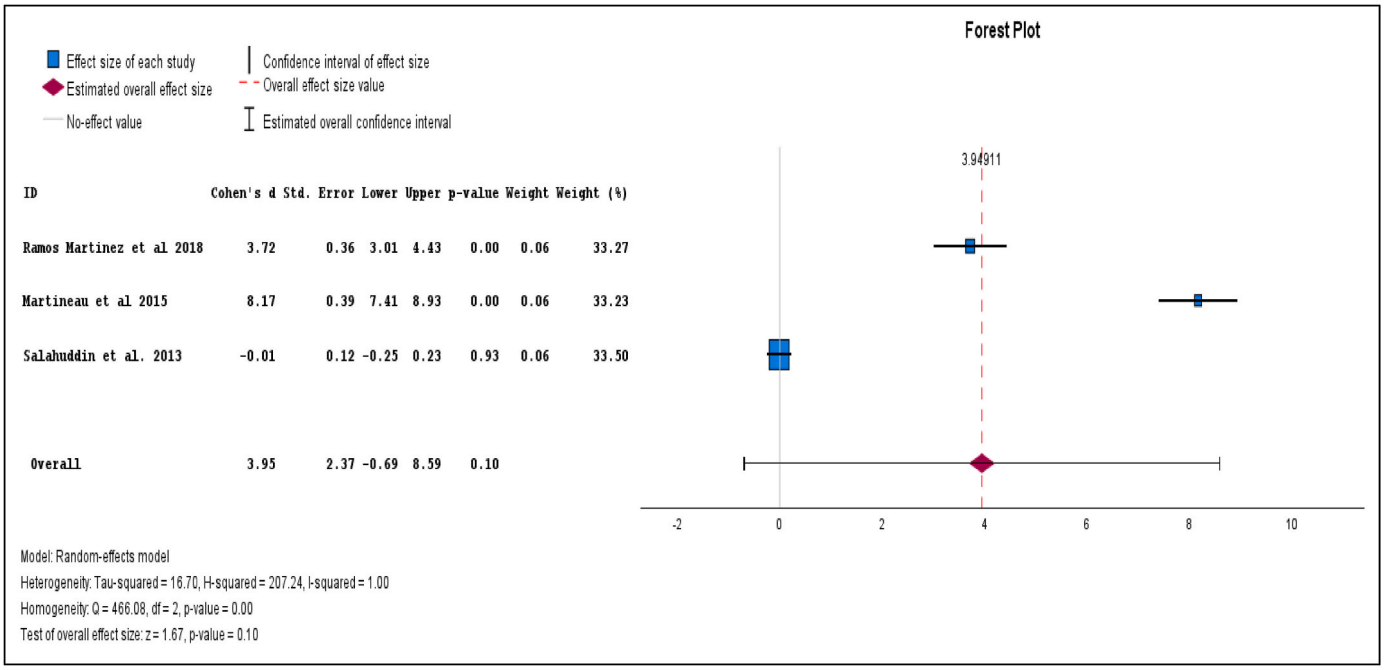

Fig. 5. Forest plot for the difference in INF gamma levels after intervention.

estimate of the vitamin D supplementation in infectious respiratory diseases. The results, however, need to be carefully interpreted as the fixed effects model favors studies with higher weight. The forest plots for the sensitivity analysis are provided in the supplementary file Figs. S1–S5.

3.3.3.2. Other outcomes reported in the included studies. Different outcomes were measured in different studies. Considering the complexity of the diseases, scores of varied outcomes were assessed by seven out of 14 studies. These included i) Sequential Organ Failure Assessment (SOFA) score, ii) Clinical Pulmonary Infection Score (CPIS) score, iii) Acute Physiology and Chronic Health Evaluation II (APACHE II) score, iv) Quality-of-life score, v) scores of respiratory tract infections (i.e., runny nose, sneezing, cough) vi) asthma control score, vii) sino-nasal outcome questionnaire test score, FEV_1/FVC ratio viii) dyspnea severity scale and ix) TB scores.

Few other studies directly measured improvement in the severity of infections following vitamin D supplementation. These included

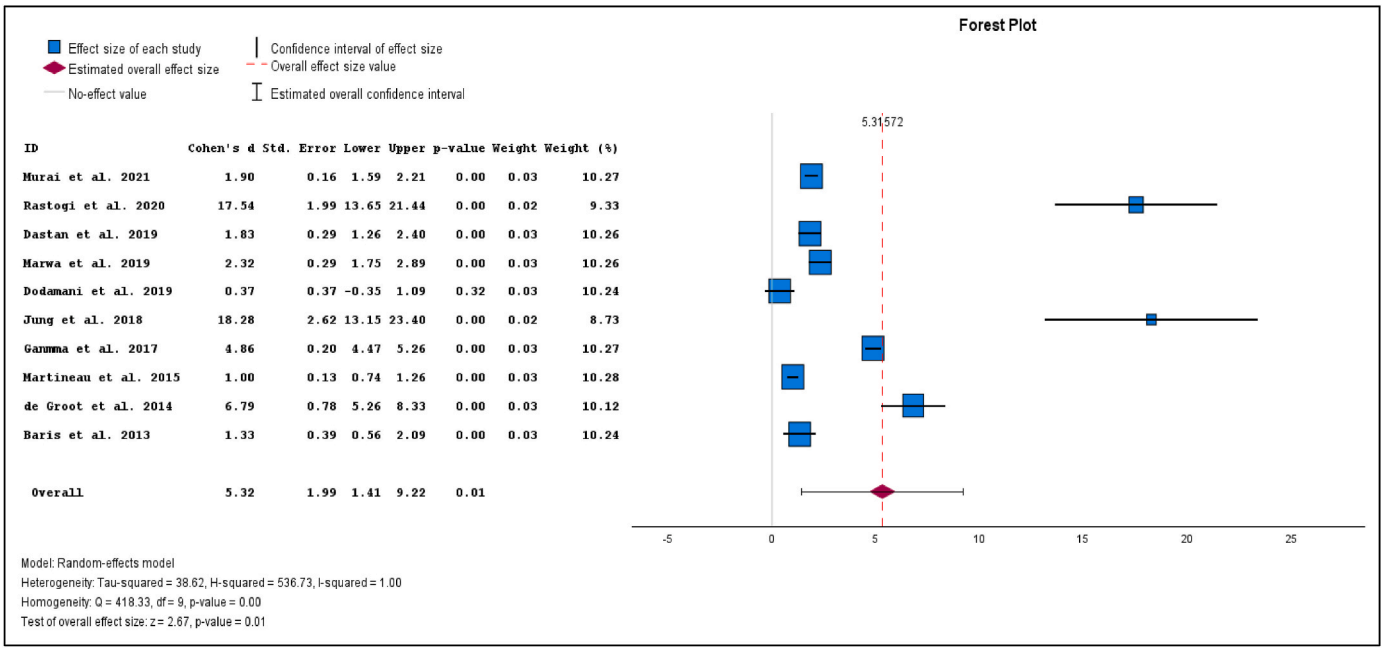

Fig. 6. Forest plot showing vitamin D levels after intervention.

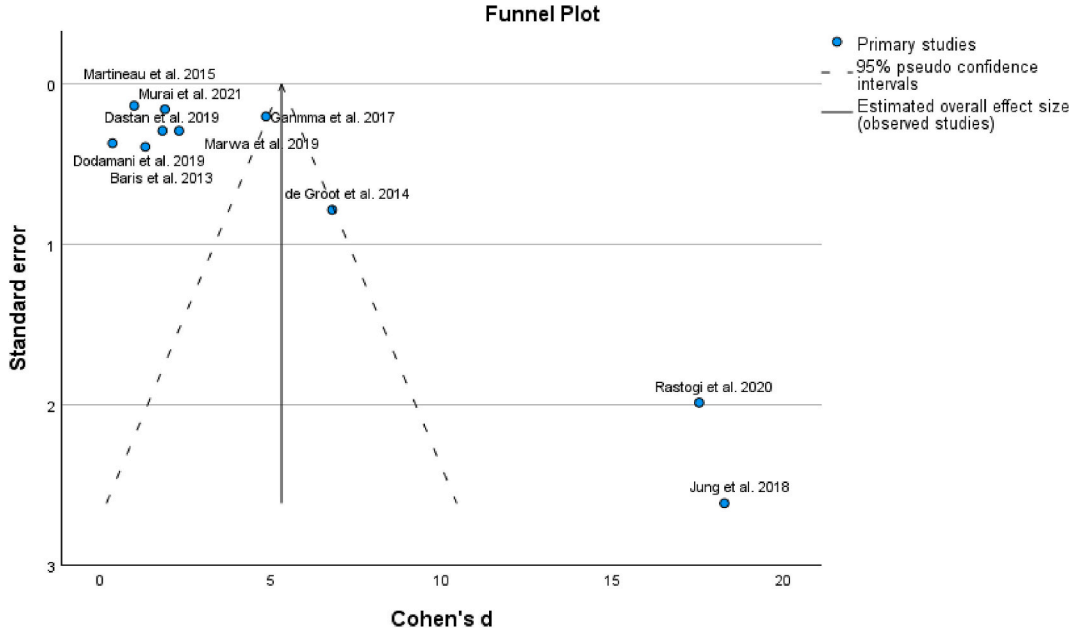

Fig. 7. Funnel plot to test publication bias.

resolving severe pneumonia and fever, sputum smear and culture conversion, pathogenic bacterial growth, sputum eosinophil, and neutrophil count. Allergic Bronchopulmonary Aspergillosis (ABPA) exacerbations were measured in studies on asthma. Indirect improvement was assessed, such as chest radiographs to assess the number of zones involved and reduction in cavity size, ICU admission, mechanical ventilation requirement, or duration of hospital stay. Mortality as an outcome was included in a few studies.

No conclusive improvements could be observed concerning the duration of hospital stay, ICU admission, or mortality. Although differences were observed between the control and intervention groups, the results were not statistically significant. Concerning infection clearance SARS-CoV- 2 infections did not show a significant difference. However, differences observed between the intervention and control group in the resolution of pneumonia were significant after adjusting for respiratory rate and other co-variates. Recurrence of pneumonia and fever clearance time did not differ between the groups. Improvements in chest radiographs by Salahuddin and co-workers [23] found that *Mycobacterium tuberculosis* antigen (MTBs) induced IFN Gamma levels in the drug intervention group significantly increased post-therapy, especially among individuals deficient in vitamin D. Studies also showed a reduction in white blood cell, neutrophil, and monocyte counts, and elevated lymphocyte to monocyte ratios in the peripheral blood. However, no significant effect of vitamin D was observed on sputum neutrophil and eosinophil count [25].

With regard to various scores related to asthma and its associated

Table 4
Sensitivity test for the meta-analysis.

A. Inflammatory marker		
CRP	Z	P
Random effects Model	−3.47	0.00*
Fixed effects Model	−3.47	0.00*
Removing lowest weight study	−3.47	0.00*
IL-6		
Random effects Model	0.59	0.56
Fixed effects Model	4.31	0.00*
Removing lowest weight study	−4.42	0.00*
INF gamma		
Random effects Model	1.67	0.10
Fixed effects Model	9.25	0.00*
Removing lowest weight study	0.99	0.32
Outlier removed[a]	2.67	0.01*
IL 10		
Random effects Model	0.93	0.35
Fixed effects Model	−9.04	0.00*
Removing lowest weight study	−0.38	0.71
Outlier removed[a]	1.06	0.29
B. Vitamin D		
Random effects Model	2.67	0.01*
Fixed effects Model	26.16	0.00*
Removing lowest weight study	3.41	0.00*

[a] Only those studies that had outliers (that gave contradictory results from the rest of the pooled studies) were removed.

quality of life, no correlations were observed between vitamin D supplementation and the scores. Vitamin D in combination with subcutaneous allergen-specific immunotherapy (SCIT) showed better scores than the placebo group. No changes were observed in the dyspnoea scale. No improvement in allergic bronchopulmonary aspergillosis (ABPA) exacerbations or sequential organ failure assessment (SOFA) and clinical pulmonary infection score (CPIS) scores was evident, but significant changes in lung function scores were observed. Genotype-specific benefits following vitamin D supplementation were observed in patients carrying the 'AA' genotype (–55 %) in the CYP2R1-gene, encoding the 25-hydroxylase enzyme, compared to AG or GG genotype carriers benefit (−6%).

4. Discussion

Given the severity of outcomes of respiratory tract infections, characterizing the role of vitamin D in attenuating inflammatory response is vital. For upper respiratory tract infections or allergic conditions in general, evidence suggests adequate vitamin D status attenuates the levels of inflammatory markers that otherwise manifest serious health outcomes. Our work adds to the existing evidence on the role of vitamin D in upper respiratory tract infections, including COVID-19 and non-infectious chronic respiratory tract diseases, and its action on inflammatory markers.

CRP concentrations rise in response to infection, inflammation, tissue damage, or injury. Respiratory infections that bring about acute and chronic inflammation could affect the quality of life [38,39]. In our metanalyses, CRP levels showed a significant decrease after vitamin D supplementation. However, variations were particularly pronounced with regard to different diseases, age groups, and duration of supplementation. For instance, among healthy women, no significant correlations between serum levels of vitamin D and CRP were observed [40]. However, among tuberculosis patients, a significant difference in CRP in short but not in longer duration of supplementation was identified [41]. Similarly, in COVID-19 infection, lower levels of CRP were observed in patients with sufficient vitamin D levels [13]. Perhaps the beneficial effect of vitamin D is pronounced during the infectious state, as also evidenced in other infections [42,43]. In consonance with our findings, previous meta-research on vitamin D supplementation indicated that supplemental vitamin D significantly decreased the circulating hs-CRP level [44]. However, few contradictory observations have been reported such as in Chens's [44] work, where baseline CRP levels, dose, and duration of intervention contributed to heterogeneity. Explanations for the anti-inflammatory effect of vitamin D come from vitamin D receptor (VDR) altering cytokine secretion patterns, suppressing T cell activation, and inducing regulatory T cells [6]. Specifically, in pulmonary tuberculosis vitamin D significantly suppressed complete Freund's adjuvant (CFA) induced pro-inflammatory cytokines [45]. In COVID-19 infection vitamin D insufficiency was associated with high levels of CRP [13]. Certain biological agents could act on IL-6 and TNF α and lower the levels possibly substantiating the findings.

Our work did not show any significant effect of vitamin D supplementation on IL-6 levels. Although vitamin D is shown to reduce oxidative stress in primary Human Bronchial Epithelial Cells (HBEC), suppress IL-6 response, and reduce proliferation, and proinflammatory cytokines, in the airway smooth muscle [46], similar results were reported in studies that focussed on other chronic conditions [47,48]. In these studies too like ours, the representation of studies was less which could have resulted in an underestimation of the effects of vitamin D. IL-6 is systemically upregulated in infections as an immune evasive strategy for virus survival [49]. The increase in IL-6 could reflect certain infectious pathologies or their severity which necessitates the need to test different doses and durations.

Interferon-gamma (IFN) showed contradictory results compared to the existing literature. For instance, studies showed vitamin D can suppress the levels of pro-inflammatory cytokines including IL-6, IFN Gamma, and TNF [50–52]. The results of our meta-analysis showed an increase in IFN Gamma after supplementation, however, the change was not significant. The three studies that were included in the meta-analysis of IFN Gamma had higher levels in the intervention group than in the control group, and yet the inherent variation between the studies perhaps contributed to this observation. Few studies suggest that vitamin D increases the serum levels of cathelicidin which in turn modulates IFN Gamma against tuberculosis [53,54] Gamma interferon and vitamin D are recognized immune modulators. The increase in IFN Gamma could be due to the immune suppression in tuberculosis, which could have improved with vitamin D supplementation. The differential regulation between bacterial and viral infections could have contributed to the increase in inflammatory markers [53–55].

Our meta-analysis did not show a significant increase in anti-inflammatory cytokine IL-10 after intervention with vitamin D. The results differ from other works that show an increase. The dosage and duration or the stage of the disease such as acute or severe could have contributed to the variations. Few studies included in the meta-analysis did show a significant association between vitamin D supplementation and decreased IgE levels. Among asthmatic patients, evidence of such an association is not concrete [56,57]. While earlier work showed a significant change in sputum eosinophils with vitamin D supplementation [58], our results differed. It has been postulated that vitamin D enables a balance between the pro and anti-inflammatory cytokines IL-6 and IL-10 respectively [59].

Our secondary outcomes did not show a significant difference in mortality among the intervention group [60] and found an inverse association between overall serum 25(OH)D concentration with risk and severity of Acute Respiratory Tract Infection (ARTI). Two of the included studies showed vitamin D3 treatment to be inversely associated with the total infectious score. Work done by Charan and co-workers [14] showed a significant reduction in the incidence of respiratory tract infection in the vitamin D supplemented as compared to the placebo group.

Some of the strengths of our work are as follows: In this systematic review and meta-analysis, we have included infectious as well as non-infectious diseases of the respiratory tract and provided evidence from 16 randomized controlled trials. To characterize the specific effects of vitamin D on the immune response we analyzed a few immune markers after vitamin D supplementation in various respiratory tract disease

outcomes.

There are several limitations to our study. The results of our findings should be carefully interpreted due to the heterogeneity of the selected studies. We have included different dosages of vitamin D and the duration of the intervention (7 days–8 months). As few studies were available on a particular disease condition, we included all types of respiratory tract diseases and dosages of vitamin D and this could explain the high heterogeneity in our meta-analysis. The expected high heterogeneity guided the use of REM. Many factors contributed to the high I^2. The clinical heterogeneity of the respiratory conditions, the variations in treatment, and fewer studies on each disease against a variety of inflammatory markers are a few factors. The pooling of respiratory tract infections, acute with chronic, and other airway obstructive diseases that vary in the inflammatory response have contributed to our study findings. This is evident from the results of the sensitivity test. Excluding airway obstruction diseases showed significant changes in the inflammatory markers. However, the number of studies included under each marker is few to derive conclusions. Some studies presented results as median which was converted to mean and standard deviation which probably influenced our results. The lack of studies on other inflammatory markers with vitamin D supplementation limits their characterization. For instance, the results of vitamin D supplementation on IL-10 identified only three studies. Although the weight of the other two studies was high, only one study showed high significance which contributed to the present results. The adiposity of the participants included in the study was not described in the studies, which could have altered the pro-inflammatory cytokines. Further, the vast majority of studies originated from Eastern countries; thus, these results cannot be extrapolated to Western populations. Further, studies were not excluded based on the ROB. Three of the selected studies suffer from significant sources of bias, and this could have impacted our study findings. Emphasis on COVID-19 and the effectiveness of vitamin D would be an important meta-analysis to conduct as our study was not designed to test the hypothesis. This study was not registered in PROSPERO which further limits overlap with similar work.

5. Conclusion

Among the biomarkers studied CRP significantly decreased, with no significant changes in the others. Our findings suggest that vitamin D supplementation modestly affects the immune response. Pooling infectious and non-infectious respiratory diseases could have underestimated our findings. More RCTs are warranted to obtain substantial results.

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CRediT authorship contribution statement

Angeline Jeyakumar: Writing – original draft, Supervision, Methodology, Formal analysis, Conceptualization. **Pooja Bhalekar:** Methodology, Investigation, Formal analysis, Data curation. **Pranita Shambharkar:** Methodology, Data curation.

Declaration of competing interest

This project was not funded and the authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.hnm.2024.200272.

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