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

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ABSTRACT

Background: Serum vitamin D level is 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 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: -4.16 – -1.25) is significantly lower.

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

Keywords: Vitamin D, Calcitriol, Pregnancy, COVID-19, SARS-CoV-2, Meta-analysis

INTRODUCTION

The emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) had 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 is 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 downregulation [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 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 whether serum vitamin D level is a determining factor for risk and severity of COVID-19 in 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.

METHODS

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.

Protocol and registration

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

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.

Exclusion criteria

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

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 (S.M-T and MH.M) evaluated the studies separately, and any disagreement was resolved through discussion and consensus by third reviewer (M.F).

Data extraction

Two reviewers (S.M-T and MH.M) separately extracted data from the eligible articles, and the 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.

Statistical analysis

The mean difference and 95% confidence interval (CI) of vitamin D level (ng/ml) between infected pregnant women and non-infected was calculated for each study. A random-effects meta-analysis and the inverse variance method was used to estimate weighted mean deference (WMD) as the pooled effect size because of underlying differences in study designs and methodologies. We assessed risk of publication bias overall 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 in Stata 17 software (StataCorp LP), and a 2-sided 0.05 level of significance was used in all cases.

RESULTS

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 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.

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 on 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 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 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]. One the other hand, three research investigated the effect of serum vitamin D on severity and risk of COVID-19 [21,22,29].

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

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

Four studies [21,22,27,29] reported a significantly lower serum vitamin D levels in cases comparing to healthy participants, however, Tekin et al [20] found significantly higher serum vitamin D levels in cases (14.64±10.72 ng/mL) than 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 significant difference between infected woman and non-infected group, even though the mean serum vitamin D level was 2.55 ng/ml less in COVID-19 group compared to healthy group (WMD=-2.55 ng/ml, 95% CI: -6.85 – 1.74) (**Figure 2**). There was considerable heterogeneity between studies (I^2=93.07%, Q' p<0.001). Egger 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.

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

All studies reported a significant higher serum vitamin D in mild cases comparing 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 which 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 significance lower (in average 2.71 ng/ml lower) serum vitamin D level in severe/moderate cases vs. mild ones (WMD=-2.71 ng/ml, 95%

CI: -4.16 – -1.25) (**Figure 3**). I^2 index as a measure of heterogeneity was near zero (I^2=0.0%, Q'p=0.84). Egger 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.

DISCUSSION

According to 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 increasing risk of pregnancy complications in COVID-19 patients [35,36]. Thus, a systematic review and meta-analysis on available literature regarding the association of 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 is significantly lower in severe cases (WMD = -2.71, 95% CI: -4.16 – -1.25). Findings of the current meta-analysis, regarding the association between vitamin D levels and risk of COVID-19 in pregnant women, is against results of some investigations in general population [17]. That might be due to high prevalence of vitamin D deficiency among participants, and even lack of sufficient studies in this field. Up to date, there is one study in Qatar which 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 contraversies exist on the efficacy of vitamin D supplementation on COVID-19 prevention, severity, and outcomes in general population [48–52] but there are no investigations on pregnant women yet.

Vitamin D deficiency, reported to associate with higher risk of serious viral infections such as hepatitis, 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 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].

Limitations and strengths

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

Beyond these, the current study has some limitations. First, there is limited data on the effect of vitamin D levels of pregnant women on risk, and severity of COVID-19. Second, existing studies take 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 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**.

CONCLUSION

Based on the current evidence, serum vitamin D level dose not associate with risk of COVID-19 incidence among pregnant women, but lower serum vitamin D level 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 comparing to vitamin D deficient individual 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 disease.

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

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REFERENCES

1. WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020 [Internet]. [cited 2022 May 5]. Available from: https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020

2. WHO Coronavirus (COVID-19) Dashboard | WHO Coronavirus (COVID-19) Dashboard With Vaccination Data [Internet]. [cited 2022 May 5]. Available from: https://covid19.who.int/

3. Al-Kaleel A, Al-Gailani L, Demir M, Aygün H. Vitamin D may prevent COVID-19 induced pregnancy complication. Medical Hypotheses. 2022 Jan 1;158.

4. Li S, Zhang Y, Guan Z, Li H, Ye M, Chen X, et al. SARS-CoV-2 triggers inflammatory responses and cell death through caspase-8 activation. Signal Transduction and Targeted Therapy 2020 5:1. 2020 Oct 9;5(1):1–10.

5. Zhang J, Wu H, Yao XH, Zhang D, Zhou Y, Fu B, et al. Pyroptotic macrophages stimulate the SARS-CoV-2-associated cytokine storm. Cellular & Molecular Immunology 2021 18:5. 2021 Mar 19;18(5):1305–7.

6. Mehta OP, Bhandari P, Raut A, Kacimi SEO, Huy NT. Coronavirus Disease (COVID-19): Comprehensive Review of Clinical Presentation. Frontiers in Public Health. 2021 Jan 15;8:1034.

7. Morelli SS, Mandal M, Goldsmith LT, Kashani BN, Ponzio NM. The maternal immune system during pregnancy and its influence on fetal development. RRB. 2015 Oct 1;6:171–89.

8. Zhang J, Shynlova O, Sabra S, Bang A, Briollais L, Lye SJ. Immunophenotyping and activation status of maternal peripheral blood leukocytes during pregnancy and labour, both term and preterm. Journal of Cellular and Molecular Medicine. 2017;21(10):2386–402.

9. Vanders RL, Gibson PG, Murphy VE, Wark PAB. Plasmacytoid Dendritic Cells and CD8 T Cells From Pregnant Women Show Altered Phenotype and Function Following H1N1/09 Infection. The Journal of Infectious Diseases. 2013 Oct 1;208(7):1062–70.

10. Wastnedge EAN, Reynolds RM, van Boeckel SR, Stock SJ, Denison FC, Maybin JA, et al. Pregnancy and COVID-19. Physiological Reviews. 2021 Jan 1;101(1):303–18.

11. Tamanna S, Lumbers ER, Morosin SK, Delforce SJ, Pringle KG. ACE2: a key modulator of the renin-angiotensin system and pregnancy. American Journal of Physiology-Regulatory, Integrative and Comparative Physiology. 2021 Dec;321(6):R833–43.

12. Amrein K, Scherkl M, Hoffmann M, Neuwersch-Sommeregger S, Köstenberger M, Tmava Berisha A, et al. Vitamin D deficiency 2.0: an update on the current status worldwide. European Journal of Clinical Nutrition 2020 74:11. 2020 Jan 20;74(11):1498–513.

13. Alhassan Mohammed H, Mirshafiey A, Vahedi H, Hemmasi G, Moussavi Nasl Khameneh A, Parastouei K, et al. Immunoregulation of Inflammatory and Inhibitory Cytokines by Vitamin D3 in Patients with Inflammatory Bowel Diseases. Scandinavian Journal of Immunology. 2017 Jun 1;85(6):386–94.

14. Bae M, Kim H. Mini-Review on the Roles of Vitamin C, Vitamin D, and Selenium in the Immune System against COVID-19. Molecules. 2020 Nov 16;25(22):E5346.

15. Getachew B, Tizabi Y. Vitamin D and COVID-19: Role of ACE2, age, gender, and ethnicity. Journal of Medical Virology. 2021 Sep 1;93(9):5285–94.

16. Malek Mahdavi A. A brief review of interplay between vitamin D and angiotensin-converting enzyme 2: Implications for a potential treatment for COVID-19. Reviews in Medical Virology. 2020 Sep 1;30(5):e2119.

17. Yisak H, Ewunetei A, Kefale B, Mamuye M, Teshome F, Ambaw B, et al. Effects of Vitamin D on COVID-19 Infection and Prognosis: A Systematic Review. Risk Manag Healthc Policy. 2021 Jan 7;14:31–8.

18. Teshome A, Adane A, Girma B, Mekonnen ZA. The Impact of Vitamin D Level on COVID-19 Infection: Systematic Review and Meta-Analysis. Front Public Health. 2021;9:624559.

19. Kiely ME, McCarthy EK, Hennessy Á. Iron, iodine and vitamin D deficiencies during pregnancy: epidemiology, risk factors and developmental impacts. Proceedings of the Nutrition Society. 2021 Aug;80(3):290–302.

20. Tekin AB, Yassa M, Birol P, Unlu SN, Sahin T, Buran AM, et al. Vitamin D status is not associated with clinical severity of COVID-19 in pregnant women. Eur J Nutr. 2022 Mar;61(2):1035–41.

21. Sinaci S, Ocal DF, Yucel Yetiskin DF, Uyan Hendem D, Buyuk GN, Goncu Ayhan S, et al. Impact of vitamin D on the course of COVID-19 during pregnancy: A case control study. J Steroid Biochem Mol Biol. 2021 Oct;213:105964.

22. Ferrer-Sánchez N, Díaz-Goicoechea M, Mayoral-Cesar V, García-Solbas S, Nievas-Soriano BJ, Parrón-Carreño T, et al. Serum 25(OH) Vitamin D Levels in Pregnant Women with Coronavirus Disease 2019 (COVID-19): A Case-Control Study. International Journal of Environmental Research and Public Health. 2022 Jan;19(7):3965.

23. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021 Mar 29;372.

24. Boutron I, Page MJ, Higgins JP, Altman DG, Lundh A, Hróbjartsson A, et al. Considering bias and conflicts of interest among the included studies. In: Cochrane Handbook for Systematic Reviews of Interventions [Internet]. John Wiley & Sons, Ltd; 2019 [cited 2022 Aug 19]. p. 177–204. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1002/9781119536604.ch7

25. Lefebvre C, Glanville J, Briscoe S, Littlewood A, Marshall C, Metzendorf MI, et al. Searching for and selecting studies. In: Cochrane Handbook for Systematic Reviews of Interventions [Internet]. John Wiley & Sons, Ltd; 2019 [cited 2022 Aug 19]. p. 67–107. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1002/9781119536604.ch4

26. Orwin RG, Vevea JL. Evaluating coding decisions. The handbook of research synthesis and meta-analysis. 2009;2:177–203.

27. Yalcin Bahat P, Aldikactioglu Talmac M, Bestel A, Topbas Selcuki NF, Aydın Z, Polat İ. Micronutrients in COVID-19 Positive Pregnancies. Cureus. 2020 Sep 23;12(9):e10609.

28. Moreno-fernandez J, Ochoa JJ, De Paco Matallana C, Caño A, Martín-alvarez E, Sanchez-romero J, et al. COVID-19 during Gestation: Maternal Implications of Evoked Oxidative Stress and Iron Metabolism Impairment. Antioxidants. 2022;11(2).

29. Schmitt G, Labdouni S, Soulimani R, Delamare C, Bouayed J. Oxidative stress status and vitamin D levels of asymptomatic to mild symptomatic COVID-19 infections during the third trimester of pregnancy: A retrospective study in Metz, France. J Med Virol. 2022 May;94(5):2167–73.

30. Seven B, Gunduz O, Ozgu-Erdinc AS, Sahin D, Moraloglu Tekin O, Keskin HL. Correlation between 25-hydroxy vitamin D levels and COVID-19 severity in pregnant women: a cross-sectional study. J Matern Fetal Neonatal Med. 2021 Nov 23;1–6.

31. Pechlivanidou E, Vlachakis D, Tsarouhas K, Panidis D, Tsitsimpikou C, Darviri C, et al. The prognostic role of micronutrient status and supplements in COVID-19 outcomes: A systematic review. Food Chem Toxicol [Internet]. 2022;162((Pechlivanidou E.; Bacopoulou F., fbacopoulou@med.uoa.gr) Center for Adolescent Medicine and UNESCO Chair in Adolescent Health Care, First Department of Pediatrics, School of Medicine, National and Kapodistrian University of Athens, Aghia Sophia Children's Hospital, Athens, Greece). Available from: https://www.embase.com/search/results?subaction=viewrecord&id=L2017106728&from=export

32. Pereira M, Dantas Damascena A, Galvão Azevedo LM, de Almeida Oliveira T, da Mota Santana J. Vitamin D deficiency aggravates COVID-19: systematic review and meta-analysis. Crit Rev Food Sci Nutr. 2022;62(5):1308–16.

33. Kaya MO, Pamukçu E, Yakar B. The role of vitamin D deficiency on COVID-19: a systematic review and meta-analysis of observational studies. Epidemiol Health. 2021;43:e2021074.

34. Szarpak L, Rafique Z, Gasecka A, Chirico F, Gawel W, Hernik J, et al. A systematic review and meta-analysis of effect of vitamin D levels on the incidence of COVID-19. Cardiol J. 2021;28(5):647–54.

35. Wei SQ, Bilodeau-Bertrand M, Liu S, Auger N. The impact of COVID-19 on pregnancy outcomes: a systematic review and meta-analysis. CMAJ. 2021 Apr 19;193(16):E540–8.

36. Jamieson DJ, Rasmussen SA. An update on COVID-19 and pregnancy. Am J Obstet Gynecol. 2022 Feb;226(2):177–86.

37. Hernandez TMF. Comparison of Pregnant and Non-pregnant Women With COVID-19 Infection. Journal of Clinical Medicine and Surgery. 2022;1(1):3.

38. Hossein-nezhad A, Holick MF. Vitamin D for health: a global perspective. Mayo Clin Proc. 2013 Jul;88(7):720–55.

39. Wang L, Zhang C, Song Y, Zhang Z. Serum vitamin D deficiency and risk of gestational diabetes mellitus: a meta-analysis. Arch Med Sci. 2020;16(4):742–51.

40. Hu KL, Zhang CX, Chen P, Zhang D, Hunt S. Vitamin D Levels in Early and Middle Pregnancy and Preeclampsia, a Systematic Review and Meta-Analysis. Nutrients. 2022 Jan;14(5):999.

41. Woo J, Giurgescu C, Wagner CL. Evidence of an Association Between Vitamin D Deficiency and Preterm Birth and Preeclampsia: A Critical Review. J Midwifery Womens Health. 2019 Sep;64(5):613–29.

42. Dovnik A, Mujezinović F. The Association of Vitamin D Levels with Common Pregnancy Complications. Nutrients. 2018 Jul;10(7):867.

43. Zhao R, Zhou L, Wang S, Yin H, Yang X, Hao L. Effect of maternal vitamin D status on risk of adverse birth outcomes: a systematic review and dose-response meta-analysis of observational studies. Eur J Nutr. 2022 Mar 22;

44. Merewood A, Mehta SD, Chen TC, Bauchner H, Holick MF. Association between vitamin D deficiency and primary cesarean section. J Clin Endocrinol Metab. 2009 Mar;94(3):940–5.

45. ACOG Committee Opinion No. 495: Vitamin D: Screening and supplementation during pregnancy. Obstet Gynecol. 2011 Jul;118(1):197–8.

46. Institute of Medicine (US) Committee to Review Dietary Reference Intakes for Vitamin D and Calcium. Dietary Reference Intakes for Calcium and Vitamin D [Internet]. Ross AC, Taylor CL, Yaktine AL, Del Valle HB, editors. Washington (DC): National Academies Press (US); 2011 [cited 2022 Jun 6]. (The National Academies Collection: Reports funded by National Institutes of Health). Available from: http://www.ncbi.nlm.nih.gov/books/NBK56070/

47. Pérez-López FR, Pilz S, Chedraui P. Vitamin D supplementation during pregnancy: an overview. Curr Opin Obstet Gynecol. 2020 Oct;32(5):316–21.

48. Hosseini B, El Abd A, Ducharme FM. Effects of Vitamin D Supplementation on COVID-19 Related Outcomes: A Systematic Review and Meta-Analysis. Nutrients. 2022 Jan;14(10):2134.

49. Rawat D, Roy A, Maitra S, Shankar V, Khanna P, Baidya DK. Vitamin D supplementation and COVID-19 treatment: A systematic review and meta-analysis. Diabetes Metab Syndr. 2021 Aug;15(4):102189.

50. Pal R, Banerjee M, Bhadada SK, Shetty AJ, Singh B, Vyas A. Vitamin D supplementation and clinical outcomes in COVID-19: a systematic review and meta-analysis. J Endocrinol Invest. 2022 Jan;45(1):53–68.

51. Tentolouris N, Samakidou G, Eleftheriadou I, Tentolouris A, Jude EB. The effect of vitamin D supplementation on mortality and intensive care unit admission of COVID-19 patients. A systematic review, meta-analysis and meta-regression. Diabetes Metab Res Rev. 2022 Jan 15;e3517.

52. Shah K, V P V, Sharma U, Mavalankar D. Does vitamin D supplementation reduce COVID-19 severity? - a systematic review. QJM. 2022 Feb 15;hcac040.

53. Siddiqui M, Manansala JS, Abdulrahman HA, Nasrallah GK, Smatti MK, Younes N, et al. Immune Modulatory Effects of Vitamin D on Viral Infections. Nutrients. 2020 Sep;12(9):2879.

54. Zdrenghea MT, Makrinioti H, Bagacean C, Bush A, Johnston SL, Stanciu LA. Vitamin D modulation of innate immune responses to respiratory viral infections. Rev Med Virol. 2017 Jan;27(1).

55. Martineau AR, Jolliffe DA, Hooper RL, Greenberg L, Aloia JF, Bergman P, et al. Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data. BMJ. 2017 Feb 15;356:i6583.

56. Grant WB, Lahore H, McDonnell SL, Baggerly CA, French CB, Aliano JL, et al. Evidence that vitamin d supplementation could reduce risk of influenza and covid-19 infections and deaths. Nutrients [Internet]. 2020;12(4). Available from: https://www.embase.com/search/results?subaction=viewrecord&id=L2004142748&from=export

57. Akoh CC, Pressman EK, Cooper E, Queenan RA, Pillittere J, O'Brien KO. Low Vitamin D is Associated With Infections and Proinflammatory Cytokines During Pregnancy. Reprod Sci. 2018 Mar;25(3):414–23.

58. Greiller CL, Martineau AR. Modulation of the immune response to respiratory viruses by vitamin D. Nutrients. 2015 May 29;7(6):4240–70.

59. Charoenngam N, Holick MF. Immunologic Effects of Vitamin D on Human Health and Disease. Nutrients. 2020 Jul;12(7):2097.

60. Martens PJ, Gysemans C, Verstuyf A, Mathieu C. Vitamin D's Effect on Immune Function. Nutrients. 2020 May;12(5):1248.

61. Mohan M, Cherian JJ, Sharma A. Exploring links between vitamin D deficiency and COVID-19. PLoS Pathog. 2020 Sep;16(9):e1008874.

62. Wang Y, Zheng J, Islam MS, Yang Y, Hu Y, Chen X. The role of CD4+FoxP3+ regulatory T cells in the immunopathogenesis of COVID-19: implications for treatment. Int J Biol Sci. 2021;17(6):1507–20.

63. Al Emadi S, Hammoudeh M. Vitamin D study in pregnant women and their babies. Qatar Med J. 2013;2013(1):32–7.

64. Chen B, Chen Y, Xu Y. Vitamin D deficiency in pregnant women: Influenced by multiple risk factors and increase the risks of spontaneous abortion and small-for-gestational age. Medicine (Baltimore). 2021 Oct 15;100(41):e27505.

65. Doaei S, Jarrahi S, Torki S, Haghshenas R, Jamshidi Z, Rezaei S, et al. Serum vitamin D level may be associated with body weight and body composition in male adolescents; a longitudinal study. Pediatr Endocrinol Diabetes Metab. 2020;26(3):125–31.

66. Elizondo-Montemayor L, Castillo EC, Rodríguez-López C, Villarreal-Calderón JR, Gómez-Carmona M, Tenorio-Martínez S, et al. Seasonal Variation in Vitamin D in Association

with Age, Inflammatory Cytokines, Anthropometric Parameters, and Lifestyle Factors in Older Adults. Mediators Inflamm. 2017;2017:5719461.

67. Rontoyanni VG, Avila JC, Kaul S, Wong R, Veeranki SP. Association between Obesity and Serum 25(OH)D Concentrations in Older Mexican Adults. Nutrients. 2017 Jan 31;9(2):E97.

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

Table 2. Quality assessment of included studies

Study	Design	Items of NIH quality assessment tool*														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

* NIH quality assessment tool has 12 questions for Case-Control studies and 14 questions for observational Cohort and Cross-sectional studies

Table 3. Included studies in the systematic review

Author	Date	Country	Design	Participants	Trimester (n) 1st	2nd	3rd	Age (year)[1]	Vitamin D (ng/mL)[1]	Vit D normal range (ng/mL)	Outcome	Main finding
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

				8 symptomatic COVID-19 cases	0	0	8	29.5	10.35±6.12			in symptomatic cases (p<0.05)
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			

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

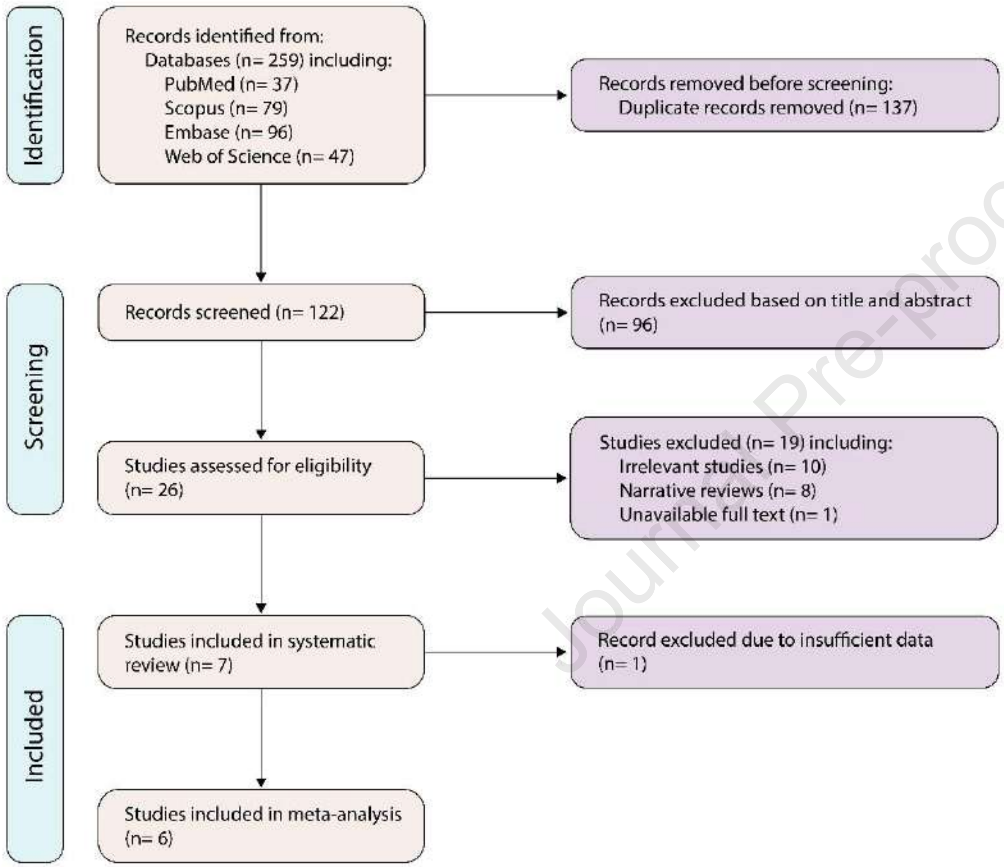

Figure 1. PRISMA diagram for study selection process.

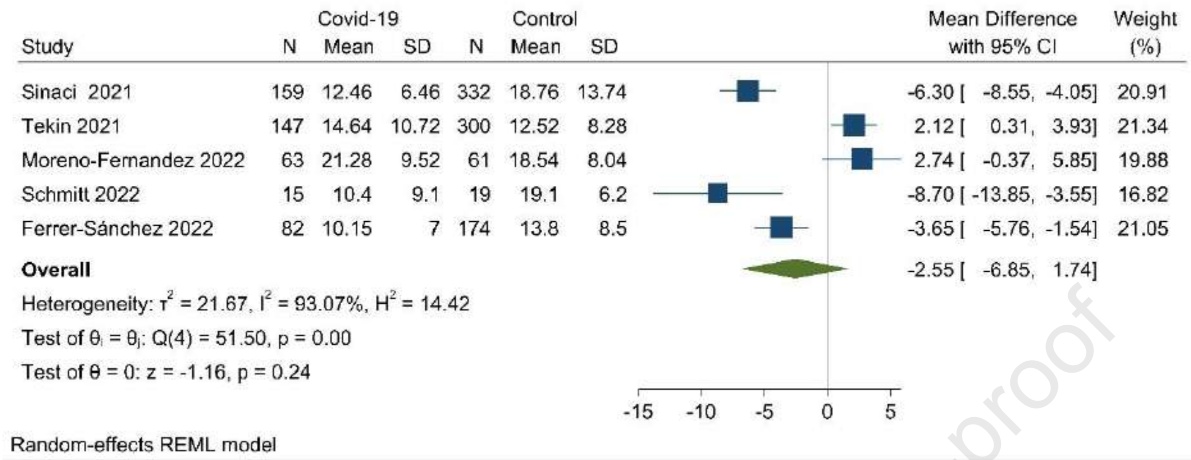

Figure 2. Comparing the mean vitamin D level (ng/ml) in COVID-19 infected pregnant women vs. no-infected ones.

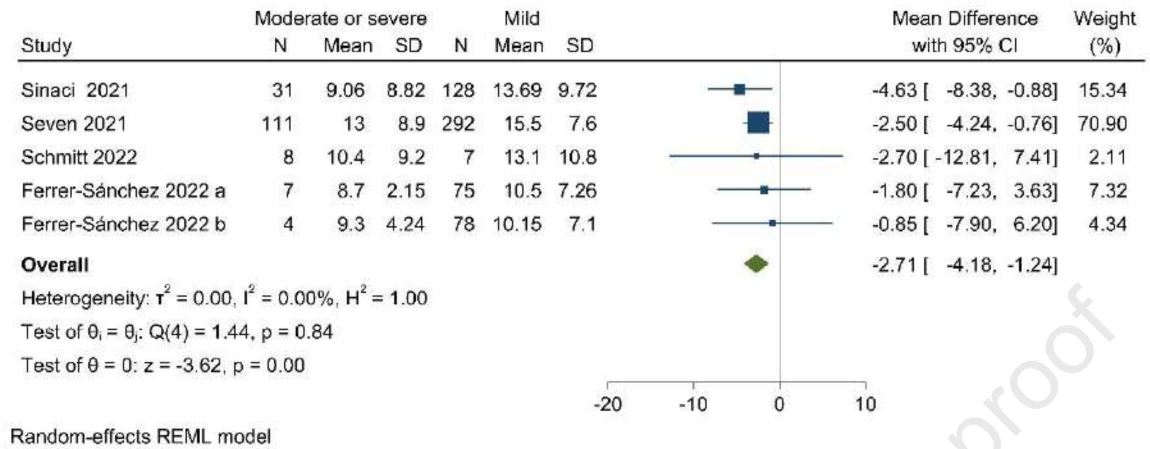

Figure 3. Comparing the mean vitamin D level (ng/ml) between pregnant women who infected to sever/moderate COVID-19 vs. those who infected to mild COVID-19.