NICE National Institute for Health and Care Excellence

Evidence review

Vitamin D for COVID-19

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This evidence review sets out the best available evidence on vitamin D for preventing or treating COVID-19, or for the susceptibility to COVID-19 based on vitamin D status. Treating or preventing acute respiratory tract infections more generally was out of scope. This evidence review includes the key messages and an advisory statement on vitamin D for COVID-19.

Disclaimer

The content of this evidence review was up-to-date on 18 June 2020. See summaries of product characteristics (SPCs), British national formulary (BNF) or the Medicines and Healthcare products Regulatory Agency (MHRA), NHS or NICE websites for up-to-date information.

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Key messages

Vitamin D is important for bone and muscle health. It has also been hypothesised that vitamin D may have a role in the body's immune response to respiratory viruses. Although sunlight exposure is the major source of vitamin D for most people, it can also be obtained from the diet or supplements. The 2 major forms of vitamin D, vitamin D3 (colecalciferol) and vitamin D2 (ergocalciferol), are licensed for the prevention and treatment of vitamin D deficiency. Vitamin D supplements are not specifically licensed for preventing or treating any infection, including the novel coronavirus infection that causes COVID-19.

This evidence review sets out the best available evidence on vitamin D for preventing or treating COVID-19, or for the susceptibility to COVID-19 based on vitamin D status. Treating or preventing acute respiratory tract infections more generally was out of scope. The Scientific Advisory Committee on Nutrition (SACN) has published a report on vitamin D and acute respiratory tract infections.

Advisory statement on likely place in therapy

There is no evidence to support taking vitamin D supplements to specifically prevent or treat COVID-19. However, all people should continue to follow UK Government advice on daily vitamin D supplementation to maintain bone and muscle health during the COVID-19 pandemic.

Rationale

To protect bone and muscle health, the UK Government advises that everyone needs vitamin D equivalent to an average daily intake of 10 micrograms (400 international units). They advise that all people should consider taking a daily supplement containing 10 micrograms vitamin D during autumn and winter months. They also advise that people whose skin has little to no exposure to sunlight and ethnic minority groups with dark skin, from African, Afro-Caribbean and South Asian backgrounds, should consider taking a vitamin D supplement all year round. This advice would also apply to people whose skin has little to no exposure to sunlight because they are indoors shielding or self-isolating. Therefore, UK Government advice during the COVID-19 pandemic is that everyone should consider taking 10 micrograms of vitamin D a day because they might not be getting enough from

sunlight if they're indoors most of the day. See also NICE guidance on Vitamin D: supplement use in specific population groups.

Following appropriate testing and clinical management, people with vitamin D deficiency may also be prescribed higher therapeutic doses of vitamin D.

Factors for decision making

Effectiveness and safety

Evidence was from 5 published studies in peer-reviewed journals. One observational cohort study (D'Avolio et al. 2020), 3 observational prognostic studies involving published data sets using correlation or regression (Hastie et al. 2020, Ilie et al. 2020 and Laird et al. 2020) and 1 case-control survey (Fasano et al. 2020) looked retrospectively at the association between vitamin D status and development of COVID 19. None of the studies were intervention trials of vitamin D supplementation for the prevention or treatment of COVID-19.

Four of the studies found an association or correlation between a lower vitamin D status and subsequent development of COVID-19. However, confounders such as body mass index (BMI) or underlying health conditions, which may have independent correlations with vitamin D status or COVID-19, were not adjusted for (D'Avolio et al. 2020, Fasano et al. 2020, Ilie et al. 2020 and Laird et al. 2020). Vitamin D status was based on serum 25-hydroxyvitamin D (25(OH)D) levels in 3 studies and the proportion of participants taking a vitamin D supplement in 1 study. The largest UK study (Hastie et al. 2020) found an association between vitamin D status and COVID-19 only in a univariable analysis (with this single potential causative factor). Importantly, no causal relationship between vitamin D status and COVID-19 was found after adjustment for confounders such as comorbidity, socio-demographics, ethnicity, BMI and other baseline factors.

Limitations of the evidence

All 5 studies were assessed as being at high risk of bias (very low quality of evidence). None of the studies were intervention studies of vitamin D supplementation (for example randomised controlled trials), so no data on appropriate doses or adverse events was given.

Apart from Hastie et al. 2020, none of the studies adjusted for confounding factors, such as BMI, higher socioeconomic deprivation and poorer self-reported health, which may have independent correlations with vitamin D status or COVID-19. Three studies (Hastie et al. 2020, Ilie et al. 2020 and Laird et al. 2020) used historic data up to 20 years old on serum 25(OH)D levels for their included populations. The use or reporting of COVID-19 case and mortality data is also limited in all 3 studies, with differences in national and international reporting and screening meaning some countries data may not include milder or asymptomatic cases. All 3 of these studies had poorly reported methods for model selection, model fit and checking (either correlation or regression). Two studies (D'Avolio et al. 2020 and Fasano et al. 2020) are limited by the representativeness of their samples and issues with diagnostic criteria for either COVID-19 or its sequelae.

Person-centred factors

A person's individual risk of vitamin D deficiency may have changed during the COVID-19 pandemic, particularly if they are spending more time indoors. Sunlight is the major source of vitamin D for most people, therefore vitamin D status will be influenced by sunlight exposure. People from ethnic minority groups with dark skin are also at particular risk of having a low vitamin D status.

For most people, 10 micrograms of vitamin D a day will be enough and people should not take more than 100 micrograms a day because it could be harmful. If people take higher therapeutic doses of vitamin D, monitoring is recommended.

There are many different brands and formulations of vitamin D supplements, often combined with other supplements (such as calcium), with different dosing regimens. This can make deciding which supplement to take, if any, difficult without health professional advice.

Background

Vitamin D is required for calcium and phosphorus regulation in the body. It is synthesised in the skin when exposed to ultraviolet B (UVB) radiation from sunlight. Although sunlight exposure is the major source of vitamin D for most people, it can also be obtained from the diet or supplements. The 2 major forms of vitamin D are vitamin D3 (colecalciferol) and vitamin D2 (ergocalciferol).

Vitamin D status is measured using serum total 25-hydroxyvitamin D (25(OH)D) level, the major circulating metabolite of vitamin D.

The 2016 Scientific Advisory Committee on Nutrition (SACN) report on vitamin D and health concluded that people with serum or plasma 25(OH)D levels below 25 nmol/L are at increased risk of poor musculoskeletal health outcomes, including rickets and osteomalacia. To protect musculoskeletal health, they recommend that serum or plasma 25(OH)D levels should not fall below 25 nmol/L at any time of the year. SACN recommend a reference nutrient intake for vitamin D of 10 micrograms (400 international units) per day for the UK population aged 4 years and above. This is the average amount needed by 97.5% of the population to maintain a plasma 25(OH)D level of 25 nmol/L or above when UVB sunshine exposure is minimal.

UK Government advice that all people should consider taking a daily supplement containing 10 micrograms vitamin D during autumn and winter months is based on these SACN recommendations. The Government also advises that people whose skin has little to no exposure to sunlight and ethnic minority groups with dark skin, from African, Afro-Caribbean and South Asian backgrounds, should consider taking a supplement all year round. This advice would also apply to people whose skin has little to no exposure to sunlight because they are indoors shielding or self-isolating due to the COVID-19 pandemic. UK Government advice during the pandemic is that everyone should consider taking 10 micrograms of vitamin D a day to keep bones and muscles healthy because they might not be getting enough vitamin D from sunlight if they are indoors most of the day. See also NICE guidance on Vitamin D: supplement use in specific population groups.

It has been hypothesised that vitamin D may also have a role in the body's immune response to respiratory viruses. *In vitro* studies suggest that vitamin D metabolites

could modulate immune and inflammatory responses in human respiratory epithelial cells (Greiller and Martineau 2015). SACN considered a range of non-musculoskeletal health outcomes in their 2016 report, and found that there was insufficient evidence in relation to vitamin D and the risk of infections, such as respiratory tract infections. SACN has considered more recent evidence on vitamin D and acute respiratory tract infections, and have published a more recent report on vitamin D and acute respiratory tract infections.

A systematic review and meta-analysis of individual participant data from randomised controlled trials (RCTs; Martineau et al. 2017) found that vitamin D supplementation reduced the risk of acute respiratory tract infection, with the greatest benefit seen in people with baseline plasma 25(OH)D level below 25 nmol/L. However, there were limitations with this systematic review. There was a high degree of heterogeneity between studies and the definitions of acute respiratory tract infection were diverse. A second systematic review and meta-analysis of RCTs involving healthy people found that vitamin D supplementation did not reduce the risk of respiratory tract infections (Vuichard Gysin et al. 2016). Heterogeneity between studies was a major limitation of this review also.

This evidence review only covers vitamin D for treating or preventing COVID-19, not treating or preventing acute respiratory tract infections more generally. It has been hypothesised that people with low serum 25(OH)D levels might be at higher risk of COVID-19, or experience worse outcomes with the disease.

As of 18 June 2020, over 8.2 million people globally and 299,255 people in the UK have developed COVID-19 (World Health Organisation [WHO] 2020), a disease caused by a novel coronavirus which emerged in Wuhan, China in December 2019. Other diseases caused by coronaviruses include severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS) as well as the common cold. It has caused a fast-moving public health crisis globally, as countries impose a range of restrictions on daily life to contain the spread of disease.

Product overview

Vitamin D3 (colecalciferol) and vitamin D2 (ergocalciferol) are licensed for the prevention and treatment of vitamin D deficiency (BNF: colecalciferol and

ergocalciferol). Vitamin D supplements are not specifically licensed for the prevention or treatment of any infection, including the novel coronavirus infection that causes COVID-19.

To protect bone and muscle health, the UK Government advises that everyone needs vitamin D equivalent to an average daily intake of 10 micrograms (400 international units) daily.

Doses for vitamin D3 (colecalciferol) and D2 (ergocalciferol) in the BNF are 400 international units for prevention of deficiency and 800 international units for treatment of deficiency. Higher doses can be used for the treatment of severe deficiency following appropriate clinical testing and management.

Individual brands and formulations of vitamin D supplements have different licensed dosing regimens, for example:

- 20 to 40 micrograms (800 to 1,600 international units) of vitamin D3 (colecalcifierol) daily for prevention of deficiency
- 20 to 80 micrograms (800 to 3,200 international units) of vitamin D3 (colecalcifierol) daily for up to 12 weeks for treatment of deficiency (with higher doses used for severe deficiency).

For more detailed dosing information see the summaries of product characteristics for colecalciferol and ergocalciferol.

Objective

This evidence review aims to review the best available evidence on the effectiveness and safety of vitamin D supplementation for the treatment or prevention of COVID-19, or the susceptibility to COVID-19 based on vitamin D status, in adults, young people and children.

Review questions

A description of the relevant Population, Intervention, Comparison and Outcomes (PICO) for this review was developed by NICE for the topic (see appendix A for more information). The review questions for this evidence review are:

1. What is the effectiveness and safety of vitamin D supplementation for the treatment of COVID-19 in adults, young people and children?

2. What is the effectiveness and safety of vitamin D supplementation for the prevention of COVID-19 in adults, young people and children?

3. Is vitamin D status associated with susceptibility to COVID-19 in adults, young people and children?

4. From the evidence selected, are there any subgroups of people who may benefit from vitamin D supplementation more than the wider population of interest?

Summary of included studies

A literature search of vitamin D for COVID-19 identified 187 references (see appendix E for full details). These references were screened using their titles and abstracts and 7 full text references were obtained and assessed for relevance against the PICO (see appendix A for details).

Five studies identified from the search are included. One study is an observational retrospective cohort design (D'Avolio et al. 2020), 1 study is a case-control survey (Fasano et al. 2020), 1 study is an observational prognostic study (Hastie et al. 2020) using univariable and multivariable regression, and 2 studies (Ilie et al. 2020 and Laird et al. 2020) are observational prognostic studies using correlation. Three of the studies (D'Avolio et al. 2020, Hastie et al. 2020 and Ilie et al. 2020) were in general populations and related to review question 3 (Is vitamin D status associated with susceptibility to COVID-19 in adults, young people and children?). Two studies (Fasano et al. 2020 and Laird et al. 2020) were in selected populations (older adults and people with Parkinson's disease) and related to review question 4 (From the evidence selected, are there any subgroups that may benefit from vitamin D supplementation more than the wider population of interest?).

A summary of the included studies is shown in appendix B . Appendix F gives details of studies identified in the literature search that were then excluded. For information,

see also appendix G for a list of preprints that were excluded from the review and appendix H for a list of ongoing studies.

Effectiveness and safety

See appendix D for full details of the results of the included studies.

Review question 1: What is the clinical effectiveness and safety of vitamin D supplementation for the treatment of COVID-19 in adults, young people and children?

No evidence was identified for this review question.

Review question 2: What is the clinical effectiveness and safety of vitamin D supplementation for the prevention of COVID-19 in adults, young people and children?

No evidence was identified for this review question.

Review question 3: Is vitamin D status associated with susceptibility to COVID-19 in adults, young people and children?

A Swiss retrospective, observational, cohort study (D'Avolio et al. 2020) investigated whether 25(OH)D levels were lower in people with a positive polymerase chain reaction (PCR) test for COVID-19 compared with people with a negative PCR test and a historical cohort of people from the same period in 2019. In the 2020 cohort of PCR test positive and negative patients (n=107), the median serum 25(OH)D level was 22.0 ng/mL (IQR 8.9–30.5; to convert ng/mL to nmol/L multiply result by 2.5). This included 27 patients with a positive test (70.4% male, median age 74 years) with a median vitamin D level of 11.1 ng/mL (IQR 8.2–21.0), and 80 patients with a negative test (48.8% male, median age 73 years) with a median vitamin D level of 24.6 ng/mL (IQR 8.9–30.5). The 2019 cohort of controls (n=1,377; 45.3% male, median age 63 years) had a median serum 25(OH)D level of 24.6 ng/mL (IQR 16.2–33.0). The study also analysed the total number of sun hours during the periods.

The study found that median serum 25(OH)D levels in the 2020 PCR positive cohort were statistically significantly lower compared with those in the 2020 PCR negative

cohort (n=107, 11.1 ng/ml versus 24.6 ng/ml, p value [p]=0.004) and compared with the 2019 cohort of controls (n=1,404, 11.1 ng/ml versus 24.6 ng/ml, p<0.001). No statistically significant difference was found for median serum 25(OH)D levels between the 2020 PCR negative cohort and the 2019 cohort.

The results of the study were stratified by gender and age. When stratified by gender, for women there was no statistically significant difference between median serum 25(OH)D levels in the 2020 PCR positive and negative cohorts, but the 2020 PCR positive cohort had median serum 25(OH)D levels which were statistically significantly lower compared to the 2019 cohort (n=761, 9.3 ng/ml versus 25.6 ng/ml, p=0.019). For men there was no statistically significant difference between median serum 25(OH)D levels in the 2020 PCR positive and negative cohorts, but the 2020 PCR positive cohort median serum 25(OH)D levels were statistically significantly lower than the 2019 cohort (n=643, 11.4 ng/ml versus 22.9 ng/ml, p=0.005).

When stratified by age, for those aged 0 to 70 years there was no statistically significant difference between the median serum 25(OH)D levels in the 2020 PCR test negative and positive cohorts or between the 2020 PCR positive cohort and the 2019 cohort. For those aged over 70 years the 2020 PCR test positive cohort had a statistically significantly lower median serum 25(OH)D level than both the 2020 negative (n=61, 9.3 ng/ml versus 23.1 ng/ml, p=0.037) and 2019 cohort (n=519, 9.3 ng/ml versus 26.4 ng/ml, p<0.001).

A UK observational prognostic study (Hastie et al. 2020) used univariable and multivariable prediction models with logistic regression to examine 2 potential prognostic factors (serum vitamin D level and ethnicity) for the development of COVID-19. Data for the period 16 March to 14 April 2020 on 2,724 COVID-19 test results (PCR swab results) from 1,474 individuals were provided by Public Health England and these were linked to baseline data (obtained at time of enrolment) on serum 25(OH)D levels from UK Biobank for a cohort of people aged 37 to 73 years at enrolment between 2006 and 2010 (n=348,598). Univariable logistic regression examined the association between serum 25(OH)D and confirmed COVID-19. The model was then adjusted (multivariable analysis) for confounders using the UK Biobank data including smoking status, blood pressure, height, weight, history of type1 or type 2 diabetes, self-reported health status, self-reported presence of long

standing illness, socioeconomic deprivation and annual household income. The model was also repeated using participants categorised as vitamin D deficient (serum 25(OH)D <25 nmol/L) or not deficient, and then as insufficient (serum 25(OH)D <50 nmol/L) or sufficient. Univariable logistic regression was also used to examine the association between ethnicity and confirmed COVID-19.

The study found that median serum 25(OH)D level measured at baseline was statistically significantly lower in people who subsequently developed COVID-19 in univariable analysis (28.7 nmol/L versus 32.7 nmol/L; odds ratio [OR] 0.99, 95% CI 0.99 to 0.999, p=0.013) but not after adjustment for confounders (OR 1.00, 95% CI 0.998 to 1.01, p=0.208). The study found that having a serum 25(OH)D level less than 25 nmol/L had a statistically higher odds of subsequently developing COVID-19 in univariable analysis (OR 1.37, 95% CI 1.07 to 1.76, p=0.011) but not after adjustment for confounders (OR 0.92, 95% CI 0.71 to 1.21, p=0.564). There was no statistically significant difference in odds for developing COVID-19 for those with a median serum 25(OH)D level less than 50 nmol/L in either univariable (OR 1.19, 95% CI 0.99 to 1.44, p=0.068) or multivariable analysis with adjustment for confounders (OR 0.88, 95% CI 0.72 to 1.08, p=0.232).

In logistic regression (for dichotomous outcomes) black, South Asian and other ethnicity were all statistically significantly associated with confirmed COVID-19 compared with white ethnicity. Adjustment for baseline median serum 25(OH)D level made little difference to the magnitude of effect for subsequent COVID-19, and the results remained statistically significant in multivariable analysis (adjusted for confounders). There was no significant interaction between ethnicity and vitamin D deficiency.

A retrospective observational prognostic study (Ilie et al. 2020) examined whether there was an association between the mean levels of serum 25(OH)D and the number of cases and deaths from COVID-19 across 20 European countries. The study was in part archival using mean serum 25(OH)D levels from another study (Lips et al. 2019; with data that went back over at least 10 years) and examined whether these were correlated with the reported number of cases and deaths from COVID-19 for the same countries from current data (data sources not reported). The study found a statistically significant moderate degree of negative correlation

between mean serum 25(OH)D levels (mean 56.79 nmol/L, standard deviation [SD] 10.61) and the number of cases of COVID-19 per 1 million population across 20 European countries (mean 1,393.4, SD±1,129.984; Pearson's r(20)=−0.4435; p=0.050). The study also found a statistically significant moderate degree of negative correlation between mean serum 25(OH)D levels and the number of deaths caused by COVID-19 per 1 million population across 20 European countries (mean 80.42, SD±94.61; Pearson's r(20)=−0.4378; p=0.05).

Review question 4: From the evidence selected, are there any subgroups that may benefit from vitamin D more than the wider population of interest?

For details of the Hastie et al. (2020) outcomes for black, South Asian and other ethnicity study population outcomes see review question 3.

A case-control telephone survey study (Fasano et al. 2020) cross-sectionally interviewed 1,486 people with Parkinson's disease and 1,207 controls (members of the same household without Parkinson's disease) in Lombardy, Italy. The study examined whether people with Parkinson's disease were more at risk of COVID-19; if there were any risk factors for people with Parkinson's disease developing COVID-19; what the clinical presentation of COVID-19 looked like in people with Parkinson's disease; and what the outcomes (hospitalisation or death) of people with Parkinson's disease developing COVID-19 were.

The study found no statistically significant difference in developing COVID-19 between people with Parkinson's disease and controls (n=197, 7.1% versus 7.6%, NICE analysis relative risk [RR] 0.93, 95% CI 0.71 to 1.21). People with Parkinson's disease who developed COVID-19 were statistically significantly younger than those people with Parkinson's disease who did not, but other baseline characteristics were similar between groups. The study found that people with Parkinson's disease who developed COVID-19 had statistically significantly more obesity and chronic obstructive pulmonary disease compared with people who had Parkinson's disease but did not develop COVID-19, but not for other comorbidities (hypertension, diabetes and cancer).

People with Parkinson's disease who developed COVID-19 were statistically significantly less likely to be taking vitamin D supplements (n=1,486, 12.4% versus

22.9%, age-adjusted OR 0.56, 95% CI 0.32 to 0.99, p=0.048) compared with people who had Parkinson's disease but did not develop COVID-19. However, there was no statistically significant difference for other medicines and/or supplements (levodopa, dopamine agonists, monoamine-oxidase B inhibitors, catechol-O-methyltransferase inhibitors, amantadine, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, immunosuppressive agents or non-steroidal anti-inflammatory drugs).

People with Parkinson's disease who developed COVID-19 reported statistically significantly more shortness of breath than controls with COVID-19 infection, but not for any other symptom (fever, cough, nasal congestion, olfactory or gustatory dysfunction, nausea or vomiting, diarrhoea, myalgia or arthralgia, fatigue or conjunctivitis). Additionally, there were no statistically significant differences in patterns of symptoms between people with Parkinson's disease who developed COVID-19 and controls with COVID-19 (respiratory, gastrointestinal, systemic, unspecified/mild or asymptomatic illness). People with Parkinson's disease who developed COVID-19 had statistically significantly fewer hospital admissions than controls with COVID-19 infection, but there was no statistically significant difference in deaths.

A retrospective observational prognostic study (Laird et al. 2020) examined whether there was an association between mean serum 25(OH)D levels and the number of deaths from COVID-19 in older adults across 12 European countries. The study undertook a literature search for data on mean serum 25(OH)D levels in older adults, data on vitamin D levels was from included studies published between 1999 and 2019. The study examined whether these correlated with the reported number of deaths from COVID-19 for the same countries from current data (World Health Organisation, Public Health England and National Records Office Scotland). The study found a statistically significant degree of negative correlation between mean serum 25(OH)D levels and the number of deaths from COVID-19 per 1 million population across 12 European countries (p=0.046).

Safety

None of the included studies reported safety or adverse events of vitamin D supplementation as an outcome.

The BNF states that common or very common side effects with vitamin D supplements are abdominal pain, headache, hypercalcaemia, hypercalciuria, nausea and skin reactions. Uncommon side effects are decreased appetite, constipation, thirst and vomiting.

The SACN report gives a guidance level for supplemental vitamin D intake (in addition to dietary intake) of 25 micrograms (1000 international units) per day for adults. This is an approximate indication of intake that would not be expected to cause adverse effects. It also gives a tolerable upper intake level of 100 micrograms (4000 international units), which represents the highest average daily intake that is likely to pose no risk of adverse health effects to nearly all people in the population.

NHS advice to adults in the UK is that taking too many vitamin D supplements over a long period of time can cause hypercalcaemia, which can weaken the bones and damage the kidneys and the heart. For most people, 10 micrograms of vitamin D a day will be enough and people should not take more than 100 micrograms a day as it could be harmful.

Symptoms of overdosage include anorexia, lassitude, nausea and vomiting, diarrhoea, constipation, weight loss, polyuria, sweating, headache, thirst, vertigo, and raised concentrations of calcium and phosphate in plasma and urine. The BNF states that all patients receiving pharmacological doses of vitamin D (which are likely to be higher therapeutic doses following appropriate clinical testing and management) should have their plasma-calcium concentration checked at intervals (initially once or twice weekly) and whenever nausea or vomiting occurs.

Person-centred factors

A person's individual risk of vitamin D deficiency may have changed during the COVID-19 pandemic, particularly if they are spending more time indoors. Sunlight is the major source of vitamin D for most people, therefore vitamin D status will be influenced by sunlight exposure. People from ethnic minority groups with dark skin are also at particular risk of having a low vitamin D status.

For most people, 10 micrograms of vitamin D a day will be enough and people should not take more than 100 micrograms a day because it could be harmful. If

people are prescribed higher therapeutic doses of vitamin D, monitoring is recommended.

There are many different brands and formulations of vitamin D supplements, often combined with other supplements (such as calcium), with different dosing regimens. This can make deciding which supplement to take, if any, difficult without health professional advice.

Limitations of the evidence

All 5 of the included studies were assessed as being at high risk of bias (very low quality of evidence). None of the studies were intervention studies of vitamin D supplementation (for example RCTs), so no data on appropriate doses or adverse events was given.

In the study by D'Avolio et al. 2020 the main limitations arise from potential sample selection bias; it is unclear how the people in the study were identified and recruited. The study participants were required to be symptomatic, so asymptomatic or milder cases of COVID-19 were excluded. Similarly the historic controls may be biased because they may have had a vitamin D test in 2019 due to suspected deficiency and not be representative of the local population. Although the results were stratified by gender and age, other important confounders such as body mass index (BMI), ethnicity, socioeconomic status, comorbidities and smoking status are not reported. It is difficult to estimate the precision of the findings because actual differences and 95% confidence intervals are not reported. The median serum 25(OH)D levels presented in the analysis would largely not represent vitamin D deficiency in the UK. The lowest median in the study, for example, is 9.3 ng/ml (23.25 nmol/L), which is only just less than 25 nmol/L, although the interquartile range (IQR) demonstrates some participants had lower vitamin D levels than the median level.

The UK study by Hastie et al. 2020 is limited by the use of historic vitamin D status data, the use of English swab test data and the non-reporting of model fit and model regression diagnostics. The study used historic baseline data on serum 25(OH)D levels collected between 2006 and 2010, and these levels may have changed since participant assessment. Not all participants enrolled in the UK Biobank study had vitamin D status assessed, and it is unclear if there are systematic differences

between those who did and did not, also the representativeness of the UK Biobank population to a wider UK population is not reported. It is further unknown if any of those having received a test for 25(OH)D levels subsequently received vitamin D supplementation. The study uses other data to adjust for confounders; with the exception of age, gender and ethnicity, these confounders may have changed since assessment at baseline, such as smoking status, BMI, blood pressure, deprivation and household income. Apart from diabetes, other comorbidities are not adjusted for in the model. The data used for the COVID-19 test result is based on the second generation surveillance system database covering English microbiology laboratories for the period 16 March to 14 April 2020. The England response to COVID-19 encouraged people with symptoms to self-isolate in the early stages of the pandemic meaning that only selected cohorts of people received tests, so people with mild to moderate symptoms and asymptomatic individuals are unlikely to have been included in the study. No information on model calibration or discrimination is reported. No information on internal validation of the final prediction model is presented.

In the study by Ilie et al. 2020 the main limitations were associated with the use of historical data for vitamin D status. The study has multiple limitations from the vitamin D status population data which is not reported as being searched for systematically and is taken instead from a single study which is not a systematic review. In some instances the data comes from studies which are over 15 years old. The vitamin D data from each country in the source study are heterogenous with regards to the included populations in the included studies (men, women, children and older people) and many of the included studies are reported as regionally rather than nationally representative. The method of 25(OH)D serum sampling may also be heterogeneous in the source study. Where there was more than 1 study for a country, data was averaged across the studies but in others a single source of data was used, no rationale is given for these decisions. None of the mean serum 25(OH)D levels from the 20 European countries included in the study had a mean less than 39 nmol/L (range 39 to 81.5 nmol/L) and only 5 countries in the study had a mean below 50 nmol/L. There is uncertainty over the COVID-19 population used. It is unclear where the data on cases and mortality per 1 million population (or European country population data if sourced separately) have been obtained from.

The correlation model itself has uncertainty of model fit and although the assumptions of independence of case and linearity appear to be fulfilled, homoscedasticity is not formally assessed in the analysis. Additionally the normality of data is not reported as being assessed so it is unclear if the selection of the parametric Pearson's correlation coefficient is appropriate. The correlation found does not imply causation or address other factors that may influence the results. Confounding may occur at a country or regional level due to differences in response to the pandemic (for example, tracing, testing and lockdown policies) which will affect outcomes. At the personal and population level confounders may include BMI, age, gender, latitude/sunshine, time spent outdoors, vitamin D supplementation, income differential, and ethnicity differences between countries. None of these potential confounders are adjusted for in the study.

The study by Fasano et al. 2020 is mainly limited by the survey methods chosen (telephone survey) which can have response biases. This was shown in the study as non-responders had a statistically significantly longer duration of Parkinson's disease illness than responders. Additionally, the inclusion criteria of visiting a specialist centre within 12 months may have excluded more frail or housebound people from the start. No sample size or power calculation is reported and there was a 77% response rate to the survey. The study comparison was participants with Parkinson's disease who did not develop COVID-19 and controls from the same household without Parkinson's disease who did and did not develop COVID-19, the latter not being described. The controls in the study are limited as they had statistically significant differences in baseline characteristics to participants with Parkinson's disease who developed COVID-19. The results of the study were adjusted for age but other confounders were not adjusted for in the study although comorbidity was assessed as were physical characteristics of the included population (stage of Parkinson's disease and BMI). The diagnosis of COVID-19 in the study is problematic because in most cases this was done by self-reporting of historical symptoms rather than a test, presenting issues with recall bias. The time period of the study may mean that these 'probable' COVID-19 cases could actually have been other seasonal upper respiratory tract infections. The study does not adjust for confounders such as BMI, gender, ethnicity or socioeconomic factors. The association between those who were not supplemented with vitamin D and higher

rates of COVID-19 is difficult to interpret. The reason some participants were not receiving vitamin D supplementation could be due to vitamin D deficiency either not being tested for, or because it may have been tested for, but not found, resulting in no requirement for vitamin D supplementation. It is important to note that this study did not directly measure serum 25(OH)D levels, it assessed the proportion of participants taking a vitamin D supplement.

For the study by Laird et al. 2020 the main limitations of the study were associated with the use of historical data for vitamin D status used and poor reporting of results. A literature search was conducted to identify data on serum 25(OH)D levels in older people from 12 countries, which includes 17 studies published between 1999 and 2019, with 1 study not having a date of publication. Only 1 study had a serum 25(OH)D level <25 nmol/L and only 5 studies demonstrated levels >50 nmol/L but it is unclear if the levels are means or medians. Only limited baseline characteristics are reported for the participants of the included studies. The study acknowledges that different methods of measurement of serum 25(OH)D levels and at different times of year have been used by different studies, although averages were used where possible. Some studies were reported as being regionally rather than nationally representative. The source data for the outcomes were reported but this may be affected by different national or regional reporting of deaths from COVID-19. The correlation model itself has uncertainty of model fit and although the assumptions for the use of the non-parametric Spearman's rank correlation are less conditional than for a parametric test, additional data on model fit and assumptions are not presented. Additionally the test statistic for Spearman's rank correlation coefficient is not presented, so although the scatter suggests monotonic decrease, the strength of the correlation is unclear. Confounding factors were discussed but not adjusted for in the model (for example BMI, socioeconomic, smoking status, age, gender and ethnicity), resulting in similar limitations to those described for the study by Ilie et al. 2020.

See appendix C for full quality assessment of the included studies.

References

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Development of the evidence review

Process

The evidence summary: process guide sets out the process NICE uses to select topics for evidence summaries and details how the summaries are developed, quality assured and approved for publication.

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Details of reviewers declarations of interests can be found in the register of interests.

Appendices

Appendix A: PICO

PICO table

Criteria	Details
P - Population and indication	Treatment or prevention of COVID-19, or the susceptibility to COVID-19 infection in adults, young people and children (or any population subgroup) For treatment: people with confirmed or suspected COVID-19 infection For prevention: all people to prevent COVID-19 infection
I - Intervention	Vitamin D (all strengths, formulations and route of administration) alone or in combination with other treatments Vitamin D status
C - Comparator(s)	Any other plausible strategy or comparator, including placebo or no treatment
O - Outcomes	Treatment: Critical outcomes: mortality Important outcomes: hospitalisation, ventilation, complications, infection cure rates, time to clinical cure, reduction in symptoms, rate of complications, safety, tolerability and adverse events Prevention: Critical outcomes: incidence of COVID-19 infection Important outcomes: safety, tolerability, adherence, morbidity
Inclusion criteria	
Study design	Published systematic reviews, randomised controlled trials, controlled clinical trials, observational studies including case series. If no higher-level quality evidence is found, case reports can be considered
Language	English language
Patients	Human studies only Patients with COVID-19 infection or other coronavirus infections such as severe acute respiratory syndrome (SARS CoV 1) and Middle East respiratory syndrome (MERS)
Age	All ages
Date limits	2002 to present day
Exclusion criteria	
Publication type	Pre-prints prior to peer review, conference abstracts or studies that have not been published in full
Study design	Ecological studies which used either weather patterns (ultraviolet index) or geographical latitude of locations as a

Criteria	Details
	proxy for vitamin D alone (not measuring vitamin D or supplementation) will not be included.

Appendix B: Summary of included studies

Included studies

Study	Number of participants	Population	Comparison	Outcomes
D'Avolio et al. 2020 Observational retrospective cohort study Switzerland	n=1,484 (n=107 COVID-19 2020-cohort and n=1,377 historic controls)	People with and without PCR positive COVID-19 (from 1 March to 14 April 2020) and historic controls for same time period in 2019 COVID-19 group: 54.2% male; median age 73 years (IQR 63 to 81)	Between those who were PCR positive and negative for COVID-19 and historic controls	**Primary outcome:** Association of serum 25(OH)D and COVID-19 infection status **Secondary outcome:** Results stratified by gender and age (≤70 and >70 years)
Fasano et al. 2020 Case-control survey Italy	n=2,693 (n=1,486 with Parkinson's disease and 1,207 controls)	Parkinson's disease group: 56.8% male; mean age 70.5 years [SD±10.1] (COVID-19) to 73 years [SD±9.5] (non-COVID-19)	Between people with Parkinson's disease and non-Parkinson's disease controls who were COVID-19 positive and negative (self-reported [probable] and confirmed cases)	**Primary outcome:** Are Parkinson's disease patients more at risk of being infected by SARS-CoV-2 and developing COVID-19? **Secondary outcomes:** What are the risk factors for COVID-19 in Parkinson's disease patients? How is the clinical expression of COVID-19 in Parkinson's disease patients? What is the COVID-19 outcome in an unselected cohort of Parkinson's disease patients?
Hastie et al. 2020 Prognostic cohort study UK (England)	n=348,598	UK population enrolled into the UK Biobank study aged 37 to 73 years between 2006 and 2010	Between those who developed a confirmed (PHE second generation surveillance system	**Primary outcome:** Is baseline serum 25(OH)D level associated with subsequent development of COVID-19 infection?

Study	Number of participants	Population	Comparison	Outcomes
			recorded) case of COVID-19 and those who did not	**Secondary outcome:** What other factors are deterministic of COVID-19 infection including ethnicity?
Ilie et al. 2020 Prognostic study using correlation Data for 20 European countries	n≥45,000 individuals for vitamin D status Populations for countries and COVID-19 data not reported	People from 20 European countries included in a non-systematic review of serum 25(OH)D levels correlated against COVID-19 cases and deaths for each country	Between serum 25(OH)D level by country and COVID-19 cases and deaths	**Primary outcome:** Crude Pearson's correlation between serum 25(OH)D level and COVID-19 cases and deaths by country
Laird et al. 2020 Prognostic study using correlation Data for 12 European countries	n=21,769 individuals for vitamin D status	Older people from 12 European countries in a literature review of serum 25(OH)D levels correlated against COVID-19 mortality data from the World Health Organisation, PHE and National Records Office Scotland	Between serum 25(OH)D level by country and COVID-19 deaths	Primary outcome: Crude Spearman's correlation between 25(OH)D level and COVID-19 cases and deaths by country

Appendix C: Quality assessment of included studies

Table 1. Quality of Cohort study

CASP Cohort study Checklist

Studies	D'Avolio et al. 2020
Did the study address a clearly focused issue?	The population was not specifically focused but included anyone attending who underwent a nasopharyngeal swab PCR for symptoms of COVID-19 during a 6 week period in 2020. The risk factor considered was focused, a measurement of serum 25(OH)D level, and duration of sunshine (total sun hours) was factored in. The main outcome was focused as the difference in serum 25(OH)D levels between those who were PCR positive and PCR negative (and also a historical control group). It is clear that the study is trying to detect a harmful effect (PCR positive result) associated with low vitamin D status.
Was the cohort recruited in an acceptable way?	The sample selection is not free from potential bias. It is unclear how the sample was obtained i.e. self-selected attendances, referred from a primary screening service etc. Although the use of historical controls may confirm the PCR negative serum 25(OH)D sample values, there may be bias in how the historical controls were themselves selected for serum 25(OH)D level assessment i.e. were they suspected of having low levels and therefore tested. An independent sample may have yielded different results.
Was the exposure accurately measured to minimise bias?	The measure of exposure (serum 25(OH)D sampling) was objectively measured in the cohort within 7 weeks of the PCR test. The historical controls were all people who had had a serum 25(OH)D level assessed during the same 6 week period in the year prior (2019).
Was the outcome accurately measured to minimise bias?	The measurement of outcome was objective, although presence of symptoms of COVID-19 were necessary before PCR testing which

	may rule out a large cohort of asymptomatic or mild COVID-19 cases. PCR itself has a known false positive and false negative rate which may act as a confounder. It is further unclear if the rules on who was able to have a PCR test were adhered to during the trial as no report is made of symptoms of the cohort. As the exposure was a blood test neither the participants or outcome assessor could be blind to exposure.
Have the authors taken account of : a) all important confounding factors? b) confounding factors in the design and/or analysis?	The authors have stratified the results by age (≤70years and >70 years) and gender. Other important confounders were not considered (socioeconomic, ethnicity, smoking status etc.).
Was the follow-up of subjects: a) complete enough? b) long enough?	Broadly the length of follow-up was sufficient, although it could be argued that follow-up of PCR negative cases may yield people with a first time false negative PCR who subsequently required repeat testing and positivity.
What are the results?	See results table.
How precise are the results?	See results table.
Do you believe the results?	See limitations of the evidence.
Can the results be applied to the local population?	According to the European Centre for Disease Control (11 June 2020) Switzerland (population≈8.5 million) has had around 10% the number of cases (31,000) and few deaths (1,674) compared to the UK (Population≈68 million; 290,000 cases and 41,128 deaths) despite similar latitude (46 versus 55 degrees). However, surveys of vitamin D levels for the countries (Lips et al. 2019) suggest they are similar (Switzerland median 46 nmol/L versus UK 47.4±[SD] 19.8 nmol/L). So the results suggest that although vitamin D levels in the UK are similar to Switzerland other factors may contribute to both number of cases and mortality.
Do the results of this study fit with other available evidence?	This study demonstrates, similar to other evidence in the review, an association between low vitamin D status and increased COVID-19 infection. However, it does not show that the effect is causal.

What are the implications of this study for practice?	The main implication is that the lowest rates of serum 25(OH)D levels were seen in the over 70 years age group who were COVID-19 PCR positive.

Table 2. Quality of Case Control study

CASP Case Control Study Checklist

Studies	**Fasano et al. 2020**
Did the study address a clearly focused issue?	The study has a very focused population of a clinical diagnosis of Parkinson's disease, at least 1 evaluation in a Parkinson's disease specialist centre in 2019 and resident in Lombardy, Italy. Risks included were COVID-19 symptoms, nasopharyngeal swabs, chest x-ray or CT scan or hospitalisation. Other clinical data including mortality data, comorbidities, and demographic data were obtained or recorded.
Did the authors use an appropriate method to answer their question?	The study set out 4 questions: 1. 'Are Parkinson's disease patients more at risk of being infected by SARS-CoV2 and developing COVID-19? 2. What are the risk factors for COVID-19 in Parkinson's disease patients? 3. How is the clinical expression of COVID-19 in Parkinson's disease patients? 4. What is the COVID-19 outcome in an unselected cohort of Parkinson's disease patients?' It would appear that a prospective cohort study or prognostic study would have been a more appropriate way to answer these questions.
Were the cases recruited in an acceptable way?	The method used to contact and recruit the sample (phone contact) is potentially open to bias as not everyone may be contactable by

	that route alone. Use of phones as the only means of contact has led to bias historically in survey results. The additional criteria of having visited a specialist centre may have excluded from the sample more frail or housebound individuals or those economically unable to travel. This may be supported by the fact that non-responders were similar to responders apart from longer disease duration. No power or sample size calculation is reported. The authors attempted to contact 1,926 people, 1,486 were available (response rate 77.2%).
Were the controls selected in an appropriate way?	Controls for the survey were family member(s) of the person with Parkinson's disease in order to gather data from people with similar environmental exposure. No specific criteria are described and it is unknown if more than 1 control came from the same household. There were differences noted between the controls with COVID-19 and cases with COVID-19; they were statistically significantly younger than cases and had statistically significantly more outings per week than cases.
Was the exposure accurately measured to minimise bias?	Exposure to COVID-19 was not clearly or accurately measured as participants were considered to have COVID-19 if they had received a positive nasopharyngeal swab (despite the false positive rate) or had probable COVID-19 based on self-reported symptoms which may be subject to recall bias or a differential cause of symptoms (other non-COVID-19 respiratory tract infection for example). Out of 105 cases with COVID-19, only 32 had a confirmed case (73 probable cases). Of the 92 cases of COVID-19 in the controls it is not reported how many were confirmed or probable.
Have the authors taken account of: a) confounding factors? b) potential confounding factors in the design and/or analysis?	The study does not take account of many confounders such as adjusting for gender, ethnicity or socioeconomic factors.
What are the results of this study?	See results table.
How precise are the results/estimate of risk?	See results table.
Do you believe the results?	See limitations of the evidence.

Can the results be applied to the local population?	It is uncertain if this study is representative of people with Parkinson's disease resident in Lombardy, Italy. Many of the findings may be due to chance, bias or suffer from the effects of confounding. Therefore it is unknown if the results could be extrapolated to a UK setting.
Do the results of this study fit with other available evidence?	The finding regarding vitamin D supplementation may fit with other studies which show an association between low levels of serum 25(OH)D level and COVID-19 infection. However, given that it is not known how many of the people in the study had actually had a serum 25(OH)D level taken (or when) we cannot assume that all those without supplementation were deficient. It may be the case that the reason for not being on a supplement was that they were not measured, or were measured, and were not found to be vitamin D deficient.

Table 3. Quality of Prognostic Studies

PROBAST Checklist

Studies	**Hastie et al. 2020**
Were appropriate data sources used?	Yes, the data sources used in the study were the UK Biobank cohort (covers 500,000 people from England, Wales and Scotland who were aged 40 to 69 years in 2006 to 2010 when recruited - according to UK Biobank website but reported as 502,624 people aged 37 to 73 years in the paper) and Public Health England COVID-19 testing data from the Second Generation Surveillance System is a centralised microbiology database covering English clinical diagnostics laboratories that provides national surveillance of legally notifiable infections, bacterial isolations and antimicrobial resistance.

Were all inclusions and exclusions of participants appropriate?	No information regarding inclusion or exclusion or participants are discussed.
Does the included population and setting match the review question?	High risk of bias. There appears to be a mismatch in geographical coverage between the 2 systems (one is UK the other England only). The data on serum 25(OH)D levels was collected at baseline (2006 to 2010), in some cases up to 14 years prior to the COVID-19 testing data to which it is linked. Additionally, the testing data is an underestimate of the number of cases of COVID-19 as not all English cases were tested (mild cases) due to restrictions on testing in England.
Were the predictors defined and assessed in a similar way for all participants?	Yes, most of the predictor data was collected at baseline (serum 25(OH)D level, ethnicity, smoking status, BMI, area level socioeconomic deprivation, diabetes, household income, self-rated health). However, some of these data will have altered since baseline assessment (up to 14 years ago).
Were predictor assessments made without knowledge of outcome data?	Yes at the time of recruitment and assessment of predictors COVID-19 was not yet a consideration for UK healthcare providers.
Are all predictors available at the time the model is intended to be used?	Probably yes, the predictors used in the model would be available at the time the model would be intended to be used, apart from area level socioeconomic deprivation which would not routinely be available to clinicians at the time of consultation.
Does the definition, assessment or timing of predictors match the review question?	The risk of bias from predictors or their assessment is moderate due to the time from baseline assessment of predictor information.
Was the outcome determined appropriately?	No, the outcome determination is based on laboratory testing for swabs for PCR testing. It is highly likely that (especially during the early phase of COVID-19 pandemic in England when testing was not universally available) that the linked PHE data highly under reports the totality of cases, particularly the asymptomatic or mild cases not presenting to health services who were advised not to attend care facilities and self-isolate.
Was a pre-specified or standard outcome definition used?	Yes, COVID-19 was defined as at least 1 positive test result.
Were predictors excluded from the outcome definition?	Yes, none of the predictors are included in the outcome definition.

Was the outcome defined and determined in a similar way for all participants?	Yes, although the setting may have varied testing was primarily nasopharyngeal swab RT-PCR testing in line with guidelines in England.
Was the outcome determined without knowledge of predictor information?	No information was reported on outcome determination and knowledge of predictor information.
Was the time interval between predictor assessment and outcome determination appropriate?	No, information of predictors was taken in advance of outcome determination by at least a decade. The predictors may have altered for each individual over time.
Does the outcome, its definition, timing or determination match the review question?	There is potential risk of bias for outcome determination and timing.
Were there a reasonable number of participants with the outcome?	Yes, there were 449 people with a COVID-19 positive test and 8 predictive factors in the model, therefore a crude events per variable >20 (56).
Were continuous and categorical predictors handled appropriately?	Yes, continuous variables were categorised appropriately using prespecified and logical/plausible categorisations.
Were all enrolled participants included in the analysis?	No, all UK Biobank enrolled participants were not included in the analysis. Only those with a recorded vitamin D result (n=348,598) were included. Although this still represents a large cohort. It is not known if there are significant differences between the enrolled and unenrolled UK Biobank participants.
Were participants with missing data handled appropriately?	Probably no, if we include the UK Biobank participants who have a missing value for serum 25(OH)D level as missing data, these were subsequently excluded from the analysis.
Was selection of predictors based on univariable analysis avoided?	Yes, all predictors were included in the multivariable modelling.
Were complexities in the data (e.g. censoring, competing risks, sampling of controls) accounted for appropriately?	Yes, the outcome was discrete (presence of COVID-19), therefore the duration of follow-up to the time of data extraction and analysis was short and no need for data censoring, little competing risk (such as death from other causes) or need for sampling of additional controls.
Were relevant model performance measures evaluated appropriately?	No information, model calibration and discrimination is not reported.

Were model overfitting and optimism in model performance accounted for?	No information is provided on whether internal validation techniques, including all model development procedures, have been applied.
Do predictors and their assigned weights in the final model correspond to the results from the reported multivariable analysis?	No information, it is unclear whether the regression coefficients in the final model correspond to reported results from multivariable analysis.
Overall assessment of risk of bias	There is a moderate/high risk of bias across all the domains measured.

Table 4. Quality of Prognostic Studies

QUIPS Checklist

Studies	**Ilie et al. 2020**	**Laird et al. 2020**
Source of target population	N – source for vitamin D population linked to but not described or how the included paper was searched for. For COVID-19 population data not linked to or described.	Y – a literature review was undertaken to inform the vitamin D population, COVID-19 population data was taken from WHO, PHE and NROS (see below).
Method used to identify population	N – the methods used to search for the populations used are not described. The paper for vitamin D population data (Lips et al. 2019) did not use systematic review methods. For Portugal, Spain and Italy the data does not appear to be presented in the main table or at all.	P – search parameters for the vitamin D search were outlined but not reported in detail. No inclusion or exclusion criteria or quality assessment were reported.
Recruitment period	N – the period searched for the population is not described. The vitamin D population data was from over 10 years or more so not necessarily up to date estimates.	Y – studies for the vitamin D population were from 1999 onwards and the rationale (measurements for older adults became more available after this date).

Place of recruitment	Y – the countries included are set out clearly, but the population statistics source is not described.	Y – the countries and regions are reported for each study.
Inclusion and exclusion criteria	N – not reported.	N – not reported.
Adequate study participation	N/A – uses archival (published) data.	N/A – uses archival (published) data.
Baseline characteristics	N – not reported in the Ilie et al. 2020 paper but in the Lips et al. 2019 study the populations are very heterogenous with many regionally rather than nationally representative and only Estonia gave summer and winter estimates of vitamin D levels.	P – the sample size, age and % aged >65 years are reported. Gender and other characteristics are not reported.
Proportion of baseline sample available for analysis	N/A – uses archival (published) data.	N/A – uses archival (published) data.
Attempts to collect information on participants who dropped out	N/A – uses archival (published) data.	N/A – uses archival (published) data.
Reasons and potential impact of subjects lost to follow-up	N/A – uses archival (published) data.	N/A – uses archival (published) data.
Outcome prognostic factor information on those lost to follow-up	N/A – uses archival (published) data.	N/A – uses archival (published) data.
Definition of the prognostic factor	P – describes vitamin D deficiency using ECTS (Lips et al. 2019) definition (serum 25(OH)D level <30 nmol/L) but not further described. NB <25 nmol/L is generally considered deficient in the UK.	P - defines vitamin deficiency as serum 25(OH)D level <25 nmol/L and <30 nmol/L, with low being <50 nmol/L. The rates of deficiency are reported for each vitamin D population study. NB <25 nmol/L is generally considered deficient in the UK.
Valid and reliable measurement of prognostic factor	P – continuous variable measurement reported for mean serum 25(OH)D level by country (however, 95% CI and proportion of those <25 nmols/L were reported in the source paper).	P - continuous variable measurement reported for serum 25(OH)D level by country or region, unclear if measures were mean or median values.

Method and setting of prognostic factor measurement	N – measurement of serum 25(OH)D level in the included studies used may have varied (the ECTS (Lips et al. 2019) paper states the serum 25(OH)D measurement promoted by the Vitamin D Standardization Program (VDSP) was reported to be the preferred option, although not discussed further). Only the mean serum 25(OH)D level data was used from the source ECTS paper which also reported the standard deviations and proportion of people with <25 nmol/L in each study (where known)	N - the authors acknowledge that serum 25(OH)D levels have been measured by different methodologies and some have been measured winter/summer, averages were used where possible. No standard deviations or 95% CI were reported for the estimates used.
Proportion of data on prognostic factor available for analysis	N – vitamin D status data was available for each included country but the sample data in some cases was reported as regionally not nationally representative.	N – vitamin D status data was available for each included country but the sample data in some cases was reported as regionally not nationally representative.
Method used for missing data	N/A – uses archival (published) data.	N/A – uses archival (published) data.
Definition of the outcome	Y – number of cases and deaths from COVID-19 by country.	Y - COVID-19 mortality, rate and number of cases by country.
Valid and reliable measurement of outcome	U – the source for the data used for outcomes is not correctly linked to or described only the date (8 April 2020) data was accessed.	P - the source data for outcomes is reported (World Health Organisation, Public Health England and National Records Office Scotland) but the date accessed and are not reported.
Method and setting of the outcome measurement	N – the method of diagnosis of cases and recording of death from COVID-19 may vary country and region.	N – the method of diagnosis of cases and recording of death from COVID-19 may vary country and region.
Important confounders measured	N – there was no measurement of confounders.	N – there was no measurement of confounders.
Definition of the confounding factor	N – there was no definition of confounding factors, except as limitations.	P - the authors acknowledge that varied rates of infection, approaches to screening, differences in demographics etc. will be confounders for the study.

Valid and reliable measurement of confounders	N – not measured.	N – not measured.
Method and setting of confounding measurement	U – measurement of confounders not measured by may vary by country or region.	U – measurement of confounders not measured by may vary by country or region.
Method used for missing data	N/A – uses archival (published) data.	N/A – uses archival (published) data.
Appropriate accounting for confounders	N – No adjustment or accounting for confounders are made.	N – No adjustment or accounting for confounders are made.
Presentation of analytical strategy	P – the data used to perform the analysis is presented, however, it is unclear if the data meets all assumptions (independence of data, linearity, homoscedasticity, and normality) to support the parametric analysis.	P – the data used to perform the analysis is presented, however, it is unclear if the data meets all assumptions (independence of data, linearity, homoscedasticity, and normality) although uses non-parametric analysis.
Model development strategy	U – the key assumption of normality to support use of Pearson's r is not demonstrated.	Y - despite not presenting evidence of normality of data the use of Spearman's rank correlation is appropriate.
Reporting of results	Y – there was no selective reporting of results.	Y – there was no selective reporting of results.
Overall assessment of quality	There are multiple issues for risk of bias across nearly all domains therefore the risk of bias is assessed as high. See also the discussion of limitations of the evidence.	There are many issues for risk of bias across nearly all domains therefore the risk of bias is assessed as high. See also the discussion of limitations of the evidence.

Key

Y=Yes
N=No
P=Partial
U=Unclear
N/A= Not applicable.

Appendix D: Results tables

D'Avolio et al. (2020)

	2019 Cohort	2020 Cohort (PCR negative)	2020 Cohort (PCR positive)	Analysis
N	**1,377**	**80**	**27**	
Primary outcome				
Median 25(OH)D (ng/ml[1])	24.6 ng/ml (IQR 16.2 to 33.0)	24.6 ng/ml (IQR 8.9 to 30.5)		No significant difference in 25(OH)D between 2020 PCR negative cohort and 2019 cohort (p=0.076[2]).
Median 25(OH)D (ng/ml[1])	24.6 ng/ml (IQR 16.2 to 33.0)		11.1 ng/ml (IQR 8.2 to 21.0)	Significantly lower 25(OH)D in 2020 PCR positive cohort compared with 2019 cohort (p<0.001[2]).
Median 25(OH)D (ng/ml[1])		24.6 ng/ml (IQR 8.9 to 30.5)	11.1 ng/ml (IQR 8.2 to 21)	Significantly lower 25(OH)D in 2020 PCR positive cohort compared with 2020 PCR negative cohort (p=0.004[2]).
Secondary outcomes (data stratified by gender and age [0 to 70 years and >70 years])				
Median 25(OH)D (ng/ml[1]) Males (n=58)		23.8 ng/ml (IQR 7.13 to 32.7)	11.4 ng/ml (IQR 8.9 to 23.6)	No significant difference in 25(OH)D between 2020 PCR positive and negative cohorts (p=0.131[2]).
Median 25(OH)D (ng/ml[1]) Males (n=643)	22.9 ng/ml (IQR 14.7 to 33.1)		11.4 ng/ml (IQR 8.9 to 23.6)	Significantly lower 25(OH)D in 2020 PCR positive cohort compared with 2019 cohort (p=0.005[2]).

	2019 Cohort	2020 Cohort (PCR negative)	2020 Cohort (PCR positive)	Analysis
Median 25(OH)D (ng/ml[1]) Females (n=49)		24.8 ng/ml (IQR 14.5 to 30.9)	9.3 ng/ml (IQR 7.3 to 20.5)	No significant difference in 25(OH)D between 2020 PCR positive and negative cohorts (p=0.062[2]).
Median 25(OH)D (ng/ml[1]) Females (n=761)	25.6 ng/ml (IQR 17.3 to 33.3)		9.3 ng/ml (IQR 7.3 to 20.5)	Significantly lower 25(OH)D in 2020 PCR positive cohort compared with 2019 cohort (p=0.019[2]).
Median 25(OH)D (ng/ml[1]) Age 0 to 70 years (n=46)		25.9 ng/ml (IQR 15.9 to 32.1)	17.2 (IQR 11.7 to 31.6)	No significant difference in 25(OH)D between 2020 PCR positive and negative cohorts (p=0.277[2]).
Median 25(OH)D (ng/ml[1]) Age 0 to 70 years (n=885)	23.9 ng/ml (IQR 16.4 to 31.6)		17.2 (IQR 11.7 to 31.6)	No significant difference in 25(OH)D between 2020 positive cohort and 2019 cohort (p=0.287[2]).
Median 25(OH)D (ng/ml[1]) Age >70 years (n=61)		23.1 ng/ml (IQR 8.5 to 31.7)	9.3 ng/ml (IQR 8.1 to 19.9)	Significantly lower 25(OH)D in 2020 PCR positive cohort compared with 2020 PCR negative cohort (p=0.037[2]).
Median 25(OH)D (ng/ml[1]) Age >70 years (n=519)	26.4 ng/ml (IQR 15.7 to 36.4)		9.3 ng/ml (IQR 8.1 to 19.9)	Significantly lower 25(OH)D in 2020 PCR positive cohort compared with 2019 cohort (p<0.001[2]).

[1]To convert ng/ml to nmol/L multiply by result by 2.5 (24.6 ng/ml is therefore equal to 61.5 nmol/L)
[2] Spearman's rank correlation

Fasano et al. (2020)

	People with Parkinson's disease COVID	People with Parkinson's disease non-COVID	Controls COVID	Analysis
N	**105 (32 confirmed cases 73 probable)**	**1,381**	**92 cases[1] of 1,115 controls surveyed**	
Primary outcome				
Risk of developing COVID-19	7.1% of those surveyed		7.6% of those surveyed	NICE analysis RR 0.93 (95% CI 0.71 to 1.21)
Secondary outcome (medicines or supplements as risk factors for developing COVID-19 in people with Parkinson's disease)				
Levodopa	100 (95.2%)	1324 (95.9%)		Age adjusted OR 1.19 (95% CI 0.45 to 3.13; p=0.72)
Dopamine agonists	50 (47.6)	649 (47%)		Age adjusted OR 1.05 (95% CI 0.69 to 1.61; p=0.82)
MAO-B inhibitors	23 (21.9%)	271 (19.6%)		Age adjusted OR 1.09 (95% CI 0.67 to 1.77; p=0.72)
COMT inhibitors	6 (5.7%)	66 (4.8%)		Age adjusted OR 1.19 (95% CI 0.67 to 2.11; p=0.56)
Amantadine	1 (1%)	28 (2.0%)		Age adjusted OR 0.41 (95% CI 0.05 to 3.08; p=0.39)
ACE inhibitors	15 (14.3%)	173 (12.5%)		Age adjusted OR 0.79 (95% CI 0.42 to 1.48; p=0.46)
ARBs	13 (12.4%)	125 (9%)		Age adjusted OR 1.02 (95% CI 0.53 to 1.97; p=0.95)
Immunosuppressive agents	5 (4.8%)	42 (3%)		Age adjusted OR 1.41 (95% CI 0.49 to 4.03; p=0.52)

	People with Parkinson's disease COVID	People with Parkinson's disease non-COVID	Controls COVID	Analysis
NSAIDs	6 (5.7%)	70 (5.1%)		Age adjusted OR 1.11 (95% CI 0.47 to 2.63; p=0.82)
Vitamin D supplementation	13 (12.4%)	316 (22.9%)		Age adjusted OR 0.56 (95% CI 0.32 to 0.99; p=0.048)
Secondary outcome (comorbidities as risk factors for developing COVID-19 in people with Parkinson's disease)				
Obesity	19 (18.1%)	151 (10.9%)		Age adjusted OR 1.72 (95% CI 1.00 to 2.94; p=0.048)
Hypertension	44 (41.9%)	535 (38.7%)		Age adjusted OR 1.29 (95% CI 0.86 to 1.95; p=0.22)
COPD	6 (5.7%)	24 (1.7%)		Age adjusted OR 3.82 (95% CI 1.51 to 9.65; p=0.005)
Diabetes	8 (7.6%)	111 (8.0%)		Age adjusted OR 1.03 (95% CI 0.48 to 2.17; p=0.95)
Cancer	1 (0.9%)	45 (3.3%)		Age adjusted OR 0.31 (95% CI 0.04 to 2.25; p=0.24)
Clinical features of COVID-19 in people with Parkinson's disease compared with controls				
Gender (n/% male)	55 (52.4%)		44 (47.8%)	p=0.57[2]
Age (years)	70.5±10.1		65.4±11.0	p=0.002[2]
BMI (kg/m^2)	25.6±4.9		25.2±4.4	p=0.93[2]
Obesity	19 (18.1%)		13 (14.1%)	p=0.56[2]
Outings (n/week)	0.8±1.9		2.9±2.5	p<0.001[2]
Total reported symptoms	3.4±1.8		3.5±1.8	p=0.70[2]
Fever	74 (70.5%)		67 (72.8%)	Age adjusted OR 0.85 (95% CI 0.45 to 1.61; p=0.61))

	People with Parkinson's disease COVID	People with Parkinson's disease non-COVID	Controls COVID	Analysis
Cough	62 (59.0%)		55 (59.8%)	Age adjusted OR 0.91 (95% CI 0.50 to 1.63; p=0.74)
Shortness of breath	17 (16.2%)		26 (28.3%)	Age adjusted OR 0.33 (95% CI 0.15 to 0.70; p=0.004)
Nasal congestion	44 (41.9%)		35 (38%)	Age adjusted OR 1.39 (95% CI 0.76 to 2.52; p=0.29)
Olfactory dysfunction	17 (16.2%)		17 (18.5%)	Age adjusted OR 0.78 (95% CI 0.36 to 1.67; p=0.52)
Gustatory dysfunction	19 (18.1%)		16 (17.4%)	Age adjusted OR 1.08 (95% CI 0.51 to 2.30; p=0.84)
Nausea or vomiting	15 (14.3%)		15 (16.3%)	Age adjusted OR 1.05 (95% CI 0.47 to 2.35; p=0.91)
Diarrhoea	28 (26.7%)		20 (21.7%)	Age adjusted OR 1.58 (95% CI 0.8 to 3.14; p=0.19)
Myalgia or arthralgia	35 (33.3%)		30 (32.6%)	Age adjusted OR 1.14 (95% CI 0.62 to 2.11; p=0.67)
Fatigue	40 (38.1%)		31 (33.7%)	Age adjusted OR 1.31 (95% CI 0.71 to 2.38; p=0.39)
Conjunctivitis	10 (9.5%)		7 (7.6%)	Age adjusted OR 1.18 (95% CI 0.42 to 3.32; p=0.75)
Patterns of symptoms of COVID-19 in people with Parkinson's disease compared with controls				
Respiratory	50 (47.6%)		52 (56.5%)	Age adjusted OR 0.64 (95% CI 0.36 to 1.14; p=0.13)
Gastrointestinal	13 (12.4%)		10 (10.9%)	Age adjusted OR 1.42 (95% CI 0.57 to 3.56; p=0.45)

	People with Parkinson's disease COVID	People with Parkinson's disease non-COVID	Controls COVID	Analysis
Systemic	22 (21%)		11 (12%)	Age adjusted OR 2.05 (95% CI 0.91 to 4.59; p=0.08)
Unspecified/mild	18 (17.1%)		14 (15.2%)	Age adjusted OR 1.18 (95% CI 0.54 to 2.57; p=0.68)
Asymptomatic	2 (1.9%)		5 (5.4%)	Age adjusted OR 0.27 (95% CI 0.05 to 1.50; p=0.14)
Outcome of COVID-19 in people with Parkinson's disease compared with controls				
Death	6 (5.7%)		7 (7.6%)	Age adjusted OR 0.45 (95% CI 0.13 to 1.53; p=0.20)
Hospitalisation	18 (17.1%)		25 (27.2%)	Age adjusted OR 0.41 (95% CI 0.20 to 0.86; p=0.018)

[1] Not reported how many were confirmed or probable COVID-19 cases
[2] Student's t-test

Hastie et al. (2020)

	No COVID-19	COVID-19	Authors univariable analysis	Authors multivariable analysis[1]
N	**348,149**	**449**		
Primary outcome - association between vitamin D and confirmed COVID-19				
Median 25(OH)D (IQR)	32.7 nmol/L (10.0 to 47.2)	28.7 nmol/L (10.0 to 43.8)	Odds ratio [OR] 0.99 (95% CI 0.99 to 0.999; p=0.013)	OR 1.00 (95% CI 0.998 to 1.01: p=0.208)
Vitamin D deficient (25(OH)D <25 nmol/L)			OR 1.37 (95% CI 1.07 to 1.76; p=0.011)	OR 0.92 (95% CI 0.71 to 1.21; p=0.564)

	No COVID-19	COVID-19	Authors univariable analysis	Authors multivariable analysis[1]
Vitamin D insufficient (25(OH)D <50 nmol/L)			OR 1.19 (95% CI 0.99 to 1.44; p=0.068)	OR 0.88 (95% CI 0.72 to 1.08; p=0.232)
Secondary outcome - association between ethnicity and confirmed COVID-19				
White (n(%)) Reference	331,464 (95.2%)	385 (85.75%)	1	1
Black (n(%))	5,054 (1.45%)	32 (7.13%)	OR 5.49 (95% CI 3.82 to 7.88; p<0.001)[2]	OR 4.30 (95% CI 2.92 to 6.31; p<0.001)
South Asian (n(%))	5,936 (1.70%)	19 (4.23%)	OR 2.76 (95% CI 1.74 to 4.39; p<0.001)[2]	OR 2.42 (95% CI 1.50 to 3.93; p<0.001)
Other (n(%))	5,759 (1.65%)	13 (2.90%)	OR 1.95 (95% CI 1.12 to 3.39; p=0.018)[2]	OR 1.87 (95% CI 1.07 to 3.28; p=0.029)
Interaction term ethnicity*vitamin D deficiency			OR 0.90 (95% CI 0.66 to 1.23; p=0.515)	
Secondary outcomes - factors predictive[3] of COVID-19 status in multivariate logistic regression				
Male sex	168,391 (48.37%)	265 (59.02%)		OR 1.41 (95% CI 1.16 to 1.71; p=0.001)
Higher socioeconomic deprivation (least versus most deprived (1 versus 5) Townsend quintile)	1) 70,669 (20.3%) 5) 65,840 (18.91%)	1) 61 (13.59 %) 5) 143 (31.85%)		OR 1.89 (95% CI 1.37 to 2.60; p<0.001)
Poorer self-reported health status (excellent versus poor)	Excellent 60,508 (17.38%) Poor 14,325 (4.11%)	Excellent 45 (10.02%) Poor 44 (9.8%)		OR 2.32 (95% CI 1.45 to 3.72; p<0.001)
Age at assessment (median (IQR))	49 years (IQR 38 to 57)	49 years (IQR 40 to 58)		OR 1.02 (95% CI 1.00 to 1.03; p=0.016)
Overweight	148,210 (42.57%)	194 (43.21%)		OR 1.34 (95% CI 1.04 to 1.72; p=0.024)

	No COVID-19	COVID-19	Authors univariable analysis	Authors multivariable analysis[1]
Obese	82,770 (23.77%)	158 (35.19%)		OR 1.62 (95% CI 1.23 to 2.14; p=0.001)
Non-white ethnicity (black)	5,054 (1.45%)	32 (7.13%)		OR 4.30 (95% CI 2.92 to 6.31; p<0.001)
Non-white ethnicity (south Asian)	5,936 (1.7%)	19 (4.23%)		OR 2.42 (95% CI 1.50 to 3.93; p<0.001)
Other ethnicity				OR 1.87 (95% CI 1.07 to 3.28; p=0.029)

[1] Adjusted for ethnicity, sex, month of assessment, Townsend deprivation quintile, household income, self-reported health rating, smoking status, BMI category, age at assessment, diabetes, blood pressure, long standing illness, disability or infirmity.

[2] Adjustment for median 25(OH)D (or as categorical variable deficient or insufficiency) in each ethnicity made little difference to the magnitude of the associations. Median 25(OH)D concentration was 33.8 (IQR 10.0 to 48.1) nmol/L in white participants, 21.0 (IQR 10.0 to 29.9) in black participants, 14.5 (IQR 15.5 to 22.1) in South Asian participants, and 23.3 (IQR 10.0 to 33.7) nmol/L in other ethnicity participants. In this study 38,778 (11.69%) white, 1,834 (36.29%) black, 3,403 (57.33%) South Asian, and 1,671 (29.02%) of other ethnicity participants were vitamin D deficient (25(OH)D <25 nmol/L) at baseline.

[3] Factors used as reference or not predictive of COVID-19 status in multivariate logistic regression: white ethnicity (reference), female sex (reference), smoking status (not predictive p=0.613), normal weight (reference), underweight (not predictive p=0.754), Townsend quintiles 1 (reference) versus 2 (not predictive p=0.262) versus 3 (not predictive p=0.999) versus 4 (predictive OR 1.55, 95% CI 1.12 to 2.14; p=0.007), self-reported health excellent (reference) versus good (not predictive p=0.12) versus fair (predictive

OR 1.72, 95% CI 1.19 to 2.48; p=0.004), long standing illness, disability or infirmity yes versus no (not predictive p=0.316), systolic and diastolic blood pressure (not predictive p=0.284 and 0.146 respectively)

Ilie et al. (2020)

		Analysis
N	**≥45,000 people (for vitamin D data), source populations for COVID-19 not reported**	
Primary outcomes		
Correlation between mean serum 25(OH)D level and the number of cases of COVID-19 in 20 European countries	Iceland, Norway, Sweden, Finland, Denmark, UK, Ireland, Netherlands, Belgium, Germany, France, Switzerland, Italy, Spain, Estonia, Czech Republic, Slovakia, Hungary, Turkey and Portugal.	Statistically significant negative correlation (using Pearson's r) between mean levels of serum 25(OH)D (average 56.79 nmol/L, standard deviation [SD] ±10.61) and number of cases of COVID-19 per 1 million population in each country (average 1393.4, SD±1129.984, r(20)=−0.4435; p=0.050)
Correlation between mean 25(OH)D level and the number of deaths from COVID-19 in 20 European countries		Statistically significant negative correlation (using Pearson's r) between mean levels of serum 25(OH)D (average 56.79 nmol/L, SD±10.61) and the number of deaths caused by COVID-19 per 1 million population in each country (average 80.42, SD±94.61, r(20)=−0.4378; p=0.05)

Laird et al. (2020)

		Analysis
N	**21,769 older people (for vitamin D data), source populations for COVID-19 not reported**	
Primary outcomes		
Correlation between mean 25(OH)D level and the number of deaths from COVID-19 in 12 European countries	Italy, Spain, Sweden, Norway, Finland, UK, Ireland, Scotland, Germany, France, Portugal, Netherlands.	Statistically significant negative correlation (using Spearman's rank correlation) between mean serum 25(OH)D levels (average and range or SD data not reported) and the number of deaths caused by COVID-19 per 1 million population in each country (average and range or SD data not reported; p=0.046)

Appendix E: Literature search strategy

Database: Medline

Platform: Ovid medline
Version: 1946 to 05/06/2020
Search date: 08-09/06/2020
Number of results retrieved: 69
Database: Ovid MEDLINE(R) <1946 to 5th June 2020>
Search Strategy:
---

1 exp Vitamin D/ (58714)
2 exp Vitamin D Deficiency/ (27641)
3 ((vitamin* adj5 D*2) or vitaminD*2).af. (97423)
4 (ergocalciferol* or calciferol* or vs041h42xc or dihydrotachysterol* or dihydrotachysterin* or calcamine or 67-96-9 or r5lm3h112r or Hydroxyvitamin D*2 or 25Hydroxyvitamin D*2 or HydroxyvitaminD*2 or 25HydroxyvitaminD*2 or hydroxycalciferol* or 25hydroxycalciferol* or hydroxyergocalciferol* or 25hydroxyergocalciferol* or ercalcidiol or "25(OH)D" or 21343-40-8 or alfacalcidol*).af. (24241)
5 (cholecalciferol* or colecalciferol* or calciol or 67-97-0 or 1c6v77qf41 or hydroxycholecalciferol* or hydroxycolecalciferol* or 25hydroxycholecalciferol* or 25hydroxycolecalciferol* or calcifediol* or calcidiol* or "19356-17-3" or p6yz13c99q or t0wxw8f54e or dihydroxycholecalciferol* or dihydroxycolecalciferol* or 25dihydroxycholecalciferol* or 25dihydroxycolecalciferol* or dihydroxyvitamin D*2 or 25dihydroxyvitamin* or dihydroxyvitaminD*2 or calcitriol* or 32222-06-3 or 40013-87-4 or 55721-11-4).af. (38257)
6 or/1-5 (118522)
7 exp coronavirus/ (15512)
8 exp Coronavirus Infections/ (14522)
9 ((corona* or corono*) adj1 (virus* or viral* or virinae*)).ti,ab,kw,kf. (1166)
10 (coronavirus* or coronovirus* or coronavirinae* or CoV or HCoV* or Betacoronavirus* or Betacoronovirus*).ti,ab,kw,kf. (23202)
11 ("2019-nCoV*" or 2019nCoV* or "19-nCoV*" or 19nCoV* or nCoV2019* or "nCoV-2019*" or nCoV19* or "nCoV-19*" or "COVID-19*" or COVID19* or "COVID-2019*" or COVID2019* or "HCoV-19*" or HCoV19* or "HCoV-2019*" or HCoV2019* or "2019 novel*" or Ncov* or "n-cov" or "SARS-CoV-2*" or "SARSCoV-2*" or "SARSCoV2*" or "SARS-CoV2*" or SARSCov19* or "SARS-Cov19*" or "SARSCov-19*" or "SARS-Cov-19*" or SARSCov2019* or "SARS-Cov2019*" or "SARSCov-2019*" or "SARS-Cov-2019*" or SARS2* or "SARS-2*" or SARScoronavirus2* or "SARS-coronavirus-2*" or "SARScoronavirus 2*" or "SARS coronavirus2*" or SARScoronovirus2* or "SARS-coronovirus-2*" or "SARScoronovirus 2*" or "SARS coronovirus2*" or covid).ti,ab,kw,kf. (19703)
12 (respiratory* adj2 (symptom* or disease* or illness* or condition*) adj5 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)).ti,ab,kw,kf. (262)
13 (("seafood market*" or "food market*") adj10 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)).ti,ab,kw,kf. (63)
14 (pneumonia* adj3 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)).ti,ab,kw,kf. (420)

15 ((outbreak* or wildlife* or pandemic* or epidemic*) adj1 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)).ti,ab,kw,kf. (241)
16 Middle East Respiratory Syndrome Coronavirus/ (1064)
17 ("middle east respiratory syndrome*" or "middle eastern respiratory syndrome*" or MERSCoV* or "MERS-CoV*" or MERS).ti,ab,kw,kf. (5005)
18 ("severe acute respiratory syndrome*" or SARS).ti,ab,kw,kf. (15820)
19 ("SARS-CoV-1*" or "SARSCoV-1*" or "SARSCoV1*" or "SARS-CoV1*" or SARSCoV or "SARS-CoV" or SARS1* or "SARS-1*" or SARScoronavirus1* or "SARS-coronavirus-1*" or "SARScoronavirus 1*" or "SARS coronavirus1*" or SARScoronovirus1* or "SARS-coronovirus-1*" or "SARScoronovirus 1*" or "SARS coronovirus1*").ti,ab,kw,kf. (8128)
20 or/7-19 (46798)
21 6 and 20 (69)

Database: Embase

Platform: Embase
Version: <1974 to 5th June 2020>
Search date: 05/06/2020
Number of results retrieved: 114
Database: Embase<1974 to 05/06/2020>
Search Strategy:
---
1 exp vitamin D/ (140837)
2 vitamin D deficiency/ (29625)
3 ((vitamin* adj5 D*2) or vitaminD*2).af. (148369)
4 (ergocalciferol* or calciferol* or vs041h42xc or dihydrotachysterol* or dihydrotachysterin* or calcamine or 67-96-9 or r5lm3h112r or Hydroxyvitamin D*2 or 25Hydroxyvitamin D*2 or HydroxyvitaminD*2 or 25HydroxyvitaminD*2 or hydroxycalciferol* or 25hydroxycalciferol* or hydroxyergocalciferol* or 25hydroxyergocalciferol* or ercalcidiol or "25(OH)D" or 21343-40-8 or alfacalcidol*).af. (45511)
5 (cholecalciferol* or colecalciferol* or calciol or 67-97-0 or 1c6v77qf41 or hydroxycholecalciferol* or hydroxycolecalciferol* or 25hydroxycholecalciferol* or 25hydroxycolecalciferol* or calcifediol* or calcidiol* or "19356-17-3" or p6yz13c99q or t0wxw8f54e or dihydroxycholecalciferol* or dihydroxycolecalciferol* or 25dihydroxycholecalciferol* or 25dihydroxycolecalciferol* or dihydroxyvitamin D*2 or 25dihydroxyvitamin* or dihydroxyvitaminD*2 or calcitriol* or 32222-06-3 or 40013-87-4 or 55721-11-4).af. (61499)
6 or/1-5 (180317)
7 exp Coronavirinae/ (19760)
8 exp Coronavirus infection/ (17348)
9 ("coronavirus disease 2019" or "severe acute respiratory syndrome coronavirus 2").sh,dj. (14137)
10 ((corona* or corono*) adj1 (virus* or viral* or virinae*)).ti,ab,kw. (1017)
11 (coronavirus* or coronovirus* or coronavirinae* or CoV or HCoV* or Betacoronavirus* or Betacoronovirus*).ti,ab,kw. (29619)
12 ("2019-nCoV*" or 2019nCoV* or "19-nCoV*" or 19nCoV* or nCoV2019* or "nCoV-2019*" or nCoV19* or "nCoV-19*" or "COVID-19*" or COVID19* or "COVID-2019*" or COVID2019* or "HCoV-19*" or HCoV19* or "HCoV-2019*" or HCoV2019*

or "2019 novel*" or Ncov* or "n-cov" or "SARS-CoV-2*" or "SARSCoV-2*" or "SARSCoV2*" or "SARS-CoV2*" or SARSCov19* or "SARS-Cov19*" or "SARSCov-19*" or "SARS-Cov-19*" or SARSCov2019* or "SARS-Cov2019*" or "SARSCov-2019*" or "SARS-Cov-2019*" or SARS2* or "SARS-2*" or SARScoronavirus2* or "SARS-coronavirus-2*" or "SARScoronavirus 2*" or "SARS coronavirus2*" or SARScoronovirus2* or "SARS-coronovirus-2*" or "SARScoronovirus 2*" or "SARS coronovirus2*" or covid).ti,ab,kw. (17444)
13 (respiratory* adj2 (symptom* or disease* or illness* or condition*) adj5 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)).ti,ab,kw. (323)
14 (("seafood market*" or "food market*") adj10 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)).ti,ab,kw. (67)
15 (pneumonia* adj3 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)).ti,ab,kw. (443)
16 ((outbreak* or wildlife* or pandemic* or epidemic*) adj1 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)).ti,ab,kw. (112)
17 Middle East respiratory syndrome/ (1275)
18 ("middle east respiratory syndrome*" or "middle eastern respiratory syndrome*" or MERSCoV* or "MERS-CoV*" or MERS).ti,ab,kw. (6368)
19 ("severe acute respiratory syndrome*" or SARS).ti,ab,kw. (18786)
20 ("SARS-CoV-1*" or "SARSCoV-1*" or "SARSCoV1*" or "SARS-CoV1*" or SARSCoV or "SARS-CoV" or SARS1* or "SARS-1*" or SARScoronavirus1* or "SARS-coronavirus-1*" or "SARScoronavirus 1*" or "SARS coronavirus1*" or SARScoronovirus1* or "SARS-coronovirus-1*" or "SARScoronovirus 1*" or "SARS coronovirus1*").ti,ab,kw. (8990)
21 or/7-20 (57296)
22 limit 21 to medline (15414)
23 21 not 22 (41882)
24 6 and 23 (114)

Database: Cochrane Central Register of Controlled Trials (CENTRAL)

Platform: CENTRAL
Version: Issue 6 of 12, 2020
Search date: 08/06/2020 10:10:27
Number of results retrieved: 0
Database: CENTRAL 08/06/2020 10:10:27
Search Strategy:

ID Search Hits
#1 MeSH descriptor: [Vitamin D] explode all trees 5254
#2 MeSH descriptor: [Vitamin D Deficiency] explode all trees 1409
#3 ((vitamin* near/5 D*) or vitaminD*) 23780
#4 (ergocalciferol* or calciferol* or vs041h42xc or dihydrotachysterol* or dihydrotachysterin* or calcamine or "67-96-9" or "r5lm3h112r" or "Hydroxyvitamin D*" or "25Hydroxyvitamin D*" or "HydroxyvitaminD*" or "25HydroxyvitaminD*" or hydroxycalciferol* or 25hydroxycalciferol* or hydroxyergocalciferol* or 25hydroxyergocalciferol* or ercalcidiol or "25(OH)D" or "21343-40-8" or alfacalcidol*) 5303
#5 (cholecalciferol* or colecalciferol* or calciol or "67-97-0" or 1c6v77qf41 or hydroxycholecalciferol* or hydroxycolecalciferol* or 25hydroxycholecalciferol* or

25hydroxycolecalciferol* or calcifediol* or calcidiol* or "19356-17-3" or p6yz13c99q or t0wxw8f54e or dihydroxycholecalciferol* or dihydroxycolecalciferol* or 25dihydroxycholecalciferol* or 25dihydroxycolecalciferol* or dihydroxyvitamin D* or 25dihydroxyvitamin* or dihydroxyvitaminD* or calcitriol* or "32222-06-3" or "40013-87-4" or "55721-11-4") 5697
#6 #1 or #2 or #3 or #4 or #5 25473
#7 MeSH descriptor: [Coronavirus] explode all trees 18
#8 MeSH descriptor: [Coronavirus Infections] explode all trees 179
#9 ((corona* or corono*) near/1 (virus* or viral* or virinae*)):ti,ab,kw 40
#10 (coronavirus* or coronovirus* or coronavirinae* or CoV or HCoV* or Betacoronavirus* or Betacoronovirus*):ti,ab,kw 460
#11 ("2019 nCoV" or 2019nCoV* or "19 nCoV" or 19nCoV* or nCoV2019* or "nCoV 2019" or nCoV19* or "nCoV 19" or "COVID 19" or COVID19* or "COVID 2019" or COVID2019* or "HCoV 19" or HCoV19* or "HCoV 2019" or HCoV2019* or "2019 novel" or Ncov* or "n cov" or "SARS CoV 2" or "SARSCoV 2" or "SARSCoV2" or "SARS CoV2" or SARSCov19* or "SARS Cov19" or "SARSCov 19" or "SARS Cov 19" or SARSCov2019* or "SARS Cov2019" or "SARSCov 2019" or "SARS Cov 2019" or SARS2* or "SARS 2" or SARScoronavirus2* or "SARS coronavirus 2" or "SARScoronavirus 2" or "SARS coronavirus2" or SARScoronovirus2* or "SARS coronovirus 2" or "SARScoronovirus 2" or "SARS coronovirus2" or covid):ti,ab,kw 599
#12 (respiratory* near/2 (symptom* or disease* or illness* or condition*) near/5 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)):ti,ab,kw 20
#13 (("seafood market" or "seafood markets" or "food market" or "food markets") near/10 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)):ti,ab,kw 2
#14 (pneumonia* near/3 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)):ti,ab,kw 23
#15 ((outbreak* or wildlife* or pandemic* or epidemic*) near/1 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)):ti,ab,kw 3
#16 MeSH descriptor: [Middle East Respiratory Syndrome Coronavirus] explode all trees 1
#17 ("middle east respiratory syndrome" or "middle eastern respiratory syndrome" or "middle east respiratory syndromes" or "middle eastern respiratory syndromes" or MERSCoV* or "MERS CoV" or MERS):ti,ab,kw 68
#18 ("severe acute respiratory syndrome" or "severe acute respiratory syndromes" or SARS):ti,ab,kw 456
#19 ("SARS CoV 1" or "SARSCoV 1" or "SARSCoV1" or "SARS CoV1" or SARSCoV or SARS CoV or SARS1 or "SARS 1" or SARScoronavirus1 or "SARS coronavirus 1" or "SARScoronavirus 1" or "SARS coronavirus1" or SARScoronovirus1 or "SARS coronovirus 1" or "SARScoronovirus 1" or "SARS coronovirus1"):ti,ab,kw 233
#20 {or #7-#19} 955
#21 #6 and #20 14
#22 (clinicaltrials or trialsearch):so 327468
#23 #21 not #22 0

Appendix F: Excluded studies

Table of excluded studies

Study reference	Reason for exclusion
Faul, JL; Kerley, B; Love, E et al. (2020) Vitamin D Deficiency and ARDS after SARS-CoV-2 Infection. Irish Medical Journal. Vol. 113. No.5; P84	Study type (Letter)
Rogza, M; Cheng, FW; Moloney, L et al. (2020) Effects of Micronutrients or Conditional Amino Acids on COVID-19 Related Outcomes. An Evidence Analysis Center Scoping Review. Journal of the Academy of Nutrition and Dietetics. 20th May [online ahead of print].	Poor relevance for population (single study of vitamin D in ventilator associated bacterial pneumonia)

Appendix G: Preprint studies

Study reference (preprints: not yet published in peer-reviewed journals)

Alipio et al 2020 Vitamin D Supplementation Could Possibly Improve Clinical Outcomes of Patients Infected with Coronavirus-2019 (COVID-19). SSRN (Elsevier)

Backer and Mageswaran 2020. Double COVID-19 Confirmed Case Fatality Rate in Countries with High Elderly Female Vitamin D Deficiency Prevalence. MedRxiv preprint

Daneshkhah et al 2020. The Possible Role of Vitamin D in Suppressing Cytokine Storm and Associated Mortality in COVID-19 Patients. Withdrawn from MedRxiv

Darling et al 2020. Vitamin D status, body mass index, ethnicity and COVID-19: Initial analysis of the first-reported UK Biobank COVID-19 positive cases (n 580) compared with negative controls (n 723). MedRxiv preprint

Davies G et al 2020. Evidence Supports a Causal Role for Vitamin D Status in COVID-19 Outcomes. MedRixv preprint

De Smet et al 2020. Vitamin D deficiency as risk factor for severe 1 COVID-19: a convergence of two pandemics. MedRxiv preprint

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Li M et al 2020. Identifying novel factors associated with COVID-19 transmission and fatality using the machine learning approach. MedRxiv preprint

Meltzer et al 2020. Association of Vitamin D Deficiency and Treatment with COVID-19 Incidence. MedRxiv preprint

Raharusun et al 2020. Patterns of COVID-19 Mortality and Vitamin D: An Indonesian Study. SSRN (Elsevier)

Raisi-Estabragh 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 preprint

Tan et al 2020. 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. MedRixv preprint

Appendix H: Ongoing studies

Study reference (ongoing studies: not yet completed)

Open-label RCT of vitamin D3 2000 IU (50 µg) plus 30 mg of zinc gluconate per day for 2 months versus usual care in adults >60 years who are 'institutionalised' but asymptomatic. Incidence of COVID-19 infection is a secondary outcome (Seguy D. Impact of Zinc and Vitamin D3 Supplementation on the Survival of Aged Patients Infected With COVID-19 (ZnD3-CoVici)
https://clinicaltrials.gov/ct2/show/NCT04351490

Randomised controlled trial of a single oral dose of 25,000 IU (625 µg) vitamin D (form not specified) versus usual care in patients who are infected with SARS-CoV-2 but do not have severe symptoms (Castillo MJ. Vitamin D on Prevention and Treatment of COVID-19 (COVITD-19)
https://clinicaltrials.gov/ct2/show/NCT04334005

RCT comparing single doses of vitamin D3, 50,000 IU to 200,000 IU (1250 Vs 5000 µg) in people with COVID-19 pneumonia >75 years of age, or >70 with low oxygen saturations (Annweiler C. COvid-19 and Vitamin D Supplementation: a Multicenter Randomized Controlled Trial of High Dose Versus Standard Dose Vitamin D3 in High-risk COVID-19 Patients (CoVitTrial)
https://clinicaltrials.gov/ct2/show/record/NCT04344041

Single group open-label study of a combination of hydroxychloroquine, vitamins C and D (form not specified), and zinc as prophylaxis in healthy healthcare workers who are at risk of COVID-19 (Haza S. A Study of Hydroxychloroquine, Vitamin C, Vitamin D, and Zinc for the Prevention of COVID-19 Infection (HELPCOVID-19)
https://clinicaltrials.gov/ct2/show/record/NCT04335084

Single group open-label study of a combination of hydroxychloroquine, vitamins C and D (form not specified), and zinc plus azithromycin as treatment for COVID-19 (Haza S. A Study of Quintuple Therapy to Treat COVID-19 Infection (HAZDpaC)
https://clinicaltrials.gov/ct2/show/NCT04334512

Open-label RCT of vitamin D (form not specified; 50,000 IU once weekly for 2/52) added to aspirin 81 mg daily for 2/52. Investigating whether early treatment with

aspirin and vitamin D in COVID-19 can mitigate COVID-19-associated coagulopathy and reduce hospitalization rates. (The LEAD COVID-19 Trial: Low-risk, Early Aspirin and Vitamin D to Reduce COVID-19 Hospitalizations) https://clinicaltrials.gov/ct2/show/NCT04363840

Case-control study investigating whether serum 25(OH)D level correlates to COVID-19 disease severity in people not treated in critical care. (Do Vitamin D Levels Really Correlated With Disease Severity in COVID-19 Patients? (COVIDVIT)) https://clinicaltrials.gov/ct2/show/NCT04394390

RCT comparing vitamin D3 (500,000 IU single dose) to placebo in adults admitted to hospital with COVID-19. Primary outcomes are respiratory SOFA at one week and need for high dose oxygen or mechanical ventilation at 30 days. (Cholecalciferol to Improve the Outcomes of COVID-19 Patients (CARED)) https://clinicaltrials.gov/ct2/show/NCT04411446

Single group open-label study of vitamin D supplementation (form not specified) in adults with COVID-19 and vitamin D deficiency (threshold for deficiency not defined). Participants to receive 2 weeks of vitamin D supplementation (10-15,000 IU based on age), with a further 3 weeks treatment if vitamin D levels remain low. Outcomes include 25(OH)D level and COVID-19 symptoms. (Vitamin D Testing and Treatment for COVID 19) https://clinicaltrials.gov/ct2/show/NCT04407286

Randomised controlled trial comparing 2 doses of vitamin D3 (50,000 IU twice/once weekly and 1,000 IU daily) with low dose vitamin D3 in adults with COVID-19. Primary outcome: COVID-19 symptom recovery at 3 weeks. (Vitamin D and COVID-19 Management) https://clinicaltrials.gov/ct2/show/NCT04385940

Case-series investigating differences in vitamin D blood levels between COVID-19 patients with different degrees of disease severity (mild-severe disease compared with patients requiring critical care). (VITACOV: Vitamin D Polymorphisms and Severity of COVID-19 Infection) https://clinicaltrials.gov/ct2/show/NCT04370808

Case-control study investigating serum zinc, vitamin D and vitamin B12 levels in pregnant women with COVID-19. (Evaluation of the Relationship Between Zinc

Vitamin D and b12 Levels in the Covid-19 Positive Pregnant Women) https://clinicaltrials.gov/ct2/show/NCT04407572

Case-control study investigating whether vitamin D levels affect outcomes in COVID-19 infection and whether vitamin D deficiency is associated with increased risk. (Investigating the Role of Vitamin D in the Morbidity of COVID-19 Patients) https://clinicaltrials.gov/ct2/show/NCT04386044

Open label RCT investigating interventions to prevent progression of COVID-19. Interventions include hydroxychloroquine, azithromycin, zinc, vitamin D, vitamin B12 with or without vitamin C. (International ALLIANCE Study of Therapies to Prevent Progression of COVID-19) https://clinicaltrials.gov/ct2/show/NCT04395768

Prospective cohort study investigating the association between vitamin D deficiency and worse outcomes in people admitted to hospital for COVID-19. (Increased Risk of Severe Coronavirus Disease 2019 in Patients With Vitamin D Deficiency (COVIT-D)) https://clinicaltrials.gov/ct2/show/NCT04403932