Association between vitamin D supplementation or serum vitamin D level and susceptibility to SARS-CoV-2 infection or COVID-19 including clinical course, morbidity and mortality outcomes? A systematic review

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ABSTRACT

Objective To systemically review and critically appraise published studies of the association between vitamin D supplementation or serum vitamin D level and susceptibility to SARS-CoV-2 infection or COVID-19, including clinical course, morbidity and mortality outcomes.

Design Systematic review.

Data sources MEDLINE (OVID), Embase (OVID), Cochrane Central Register of Controlled Trials, MedRxiv and BioRxiv preprint databases. COVID-19 databases of the WHO, Cochrane, CEBS Oxford and Bern University up to 10 June 2020.

Study selection Studies that assessed vitamin D supplementation and/or low serum vitamin D in patients acutely ill with, or at risk of, severe betacoronavirus infection (SARS-CoV, MERS-CoV, SARS-CoV-2).

Data extraction Two authors independently extracted data using a predefined data extraction form and assessed risk of bias using the Downs and Black Quality Assessment Checklist.

Results Searches elicited 449 papers, 59 studies were eligible full-text assessment and 4 met the eligibility criteria of this review. The four studies were narratively synthesised and included (1) a cross-sectional study (n=107) suggesting an inverse association between serum vitamin D and SARS-CoV-2; (2) a retrospective cohort study (348 598 participants, 449 cases) in which univariable analysis showed that vitamin D protects against COVID-19; (3) an ecological country level study demonstrating a negative correlation between vitamin D and COVID-19 case numbers and mortality; and (4) a case–control survey (n=1486) showing cases with confirmed/probable COVID-19 reported lower vitamin D supplementation. All studies were at high/unclear risk of bias.

Conclusion There is no robust evidence of a negative association between vitamin D and COVID-19. No relevant randomised controlled trials were identified and there is no robust peer-reviewed published evidence of association between vitamin D levels and severity of symptoms or mortality due to COVID-19. Guideline producers should acknowledge that benefits of vitamin D supplementation in COVID-19 are as yet unproven despite increasing interest.

INTRODUCTION

COVID-19, a novel viral infection caused by SARS-CoV-2, was declared a pandemic by the WHO on 11 March 2020. Mild COVID-19 may manifest as high temperature, a continuous cough and a loss of or change in sense of smell or taste. However, more severe and critical cases can result in inflammation of the lungs, low oxygen levels and acute respiratory distress syndrome. Interest is mounting regarding the association of vitamin D supplementation or level with susceptibility to COVID-19 due to the recognised modulating
effects of vitamin D on the immune system and immune response.

Vitamin D can modulate the immune system through highly expressed receptors in most non-skeletal tissues. Two of the most common analogues of vitamin D which are found in food and used as a dietary supplement are D$_2$ (ergocalciferol) and D$_3$ (cholecalciferol, also made by the skin when exposed to sunlight). Both D$_2$ and D$_3$ can be hydroxylated by liver enzymes CYP2R1 and CYP27A1 to form calcidiol (25(OH)D). The active metabolite of vitamin D, calcitriol (1α,25(OH)2D), results from the action of CYP27B enzyme on calcidiol. CYP27B is found in several tissues including the kidney, skin, bones and immune system. Tumour necrosis factor-α (TNF-α) and interferon-γ (IFN-γ) are examples of inflammatory cytokines that stimulate the CYP27B enzymes of the immune system. Vitamin D can interact with both the innate and the cellular immune systems through these mechanisms.

Current Public Health England (PHE), National Institutes of Health and European Food Safety Authority recommendations highlight the importance of vitamin D to population health. Vitamin D deficiency is defined as less than 25 nmol/L (10 ng/mL) measured in blood serum. The UK guideline recommendations suggest that people take a supplement of 10 μg of vitamin D per day during the winter months or throughout the year if they do not spend time outdoors or if they cover the majority of their skin when outside. Published editorials, journal commentaries and news media reports suggest that individuals with low blood serum concentrations of vitamin D might be at higher risk of infection with COVID-19, or on infection have worse outcomes than individuals with normal/high serum vitamin D.

Several observational studies have reported associations between low serum vitamin D and chronic and acute conditions such as susceptibility to acute respiratory tract infections (RTI). Most recently, Martineau and colleagues conducted a systematic review and meta-analysis of individual participant data from randomised controlled trials (RCTs) to assess the overall effect of vitamin D supplementation on risk of acute RTI. They reported vitamin D supplementation to be safe while protecting against acute RTI overall (adjusted OR 0.88, 95% CI 0.81 to 0.96; p for heterogeneity <0.001). Patients very deficient in vitamin D benefited the most (adjusted OR 0.75, 0.60 to 0.95; p for interaction=0.006). Critiques of this review have suggested that the findings should be interpreted as hypothesis generating only, as the results are heterogeneous and not sufficiently applicable to the general population. Recent rapid reviews of vitamin D for treatment or prevention in COVID-19 reported no evidence to assess the association of vitamin D supplementation or level with susceptibility to SARS-CoV-2 infection or COVID-19 including clinical course, morbidity and mortality outcomes.

METHODS

Protocol registration

The methods were prespecified in a protocol that was registered with the PROSPERO International Prospective Register of Systematic Reviews (https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020182876). Research ethics committee approval was not required for this study.

We undertook a systematic review to answer the following question: Is vitamin D supplementation or level associated with susceptibility to severe betacoronavirus infection (SARS-CoV, Middle East respiratory syndrome (MERS-CoV), SARS-CoV-2) including clinical course, morbidity and mortality outcomes?

Our review was conceptualised and written in accordance with the PRISMA statement.

Data sources and search

The search strategy was developed by the information specialists in collaboration with the research team and clinical advisors. We searched MEDLINE (OVID interface), Embase (OVID interface), Cochrane Central Register of Controlled Trials, MedRxiv and BioRxiv preprint databases on 6–8 May 2020. We searched the global research on COVID-19 developed by the WHO, CEBM Oxford and the living systematic review developed by Bern University on 10 May 2020. We updated the database searches on 10 June 2020 to capture articles which may have been published since the initial search was conducted.

We searched additional resources including relevant systematic reviews in MEDLINE (OVID interface), Embase (OVID interface) and Cochrane Database of Systematic Reviews, 19 May 2020), relevant references and contacted experts for additional evidence. Our full search record is included in the online supplemental file 1.

Study eligibility

We developed predefined study eligibility criteria aligned to the research question (box 1). We imposed a date restriction of January 2002 to capture all published articles since SARS-CoV was first discovered in Asia in February 2003. We limited to English language only.

Article selection

Following the article search, we systematically identified and removed any duplicate citations using EndNote V.X9 software. Using titles and abstracts, deduplicated citations were screened by two independent reviewers (OO, MZ, AM, AG) and checked by a third (AC). All articles deemed ineligible were excluded at this stage. We
identified and obtained all remaining articles for full-text screening, which was performed independently by at least two reviewers against the prespecified eligibility criteria (box 1). Where disagreements regarding the inclusion of articles arose, a third reviewer (AC) was consulted to reach a final decision.

Data extraction

Two reviewers independently (LA-K, MZ, OO, AM) extracted data from eligible full-text papers using a prespecified data extraction form. The accuracy of all the data extraction was independently assessed by a third reviewer (AG). Where reported, we sought to extract data from each article relevant to the research question, including details of population, intervention/exposure, comparator, outcomes and any detail related to the two prespecified subgroups: ethnicity characteristics and age characteristics. Disagreements between reviewers were resolved by discussion and agreement or via consultation with a third reviewer (AC).

Risk of bias

The included studies had observational study designs aimed at answering a specific question. Therefore, risk of bias of included full-text papers was assessed using the Downs and Black Quality Assessment Checklist.48 Two reviewers (AM, MZ, OO) independently assessed the risk of bias of the included studies and the accuracy of the assessment was evaluated by a third reviewer (LA-K).

Data analysis

We anticipated that identified studies would be too heterogeneous to facilitate pooling of study data and planned a narrative synthesis. Nevertheless, we intended to consider pooling outcomes data in a meta-analysis using a random-effects model if appropriate.

Patient and public involvement

Due to the rapid timeframe of this systematic review, it was not possible for our research team to involve patients or the public in the design, conduct or reporting of our study.

RESULTS

After searching databases, assessing the reference lists of 17 narrative reviews27 28 33 49–62 and one additional article identified through consultation with clinical experts,38 we identified 499 citations. Following removal of duplicates and screening of titles and abstracts, we retrieved 59 full-text papers, of which 4 met the full eligibility criteria (see figure 1). The electronic supplement includes a list of reasons for excluding studies at full-text review. Seven articles closely met the eligibility criteria but were excluded as they were not available as peer-reviewed publications at the time of our narrative synthesis, details of these seven studies63–69 is provided in the online supplemental material.

The characteristics of the four included studies are presented in table 1. All four included studies were conducted in Europe and published in April or May 2020. One study was based on data from UK residents exclusively,70 another included data on residents in 20 European countries, including the UK.71 The studies were observational design and no relevant RCT were identified or included in the review. All four studies were at high or unclear risk of bias and scored poorly across several domains of the Downs and Black Quality Assessment Checklist,48 including external validity, internal validity and power. A prominent issue among the included studies was that the authors did not perform adequate multivariable adjustment to correct for confounding.72–74 Ecological bias was present in Ilie et al,71 which may result from spatial and temporal scale differences between country level mean levels of vitamin D. However, several domains in each risk of bias assessment were not applicable or not reported and, therefore, could not be scored using the Downs and Black Quality Assessment Checklist.48 Detailed risk of bias scores are provided in the online supplemental material.

Serum vitamin D

D’Avolio et al73 used a cross-sectional design with data on nasopharyngeal swab PCR analysis for SARS-CoV-2 and a 25(OH)D measurement taken from patients between 1 March and 14 April 2020. PCR positives (median age=74 years (IQR 65–81); male=70.4%) had significantly (p=0.004) lower serum 25(OH)D levels (median=11.1
ng/mL (IQR 8.2–21.0)) than PCR negatives (median age=73 years (IQR 61–82); male=48.8%; median 25(OH)D=24.6 ng/mL (IQR 8.9–30.5)). Although gender-stratified and age-stratified analysis showed no significant differences, older (>70 years) SARSCoV-2 positive (n=18) participants had significantly lower median serum 25(OH)D levels (9.3 ng/mL (IQR 8.1–19.9)) than older SARS-CoV-2 negatives (n=43) (23.1 ng/mL (IQR 8.5–31.7)) (p=0.037).

Hastie et al70 is a retrospective cohort study that used data from the UK Biobank,72 using data from 348,998 people with complete information on vitamin D and covariates; 449 people tested positive for COVID-19. COVID-19 positives were older (median=49 years; IQR=40–58) than COVID-19 negatives (median=49 years; IQR=38–57) with p value of <0.05. Multivariable analysis showed that age at assessment (OR=1.02; 95% CI=1.00 to 1.03; p=0.016) and non-white ethnicity (black OR=4.30, 95% CI=2.92 to 6.31, p=<0.001; South Asian OR=2.42, 95% CI=1.50 to 3.93, p=<0.001) were associated with confirmed COVID-19. There was no significant interaction between ethnicity and vitamin D deficiency (OR=0.90; 95% CI=0.66 to 1.23; p=0.515). Median vitamin D concentration at recruitment was lower for people with subsequent confirmed COVID-19 (28.7 (IQR 10.0–43.8) nmol/L) than for other participants (32.7 (IQR 10.0–47.2) nmol/L) (p<0.01).

Although univariable analysis suggested an association between vitamin D and COVID-19 (OR=0.99; 95% CI 0.99 to 0.999; p=0.013), this association became insignificant (OR=1.00; 95% CI=0.998 to 1.01; p=0.208) after adjustment for covariates.70

Ilie et al71 used an ecological study design reporting on 20 European countries as at 8 April 2020; the data pertain to mean levels of vitamin D, cases of COVID-19 per million population and deaths from COVID-19 per million population. The authors performed Pearson’s correlation coefficient calculations and reported a negative correlation between mean levels of vitamin D (mean 56.79 nmol/L, SD 10.61) and numbers of cases of COVID-19 per million population in each country (mean cases 1393.4, SD 1129.984, r(20) = −0.44; p=0.05). Additionally, a negative correlation was reported between mean vitamin D levels and the number of deaths caused by COVID-19 per million population in each country (mean 80.42, SD 94.61, r(20) = −0.4378; p=0.05). Sweden had the highest mean level of vitamin D (73.5 nmol/L) compared with Spain which had a mean level of 42.5 nmol/L. The number of cases of COVID-19 per million population was 834 in Sweden and 3137 in Spain. Likewise, at the time of the study, there were 68 deaths from

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**Figure 1** PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram for the selection of studies.
<table>
<thead>
<tr>
<th>Study</th>
<th>Design/setting</th>
<th>Population</th>
<th>Exposure/intervention</th>
<th>Outcomes</th>
<th>Results</th>
<th>Limitations</th>
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<tbody>
<tr>
<td><strong>Serum vitamin D</strong></td>
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<tr>
<td>D’Avolio et al&lt;sup&gt;73&lt;/sup&gt;</td>
<td>Cross-sectional study&lt;br&gt;Canton of Tessin, Switzerland</td>
<td>107 patients with data on SARS-CoV-2 and 25(OH)D measurement</td>
<td>Vitamin D analysis, conducted within 7 weeks of the SARS-CoV-2 PCR result. Control patients with 25(OH)D data during the same period.</td>
<td>SARS-CoV-2 infection</td>
<td>Group 1 comprised 27 patients with positive PCR test results for SARS-CoV-2, while group 2 comprised 80 patients with a negative PCR result for SARS-CoV-2. Significantly lower 25(OH)D levels (p=0.004) in SARS-CoV-2 patients even after stratifying patients according to age &gt;70 years.</td>
<td>Few patients from a single hospital. No available clinical information about the severity of COVID-19 symptoms. No data on other potential confounding variables. SARS-CoV-2 and the 25(OH)D status were performed on different days.</td>
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<tr>
<td>Hastie et al&lt;sup&gt;70&lt;/sup&gt;</td>
<td>Retrospective cohort study&lt;br&gt;UK Biobank Cohort including England, Scotland and Wales</td>
<td>502624 participants aged 37–73 years between 2006 and 2010</td>
<td>Biochemical assay of 25(OH)D, a measure of vitamin D status. Vitamin D was imputed if it was below or above the limit of detection.</td>
<td>Confirmed COVID-19 (at least one positive test result)</td>
<td>Complete data on 348598 UK Biobank participants 449 had confirmed COVID-19. Of these, 385 (85.8%) were white compared with 64 (14.2%) non-white (black, South Asian and others). Vitamin D was associated with COVID-19 univariately but not after adjustment for confounders. Ethnicity was associated with COVID-19.</td>
<td>UK Biobank is not representative of the general population. Baseline measurements, including 25(OH)D concentration and health status, were obtained a decade prior to the conduct of the study.</td>
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<td>Ilie et al&lt;sup&gt;71&lt;/sup&gt;</td>
<td>Ecological study&lt;br&gt;20 European countries</td>
<td>Population of 20 included European countries</td>
<td>Mean levels of vitamin D in each country</td>
<td>Cases of COVID-19 per 1 million population in each country. Deaths from COVID-19 per 1 million population.</td>
<td>Negative correlations between mean levels of vitamin D and the number of COVID-19 cases per 1 million, and mortality per 1 million.</td>
<td>The number of cases per country is affected by the number of tests performed and by the different measures taken by each country to prevent the spread of infection.</td>
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<td><strong>Vitamin D supplementation</strong></td>
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<td>Fasano et al&lt;sup&gt;74&lt;/sup&gt;</td>
<td>Case–control survey.&lt;br&gt;A single tertiary centre in Lombardy, Italy</td>
<td>1486 Parkinson’s disease (PD) patients were included in the survey 1207 family members (controls)</td>
<td>Vitamin D ‘Confirmed’ or ‘probable’ diagnosis of COVID-19</td>
<td>12.4% of PD patients with confirmed or probable COVID-19 had been taking vitamin D. 22.9% of PD patients without COVID-19 had been taking vitamin D.</td>
<td>Well-known limitation of a telephone survey. Community-dwelling PD patients. Some patients could not be reached possibly due to death from COVID-19. COVID-19 diagnosis could not be confirmed in many cases. Younger age of non-PD COVID-19 cases.</td>
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COVID-19 per million population in Sweden and 314 in Spain.

Vitamin D supplementation

Fasano et al\textsuperscript{44} investigated patients in a case–control phone survey in Lombardy, Italy. COVID-19 diagnosis was confirmed using a nasopharyngeal swab or probable based on (1) the presence of persistent COVID-19-related symptoms (≥3 including fever or ≥5 without fever); or (2) ≥1 symptom in the presence of suggestive chest radiologic signs; and/or (3) living with a family member with a confirmed diagnosis of COVID-19. A total of 1486 participants were included in the survey (32 confirmed COVID-19, 73 probable COVID-19 and 1381 unaffected). Confirmed/probable COVID-19 cases (mean age=70.5 (SD=10.1); male=53%) self-reported a significantly lower intake of vitamin D supplementation (12.4%) compared with unaffected cases (22.9%; mean age=73.0 (SD=9.5), male=57%). The age-adjusted OR (OR 0.56 (95% CI=0.32 to 0.99), p=0.048) suggested a protective effect of vitamin D intake.

Subgroup evaluation

We planned to perform subgroup analyses by age and ethnicity. According to Hastie et al\textsuperscript{20} multivariable analysis showed that age at assessment (OR=1.02; 95% CI=1.00 to 1.03; p=0.016) and non-white ethnicity (black OR=4.30, 95% CI=2.92 to 6.31, p<0.001; South Asians OR=2.42, 95% CI=1.50 to 3.93, p<0.001) were associated with confirmed COVID-19. However, Hastie et al\textsuperscript{20} found no significant interaction between ethnicity and vitamin D deficiency (OR=0.90; 95% CI=0.66 to 1.23; p=0.515).

DISCUSSION

This systematic review of non-randomised studies has shown no robust evidence of an association between vitamin D and COVID-19. We identified four studies for inclusion in a narrative synthesis which were all at high or unclear risk of bias. A univariable analysis of data from the UK Biobank database revealed an association between vitamin D and COVID-19 (OR=0.99; 95% CI 0.99 to 0.999, p=0.013). However, this association became insignificant (OR=1.00; 95% CI=0.998 to 1.01; p=0.208) after adjustment for 13 other covariates, suggesting that the initial association was due to one or more confounding variables.\textsuperscript{70} This view is further strengthened by the demonstration of highly significant associations between age and ethnicity characteristics as predictor variables and COVID-19 as the outcome variable. Overall, the UK Biobank study showed no effect; however, it should be noted that the UK Biobank data included only one measurement of vitamin D levels taken between 10 and 14 years prior to the outbreak of COVID-19. This is a significant study limitation.

Liu et al\textsuperscript{75} concluded that patients over 60 years experienced more severe manifestations and had longer disease courses of COVID-19 compared with patients below 60 years.\textsuperscript{75} And other studies have shown that older (rather than younger) people are more likely to die from COVID-19.\textsuperscript{76–79}

Non-white people are known to be more susceptible to COVID-19 and tend to develop worse outcomes,\textsuperscript{80} a finding that our review has further substantiated.\textsuperscript{70} Ethnicity is a multifaceted construct that includes genetic makeup, sociocultural identity and behavioural patterns.\textsuperscript{81} It has been shown to be associated with differing susceptibility and treatment outcomes in a number of diseases.\textsuperscript{82–84} Hastie et al\textsuperscript{20} did not find any interaction between ethnicity and vitamin D deficiency and although Ilie et al\textsuperscript{71} identified a relationship, the study is subject to ecological bias. Ilie et al\textsuperscript{71} compared vitamin D levels and rates of COVID-19 across 20 European countries, and therefore many relevant factors were not accounted for in the analysis. Given the findings so far from our review, we consider that there is paucity of data on vitamin D levels and morbidity and mortality from COVID-19 and there is no evidence from RCTs on outcomes of vitamin D supplementation on severity of symptoms or mortality to date. However, a relationship between ethnicity, vitamin D (serum levels or supplementation) and susceptibility to or severity of COVID-19 cannot yet be ruled out.

Risk of bias assessments demonstrate that all studies were at high or unclear risk of bias. All studies were observational designs and therefore, subject to confounding. The persistent calls for high-dose vitamin D supplementation\textsuperscript{85} arise from speculation about presumed mechanisms.\textsuperscript{86,87} Our systematic review found no robust evidence that low levels of vitamin D are associated with an increased likelihood of COVID-19. More robust prognostic studies could be combined in a systematic review where a prognostic factor research question is phrased, and considerations of participation, attrition, prognostic factor measurement, confounding measurement and account, outcome measurement, and analysis and reporting are evaluated.

Our systematic review identified no relevant RCTs; nevertheless, we are aware of two ongoing RCTs investigating the effects of vitamin D on COVID-19, the ZnD3-CoVici study, France (NCT04351490)\textsuperscript{88} and the CoVitTrial, France (NCT04344041).\textsuperscript{89} Both trials have an estimated study completion date of July 2020. Inclusion of data from these studies in future systematic reviews and meta-analyses may enable us to potentially draw better stronger conclusions on this topic. Results from the ongoing international VITDALIZE study (NCT03188796) may also contribute to our understanding of the effect of high-dose vitamin D\textsubscript{3} on mortality.\textsuperscript{90}

Study limitations

We performed a full systematic review of the published evidence available, and simultaneous independent screening, data extraction and risk of bias assessments. However, our study is limited by the small amount of evidence available which was, moreover, at risk of bias. This limits the inferences that can be drawn. Seven
eligible studies were excluded because they are not available as peer-reviewed publications. If published, these seven studies would be included in a future update of this review. A final limitation is that the review was restricted to English language only. Therefore, articles published in other languages may have been excluded.

Implications for practice
Our review does not provide evidence for or against additional or high-dose vitamin D supplementation specifically in relation to COVID-19. Treatment as standard practice for people who are deficient is pre-existing practice across Europe, the USA, and in the UK. Current guidelines from PHE suggest that the entire UK population should take vitamin D supplements to prevent vitamin D deficiency in winter or with inadequate sunlight exposure to sun in summer. This review does not give evidence to drive a change in this current advice. Treatment recommendations for patients should be updated following the publication of results from ongoing and new well-designed adequately powered randomised controlled trials.

CONCLUSION
This systematic review identified no robust evidence to enable us to assess an association between vitamin D supplementation or serum vitamin D level with susceptibility to COVID-19 including clinical course, morbidity and mortality outcomes. All studies were at high or unclear risk of bias. Both age and ethnicity were associated with vitamin D levels even after multivariable adjustment. Black and South Asian people had a much higher risk of confirmed COVID-19 compared with white people. However, there was no interaction between the association of ethnicity and vitamin D deficiency with COVID-19. There were no papers reporting association of vitamin D with severity of symptoms or mortality due to COVID-19.

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Contributors
SK, AG and AC conceived the study. AG, AC, NM, SK, ST-P and OAU designed the study. RC and AB developed the search strategies, performed all searches and database management, and created the bibliography. AG, AC, AM, OM, MZ screened titles and abstracts for inclusion. AG, OM, MZ, LA-K and AC screened at full text and extracted and analysed data. OM, AM, MZ and LA-K performed risk of bias assessments. AG, SK and NM assisted in the interpretation from a clinical perspective. ST-P, LA-K and OU offered technical and methodological support. AG, OM and MZ wrote the first draft, all authors revised content. All authors approved the final manuscript. AG and AC are the guarantors. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Competing interests
None declared.

Patient consent for publication
Not required.

Provenance and peer review
Not commissioned; externally peer reviewed.

Data availability statement
Data are available on reasonable request. All data relevant to the study are included in the article or uploaded as supplementary information. The study protocol is available systematic review protocol registration: CRD42020182876 available online via PROSPERO at https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020182876. All included studies are publicly available. Additional data are available on reasonable request by emailing the corresponding author.

Supplemental material
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69 Tan CW, LP H, Kalimuddin S. A cohort study to evaluate the effect of combination vitamin D magnesium and vitamin B12 (DMB) on progression to severe outcome in older COVID-19 patients. medRxiv 2020.


Supplemental file

Contents

1. Full record of search
2. Full details of the study eligibility criteria
3. List of studies excluded at full text review
4. Articles included at full text, but later excluded at time of narrative synthesis
5. Quality assessment of included studies

1. Full record of search

Medline (Ovid)

Search date: 06/05/2020
Database: Ovid MEDLINE(R) ALL <1946 to May 05, 2020>
Search Strategy:

1 exp Vitamin D/ (58492)
2 Vitamin D Deficiency/ (15552)
3 (vitamin D? or vit D? or D vitamin? or ergocalciferol or cholecalciferol or colecalciferol or calciferol or dihydroergocalciferol or sitocalciferol or dihydroachysteroxy or dihydroxycholecalciferol? or hydroxycholecalciferol? or "25(OH)D?" or 25OHD? or calcidiol or hydroxyergocalciferol or alfalcaldiol or alphacalcidol or "1,25(OH)2D" or hydroxyvitamin D? or dihydroxyvitamin D?).ab,kf,ti. (78232)
4 (paricalcitol or doxercalciferol or doxercalciferol or calcifediol or calcitriol).ab,kf,ti. (5577)
5 hypovitaminosis D?.ab,kf,ti. (1775)
6 ((D or D2 or D3) adj3 supplement*).ab,kf,ti. (12158)
7 1 or 2 or 3 or 4 or 5 or 6 (92560)
8 coronavirus/ or betacoronavirus/ or betacoronavirus 1/ or coronavirus oc43, human/ or middle east respiratory syndrome coronavirus/ or sars virus/ (7431)
9 coronavirus infections/ or severe acute respiratory syndrome/ (10675)
10 (((corona* or corono*) adj1 (virus* or viral* or virinae*)) or coronavirus* or coronavirus* or coronavirinae* or Coronavirus* or Coronavirus* or Wuhan* or Hubei* or Huanan or "2019-nCoV" or 2019nCoV or nCoV2019 or "nCoV-2019" or "COVID-19" or COVID19 or "CORVID-19" or CORVID19 or "WN-CoV" or WNCoV or "HCoV-19" or HCoV19 or CoV or "2019 novel*" or Ncov or "n-cov" or "SARS-CoV-2" or "SARSCoV-2" or "SARS-CoV2" or "SARS-CoV2" or SARSCoV19 or "SARS-Cov19" or "SARS-CoV-19" or "SARS-Cov-19" or Ncovor or Ncorona* or Ncoron* or NcovWuhan* or NcovHubei* or NcovChina* or NcovChinese*).ab,kf,ti. (26891)
11 (severe acute respiratory syndrome or SARS or Middle East respiratory syndrome or MERS).ab,kf,ti. (16560)
12 (betacoronavirus* or betacoronavirinae*).ab,kf,ti. (280)
13 8 or 9 or 10 or 11 or 12 (37180)
14 7 and 13 (32)
15 exp Animals/ (23144176)
16  exp Humans/ (18448248)
17  15 not 16 (4695928)
18  14 not 17 (30)
19  limit 18 to yr="2002 -Current" (30)

Update
Search date: 10/6/2020
Actual databases searched: Ovid MEDLINE All <1946 to June 09, 2020>
Search strategy:
Re-ran search above plus...
20  limit 19 to ed=20200506-20200610 (8)
21  limit 19 to ep=20200506-20200610 (39)
22  limit 19 to dt=20200506-20200610 (43)
23  limit 19 to ez=20200506-20200610 (27)
24  20 or 21 or 22 or 23 (46)

Embase (Ovid)
Search date: 06/05/2020
Database: Embase <1974 to 2020 May 05>
Search Strategy:
--------------------------------------------------------------------------------
1  exp vitamin D/ (139781)
2  vitamin D deficiency/ (29333)
3  (vitamin D? or vit D? or D vitamin? or ergocalciferol or cholecalciferol or colecalficoler or calciferol or dihydroergocalciferol or sitocalciferol or dihydrotachysterol or dihydroxycholecalciferol? or hydroxycholecalciferol? or "25(OH)D?" or 25OHD? or calcidiol or hydroxyergocalciferol or alfalcaiold or alphacalciold or "1,25(OH)2D" or hydroxyvitamin D? or dihydroxyvitamin D?).ab,kw,ti. (112459)
4  (paricalcitol or doxercalciferol or doxercalciferol or calcifediol or calcitriol).ab,kw,ti. (8478)
5  hypovitaminosis D?.ab,kw,ti. (3012)
6  ((D or D2 or D3) adj3 supplement*).ab,kw,ti. (19177)
7  1 or 2 or 3 or 4 or 5 or 6 (163395)
8  betacoronavirus 1/ or betacoronavirus/ or human coronavirus oc43/ (696)
9  Middle East respiratory syndrome coronavirus/ (2028)
10  sars-related coronavirus/ or sars coronavirus/ (6354)
11  Coronavirus/ (2231)
12  coronavirus infection/ or middle east respiratory syndrome/ or severe acute respiratory syndrome/ (11950)
13  (((corona* or corono*) adj1 (virus* or viral* or virinae*)) or coronavirus* or coronavirus* or coronavirine* or Coronavirus* or Coronavirus* or Wuhan* or Hubei* or Huanan or "2019-nCoV" or 2019nCoV or nCoV2019 or "nCoV-2019" or "COVID-19" or COVID19 or "CORVID-19" or CORVID19 or "WN-CoV" or WNCov or "HCoV-19" or HCoV19 or CoV or "2019 novel*" or Ncov or "n-cov" or "SARS-CoV-2" or "SARS-CoV-2" or "SARS-CoV2" or "SARS-CoV2" or SARS-CoV19 or "SARS-CoV19" or "SARS-CoV-19" or "SARS-Cov-19" or "SARS-Cov19" or Ncov or Ncorona* or Ncorona* or Ncorona* or Ncorona* or Ncorona* or Ncorona* or Ncorona* or Ncorona* or NcorWuhan* or NcoveHubei* or NcoveChina* or NcoveChinese*).ab,kw,ti. (27686)
14  (severe acute respiratory syndrome or SARS or Middle East respiratory syndrome or MERS).ab,kw,ti. (17146)
15  (betacoronavirus* or betacoronavirusine*).ab,kw,ti. (275)
16  8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 (40716)
Update
Search date: 10/6/2020
Actual databases searched: Ovid Embase <1974 to 2020 June 09>
Search strategy:
Re-ran search above plus...
22 limit 21 to yr="2002 -Current" (123)
23 limit 22 to dd=20200506-20200610 (39)
24 limit 22 to em=202005-202006 (0)
25 limit 22 to dc=20200506-20200610 (62)
26 23 or 24 or 25 (62)

MedRxiv (searched via Medrxivr https://mcguinlu.shinyapps.io/medrxivr/)
Search date: 07/05/2020
Search Strategy:

Topic 1:
[Vv]itamin D
[Vv]itamin D2
[Vv]itamin D3
calciferol
25OHD
25OHD3
[Hh]ypovitaminosis D

Topic 2:
[Cc]oronavirus
[Cc]orona(\s){0,1}virus
[Cc]oronavirinae
[Cc]ovid
nCoV
NCOV
Ncov
[Nn]-cov
N-COV
2019ncov
2019-ncov
ncov2019
ncov-2019
SARS
[Severe Acute Respiratory Syndrome]
Middle East Respiratory Syndrome

MERS

Earliest record date
20190101
Latest record date
20200507
Remove older versions of the same record

6 results

Update
Search date: 10/6/2020
Re-ran search above changing record dates as follows:
Earliest record date
20200507
Latest record date
20200610
Remove older versions of the same record

11 results

BioRxiv
https://www.biorxiv.org/

Search date: 07/05/2020

65 Results
for abstract or title "vitamin D" (match phrase words)

22 Results
for full text or abstract or title "ergocalciferol cholecalciferol colecalciferol" (match whole any)

41 Results
for full text or abstract or title "25OHD 25OHD3" (match whole any)

Imported into EndNote and de-duplicated
92 results after deduplication

Searched in Endnote using the following search strategy:
coronavirus or corona or covid or SARS or MERS or betacoronavirus or ncov
Any Field

5 results

Update
Search date: 10/6/2020
1 Results
for abstract or title "vitamin D" (match phrase words) and posted between "07 May, 2020 and 10 Jun, 2020" – animal study (also in both results sets below) so not exported to EndNote

3 Results
for full text or abstract or title "ergocalciferol cholecalciferol colecalciferol" (match whole any) and posted between "07 May, 2020 and 10 Jun, 2020" - 2 animal studies and 1 on sertraline in TB

2 Results
for full text or abstract or title "25OHD 25OHD3" (match whole any) and posted between "07 May, 2020 and 10 Jun, 2020" - 1 animal study, 1 non-clinical / non-coronavirus

0 results relevant to coronaviruses

Cochrane Library

Search date: 08/05/2020

ID Search Hits
#1 MeSH descriptor: [Vitamin D] explode all trees 5224
#2 MeSH descriptor: [Vitamin D Deficiency] this term only 1226
#3 (vitamin NEXT D?) or (vit NEXT D?) or (D NEXT vitamin?) or ergocalciferol or cholecalciferol or colecalciferol or calciferol or dihydroergocalciferol or sitocalciferol or dihydrotachysterol or dihydroxycholecalciferol? or hydroxycholecalciferol? or "25(OH)D" or "25(OH)D3" or 25OHD? or calcidiol or hydroxyergocalciferol or alfalcacidol or alphacalcidol or "1,25(OH)2D" or (hydroxyvitamin NEXT D?) or (dihydroxyvitamin NEXT D?):ti,ab,kw 12959
#4 (paricalcitol or doxercalciferol or doxerocalciferol or calcifediol or calcitriol):ti,ab,kw 2417
#5 hypovitaminosis NEXT D? 303
#6 ((D OR D2 OR D3) NEAR/3 supplement*):ti,ab,kw 5633
#7 #1 or #2 or #3 or #4 or #5 or #6 14461
#8 MeSH descriptor: [Coronavirus] this term only 2
#9 MeSH descriptor: [Betacoronavirus] this term only 2
#10 MeSH descriptor: [Betacoronavirus 1] this term only 0
#11 MeSH descriptor: [Coronavirus OC43, Human] this term only 0
#12 MeSH descriptor: [Middle East Respiratory Syndrome Coronavirus] explode all trees 1
#13 MeSH descriptor: [SARS Virus] this term only 9
#14 MeSH descriptor: [Coronavirus Infections] this term only 137
#15 MeSH descriptor: [Severe Acute Respiratory Syndrome] this term only 107
#16 (((corona* or corono*) near/1 (virus* or viral* or virinae*)) or coronavirus* or coronavirus* or coronaviinae* or Coronavirus* or Coronavirus* or Wuhan* or Hubei* or Huanan or "2019-nCoV" or 2019nCoV or nCoV2019 or "nCoV-2019" or "COVID-19" or COVID19 or "CORVID-19" or CORVID19 or "WN-CoV" or WNCov or "HCoV-19" or HCoV19 or CoV or "2019 novel*" or Ncov or "n-cov" or "SARS-CoV-2" or "SARS-CoV-2" or "SARS-CoV2" or SARS-CoV19 or "SARS-Cov19" or "SARS-Cov-19" or "SARS-Cov-19" or Ncovor or Ncorona* or Ncorono* or NcovWuhan* or NcOvHubei* or NcOvChina* or NcOvChinese*):ti,ab,kw 614
#17 ("severe acute respiratory syndrome" or SARS or "Middle East respiratory syndrome" or MERS):ti,ab,kw 350
#18 (betacoronavirus* or betacoronaviinae*):ti,ab,kw 4
Update
Search date: 10/06/2020
Re-ran search exactly as above and retrieved 5 results, all from CENTRAL. All 5 results exported to EndNote for deduplication.

Database of publications (living map of evidence) on coronavirus disease (COVID-19) developed by the University of Bern

Living Evidence on COVID-19
Contributors: Michel Counotte, Hira Imeri, Mert Ipekci, Nicola Low

https://zika.ispm.unibe.ch/assets/data/pub/ncov/

Search date: 10/05/2020 (14,988 entries)

Search: Title, Abstract
Search:

vitamin D 13
vitamin D2 0
vitamin D3 0
ergocalciferol 0
cholecalciferol 0
colecalciferol 0
25(OH)D 0
25OHD 0
25(OH)D3 0
25OHD3 0
hypovitaminosis D 1
Vitamin D Deficiency 1

Oxford COVID-19 Evidence Service
https://www.cebm.net/oxford-covid-19-evidence-service/
The Centre for Evidence-Based Medicine (CEBM) The University of Oxford

Search date: 10/05/2020 (142 articles)
vitamin D 1
vitamin D2 0
vitamin D3 0
ergocalciferol 0
cholecalciferol 0
colecalciferol 0
25(OH)D 0
25OHD 0
25(OH)D3 0
25OHD3 0
hypovitaminosis D 0
Vitamin D Deficiency 0

Database of publications on coronavirus disease (COVID-19) developed by WHO

Search date: 10/05/2020  (15,253 entries)

Search: Title, Abstract, Subject

vitamin D 19
vitamin D2 0
vitamin D3 2
ergocalciferol 0
cholecalciferol 1
colecalciferol 0
25(OH)D 0
25OHD 0
25(OH)D3 0
25OHD3 0
hypovitaminosis D 1
Vitamin D Deficiency 2

Total: 25
After de-duplication: 20

Searches for systematic reviews, for reference checking

Medline

Search date: 19/05/2020
Database: Ovid MEDLINE(R) ALL <1946 to May 18, 2020>
Search Strategy:

1 exp Vitamin D/ (58577)
2 Vitamin D Deficiency/ (15588)
3 (vitamin D? or vit D? or D vitamin? or ergocalciferol or cholecalciferol or colecalciferol or calciferol or dihydroergocalciferol or sitocalciferol or dihydrotachysterol or dihydroxycholecalciferol? or hydroxycholecalciferol? or “25(OH)D?” or 25OHD? or calcidiol or hydroxyergocalciferol or alfalcacidol or alphacalcidol or “1,25(OH)2D” or hydroxyvitamin D? or dihydroxyvitamin D?).ab,kf,ti. (78395)
4 (paricalcitol or doxercalciferol or doxercalciferol or calcitriol).ab,kf,ti. (5588)
5 hypovitaminosis D?.ab,kf,ti. (1780)
6 ((D or D2 or D3) adj3 supplement*).ab,kf,ti. (12198)
7 1 or 2 or 3 or 4 or 5 or 6 (92747)
8  coronavirus/ or betacoronavirus/ or betacoronavirus 1/ or coronavirus oc43, human/ or middle east respiratory syndrome coronavirus/ or sars virus/ (8161)
9  coronavirus infections/ or severe acute respiratory syndrome/ (11614)
10  (((corona* or corono*) adj1 (virus* or viral* or virinae*)) or coronavirus* or coronavirinae* or Coronavirus* or Coronovirus* or Wuhan* or Hubei* or Huanan or "2019-nCoV" or 2019nCoV or nCoV2019 or "nCoV-2019" or "COVID-19" or COVID19 or "CORVID-19" or CORVID19 or "WN-CoV" or WNCov or "HCoV-19" or HCoV19 or CoV or "2019 novel*" or Ncov or "n-cov" or "SARS-CoV-2" or "SARS-CoV2" or "SARS-CoV-2" or SARS-CoV19 or "SARS-Cov19" or "SARS-Cov-19" or "SARS-Cov-19" or Ncov or Ncorona* or Ncorono* or NcovWuhan* or NcovHubei* or NcovChina* or NcovChinese*).ab,kf,ti. (31115)
11  (severe acute respiratory syndrome or SARS or Middle East respiratory syndrome or MERS).ab,kf,ti. (17795)
12  (betacoronavirus* or betacoronavirinae*).ab,kf,ti. (294)
13  exp Respiratory Tract Infections/. (356696)
14  (acute respiratory infection* or severe respiratory infection* or acute respiratory tract infection* or severe respiratory tract infection* or influenza or common cold or pneumonia or bronchitis).ab,kf,ti. (234266)
15  8 or 9 or 10 or 11 or 12 or 13 or 14 (503079)
16  7 and 15 (1062)
17  (metanayls* or "meta analys*" or "meta-analys*").tw. (169008)
18  (systematic* adj3 review*).mp. (200684)
19  meta analysis.pt. (114746)
20  17 or 18 or 19 (301767)
21  16 and 20 (55)

Embase

Search date: 19/05/2020

Database: Embase Classic+Embase <1947 to 2020 Week 20>
Search Strategy:

--------------------------------------------------------------------------------
1  exp vitamin D/ (147053)
2  vitamin D deficiency/ (30106)
3  (vitamin D? or vit D? or D vitamin? or ergocalciferol or cholecalciferol or colecalciferol or calciferol or dihydroergocalciferol or sitocalciferol or dihydrotachysterol or dihydroxycholecalciferol? or hydroxycholecalciferol? or "25(OH)D?" or 25OHD? or calcidiol or hydroxyergocalciferol or alfalcacidol or alphacalcidol or "1,25(OH)2D" or hydroxyvitamin D? or dihydroxyvitamin D?).ab,kw,ti. (118981)
4  (paricalcitol or doxercalciferol or doxercalciferol or calcifiol or calcitriol).ab,kw,ti. (8485)
5  hypovitaminosis D?.ab,kw,ti. (3033)
6  (((D or D2 or D3) adj3 supplement*).ab,kw,ti. (19335)
7  1 or 2 or 3 or 4 or 5 or 6 (172654)
8  betacoronavirus 1/ or betacoronavirus/ or human coronavirus oc43/ (1085)
9  Middle East respiratory syndrome coronavirus/ (2082)
10  sars-related coronavirus/ or sars coronavirus/ (6062)
11  Coronavirusae/ (2060)
12  coronavirus infection/ or middle east respiratory syndrome/ or severe acute respiratory syndrome/ (12565)
Cochrane Database of Systematic Reviews (Cochrane Library)

Search Name: Vitamin D Covid and Acute Respiratory Infections SRs
Date Run: 20/05/2020 18:30:28
Comment:

ID   Search   Hits
#1   MeSH descriptor: [Vitamin D] explode all trees   5224
#2   MeSH descriptor: [Vitamin D Deficiency] this term only   1226
#3   (vitamin NEXT D?) or (vit NEXT D?) or (D NEXT vitamin?) or ergocalciferol or cholecalciferol or colecalferror or calciferor or dihydroergocalciferor or sitocalciferor or dihydrotachysterol or dihydroxchocalciferor? or hydroxycholecalciferor? or "25(OH)D" or "25(OH)D3" or 25OHD? or calcidiol or hydroxyergocalciferor or alfacalcidiol or alphacalcidiol or "1,25(OH)2D" or (hydroxyvitamin NEXT D?) or (dihydroxyvitamin NEXT D?):ti,ab,kw   12959
#4   (paricalcitol or doxercalciferor or doxocalciferor or calcifediol or calcitriol):ti,ab,kw   2417
#5   hypovitaminosis NEXT D?   303
#6   ((D OR D2 OR D3) NEAR/3 supplement*):ti,ab,kw   5632
#7   #1 or #2 or #3 or #4 or #5 or #6   14461
#8   MeSH descriptor: [Coronavirus] this term only   2
#9   MeSH descriptor: [Betacoronavirus] this term only   2
#10  MeSH descriptor: [Betacoronavirus 1] this term only   0
#11  MeSH descriptor: [Coronavirus OC43, Human] this term only   0
#12  MeSH descriptor: [Middle East Respiratory Syndrome Coronavirus] explode all trees   1
Supplemental material

One additional study identified:

2. **Full details of the study eligibility criteria**

<table>
<thead>
<tr>
<th>Include</th>
<th>Exclude</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>P - Population</strong></td>
<td>Animals studies, modelling studies</td>
</tr>
<tr>
<td>1) Patients acutely ill with Betacoronavirus infection [SARS-CoV, MERS-CoV, SARS-CoV-2]</td>
<td></td>
</tr>
<tr>
<td>2) or at risk of acute illness with Betacoronavirus infection</td>
<td></td>
</tr>
<tr>
<td><strong>I - Intervention/exposure</strong></td>
<td></td>
</tr>
<tr>
<td>1) Vitamin D supplementation</td>
<td></td>
</tr>
<tr>
<td>2) Low Serum Vitamin D</td>
<td></td>
</tr>
<tr>
<td><strong>O - Outcomes</strong></td>
<td></td>
</tr>
<tr>
<td>1) Betacoronavirus infection (to include serological evidence of infection or clinically confirmed symptomatic infection);</td>
<td></td>
</tr>
<tr>
<td>2) severity of Betacoronavirus infection (to include patients admitted to hospital or admitted to intensive care); mortality due to Betacoronavirus.</td>
<td></td>
</tr>
<tr>
<td>3) Mortality due to Betacoronavirus</td>
<td></td>
</tr>
<tr>
<td><strong>C - Comparator</strong></td>
<td></td>
</tr>
<tr>
<td>1) No Vitamin D supplementation</td>
<td></td>
</tr>
<tr>
<td>2) high or normal Serum Vitamin D</td>
<td></td>
</tr>
<tr>
<td><strong>S - Study design</strong></td>
<td>Qualitative studies, Non-primary research- reviews, editorials etc, guidelines and non-systematic reviews.</td>
</tr>
<tr>
<td>Randomised controlled trials and non-randomized studies will be eligible for inclusion in the review including, non randomized controlled trials, interrupted time series, controlled before-and-after studies, cohort studies, ecological studies, case reports and case series.</td>
<td></td>
</tr>
<tr>
<td><strong>Subgroups</strong></td>
<td>Non-English language. Non peer reviewed publication.</td>
</tr>
<tr>
<td>1. Ethnicity characteristics (White British, All Other White, Mixed, Asian, Black, Other)</td>
<td></td>
</tr>
<tr>
<td>2. Age characteristics (population by five-year age groups)</td>
<td></td>
</tr>
</tbody>
</table>
### List of studies excluded at full text review

<table>
<thead>
<tr>
<th>Excluded studies</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>ID</td>
<td>Author(s)</td>
</tr>
<tr>
<td>----</td>
<td>-----------</td>
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<tr>
<td>15</td>
<td>Faul, J. L., et al. (2020)</td>
</tr>
<tr>
<td>17</td>
<td>Grant, W. B., et al. (2020)</td>
</tr>
<tr>
<td>19</td>
<td>Hribar, C. A., et al. (2020)</td>
</tr>
<tr>
<td>22</td>
<td>Kalippurayil Moozhipurath, R., et al. (2020)</td>
</tr>
<tr>
<td>Page</td>
<td>Reference</td>
</tr>
<tr>
<td>------</td>
<td>-----------</td>
</tr>
<tr>
<td>No.</td>
<td>Authors</td>
</tr>
<tr>
<td>-----</td>
<td>--------------------</td>
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<tr>
<td>34</td>
<td>Mitchell, F.</td>
</tr>
<tr>
<td>35</td>
<td>Molloy, E. J. and N. Murphy</td>
</tr>
<tr>
<td>37</td>
<td>Rabbitt, L. and E. Slattery</td>
</tr>
<tr>
<td>38</td>
<td>Ribeiro, H., et al.</td>
</tr>
<tr>
<td>40</td>
<td>Silberstein, M.</td>
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<tr>
<td>41</td>
<td>Speeckaert, M. M. and J. R. Delanghe</td>
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<tr>
<td>43</td>
<td>Suresh, P. S.</td>
</tr>
<tr>
<td>47</td>
<td>Zabetakis, I., et al.</td>
</tr>
</tbody>
</table>
### 4. Articles included at full text, but later excluded at time of narrative synthesis

<table>
<thead>
<tr>
<th>Citation record</th>
<th>Exclusion reason</th>
<th>Update performed 8th October 2020</th>
</tr>
</thead>
<tbody>
<tr>
<td>De Smet, D., et al. (2020). Vitamin D deficiency as risk factor for severe COVID-19: a convergence of two pandemics. medRxiv. <a href="https://www.medrxiv.org/content/10.1101/2020.05.01.20079376v2">https://www.medrxiv.org/content/10.1101/2020.05.01.20079376v2</a></td>
<td>Not peer reviewed publication at time of narrative synthesis</td>
<td>No update available</td>
</tr>
<tr>
<td>Reference</td>
<td>Title</td>
<td>doi</td>
</tr>
<tr>
<td>--------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------</td>
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</tbody>
</table>
| https://www.medrxiv.org/content/10.1101/2020.05.08.20095083v1?versioned=TRUE | Raisi-Estabragh, Z., et al. (2020). “Greater risk of severe COVID-19 in non-White ethnicities is not explained by cardiometabolic, socioeconomic, or behavioural factors, or by 25(OH)-vitamin D status: study of 1,326 cases from the UK Biobank.” MedRxiv: the Preprint Server for Health Sciences. | An updated publication is available at https://academic.oup.com/pubhealth/article/42/3/5859581 | Citation
Zahra Raisi-Estabragh, Celeste McCracken, Mae S Bethell, Jackie Cooper, Cyrus Cooper, Mark J Caulfield, Patricia B Munroe, Nicholas C Harvey, Steffen E Petersen, Greater risk of severe COVID-19 in Black, Asian and Minority Ethnic populations is not explained by cardiometabolic, socioeconomic or behavioural factors, or by 25(OH)-vitamin D status: study of 1326 cases from the UK Biobank, *Journal of Public Health*, Volume 42, Issue 3, September 2020, Pages 451–460, [https://doi.org/10.1093/pubmed/fdaa095](https://doi.org/10.1093/pubmed/fdaa095) |
<table>
<thead>
<tr>
<th>Study</th>
<th>Design/setting</th>
<th>Population</th>
<th>Exposure/Intervention</th>
<th>Outcomes</th>
<th>Results</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Darling, A. L., et al. (2020)</td>
<td>Retrospective cohort study UK Biobank cohort only</td>
<td>COVID-19 positive cases (n 580) Mean age 57.5 (SD 9.7) COVID-19 negative controls (n 723) Mean age 57.9 (SD 8.7)</td>
<td>Serum 25(OH)D status Median (IQR) nmol/L by gender (Male/Female), body mass index (Normal/underweight, overweight, obesity), ethnicity (Asian, Black, Mixed and Other, White)</td>
<td>COVID-19 test result</td>
<td>Serum 25(OH)D status similar in both groups: COVID-19 positive cases (median IQR) = 43.3 (32.1) nmol/L COVID-19 negative controls (median (IQR) 44.1 (31.2) nmol/L) for COVID-19.</td>
<td>A logistic regression model suggests that being overweight (OR 1.51 CI 1.13-2.02) or obese (OR 1.67 CI 1.24-2.26); living in London (OR 1.45 CI 1.05-2.00); being male (OR 1.28 CI 1.01-1.61) and being of Asian, Black or Mixed ethnicity (OR 1.66 CI 1.08-2.54) is associated with a higher odds of testing positive for COVID-19 UK Biobank baseline samples collected in 2006-2010.</td>
</tr>
<tr>
<td>De Smet, D., et al. (2020)</td>
<td>Retrospective observational study Central network hospital, West Flanders, Belgium</td>
<td>186 SARS-CoV-2 infected patients hospitalised from March 1, 2020 to April 7, 2020 (109 males [median age 68 years, IQR 53-79] 77 females [median age 71 years, IQR 65-74]) 25(OH)D in COVID-19 patients was compared a control group of 2717 patients with similar age distribution, sampled from March 1, 2019 to April 30, 2019. (999 males [median age 69 years, IQR 53-81] and 1718 females [median age 68 years, IQR 43-83]).</td>
<td>25(OH)D levels</td>
<td>SARS-CoV-2 infection COVID-19 patients had a lower median 25(OH)D on admission (18.6 ng/mL, IQR 12.6-25.3) than controls (21.5 ng/mL, IQR 13.9-20.8, P=0.0016) and a higher percentage of vitamin D deficiency (defined as 25(OH)D &lt; 20ng/mL): 58.6% versus 45.2% (P=0.0005). In male COVID-19 patients, vitamin D deficiency was lower median 25(OH)D (17.6 ng/mL, IQR 12.7-24.0 versus 20.3 ng/mL, IQR 13.7-28.3, P=0.0234) and a higher deficiency rate (67.0% versus 49.2%, P=0.0006) than male controls.</td>
<td>The prevalence and age/sex/seasonal-distribution of vitamin D status was derived from the general population sampled from 16274 consecutive, unselected and unique patients from January 1, 2019 to December 31, 2019.</td>
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Lau, F. H., et al. (2020)  
Retrospective observational study  
A single, tertiary care academic (university) medical centre, Louisiana, New Orleans, USA  
COVID-19 ICU patients (n 13)  
- Mean age 61.5 (SD 15.7)  
- COVID-19 floor patients (n 7)  
- Mean age 72.0 (SD 14.8)  
Medical records of COVID-19 patients between March 27, 2020 and April 21, 2020  
Vitamin D insufficiency (VDI) and COVID-19 metrics in ICU vs. floor patients  
VDI: defined as serum 25(OH) D < 30 ng/mL  
- Serum 25(OH) D status Mean (SD) ng/mL by gender (Male/Female), body mass index (Normal, obesity), race (African American), age (elderly>65 years), hypertension  
- Overall, few significant differences were identified between ICU and floor patients: Lactate dehydrogenase was significantly higher among ICU patients (441.8 vs. 223.0, P=0.001). Also, body mass index was significantly higher among ICU patients (35.2 vs. 24.5, P=0.02).  
- Among ICU subjects, 11 (84.6%) had VDI, vs. 4 (57.1%) of floor subjects. 100% of ICU patients less than 75 years old had VDI (n=11). Among these, 64.6% (n=7) had critically low 25(OH) D (<20 ng/mL) and 3 had <10 ng/mL.  
- VDI is highly prevalent in dark-skinned people (82.1% of African Americans vs. 41.6% overall).  
- Male/Female ratio was 1.24 and 1.44 for COVID-19 and VDI respectively.  

Statistical analysis was limited by the small number of subjects.

Meltzer, D. O., et al. (2020)  
Retrospective cohort study  
University of Chicago Medicine, USA  
4,314 patients tested for COVID-19 from 3/3/2020 to 4/10/2020. Among these, 499 had a vitamin D level in the year before testing.  
COVID-19 positive cases with vitamin D deficient (n 178)  
- Mean age 45.6  
COVID-19 positive cases with not vitamin D deficient (n 321)  
- Mean age 50.7  
Vitamin D deficiency: defined by the most recent 25(OH) D <20ng/ml or 1,25-dihydroxycholecalciferol <18pg/ml within 1 year before COVID-19 testing. Treatment: defined by the most recent vitamin D type and dose, and treatment changes between the time of the most recent vitamin D level and time of COVID-19 testing  
Vitamin D deficiency and treatment changes were combined to categorize vitamin D status at the time of COVID-19 testing as:  
1)Likely deficient (last-level-deficient/treatment-not-increased)  
2)Likely sufficient (not-deficient/treatment-not-decreased)  
3)Likely increased (deficient/treatment-increased)  
4)Likely normal (not-deficient/treatment-not-decreased)  
5)Likely decreased (deficient/treatment-decreased)  
Testing positive for COVID-19  
In multivariable analysis, testing positive for COVID-19 was associated with increasing age (RR (age<50)=1.05, P<0.021; RR (age≥50)=1.02, P=0.064)), non-white race (RR=2.54, P<0.01) and being likely vitamin D deficient (deficient/treatment-not-increased: RR=1.77, P<0.02) as compared to likely vitamin D sufficient (not-deficient/treatment-not-decreased), with predicted COVID-19 rates in the vitamin D deficient group of 21.6% (95%CI [14.0%-29.2%]) vs 12.2% (95%CI [8.9%-15.4%]) in the vitamin D sufficient group.  
Vitamin D deficiency declined with increasing vitamin D dose (especially of vitamin D3). Vitamin D dose was not significantly associated with testing positive for COVID-19 (P=0.18).  
The associations observed might not reflect causal effects of vitamin D deficiency on COVID-19. This is because vitamin D deficiency can reflect a range of chronic health conditions or behavioural factors which plausibly decrease the likelihood of treatment of vitamin D.
2) Likely sufficient (last-level-not-deficient/treatment-not-decreased)  
3) Uncertain deficiency (last-level-deficient/treatment-increased or last-level-not-deficient/treatment-decreased)  
by age (<50, ≥50), gender (Male/Female), race (White, other than White), ethnicity (Hispanic, not Hispanic), body mass index, employee status, comorbidity indicators (e.g. hypertension)  

<p>| Notari, A. and G. Torrieri (2020) | Correlational study | The number of cases follows in its early stages an almost exponential expansion. A starting point in each country was chosen: the first day (d_i) with 30 cases and fitted for 12 days. Thus, capturing the early exponential growth. Countries with too small total population (less than 300 thousands inhabitants) were excluded. | They analysed risk factors correlated with the initial transmission growth rate of COVID-19. Average annual level of serum Vitamin D and the seasonal level. The seasonal level is defined as: the amount during March or during winter for northern hemisphere, or during summer for southern hemisphere or the annual level for countries with little seasonal variation. | Growth rate of COVID-19: They looked for linear correlations of the exponents with other variables, for a sample of 126 countries. They found a positive correlation, i.e. faster spread of COVID-19, with high confidence level with the following variables, with respective (p)-value: low Temperature ((4 \cdot 10^{-7})), high ratio of old vs. working-age people ((3 \cdot 10^{-5})), life expectancy ((8 \cdot 10^{-6})), number of international tourists ((1 \cdot 10^{-5})), earlier epidemic starting date (d_i) ((2 \cdot 10^{-5})), high level of physical contact in greeting habits ((6 \cdot 10^{-5})), lung cancer prevalence ((6 \cdot 10^{-5})), obesity in males ((3 \cdot 10^{-5})), share of population in urban areas ((2 \cdot 10^{-6})), cancer prevalence ((3 \cdot 10^{-6})), alcohol consumption ((0.0019)), daily smoking prevalence ((0.0036)), UV index ((0.004), smaller sample, 73 countries), low Vitamin D serum levels ((0.002-0.006), smaller sample, 50 countries). There is highly significant correlation also with blood type. Also, positive correlation with moderate CI ((p)-value of 0.02-0.03) with: CO2/SO emissions, type-1 diabetes in children, and low vaccination coverage for Tuberculosis (BCG). | The dataset for the annual vitamin D was built with the available literature, which is quite inhomogeneous. The dataset for the seasonal levels is more restricted. This is because the relative literature is less complete. So, for this the authors have included only 42 countries. |</p>
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Sample Size</th>
<th>Methods</th>
<th>Findings</th>
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<tr>
<td>Raisi-Estabragh, Z., et al. (2020)</td>
<td>Retrospective cohort study</td>
<td>4,510 UK participants tested for COVID-19. Latest data release (29/05/2020) includes test results from 16/03/2020 to 18/05/2020. COVID-19 positive cases (n 1,326) Mean age 68.11 (SD 9.23) COVID-19 negative controls (n 3,184) Mean age 68.91 (SD 8.72)</td>
<td>Serum 25(OH) D levels nmol/L Multivariate logistic regression models by age, gender (Male/Female), ethnicity (Caucasian (any White background) and non-Caucasian: Black, Asian, Chinese) to test whether addition of: 1) cardio metabolic factors (e.g. hypertension, body mass index); 2) 25(OH)-vitamin D; 3) poor diet; 4) Townsend deprivation score; 5) housing; or 6) behavioural factors attenuated sex/ethnicity associations with COVID-19 status</td>
<td>Vitamin D is not highly correlated with UV index due to different food consumption in different countries. COVID-19 test result Greater risk of severe COVID-19 Over-representation of men and non-White ethnicities in the COVID-19 positive group. Non-Whites had, on average, poorer cardio metabolic profile, lower 25(OH)-vitamin D, greater material deprivation, and were more likely to live in larger households and flats. Male sex, non-White ethnicity, higher body mass index, Townsend deprivation score, and household overcrowding were independently associated with significantly greater odds of COVID-19. The pattern of association was consistent for men and women; cardio metabolic, socio-demographic and behavioural factors did not attenuate sex/ethnicity associations.</td>
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<td>Tan, C. W., et al. (2020)</td>
<td>Cohort observational study</td>
<td>All 43 consecutive hospitalized COVID-19 patients aged 50 and above. Between 15 January and 15 April 2020.</td>
<td>DMB = a single daily oral dose of vitamin D3 1000 IU, magnesium 150mg and vitamin B12 500mcg for up to 14 days Adjusted for age, gender and comorbidities</td>
<td>Deterioration post-DMB administration leading to any form of oxygen therapy and/or intensive care Duration of therapy: days, Median 5 (IQR 4-7) Significantly fewer DMB patients than controls required initiation of oxygen therapy subsequently throughout their hospitalization (17.6% vs 61.5%, P=0.006). On univariate analysis, increasing age and presence of comorbidities were associated</td>
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17 patients received Vitamin D, Magnesium, Vitamin B12 (DMB): Mean age 58.4 (SD 7.0)
26 patients did not: Mean age 64.1 (SD 7.9)

| support for COVID-19 patients | with significantly higher OR for oxygen therapy, while exposure to DMB therapy was associated with a significantly improved OR 0.13 (95% CI: 0.03 – 0.59, P=0.008).
On multivariate analysis, increasing age was associated with significantly higher OR for oxygen therapy, while exposure to DMB therapy was associated with a significantly improved OR 0.15 (95% CI: 0.025 – 0.93, P=0.041). |
5. **Risk of bias of included studies**

Risk of bias assessment using the Downs and Black Checklist

<table>
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<tr>
<th>Study</th>
<th>Quality score</th>
<th>Reviewer notes</th>
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</thead>
<tbody>
<tr>
<td>Hastie et al., 2020⁹</td>
<td>14/20</td>
<td>The study could not be scored for 3 questions as we were unable to determine; 1) the representativeness of the subjects who were prepared to participate from the entire population from which they were recruited, 2) whether losses to follow-up were taken into account as patients lost to follow-up were not reported and 3) whether the study had sufficient power to detect a clinically important effect. The study did not score a point for 3 questions; 1) providing the number and a description of the characteristics of patients lost to follow-up, 2) stating whether study subjects in different intervention groups were recruited over the same period of time and 3) for assignment concealment as it was a non-randomised study. The study scored partially (only 1 point not two) for clearly described distributions of principal confounders in each group of subjects to be compared.</td>
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<tr>
<td>D’Avolio et al., 2020¹⁰</td>
<td>13/15</td>
<td>The study could not be scored for the ‘power’ domain as we were unable to determine from the article whether the study had sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%. The study did not score 1 point in the ‘external validity’ domain as those subjects who were prepared to participate were not representative of the entire population from which they were recruited.</td>
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<td>Fasano et al., 2020¹¹</td>
<td>12/17</td>
<td>The study could not be scored for 4 items, the ‘power’ domain and one question in the ‘Internal validity - confounding (selection bias)’ as the study did not specify the time period over which patients were recruited. It could also not be scored for 2 questions in the ‘External validity domain’, 1) the representativeness of the subjects asked to participate in the study compared to the entire population from which they were recruited and 2) the representativeness of those subjects who were prepared to participate compared to the entire population from which they were recruited. The study did not score 1 point as the effect of the main confounders was not investigated or confounding was demonstrated but no adjustment was made in the final analyses. The study scored two points for presentation of potential confounders.</td>
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<td>Ilie et al., 2020&lt;sup&gt;12&lt;/sup&gt;</td>
<td>4/20</td>
<td>The study could not be scored for 9 questions. Two in the 'reporting' domain, 1) interventions of interest not clearly described, 2) the main findings of the study are not clearly described. Two ‘External validity’ questions 1) the representativeness of the subjects asked to participate in the study compared to the entire population from which they were recruited and 2) the representativeness of those subjects who were prepared to participate compared to the entire population from which they were recruited. Two ‘Internal validity – bias’ domain questions 1) all analyses that had not been planned at the outset of the study were not clearly indicated (results of the study based on “data dredging”, were not made clear), and 2) it was not clear is the statistical techniques used were appropriate to the data. Three ‘Internal validity – confounding (selection bias)’ domain questions, 1) no information provided concerning the source of patients included in the study 2) does not specify the time period over which patients were recruited, and 3) the numbers of patients lost to follow-up are not reported. The study did not score 7 points for the following; 3 reporting issues 1) no description of the characteristics of participants included in the study 2) no description of the distributions of principal confounders in each group of subjects to be compared, and 3) no description of the characteristics of patients lost to follow-up. Two internal validity bias issues 1) differences in follow-up were ignored and 2) no evidence that the main measure used were accurate (valid and reliable).</td>
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**Note:** For each included study, the maximum possible quality score was dependent on which domains could be assessed based on the study design. The higher the score assigned to a study, the lower the risk of bias. For example, Hastie et al. 2020<sup>9</sup> was assigned a score of 14 out of a maximum possible score of 20, suggesting good quality and therefore low risk of bias compared to the other studies.

### References


8. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health* 1998;52(6):377-84. doi: 10.1136/jech.52.6.377


