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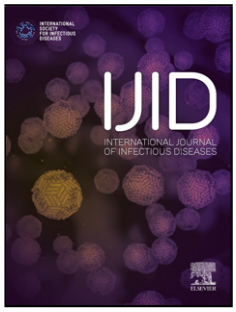

Low vitamin D status is associated with coronavirus disease 2019 outcomes: A systematic review and meta-analysis

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Title page

Low vitamin D status is associated with coronavirus disease 2019 outcomes： a systematic review and meta-analysis

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Highlights

- COVID-19-positive patients have a higher incidence of low vitamin D levels than COVID-19-negative patients.
- COVID-19-positive patients have lower vitamin D levels than COVID-19-negative patients.
- Vitamin D supplementation may be beneficial for the prevention and treatment of COVID-19, although formal proof for an effect remains to be determined by randomized controlled trials.

Abstract

Background: Observational studies suggest that the risk and clinical prognosis of coronavirus disease 2019 (COVID-19) are related to low vitamin D status; however, the data are inconsistent.

Objectives: We conducted a systematic review and meta-analysis to assess the association between low vitamin D status and COVID-19.

Methods: The systematic search was conducted with PubMed, Embase, and the Cochrane Library from database inception to September 25, 2020. The standardized mean difference (SMD) or odds ratio (OR) and corresponding 95% confidence interval (CI) were applied to estimate pooled results. Random - or fixed - effect models based on heterogeneity were used for the meta-analysis. Funnel plots and Egger regression tests were used to assess publication bias.

Results: A total of 10 articles with 361, 934 participants were selected for meta-analysis.

Overall, the pooled OR in the fixed-effect model showed that vitamin D deficiency or insufficiency was associated with an increased risk of COVID-19 (OR = 1.43, 95% CI 1.00 to 2.05). In addition, COVID-19-positive individuals had lower vitamin D levels than those with COVID-19-negative individuals (SMD = -0.37, 95% CI = -0.52 to -0.21). Significant heterogeneity existed in both endpoints. Funnel plots and Egger regression tests revealed significant publication bias.

Conclusions: This systematic review and meta-analysis indicated that low vitamin D status may be associated with an increased risk of COVID-19 infection. Further studies are needed to evaluate the impact of vitamin D supplementation on the clinical severity and prognosis in patients with COVID-19.

Systematic Review Registration: PROSPERO registration no: CRD42020216740

Keywords: Coronavirus disease 2019; Vitamin D; Meta-analysis; Low vitamin D status; 25-hydroxyvitamin D

Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has had a catastrophic impact worldwide(Walker et al., 2020). Although it is difficult to compare national data, mortality from COVID-19 is significantly higher in some countries than in others(Li 2020). For example, Spain, Italy, and the United Kingdom have higher mortality rates

than the United States and Germany. Multiple factors contribute to this difference, including differences in aging, general health, government decisions, accessibility and quality of healthcare, and socioeconomic status(Patel et al., 2020; Raifman MA and Raifman JR., 2020). Recent observational studies have linked the population's relative vitamin D status to COVID-19 outcomes.

Vitamin D is also called cholecalciferol (vitamin D3) or ergocalciferol (vitamin D2), which are precursors of hormones and play an important role in regulating the metabolism of calcium and phosphate (Kulda 2012). The vitamin D biosynthetic pathway begins with ultraviolet B radiation of 7-dehydrocholesterol on the bare skin exposed to strong sunlight, which is the primary source, as few foods contain vitamin D (Bouillon 2017). 1,25-dihydroxyvitamin D is responsible for the function of vitamin D, not 25-hydroxyvitamin D ([25(OH)D]), which requires CYP27B1 to transform into active vitamin D. A substantial body of evidence shows that local synthesis of active vitamin D is critical for the immunomodulatory role of vitamin D against inflammation and microbes beyond the systemic level of 25-hydroxyvitamin D and bone; however, extrarenal vitamin D metabolism and its regulatory loop are not yet fully understood (Xu et al., 2020). Various studies now support that vitamin D inhibits lymphocyte proliferation, antibody production, and cytokine synthesis through monocyte and cell-mediated immune stimulation(Kara et al., 2020). Low vitamin D status is also regarded as an epidemic and a global public health problem, especially in Europe. It is related to an increase in infectious and noninfectious diseases, especially upper respiratory tract infections.(De Lapuente-Yague et al., 2018; Jagannath et al., 2018; Martineau et al.,

2017). This association was confirmed by a meta-analysis including 25 randomized controlled trials, which showed that vitamin D supplementation is beneficial for respiratory diseases. Recently, a substantial body of evidence has clearly linked COVID-19 outcomes with low vitamin D status, but the results from those published to date are conflicting: two retrospective studies reported independent associations between low prepandemic 25(OH)D levels and the subsequent incidence and severity of COVID-19(Meltzer et al., 2020) (D'Avolio et al. 2020), while an analogous study in the UK did not support the potential link between 25(OH)D concentration and the risk of severe COVID-19 infection and mortality(Hastie et al., 2020).

Considering the impact of the COVID-19 risk potentially resulting from low vitamin D status, several studies have explored their association. However, the results of these studies are conflicting. To clarify these contradictory results and more accurately assess the relationship between low vitamin D status and COVID-19 risk, we performed a meta-analysis of published studies to provide a clinical reference.

Methods

The preferred reporting item for systematic review and meta-analysis protocol (PRISMA) guidelines were followed for reporting the results of this review **(Appendix S1)**(Moher D 2009).

Data Sources and Searches

We conducted a systematic search of the PubMed, Embase, and Cochrane Library databases from database inception to September 25, 2020, using thesaurus terms and keywords using following search terms were used: (“coronavirus disease 2019” OR

"COVID-19" OR "SARS-COV-2" OR "Coronavirus") AND ("vitamin D" OR "25(OH)D" OR "25-hydroxyvitamin D" OR "hydroxycholecalciferols" OR "hypovitaminosis D"). No language restrictions were applied. We contacted the authors of the articles if the data were not available. We also manually searched the references of included articles for the latest reviews. The search strategy is presented in **Table S1**.

Study Selection

We first conducted a preliminary screening of titles and abstracts, and the second screening involved a full-text review. Two researchers independently screened information at each stage. Disagreements were resolved through consensus and, if necessary, with a third independent reviewer. In this study, the population (P) included individuals with COVID-19 who had low vitamin D status, including vitamin D deficiency or insufficiency, (E) and were compared (C) to individuals without COVID-19. The primary outcome (O) was incident COVID-19. Observational studies (S) were included in this meta-analysis. Vitamin D deficiency or insufficiency is defined as a 25(OH)D below 20 ng/ml (50 nmol/L) or as a 25(OH)D of 21–29 ng/ml (52.5–72.5 nmol/L), respectively(Bolland, Avenell and Grey 2016). Binary variables report odds ratios (ORs) and corresponding 95% confidence intervals (CIs) (or the data used to calculate them). Continuous variables report the levels of vitamin D, expressed as the mean ± standard deviation. Case reports, case series, duplicate reports, commentaries, and author responses were excluded.

Data Extraction

Standardized data collection tables were used for data extraction. We extracted the

reported OR and the corresponding 95% CI or other data used to calculate these indicators. We also extracted the characteristics of each trial and recorded the data as follows: first author, year of publication, country of publication, time of the study, characteristics of the study population, baseline age, total number of participants, number of vitamin D deficiency or insufficiency events, and average vitamin D level. Two reviewers independently performed research selection and data extraction. Any discrepancies were resolved through discussion.

Quality Assessment

The methodological quality of the included study was assessed by the modified Newcastle-Ottawa scale (NOS)(Stang 2010), which consists of three factors: patient selection, comparability of the study groups, and assessment of outcome. Each study has a score of 0-9 (assigned as stars), and observational studies with 6 or more stars are considered high quality. Two researchers conducted a quality assessment and resolved any discrepancies through discussion or consensus.

Statistical Analysis

Stata software (version 16.0, StataCorp, College Station, TX, USA) was used for pooled estimates. Dichotomous data were analyzed using the ORs computed by the Mantel Haenszel method (fixed or random models) and the corresponding 95% CIs. Continuous outcomes measured on the same scale are expressed as the mean value and standard deviation, and the standardized mean difference (SMD) was used for analysis. The I-square (I^2) test was performed to assess the impact of study heterogeneity on 他 the meta-analysis results. According to the Cochrane review guidelines, if there is a

serious heterogeneity at $I^2 > 50\%$, the random effect model is chosen; otherwise, the fixed effect model is used(Higgins et al., 2003). Sensitivity analysis of the primary endpoint was conducted by sequential removal of each trial to assess the impact of individual studies on overall pooled estimates. Subgroup analysis was performed based on the 25(OH)D measurement units (ng/ml and nmol/L). We explored publication bias using funnel plots and Egger regression tests. Statistical assessment was two-tailed and was considered statistically significant at $P < 0.05$.

Results

Selected Studies

As shown in the PRISMA flow chart **(Figure 1)**, we searched 522 related records from all electronic databases, of which 142 were excluded as duplicates. The remaining 380 records were filtered according to the titles and abstracts, of which 348 were excluded due to unrelated topics. We reviewed the full text of the remaining 32 studies and identified 10 that met the inclusion criteria of the meta-analysis(Baktash et al., 2020; Chodick et al., 2020; D'Avolio et al., 2020; Hastie, Pell and Sattar 2020; Im et al., 2020; Mardani et al., 2020; Meltzer et al., 2020; Merzon et al., 2020; Raisi-Estabragh et al., 2020; Ye et al., 2020).

Study Characteristics

Ten case-control studies involving 376,596 participants were included in the meta-analysis, including 4,178 COVID-19-positive participants and 372,418-negative participants. The sample size of the studies varied greatly, from 105 to 248,598. Most participants were at least 50 years old. Most studies were conducted in Asia (n = 5),

followed by Europe (n = 4)(Baktash et al., 2020; D'Avolio et al., 2020; Hastie, Pell and Sattar 2020; Raisi-Estabragh et al., 2020),(Chodick et al., 2020; Im et al., 2020; Mardani et al., 2020; Merzon et al., 2020; Ye et al., 2020), and the United States (n = 1)(Meltzer et al. 2020). **Table 1** lists the main descriptive statistics for all included studies.

Quality Assessment

For the quality of the included studies, 8 studies(Chodick et al., 2020; D'Avolio et al., 2020; Hastie, Pell and Sattar 2020; Mardani et al., 2020; Meltzer et al., 2020; Merzon et al., 2020; Raisi-Estabragh et al., 2020; Ye et al., 2020) were classified as high-quality, and 2 studies(Baktash et al., 2020; Im et al., 2020) were classified as medium-quality, with an average score of 7.7 **(Table 1)**. Overall, the evidence contributing to these analyses was assessed as being high quality.

Results of the Meta-Analysis

Four of the ten studies reported the association between vitamin D deficiency or insufficiency and COVID-19 infection(Im et al., 2020; Meltzer et al., 2020; Merzon et al., 2020; Ye et al., 2020). Overall, the pooled OR in a fixed-effect model showed that vitamin D deficiency or insufficiency was associated with an increased risk of COVID-19 infection (OR = 1.43, 95% CI 1.00 to 2.05). However, high heterogeneity was observed in the studies (I^2 = 64.9%, p = 0.036) **(Figure 2)**.

Seven studies evaluated the vitamin D level in COVID-19-positive and-negative participants(Baktash et al., 2020; Chodick et al., 2020; D'Avolio et al., 2020; Hastie, Pell and Sattar 2020; Im et al., 2020; Mardani et al., 2020; Raisi-Estabragh et al., 2020;

Ye et al., 2020). Overall, we found that the average vitamin D level of the COVID-19-positive group was lower than the COVID-19-negative group (SMD = -0.37, 95% CI = -0.52 to -0.21, I^2 = 89.6%) **(Figure 3)**. The robustness of the results was evaluated by deleting each study in turn and reanalyzing the data sets, which did not lead to significant changes in the pooled OR estimate **(Figure 4)**; however, there was still serious heterogeneity. We conducted a subgroup analysis based on the 25(OH)D measurement units (ng/ml and nmol/L) and found positive results (nmol/L: WMD = -7.90, 95% CI = -13.41 to -2.38, I^2 = 89.8%; ng/ml: WMD = -5.85, 95% CI = -11.23 to -0.46, I^2 = 93.6%) **(Figure 5)**.

Publication Bias

Visual inspection of the funnel plot identified substantial asymmetry **(Figure 6)**. Additionally, Egger's regression asymmetry test also indicated publication bias (p = 0.001; p = 0.009).

Discussion

This meta-analysis was conducted based on 10 studies that assessed the impact of vitamin D deficiency or insufficiency on COVID-19 outcomes. According to the available evidence, we found that low vitamin D levels are associated with an increased risk of COVID-19 infection (OR = 1.43, 95% CI 1.00 to 2.05). In addition, the findings suggest that COVID-19 individuals have lower vitamin D levels than those who are not infected (SMD = -0.37, 95% CI = -0.52 to -0.21). This study clearly links the outcomes of COVID-19 with low vitamin D status.

Of note, the study by Hastie et al. does not support a potential link between 25(OH)D concentrations and risk of severe COVID-19 infection because they collected data on vitamin D levels between 2006-2010 and link it to COVID-19 mortality today, more than a decade later. We question the validity of their results and of such a comparison because vitamin D levels vary with age and season. Therefore, we conducted a sensitivity analysis by excluding this study to observe the impact on the overall effect estimate and found that the results did not substantially change (SMD=-0.46, 95% CI: -0.65 to -0.26).

The association between low vitamin D status and metabolism, autoimmunity, and infectious diseases has received widespread attention(Holick 2017). In particular, some studies have highlighted that low vitamin D status may lead to an increased risk of respiratory infections. Chalmers et al. found that bronchitis dilated patients with vitamin D deficiency were more likely to be colonized by bacteria and have increased respiratory tract inflammation(Chalmers et al., 2013). Mamani et al. indicated that low levels of serum 25-hydroxyvitamin D (25(OH)D) were associated with a high incidence of community-acquired pneumonia and the severity of the disease(Mamani et al., 2017). In addition, Dancer et al. demonstrated that survivors with acute respiratory distress syndrome (ARDS) have higher levels of vitamin D than nonsurvivors, suggesting that vitamin D supplementation may have a therapeutic effect(Dancer et al., 2015). This led to the hypothesis that low vitamin D status might also be associated with an increased risk of COVID-19. Indeed, from clinical observations to randomized controlled trials, researchers worldwide are focusing on this issue. Based on the available evidence, we

conducted this systematic review and found that vitamin D deficiency is associated with an increased risk of COVID-19.

There may be multiple role of vitamin D in COVID-19 infection may be multiple. First, vitamin D deficiency can reduce innate cellular immunity and stimulate cytokine storms, which are related to the worsening of ARDS associated with COVID-19. Second, vitamin D supports the antimicrobial peptides produced in the epithelium of the respiratory tract, which makes viral infections and COVID-19 symptoms unlikely. Third, vitamin D may help reduce the inflammatory response to SARS-CoV-2 infection(Daneshkhah et al., 2020; Mitchell 2020). Dysregulation of this response, especially of the renin-angiotensin system, is characteristic of COVID-19, and the degree of overactivation is associated with poorer prognosis.

Several possibilities exist for the reduced vitamin D levels in COVID-19 patients. Many factors affect vitamin D levels, such as age, region, season, and race. Vitamin D is a fat-soluble vitamin produced by 7-dehydrocholesterol due to the action of ultraviolet B radiation is subsequently converted to 25(OH)D in the liver and then to the active form in the kidneys or other organs(Carpagnano et al., 2020). COVID-19 broke out in the winter with low sunlight exposure in the Northern Hemisphere, when levels of 25-hydroxyvitamin D are at their nadir. Patients with COVID-19 are required to be isolated or hospitalized after infection, during which time the skin cannot get enough sunlight. Most participants were over 50 years old, which may be one of the reasons for low vitamin D. In addition, an imbalanced diet during hospitalization cannot obtain sufficient vitamins from food, leading to vitamin D deficiency.

In previous studies, intervention trials have rarely shown the benefits of vitamin D supplementation as a treatment or preventive measure. For example, several meta-analyses of vitamin D supplementation trials failed to show significant improvement in blood pressure, insulin sensitivity or lipid parameters, failing to show a benefit even in the prevention of fracture events (Al Mheid I et al., 2017; Beveridge LA et al., 2015; Moyer VA et al., 2013). This making it challenging to investigate the benefits of vitamin D supplementation for COVID-19. However, an important exception to this general trend is upper respiratory tract infections: a meta-analysis of 25 randomized controlled trials showed that vitamin D supplementation protected against acute respiratory tract infections and that patients with serum 25(OH)D levels < 25 nmol/L gained the most benefit(Martineau et al., 2017). To date, we found 2 studies evaluating the impact of vitamin D supplementation on the clinical outcome of COVID-19. One reported 4 vitamin D-deficient patients diagnosed with COVID-19 who were provided either cholecalciferol of 1000 IU daily (standard dose) or ergocalciferol 50,000 IU daily for 5 days (high dose) as part of supplementation. The results show that patients receiving high-dose vitamin D supplements exhibited improved clinical rehabilitation, which was reflected in shorter hospital stay, lower oxygen demand, and a reduction in inflammatory marker status(Ohaegbulam et al., 2020). Another study evaluated the effect of calcifediol treatment on intensive care unit admission and mortality rate among patients hospitalized for COVID-19, demonstrating that the administration of high-dose calcifediol significantly reduced the need for ICU treatment in COVID-19-admitted patients(Entrenas et al., 2020). Pending the results of such trials, we recommend

vitamin D supplementation to reach the reference nutritional intake, ranging from 400 IU/day in the UK to 600-800 IU/day in the United States. These levels are based on the benefits of vitamin D for bone and muscle health, but there is a chance that their implementation might also reduce the impact of COVID-19 in populations with vitamin D deficiency(Martineau and Forouhi, 2020).

The present study has some limitations. First, correlation does not equal causation and whether low vitamin D levels are a cause or consequence of COVID-19 remains uncertain. Caution should be exercised when interpreting these results. Second, there are discrepancies in the number and sample size of the included studies, leading to some large variances in effect size estimates. Third, significant heterogeneity was found. The source of heterogeneity was not explored because too few studies were available for each endpoint. We only used random-effects models to address heterogeneity, which may affect the strength and extrapolation of conclusions. Fourth, publication bias may affect our results because negative studies are less likely to be published.

Conclusion

In conclusion, low serum vitamin D status may be related to the increased risk of COVID-19. Individuals with vitamin D deficiency should receive special attention, and future research should focus on the benefits of vitamin D supplementation.

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Declaration of interest: The authors have no relevant interests to declare.

Ethics

This study did not require ethical approval because the meta-analysis was based on published research and the original data are anonymous.

Conflict of Interest Statement

We declare that we do not have any commercial or associative interest that represents a conflict of interest in connection with the work submitted.

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Table 1. Summary characteristics of studies included in the meta-analysis

Study	Country	Study Design	Sample size	Age		Gender Male (%)	Definition of vitamin D status [25(OH)D]	25(OH)D level		
				COVID-19 positive	COVID-19 negative			COVID-19 positive	COVID-19 negative	NOS
Raisi-Estabragh et al. 2020	United Kingdom	case-control study	4510	68.11 (9.23) [a]	68.91 (8.72)	2201 (48.8%)	NR	33.88 ± 27.01 nmol/L	35.45 ± 26.78 nmol/L	8
Baktash et al.2020	United Kingdom	case-control study	105	mean age 81 years, range 65–102		57 (54.3%)	vitamin D-deficient (≤30 nmol/L) vitamin D-replete (>30 nmol/L)	31.33 ± 20.44 nmol/L	51.67 ± 30.92 nmol/L	5
Chodick et al. 2020	Israel	case-control study	14520	40.6 (19.1) [a]	37.0 (19.1)	6880 (47.4%)	NR	23.6 ± 8.6 ng/ml	24.1 ± 9.1 ng/ml	9
Hastie et al. 2020	United Kingdom	case-control study	348598	49 (40-58) [b]	49 (38-57)	168391 (48.3%)	vitamin D deficiency (< 25 nmol/L) vitamin D insufficiency (< 50 nmol/L)	30.0 ± 27.6 nmol/L	27.5 ± 25.1 nmol/L	8
Avolio et al. 2020	Switzerland.	case-control study	102	74 (65-81) [b]	73 (61-82)	NR	NR	13.43 ± 10.01 ng/ml	21.33 ± 16.31 ng/ml	6
Im et al. 2020	Korea	case-control study	200	52.2 (20.7) [a]	52.4 (20.2)	NR	vitamin D deficiency (< 20 ng/dl) severe vitamin D deficiency (< 10ng/dl)	15.7 ± 7.9 ng/ml	25.0 ± 13.2 ng/ml	9
Merzon et al. 2020	Israel	case-control study	7807	35.58 (34.49-36.67) [c]	47.35 (46.87-47.85)	4573 (58.6%)	vitamin D deficiency (<30 ng/mL)	NR		9
Mardani et al. 2020	Iran	case-control study	123	mean age 42 years, range 18-78		65 (52.8%)	vitamin D sufficient (>30 ng/mL) vitamin D insufficient (<30 ng/mL)	18.54 ± 11.63 ng/ml	30.17 ± 9.05 ng/ml	7
Meltzer et al. 2020	United States	case-control study	489	49.2 (18.4) [a]		123 (25.2%)	vitamin D deficient (<20 ng/mL) not deficient (≥20 ng/mL)	NR		8
Ye et al. 2020	China	case-control study	142	43 (32–59) [b]	42 (31–52)	55 (38.7%)	vitamin D deficiency was defined as a 25(OH)D<50 nmol/L, vitamin D insufficiency as 50 nmol/L≤25(OH)D<75 nmol/L and vitamin D sufficiency as 25(OH)D≥75 nmol/L	54.5 ± 18.4 nmol/L	71 ± 19.7 nmol/L	8

COVID-19 = coronavirus disease 2019; a = mean (SD); b = median (IQR); c = mean age, (years, 95% CI); NR = not report.

Figure legends

Figure 1. Flow diagram of the literature search process.

Figure 2. Results from the random-effect model that compared the odds of low vitamin D status among individuals with COVID-19 positivity and negativity. COVID-19 = coronavirus disease 2019.

Figure 3. Results from the random-effect model that compared the serum 25(OH)D levels among individuals with COVID-19 positivity and negativity. 25(OH)D = 25-hydroxyvitamin D; COVID-19 = coronavirus disease 2019.

Figure 4. Sensitivity analysis was performed by excluding each study in turn.

Figure 5. Subgroup analysis based on the 25(OH)D measurement units (ng/ml and nmol/L) that comparing the serum vitamin D levels among individuals with COVID-19 positivity and negativity. 25(OH)D = 25-hydroxyvitamin D; COVID-19 = coronavirus disease 2019.

Figure 6. The visual forest plots was performed to assess publication bias. (a) represents binary variable; (b) represents continuous variable.