# Vitamin D Deficiency Aggravates COVID-19: systematic review and meta-analysis

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**Table S1.** Database search strategy and results 11/10/2020

| **Database**  |  **Search strategy** | **Items found** |
| --- | --- | --- |
| **Embase** | ('vitamin d'/exp OR 'vitamin d') AND ('coronavirus disease 2019'/exp OR 'coronavirus disease 2019') | 340 |
| **PubMed**  | (vitamin D) AND (COVID-19) Sort by: Publication Date((("vitamin d"[MeSH Terms] OR "vitamin d"[All Fields]) OR "ergocalciferols"[MeSH Terms]) OR "ergocalciferols"[All Fields]) AND ((((((("covid 19"[All Fields] OR "covid 2019"[All Fields]) OR "severe acute respiratory syndrome coronavirus 2"[Supplementary Concept]) OR "severe acute respiratory syndrome coronavirus 2"[All Fields]) OR "2019 ncov"[All Fields]) OR "sars cov 2"[All Fields]) OR "2019ncov"[All Fields]) OR (("wuhan"[All Fields] AND ("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields])) AND (2019/12/1:2019/12/31[Date - Publication] OR 2020/1/1:2020/12/31[Date - Publication]))) | 230 |
| **Web of science** | ( " COVID-19" AND "vitamin D" ) | 161 |
| **Scopus** | ( " COVID-19" AND "vitamin D" )  | 279 |
| **ScienceDirec**t | ( " COVID-19" AND "vitamin D" )  | 325 |
| **Medrevix**  | ( " COVID-19" AND "vitamin D" )  | 204 |

**Table S2**. RTI Item Bank use in the systematic review.

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| **Uniform inclusion/exclusion criteria**:**1**. Does the article clearly state its own inclusion/exclusion criteria?  |
| 2. Did the study apply inclusion/exclusion criteria uniformly to all comparison groups of the study? |
| **Appropriate sample selectio**n:4. Is the sample appropriate? |
| **Valid assessment of inclusion/exclusion:**5. Are the inclusion/exclusion criteria measured using valid and reliable measures? |
| **Valid assessment of outcome:**6. Are outcomes assessed using valid and reliable measures, implemented consistently across all study participants? |
| 7. Were the important confounding and effect modifying variables taken into account in the design and/or analysis (e.g., through matching, stratification, interaction terms, multivariate analysis, or other statistical adjustment)? |

| **Table S3.** Objetive and results ofincluded studies between vitamin D and COVID-19.  |
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| **Authors** | **Objective** | **Results** |
| (Alipio 2020) | To predict clinical outcomes of patients infected with Covid-2019 based on 25-hydroxyvitamin D 25(OH)D] levels | Serum 25(OH)D level of cases with mild outcome was 31.2 ng/ml, 27.4 ng/ml for ordinary, 21.2 ng/ml for severe, and 17.1 ng/ml for critical. Cases identified as Vitamin D-deficient were 77 (36.3%), majority of which were severe (40.3%). |
| (Baktash et al. 2020) | To determine whether these patients have worse outcomes withCOVID-19 | COVID-19-positive arm demonstrated lower median serum 25(OH)D level of 27 nmol/L (IQR=20–47 nmol/L) compared with COVID-19-negative arm, with median level of 52 nmol/L (IQR=31.5–71.5 nmol/L) (p value=0.0008) |
| (Carpagnano et al. 2020) | To analyse vitamin D levels in patients with acute respiratory failure due to COVID-19 and to assess any correlations with disease severity and prognosis | A survival analysis highlighted that, after 10 days of hospitalization, severe vitamin D deficiency patients had a 50% mortality probability, while those with vitamin D ≥ 10 ng/mL had a 5% mortality risk (*p* = 0.019). |
| (Claire E Hastie, Pell, and Sattar 2020; C E Hastie et al. 2020) | To establish whether blood vitamin D (25(OH)D) concentration was associated with COVID-19 risk, and whether it explained the higher incidence of COVID-19 in black and South Asian people. | Vitamin D was associated with COVID-19 infection univariably (OR = 0.99; 95% CI 0.99, 0.99; p = 0.01), but not after adjustment for confounders (OR = 1.00; 95% CI = 0.99, 1.01; p = 0.20). |
| (Cuñat, Ojeda, and Calvo 2020) | To evaluate the prevalence of vitamin D deciency in a consecutive population ofCOVID-19 patients admitted to intensive care units of a single center and to evaluate its relationship with clinical outcomes. | Thirteen patients (76.5%) had 25-hydroxyvitamin D levels < 12.5 %, with 3 patients with values lower than 5 ng/ml. Hypocalcemia and hypophosphatemia were observed in 6 (35.2%) and 11 (64.7%) patients, respectively. |
| (D’Avolio et al. 2020) | To described the 25-hydroxyvitamin D (25(OH)D) plasma concentrations in a cohort of patients from Switzerland. | In this cohort, significantly lower 25(OH)D levels (p = 0.004) were found in PCR-positivefor SARS-CoV-2 (median value 11.1 ng/mL) patients compared with negative patients (24.6 ng/mL) |
| (Darling et al. 2020) | Present a preliminary assessment of the serum 25-hydroxyvitamin D status (25(OH)D), body mass index (BMI), ethnicity and other lifestyle factors in the first-reported UK Biobank COVID-19 positive cases (n=580) compared with negative controls (n=723). | Serum 25(OH)D status was almost identical in those who tested positive (median (Interquartile range, IQR)= 43.3 (32.1) nmol/L) compared to those who tested negative (median (IQR) 44.1 (31.2) nmol/L) for COVID-19. |
| (Faniyi et al. 2020) | To determine the prevalence of vitamin D deficiency in NHS staff who have isolated with symptoms suggestive of COVID-19 and relate this to vitamin D status | In those healthcare workers who have isolated due to symptoms of COVID-19, those of Black, Asian, and minority ethnic (BAME) are at the highest risk of vitamin D deficiency. Vitamin D deficiency is a risk factor for COVID-19 seroconversion for NHS healthcare workers especially in BAME male staff. |
| (Faul et al. 2020) | To explore whether 25OHD levels might be associated with an increased risk of the development of ARDS due to SARS-CoV-2 | In patients with SARS-CoV-2 related pneumonia a baseline serum 25OHD level less than 30 nmol.l-1 was associated with a hazard ratio (HR) for intubation of 3.19 (95 percent confidence interval, 1.05 to 9.7) |
| (Im et al. 2020) | To confirm the amounts of various nutrients in COVID-19 patients | Vitamin D deficiency was the most prevalent, with a deficiency (less than 20 ng/dl) in 76% of the patients and a severe deficiency (less than 10ng/dl) in 24%. |
| (Karonova, Andreeva, and Vashukova 2020) | To evaluate the vitamin D level of patients with COVID-19 hospitalized with communityacquired pneumonia and compare the value of 25(OH)D in blood serum with the clinical manifestations of the disease | Serum 25(OH)D level ranged from 3,0 to 88,8 ng /ml (16,7 ± 12,7 ng / ml). It was found that in patients with severe course, the level of 25(OH)D blood was significantly lower (11.9 ± 6.4 ng / ml) and vitamin D deficiency was more common than in patients with moderate to severe course of the disease (18,5 ± 14,0 ng / ml, p = 0,027). The same pattern was revealed in patients with a fatal outcome, where the level of 25(OH)D was 10,8 ± 6,1 ng / ml, compared with this indicator in patients discharged from the hospital (17,8 ± 13,4 ng / ml) (p = 0,02). |
| (Lau et al. 2020) | To evaluate prevalence of VDI among our COVID-19 intensive care unit (ICU) patients. | Among ICU subjects, 11 (84.6%) had VDI, vs. 4 (57.1%) of floor subjects. Strikingly, 100% of ICU patients less than 75 years old had VDI (n=11). Among these, 64.6% (n=7) had critically low 25OHD (<20ng/mL) and three had <10 ng/mL |
| (Macaya et al. 2020) | To explore the association between VDD and the development of severe COVID-19.  | VDD tended to predict an increased risk of developing severe COVID-19 after adjusting for age, gender, obesity, cardiac disease, and kidney disease [OR 3.2 (95 % CI: 0.9-11.4), p = 0.07]. Age had a negative interaction with the effect of VDD on the composite outcome (p = 0.03), indicating that the effect was more noticeable at younger ages. Furthermore, male gender was associated with VDD and with severe COVID-19 at younger ages. |
| (Maghbooli et al. 2020) | To investigate the association between serum 25-hydroxyvitamin D levels and its effect on adverse clinical outcomes, and parameters of immune function and mortality due to a SARS-CoV-2 infection. | 74% had severe COVID-19 infection and 32.8% were vitamin D sufficient. After adjusting for confounding factors, there was a significant association between vitamin D sufficiency and reduction in clinical severity, inpatient mortality serum levels of C-reactive protein (CRP) and an increase in lymphocyte percentage. Only 9.7% of patients older than 40 years who were vitamin D sufficient succumbed to the infection compared to 20% who had a circulating level of 25(OH)D< 30 ng/ml.  |
| (Mardani et al. 2020) |   To analyse vitamin D, angiotensin converting enzyme (ACE) concentrations, and neutrophil to lymphocyte ratio (NLR) in patients with confirmed COVID-19 in comparison with control group | Results demonstrated significant alterations in vitamin D and ACE levels as well as NLR in the patients’ group.  |
| (Meltzer et al. 2020) | To examine whether vitamin D deficiency and treatment are associated with testing positive for COVID-19. | Testing positive for COVID-19 was not significantly more likely for the patients classified as having vitamin D levels of uncertain sufficiency compared to patients with sufficient vitamin D levels.COVID-19 rates in the vitamin D deficient group of 21.6%(95%CI [14.0%-29.2%] ) versus 12.2%(95%CI[8.9%-15.4%]) in the vitamin D sufficient group. |
| (Mendy et al. 2020)  | Identify factors associated with hospitalizationand disease severity in a racially and ethnically diverse cohort of COVID-19 patients. | Thirty-two of 178(18%) vitamin D deficient patients tested positive for COVID-19 versus 40 of 321(11%) non-deficient patients(p=0.11). |
| (Merzon et al. 2020) | Identify factors associated with hospitalization and disease severity in a racially and ethnically diverse cohort of COVID-19 patients. | Vitamin D deficiency were associated with hospitalization ( OR = 1.77 ; 95%CI= 1.07, 2.93), disease severity ( OR= 1.95 ; 95%CI= 1.07, 3.56), admission to IC ( OR = 2.55 95%CI= 1.28, 5.08). There is no association with death (OR= 1.08 (95%CI= 0.37, 3.17) |
| (Panagiotou et al. 2020) | To evaluate our implementation of a local protocol for treatment of VDD among patients hospitalized for COVID-19; to assess the prevalence of VDD among COVID-19 in patients, and examine potential associations with disease severity and fatality. | Mean sérum 25(OH)D levels were comparable (p=0.3), only 19% of ITU patients had 25(OH)D levels greater than 50 nmol/L vs. 39.1% of non-ITU patients (p=0.02). However, there was no association with fatality, potentially due to small sample size and prompt diagnosis and treatment of VDD. |
| (Pinzon, Angela, and Pradana 2020) | To report case series of Vitamin D status in patients with conrmed COVID-19 and review recent literature on the role of Vitamin D on COVID-19. | The prevalence of vitamin D deficiency in this case was 90% and 10% of insuficiency. |
| (Pizzini et al. 2020) | To analyze vitamin D (VITD) status and its associations with clinical presentation and course of disease in COVID-19 | Eight weeks after the onset of COVID-19, a high proportion of patients presented with impaired VITD metabolism and elevated parathyroid hormone (PTH) levels. Low VITD levels at disease onset or at eight-week follow-up were not related to persistent symptom burden, lung function impairment, ongoing inflammation, or more severe CT abnormalities. VITD deficiency is frequent among COVID-19 patients but not associated with disease outcomes. |
| (Radujkovic et al. 2020) | To explore possible associations between VitD status and disease severity and survival in COVID-19 patients | A total of 41 (22%) patients were VitD deficient. When adjusted for age, gender, and comorbidities, VitD deficiency was associated with higher risk of IMV/D and death (HR 6.12, 95% CI 2.79–13.42, p < 0.001 and HR 14.73, 95% CI 4.16–52.19, p < 0.001, respectively). Similar correlations were observed in the inpatient subgroup. |
| (Raharusun et al. 2020) | The study has focused on identifying patterns of mortality among patients infected with Covid-19 and the possible associationbetween serum 25(OH)D level and mortality outcomes. | A significant association has been obtained between Vitamin D status and mortality. In particular, the odds of death was higher in cases with insufficient Vitamin D status (OR=7.63; p<0.001). When compared to cases with normal Vitamin D status, death was approximately 10.12 times more likely for Vitamin D deficiente cases (OR=10.12; p<0.001). |
| (Raisi et al. 2020) | To examine whether the greater severity of coronavirus disease 2019 (COVID-19) amongst men and Black, Asian and Minority Ethnic (BAME) individuals is explained by cardiometabolic, socio-economic or behavioural factors. | There was no significant association between season-adjusted 25(OH)-vitamin D status and COVID-19 positivity. Similarly, in a separate model, adjustment for sex, age and ethnicity demonstrated no statistically significant association between processed meat consumption and COVID-19 status |
| (Smet et al. 2020) | To investigate the level of vitamin D deficiency in West Flanders, Belgium and its correlation to severity of COVID-19 | COVID-19 patients showed lower median 25(OH)D (18.6 ng/mL, IQR 12.6-25.3, versus 21.5 ng/mL, IQR 13.9-65 30.8; P=0.0016) and higher vitamin D deficiency rates (58.6% versus 45.2%, P=0.0005). |
| (Sun et al. 2020) | To investigate the correlations between sérum calcium and clinical outcomes in patients with COVID-19 | The median 25-hydroxy-vitamin D levels were 10.20 (IQR, 8.20-12.65) ng/mL. All patients had VD deficiency. |



**Figure S1**. Means of vitamin D in COVID-19 patients compared with no positive COVID-19 test.

 **Figure S2.** Prevalence of vitamin D deficiency (A) insufficiency (B) in COVID-19 patients.



**Figure S3**. Means of vitamin D in severe COVID-19 compared with mild cases of the disease