Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Meta-analysis

Serum vitamin D levels and COVID-19 during pregnancy: A systematic review and meta-analysis

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SUMMARY

Background: Serum vitamin D levels are reported to be associated with the risk of incidence and severity of COVID-19 in the general population. During pregnancy, immune system alterations in line with changes in vitamin D metabolism may affect the course of COVID-19. Thus, we aimed to systematically review the association between vitamin D, pregnancy, and COVID-19.

Methods: A systematic literature search was conducted in PubMed, Scopus, Web of Science, Embase, and Google Scholar until the end of May 2022. Mean differences (MD) with 95% CI were used as desired effect sizes to assess the association of serum vitamin D levels with the risk of incidence and severity of COVID-19 in pregnant women.

Results: Among 259 records, 7 and 6 studies were included in the systematic review and meta-analysis, respectively. All included studies had acceptable quality. Our results demonstrated an insignificant difference between infected women and non-infected controls (MD = -2.55 ng/ml, 95% CI: −6.85 − 1.74). But serum vitamin D levels in severe/moderate cases compared to mild ones (MD = −2.71 ng/ml, 95% CI: −4.18 to −1.24) are significantly lower.

Conclusion: Based on the current evidence, serum vitamin D level does not associate with the risk of SARS-CoV-2 infection among pregnant women, but we find a significant association with the severity of the disease. These findings may be helpful in similar conditions and future studies to better understand the complex immune alterations during pregnancy.

1. Introduction

The emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has profoundly affected lives worldwide since 2019. The disease caused by SARS-CoV-2, coronavirus disease 19 (COVID-19), rapidly evolved and was declared a pandemic by the world health organization (WHO) in March 2020 [1]. Although the catastrophic days of the pandemic are over, COVID-19 is still considered a significant health issue [2].

SARS-CoV-2 is mainly transmitted through respiratory droplets and binds to pulmonary epithelial cells via membrane-bound angiotensin-converting enzyme 2 (ACE-2), resulting in its down-regulation [3]. The infection of target cells with SARS-CoV-2 activates inflammatory responses and various cell death programs, causing lung injuries [4]. Furthermore, the recruitment of pro-inflammatory immune cells to the lungs can initiate cytokine storms leading to life-threatening conditions [5].

The clinical manifestation of COVID-19 encompasses a broad spectrum ranging from asymptomatic to severe respiratory and multi-system complications leading to death [6]. Based on current knowledge, the elimination of SARS-CoV-2 primarily relies on the

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host immune system. Thus, alterations in the immune status throughout conditions like pregnancy could significantly influence the course of COVID-19 and its clinical outcomes. During gestation, immune responses shift toward T helper 2 (Th2) responses [7], circulating natural killer (NK) cells [8], and plasmacytoid dendritic cells (pDCs) [9] are reduced, and an overall capacity to confront SARS-CoV-2 is diminished [10]. Moreover, the ACE-2 is upregulated during normal pregnancies, regulating the hemodynamic changes by increasing angiotensin 1-7 [11].

The role of micronutrients, especially vitamin D, in the severity and sequelae of COVID-19 is widely investigated. However, human bodies can produce vitamin D in sunlight, but vitamin D deficiency is not rare [12]. Vitamin D has immunomodulatory effects and can reduce inflammatory cytokines, including tumor necrosis factor α (TNF-α) and interleukin 6 (IL-6), while promoting the production of anti-inflammatory cytokines such as IL-4, IL-5, and IL-10 [13,14]. Besides, vitamin D upregulates the expression of ACE-2 and decreases the ACE/ACE-2 ratio, which could be crucial in COVID-19 [15,16]. However, there are conflicting reports on whether serum vitamin D level is a determining factor for risk and severity of COVID-19 in the general population [17,18].

As aforementioned, pregnancy is a unique immunological condition that can potentially worsen the course of COVID-19, and vitamin D has proven to modulate the immune system and prominent molecules related to COVID-19. Pregnant women are at higher risk of vitamin D deficiency [19]. Moreover, contrasting evidence regarding the effect of vitamin D levels on the incidence [20,21] and severity [21,22] of COVID-19 in pregnant patients emphasizes the need to systematize the knowledge on this ground. Therefore, this study aims to evaluate the effect of vitamin D levels on the risk of infection with SARS-CoV-2 and the severity of COVID-19 in pregnant females.

2. Methods

2.1. Search strategy

This review is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) 2020 guideline [23]. A comprehensive online search was conducted using Medline (PubMed), Scopus, Web of Science, and Embase databases on published articles up to the end of May 2022 using the following search query ("Vitamin D″ OR "Vit D″ OR "calcitriol*" OR "cholecalciferol*" OR "25-Hydroxycolecalciferol" OR "25(OH)D" OR "25-hydroxyvitamin D" OR "hydroxycholecalciferol*" OR "25-hydroxyvitamin D3" OR "ergocalciferol*" OR "calcifediol*") AND (COVID-19 OR "SARS-CoV-2" OR "coronavirus" OR "cov-19" OR "2019-ncov" OR "SARS-CoV2" OR "Coronavirus disease" OR COVID OR "SARSCoV2" OR "corona virus disease 2019" OR "novel coronavirus pneumonia" OR "severe acute respiratory syndrome coronavirus 2" OR "coronavirus disease 2019" OR "COVID19" OR "novel coronavirus 2019 disease" OR "SARS-CoV2" OR "nCoV19" OR "nCoV 2019" OR "2019 nCoV" OR "novel coronavirus disease 2019") AND (Pregnancy OR pregnant OR antepartum OR prenatal OR "obstetric" OR maternal OR mother OR "pregnan*"). In addition, reference lists of relevant reviews were examined to identify missing eligible articles.

2.2. Protocol and registration

The protocol of this study is available on PROSPERO with the "CRD42022327128" registration number.

2.3. Inclusion criteria

Using PECO (patient, exposure, comparison, and outcome) strategy (summarized in Table 1), observational studies presenting original data on serum vitamin D levels and COVID-19 status in pregnant females were included.

2.4. Exclusion criteria

Studies with no control group and studies published in languages rather than English were excluded.

2.5. Quality assessment

The quality of included studies was evaluated using the National Institution of Health (NIH) Quality Assessment Tool. This tool consists of 12 questions for case–control studies and 14 questions for observational cohort and cross-sectional studies. Each question was answered by "Yes", "No" or "Other (cannot determined, not applicable, not reported)" and after that, the overall quality of each study was rated as "Good", "Fair" or "Poor". Two reviewers (SM-T and MHM) evaluated the studies separately, and any disagreement was resolved through discussion and consensus by a third reviewer (MF).

2.6. Data extraction

Two reviewers (SM-T and MHM) separately extracted data from the eligible articles, and it was checked by a third reviewer (MF). The extracted data are as follows: first author's name, publication year, country of origin, study design, number of enrolled participants (cases and controls), trimesters of pregnancy, participants' serum levels of vitamin D, normal range of vitamin D, and COVID-19 severe and mild cases if available.

2.7. Statistical analysis

The mean difference and 95% confidence interval (CI) of vitamin D level (ng/ml) between infected pregnant women and non-infected were calculated for each study. A random-effects meta-analysis and the inverse variance method were used to estimate weighted mean difference (WMD) as the pooled effect size because of underlying differences in study designs and methodologies. We assessed the risk of publication bias by Egger's test. The between-study heterogeneity was assessed with the use of the I^2 statistic. We used Kappa statistics to assess inter-rater agreement between reviewers for study inclusion and assessment of the risk of bias [24,25]. Values of kappa between 0.40 and 0.59 have been considered to reflect fair agreement, between 0.60 and 0.74 to reflect good agreement, and 0.75 or more to reflect excellent agreement [26]. All statistical analyses were conducted by Stata 17 software (StataCorp LP), and a 2-sided 0.05 level of significance was used in all cases.

3. Results

3.1. Study selection

Based on the search strategy, 259 records were identified. After duplicate removal, 122 citations were screened, of which 26 papers were potentially eligible for full-text review. Finally, seven papers

Table 1
PECO search strategy.

PECO component	Inclusion criteria
Population (P)	Pregnant females
Exposure (E)	SARS-CoV-2 infection
Comparison (C)	No COVID-19/severity of COVID-19
Outcome (O)	Differences in mean serum vitamin D levels

were qualified for inclusion in the systematic review and meta-analysis. Inter-rater agreement between reviewers for study selection was excellent (Kappa statistics = 0.92). Figure 1 summarizes the study selection process.

3.2. Description of included studies

Out of seven included studies, five utilized a case–control design [20–22,27,28], one study used a retrospective cohort analysis [29], and one was in a cross-sectional manner [30].

Included studies covered a total of 1799 pregnant women, of which 886 individuals were healthy and 913 were confirmed COVID-19 cases. The smallest sample size was a retrospective cohort study of 34 participants [29], while the largest was a case–control survey of 491 individuals [21]. Three studies assessed only pregnant women in the third trimester, while others included participants without any limitation of gestational age. The normal range of vitamin D is considered to be above 30 ng/ml in all studies except one study in Turkey by Tekin et al., which considered amounts above 50 ng/ml as an optimal serum concentration [20]. Four studies were conducted in Turkey [20,21,27,30], two in Spain [22,28], and one in France [29]. Based on the NIH quality assessment tool, six studies [20–22,28–30] possessed good quality, and one study qualified as fair [27]. Agreement on the risk of bias assessment was excellent (Kappa statistics = 0.8). Table 2 shows the details of the quality assessment process.

Three studies assessed just vitamin D concentration among COVID-19 cases and healthy individuals [20,27,28]. One study assessed only serum vitamin D within mild cases and severe ones [30]. On the other hand, three research investigated the effect of serum vitamin D on the severity and risk of COVID-19 [21,22,29].

Out of seven included studies, six were included in the meta-analysis. The study conducted by Yalcin Bahat et al. [27] was not included in the meta-analysis, due to the lack of a control group. Features of included studies were summarized in Table 3.

3.3. Vitamin D and risk of COVID-19 and main findings of the meta-analysis

Four studies [21,22,27,29] reported significantly lower serum vitamin D levels in cases compared to healthy participants. However, Tekin et al. [20] found significantly higher serum vitamin D levels in cases (14.64 ± 10.72 ng/ml) than in controls (12.52 ± 8.28 ng/ml). Moreover, a case–control study in Spain did not find any significant difference between serum vitamin D status in cases (21.28 ± 9.52 ng/ml) and controls (18.54 ± 8.04 ng/ml) [28].

Pooled results of 5 studies [20–22,28,29] did not show a significant difference between infected women and the non-infected group, even though the mean serum vitamin D level was 2.55 ng/ml less in the COVID-19 group compared to the healthy group (WMD = −2.55 ng/ml, 95% CI: −6.85 − 1.74) (Fig. 2). There was considerable heterogeneity between studies (I^2 = 93.07%, Q′

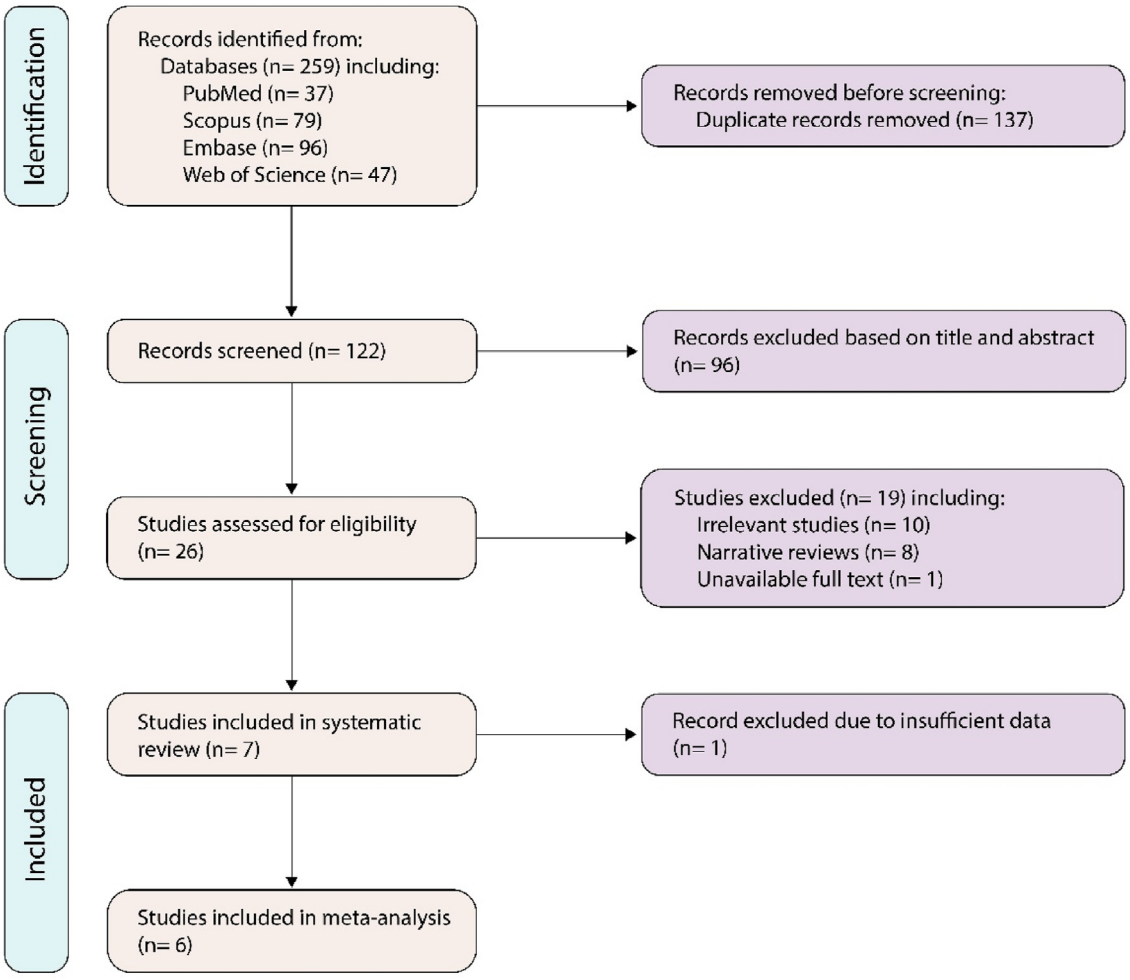

Fig. 1. PRISMA diagram for study selection process.

Table 2
Quality assessment of included studies.

Study	Design	Items of NIH quality assessment tool[a]														Summary quality
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	
Yalcin Bahat et al., 2020 [27]	Case-control	yes	yes	no	no	yes	no	no	no	yes	yes	no	no			Fair
Sinaci et al., 2021 [21]	Case-control	yes	yes	no	yes	yes	yes	yes	yes	no	yes	no	no			Good
Tekin et al., 2021 [20]	Prospective case–control	yes	yes	yes	no	yes	yes	no	yes	yes	yes	no	no			Good
Seven et al., 2021 [30]	Cross-sectional	yes	yes	yes	no	yes	no	no	yes	yes	no	yes	no	no	no	Good
Moreno-Fernandez et al., 2022 [28]	Case-control	yes	yes	yes	yes	yes	yes	no	yes	no	yes	no	no			Good
Schmitt et al., 2022 [29]	Retrospective cohort	yes	yes	yes	yes	no	yes	no	yes	yes	no	yes	no	yes	no	Good
Ferrer-Sánchez et al., 2022 [22]	Case-control	yes	yes	yes	yes	yes	yes	yes	yes	no	yes	no	yes			Good

[a] NIH quality assessment tool has 12 questions for Case-Control studies and 14 questions for observational Cohort and Cross-sectional studies.

$p < 0.001$). Egger's test did not reveal any evidence of publication bias (Egger's $p = 0.32$). After sensitivity analysis, the pooled effect size yet was not statistically significant.

3.4. Vitamin D and severity of COVID-19 and main findings of the meta-analysis

All studies reported a significantly higher serum vitamin D in mild cases compared to severe ones [21,29,30]. However, Ferrer-Sánchez et al. [22] did not find a significant difference between mild cases (10.5 ± 7.26 ng/ml) with moderate and severe ones (8.7 ± 2.15 ng/ml), and even between cases that did not admit to Intensive Care Unit (ICU) (10.15 ± 7.1 ng/ml) and admitted cases to ICU (9.3 ± 4.24 ng/ml).

Pooling the extracted mean differences resulted in a significantly lower (on average 2.71 ng/ml lower) serum vitamin D level in severe/moderate cases vs. mild ones (WMD = −2.71 ng/ml, 95% CI: −4.18 to −1.24) (Fig. 3). I^2 index as a measure of heterogeneity was near zero ($I^2 = 0.0\%$, Q'p = 0.84). Egger's test did not show evidence of publication bias (Egger's p = 0.952). Based on the sensitivity analysis, the pooled effect size did not change notably.

4. Discussion

According to the results of a primary search, more than 50 systematic reviews exist on different aspects of vitamin D and COVID-19. However, in almost all of them, pregnant women were not included [31–34]. Moreover, various studies demonstrated an increased risk of pregnancy complications in COVID-19 patients [35,36]. Thus, a systematic review and meta-analysis of available literature regarding the association between vitamin D status and COVID-19 in pregnant women might improve outcomes of pregnancy in COVID-19 patients.

Results of the current study indicate vitamin D deficiency among the majority of participants (COVID-19 cases and healthy individuals) in all investigations. Surprisingly, there is no significant difference in serum vitamin D levels between COVID-19 cases and healthy controls (WMD = −2.55, 95% CI: −6.85 − 1.74), but serum vitamin D levels are significantly lower in severe cases (WMD = −2.71, 95% CI: −4.18 to −1.24). Findings of the current meta-analysis regarding the association between vitamin D levels and the risk of COVID-19 in pregnant women are against the results of some investigations in the general population [17]. That might be due to the high prevalence of vitamin D deficiency among participants, and even the lack of sufficient studies in this field. To date, there is one study in Qatar that assessed the difference of serum vitamin D levels in pregnant and non-pregnant women with COVID-19. Its results suggested a significant risk of vitamin D deficiency among pregnant women (OR = 6.5, 95% CI = 3.6–11.8) [37].

Pregnancy is among the physiological risk factors for low serum vitamin D levels, and several studies investigated the effect of vitamin D deficiency during pregnancy [38]. It has been reported that low vitamin D levels are associated with an increased risk of pregnancy complications, including gestational diabetes mellitus [39], preeclampsia [40], preterm labor [41,42], low birth weight [43] and demand for a cesarean section [44]. The U.S. Institute of Medicine (IOM) recommendation for vitamin D intake during pregnancy and lactation is 600 IU/day, while the American College of Obstetricians and Gynecologists (ACOG) recommends supplementing 250–600 IU/day [45,46]. Nevertheless, recent clinical trials suggest even more supplementation with vitamin D to reduce the risk of pregnancy complications and adverse outcomes [47]. On the other hand, although many controversies exist on the efficacy of vitamin D supplementation on COVID-19 prevention, severity, and outcomes in the general population [48–52] but there are no investigations on pregnant women yet.

Vitamin D deficiency is reported to associate with a higher risk of serious viral infections such as hepatitis and AIDS [53]. There are also studies describing the association between serum vitamin D levels and susceptibility to respiratory tract infections, including influenza and COVID-19 [54]. It has been shown that vitamin D supplements protect against respiratory tract infections as well as SARS-CoV-2 [55,56]. During pregnancy, vitamin D status has been reported to be inversely associated with the risk of bacterial and fungal infections. In addition, maternal 1,25(OH)2D and inflammatory cytokines, including IL-6 and TNF-α, inversely associate at delivery [57].

While there is clinical evidence that vitamin D has a supportive role against infections, the molecular mechanisms of this effect need further elucidation as the effects of vitamin D on the immune system incongruously vary in nature [58]. Vitamin D has immunomodulatory effects both on innate and adaptive immunity. In the innate immune system, activation of Toll-like receptors upregulates the expression of vitamin D receptors and vitamin D-1-hydroxylase, leading to the production of cathelicidins that activate neutrophils, macrophages, and dendritic cells [59,60]. In adaptive immunity, vitamin D diminishes the proliferation of Th1 cells and skews the maturation of T lymphocytes toward regulatory T cells, causing lower levels of pro-inflammatory cytokines and hampering overwhelming immune responses against pathogens [61]. The attenuation of adaptive immunity caused by vitamin D could be beneficial in impeding cytokine storms. However, it could also predispose patients to secondary infections [61,62].

4.1. Limitations and strengths

To the best of our knowledge, this is the only meta-analysis that assessed the effect of vitamin D status in pregnancy on the risk and severity of COVID-19. Moreover, all included studies in quantitative analysis possess good quality, and there is no evidence of publication bias.

Table 3
Included studies in the systematic review.

Author	Date	Country	Design	Participants	Trimester (n)			Age (year)[a]	Vitamin D (ng/ml)[a]	Vit D normal range (ng/ml)	Outcome	Main finding
					1st	2nd	3rd					
Yalcin Bahat et al., 2020 [27]	September 2020	Turkey	Case-control	44 confirmed COVID-19 cases	5	12	27	28.5	9.7 ± 59.14	30–100	Incidence	Serum vitamin D levels were significantly lower than normal cut-off ranges ($p < 0.001$)
Sinaci et al., 2021 [21]	August 2021	Turkey	Case-control	159 confirmed COVID-19 cases	Participants are from all trimesters			29.6	12.46 ± 6.46	Above 30	Incidence	Serum vitamin D levels were significantly lower in cases ($p < 0.001$)
				332 healthy pregnant women				27.4	18.76 ± 13.74			
				128 mild COVID-19 cases	Participants are from all trimesters			NR	13.69 ± 9.72	Above 30	Severity	Serum vitamin D levels were significantly higher in mild patients compering to moderate and severe cases ($p = 0.041$)
				31 moderate & severe COVID-19 cases				NR	9.06 ± 8.82			
Tekin et al., 2021 [20]	October 2021	Turkey	Prospective case–control	147 confirmed COVID-19 cases	17	46	84	27.9	14.64 ± 10.72	Above 50	Incidence	Serum vitamin D levels were significantly higher in cases ($p = 0.001$)
				300 healthy pregnant women	NR	NR	NR	27.9	12.52 ± 8.28			
Seven et al., 2021 [30]	November 2021	Turkey	Cross-sectional	292 mild COVID-19 cases	83	102	107	28	15.5 ± 7.6	Above 30	Severity	Serum vitamin D levels were significantly higher in mild patients compared to severe cases ($p = 0.01$)
				111 severe COVID-19 cases	7	25	79	29.5	13 ± 8.9			
Moreno-Fernandez et al., 2022 [28]	January 2022	Spain	Case-control	63 COVID-19 cases	0	0	63	31.9	21.28 ± 9.52	NR	Incidence	There is no significant difference between cases and controls ($p > 0.05$)
				61 healthy pregnant women	0	0	61	31.5	18.54 ± 8.04			
Schmitt et al., 2022 [29]	January 2022	France	Retrospective cohort	15 COVID-19 cases	0	0	15	30	10.4 ± 9.1	Above 30	Incidence	Serum vitamin D levels were significantly lower in cases ($p < 0.05$)
				19 healthy pregnant women	0	0	19	31	19.1 ± 6.2			
				7 asymptomatic COVID-19 cases	0	0	7	30.7	13.04 ± 7.95	Above 30	Severity	Serum vitamin D levels were significantly lower in symptomatic cases ($p < 0.05$)
				8 symptomatic COVID-19 cases	0	0	8	29.5	10.35 ± 6.12			
Ferrer-Sánchez et al., 2022 [22]	March 2022	Spain	Case-control	82 COVID-19 cases	0	0	82	31	10.15 ± 7	Above 30	Incidence	Serum vitamin D levels were significantly lower in cases ($p = 0.005$)
				174 healthy pregnant women	0	0	174	32	13.8 ± 8.5			
				75 mild COVID-19 cases	0	0	75	NR	10.5 ± 7.26	Above 30	Severity	There is no significant difference ($p = 0.25$)
				7 moderate & severe COVID-19 cases	0	0	7	NR	8.7 ± 2.15			
				78 COVID-19 cases, did not admit to ICU	0	0	78	NR	10.15 ± 7.1	Above 30	Severity	There is no significant difference ($p = 0.41$)
				4 COVID-19 cases, admitted to ICU	0	0	4	NR	9.3 ± 4.24			

[a] Values are mean for age, and mean ± SD for serum vitamin D level.

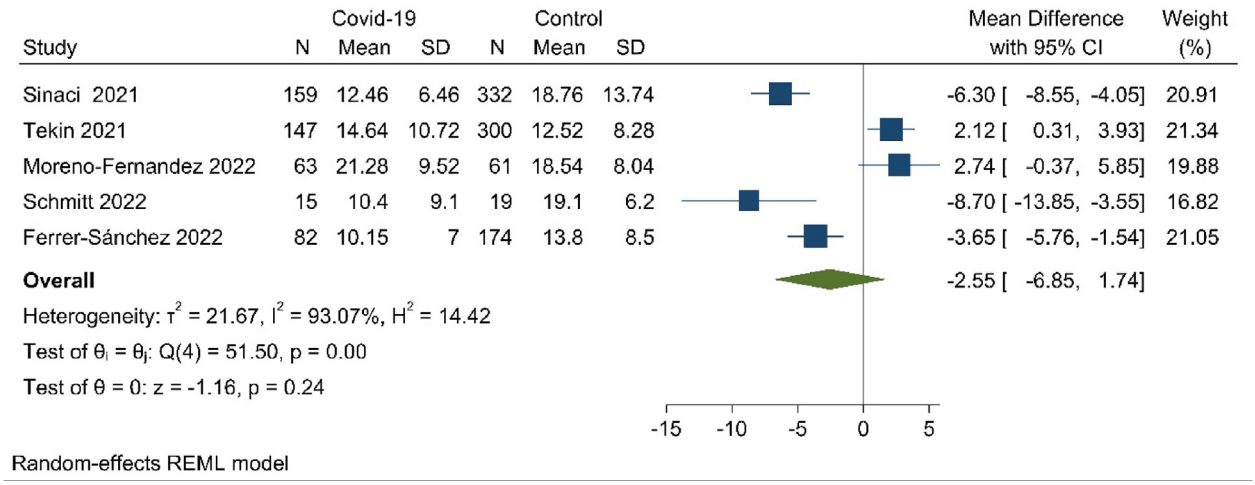

Fig. 2. Comparing the mean vitamin D level (ng/ml) in COVID-19 infected pregnant women vs. no-infected ones.

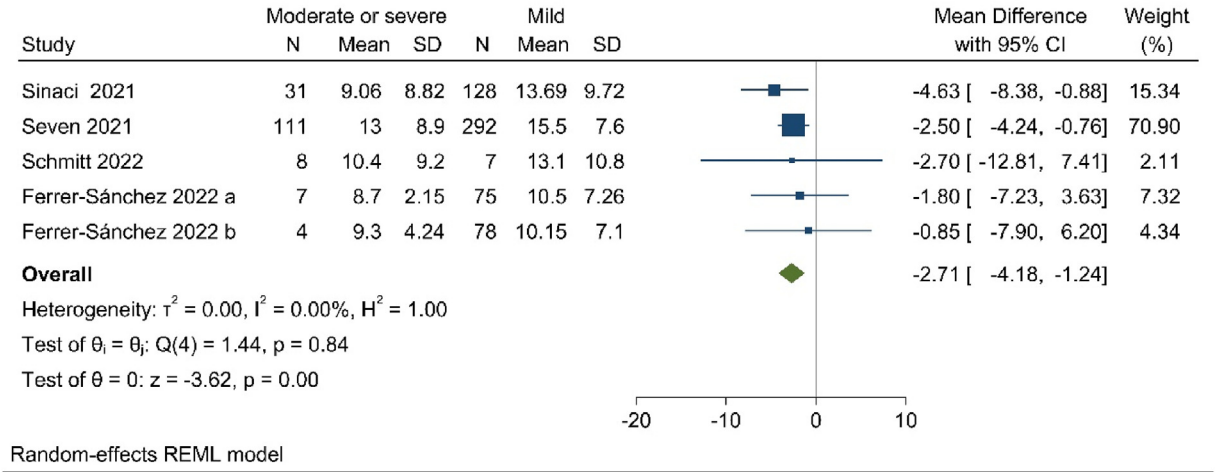

Fig. 3. Comparing the mean vitamin D level (ng/ml) between pregnant women who infected to sever/moderate COVID-19 vs. those who infected to mild COVID-19.

Beyond these, the current study has some limitations. First, there is limited data on the effect of vitamin D levels of pregnant women on the risk and severity of COVID-19. Second, existing studies took place only in three countries (Turkey, Spain, and France), which made it questionable to generalize the results to all pregnant women, because of the effect of geographical and ethnical backgrounds on vitamin D status [63]. Third, vitamin D levels of pregnant women may be influenced by gestational age (GA) [64], but none of the included articles analyzed the participants based on their trimesters or GA. Fourth, most of the participants, regardless of their health status (COVID-19 cases or healthy individuals), were vitamin D deficient; thus, it is impossible to investigate the relation between vitamin D status (deficient or not) with COVID-19. Fifth, body weight and age are two factors that might affect serum vitamin D levels [65–67]. Unfortunately, almost all of the included studies did not report the mean body weight of included participants. However, the reported mean ages of participants are extracted and shown in Table 3.

5. Conclusion

Based on the current evidence, serum vitamin D levels do not associate with the risk of COVID-19 incidence among pregnant women, but lower serum vitamin D levels are associated with higher susceptibility to severe disease. However, it seemed necessary that further studies subgroup participants based on their GA and even in different regions. More investigations on participants with optimal vitamin D status compared to vitamin D deficient individuals might better clarify the association of vitamin D status with COVID-19 in pregnant women. These findings may also be helpful in future emerging viral diseases.

Author contributions

SM-T contributed to the conception of the work, data search, screening of records, study quality assessment, manuscript preparation, manuscript revision, final approval of the manuscript, and agreed to be accountable for all aspects of the work.

MHM contributed to data search, screening of records, study quality assessment, manuscript preparation, manuscript revision, final approval of the manuscript, and agreed to be accountable for all aspects of the work.

MY contributed to statistical analysis, interpretation of data, manuscript preparation, manuscript revision, final approval of the manuscript, and agreed to be accountable for all aspects of the work.

MF contributed to manuscript preparation, manuscript revision, final approval of the manuscript, and agreed to be accountable for all aspects of the work.

APA contributed to manuscript preparation, manuscript revision, final approval of the manuscript, and agreed to be accountable for all aspects of the work.

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Data availability statement

Not applicable.

Conflict of interest

The authors declare no conflicts of interest.

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