Cochrane Library

Cochrane Database of Systematic Reviews

Vitamin D supplementation for the treatment of COVID-19: a living systematic review (Review)

Stroehlein JK, Wallqvist J, Iannizzi C, Mikolajewska A, Metzendorf MI, Benstoem C, Meybohm P, Becker M, Skoetz N, Stegemann M, Piechotta V

Stroehlein JK, Wallqvist J, Iannizzi C, Mikolajewska A, Metzendorf M-I, Benstoem C, Meybohm P, Becker M, Skoetz N, Stegemann M, Piechotta V.
Vitamin D supplementation for the treatment of COVID-19: a living systematic review.
Cochrane Database of Systematic Reviews 2021, Issue 5. Art. No.: CD015043.
DOI: 10.1002/14651858.CD015043.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Review]

Vitamin D supplementation for the treatment of COVID-19: a living systematic review

Julia Kristin Stroehlein[1], Julia Wallqvist[2], Claire Iannizzi[1], Agata Mikolajewska[3], Maria-Inti Metzendorf[4], Carina Benstoem[5], Patrick Meybohm[6], Marie Becker[1], Nicole Skoetz[7], Miriam Stegemann[3a], Vanessa Piechotta[8b]

[1]Cochrane Haematology, Department I of Internal Medicine, Center for Integrated Oncology Aachen Bonn Cologne Duesseldorf, Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany. [2]Department of Anaesthesiology and Intensive Care Medicine, Medical Faculty, RWTH Aachen University, Aachen, Germany. [3]Department of Infectious Diseases and Respiratory Medicine, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany. [4]Cochrane Metabolic and Endocrine Disorders Group, Institute of General Practice, Medical Faculty of the Heinrich-Heine-University Düsseldorf, Düsseldorf, Germany. [5]Department of Intensive Care Medicine, Medical Faculty, RWTH Aachen University, Aachen, Germany. [6]Department of Anaesthesiology, Intensive Care, Emergency and Pain Medicine, University Hospital Wuerzburg, Wuerzburg, Germany. [7]Cochrane Cancer, Department I of Internal Medicine, Center for Integrated Oncology Aachen Bonn Cologne Duesseldorf, Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany. [8]Cochrane Haematology, Department I of Internal Medicine, Center for Integrated Oncology Aachen Bonn Cologne Duesseldorf, Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany

[a]contributed equally. [b]contributed equally

Contact address: Vanessa Piechotta, vanessa.piechotta@uk-koeln.de.

Editorial group: Cochrane Haematology Group.
Publication status and date: New, published in Issue 5, 2021.

Citation: Stroehlein JK, Wallqvist J, Iannizzi C, Mikolajewska A, Metzendorf M-I, Benstoem C, Meybohm P, Becker M, Skoetz N, Stegemann M, Piechotta V. Vitamin D supplementation for the treatment of COVID-19: a living systematic review. *Cochrane Database of Systematic Reviews* 2021, Issue 5. Art. No.: CD015043. DOI: 10.1002/14651858.CD015043.

ABSTRACT

Background

The role of vitamin D supplementation as a treatment for COVID-19 has been a subject of considerable discussion. A thorough understanding of the current evidence regarding the effectiveness and safety of vitamin D supplementation for COVID-19 based on randomised controlled trials is required.

Objectives

To assess whether vitamin D supplementation is effective and safe for the treatment of COVID-19 in comparison to an active comparator, placebo, or standard of care alone, and to maintain the currency of the evidence, using a living systematic review approach.

Search methods

We searched the Cochrane COVID-19 Study Register, Web of Science and the WHO COVID-19 Global literature on coronavirus disease to identify completed and ongoing studies without language restrictions to 11 March 2021.

Selection criteria

We followed standard Cochrane methodology. We included randomised controlled trials (RCTs) evaluating vitamin D supplementation for people with COVID-19, irrespective of disease severity, age, gender or ethnicity.

We excluded studies investigating preventive effects, or studies including populations with other coronavirus diseases (severe acute respiratory syndrome (SARS) or Middle East respiratory syndrome (MERS)).

Data collection and analysis

We followed standard Cochrane methodology.

To assess bias in included studies, we used the Cochrane risk of bias tool (ROB 2) for RCTs. We rated the certainty of evidence using the GRADE approach for the following prioritised outcome categories: individuals with moderate or severe COVID-19: all-cause mortality, clinical status, quality of life, adverse events, serious adverse events, and for individuals with asymptomatic or mild disease: all-cause mortality, development of severe clinical COVID-19 symptoms, quality of life, adverse events, serious adverse events.

Main results

We identified three RCTs with 356 participants, of whom 183 received vitamin D. In accordance with the World Health Organization (WHO) clinical progression scale, two studies investigated participants with moderate or severe disease, and one study individuals with mild or asymptomatic disease. The control groups consisted of placebo treatment or standard of care alone.

Effectiveness of vitamin D supplementation for people with COVID-19 and moderate to severe disease

We included two studies with 313 participants. Due to substantial clinical and methodological diversity of both studies, we were not able to pool data. Vitamin D status was unknown in one study, whereas the other study reported data for vitamin D deficient participants. One study administered multiple doses of oral calcifediol at days 1, 3 and 7, whereas the other study gave a single high dose of oral cholecalciferol at baseline. We assessed one study with low risk of bias for effectiveness outcomes, and the other with some concerns about randomisation and selective reporting.

All-cause mortality at hospital discharge (313 participants)

We found two studies reporting data for this outcome. One study reported no deaths when treated with vitamin D out of 50 participants, compared to two deaths out of 26 participants in the control group (Risk ratio (RR) 0.11, 95% confidence interval (CI) 0.01 to 2.13). The other study reported nine deaths out of 119 individuals in the vitamin D group, whereas six participants out of 118 died in the placebo group (RR 1.49, 95% CI 0.55 to 4.04]. We are very uncertain whether vitamin D has an effect on all-cause mortality at hospital discharge (very low-certainty evidence).

Clinical status assessed by the need for invasive mechanical ventilation (237 participants)

We found one study reporting data for this outcome. Nine out of 119 participants needed invasive mechanical ventilation when treated with vitamin D, compared to 17 out of 118 participants in the placebo group (RR 0.52, 95% CI 0.24 to 1.13). Vitamin D supplementation may decrease need for invasive mechanical ventilation, but the evidence is uncertain (low-certainty evidence).

Quality of life

We did not find data for quality of life.

Safety of vitamin D supplementation for people with COVID-19 and moderate to severe disease

We did not include data from one study, because assessment of serious adverse events was not described and we are concerned that data might have been inconsistently measured. This study reported vomiting in one out of 119 participants immediately after vitamin D intake (RR 2.98, 95% CI 0.12 to 72.30). We are very uncertain whether vitamin D supplementation is associated with higher risk for adverse events (very low-certainty).

Effectiveness and safety of vitamin D supplementation for people with COVID-19 and asymptomatic or mild disease

We found one study including 40 individuals, which did not report our prioritised outcomes, but instead data for viral clearance, inflammatory markers, and vitamin D serum levels. The authors reported no events of hypercalcaemia, but recording and assessment of further adverse events remains unclear. Authors administered oral cholecalciferol in daily doses for at least 14 days, and continued with weekly doses if vitamin D blood levels were > 50 ng/mL.

Authors' conclusions

There is currently insufficient evidence to determine the benefits and harms of vitamin D supplementation as a treatment of COVID-19. The evidence for the effectiveness of vitamin D supplementation for the treatment of COVID-19 is very uncertain. Moreover, we found only limited safety information, and were concerned about consistency in measurement and recording of these outcomes.

There was substantial clinical and methodological heterogeneity of included studies, mainly because of different supplementation strategies, formulations, vitamin D status of participants, and reported outcomes.

There is an urgent need for well-designed and adequately powered randomised controlled trials (RCTs) with an appropriate randomisation procedure, comparability of study arms and preferably double-blinding. We identified 21 ongoing and three completed studies without

published results, which indicates that these needs will be addressed and that our findings are subject to change in the future. Due to the living approach of this work, we will update the review periodically.

PLAIN LANGUAGE SUMMARY

Is vitamin D an effective and safe treatment for COVID-19?

Key messages

- We did not find enough, good-quality evidence to judge whether vitamin D is an effective or safe treatment for adults with COVID-19.

- We need more research on this topic. Future research should focus on well-designed studies with robust methods.

- We identified 21 studies on this topic that are ongoing. We will update this review when more evidence becomes available.

What is the link between vitamin D and COVID-19?

Some studies have shown that people who are in hospital with severe COVID-19 also have low levels of vitamin D (vitamin D deficiency). However, the risk factors for developing severe COVID-19 are the same as those for developing vitamin D deficiency, so it is difficult to tell if vitamin D deficiency itself is a risk factor for severe COVID-19. Risk factors include general ill-health, a poor diet, and pre-existing health conditions, such as diabetes, and liver and kidney disease.

Vitamin D is important for healthy bones, teeth and muscles. It helps to regulate blood sugar, the heart and blood vessels, and the lungs and airways. It also has a role in boosting the body's immune system. These are areas affected by COVID-19, so giving vitamin D to people with COVID-19 might help them to recover more quickly or have the disease less severely.

What did we want to find out?

We wanted to find out the effects of giving vitamin D to adults with confirmed COVID-19 on the following:

- death from any cause;

- improvement or worsening of the patient's condition;

- unwanted effects; and

- quality of life.

What did we do?

We searched for studies that assessed the use of vitamin D as a treatment for adults with confirmed COVID-19 compared with a placebo (sham treatment) or another treatment. Vitamin D could be given in any form and in any dose.

We compared and summarised their results, and rated our confidence in the evidence, based on factors such as study methods and sizes.

What did we find?

We found three studies with 356 participants. One study took place in Brazil, and the other two in Spain. Two studies had participants with severe COVID-19 and one had participants with mild COVID-19 or with no symptoms. All the participants tested positive for COVID-19 with a laboratory test called 'PCR', which is currently the most accurate test available.

The studies gave their participants different doses of vitamin D. They used different timings from each other, from one large dose in one study to several smaller doses over 14 days in another study. Only two studies said that their participants were vitamin D-deficient. The other study did not say anything about their participants' vitamin D status.

Deaths from any cause
We do not know whether vitamin D helps to prevent death from COVID-19. Two studies (in participants with severe COVID-19) provided evidence about deaths from any cause. One reported no deaths in the 50 participants who had received vitamin D, but two deaths in the 26 participants who received the hospital's usual COVID-19 treatment. The other study reported nine deaths in 119 participants who had been given vitamin D and six deaths in the 118 participants given placebo. These studies were too different from each other to allow us to draw any conclusions.

Patient's condition
Vitamin D may reduce the need for patients to be put on a ventilator to help them breathe, but the evidence is uncertain. One study (in participants with severe COVID-19) reported that nine out of 119 participants given vitamin D had to be put on a ventilator and 17 out of 118 given a placebo needed a ventilator.

Unwanted effects
We do not know whether vitamin D causes unwanted effects. Only one study (in participants with severe COVID-19) reported data on unwanted effects in a way that we could use. It found that one participant out of 119 vomited shortly after being given vitamin D.

Quality of life
None of the studies reported quality of life.

What are the limitations of the evidence?

Our confidence in the evidence is very limited because the studies gave different doses of vitamin D at different times from each other, did not all report participants' vitamin D status, and did not measure and record their results using consistent methods.

We found little evidence on unwanted effects and none on quality of life.

How up to date is this evidence?

The evidence is up to date to 11 March 2021.

Summary of findings 1. Summary of Findings Table - Vitamin D compared to placebo or standard care alone for individuals with moderate to severe disease

Vitamin D compared to placebo or standard care alone for individualswith moderate to severe disease

Patient or population: individualswith moderate to severe disease **Setting**: Inpatient **Intervention**: Vitamin D **Comparison**: placebo or standard care alone

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo or standard care alone	Risk with Vitamin D				
All-cause mortality at hospital discharge	Two studies reported all cause-mortality at hospital discharge but were to heterogenous to be pooled. One study reported that 0/50 participants in the vitamin D and 2/26 participants in the control group died [RR 0.11 (95% CI 0.01 to 2.13)]. The other study reported that 9/119 participants in the vitamin D and 6/118 participants in the placebo group died [RR 1.49 (95% CI 0.55 to 4.05)].			313 (2 RCTs)	⊕⊖⊖⊖ VERY LOW [a, b, c]	We are uncertain whether vitamin D supplementation increases or decreases all-cause mortality.
Improvement of clinical status assessed with: liberation from supplemental oxygen support (for the subgroup of participants requiring any supplemental oxygen or ventilator support at baseline, i.e WHO≥5), and weaning or liberation from invasive mechanical ventilation (for the subgroup of participants requiring invasive mechanical ventilationat baseline, i.e WHO≥7)	0 per 1,000	**0 per 1,000** (0 to 0)	not estimable	(studies)	-	No study reported this outcome.
Worsening of clinical status assessed with: need for invasive mechanical ventilation (for the subgroup of participants not requiring invasive mechanical ventilationat baseline, i.e WHO≤6)	144 per 1,000	**75 per 1,000** (35 to 163)	**RR 0.52** (0.24 to 1.13)	237 (1 RCT)	⊕⊕⊖⊖ LOW [d]	Vitamin D supplementation may decrease the need for mechanical ventilation, but the evidence is uncertain.
Quality of life, including fatigue and neurological status	0 per 1,000	**0 per 1,000** (0 to 0)	not estimable	(studies)	-	No study reported this outcome.

assessed with: standardised scales (e.g. WHOQOL-100) up to longest follow-up						
Adverse events (any grade)	Low		**RR 2.98** (0.12 to 72.30)	237 (1 RCT)	⊕⊖⊖⊖ VERY LOW [d, e]	We do not know whether vitamin D supplementation is associated with a higher risk of adverse events.
	3 per 1,000	**8 per 1,000** (0 to 204)				
Serious adverse events	0 per 1,000	**0 per 1,000** (0 to 0)	not estimable	(studies)	-	No study reported this outcome.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_424522142738901140.

a. Downgraded one level for serious study limitations, because of some concerns about risk of bias in one study.
b. Downgraded two levels for very serious inconsistency, because of inconsistent directions and variations of point estimates.
c. Downgraded two levels for very serious imprecision, because of wide confidence intervals, few participants, and few events.
d. Downgraded two levels for very serious imprecision, because of only one study, wide confidence intervals, few participants, and few events.
e. Downgraded one level for serious indirectness, because the reported outcome did not match our outcome definition.

BACKGROUND

This work is part of a series of Cochrane Reviews investigating treatments and therapies for coronavirus disease 2019 (COVID-19). Reviews of this series share information in the background section and methodology based on the first published reviews about monoclonal antibodies (Kreuzberger 2021) and convalescent plasma (Chai 2020) from the German research project "CEOsys" (COVID-19 Evidence-Ecosystem).

Description of the condition

COVID-19 is a rapidly spreading infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; WHO 2020a). On the 22 March 2020 the World Health Organization (WHO) declared the current COVID-19 outbreak a pandemic. COVID-19 is unprecedented in comparison to previous coronavirus outbreaks, such as severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), with 813 and 858 deaths, respectively (WHO 2007; WHO 2019). Despite intensive international efforts to contain its spread, it has resulted in more than 120 millions confirmed cases and almost 2.7 million deaths worldwide (WHO 2021a; WHO 2021c). The emergence of SARS-CoV-2 variants, with potential for increased transmissibility, could result in a higher case incidence (WHO2021b).

Several vaccines against COVID-19 have been distributed across countries and an additional hundred 100 vaccine candidates are in development (WHO 2020d). However, the process is time consuming, and challenges that go along with vaccine hesitancy and refusal have been reported. Moreover, the duration and degree to which the vaccines can protect against the disease, but also against infection and transmission is still not clear (Grubaugh 2020).

Specific risk factors for severe disease, hospitalisation and mortality have been identified: individuals aged 65 years or older, smokers and those with certain underlying medical conditions, such as cancer, chronic kidney disease, chronic obstructive pulmonary disease (COPD), heart conditions, immunocompromised state, obesity, sickle cell disease or diabetes mellitus are more likely to have severe courses of the disease (Huang 2020; Liang 2020; WHO 2020a; Williamson 2020). COVID-19 case fatality ratios varied widely between countries and reporting periods (from 0% to more than 25%, Johns Hopkins University & Medicine). However, these numbers may be misleading as they tend to overestimate the infection fatality ratio due to varying testing frequency, lag in reporting dates, incomplete capturing of all cases, and variations in case definitions since the beginning of the pandemic (WHO 2020b).

The median incubation period is estimated to be between five and six days; 97.5% of symptomatic cases develop symptoms within 11.5 days of exposure (Lauer 2020). Sore throat, cough, fever, headache, fatigue, and myalgia or arthralgia (joint pain) are the most commonly reported symptoms (Struyf 2020). Other symptoms include dyspnoea, chills, nausea or vomiting, diarrhoea and nasal congestion (WHO 2020a). The majority of infected people have mild symptoms (approximately 80%, Wu 2020) or remain completely asymptomatic (Buitrago-Garcia 2020). A smaller proportion (approximately 14%) are affected by severe or critical disease with intensive care unit (ICU) admittance due to respiratory failure, septic shock or multiple organ dysfunction (Wu 2020). In light of the extent of the pandemic, including the pressure COVID-19 puts on health systems, especially in the face of evolving variants of the virus with the potential of increased transmissibility, the ongoing scarcity of effective treatments, and the limited global availability of vaccines, there is an urgent need for effective therapies to save lives and to reduce the burden on healthcare systems.

Description of the intervention

Therapeutic interventions to treat COVID-19 are being investigated with immense emphasis. Recently, vitamin D supplementation for treatment of COVID-19 gained attention, since studies suggested an association between vitamin D deficiency and risk or prognosis of the disease (Grant 2020). Vitamin D3 is the precursor of a potent secosteroid hormone, intervening in several metabolic processes in the human body and showing immunomodulating (Sassi 2018) and organ protective properties (Amrein 2018; Martucci 2019; Ney 2019). Vitamin D3 (cholecalciferol) is naturally absorbed from food sources or produced by the epidermis when ultraviolet radiation is present. After being metabolised by the liver into 25-hydroxyvitamin D [25(OH)D or calcidiol or calcifediol], and further converted into its biological active hormone 1,25-dihydroxyvitamin D [$1,25(OH)_2D_3$ or calcitriol] by the kidneys within two or three days, it enters various cells at different organs (Lee 2009). By binding to the nuclear vitamin D receptor, a deoxyribonucleic acid (DNA) binding protein, it can regulate the transcription of genes-not only involved in calcium/phosphorus homeostasis and bone health (Holick 1996), but also in glycaemic control (Wu 2017), in muscle and cardiovascular function (Norman 2014), in the renin-angiotensin system (Braun 2012), and in respiratory mechanisms (Hughes 2009). Some of these characteristics might play a role in critically ill patients and might have an influence on the course of COVID-19 (Grant 2020).

25-hydroxyvitamin D and 1,25-dihydroxyvitamin D serum concentrations can be measured by radioimmunoassays and competitive protein-binding assays, with a high risk for technical difficulties, or by liquid chromatography tandem mass spectroscopy (LC-MS) technique (Holick 2009), or high performance liquid chromatography (HPLC) technique (Fraser 2020). The vitamin D external quality assurance scheme (DEQAS) has contributed to improve and standardise measurement procedures of serum 25(OH)D and 1,25(OH)2D.

Vitamin D deficiency is generally defined as 25-hydroxyvitamin D values lower than 20 ng/mL (equals 50 nmol/L), while levels lower than 12 ng/mL (equals 30 nmol/L can be regarded as severely deficient (Amrein 2018). While cholecalciferol has a half life of about three months; 25-hydroxyvitamin D's half life lies within the range of two to three weeks (Jones 2008). 1,25-dihydroxyvitamin D is very unstable and only available and traceable for several hours (Brandi 2002; Leaf 2014). Each of the metabolites can be supplemented, however, keeping the physiology of vitamin D in mind, supplementation strategies must be well conceived and adjusted to the patient population.

- Right patient population: patients at need due to 25(OH)D deficit (Amrein 2014), nutrition deficits, co-morbidities and/or severe illness.
- Right substance or right timing: either supplementing the active form calcitriol or providing enough time for the body to metabolise vitamin D3 (cholecalciferol) into its biological active

form itself. Liver and kidneys must work properly in order to ensure this metabolisation process.

- Right dosing: adequate dosing is necessary in order to provide sufficient 25(OH)D levels. In-hospital, high-dose supplementation is often required due to the great deficiency at baseline.
- Right outcome: besides mortality as the overarching outcome in COVID-19, clinical status including improvement and worsening as well as need for dialysis, and quality of life are crucial outcomes to be evaluated in the context of vitamin D supplementation for the treatment of COVID-19.

Until now, evidence regarding specific vitamin D supplementation strategies as a treatment for individuals with COVID-19 are sparse (NICE 2020). Recommendations were published by the European and American Societies for Clinical Nutrition and Metabolism (ESPEN and ASPEN), which focused on including malnutrition in the management of COVID-19 patients and suggested supplementation with vitamins in these individuals if vitamin levels were deficient (Barazzoni 2020; Wells 2020). The recommendations provide guidance for those in the intensive care unit setting and align with the general principles in critical care nutrition. With this review, we aim to evaluate the role of vitamin D in the treatment of COVID-19.

How the intervention might work

Patients at risk of developing severe COVID-19 share many characteristics with patients at risk for vitamin D deficiency. Poor general health condition along with limited sunlight exposure, pre-hospital malnutrition, old age, pre-existing co-morbidities including liver and kidney dysfunction are among the primary points of focus when analysing causes for vitamin D deficiency (Lee 2009). These characteristics also are risk factors for COVID-19-related hospitalisation, intensive care unit (ICU) admission and mortality (Wu 2020a). Recent observational studies showed an association between vitamin D deficiency and worse clinical outcome (including need and duration of mechanical ventilation and mortality) in COVID-19 patients (Grant 2020; Liu 2021; Munshi 2021; Pereira 2020; Yisak 2021). These observations raise the question if vitamin D deficiency is a predictive marker or partly responsible for progression to severe COVID-19 and accordingly, a possible target for treatment.

SARS-CoV-2 infection can cause severe inflammation along with serious life-threatening complications (Wu 2020). SARS-CoV-2 can enter host cells by binding to human angiotensin-converting enzyme 2 (hACE2) receptors, which are highly expressed in the upper respiratory tract of humans. After entering the host cell, viral ribonucleic acid (RNA) replication takes place, resulting in the host response including activation of alveolar macrophages and inflammatory infiltration (Cabler 2020). Early descriptions of COVID-19 included development of a cytokine storm as a precursor for clinical instability and deterioration and still many questions related to the pathogenesis of inflammation are unanswered.

The biological active hormone 1,25-dihydroxyvitamin D (calcitriol) shows immunomodulating properties, which might help to reduce inflammation in COVID-19. Vitamin D receptors are present on several immunological cells such as T cells, B cells, macrophages and dendritic cells. Active immune cells can locally convert 25-hydroxyvitamin D into the active form of vitamin D (1,25(OH)2D) via the 1-α-hydroxylase enzyme (CYP27B1) to provide these immunoprotective properties. In addition to immune cells, the vitamin D receptor (VDR) and the 1-α-hydroxylase enzyme (CYP27B1) are expressed in lung epithelial cells, which are thus also able to produce calcitriol in case of infection. $1,25(OH)_2D$ activates several anti-inflammatory mediators (e.g. IL-4 and IL-10) and inhibits pro-inflammatory cytokines such as interferon-γ, interleukin 2 and 6 and tumour necrosis factor-α (Sassi 2018), which are part of the COVID-19 induced cytokine storm. 1,25-Dihydroxy-vitamin-D further triggers an upregulation of cathelicidin (LL-37) and defensins; antimicrobial peptides with antiviral effects (Bilezikian 2020; Malaguarnera 2020). By binding to the SARS-CoV-2 S protein, LL-37 inhibits the attachment of SARS-CoV-2 to the hACE2 receptor and thus blocks viral entry and virus replication (Roth 2020). Besides the effect on the endogenous defence system, $1,25(OH)_2D$ influences the adaptive immune system by reducing TH1 cells and by triggering the formation of TH2 and regulatory T cells (Malaguarnera 2020). Vitamin D was shown to improve clinical outcomes in patients with acute respiratory distress syndrome (ARDS) (Martineau 2017; Martineau 2019), asthma exacerbations (Jolliffe 2017; Ramos-Martinez 2018) and critical illness (Putzu 2017). These findings support the hypothesis that this vitamin could act as an disease-modifying treatment for COVID-19.

Beside its involvement in regulating the immune system, vitamin D influences arterial stiffness and is involved in the regulation of various thrombotic pathways. Calcitriol leads to an upregulation of the anticoagulants thrombomodulin and tissue factor pathway inhibitor and inhibits tissue factor mediated thrombin activation and thereby reduces hypercoagulability (Sengupta 2021). These characteristics are of particular importance for COVID-19 patients since virus-related injury of the vascular endothelium leads to an increased risk for coagulopathy and thrombosis (Wang 2020; Wu 2020) with life-threatening consequences.

ACE2 receptors are also expressed by human epithelial cells that line mucosal surfaces and cover organs of liver, heart, kidney and intestine, which could explain why multiple organs can be affected during COVID-19 (Mokhtari 2020). Rates of acute kidney injury (AKI) and the need for dialysis vary. However, AKI affects about 30% to 40% of hospitalised individuals with COVID-19, and about 50% of people with COVID-19 on ICU, of whom 20% require renal replacement therapy (Gupta 2021; Nadim 2020). Kidney injury can aggravate vitamin D deficiency as metabolisation of the active hormone calcitriol from vitamin D3 sources can be compromised.

Why it is important to do this review

There is a clear, urgent need for more information to guide clinical decision-making for COVID-19 patients. Current treatment consists of supportive care with oxygen therapy in cases with moderate disease, and with respiratory support as mechanical ventilation and extracorporeal membrane oxygenation in cases with severe disease (CDC 2020; WHO 2020f). Overall, data from randomised trials do not demonstrate a clear, major clinical benefit with most drugs evaluated so far. Data from randomized trials overall support the role of corticosteroids for severe COVID-19 and clinical guidelines recommend the use of corticosteroids (Siemieniuk 2020). Recommendations for the use of tocilizumab and remdesivir vary to a certain extent from different panels (National COVID-19 Clinical Evidence Taskforce 2021, Siemieniuk 2020). Other drugs, such as hydroxychloroquine, are not recommended for the treatment of COVID-19 (Siemieniuk 2020). Moreover, existing evidence on the effectiveness of monoclonal antibodies as

treatments for hospitalised individuals with COVID-19 remains unclear.

Extensive work in the field of systematic reviews for interventions for COVID-19 has already been undertaken, including vitamin D supplementation. For example, several systematic reviews investigated the association between vitamin D blood status, risk,and prognosis of COVID-19, mainly based on non-randomised studies (e.g. Liu 2021; Munshi 2021; Pereira 2020). Yisak 2021 and Shah 2021 additionally included randomised controlled trials (RCTs).

One of the most interesting sources is the regularly updated 'The National Institute for Health and Care Excellence' (NICE) guideline covering vitamin D use in the context of COVID-19 (published in December 2020, NICE 2020). The Australian high-priority, evidence-based clinical COVID-19 guidelines are continually updated with the latest research on emerging treatments, including recommendations for consideration of vitamin D analogues for people with COVID-19 (National COVID-19 Clinical Evidence Taskforce 2021).

This systematic review will fill current gaps by identifying, describing, evaluating and meta-analysing RCTs for vitamin D supplementation on clinical outcomes in COVID-19. Several clinical trials investigating the safety and effectiveness of vitamin D supplementation have been announced, and their results will need to be interpreted with care due to possible side effects of vitamin D overdoses. Thus, there needs to be a thorough understanding of the current body of evidence regarding the use of vitamin D supplementation for the treatment of COVID-19, and an extensive review of the available literature is required.

OBJECTIVES

To assess whether vitamin D supplementation is effective and safe for the treatment of COVID-19 in comparison to an active comparator, placebo, or standard of care alone, and to maintain the currency of the evidence, using a living systematic review. approach.

METHODS

Criteria for considering studies for this review

Types of studies

The main description of methods is based on the standard template of the Cochrane Haematology review group and is in line with a series of Cochrane Reviews investigating treatments and therapies for COVID-19. Specific adaptions related to the research question were made if necessary. The protocol for this review was registered with PROSPERO on 21 January 2021 (Stroehlein 2021a).

To assess the effectiveness and safety of vitamin D supplementation for the treatment of people with COVID-19, we included randomised controlled trials (RCTs), as this study design, if performed appropriately, provides the best evidence for experimental therapies in highly-controlled therapeutic settings. Cluster-randomised and cross-over trials were eligible for inclusion.

We excluded controlled non-randomised studies of intervention and observational studies. We also excluded animal studies, pharmacokinetic studies, and in vitro studies.

We included the following formats, if sufficient information was available on study design, characteristics of participants, interventions and outcomes.

- Full-text publications
- Preprint articles
- Abstract publications
- Results published in trials registries
- Personal communication with investigators

We included preprints and conference abstracts to have a complete overview of the ongoing research activity, especially for tracking newly emerging studies about vitamin D supplementation in COVID-19. We did not apply any limitation with respect to the length of follow-up.

Types of participants

We included adults with a confirmed diagnosis of COVID-19 (as described in the study) and we did not exclude any studies based on gender, ethnicity, disease severity, setting, or baseline vitamin D status.

We excluded studies that evaluated vitamin D supplementation for the treatment of other coronavirus diseases such as SARS or MERS, or other viral diseases, such as influenza. If studies enrolled populations with or exposed to mixed viral diseases, we had planned to only include these if trial authors provided subgroup data for SARS-CoV-2 infection.

Types of interventions

We included any type of vitamin D supplementation, including its active or non-active forms, single or multiple doses, low- or high-dose, and given alone or combined with individual care.

We included the following comparison.

- Vitamin D supplementation (any of the above specified interventions) versus placebo or no treatment. Co-interventions were allowed, but had to be comparable between intervention groups.

We had further planned to include the following comparisons.

- Vitamin D supplementation (any of the above specified interventions) versus control intervention, for example drug treatments or micronutrient supplementation.
- Low-dose vitamin D supplementation versus high-dose vitamin D supplementation (as defined in studies).
- Single-dose vitamin D supplementation versus multiple- dose Vitamin D supplementation.

We excluded studies evaluating vitamin D supplementation in combination with other active treatments, if the same treatment was not used in the control group. We also excluded studies investigating the effectiveness and safety to prevent COVID-19.

Types of outcome measures

We evaluated core outcomes in accordance with the Core Outcome Measures in Effectiveness Trials (COMET) Initiative for COVID-19 patients (COMET 2020; Marshall 2020), and additional outcomes that have been prioritised by consumer representatives and the

German guideline panel for inpatient therapy of people with COVID-19.

We defined outcome sets for two populations. Those are: hospitalised individuals with a confirmed diagnosis of COVID-19 and moderate to severe disease, and ambulatory-managed individuals with a confirmed diagnosis of SARS-CoV-2 infection and asymptomatic or mild disease, according to WHO clinical progression scale (WHO 2020e, see Table 1).

Individuals with a confirmed diagnosis of COVID-19 and moderate to severe disease

Effectiveness of vitamin D supplementation

Prioritised outcomes (included in Summary of findings table)

- All-cause mortality at day 28, day 60, time-to-event, and at hospital discharge
- Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale (WHO 2020e) (see Figure 1), WHO Ordinal Scale for Clinical Improvement (WHO 2020g) at day 28, day 60, and up to longest follow-up); including:
  - Improvement of clinical status:
    - ☐ weaning or liberation from invasive mechanical ventilation in surviving patients i.e. WHO ≤ 6, if ≥ 7 at baseline;
    - ☐ ventilator-free days; ventilator-free defined as WHO ≤ 6;
    - ☐ duration to liberation from invasive mechanical ventilation;
    - ☐ liberation from supplemental oxygen in surviving patients i.e. WHO ≤ 4, if ≥ 5 at baseline;
    - ☐ duration to liberation from supplemental oxygen.
  - Worsening of clinical status:
    - ☐ need for invasive mechanical ventilation i.e. WHO 7-9, if ≤ 6 at baseline ;
    - ☐ need for non-invasive mechanical ventilation or high flow i.e. WHO=6, if ≤ 5 at baseline;
    - ☐ need for oxygen by mask or nasal prongs i.e. WHO = 5, if ≤ 4 at baseline
- Need for dialysis (at up to 28 days)
- Quality of life, including fatigue and neurological status, assessed with standardised scales (e.g. WHOQOL-100) at up to seven days; up to 30 days, and longest follow-up available

Figure 1. WHO Clinical Progression Scale (Marshall 2020) Copyright © 2020 Elsevier Ltd. All rights reserved: reproduced with permission.

Patient State	Descriptor	Score
Uninfected	Uninfected; no viral RNA detected	0
Ambulatory mild disease	Asymptomatic; viral RNA detected	1
	Symptomatic; independent	2
	Symptomatic; assistance needed	3
Hospitalised: moderate disease	Hospitalised; no oxygen therapy*	4
	Hospitalised; oxygen by mask or nasal prongs	5
Hospitalised: severe diseases	Hospitalised; oxygen by NIV or high flow	6
	Intubation and mechanical ventilation, pO_2/FiO_2 ≥150 or SpO_2/FiO_2 ≥200	7
	Mechanical ventilation pO_2/FIO_2 <150 (SpO_2/FiO_2 <200) or vasopressors	8
	Mechanical ventilation pO_2/FiO_2 <150 and vasopressors, dialysis, or ECMO	9
Dead	Dead	10

Additional outcomes (not in Summary of findings table)

- Admission to the intensive care unit (ICU)
- Duration of hospitalisation, or time to discharge from hospital from randomisation

- Viral clearance, assessed with reverse transcription polymerase chain reaction (RT-PCR) test for SARS-CoV-2 at baseline, up to 3, 7, and 15 days
- Vitamin D serum levels

Safety of vitamin D supplementation

Prioritised outcomes (included in Summary of findings table)

- Serious adverse events, defined as number of participants with any event
- Adverse events (any grade, grade 1-2, grade 3-4), defined as number of participants with any event

Individuals with a confirmed diagnosis of COVID-19 and asymptomatic or mild disease

Effectiveness of vitamin D supplementation

Prioritised outcomes (included in Summary of findings table)

- All-cause mortality at day 28, day 60, time-to-event, and up to longest follow-up
- Admission to hospital (WHO≥ 4)
- Development of moderate to severe clinical COVID-19 symptoms, defined as WHO Clinical Progression Scale ≥ 6 (WHO 2020e), up to longest follow-up
  - Need for invasive mechanical ventilation, non-invasive mechanical ventilation or high flow i.e. WHO ≥ 6, severe disease:
    - ☐ need for invasive mechanical ventilation i.e. WHO 7-9;
    - ☐ need for non-invasive mechanical ventilation or high flow i.e. WHO = 6.
  - Need for hospitalisation with or without supplemental oxygen i.e. WHO=4-5, moderate disease:
    - ☐ Need for oxygen by mask or nasal prongs i.e. WHO=5;
    - ☐ Need for hospitalisation without oxygen therapy i.e. WHO = 4.
- Quality of life, including fatigue and neurological status, assessed with standardised scales (e.g. WHOQOL-100) at up to 7 days, up to 30 days, and longest follow-up available

Additional outcomes (not in Summary of findings table)

- Duration of hospitalisation, or time to hospital discharge from randomisation, for subgroup of participants hospitalised during course of disease
- Vitamin D serum levels

Safety of vitamin D supplementation

Prioritised outcomes (included in Summary of Findings table)

- Serious adverse events, defined as number of participants with any event
- Adverse events (any grade, grade 1-2, grades 3-4), defined as number of participants with any event

Timing of outcome measurement

In case of time-to-event analysis, e.g. for time to discharge from hospital, we included the outcome measure based on the longest follow-up time and measured from randomisation. We also collected information on outcomes from all other time points reported in the publications.

We included adverse events occurring during active treatment and included long-term adverse events as well. If sufficient data were available, we grouped the measurement time points of eligible outcomes, for example, adverse events and serious adverse events, into those measured directly after treatment (up to seven days after treatment), medium-term outcomes (up to 15 days after treatment) and longer-term outcomes (more than 30 days after treatment).

Search methods for identification of studies

Electronic searches

On 11 March 2021 our Information Specialist (MIM) conducted systematic searches in the following sources from inception of each database to 11 March 2021 (date of last search for all databases) and did not place restrictions on the language of publication:

- Cochrane COVID-19 Study Register (CCSR) (www.covid-19.cochrane.org), comprising:
  - MEDLINE (PubMed), daily updates,
  - Embase.com, weekly updates,
  - ClinicalTrials.gov (www.clinicaltrials.gov), daily updates,
  - World Health Organization International Clinical Trials Registry Platform (ICTRP) (www.who.int/trialsearch), weekly updates,
  - medRxiv (www.medrxiv.org), weekly updates,
  - Cochrane Central Register of Controlled Trials (CENTRAL), monthly updates.
- Web of Science Core Collection (from 1 January 2020 onwards):
  - Science Citation Index Expanded (1945-present),
  - Emerging Sources Citation Index (2015-present).
- WHO COVID-19 Global literature on coronavirus disease (https://search.bvsalud.org/global-literature-on-novel-coronavirus-2019-ncov/).

Database search results for Web of Science were restricted to publications from 2020 to current, as no treatment trials on COVID-19 were registered prior to January 2020. For detailed search strategies, see Appendix 1.

Searching other resources

We identified other potentially eligible studies by searching the reference lists of included studies, systematic reviews and meta-analyses. In addition, we contacted the investigators of included studies to obtain additional information on the retrieved studies.

We searched for grey literature, which we defined as searching study registries such as ClinicalTrials.gov and WHO ICTRP contained in the CCSR, as well as searching preprint servers and grey literature indexes contained in CCSR and WHO COVID-10 Global Literature database. Once we established our set of included studies, we searched for preprints via Europe PMC, to check if any preprints for included studies were published since our database search.

Data collection and analysis

Selection of studies

Two out of three review authors (JS, CI, NS) independently screened the results of the search strategies for eligibility for this review by reading the titles and abstracts using EndNote Software (EndNote X9). We coded the abstracts as either 'include' or 'exclude'. In the case of disagreement or if it was unclear whether

we should retrieve the abstract or not, we obtained the full-text publication for further discussion. Both review authors assessed the full-text articles of selected studies. If the two review authors were unable to reach a consensus, they consulted the third review author to reach a final decision.

We documented the study selection process in a flow chart, as recommended in the PRISMA statement (Moher 2009), and show the total numbers of retrieved references and the numbers of included and excluded studies. We listed all studies that we excluded after full-text assessment and the reasons for their exclusion in the 'Characteristics of excluded studies' section.

Data extraction and management

We conducted data extraction according to the guidelines proposed by Cochrane (Li 2020). Two out of three review authors (JS, VP, CI) extracted data independently and in duplicate, using a customised data extraction form developed in Microsoft Excel (Microsoft 2018). We resolved disagreements by discussion. If no agreement was obtained, a third review author was involved to resolve the disagreement.

Two out of three review authors (JS, VP, CI) independently assessed eligible studies obtained in the process of study selection (as described above) for methodological quality and risk of bias. If the review authors were unable to reach a consensus, a third review author was consulted.

We extracted the following information, if reported.

- General information: author, title, source, publication date, country, language, duplicate publications.
- Study characteristics: trial design, setting and dates, source of participants, inclusion/exclusion criteria, comparability of groups, treatment cross-overs, compliance with assigned treatment, length of follow-up.
- Participant characteristics: age, gender, ethnicity, number of participants recruited/allocated/evaluated, additional diagnoses, severity of disease, previous treatments, concurrent treatments, complementary medicine (e.g. quercetin, elderberry, zinc), co-morbidities (e.g. diabetes, immunosuppression).
- Interventions: type of vitamin D, dose, frequency, timing, duration and route of administration, setting (e.g. inpatient, ambulant, prevention), duration of follow-up.
- Control interventions: placebo, no treatment, or other intervention; dose, frequency, timing, duration and route of administration, setting, duration of follow-up.
- Outcomes: as specified under Types of outcome measures.
- 'Risk of bias' assessment: randomisation process, deviations from the intended interventions, missing outcome data, measurement of the outcome, selection of the reported result.

Assessment of risk of bias in included studies

We used the risk of bias 2.0tool (RoB 2) to analyse the risk of bias of study results (Sterne 2019). Of interest for this review is the effect of the assignment to the intervention (the intention-to-treat (ITT) effect), thus, we performed all assessments with RoB 2 on this effect. The outcomes that we assessed are those specified for inclusion in the 'Summary of findings' table.

Two out of three review authors (JS, VP, CI) independently assessed the risk of bias for each outcome. In case of discrepancies among their judgements and inability to reach consensus, we consulted the third review author to reach a final decision. We assessed the following types of bias as outlined in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2020c).

- Bias arising from the randomisation process
- Bias due to deviations from the intended interventions
- Bias due to missing outcome data
- Bias in measurement of the outcome
- Bias in selection of the reported result

For cluster-RCTs, we had planned to add an additional domain to assess bias arising from the timing of identification and recruitment of participants in relation to timing of randomisation as recommended in the archived RoB 2 guidance for cluster-randomised trials (Eldridge 2016), and in Chapter 23 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2020a).

To address these types of bias we used the signalling questions recommended in RoB 2 and make a judgement using the following options.

- 'Yes': if there is firm evidence that the question is fulfilled in the study (i.e. the study is at low or high risk of bias for the given the direction of the question).
- Probably yes': a judgement has been made that the question is fulfilled in the study (i.e. the study is at low or high risk of bias given the direction of the question).
- 'No': if there is firm evidence that the question is unfilled in the study (i.e. the study is at low or high risk of bias for the given the direction of the question).
- 'Probably no': a judgement has been made that the question is unfilled in the study (i.e. the study is at low or high risk of bias given the direction of the question).
- 'No information': if the study report does not provide sufficient information to allow any judgement.

We used the algorithms proposed by RoB 2 to assign each domain one of the following levels of bias.

- Low risk of bias
- Some concerns
- High risk of bias

Subsequently, we derived an overall 'Risk of bias' rating for each pre-specified outcome in each study in accordance with the following suggestions.

- 'Low risk of bias': we judge the trial to be at low risk of bias for all domains for this result.
- 'Some concerns': we judge the trial to raise some concerns in at least one domain for this result, but not to be at high risk of bias for any domain.
- 'High risk of bias': we judge the trial to be at high risk of bias in at least one domain for the result or we judge the trial to have some concerns for multiple domains in a way that substantially lowers confidence in the results.

We used the RoB 2 Excel tool to implement RoB 2 (available from riskofbias.info), added our judgements to the analysis for each assessed study and outcome, and stored our detailed RoB 2 assessments as supplementary online material (Stroehlein 2021b).

Measures of treatment effect

For continuous outcomes, we recorded the mean, standard deviation and total number of participants in both treatment and control groups. Where continuous outcomes used the same scale, we performed analyses using the mean difference (MD) with 95% confidence intervals (CIs). For continuous outcomes measured with different scales, we performed analyses using the standardised mean difference (SMD). For interpreting SMDs, we re-expressed SMDs in the original units of a particular scale with the most clinical relevance and impact (e.g. clinical symptoms with the WHO Clinical Progression Scale (WHO 2020e)).

For dichotomous outcomes, we recorded the number of events and total number of participants in both treatment and control groups. We reported the pooled risk ratio (RR) with a 95% CI (Deeks 2020).

If available, we extracted and report hazard ratios (HRs) for time-to-event outcomes (e.g. time to hospital discharge). If HRs were not available, we would have made every effort to estimate the HR as accurately as possible from available data using the methods proposed by Parmar and Tierney (Parmar 1998; Tierney 2007). Had sufficient studies provided HRs, we planned to use HRs rather than RRs or MDs in a meta-analysis, as they provide more information.

Unit of analysis issues

The aim of this review was to summarise trials that analysed data at the level of the individual. We planned to follow methods as recommended in Chapter 23 of the *Cochrane Handbook for Systematic Reviews of Interventions* for incorporating data from cluster-RCTs and cross-over trials (Higgins 2020a). For cross-over trials we would have only considered results from the first period before cross-over because COVID-19 is not a chronic condition and its exact course and long-term effects are yet to be defined.

Studies with multiple treatment groups

As recommended in Chapter 6 of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2020b), for studies with multiple treatment groups of the same intervention (i.e. dose, route of administration), we planned to evaluate if study arms are sufficiently homogeneous to be combined. If arms could not be pooled, we had planned to compare each arm with the common comparator separately. For pairwise meta-analysis, we planned to split the ‘shared’ group into two or more groups with smaller sample size, and include two or more (reasonably independent) comparisons. For dichotomous outcomes both the number of events and the total number of participants would have been divided, and for continuous outcomes the total number of participants would have been divided with unchanged means and SDs.

Dealing with missing data

Chapter 10 of the *Cochrane Handbook for Systematic Reviews of Interventions* suggests a number of potential sources for missing data, which we took into account: at study level, at outcome level and at summary data level (Deeks 2020). At all levels, it is important to differentiate between data 'missing at random', which may often be unbiased, and 'not missing at random', which may bias study and thus review results.

Where data were missing, we requested these data from the principal investigators of two studies (Entrenas Castillo 2020; Murai 2021). We requested additional data for our prioritised outcomes from all authors. In addition, we requested information from Rastogi 2020 regarding clinical status of participants, and from Murai 2021 and Entrenas Castillo 2020 regarding evaluation and assessment of (serious) adverse events. We received a response from Rastogi 2020 and classified participants as ambulatory managed with mild or asymptomatic disease based on their answer. We did not receive a response from the other two authors (Entrenas Castillo 2020; Murai 2021. Where data were still missing, we had to make explicit assumptions of any methods the included studies used. For example, we assumed that the data were missing at random or we assumed that missing values had a particular value, such as a poor outcome.

Assessment of heterogeneity

Because of substantial clinical heterogeneity, we did not perform a meta-analysis, but commented on results per study.

We would have assessed statistical heterogeneity of treatment effects between trials using a Chi^2 test with a significance level at $P < 0.1$. We would have used the I^2 statistic (Higgins 2003) and visual examination, to assess possible heterogeneity (I^2 statistic > 30% to signify moderate heterogeneity, I^2 statistic > 75% to signify considerable heterogeneity; Deeks 2020). If heterogeneity had been above 80%, we planned to explore potential causes through sensitivity and subgroup analyses.

Assessment of reporting biases

As mentioned above, we searched trials registries to identify completed trials that have not been published elsewhere, to minimise or determine publication bias.

We had planned to explore potential publication bias by generating a funnel plot and statistically testing this by conducting a linear regression test for meta-analyses involving at least 10 trials (Sterne 2019). We would have considered $P < 0.1$ as significant for this test.

Data synthesis

If the clinical and methodological characteristics of individual studies were sufficiently homogeneous, we would have pooled the data in meta-analysis. We would have performed analyses according to the recommendations of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2020). We would have analysed trials including different severities of disease separately, grouping them into mild, and moderate to severely ill, as these are different populations in different settings, resulting in differing outcomes (see Types of outcome measures). We had planned to treat placebo and no treatment as the same intervention, as well as standard of care at different institutions and time points.

We used the Review Manager Web (RevMan Web) software for analyses (RevMan Web 2019). One review author entered the data into the software, and a second review author checked the data for accuracy. We used the random-effects model for all analyses as we anticipated that true effects are related, but are not the same for included studies. Because we could not perform a meta-analysis, we commented on the results, with the results presented per study.

For binary outcomes, we would have based the estimation of the between-study variance using the Mantel-Haenszel method. We would have used the inverse variance method for continuous outcomes, outcomes that included data from cluster-RCTs, or outcomes where HRs were available. We would have explored heterogeneity above 80% with sensitivity analyses. If we could not find a cause for the heterogeneity, we had planned to not perform a meta-analysis, but to comment on the results as a narrative with the results from all studies presented in tables.

Subgroup analysis and investigation of heterogeneity

To explore heterogeneity, we performed subgroup analyses of the following characteristics for our prioritised outcomes.

- Vitamin D status at baseline: sufficiency being defined as 25(OH)D levels ≥20 ng/mL (equals 50 nmol/L), 25(OH)D deficiency <20 ng/mL and severe 25(OH)D deficiency <12ng/mL (equals 30nmol/L) (Amrein 2020; Holick 2011)

We used the tests for interaction to test for differences between subgroup results.

We had planned to perform additional subgroup analyses of the following characteristics.

- Age of participants (divided into applicable age groups, e.g. children; 18 to 65 years, 65 years and older)
- Pre-existing conditions (diabetes, respiratory disease, hypertension, immunosuppression)
- Severity of the disease (moderate (WHO 4-5) vs. severe disease (WHO 6-9), according to WHO clinical progression scale (WHO 2020c); if meaningful further divided into moderate disease without oxygen support (WHO = 4) versus moderate disease with low-flow oxygen (WHO = 5) versus severe disease with high-flow oxygen or non-invasive mechanical ventilation (WHO = 6) versus severe disease with invasive mechanical ventilation (WHO 7-9))
- Duration since symptom onset
- Formulation of vitamin D (active or non-active forms)
- Doses of vitamin D (single or multiple doses)
- Administration of vitamin D (oral or intravenous)
- Co-treatments (e.g. steroids used as co-treatment in up to 20% of participants vs. used in at least 80% of participants)

Sensitivity analysis

We had planned to perform sensitivity analysis of the following characteristics for our prioritised outcomes.

- 'Risk of bias' assessment components (studies with a low risk of bias or some concerns versus studies with a high risk of bias)
- Comparison of preprints of COVID-19 interventions versus peer-reviewed articles
- Comparison of premature termination of studies with completed studies

Summary of findings and assessment of the certainty of the evidence

We created one 'Summary of findings' table and evaluated the certainty of the evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach for interventions evaluated in RCTs.

Summary of findings

We used the MAGICapp software to create the 'Summary of findings' table (MAGICapp). For time-to-event outcomes, we planned to calculate absolute effects at specific time points, as recommended in the GRADE guidance 27 (Skoetz 2020).

According to Chapter 14 of the updated *Cochrane Handbook for Systematic Reviews of Interventions*, the "most critical and/or important health outcomes, both desirable and undesirable, limited to seven or fewer outcomes" should be included in the 'Summary of findings' table(s) (Schünemann 2020). We included outcomes prioritised according to the following Core Outcome Set for intervention studies (COMET 2020), and patient-relevance.

Hospitalised individuals with a confirmed diagnosis of COVID-19 and moderate to severe disease

- All-cause mortality; *all-cause mortality at hospital discharge most favourable; if not reported all-cause mortality day 60, followed by day 28, or time-to-event estimate will be included in SoF table*
- Improvement of clinical status, assessed with liberation from supplemental oxygen support or invasive mechanical ventilation, in accordance with WHO Clinical Progression Scale (WHO 2020e) at longest follow-up available
  - For all hospitalised individuals with oxygen support (WHO ≥5 at baseline on the WHO Clinical Progression Scale (WHO 2020e)): *Liberation from supplemental oxygen in surviving patients most favourable, if not reported duration to liberation from supplemental oxygen will be included in SoF*
  - For subgroup of severely ill individuals (WHO ≥ 7 at baseline on the WHO Clinical Progression Scale (WHO 2020e)): *Liberation from invasive mechanical ventilation in surviving patients most favourable, if not reported ventilator-free days, followed by duration to liberation from invasive mechanical ventilation will be included in SoF*
- Worsening of clinical status assessed by need for invasive mechanical ventilation i.e. WHO 7-9 (if ≤ 6 at baseline) on the WHO Clinical Progression Scale (WHO 2020e) at longest follow-up available
- Quality of life, including fatigue and functional independence; assessed with standardised scales (e.g. WHOQOL-100) at longest follow-up available
- Adverse events
- Serious adverse events

Ambulatory managed individuals with a confirmed diagnosis of SARS-CoV-2 infection and asymptomatic or mild disease

- All-cause mortality; *all-cause mortality at longest follow-up and > 60 days most favourable; if not reported all-cause mortality day 60, followed by day 28, or time-to-event estimate, will be included in SoF table*
- Development of severe clinical COVID-19 symptoms, defined as WHO Clinical Progression Scale ≥ 6 (WHO 2020e) at longest follow-up available

- Quality of life, including fatigue and functional independence; assessed with standardised scales (e.g. WHOQOL-100) at longest follow-up available
- Adverse events
- Serious adverse events

Assessment of the certainty in the evidence

We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to assess the certainty in the evidence for the outcomes listed in the previous section.

The GRADE approach uses five domains (risk of bias, consistency of effect, imprecision, indirectness and publication bias) to assess the certainty in the body of evidence for each prioritised outcome.

We downgraded our certainty of evidence for:

- serious (-1) or very serious (- 2) risk of bias;
- serious (-1) or very serious (- 2) inconsistency;
- serious (-1) or very serious (- 2) uncertainty about directness;
- serious (-1) or very serious (- 2) imprecise or sparse data;
- serious (-1) or very serious (- 2) probability of reporting bias.

The GRADE system used the following criteria for assigning grade of evidence.

- High: we are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different.
- Low: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
- Very low: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

We followed the current GRADE guidance for these assessments in its entirety as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions*, Chapter 14 (Schünemann 2020).

We used the overall 'Risk of bias' judgement, derived from the RoB 2 Excel tool, to inform our decision on downgrading for risk of bias. We phrased the findings and certainty in the evidence as suggested in the informative statement guidance (Santesso 2020).

Methods for future updates

Living systematic review considerations

Our information specialist (MIM) will provide us with new search records each week, which two review authors will screen, extract, evaluate, and integrate following the guidance for Cochrane living systematic reviews (Cochrane LSR).

We will manually check platform trials that were previously identified and listed as 'studies awaiting classification' for additional treatment arms.

We will wait until the accumulating evidence changes our conclusions of the implications of research and practice before republishing the review. We will consider one or more of the following components to inform this decision.

- The findings of one or more prioritised outcomes.
- The credibility (e.g. GRADE rating) of one or more prioritised outcomes.
- New settings, populations, interventions, comparisons or outcomes studied.

In case of emerging policy relevance because of global controversies around the intervention, we will consider republishing an updated review even though our conclusions remain unchanged. We will review the review scope and methods approximately monthly, or more frequently if appropriate, in light of potential changes in COVID-19 research (for example, when additional comparisons, interventions, subgroups or outcomes, or new review methods become available).

RESULTS

Description of studies

Results of the search

The literature search resulted in 245 records. One record was additionally identified via handsearching reference lists, resulting in overall 246 records. After removing duplicates, 244 records remained and were screened based on their titles and abstracts. 189 records did not meet the prespecified inclusion criteria and were excluded. We screened the full texts, or, if these were not available, the trial register entries, of the remaining 56 references. 20 records were excluded after full-text assessment. Thirteen studies investigated a combined treatment including vitamin D, five studies investigated preventive effects, and two studies were no RCTs. We identified 24 ongoing records (21 studies) and three studies awaiting assessment. Finally, we included seven records (three studies) in our narrative synthesis. The search process is visualised in Figure 2 (Moher 2009).

Figure 2.

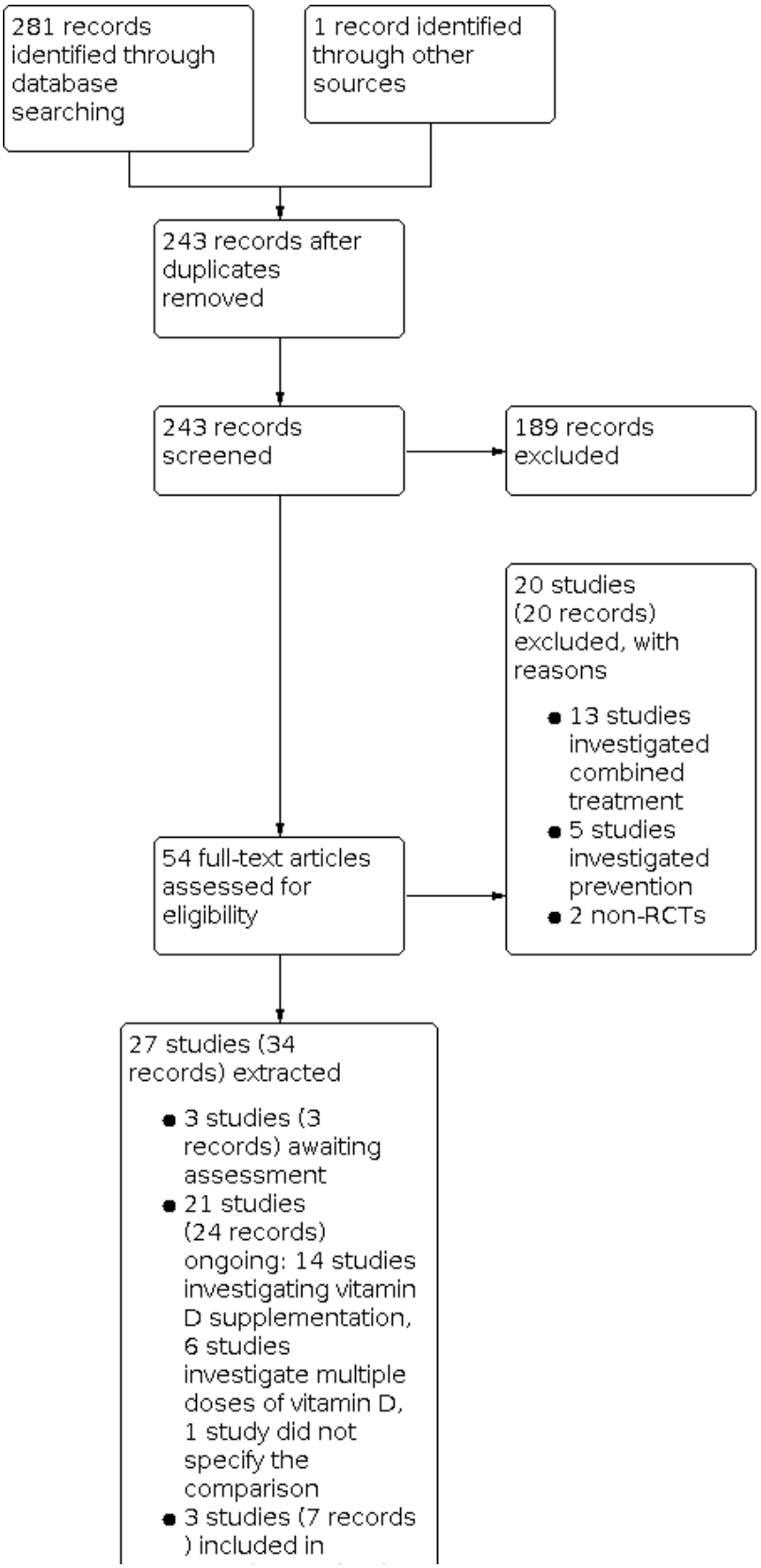
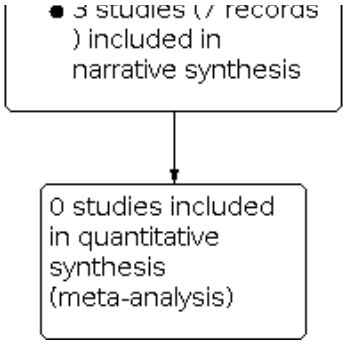


Figure 2. (Continued)



Included studies

Designs of the studies and involved study-centres

We included three randomised controlled trials (RCTs) describing 356 adult participants (Entrenas Castillo 2020; Murai 2021; Rastogi 2020). One of the studies (Entrenas Castillo 2020) had an open-label design; the other two studies (Murai 2021; Rastogi 2020) were double-blinded and placebo-controlled. Murai 2021 performed a multicentre study in two sites in Brazil. The other two studies (Entrenas Castillo 2020; Rastogi 2020) were performed each in one centre, in Spain (Entrenas Castillo 2020) and in India (Rastogi 2020).

Participants

Two of the three studies were conducted with hospitalised participants with COVID-19 (Entrenas Castillo 2020; Murai 2021). In Entrenas Castillo 2020, all participants had both a polymerase chain reaction (PCR)-confirmed diagnosis of COVID-19, and radiological signs of pneumonia. At least one of these criteria (PCR or radiological signs) was necessary for inclusion in the study in Murai 2021 and 61.2% of participants had a positive PCR-result for COVID-19. Rastogi 2020 investigated outpatients with mild or asymptomatic disease, and all randomised participants were positive for COVID-19. The other studies (Entrenas Castillo 2020; Murai 2021) included participants with clinical signs of an acute respiratory infection with moderate to severe illness. In Entrenas Castillo 2020, all participants had a Confusion-Respiratory rate-Blood pressure (CRB)-65-score > 1, independently of the components of the score. There were no details on oxygen supplementation and the only detail regarding the extent of respiratory insufficiency is the mean of partial pressure of oxygen/fraction of inspired oxygen (PaO_2/FiO_2) ratio at baseline. However, the participants did not need intensive care unit (ICU) treatment at baseline. In Murai 2021, all participants had moderate or severe COVID-19 as defined by respiratory rate greater than 24/min, saturation less than 93% while breathing room air or risk factors for complications. The vast majority of participants in this study needed oxygen supplementation (71.7% of patients in the intervention arm versus 80.8% of patients in the control arm), while non-invasive ventilation was necessary in 15% and 11.7% of participants in each group. Participants requiring invasive ventilation before randomisation were excluded.

In Rastogi 2020, the participants were slightly younger than in the other two studies (between 36 and 51 years in the intervention arm and 39 and 49 years in the control arm), while in Entrenas Castillo 2020 and Murai 2021, the approximate mean age of participants was 53.14 +/- 10.77 years (intervention group) and 52.77 +/- 9.35 years (control group) or 56.8 +/- 14.2 years (intervention group) and 55.8 +/- 15.0 years (control group), respectively. In Entrenas Castillo 2020, the risk factors arterial hypertension and diabetes mellitus were less common in the intervention group (in the case of arterial hypertension this difference was statistically significant), while these risk factors were balanced between intervention and control group in Murai 2021. Comparing these two studies, diabetes mellitus and arterial hypertension were more frequent in Murai 2021 than in Entrenas Castillo 2020, in particular in the intervention arm (diabetes mellitus 40.8% versus 6% and arterial hypertension 56.7% versus 24.19%, respectively). In Murai 2021, more participants in both study arms had cardiovascular disease compared with those in Entrenas Castillo 2020 (13%versus 4%, respectively). Body mass index (BMI) and percentage of participants with obesity were reported only in Murai 2021. Rastogi 2020 did not report details on comorbidities of participants.

Only one study (Murai 2021) provided information on mean 25-hydroxyvitamin D level at baseline as well as rough information on previous vitamin D supplementation, since supplementation > 1000 IU/day was one of the exclusion criteria. In Rastogi 2020, all participants randomised had 25(OH)Vitamin D_3 level <= 20 ng/mL.

Interventions and comparators

Participants in the intervention arm of Entrenas Castillo 2020 received calcifediol (25(OH)Vitamin D_3) at day 1 (0.532 mg) and continued with 0.266 mg on days 3 and 7, and then weekly until discharge or ICU admission. In Murai 2021 and Rastogi 2020, participants in the intervention arm received cholecalciferol (vitamin D_3) as a single, oral dose of 200, 000 IU (Murai 2021) or in multiple, daily doses of 60, 000 IU over seven days (Rastogi 2020). Rastogi 2020 continued daily supplementation until day 14, if 25-hydroxyvitamin D levels at day 7 achieved < 50 ng/mL. If 25-hydroxyvitamin D levels at day 7 achieved > 50 ng/mL, participants continued with weekly supplementation of 60, 000 IU. Murai 2021 and Rastogi 2020 were placebo-controlled. In Murai 2021, participants in the control arm received a single, oral dose of placebo (a peanut oil solution). In Rastogi 2020, participants received 5 mL distilled water as placebo up to day 7.

In Entrenas Castillo 2020, all participants received "best available therapy", which consisted of a combination of hydroxychloroquine (400 mg every 12 h on the first day, and 200 mg every 12 h for the following 5 days), azithromycin (500 mg orally for 5 days)

and for participants with pneumonia and National Early Warning Score (NEWS) ≥ 5, a broad-spectrum antibiotic (ceftriaxone 2 g intravenously every 24 h for 5 days). Standard care therapy was not prespecified in Murai 2021 and Rastogi 2020. However, in the study by Murai 2021 the majority of participants in both intervention and control arm received a concomitant corticosteroid therapy (64.7% vs. 61.9%, respectively).

Outcome measures

Primary outcomes were different in all three studies, including rate of ICU admissions and 28-day mortality (Entrenas Castillo 2020), length of hospital stay (Murai 2021) and viral clearance before week three (Rastogi 2020). Overall mortality and rate of ICU admissions were secondary outcomes in Murai 2021. Other secondary outcomes in this study were number of participants requiring mechanical ventilation, as well as duration of mechanical ventilation and 25-hydroxyvitamin D levels, calcium, creatinine, C-reactive protein (CRP) and D-dimer. Other outcomes, like differences in length of hospital stay, mortality, admission to ICU, mechanical ventilation requirement and duration, were reported in post-hoc analysis for subgroups with and without vitamin D deficiency. The change of vitamin D serum levels and inflammatory markers (procalcitonin, CRP, fibrinogen, D-dimer) were secondary outcomes in Rastogi 2020.

Ongoing studies

Of the 21 ongoing studies, 14 RCTs are comparing the effects of vitamin D supplementation with either placebo or no intervention, (CTRI/2020/12/030083; EUCTR2020-001717-20-ES; EUCTR2020-001960-28-ES; NCT04334005; NCT04363840; NCT04386850; NCT04411446; NCT04489628; NCT04502667; NCT04536298; NCT04552951; NCT04621058; NCT04636086; NCT04641195).

Of these, three studies were expected to be completed in 2020 and planned to evaluate between 30 and 1080 participants, but according to the trial registry, two are not yet recruiting (NCT04334005; NCT04363840) and one is still recruiting (NCT04552951). Six studies are expected to be completed in 2021, and plan to evaluate between 40 and 2700 participants (CTRI/2020/12/030083; NCT04411446; NCT04489628; NCT04502667; NCT04536298; NCT04621058) and two studies were scheduled to be completed by the time of writing and planned to evaluate between 100 and 1500 participants (NCT04386850; NCT04636086). One study is expected to be completed in 2022, and plans to evaluate 700 participants (NCT04641195). Two studies are not indicating an expected completion date, and plan to evaluate 108 and 1008 participants (EUCTR2020-001717-20-ES; EUCTR2020-001960-28-ES).

Six of the 21 ongoing studies investigate different doses of vitamin D supplementation, of which all are RCTs (CTRI/2020/06/026189; EUCTRCT2020-002312-43-ES; NCT04344041; NCT04385940; NCT04482673; NCT04525820 and plan to evaluate between 64 and 210 participants. Of these, one RCT was expected to be completed in 2020, but according to the trial registry, is not yet recruiting (NCT04385940), two RCTs are expected to be completed in 2021 (NCT04482673; NCT04525820), one RCT is expected to be completed in 2022 (CTRI/2020/06/026189), and one RCT is not indicating any completion date (EUCTRCT2020-002312-43-ES). Further, one RCT (NCT04344041) has two different trial registrations, one in ClinicalTrials.gov and one in the EU Clinical Trial Registry. In the first registry, the study is expected to be completed in 2021 and in the second registry, the study is indicated to be completed already, but no results are available yet.

One of the ongoing studies is an RCT, but it is unclear what comparison the study performs with vitamin D (EUCTR2020-002274-28-ES).

Studies awaiting classification

We identified three completed RCTs from trial register entries, but no results are available or have been published yet. Of these, one RCT investigates different doses of vitamin D supplementation (IRCT20110726007117N11), whereas the other two RCTs investigate vitamin D treatment versus placebo (IRCT20200324046850N1; NCT04733625).

Excluded studies

We excluded 20 references (20 studies) that did not match our inclusion criteria.

- Five studies investigated the effect of Vitamin D on prevention: NCT04535791; NCT04579640; NCT04476680; NCT04483635; NCT04596657.
- 13 studies evaluated a combination of vitamin D with other treatments: NCT04507867; IRCT20200319046819N1; NCT04565392; Euctr2020-001903-17; NCT04399746; IRCT20200705048013N1; NCT04395768; Euctr2020-001363-85-dk; NCT04482686; CTRI/2020/06/026191; IRCT20200319046819N1; NCT04780061; NCT04351490.
- Two studies were non-RCTs. Nogues 2021 investigated the potential role of vitamin on mortality and intensive care treatment in hospitalised patients, but we had serious concerns about adequacy of the randomisation procedure, as participants were randomised to hospitals and not to treatments. the other study was a single-arm trial (NCT04407286).

Risk of bias in included studies

Risk of bias in randomised controlled trials

We assessed methodological quality and risk of bias for two RCTs (Entrenas Castillo 2020; Murai 2021) using RoB 2 tool to analyse the risk of bias of our prioritised outcomes (Sterne 2019), recommended in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions (* Higgins 2020c). We did not judge risk of bias for Rastogi 2020, as they reported none of our prioritised outcomes. The completed RoB 2 tool with responses to all assessed signalling questions is available online at https://zenodo.org/record/4771734#.YKTEFKj7Ryw (Stroehlein 2021b).

Overall judgement for studies including individuals with a confirmed diagnosis of COVID-19 and moderate to severe disease

Overall, we rated the risk of bias, among those studies having reported a mortality outcome, to be of some concerns in Entrenas Castillo 2020 and to be low in Murai 2021. For the reported outcome worsening of clinical status, we judged the risk of bias to be low for Murai 2021.

All-cause mortality

We assessed this outcome on a study level at day 28, day 60, time-to-event, and at hospital discharge. For Entrenas Castillo 2020, there were some concerns arising form the randomisation process, as the randomisation list was accessible to "study specialists" and some concerns for bias arising from the selection of reported mortality results. The definition of mortality differed between the trial registry and the journal publication, making it unclear how long participants were followed and how the outcome was defined at protocol stage. For Murai 2021, we did not identify any concerns for the mortality outcome, and judged the risk of bias to be low (Risk of bias for analysis 1.1 All-cause mortality).

Clinical status

We assessed this outcome on a study level, by the need for respiratory support in accordance with standardised scales (WHO 2020e), and included both clinical improvement and clinical worsening in our assessment.

Improvement of clinical status

We could not assess the risk of bias for this outcome, because none of the studies reported measures of improvement.

Worsening of clinical status: assessed with need for invasive mechanical ventilation

The outcome was only reported in one study (Murai 2021). We did not identify any concerns that could have biased the reported outcome, and therefore judged the risk of bias to be low (Risk of bias for analysis 1.2 Worsening of clinical status: need for mechanical ventilation).

Quality of life

We could not assess the risk of bias for this outcome, because none of the studies reported quality of life.

Serious adverse events

We could not assess the risk of bias for this outcome, because none of the studies reported serious adverse events.

Adverse events (any grade)

Adverse events of any grade were reported in one study Murai 2021. We had concerns about selection bias due to insufficient information about recording and reporting of adverse events, and judged risk of bias with some concerns (Risk of bias for analysis 1.6 Adverse events (any grade)).

Overall judgement for studies including individuals with a confirmed diagnosis of COVID-19 and asymptomatic or mild disease

Overall, the one study (Rastogi 2020) including individuals with asymptomatic and mild disease did not report our prioritised outcomes, and thus risk of bias could not be formally assessed for this study using RoB 2.0.

Effects of interventions

See: **Summary of findings 1** Summary of Findings Table - Vitamin D compared to placebo or standard care alone for individuals with moderate to severe disease

We identified three studies and included them in this review (Entrenas Castillo 2020; Murai 2021; Rastogi 2020). We requested disease status of participants in Rastogi 2020. Based on their reply, we included the study for our population with a confirmed diagnosis of COVID-19 and asymptomatic or mild disease. We also investigated additional outcomes for effectiveness of vitamin D supplementation which were not included in the summary of findings table.

Individuals with a confirmed diagnosis of COVID-19 and moderate to severe disease

The evidence profile for vitamin D supplementation for individuals with a confirmed diagnosis of COVID-19 and moderate to severe disease is presented in Summary of findings table 1. Two studies were included (Entrenas Castillo 2020; Murai 2021).

Effectiveness of vitamin D supplementation

All-cause mortality

Both studies reported data for mortality at hospital discharge for 313 participants (Entrenas Castillo 2020; Murai 2021). Entrenas Castillo 2020 reported that none of the 50 participants treated with vitamin D died, compared to two of 26 participants in the control group (risk ratio (RR) 0.11, 95% confidence interval (CI) 0.01 to 2.13). Murai 2021 reported nine deaths out of 119 individuals treated with vitamin D, and six deaths out of 118 participants in the placebo group (RR 1.49, 95% CI 0.55 to 4.05). The evidence is very uncertain whether vitamin D supplementation has an effect on all-cause mortality at hospital discharge (very low-certainty evidence, see Analysis 1.1).

Our main reasons for downgrading were serious study limitations due to unclear risk of bias in Entrenas Castillo 2020, very serious inconsistency due to inconsistent directions of point estimates, as well as due to very serious imprecision because of wide confidence intervals along with a low number of participants and events.

We did not find any data for mortality up to day 28, day 60 or time-to-event.

Subgroup analysis

As we are comparing two studies with substantial clinical and methodological diversity, subgroup analyses regarding dose, administration, formulation and other subgroups will rather reflect effects of these differences. Therefore, we conducted subgroup analysis for vitamin D status only, but not for other subgroups. Vitamin D status at baseline was unknown for participants in Entrenas Castillo 2020 and we therefore did not include the study for subgroup analyses.

Murai 2021 reported data for 115 participants with vitamin D deficiency at baseline. We did not find evidence for subgroup differences between vitamin D deficient and non-deficient individuals for all-cause mortality at hospital discharge (see Analysis 2.1).

Clinical Status (assessed by need for respiratory support with standardised scales)

We did not find data for outcomes for improvement of clinical status (weaning or liberation from invasive mechanical ventilation in surviving patients, ventilator-free days, duration to liberation from invasive mechanical ventilation, liberation from

supplemental oxygen in surviving patients, duration to liberation from supplemental oxygen).

One study reported data for worsening of clinical status for 237 participants, measured as need for mechanical invasive ventilation (Murai 2021). Nine out of 119 participants treated with vitamin D needed invasive mechanical ventilation compared to 17 out of 118 participants in the control group (RR 0.52, 95% CI 0.24, 1.13). Vitamin D supplementation may decrease need for invasive mechanical ventilation, but the evidence is uncertain (low-certainty evidence, see Analysis 1.2). We graded down due to very serious imprecision because of the low number of participants and events as well as because of data from only one study.

We did not find any data for other outcomes regarding worsening of clinical status (need for non-invasive mechanical ventilation or high flow, need for oxygen by mask or nasal prongs).

Subgroup analysis

115 participants with vitamin D deficiency at baseline were included (Murai 2021). We did not find evidence for subgroup differences between vitamin D deficient and non-deficient individuals for invasive mechanical ventilation (see Analysis 2.2), and confidence intervals were overlapping.

Need for dialysis (at up to 28 days)

We did not find any data for this outcome.

Quality of life (including fatigue and neurological status)

We did not find any data for this outcome (at up to seven days, up to 30 days, longest follow-up available).

Additional outcomes for effectiveness of vitamin D supplementation (not included in summary of findings table)

Admission to intensive care unit (ICU)

Both studies reported the outcome for 313 participants (Entrenas Castillo 2020; Murai 2021). Entrenas Castillo 2020 reported one participant out of 50 treated with vitamin D that was referred to ICU, compared to 13 out of 26 participants in the control group (RR 0.04, 95% CI 0.01 to 0.29). 19 out of 119 participants in the vitamin D group were referred to ICU, and 25 out of 118 in the control group in Murai 2021 (RR 0.75, 95% CI 0.44 to 1.29), see Analysis 1.5].

Subgroup analysis

Murai 2021 reported data for 115 participants with vitamin D deficiency. We did not find evidence for subgroup differences between vitamin D deficient and non-deficient individuals for admission to ICU (see Analysis 2.3).

Duration of hospitalisation

One study reported data for this outcome for 237 participants (Murai 2021). The median duration of hospitalisation was 7 (interquartile range (IQR) 4-10) days in the vitamin D group and 7 (IQR 5-13) days in the control group (Hazard ratio (HR) 1.07, 95% CI 0.81 to 1.41), see Analysis 1.3].

Viral clearance (assessed with RT-PCR test for SARS-CoV-2)

We did not find any data for this outcome (at baseline, up to 3, 7, and 15 days).

Vitamin D serum levels

Only Murai 2021 reported data for this outcome for 237 participants. 25-hydroxyvitamin D levels increased in individuals treated with vitamin D (119 participants, baseline: 21.2 (standard deviation (SD) 10.1) ng/mL to 44.4 (SD 15) ng/mL), but not in the placebo group (118 participants, baseline: 20.6 (SD 8.1) ng/mL to 19.8 (SD 10.5) ng/mL [mean difference after intervention 24.70 ng/mL (95% CI 21.41 to 27.99), see Analysis 1.4].

Safety of vitamin D supplementation

Serious adverse events

The authors reported that no serious adverse events were observed throughout the trial. There was insufficient information provided to assess whether serious adverse reactions have been assessed in a consistent manner for all participants.

Adverse events (any grade, grade 1-2, grade 3-4)

One study reported adverse events (any grade) for 237 participants. One out of 119 participants treated with vitamin D had an adverse event (vomiting) compared to none participant out of 118 control group (RR 2.98, 95% CI 0.12 to 72.30). We are very uncertain whether vitamin D supplementation is associated with a higher risk of adverse events (very low-certainty evidence, see Analysis 1.6). We graded down due to very serious imprecision because of the low number of participants and events, data from only one study as well as due to serious indirectness, as outcome definition did not match our definition.

Individuals with a confirmed diagnosis of COVID-19 and asymptomatic or mild disease

Rastogi 2020 investigated individuals with a confirmed diagnosis of COVID-19 and asymptomatic or mild disease. However, we could not find any data for our prioritised outcomes. Instead, authors reported data for viral clearance, vitamin D serum levels and inflammatory markers.

Effectiveness of vitamin D supplementation

All-cause mortality

We could not find any data for mortality at day 28, at day 60, time-to-event, and up to longest follow-up.

Admission to hospital (WHO ≥ 4)

We could not find any data for this outcome.

Development of moderate to severe clinical COVID-19 symptoms

We did not find data for need for invasive mechanical ventilation, need for non-invasive mechanical ventilation or high flow, need for hospitalisation, with or without supplemental oxygen (need for oxygen by mask or nasal prongs, need for hospitalisation without oxygen therapy).

Quality of life (including fatigue and neurological status)

We could not find any data for this outcome (at up to seven days, 30 days, and longest follow-up available).

Additional outcomes for effectiveness of vitamin D supplementation (not included in summary of findings table)

Duration of hospitalisation (for subgroup of participants hospitalised during course of disease)

We could not find any data for this outcome.

Time to hospital discharge (for subgroup of participants hospitalised during course of disease)

We could not find any data for this outcome.

Vitamin D serum levels

The outcome was reported in Rastogi 2020 for 40 individuals with vitamin D deficiency at baseline (defined as < 20 ng/mL). Baseline 25-hydroxyvitamin D levels were comparable between groups [median 8.6 (IQR 7.1-13.2) for vitamin D group and 9.54 (IQR 8.1-12.5) for placebo group]. 25-hydroxyvitamin D levels increased in individuals treated with vitamin D (16 participants, median increase 42.4 (IQR 39 to 48.8) ng/mL), but not in the placebo group (24 participants, median increase of 5.1 (IQR 0-12.3) ng/mL). The median 25-hydroxyvitamin D levels at day 14 were 51.7 (IQR 48.9-59.9) ng/mL in the vitamin D group and 15.2 (IQR 12.7-19.5) ng/mL in the placebo group.

Safety of vitamin D supplementation

Serious adverse events

We did not find data for this outcome.

Adverse events (any grade, grade 1-2, grade 3-4)

Rastogi 2020 reported that no events of hypercalcaemia were observed during the intervention in both groups. Information about other adverse events was missing. We did not include data of this study for this outcome as we found only insufficient information provided to assess whether adverse reactions have been assessed in a consistent manner for all participants.

DISCUSSION

Summary of main results

The aim of this review was to investigate the effectiveness and safety of vitamin D supplementation in individuals with confirmed COVID-19 and moderate to severe disease or asymptomatic to mild disease. We identified three randomised controlled trials (RCTs) (Entrenas Castillo 2020; Murai 2021; Rastogi 2020, n = 356), of which two reported all-cause mortality (Entrenas Castillo 2020; Murai 2021, n = 313), and one reported the need for invasive mechanical ventilation and adverse events (Murai 2021, n = 237) in individuals with COVID-19 and moderate to severe disease. We could not find data for any other of our prioritised outcomes. We found one RCT with participants with confirmed COVID-19 and asymptomatic or mild disease (Rastogi 2020), which did not report data for our prioritised outcomes.

We identified a further 21 ongoing studies evaluating the effectiveness and safety of vitamin D supplementation and three completed studies, but without any results published yet that are awaiting classification.

Risk of bias

We judged risk of bias with some concerns for Entrenas Castillo 2020, and as low for Murai 2021 for mortality outcomes. Moreover, we judged risk of bias for outcomes regarding worsening of clinical status (need for invasive mechanical ventilation) as low-certainty evidence for one study (Murai 2021). We were not able to conduct bias assessment for Rastogi 2020, as the authors did not report our prioritised outcomes.

Effectiveness of vitamin D supplementation for hospitalised individuals with a confirmed diagnosis of COVID-19 and moderate to severe disease

We identified two RCTs that evaluated effectiveness of vitamin D supplementation in hospitalised individuals with confirmed COVID-19 and moderate to severe disease. Due to substantial clinical and methodological diversity between Entrenas Castillo 2020 and Murai 2021, we were unable to calculate pooled effect estimates. Therefore, results are presented individually for each study.

All-cause mortality

Both included studies evaluated all-cause mortality at hospital discharge. We are very uncertain whether vitamin D supplementation has an effect on this outcome.

Subgroup analysis

Murai 2021 reported data for 115 participants with vitamin D deficiency at baseline. We did not find evidence for subgroup differences for all-cause mortality at hospital discharge

Clinical status

We did not find data for improvement of clinical status.

Murai 2021 reported data for worsening of clinical status (outcome need for invasive mechanical ventilation) for 237 participants. Vitamin D supplementation may decrease need for invasive mechanical ventilation, but the evidence is uncertain.

Subgroup analysis

Murai 2021 reported data for 115 participants with vitamin D deficiency at baseline. We did not find evidence for subgroup differences for invasive mechanical ventilation.

Quality of life (including fatigue and neurological status)

We could not find data for this outcome.

Safety of vitamin D supplementation for hospitalised individuals with a confirmed diagnosis of COVID-19 and moderate to severe disease

We did not include data because insufficient information provided in Murai 2021 about evaluation and assessment of serious adverse events. Murai 2021 reported one adverse event (any grade) for 237 participants. We are very uncertain whether vitamin D supplementation is associated with a higher risk of adverse events.

Effectiveness of vitamin D supplementation for individuals with a confirmed diagnosis of COVID-19 and asymptomatic or mild disease

We identified one RCT which investigated outpatients with COVID-19 and asymptomatic or mild disease (Rastogi 2020). However, we did not find data for our prioritised outcomes (all-cause mortality, development of severe clinical COVID-19 symptoms, quality of life).

Safety of vitamin D supplementation for individuals with a confirmed diagnosis of COVID-19 and asymptomatic or mild disease

We did not include data for safety outcomes due to insufficient information provided in Rastogi 2020 about evaluation and assessment of adverse events or serious adverse events. We did not identify other RCTs that reported these outcomes (serious adverse events, adverse events).

Overall completeness and applicability of evidence

We identified three RCTs with 356 participants, either with hospitalised participants with moderate to severe disease (Entrenas Castillo 2020; Murai 2021), or with ambulatory-managed individuals with mild or asymptomatic disease (Rastogi 2020).

Hospitalised participants with moderate to severe disease

Two studies investigated vitamin D supplementation in 316 hospitalised participants with moderate or severe COVID-19 (Entrenas Castillo 2020; Murai 2021), of whom 170 received vitamin D supplementation.

Most of the hospitalised participants with moderate or severe disease received concomitant medication, either solely or in combination. These included corticosteroids, hydroxychloroquine, and antibiotics, as azithromycin. Moreover, most participants received respiratory support (i.e. oxygen therapy or noninvasive ventilation).

In both studies, some relevant confounding factors, like age, gender, severity of disease, and co-morbidities, were considered by authors in the analyses. Entrenas Castillo 2020 reported that more participants in the placebo control group had diabetes and hypertension, which are risk factors for developing severe disease. This may have confounded the results of the study.

Murai 2021 reported baseline 25-hydroxyvitamin D levels for all participants, as well as baseline demographics and clinical characteristics from participants with vitamin D deficiency. Post hoc analysis revealed that patients with vitamin D deficiency and no treatment had the best clinical outcome questioning the applicability of these study results. Entrenas Castillo 2020 did not report vitamin D status of participants. In addition, Murai 2021 also excluded participants who had received previous vitamin D supplementation (> 1000 international units (IU)/day), which was not reported in Entrenas Castillo 2020.

Outpatients with mild or asymptomatic disease

Rastogi 2020 reported data for 40 outpatients with COVID-19 and mild or asymptomatic disease, of whom 16 were treated with vitamin D, but not for our prioritised outcomes. Moreover, only participants with vitamin D deficiency (defined as < 20 ng/mL) were included in the study. Despite age and gender, authors did not report important prognostic factors of COVID-19 (e.g. co-morbidities, obesity) of participants at baseline, thus comparability of both groups remains uncertain. Despite this trial with a small number of participants, no other studies were identified.

Ongoing studies

We identified 21 ongoing studies investigating either effectiveness of vitamin D supplementation versus placebo or no treatment, or different doses of vitamin D (CTRI/2020/06/026189; CTRI/2020/12/030083; EUCTR2020-001717-20-ES; EUCTR2020-001960-28-ES; EUCTRCT2020-002312-43-ES; NCT04334005; NCT04344041; NCT04363840; NCT04385940; NCT04386850; NCT04411446; NCT04482673; NCT04489628; NCT04502667; NCT04525820; NCT04536298; NCT04552951; NCT04621058; NCT04636086; NCT04641195; EUCTR2020-002274-28-ES). Of these, three studies were expected to be completed in 2020, but according to the trial registry, two are not yet recruiting (NCT04334005; NCT04363840), and one is still recruiting (NCT04552951). Six studies are expected to be completed in 2021, and plan to evaluate between 40 and 2700 participants (CTRI/2020/12/030083; NCT04411446; NCT04489628; NCT04502667; NCT04536298; NCT04621058). Two studies were scheduled to be completed by the time of writing and planned to evaluate between 100 and 1500 participants (NCT04386850; NCT04636086).

Three studies are reported to be completed, but no results are available or have been published yet. Of these, one RCT investigates different doses of vitamin D supplementation (IRCT20110726007117N11), whereas the other two RCTs investigate vitamin D treatment versus placebo (NCT04733625; IRCT20200324046850N1).

Currently, there is only low-certainty evidence regarding the effects and safety of vitamin D supplementation. Publication of the identified ongoing RCTs will necessitate an update of this review. The conclusions of the updated review could differ from those of the present review, and may allow for a better judgement regarding the effectiveness and safety of vitamin D supplementation for the treatment of COVID-19.

Quality of the evidence

We assessed two studies for risk of bias (Entrenas Castillo 2020; Murai 2021), as Rastogi 2020 did not report our prioritised outcomes. Risk of bias was in general low for Murai 2021, except for adverse events, which we judged with some concerns due to selective reporting. We had concerns about randomisation in Entrenas Castillo 2020, as the list was accessible to "study specialists". Moreover, we observed differences between regarding outcome definition in the trial registry and the journal article.

Due to substantial clinical and methodological diversity of the studies, we did not conduct meta-analysis. We included data for all-cause mortality (at hospital discharge), worsening of clinical status (need for mechanical ventilation) and adverse events (any grade). All other prioritised outcomes of this review were not reported by trial authors.

In individuals with a confirmed diagnosis of COVID-19 and moderate to severe disease, we graded the certainty of the evidence for all-cause mortality (at hospital discharge) as very low due

to serious risk of bias (1 point, unclear risk of bias because of randomisation process in Entrenas Castillo 2020), due to very serious imprecision (2 points, inconsistent directions and variations of point estimates), and due to very serious inconsistency (2 points, wide confidence intervals along with a low number of participants and events). We graded the certainty of the evidence for worsening of clinical status (need for mechanical ventilation) as low due to very serious imprecision (low number of participants and events). For adverse events (any grade), we graded certainty in the evidence as very low due to serious indirectness and very serious imprecision.

Regarding individuals with a confirmed diagnosis of COVID-19 and asymptomatic or mild disease, we identified one RCT Rastogi 2020, but trial authors did not report any of our prioritised outcomes.

Potential biases in the review process

To avoid potential bias in the review process, we were committed at all times to conduct a systematic review that followed published guidance provided by the *Cochrane Handbook for Systematic Reviews of Interventions (* Higgins 2020d).

Experienced medical information specialists of the CEOsys consortium developed an all-encompassing search strategy to identify available evidence to answer our research question. We aimed at identifying all completed, but also ongoing studies for inclusion in our review. The sensitive search included relevant electronic databases as well as clinical trial registries. As a supplement, we screened reference lists of included studies. In addition to peer-reviewed full-text articles, we also included preprints. We are aware of the potentially lower quality of preprint publications, and that results could change once the peer-reviewed journal publications are available. In cases of missing data, we contacted study authors for additional data or relevant details if we needed more information, details are provided in the 'Characteristics of included studies' tables. We are confident that we identified all relevant studies and will monitor ongoing studies as well as full publication of preprints closely after the publication of this review.

We outlined the study selection process comprehensively and in full detail (Figure 2). Two out of three review authors performed all levels of the selection process (judgement on eligibility, data extraction and judgement on risk of bias) independently and in duplicate; analyses were conducted by one review author and checked by a colleague. We provide reasons for the exclusion of studies from this systematic review and describe each included study in full detail and made explicit judgements on individual risk of bias. We identified no other potential sources of bias in our review process.

Agreements and disagreements with other studies or reviews

We identified (very) lo- certainty evidence for vitamin D supplementation as a treatment for COVID-19, which is similar to findings of the rapid guideline by NICE 2020 published in December 2020. Authors included only one RCT, which we also identified in this review (Entrenas Castillo 2020). Based on this RCT, they reported that people treated with vitamin D are less likely to be admitted to intensive care unit or to die, but certainty in the evidence was very low for both outcomes due to very serious risk of bias and the low number of participants in the study. Author's recommendations for future research were the investigation of vitamin D supplementation in randomised controlled designs, including subgroup analyses with a focus on age (older than 75 years), ethnicity, and co-morbidities (obesity) and with a minimum eight-week follow-up.

Liu 2021 investigated the association of vitamin D status with risk of COVID-19 infection, which was not the scope of this review. However, we identified several systematic reviews and meta-analyses which studied the association of vitamin D levels and prognosis of COVID-19 based mainly on non-randomised trials (Munshi 2021; Pereira 2020; Shah 2021; Yisak 2021). Pereira 2020 included data for 8176 individuals with COVID-19 and suggests a positive association of vitamin D deficiency (25-hydroxyvitamin D levels < 50 nmol/L) and COVID-19 severity. Additionally, authors reported that participants with vitamin D levels < 75 nmol/L had a higher likelihood for hospitalisation and mortality (Pereira 2020). Similar results were found by Munshi 2021, who investigated prognosis of COVID-19 in 1368 individuals. In this study, a poor prognosis was associated with lower vitamin D levels and vice versa. Yisak 2021 and colleagues included nine studies and reported an association between vitamin D deficiency (not defined) and hospitalisation, admission to intensive care unit (ICU) and severity of COVID-19. Shah 2021 included data from 532 hospitalised participants based on two RCTs and one retrospective study. They reported a significant effect on admission to ICU, and a comparable risk for mortality.

Authors of all relevant reviews reported significant heterogeneity and high risk of bias for included studies, and results should therefore be interpreted with caution. Despite Shah 2021, who included two RCTs, none of these reviews or studies were able to show causality of findings because of the design of the included studies. For example, retrospective and cross-sectional analyses (Pereira 2020; Munshi 2021; Yisak 2021) do not provide information whether vitamin D deficiency was present before diagnosis of COVID-19 or if it was rather a consequence of the disease. In addition, risk factors for severe COVID-19, such as older age, obesity, hypertension, diabetes mellitus and others, often overlap with risk factors for vitamin D deficiency. This exacerbates interpretation and the assumption of causality.

We further identified a non-randomised controlled study with 930 participants (Nogues 2021), suggesting that vitamin D supplementation decreases mortality and admission to ICU. However, the study was removed from the preprint server due to serious concerns about the methodological proceeding.

Currently, there is a lack of adequately powered randomised controlled trials investigating the effectiveness of vitamin D supplementation on COVID-19. It also remains unclear which populations (e.g. critical ill individuals with vitamin D deficiency) benefit from vitamin D supplementation. Therefore, based on the limited evidence, neither this work nor other published reviews or studies can draw conclusions about the therapeutic effect and safety of vitamin D supplementation for individuals with COVID-19.

AUTHORS' CONCLUSIONS

Implications for practice

Based on the current evidence, we are very uncertain about the effectiveness of vitamin D supplementation for participants with COVID-19. Moreover, inconsistency in the reporting of adverse and serious adverse events impeded evaluation of safety of vitamin D supplementation. Therefore, we cannot draw conclusions about vitamin D supplementation as a treatment for individuals with COVID-19. With respect to the identified studies in trial registries, our results are subject to change in the future.

Implications for research

To elucidate the effectiveness and safety of vitamin D supplementation for individuals with COVID-19, more randomised controlled trials (RCTs) are necessary. Heterogeneity of studies was problematic in this review and impeded conduction of meta-analysis. Studies were mainly heterogenous because of different supplementation strategies, formulations, vitamin D statuses of participants, and reported outcomes. Moreover, measurement and reporting of serious adverse events was inconsistent across included studies as well, which exacerbate the evaluation of safety.

Currently, there is an urgent need for good-quality evidence, ideally based on RCTs with appropriate randomisation procedures, comparability of study arms and a preferably double-blinded design. We identified 21 ongoing RCTs in trial registries, which might increase the evidence about vitamin D supplementation as a treatment for COVID-19 in the future. In accordance with the living approach of this review, we will continually update our search and include eligible trials.

ACKNOWLEDGEMENTS

This work is part of a series of reviews investigating treatments and therapies for COVID-19 as part of the project CEOsys. Text passages in the background section (e.g. "description of the condition" and "why it is important to do this review") are shared between reviews of this series. We thank the authors of the first published reviews of this series for providing and sharing this information. Moreover, we thank the Cochrane Haematology working group for using the template for the description of methods.

This review was published in collaboration with the Cochrane Editorial and Methods Department. We particularly thank Liz Bickerdike (Managing Editor), Robin Featherstone (Information Specialist), Tess Moore (Methods Editor), and Heather Maxwell (Copy Editor) for their excellent support, their valuable comments on the review and timely management of the editorial process. We thank Robert Walton of the Analysis of Review Group Output (ARGO) for his comments on the abstract, and Denise Mitchell for writing the Plain Language Summary.

We thank all external peer reviewers who read and commented on this review. We thank Saurabh Mehta (Division of Nutritional Sciences, Cornell University, Ithaca and Samantha Huey, Division of Nutritional Sciences, Cornell University, Ithaca), John White (Department of Physiology, McGill University), and our consumer referee Abhijit Dutta (PDMJ, Research Scientist, Office of Medical Research &Data Management, Sanjiban Hospital, Howrah, India), who greatly helped to improve this review.

The research was part of a project supported by the German Federal Ministry of Education and Research (NaFoUniMedCovid19, funding number: 01KX2021; part of the project "CEOSys"). The contents of this document reflect only the authors' views and the German Ministry is not responsible for any use that may be made of the information it contains.

REFERENCES

References to studies included in this review

Entrenas Castillo 2020 *{published data only}*

* Entrenas Castillo E, Entrenas Costa LM, Vaquero Barrios JM, Alcalá Diaz JF, López Miranda J, Bouillon R, et al. Effect of calcifediol treatment and best available therapy versus bestavailable therapy on intensive care unit admission and mortality among patients hospitalized for COVID-19: a pilot randomized clinical study. *Journal of Steroid Biochemistry and Molecular Biology* 2020;**203**:105-751. [DOI: 10.1016/j.jsbmb.2020.105751]

Murai 2021 *{published data only}*

Murai IH, Fernandes AL, Sales LP, Pinto AJ, Giessler KF, Curan CS, et al. Effect of vitamin D $_3$ supplementation vs placebo on hospital length of stay in patients with severe COVID-19: a multicenter, double-blind, randomized controlled trial (preprint). Medrxiv. [DOI: https://doi.org/10.1101/2020.11.16.20232397]

* Murai IH, Fernandes AL, Sales LP, Pinto AJ, Goessler KF, Duran CS, et al. Effect of a single high dose of vitamin D $_3$ on hospital length of stay in patients with moderate to severe COVID-19: a randomized clinical trial. *JAMA* 2021;**Published online February 17, 2021**:E1-8. [DOI: 10.1001/jama.2020.26848]

Rastogi 2020 *{published data only}*

Rastogi A, Bhansali A, Khare N, Suri V, Yaddanapudi N, Sachdeva N, et al. Short term, high-dose vitamin D supplementation for COVID-19 disease: a randomised, placebo-controlled, study (SHADE study). *Postgraduate Medical Journal* 2020;**0**:1-4.

References to studies excluded from this review

Beigmohammadi 2020 *{published data only}*

Beigmohammadi MT, Bitarafan S, Hoseindokht A, Abdollahi A, Amoozadeh L, Mahmoodi Ali Abadi M, et al. Impact of vitamins A, B, C, D, and E supplementation on improvement and mortality rate in ICU patients with coronavirus-19: a structured summary of a study protocol for a randomized controlled trial. *Trials* 2020;**21**(1):614. [PMID: 10.1186/s13063-020-04547-0]

CTRI/2020/06/026191 *{published data only}*

CTRI/2020/06/026191. To study the safety and efficacy of vitamin D3,vitamin K2-7 & magnesium, in prevention of COVID 19 infection in health care professional (HCP). www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=45075 2020.

Euctr2020-001363-85-dk *{published data only}*

Odense University, Hospital. Medication for prevention of Corona-virus for Danish nursing home residents. https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2020-001363-85.

Euctr2020-001903-17 *{unpublished data only}*

2020-001903-17. A randomized clinical trial (IIIb) of eficacy of a single dose of Tocilizumab or a combination of Tocilizumab plus vitamin D (single i.m. dose) for the treatment of the COVID-19 hyperimmune complication. Assessment of IL-6. https://www.clinicaltrialsregister.eu/ctr-search/trial/2020-001903-17/ES.

IRCT20200319046819N1 *{published data only}*

* Beigmohammadi MT, Bitarafan S, Hoseindokht A, Abdollahi A, Amoozadeh L, Mahmoodi Ali Abadi M, et al. Impact of vitamins A, B, C, D, and E supplementation on improvement and mortality rate in ICU patients with coronavirus-19: a structured summary of a study protocol for a randomized controlled trial. *Trials* 2020;**21**(1):614. [DOI: 10.1186/s13063-020-04547-0]

IRCT20200319046819N1. Impact of vitamin B, A, D, E, C supplementation on improvement and mortality rate in patients with COVID-19 admitted in intensive care unit. https://www.irct.ir/trial/46838 (first received April 4, 2020).

IRCT20200705048013N1 *{published data only}*

Karaj University of Medical Sciences. The effect of Pentoxifylline in patients with Covid-19. http://en.irct.ir/trial/49525.

NCT04351490 *{published data only}*

NCT04351490. Influence of zinc and vitamin D3 supplementation on survival in elderly institutionalized individuals with CoV-2 SARS infection. https://clinicaltrials.gov/ct2/show/NCT04351490 (first received April 17, 2020).

NCT04395768 *{published data only}*

National Institute of Integrative Medicine, Australia. Therapies to Prevent Progression of COVID-19, Including Hydroxychloroquine, Azithromycin, Zinc, vitamin D, vitamin B12 with or without vitamin C, a multi-centre, international, randomized trial: the International ALLIANCE Study. https://clinicaltrials.gov/show/NCT04395768.

NCT04399746 *{published data only}*

NCT04399746. Ivermectin-Azithromycin-Cholecalciferol (IvAzCol) combination therapy for COVID-19. https://clinicaltrials.gov/show/NCT04399746.

NCT04407286 *{published data only}*

NCT04407286. Vitamin D testing and treatment for COVID 19. https://clinicaltrials.gov/ct2/show/NCT04407286 (First received: May 29, 2020).

NCT04476680 *{published data only}*

NCT04476680. Reducing asymptomatic infection with vitamin D in coronavirus disease. https://clinicaltrials.gov/ct2/show/NCT04476680 (first received July 20, 2020).

NCT04482686 *{published data only}*

ProgenaBiome. Trial of combination therapy to treat COVID-19 infection. https://clinicaltrials.gov/show/NCT04482686.

NCT04483635 *{published data only}*

NCT04483635. Preventing COVID-19 with high-dose vitamin D supplements. https://clinicaltrials.gov/ct2/show/NCT04483635 (first received July 23, 2020).

NCT04507867 *{published data only}*

NCT04507867. Effect of a Nss to reduce complications in patients with Covid-19 and comorbidities in stage III. https://clinicaltrials.gov/ct2/show/NCT04507867 (first received 11 August 2020).

NCT04535791 *{published data only}*

NCT04535791. Efficacy of vitamin D supplementation to prevent the risk of acquiring COVID-19 in healthcare workers (COVID-19). https://clinicaltrials.gov/ct2/show/NCT04535791 (first received September 2, 2020).

NCT04565392 *{published data only}*

drpykessupplementscom. Proof-of-concept randomized placebo-controlled trial of Famotidine for outpatients With COVID-19. https://clinicaltrials.gov/show/NCT04565392.

NCT04579640 *{published data only}*

NCT04579640. Trial of vitamin D to reduce risk and severity of COVID-19 and other acute respiratory infections (CORONAVIT). https://clinicaltrials.gov/ct2/show/NCT04579640 (first received October 8, 2020).

NCT04596657 *{published data only}*

NCT04596657. Vitamin D3 supplementation to prevent respiratory tract infections. https://clinicaltrials.gov/ct2/show/NCT04596657 (first received October 22, 2020).

NCT04780061 *{published data only}*

The Canadian College of Naturopathic, Medicine. Dietary supplements for COVID-19. https://clinicaltrials.gov/show/NCT04780061.

Nogues 2021 *{published data only}*

* Nogues X, Ovejero D, Quesada-Gomez JM, Bouillon R, Arenas D, Pasqual J, et al. Calcifediol treatment and COVID-19-related outcomes (preprint). SSRN. [DOI: http://dx.doi.org/10.2139/ssrn.3771318]

References to studies awaiting assessment

IRCT20110726007117N11 *{published data only}*

IRCT20110726007117N11. Effect of vitamin D supplementation in novel corona virus 2019. https://en.irct.ir/trial/48287 (first received 2020-07-05).

IRCT20200324046850N1 *{published data only}*

IRCT20200324046850N1. Comparison of vitamin D3 and N-acetylcysteine prescription in COVID-19 patients and their effect on recovery process. https://en.irct.ir/trial/46732 (first received 29 March 2020).

NCT04733625 *{published data only}*

Kasr El Aini Hospital. TheeEffect of vitamin D tn morbidity and moratlity in patients with SARS-CoV 2 infection. https://clinicaltrials.gov/show/NCT04733625.

References to ongoing studies

CTRI/2020/06/026189 *{published data only}*

CTRI/2020/06/026189. To compare the safety and efficacy of vitamin D, with magnesium in mild to moderate Covid 19 patients. www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=45029 (first received 26/06/2020).

CTRI/2020/12/030083 *{published data only}*

CTRI/2020/12/030083. To study the role of vitamin D in the treatment of confirmed COVID-19 infection. ctri.nic.in/Clinicaltrials/showallp.php?mid1=46899&EncHid=&userName=CTRI/2020/12/030083 (first received 29 December 2020).

EUCTR2020-001717-20-ES *{published data only}*

EUCTR2020-001717-20-ES. Prevention and treatment with Calcifediol of respiratory problems caused by COVID-19. https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2020-001717-20 (first received 20 April 2020).

EUCTR2020-001960-28-ES *{published data only}*

EUCTR2020-001960-28-ES. Efficacy of vitamin D treatment in patients diagnosed with pneumonia who require hospital admission and have vitamin D deficiency and a positive diagnosis for SARS-Cov-2 (COVID-19). https://www.clinicaltrialsregister.eu/ctr-search/trial/2020-001960-28/ES (first received 26 Mai 2020).

EUCTR2020-002274-28-ES *{published data only}*

EUCTR2020-002274-28-ES. Usefulness of vitamin D on morbidity and mortality of SARS-COV-2 virus infection (Covid-19) at the Central University Hospital of Asturias. https://www.clinicaltrialsregister.eu/ctr-search/trial/2020-002274-28/ES (first received 2020-05-21).

EUCTRCT2020-002312-43-ES *{published data only}*

EUCTR2020-002312-43-ES. Clinical trial, randomized, open-label, to evaluate the efficacy of high-dose vitamin D in patients with COVID-19 pneumonia. https://www.clinicaltrialsregister.eu/ctr-search/trial/2020-002312-43/ES (first received 2020-05-31).

NCT04334005 *{published data only}*

NCT04334005. Vitamin D on prevention and treatment of COVID-19. https://clinicaltrials.gov/ct2/show/NCT04334005 (first received April 3, 2020).

NCT04344041 *{published data only}*

* Annweiler C, Beaudenon M, Gautier J, Simon R, Dubee V, Gonsard J, et al. COvid-19 and high-dose VITamin D supplementation trial in high-risk older patients (COVIT-TRIAL): study protocol for a randomized controlled trial. *Trials* 2020;**21**(1):1031. [DOI: 10.1186/s13063-020-04928-5]

EUCTR2020-001602-34-FR. 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. https://www.clinicaltrialsregister.eu/ctr-search/trial/2020-001602-34/FR (first received on 3 April 2020).

NCT04344041. COvid-19 and high-dose VITamin D supplementation TRIAL in high-risk older patients (COVIT-TRIAL): study protocol for a randomized controlled trial. https://clinicaltrials.gov/ct2/show/NCT04344041 (first received 14 April 2020).

NCT04363840 *{published data only}*

NCT04363840. The LEAD COVID-19 trial: Low-risk, early aspirin and Vitamin D to reduce COVID-19 hospitalizations. https://clinicaltrials.gov/ct2/show/NCT04363840 (first received April 27, 2020).

NCT04385940 *{published data only}*

NCT04385940. Vitamin D and COVID-19 management. https://clinicaltrials.gov/ct2/show/NCT04385940 (First posted: 13 May 2020).

NCT04386850 *{published data only}*

NCT04386850. Oral 25-hydroxyvitamin D3 and COVID-19. https://clinicaltrials.gov/ct2/show/NCT04386850 (first received May 13, 2020).

NCT04411446 *{published data only}*

* Mariani J, Tajer C, Antonietti L, Inserra F, Ferder L, Manucha W. High-dose vitamin D versus placebo to prevent complications in COVID-19 patients: a structured summary of a study protocol for a randomised controlled trial (CARED-TRIAL). *Trials* 2021;**22**(1):111. [DOI: 10.1186/s13063-021-05073-3]

NCT04411446. Cholecalciferol to improve the outcomes of COVID-19 patients (CARED). https://clinicaltrials.gov/ct2/show/NCT04411446 (First posted June 2, 2020).

NCT04482673 *{published data only}*

NCT04482673. Vitamin D supplementation in the prevention and mitigation of COVID-19 infection (VitD-COVID19). https://clinicaltrials.gov/ct2/show/NCT04482673 (first received July 22, 2020).

NCT04489628 *{published data only}*

NCT04489628. Tele-health enabled clinical trial for COVID-19. https://clinicaltrials.gov/ct2/show/NCT04489628 (First posted 28 July 2020).

NCT04502667 *{published data only}*

NCT04502667. Efficacy of vitamin D treatment in pediatric patients hospitalized by COVID-19 (COVID-19). https://clinicaltrials.gov/ct2/show/NCT04502667 (first received August 6, 2020).

NCT04525820 *{published data only}*

NCT04525820. High dose vitamin-D substitution in patients with COVID-19: a randomized controlled, multi center study. https://clinicaltrials.gov/ct2/show/NCT04525820 (first received August 25, 2020).

NCT04536298 *{published data only}*

NCT04536298. Vitamin D and COVID-19 trial (VIVID). https://clinicaltrials.gov/ct2/show/NCT04536298 (First posted 2 September 2020).

* Wang R, DeGruttola V, Lei Q, Mayer KH, Redline S, Hazra A, et al. The vitamin D for COVID-19 (VIVID) trial: a pragmatic cluster-randomized design. *Contemporary clinical trials* January 2021;**100**:106176. [DOI: https://doi.org/10.1016/j.cct.2020.106176]

NCT04552951 *{published data only}*

NCT04552951. Effect of vitamin D on morbidity and mortality of the COVID-19 (COVID-VIT-D). https://clinicaltrials.gov/ct2/show/NCT04552951 (first received September 17, 2020).

NCT04621058 *{published data only}*

NCT04621058. Efficacy of vitamin D treatment in mortality reduction due to COVID-19. https://clinicaltrials.gov/ct2/show/NCT04621058 (first received November 9, 2020).

NCT04636086 *{published data only}*

NCT04636086. Effect of vitamin D on hospitalized adults with COVID-19 infection. https://clinicaltrials.gov/ct2/show/NCT04636086 (First posted 19 November 2020).

NCT04641195 *{published data only}*

NCT04641195. Vitamin D and zinc supplementation for improving treatment outcomes among COVID-19 patients in India. https://clinicaltrials.gov/ct2/show/NCT04641195 (first received November 23, 2020).

Additional references

Amrein 2014

Amrein K, Schnedl C, Holl A, Riedl R, Christopher KB, Pachler C, et al. Effect of high-dose vitamin D3 on hospital length of stay in critically ill patients with vitamin D deficiency: the VITdAL-ICU randomized clinical trial. *Jama* 2014;**312**(15):1520-30.

Amrein 2018

Amrein K, Papinutti A, Mathew E, Vila G, Parekh D. Vitamin D and critical illness: what endocrinology can learn from intensive care and vice versa. *Endocrine Connections* 2018;**7**(12):304-15.

Amrein 2020

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

Barazzoni 2020

Barazzoni R, Bischoff SC, Breda J, Wickramasinghe K, Krznaric Z, Nitzan D, et al. ESPEN expert statements and practical guidance for nutritional management of individuals with SARS-CoV-2 infection. *Clinical Nutrition* 2020;**39**(6):1631-8.

Bilezikian 2020

Bilezikian JP, Bikle D, Hewison M, Lazaretti-Castro M, Formenti AM, Gupta A, et al. Mechanisms in endocrinology: Vitamin D and COVID-19. *European Journal of Endocrinology* 2020;**183**(5):R133-R47.

Brandi 2002

Brandi L, Egfjord M, Olgaard K. Pharmacokinetics of 1,25(OH)(2)D(3) and 1alpha(OH)D(3) in normal and uraemic men. *Nephrology Dialysis Transplantation* 2002;**17**(5):829-42.

Braun 2012

Braun AB, Litonjua AA, Moromizato T, Gibbons FK, Giovannucci E, Christopher KB. Association of low serum 25-hydroxyvitamin D levels and acute kidney injury in the critically ill. *Critical Care Medicine* 2012;**40**(12):3170-9.

Buitrago-Garcia 2020

Buitrago-Garcia D, Egli-Gany D, Counotte MJ, Hossmann S, Imeri H, Ipekci Aziz M, et al. Occurrence and transmission potential of asymptomatic and presymptomatic SARS-CoV-2 infections: a living systematic review and meta-analysis. *PLOS Medicine* 2020;**17**(9):e1003346.

Cabler 2020

Cabler SS, French AR, Orvedahl A. A cytokine circus with a viral ringleader: SARS-CoV-2-associated cytokine storm syndromes. *Trends in Molecular Medicine* 2020;**26**(12):1078-85.

CDC 2020

Centers for Disease Control and Prevention. Interim clinical guidance for management of patients with confirmed coronavirus disease (COVID-19). www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html (accessed 22 March 2021).

Chai 2020

Chai KL, Valk SJ, Piechotta V, Kimber C, Monsef I, Doree C, et al. Convalescent plasma or hyperimmune immunoglobulin for people with COVID-19: a living systematic review. *Cochrane Database of Systematic Reviews* 2020, Issue 7. Art. No: CD013600. [DOI: 10.1002/14651858.CD013600.pub3]

Cochrane LSR

Guidance for the production and publication of Cochrane living systematic reviews: Cochrane Reviews in living mode. Available from community.cochrane.org/review-production/production-resources/living-systematic-reviews (accessed 22 March 2021).

COMET 2020

Core outcome set developers' response to COVID-19. Available from www.comet-initiative.org/Studies/Details/1538 (accessed 22 March 2021).

Deeks 2020

Deeks JJ, Higgins JP, Altman DG, editor(s). Chapter 10: Analysing data and undertaking meta-analyses. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al, editor(s). Cochrane Handbook for Systematic Reviews of Interventionsversion 6.1 (updated September 2020). Cochrane, 2020. Available from training.cochrane.org/handbook.

Eldridge 2016

Eldridge S, Campbell M, Campbell M, Dahota A, Giraudeau B, Higgins JT, et al. Revised Cochrane risk of bias tool for randomized trials (RoB 2.0). Additional considerations for cluster-randomized trials. www.riskofbias.info/welcome/rob-2-0-tool/archive-rob-2-0-cluster-randomized-trials-2016 (accessed 22 March 2021).

EndNote X9 [Computer program]

EndNote X9. The EndNote Team. Clarivate, 2013.

Fraser 2020

Fraser WD, Tang JC, Dutton JJ, Schoenmakers I. Vitamin D measurement, the debates continue, new analytes have emerged, developments have variable outcomes. *Calcified Tissue International* 2020;**106**(1):3-13.

Grant 2020

Grant WB, Lahore H, McDonnell SL, Baggerly CA, French CB, Aliano JL, et al. Evidence that vitamin D supplementation could reduce risk of influenza and COVID-19 infections and deaths. *Nutrients* 2020;**12**(4):988.

Grubaugh 2020

Grubaugh ND, Hanage WP, Rasmussen AL. Making sense of mutation: what D614G means for the COVID-19 pandemic remains unclear. *Cell* 2020;**182**(4):794-95. [DOI: https://doi.org/10.1016/j.cell.2020.06.040]

Gupta 2021

Gupta S, Coca SG, Chan L, Melamed ML, Brenner SK, Hayek SS, et al. AKI treated with renal replacement therapy in critically ill patients with COVID-19. *Journal of the American Society of Nephrology* 2021;**32(1)**:161-76.

Higgins 2003

Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**:557-60.

Higgins 2020a

Higgins JP, Eldridge S, Li T. Chapter 23: Including variants on randomized trials. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.1 (updated September 2020). Cochrane, 2020. Available from training.cochrane.org/handbook.

Higgins 2020b

Higgins JP, Tianging L, Deeks JJ, editor(s). Chapter 6: Choosing effect measures and computing estimates of effect. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.1 (updated September 2020). Cochrane, 2020. Available from training.cochrane.org/handbook.

Higgins 2020c

Higgins JP, Savović J, Page MJ, Elbers RG, Sterne JA. Chapter 8: Assessing risk of bias in a randomized trial. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.1 (updated September 2020). Cochrane, 2020. Available from training.cochrane.org/handbook.

Higgins 2020d

Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al (editors). Cochrane Handbook for Systematic Reviews of

Interventions version 6.1 (updated September 2020). Available from: training.cochrane.org/handbook 2020.

Holick 1996

Holick MF. Vitamin D and bone health. *Journal of Nutrition* 1996;**126**(4 Suppl):1159s-64s.

Holick 2009

Holick MF. Vitamin D status: measurement, interpretation, and clinical application. *Annals of Epidemiology* 2009;**19**(2):73-8.

Holick 2011

Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *Journal of Clinical Endocrinology and Metabolism* 2011;**96**(7):1911-30.

Huang 2020

Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020;**395**(10223):497-506.

Hughes 2009

Hughes DA, Norton R. Vitamin D and respiratory health. *Clinical and Experimental Immunology* 2009;**158**(1):20-5.

Johns Hopkins University & Medicine

Johns Hopkins University & Medicine Coronavirus Resource Center. Mortality analyses. Available from https://coronavirus.jhu.edu/data/mortality (accessed at 22 March 2021).

Jolliffe 2017

Jolliffe DA, Greenberg L, Hooper RL, Griffiths CJ, Camargo CA, Kerley CP, et al. Vitamin D supplementation to prevent asthma exacerbations: a systematic review and meta-analysis of individual participant data. *The Lancet Respiratory Medicine* 2017;**5**(11):881-90.

Jones 2008

Jones G. Pharmacokinetics of vitamin D toxicity. *American Journal of Clinical Nutrition* 2008;**88**(2):582S-586S.

Kreuzberger 2021

Kreuzberger N, Hirsch C, Chai KL, Piechotta V, Valk SJ, Estcourt LJ, et al. SARS-CoV-2-neutralising monoclonal antibodies for treatment of COVID-19. *Cochrane Database of Systematic Reviews* 2021, Issue 1. Art. No: CD013825. [DOI: 10.1002/14651858.CD013825]

Lauer 2020

Lauer SA, Grantz KH, Bi Q, Jones FK, Zheng Q, Meredith HR, et al. The incubation period of coronavirus disease 2019 (COVID-19) from publicly reported confirmed cases: estimation and application. *Annals of Internal Medicine* 2020;**172**(9):577–82. [DOI: 10.7326/M20-0504]

Leaf 2014

Leaf DE, Raed A, Donnino MW, Ginde AA, Waikar SS. Randomized controlled trial of calcitriol in severe sepsis. *American Journal of Respiratory and Critical Care Medicine* 2014;**190**(5):533-41.

Lee 2009

Lee P, Eisman JA, Center JR . Vitamin D deficiency in critically ill patients. *New England Journal of Medicine* 2009;**360**(18):1912-4.

Li 2020

Li T, Higgins JP, Deeks JJ. Chapter 5: Collecting data. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.1 (updated September 2020). Cochrane, 2020. Available from training.cochrane.org/handbook.

Liang 2020

Liang W, Guan W, Chen R, Wang W, Li J, Xu K, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. *Lancet Oncology* 2020;**21**(3):335-7.

Liu 2006

Liu PT, Stenger S, Li H, Wenzel L, Tan BH, Krutzik SR, et al. Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response. *Science* 2006;**311**(5768):1770-3.

Liu 2021

Liu N, Sun J, Wang X, Zhang T, Zhao M, Li H. Low vitamin D status is associated with coronavirus disease 2019 outcomes: a systematic review and meta-analysis. *International Journal of Infectious Diseases* 2021;**104**:58-64. [DOI: 10.1016/j.ijid.2020.12.077]

MAGICapp [Computer program]

Norwegian MAGIC Evidence Ecosystem Foundation (powered by UserVoice Inc.) MAGICapp. Brønnøysund (NOR): Norwegian MAGIC Evidence Ecosystem Foundation (powered by UserVoice Inc.), accessed 25 February 2021. Available at magicapp.org.

Malaguarnera 2020

Malaguarnera L. Vitamin D3 as potential treatment adjuncts for COVID-19. *Nutrients* 2020;**12**(11):3512.

Marshall 2020

Marshall JC, Murthy S, Diaz J, Adhikari NK, Angus DC, Arabi YM, et al. A minimal common outcome measure set for COVID-19 clinical research. *Lancet Infectious Diseases* 2020;**20**(8):e192-7. [DOI: 10.1016/S1473-3099(20)30483-7]

Martineau 2017

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

Martineau 2019

Martineau AR, Jolliffe DA, Greenberg L, Aloia JF, Bergman P, Dubnov-Raz G, et al. Vitamin D supplementation to prevent acute respiratory infections: individual participant data meta-analysis. *Health Technology Assessment* 2019;**23**(2):1-44.

Martucci 2019

Martucci G, Amrein K, Ney J. Vitamin D deficiency in ICU patients. *ICU Management & Practice* 2019;**19(2)**:114-6.

Microsoft 2018 [Computer program]

Mircosoft Excel. Microsoft Corporation. Microsoft Corporation, 2018. office.microsoft.com/excel.

Moher 2009

Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Journal of Clinical Epidemiology* 2009;**62**(10):1006-12.

Mokhtari 2020

Mokhtari T, Hassani F, Ghaffari N, Ebrahimi B, Yarahmadi A, Hassanzadeh G. COVID-19 and multiorgan failure: a narrative review on potential mechanisms. *Journal of Molecular Histology* 2020;**51(6)**:613-28.

Munshi 2021

Munshi R, Hussein MH, Toraih EA, Elshazli RM, Jardak C, Sultana N, et al. Vitamin D insufficiency as a potential culprit in critical COVID-19 patients. *Journal of Medical Virology* 2021;**93**(2):733-40.

Nadim 2020

Nadim MK, Forni LG, Mehta RL, Connor MJ Jr, Liu KD, Ostermann M, et al. COVID-19-associated acute kidney injury: consensus report of the 25th Acute Disease Quality Initiative (ADQI) Workgroup. *Nature Reviews Nephrology* 2020;**16(12)**:747-64.

National COVID-19 Clinical Evidence Taskforce 2021

National COVID-19 Clinical Evidence Taskforce. Caring for people with COVID-19: supporting Australia's healthcare professionals with continually updated, evidence-based clinical guidelines. Available from covid19evidence.net.au/#living-guidelines (accessed 22 March 2021).

Ney 2019

Ney J, Heyland DK, Amrein K, Marx G, Grottke O, Choudrakis M, et al. The relevance of 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D concentration for postoperative infections and postoperative organ dysfunctions in cardiac surgery patients: The eVIDenCe study. *Clinical Nutrition* 2019;**38**(6):2756-2762.

NICE 2020

National Institute for Health and Care Excellence. COVID-19 rapid guideline: vitamin D. Available from https://www.nice.org.uk/guidance/ng187/evidence (assessed 22 March 2021).

Nogues 2021

Nogues X, Ovejero D, Quesada-Gomez JM, Bouillon R, Arenas D, Pascual J et al. Calcifediol treatment and COVID-19 related outcomes. Available from https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3771318 (assessed 22 March 2021).

Norman 2014

Norman PE, Powell JT. Vitamin D and cardiovascular disease. *Circulation Research* 2014;**114**(2):379-93.

Parmar 1998

Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. *Statistics in Medicine* 1998;**17**(24):2815-34. [DOI: 10.1002/(SICI)1097-0258(19981230)17:24<2815::AID-SIM110>3.0.CO;2-8]

Pereira 2020

Pereira M, Dantas Damascena A, Galvao Azevedo LM, de Almeida Oliveira T, da Mota Santana J. Vitamin D deficiency aggravates COVID-19: systematic review and meta-analysis. *Critical Reviews in Food Science and Nutrition* 2020;**1-9**:Epub ahead of print.. [DOI: 10.1080/10408398.2020.1841090.]

Piechotta 2020

Piechotta V, Valk SJ, Chai KL, Wood EM, Lamikanra A, Kimber C, et al. Safety and effectiveness of convalescent plasma or hyperimmune globulin for people with COVID-19: a rapid review. osf.io/dwf53 2020. [DOI: 10.17605/OSF.IO/DWF53]

Putzu 2017

Putzu A, Belletti A, Cassina T, Clivio S, Monti G, Zangrillo A, et al. Vitamin D and outcomes in adult critically ill patients. A systematic review and meta-analysis of randomized trials. *Journal of Critical Care* 2017;**38**:109-14.

Ramos-Martinez 2018

Ramos-Martinez E, Lopez-Vancell MR, Fernandez de Cordova-Aguirre JC, Rojas-Serrano J, Chavarria A, Velasco-Medina A, et al. Reduction of respiratory infections in asthma patients supplemented with vitamin D is related to increased serum IL-10 and IFNgamma levels and cathelicidin expression. *Cytokine* 2018;**108**:239-46.

RevMan Web 2019 [Computer program]

The Cochrane Collaboration Review Manager Web (RevMan Web). The Cochrane Collaboration, 2019. revman.cochrane.org.

Roth 2020

Roth A, Lütke S, Meinberger D, Hermes G, Sengle G, Koch M, et al. LL-37 fights SARS-CoV-2: The vitamin D-inducible peptide LL-37 inhibits binding of SARS-CoV-2 spike protein to its cellular receptor angiotensin converting enzyme 2 in vitro. bioRxiv 2020/01/01. [DOI: https://doi.org/10.1101/2020.12.02.408153]

Santesso 2020

Santesso N, Glenton C, Dahm P, Garner P, Akl A, Alper B, et al. GRADE guidelines 26: informative statements to communicate the findings of systematic reviews of interventions. *Journal of Clinical Epidemiology* 2020;**119**:126-35. [DOI: 10.1016/j.jclinepi.2019.10.014]

Sassi 2018

Sassi F, Tamone C, D'Amelio P. Vitamin D: Nutrient, hormone, and immunomodulator. *Nutrients* 2018;**10**(11):1656.

Schünemann 2020

Schünemann HJ, Higgins JP, Vist GE, Glasziou P, Akl EA, Skoetz N, et al. Chapter 14: Completing 'Summary of findings' tables and grading the certainty of the evidence. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.1 (updated September 2020). Cochrane, 2020. Available from www.training.cochrane.org/handbook.

Sengupta 2021

Sengupta T, Majumder R, Majumder S. Role of vitamin D in treating COVID-19-associated coagulopathy: problems and perspectives. *Molecular and Cellular Biochemistry* 2021;**(no indication)**:(no indication). [DOI: https://doi.org/10.1007/s11010-021-04093-6]

Shah 2021

Shah K, Saxena D, Mavalankar D. Vitamin D supplementation, COVID-19 and disease severity: a meta-analysis. *QJM: An International Journal of Medicine* 24 January 2021;**0**:1-7.

Siemieniuk 2020

Siemieniuk R, Rochwerg B, Agoritsas T, Lamontagne F, Leo Y S, Macdonald H, et al. A living WHO guideline on drugs for Covid-19. *BMJ* 2020;**370: m3379**:1-14. [DOI: https://doi.org/10.1136/bmj.m3379]

Skoetz 2020

Skoetz N, Goldkuhle M, Van Dalen EC, Akl EA, Trivella M, Mustafa RA, et al. GRADE guidelines 27: how to calculate absolute effects for time-to-event outcomes in summary of findings tables and evidence profiles. *Journal of Clinical Epidemiology* 2020;**118**:124-31. [DOI: 10.1016/j.jclinepi.2019.10.015]

Sterne 2019

Sterne JA, Savovic J, Page MJ, Elbers RG, Blencowe N, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;**366**:l4898. [DOI: 10.1136/bmj.l4898]

Struyf 2020

Struyf T, Deeks JJ, Dinnes J, Takwoingi Y, Davenport C, Leeflang MM, et al. Signs and symptoms to determine if a patient presenting in primary care or hospital outpatient settings has COVID-19 disease. *Cochrane Database of Systematic Reviews* 2020, Issue 7. Art. No: CD013665. [DOI: 10.1002/14651858.CD013665]

Tierney 2007

Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. *Trials* 2007;**8**:16. [DOI: 10.1186/1745-6215-8-16]

Wang 2020

Wang Q, Zhang Y, Wu L, Niu S, Song C, Zhang Z, et al. Structural and functional basis of SARS-CoV-2 entry by using human ACE2. *Cell* 2020;**181**(4):894-904 e9..

Wells 2020

Wells Mulherin D, Walker R, Holcombe B, Guenter P. ASPEN report on nutrition support practice processes with COVID-19: The first response. *Nutrition in Clinical Practice* 2020;**35**(5):783-91.

WHO 2007

World Health Organization. Cumulative number of reported probable cases of SARS. Available from www.who.int/csr/sars/country/2003_07_11/en (accessed 22 March 2021).

WHO 2019

World Health Organization. Middle East respiratory syndrome coronavirus (MERS-CoV). Available from www.who.int/emergencies/mers-cov/en (accessed 22 March 2021).

WHO 2020a

World Health Organization. Report of the WHO-China Joint Mission on coronavirus disease 2019 (COVID-19). Available from www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report (accessed 22 March 2021).

WHO 2020b

World Health Organization. Estimating mortality from COVID-19 - scientific brief. Available from www.who.int/publications/i/item/WHO-2019-nCoV-Sci-Brief-Mortality-2020.1 (accessed 22 March 2021).

WHO 2020c

World Health Organization. Corticosteroids for COVID-19 - living guidance 2 September 2020. Available from www.who.int/publications/i/item/WHO-2019-nCoV-Corticosteroids-2020.1 (accessed 22 March 2021).

WHO 2020d

World Health Organization. Draft landscape of COVID-19 candidate vaccines. Available from www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines (accessed 22 March 2021).

WHO 2020e

WHO working group on the clinical characterisation and management of COVID-19 infection. A minimal common outcome measure set for COVID-19 clinical research. Lancet Infectious Diseases 2020;**20**(8):e192-7.

WHO 2020f

World Health Organization (WHO). Clinical management of COVID-19 - interim guidance, 27 May 2020. WHO/2019-nCoV/clinical/2020.4.

WHO 2020g

World Health Organization. COVID-19 Therapeutic Trial Synopsis. Available from www.who.int/blueprint/priority-diseases/key-action/COVID-19_Treatment_Trial_Design_Master_Protocol_synopsis_Final_18022 (assessed 27 April 2021).

WHO 2021a

World Health Organization. WHO Coronavirus Disease (COVID-19) Dashboard. covid19.who.int (accessed 22 March 2021).

WHO2021b

World Health Organization. SARS-CoV-2 Variants. Available from https://www.who.int/csr/don/31-december-2020-sars-cov2-variants/en/ (accessed 22 March 2021).

WHO 2021c

World Health Organization. Weekly epidemiological update - 23 February 2021. https://www.who.int/publications/m/item/weekly-epidemiological-update---23-february-2021 (accessed 22 March 2021).

Williamson 2020

Williamson E, Walker AJ, Bhaskaran KJ, Bacon S, Bates C, Morton CE, et al. Factors associated with COVID-19-related death using OpenSAFELY. *Nature* 2020;**584**:430-6. [DOI: 10.1038/s41586-020-2521-4]

Wu 2017

Wu C, Qiu S, Zhu X, Li L. Vitamin D supplementation and glycemic control in type 2 diabetes patients: a systematic review and meta-analysis. *Metabolism* 2017;**73**:67-76.

Wu 2020

Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72314 cases from the Chinese Center for Disease Control and Prevention. *JAMA* 2020;**323**(13):1239-42. [DOI: 10.1001/jama.2020.2648]

Wu 2020a

Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: Summary of a report of 72314 cases from the Chinese Center for Disease Control and Prevention. *JAMA* 2020;**323**(13):1239-42.

Yisak 2021

Yisak H, Ewunetei A, Kefale B, Mamuye M, Teshome F, Ambaw B, et al. Effects of vitamin D on COVID-19 infection and prognosis: A systematic review. *Risk management and healthcare policy* 2021;**14**:31-8.

References to other published versions of this review

Stroehlein 2021a

Stroehlein JK, Wallqyist J, Iannizzi C, Benstoem C, Meybohm P, Mikolajewska A, et al. Effects of vitamin D supplementation on clinical outcomes of COVID-19 patients (part of German Evidence Ecosystem CEO-sys). PROSPERO 21 January 2021 (available from https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021232283). [PROSPERO: CRD42021232283]

Stroehlein 2021b

Stroehlein JK, Wallqvist J, Iannizzi C, Mikolajewska A, Metzendorf MI, Benstoem C, et al. Risk of bias assessments for the Cochrane review 'Vitamin D supplementation for the treatment of COVID-19: a living systematic review'. https://zenodo.org/record/4771734#.YKTEFKj7Ryw 2021. [DOI: 10.5281/zenodo.4771734]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Entrenas Castillo 2020

Study characteristics	
Methods	• Trial design: RCT, open-label • Type of publication: journal publication • Setting: inpatient • Recruitment dates: not reported • Country: Spain • Language: English • Number of centres: 1 • Trial registration number: NCT04366908 (ClinicalTrials.gov) • Date of trial registration: 29th April 2020
Participants	• Age (mean and standard deviation): intervention group 53.14 (10.77), control group 52.77 (9.35) • Gender [males, n(%)]: intervention group 27 (54), control group 18 (69%) • Ethnicity: NR • Number of participants (recruited/allocated/evaluated): 76 • Severity of condition according to study definition: hospitalised

Entrenas Castillo 2020 *(Continued)*

- Severity of condition according to WHO score: 4, 5 (not specified for intervention and control group)
- Co-morbidities: diabetes, respiratory diseases, hypertension, cardiovascular disease, immunosuppression
- Inclusion criteria: hospitalised patients with COVID-19 infection, clinical picture of acute respiratory infection, confirmation by radiographic pattern of viral pneumonia and a positive SARS-CoV-2 PCR
- Exclusion criteria: patients < 18 years, pregnant women
- Previous treatments: not reported

Interventions

- Treatment details of intervention group (e.g dose, route of administration, number of doses): Calcifediol (25(OH)Vitamin D_3) 0.532 mg orally on day 1, than calcifediol (0.266 mg) on days 3 and 7, and then weekly until discharge or ICU admission and standard care
- Treatment details of control group (e.g. dose, route of administration, number of doses): standard care alone
- Concomitant therapy (e.g. description of standard of care): a combination of hydroxychloroquine (400 mg orally every 12 hours on the first day, and 200 mg every 12 hours for the following 5 days), azithromycin (500 mg orally for 5 days) and for patients with pneumonia and NEWS score ≥ 5, a broad-spectrum antibiotic (ceftriaxone 2 g intravenously (i.v.)for 5 days)
- Duration of follow-up: until admission to ICU, hospital discharge or death.
- Treatment cross-overs: no
- Compliance with assigned treatment: yes

Outcomes

Primary study outcome: admission to ICU, mortality at hospital discharge

Review outcomes

- All-cause mortality at day 28, day 60, time-to-event, and at hospital discharge: reported
- Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale (WHO 2020c), WHO Ordinal Scale for Clinical Improvement (WHO 2020d)) at day 28, day 60, and up to longest follow-up); including:
  * Improvement of clinical status:
    - ☐ Weaning or liberation from invasive mechanical ventilation in surviving patients i.e. WHO ≤ 6, if ≥7 at baseline: NA;
    - ☐ Ventilator free days; ventilator free defined as WHO ≤6: NA;
    - ☐ Duration to liberation from invasive mechanical ventilation: NA;
    - ☐ Liberation from supplemental oxygen in surviving patients i.e. WHO ≤4, if ≥5 at baseline: NR;
    - ☐ Duration to liberation from supplemental oxygen: NR;
  * Worsening of clinical status:
    - ☐ Need for invasive mechanical ventilation i.e. WHO 7-9, if ≤6 at baseline: NR;
    - ☐ Need for non-invasive mechanical ventilation or high flow i.e. WHO=6, if ≤ 5 at baseline: NR;
    - ☐ Need for oxygen by mask or nasal prongs i.e. WHO = 5, if ≤ 4 at baseline: NR;
- Need for dialysis (at up to 28 days): NR;
- Quality of life, including fatigue and neurological status, assessed with standardised scales (e.g. WHO-QOL-100) at up to seven days; up to 30 days, and longest follow-up available: NR;
- Admission to ICU: reported;
- Duration of hospitalisation: NR;
- Time to discharge from hospital: NR;
- Viral clearance, assessed with reverse transcription polymerase chain reaction (RT-PCR) test for SARS-CoV-2 at baseline, up to 3, 7, and 15 days: NR;
- Vitamin D serum levels: NR;
- Serious adverse events, defined as number of participants with event: NR;
- Adverse events (any grade, grade 1-2, grade 3-4), defined as number of participants with event: NR;

Additional study outcomes: -

Notes

- Date of publication: 29th August 2020

Entrenas Castillo 2020 *(Continued)*

- Sponsor/funding: Maimónides Biomedical Research Institute of Córdoba

Murai 2021

Study characteristics	
Methods	• Trial design: RCT, double-blind, placebo-controlled • Type of publication: journal publication • Setting: inpatient • Recruitment dates: between June 2, 2020 to August 27, 2020 • Country: Brazil • Language: English • Number of centres: two • Trial registration number: NCT04449718 • Date of trial registration: 16th June, 2020
Participants	• Age (mean and standard deviation): Intervention group 56.8 (14.2), control group 55.8 (15.0) • Gender [males, n(%)]: Intervention group 70 (58.3), control group 65 (54.2) • Ethnicity [intervention group vs. control group, n(%)]: White: 62 (51.7) vs. 70 (58.3); Brown: 37 (30.8) vs. 36 (30.0); Black: 20 (16.7) vs. 14 (11.7); Asian: 1 (0.8) vs. 0 (0.0) • Number of participants (recruited/allocated/evaluated): 240 • Severity of condition according to study definition: severe COVID-19 • Severity of condition according to WHO score [intervention group vs. control group, n(%)]: WHO 4: 16 (13.3) vs. 9 (7.5); WHO 5: 86 (71.7) vs. 97 (80.8); WHO 6: 18 (15.0) vs. 14 (11.7) • Co-morbidities: hypertension, cardiovascular disease, diabetes, chronic obstructive pulmonary disease, asthma, chronic kidney disease, rheumatic disease • Inclusion criteria: adults aged 18 years or older; diagnosis of COVID-19 by either polymerase chain reaction (PCR) for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) from nasopharyngeal swabs or computed tomography scan findings (bilateral multifocal ground-glass opacities ≥ 50%) compatible with the disease; diagnosis of flu syndrome with hospitalisation criteria on hospital admission, presenting respiratory rate ≥ 24 breaths per minute, saturation < 93% on room air or risk factors for complications, such as heart disease, diabetes mellitus, systemic arterial hypertension, neoplasms, immunosuppression, pulmonary tuberculosis, and obesity, followed by COVID-19 confirmation before randomisation. • Exclusion criteria: patient unable to read and sign the written informed consent; patient already admitted under invasive mechanical ventilation; previous vitamin 7 D3 supplementation (> 1000 IU/day); renal failure requiring dialysis or creatinine ≥ 8 2.0 mg/dL; hypercalcaemia defined by total calcium > 10.5 mg/dL; pregnant or lactating women; and patients with expected hospital discharge in less than 24 hours. • Previous treatments: NR
Interventions	• Treatment details of intervention group (e.g dose, route of administration, number of doses): 25(OH)-vitamin D 200,000 IU in a 10 mL of peanut oil solution as a single dose orally • Treatment details of control group (e.g. dose, route of administration, number of doses): 10 mL of peanut oil solution as a single dose orally • Concomitant therapy (e.g. description of standard of care): no specific standard of care; other concomitant treatments (intervention group vs. control): corticosteroids (not specified) 64.2% vs. 60.8% ; antivirals (not specified) 3.3% vs. 3.3%, antibiotics (not specified) 85.0% vs. 87.5% , anticoagulant (not specified) 91.7% vs. 85.8% , antihypertensive 56.3% vs. 48.3, proton-pump inhibitor 39.5% vs. 41.5%, antiemetic 37.8% vs. 46.6%, analgesic 37.5% vs. 43.7%, hypoglycaemic 21.8% vs. 20.3%, hypolipidaemic 12.6% vs. 15.3%, thyroid 8.4% vs. 8.5% • Duration of follow-up: until hospital discharge or death • Treatment cross-overs: no

Murai 2021 *(Continued)*

- Compliance with assigned treatment: 3 patients in intervention arm did not receive vitamin D, two patients in control arm did not receive placebo

Outcomes	Primary study outcome: Hospital length of stay Review outcomes • All-cause mortality at day 28, day 60, time-to-event, and at hospital discharge: reported; • Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale (WHO 2020e), WHO Ordinal Scale for Clinical Improvement (WHO 2020f)) at day 28, day 60, and up to longest follow-up); including: * Improvement of clinical status: ☐ Weaning or liberation from invasive mechanical ventilation in surviving patients i.e. WHO ≤ 6, if ≥7 at baseline: NA; ☐ Ventilator-free days; ventilator-free defined as WHO ≤ 6: NA; ☐ Duration to liberation from invasive mechanical ventilation: NA; ☐ Liberation from supplemental oxygen in surviving patients i.e. WHO ≤ 4, if ≥ 5 at baseline: NR; ☐ Duration to liberation from supplemental oxygen: NR; * Worsening of clinical status: ☐ Need for invasive mechanical ventilation i.e. WHO 7-9, if ≤6 at baseline: reported; ☐ Need for non-invasive mechanical ventilation or high flow i.e. WHO = 6, if ≤ 5 at baseline: NR; ☐ Need for oxygen by mask or nasal prongs i.e. WHO = 5, if ≤ 4 at baseline: NR; • Need for dialysis (at up to 28 days): NR; • Quality of life, including fatigue and neurological status, assessed with standardised scales (e.g. WHO-QOL-100) at up to seven days; up to 30 days, and longest follow-up available: NR; • Admission to ICU: reported; • Duration of hospitalisation: reported • Time to discharge from hospital: reported • Viral clearance, assessed with reverse transcription polymerase chain reaction (RT-PCR) test for SARS-CoV-2 at baseline, up to 3, 7, and 15 days: NR; • Vitamin D serum levels: reported; • Serious adverse events, defined as number of participants with event: reported; • Adverse events (any grade, grade 1-2, grade 3-4), defined as number of participants with event: reported Additional study outcomes: serum levels of calcium, C-reactive protein and D-dimer, duration of mechanical ventilation
Notes	• Date of publication: 17th February, 2021 (journal publication) • Sponsor/funding: University of Sao Paulo

Rastogi 2020

Study characteristics

Methods	• Trial design: RCT, double-blind, placebo-controlled • Type of publication: journal publication • Setting: outpatient • Recruitment dates: not reported in the publication, according to study register: 15th July 2020 until 30th August 2020 (estimated primary completion date) • Country: India • Language: English • Number of centres: one • Trial registration number: NCT04459247

Rastogi 2020 *(Continued)*

	• Date of trial registration: 3rd July, 2020 ("first submitted" in study register)
Participants	• Age (means not reported): median and interquartile range (IQR): intervention group 50.0 (36 to 51), control group 47.5 (39.3 to 49.2) • Gender [males, n(%)]: intervention group 6 (37.5), control group 14 (58.3) • Ethnicity [intervention group vs. control group, n(%)]: NR • Number of participants (recruited/allocated/evaluated): 40 • Severity of condition according to study definition: mildly symptomatic or asymptomatic individuals (based on additional information provided by the authors) • Severity of condition according to WHO score: 1-3 (not specified for the intervention and control group) • Co-morbidities: not specified (individuals with or without co-morbidities (hypertension, diabetes mellitus, chronic obstructive airway disease, chronic liver disease, chronic kidney disease) • Inclusion criteria: adults aged 18 years or older, SARS-CoV-2 RNA positive mildly symptomatic or asymptomatic individuals (according to the publication and information provided by the authors) • Exclusion criteria: uncontrolled diabetes, uncontrolled hypertension, chronic liver disease, chronic obstructive pulmonary disease requiring invasive ventilation • Previous treatments: NR
Interventions	• Treatment details of intervention group (e.g dose, route of administration, number of doses): 25 (OH)-vitamin D 60,000 IU in daily doses of 60, 000 international units (IU) over seven days followed by further daily supplementation until day-14, if 25(OH)Vitamin D_3 level at day-7 achieved < 50 ng/mL. If the 25(OH)Vitamin D_3 level at day-7 achieved >50 ng/mL, the participants continued with weekly supplementation of 60, 000 IU. • Treatment details of control group (e.g dose, route of administration, number of doses): 5 mL distilled water as placebo up to day-7 orally • Concomitant therapy (e.g description of standard of care): NR • Duration of follow-up: NR • Treatment cross-overs: no • Compliance with assigned treatment: all patients randomised received intervention or placebo

Outcomes	• All-cause mortality at day 28, day 60, time-to-event, and at hospital discharge: NR;
	• Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale (WHO 2020e), WHO Ordinal Scale for Clinical Improvement (WHO 2020f)) at day 28, day 60, and up to longest follow-up); including:
	  * Improvement of clinical status:
	  ☐ Weaning or liberation from invasive mechanical ventilation in surviving patients i.e. WHO ≤ 6, if ≥7 at baseline: NA;
	  ☐ Ventilator-free days; ventilator-free defined as WHO ≤ 6: NA;
	  ☐ Duration to liberation from invasive mechanical ventilation: NA;
	  ☐ Liberation from supplemental oxygen in surviving patients i.e. WHO ≤ 4, if ≥ 5 at baseline: NA;
	  ☐ Duration to liberation from supplemental oxygen: NA;
	  * Worsening of clinical status:
	  ☐ Need for invasive mechanical ventilation i.e. WHO 7-9, if ≤ 6 at baseline: NR;
	  ☐ Need for non-invasive mechanical ventilation or high flow i.e. WHO = 6, if ≤5 at baseline: NR;
	  ☐ Need for oxygen by mask or nasal prongs i.e. WHO = 5, if ≤4 at baseline: NR;
	• Need for dialysis (at up to 28 days): NR;
	• Quality of life, including fatigue and neurological status, assessed with standardised scales (e.g. WHO-QOL-100) at up to seven days; up to 30 days, and longest follow-up available: not reported;
	• Admission to ICU: NR;
	• Duration of hospitalisation: NA;
	• Time to discharge from hospital: NA;
	• Viral clearance, assessed with reverse transcription polymerase chain reaction (RT-PCR) test for SARS-CoV-2 at baseline, up to 3, 7, and 15 days: reported;
	• Vitamin D serum levels: reported;

Rastogi 2020 *(Continued)*	• Serious adverse events, defined as number of participants with event: NR; • Adverse events (any grade, grade 1-2, grade 3-4), defined as number of participants with event: NR Additional study outcomes: the change in the level of inflammatory markers with treatment
Notes	• Date of publication: 12th November 2020 • Sponsor/funding: Postgraduate Institute of Medical Education and Research, India

ICU: intensive care unit; NA: not applicable; NR: not reported; PCR: polymerase chain reaction; RCT: randomised controlled trial

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Beigmohammadi 2020	combination of vitamin D with other treatments
CTRI/2020/06/026191	prevention
Euctr2020-001363-85-dk	prevention
Euctr2020-001903-17	combination of vitamin D with other treatments
IRCT20200319046819N1	combination of vitamin D with other treatments
IRCT20200705048013N1	combination of vitamin D with other treatments
NCT04351490	study withdrawn: the study stopped early, before enrolling its first participant. Combination of vitamin D with other treatments
NCT04395768	combination of vitamin D with other treatments
NCT04399746	combination of vitamin D with other treatments
NCT04407286	single-arm study
NCT04476680	prevention
NCT04482686	combination of vitamin D with other treatments
NCT04483635	prevention
NCT04507867	combination of vitamin D with other treatments
NCT04535791	prevention
NCT04565392	combination of vitamin D with other treatments
NCT04579640	prevention
NCT04596657	prevention
NCT04780061	combination of vitamin D with other treatments
Nogues 2021	non-randomised study; paper removed from preprint server quote: "due to concerns about the description of the research in this paper"

Characteristics of studies awaiting classification *[ordered by study ID]*

IRCT20110726007117N11

Methods	• Trial design: RCT • Sample size: 210 • Setting: inpatient • Language: English (Iran) • Number of centres: NA • Type of intervention (treatment/prevention): treatment

Participants	• Inclusion criteria:
	  * age 30- 60 years old
	  * serum vitamin D level lower than 30 nanograms per mL
	  * cases who diagnosed as novel coronavirus 2019 infection by clinical features (sore throat, dry cough, dyspnoea), laboratory findings (positive C- reactive protein, lymphocyte<1100 per mL), or radiological findings (lung patchy infiltrations in chest X-ray or CT scan)
	• Exclusion criteria:
	  * serum Vitamin D level upper than 30 nanograms per mL
	  * use of medications that interfere with vitamin D metabolism
	  * history of hypercalcemia, kidney disorders, cirrhosis

Interventions	• Details of intervention:
	  * dose: 50000 International Units (IU) pearl vitamin D as single dose made in ZAHRAVI manufacture and then 10,000 IU vitamin D syrup
	  * route of administration: 30 days, with lunch
	• Treatment details of control group (e.g. dose, route of administration): 1000 IU syrup vitamin D daily, 30 days, with lunch
	• Concomitant therapy: none

Outcomes	Primary study outcome
	• erythrocyte sedimentation rate (ESR) level
	Review outcomes
	• All-cause mortality at day 28, day 60, time-to-event, and up to longest follow-up - NP
	• Admission to hospital (WHO≥ 4) - NP
	• Development of moderate to severe clinical COVID-19 symptoms, defined as WHO Clinical Progression Scale ≥ 6 (WHO 2020e), up to longest follow-up
	  * Need for invasive mechanical ventilation, non-invasive mechanical ventilation or high flow i.e. WHO ≥6, severe disease;
	  ☐ Need for invasive mechanical ventilation i.e. WHO 7-9;
	  ☐ Need for non-invasive mechanical ventilation or high flow i.e. WHO = 6.
	  * Need for hospitalisation with or without supplemental oxygen i.e. WHO = 4-5, moderate disease;
	  ☐ Need for oxygen by mask or nasal prongs i.e. WHO = 5;
	  ☐ Need for hospitalisation without oxygen therapy i.e. WHO = 4.
	  * NP
	• Quality of life, including fatigue and neurological status, assessed with standardised scales (e.g. WHOQOL-100) at up to 7 days, up to 30 days, and longest follow-up available - NP
	• Duration of hospitalisation, for subgroup of participants hospitalised during course of disease - NP
	• Time to hospital discharge, for subgroup of participants hospitalised during course of disease - NP
	• Vitamin D serum levels - reported
	• Serious adverse events, defined as number of participants with event - NP
	• Adverse events (any grade, grade 1-2, grade 3-4), defined as number of participants with event - NP

IRCT20110726007117N11 *(Continued)*

	Additional study outcomes: • neutrophil to lymphocyte ratio level • serum vitamin D level • low- density lipoprotein(LDL) Level • high-density lipoprotein (HDL) level • total cholesterol level • triglyceride level • fasting blood glucose level
Notes	• Recruitment status: complete • Prospective completion date: NI • Date last update was posted: NI • Sponsor/funding: Mashhad University of Medical Sciences

IRCT20200324046850N1

Methods	• Trial design: randomised, double-blind, phase III clinical trial • Sample size: 100 • Setting: inpatient • Language: English (Iran) • Number of centres: 1 • Type of intervention (treatment/prevention): treatment
Participants	• Inclusion criteria: * COVID-19 patients that have positive polymerase chain reaction (PCR) test of nasopharyngeal sample or have positive computed tomography (CT) scan for COVID-19. * age > 18 * men and women • Exclusion criteria: * pregnant or breast-feeding women Patients under 18 years of age. Any life-threatening factor
Interventions	• Details of intervention (4 Groups) * Intervention group 1: standard country protocol drugs (lopinavir (50 mg) –ritonavir (200 mg) 2 tablets every 12 hours until the patient's clinical symptoms improve + hydroxychloroquine (200 mg) two tablets one dose) with vitamin D3 ampoules of 50,000 units once a week and N-acetylcysteine placebo tablets every 12 hours * Intervention group 2: standard country protocol drugs (lopinavir (50 mg) –ritonavir (200 mg) 2 tablets every 12 hours until the patient's clinical symptoms improve + hydroxychloroquine (200 mg) two tablets one dose) with 600 mg N-acetylcysteine tablet every 12 hours and vitamin D3 placebo once a week * Intervention group 3: standard country protocol drugs (lopinavir (50 mg) –ritonavir (200 mg) 2 tablets every 12 hours until the patient's clinical symptoms improve + hydroxychloroquine (200 mg) two tablets one dose) with 600mg N-acetylcysteine tablets every 12 hours and 500,000 units of vitamin D3 once a week * Intervention group 4: standard country protocol drugs (lopinavir (50 mg) –ritonavir (200 mg) 2 tablets every 12 hours until the patient's clinical symptoms improve + hydroxychloroquine (200 mg) two tablets one dose) with placebo vitamin D3 once a week and placebo tablets N-acetylcysteine every 12 hours • Concomitant therapy: none
Outcomes	Primary study outcome • Time to clinical improvement defined as start of taking medication time to discharge time.

IRCT20200324046850N1 *(Continued)*

Review outcomes (add for each outcome if planned or not planned)

- All-cause mortality at day 28, day 60, time-to-event, and at hospital discharge - probably reported
- Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale (WHO 2020e), WHO Ordinal Scale for Clinical Improvement (WHO 2020f)) at day 28, day 60, and up to longest follow-up); including:
  * Improvement of clinical status:
    - ☐ weaning or liberation from invasive mechanical ventilation in surviving patients i.e. WHO ≤6, if ≥7 at baseline;
    - ☐ ventilator-free days; ventilator-free defined as WHO ≤ 6;
    - ☐ duration to liberation from invasive mechanical ventilation;
    - ☐ liberation from supplemental oxygen in surviving patients i.e. WHO ≤ 4, if ≥5 at baseline;
    - ☐ duration to liberation from supplemental oxygen
  * Worsening of clinical status:
    - ☐ need for invasive mechanical ventilation i.e. WHO 7-9, if ≤ 6 at baseline;
    - ☐ need for non-invasive mechanical ventilation or high flow i.e. WHO = 6, if ≤ 5 at baseline;
    - ☐ need for oxygen by mask or nasal prongs i.e. WHO=5, if ≤4 at baseline
  * NP
- Need for dialysis (at up to 28 days) - NP
- Quality of life, including fatigue and neurological status, assessed with standardised scales (e.g. WHOQOL-100) at up to seven days; up to 30 days, and longest follow-up available - NP
- Admission to ICU - probably reported
- Duration of hospitalisation - NP
- Time to discharge from hospital - reported
- Viral clearance, assessed with reverse transcription polymerase chain reaction (RT-PCR) test for SARS-CoV-2 at baseline, up to 3, 7, and 15 days - NP
- Vitamin D serum levels - NP
- Serious adverse events, defined as number of participants with event - NP
- Adverse events (any grade, grade 1-2, grade 3-4), defined as number of participants with event - reported

Additional study outcomes:

- complete blood count
- venous blood gas
- C-reactive-protein
- creatinine
- aspartate amino transferase
- alanine amino transferase
- prothrombin time
- partial thromboplastin time
- cough
- level of consciousness
- shortness of breath
- fatigue
- severe and frequent diarrhoea
- abdominal pain
- nausea and vomiting
- olfactory disturbances
- appetite
- duration of ICU stay
- adverse events
- the patient's condition is based on inpatient or outpatient
- mortality rate

IRCT20200324046850N1 *(Continued)*

	• taste disturbances
Notes	• Recruitment status: complete • Prospective completion date: NI • Date last update was posted: 03/06/2020 • Sponsor/funding: Abadan University of Medical Sciences

NCT04733625

Methods	• Trial design: RCT, double-blinded • Sample size: 56 • Setting: inpatient • Language: English (Egypt) • Number of centres: NA • Type of intervention (treatment/prevention): treatment
Participants	• Inclusion criteria: * elderly type II diabetes adult with age more than 60 years males and females having deficient serum vitamin D levels (less than 25 ng/mL). * diabetes patients recruited to the control group were only included in the study if not known to have cholecalciferol supplementation within last 6 weeks. All elderly vitamin D deficient diabetes patients were diagnosed with COVID-19 when throat-swab specimens for SARS-CoV-2 PCR were positive. • Exclusion criteria: * patients with known history of renal stones * diagnosis of hypercalcaemia with the past year * baseline serum total calcium more than 10mg/dL * established diagnosis associated with increase the risk of hypercalcaemia (e.g. metastatic cancer, sarcoidosis, multiple myeloma, primary hyperparathyroidism) * current vitamin D supplementation * known malignancy, organ transplant and known chronic autoimmune diseases * individuals on systemic steroid for any cause
Interventions	• Details of intervention: * dose: single injection of cholecalciferol (200000 IU) * Route of administration: • Treatment details of control group (e.g. dose, route of administration): placebo medication • Concomitant therapy: none
Outcomes	Primary study outcome • mortality (in hospital) of need for intubation (6 weeks) Review outcomes • All-cause mortality at day 28, day 60, time-to-event, and up to longest follow-up: reported • Admission to hospital (WHO≥ 4) - NP

NCT04733625 *(Continued)*

- Development of moderate to severe clinical COVID-19 symptoms, defined as WHO Clinical Progression Scale ≥ 6 (WHO 2020e), up to longest follow-up
  * Need for invasive mechanical ventilation, non-invasive mechanical ventilation or high flow i.e. WHO ≥ 6, severe disease;
    ☐ Need for invasive mechanical ventilation i.e. WHO 7-9; reported
    ☐ Need for non-invasive mechanical ventilation or high flow i.e. WHO = 6.
  * Need for hospitalisation with or without supplemental oxygen i.e. WHO = 4-5, moderate disease;
    ☐ Need for oxygen by mask or nasal prongs i.e. WHO = 5;
    ☐ Need for hospitalisation without oxygen therapy i.e. WHO = 4.
- Quality of life, including fatigue and neurological status, assessed with standardised scales (e.g. WHOQOL-100) at up to 7 days, up to 30 days, and longest follow-up available - NP
- Duration of hospitalisation, for subgroup of participants hospitalised during course of disease - NP
- Time to hospital discharge, for subgroup of participants hospitalised during course of disease - NP
- Vitamin D serum levels - reported
- Serious adverse events, defined as number of participants with event - NP
- Adverse events (any grade, grade 1-2, grade 3-4), defined as number of participants with event - NP

Additional study outcomes: no

Notes	• Recruitment status: complete • Prospective completion date: December 17, 2020 • Sponsor/funding: Kasr El Aini Hospital

NA: not applicable; NI: no information; NP: not planned; NR: not reported; RCT: randomised controlled trial

Characteristics of ongoing studies *[ordered by study ID]*

CTRI/2020/06/026189

Study name	Randomized, double blind, parallel group study of vitamin D3 & magnesium in Covid 19 infection
Methods	• Trial design: RCT • Sample size: 210 • Setting: inpatient • Language: English (India) • Number of centres: 1 • Type of intervention (treatment/prevention): treatment
Participants	• Inclusion criteria * Patients of either sex, 20 to 60 years of age with mild – moderate COVID -19 infection, found positive for COVID -19 test by RT_PCR are requiring clinical management symptomatic patients who present with cough, fever, nasal congestion, gastrointestinal symptoms, fatigue, insomnia, ageusia or alternative signs of respiratory infections.) * Participants who are willing to provide inform consent and willing to come for schedule follow-up visit. * Participants who are having normal hematological renal hepatic parameters * Participants not having contra indication to take standard treatmentvitamin D, magnesium * Participants tested positive for COVID 19 by nose throat swab using PCR technique * Signed informed consent, demonstrating that the participant understands the procedures required for the study and the purpose of the study.

CTRI/2020/06/026189 *(Continued)*

- Exclusion criteria
  * Participants having severe COVID -19 infection
  * Participants presenting severe respiratory and/or multi systemic symptoms compatible with advanced COVID-19 and inter current acute or severe chronic diseases (i.e. active cancer).
  * Participants with hypersensitivity or intolerance or contraindication to the use of standard treatment
  * Participants with known allergy or contraindication to Vitamin D, magnesium
  * History of having received any investigational drug in the preceding one month.
  * History of taking any kind of formulation or any other form of therapy for COVID 19 prophylaxis .
  * Unwilling to come for regular follow-up for the entire duration of the study.
  * COVID -19 RT-PCR negative
  * Any condition that, in the opinion of the investigator, does not justify the participant's inclusion in the study.
  * Participants participating in other clinical study.
  * Participant receiving other immune enhancers.
  * Refusal to sign informed consent form
  * Symptomatic for sever COVID-19 infection needing ICU
  * Atherosclerotic coronary artery disease

Interventions

- Details of intervention
  * Dose: vitamin D 400,000 IU single dose + magnesium glycinate 250 mg twice daily
  * Route of administration: for 14 days
- Treatment details of control group (e.g. dose, route of administration):
  * Dose: vitamin D 60,000 IU single dose + magnesium glycinate 250 mg twice daily
  * Route of administration: for 14 days
- Concomitant therapy: standard COVID-19 treatment

Outcomes

Primary study outcome

- Negative RT- PCR test for COVID 19 infection
- Improvement in signs and symptoms of COVID 19 infection, use of ventilator, length of stay in ICU
- Reduction in CRP levels
- Reduction in rate of COVID -19 complication .
- Speed of recovery and duration to becoming asymptomatic
- Length of hospital stay

Review outcomes

- All-cause mortality at day 28, day 60, time-to-event, and at hospital discharge - NP
- Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale (WHO 2020e), WHO Ordinal Scale for Clinical Improvement (WHO 2020f)) at day 28, day 60, and up to longest follow-up); including:
  * Improvement of clinical status:
    - ☐ weaning or liberation from invasive mechanical ventilation in surviving patients i.e. WHO ≤ 6, if ≥7 at baseline;
    - ☐ ventilator-free days; ventilator free defined as WHO ≤ 6;
    - ☐ duration to liberation from invasive mechanical ventilation;
    - ☐ liberation from supplemental oxygen in surviving patients i.e. WHO ≤ 4, if ≥5 at baseline;
    - ☐ duration to liberation from supplemental oxygen
  * Worsening of clinical status:
    - ☐ need for invasive mechanical ventilation i.e. WHO 7-9, if ≤ 6 at baseline;
    - ☐ need for non-invasive mechanical ventilation or high flow i.e. WHO = 6, if ≤5 at baseline;
    - ☐ need for oxygen by mask or nasal prongs i.e. WHO = 5, if ≤4 at baseline
    - ☐ NP
- Need for dialysis (at up to 28 days) - not planned

CTRI/2020/06/026189 *(Continued)*

	• Quality of life, including fatigue and neurological status, assessed with standardised scales (e.g. WHOQOL-100) at up to 7 days; up to 30 days, and longest follow-up available - NP • Admission to ICU - probably reported • Duration of hospitalisation - reported • Time to discharge from hospital - probably reported • Viral clearance, assessed with reverse transcription polymerase chain reaction (RT-PCR) test for SARS-CoV-2 at baseline, up to 3, 7, and 15 days - reported • Vitamin D serum levels - NP • Serious adverse events, defined as number of participants with event - probably reported • Adverse events (any grade, grade 1-2, grade 3-4), defined as number of participants with event - probably reported Additional study outcomes: • safety and efficacy
Starting date	01/08/2020
Contact information	AVN Sridhar suraksha pharma 8-3-898/5, suraksha towers, Ameerpet, Hyderabad TELANGANA 500073 India svp@surakshapharma.com
Notes	• Recruitment status: not yet recruiting • Prospective completion date: 01.02.2022 • Date last update was posted: NR • Sponsor/funding: suraksha pharma

CTRI/2020/12/030083

Study name	To study the role of vitamin D in the treatment of confirmed COVID-19 infection
Methods	• Trial design: RCT • Sample size: 100 • Setting: inpatient • Language: English (India) • Number of centres: 1 • Type of intervention (treatment/prevention): treatment
Participants	• Inclusion criteria * Patients aged above 18 years either gender with positive RT-PCR for novel Corona Virus causing Covid-19 pandemic. * Only patients categorised as suffering from uncomplicated illness (category 1), mild pneumonia (category 2) and severe pneumonia (category 3) as defined by ICMR dt. 31-03-2020, will be selected to participate in the study. * Women of childbearing potential must agree to use contraception for the duration of the study. * Patients or their legally acceptable representative willing to sign the informed Consent form.

CTRI/2020/12/030083 *(Continued)*

- Exclusion criteria
  * Patients less than 18 years of age.
  * Patience who have taken high-dose vitamin D (i.e. 60,000 IU of Vitamin D) In the last 3months either daily, weekly or monthly or whose 25 (OH) D level is above 30 ng/mL.
  * Refusal to participate expressed by patient or legally authorised representative if they are present. Refusal to sign the informed Consent form.
  * Patients of category 4, 5, 6 (ARDS, Sepsis, septic shock) respectively as a defined by ICMR.
  * Patients suffering from active malignancy.
  * Severe chronic kidney disease or requiring dialysis (i.e. eGFR < 30 mL/minute).
  * Pregnancy and breast-feeding.
  * Anticipated transfer to another hospital which is not a study site within 72 hours.
  * Contraindication to any study medication including allergy.
  * Human immunodeficiency virus infection under highly active antiretroviral therapy (HAART).

Interventions

- Details of intervention
  * Dose:
    - ☐ Uncomplicated illness: **3,60,000-6,00,000** IU 6-10 days once a day
    - ☐ Mild pneumonia: **3,60,000-6,00,000** IU 6-10 days once a day
    - ☐ Severe pneumonia:**3,60,000-6,00,000** IU 3-5 days twice a day
  * Route of administration: orally (syrup)
- Treatment details of control group (e.g dose, route of administration): Standard treatment according to physician's decision, based on the current recommendations.
- Concomitant therapy: none

Outcomes

Primary study outcome

- Difference in two study groups with respect to the duration and severity of signs and symptoms.
- Time taken for double negative RT-PCR between the two study groups
- Duration of hospital stay.
- Difference in the blood parameters and comparable symptoms between the two groups after the intervention.

Review outcomes

- All-cause mortality at day 28, day 60, time-to-event, and at hospital discharge - reported
- Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale (WHO 2020e), WHO Ordinal Scale for Clinical Improvement (WHO 2020f)) at day 28, day 60, and up to longest follow-up); including:
  * Improvement of clinical status:
    - ☐ weaning or liberation from invasive mechanical ventilation in surviving patients i.e. WHO ≤6, if ≥7 at baseline;
    - ☐ ventilator free days; ventilator free defined as WHO ≤ 6;
    - ☐ duration to liberation from invasive mechanical ventilation;
    - ☐ liberation from supplemental oxygen in surviving patients i.e. WHO ≤4, if ≥5 at baseline;
    - ☐ duration to liberation from supplemental oxygen
  * Worsening of clinical status:
    - ☐ need for invasive mechanical ventilation i.e. WHO 7-9, if ≤6 at baseline;
    - ☐ need for non-invasive mechanical ventilation or high flow i.e. WHO=6, if ≤ 5 at baseline;
    - ☐ need for oxygen by mask or nasal prongs i.e. WHO = 5, if ≤ 4 at baseline
  * probably reported
- Need for dialysis (at up to 28 days) - NP
- Quality of life, including fatigue and neurological status, assessed with standardised scales (e.g. WHOQOL-100) at up to seven days; up to 30 days, and longest follow-up available - NP
- Admission to ICU - reported
- Duration of hospitalisation - reported

CTRI/2020/12/030083 *(Continued)*

- Time to discharge from hospital - NP
- Viral clearance, assessed with reverse transcription polymerase chain reaction (RT-PCR) test for SARS-CoV-2 at baseline, up to 3, 7, and 15 days - probably reported
- Vitamin D serum levels - probably reported
- Serious adverse events, defined as number of participants with event - NP
- Adverse events (any grade, grade 1-2, grade 3-4), defined as number of participants with event - NP

Additional study outcomes

- Intensive care unit admission.
- Recovery
- Composite of cumulative death, i.e. all causes and specific causes mortality

Starting date	31/12/2020
Contact information	Dr I Shyam Sundar Varaprasad Raju Gandhi Medical College and Hospital Musheerabad Padmarao Nagar Secunderabad Hyderabad TELANGANA 500003 India 9848152349 drgsgmbbs@gmail.com
Notes	• Recruitment status: not yet recruiting • Prospective completion date: 30/06/2021 • Date last update was posted: 01/01/2021 • Sponsor/funding: Pulse Pharmaceuticals Pvt Ltd

EUCTR2020-001717-20-ES

Study name	Prevention and treatment with Calcifediol of Coronavirus COVID-19-induced acute respiratory syndrome (SARS)
Methods	• Trial design: RCT • Sample size: 1008 • Setting: inpatient • Language: English / Spanish (Spain) • Number of centres: NI • Type of intervention (treatment/prevention): treatment

Participants	• Inclusion criteria
	  * Age ≥ 18 and < 90 years
	  * Diagnosis confirmed by COVID-19 PCR
	  * Radiological image compatible with inflammatory pleuropulmonary exudate
	  * Signature of direct or delegated informed consent
	• Exclusion criteria
	  * Being on treatment with calcifediol or colecalciferol in any of its presentations and dosage
	  * Intolerance or allergy to calcifediol or its components
	  * Pregnancy

EUCTR2020-001717-20-ES *(Continued)*

Interventions	• Details of intervention
	  * Dose: 0.266 mg of Vitamin D3 (calcifediol)
	  * Route of administration: orally
	• Treatment details of control group (e.g dose, route of administration): best standard care
	• Concomitant therapy: none

Outcomes	Primary study outcome
	
	• Admission to the ICU
	• Death
	
	Review outcomes
	
	• All-cause mortality at day 28, day 60, time-to-event, and at hospital discharge - reported
	• Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale (WHO 2020e), WHO Ordinal Scale for Clinical Improvement (WHO 2020f)) at day 28, day 60, and up to longest follow-up); including:
	  * Improvement of clinical status:
	  ☐ weaning or liberation from invasive mechanical ventilation in surviving patients i.e. WHO ≤ 6, if ≥ 7 at baseline;
	  ☐ ventilator-free days; ventilator-free defined as WHO ≤ 6;
	  ☐ duration to liberation from invasive mechanical ventilation;
	  ☐ liberation from supplemental oxygen in surviving patients i.e. WHO ≤ 4, if ≥ 5 at baseline;
	  ☐ duration to liberation from supplemental oxygen.
	  * Worsening of clinical status:
	  ☐ need for invasive mechanical ventilation i.e. WHO 7-9, if ≤n6 at baseline;
	  ☐ need for non-invasive mechanical ventilation or high flow i.e. WHO=6, if ≤5 at baseline;
	  ☐ need for oxygen by mask or nasal prongs i.e. WHO = 5, if ≤ 4 at baseline.
	  * probably reported
	• Need for dialysis (at up to 28 days) - NP
	• Quality of life, including fatigue and neurological status, assessed with standardised scales (e.g. WHOQOL-100) at up to seven days; up to 30 days, and longest follow-up available - NP
	• Admission to ICU - reported
	• Duration of hospitalisation - probably reported
	• Time to discharge from hospital - reported
	• Viral clearance, assessed with reverse transcription polymerase chain reaction (RT-PCR) test for SARS-CoV-2 at baseline, up to 3, 7, and 15 days - probably reported
	• Vitamin D serum levels -probably reported
	• Serious adverse events, defined as number of participants with event - reported
	• Adverse events (any grade, grade 1-2, grade 3-4), defined as number of participants with event - reported
	
	Additional study outcomes
	
	• Clinical evolution
	  * Time from the onset of symptoms to discharge of patients in conventional hospitalisation.
	  * In patients who in the course of evolution required admission with mechanical ventilation in the ICU:
	  ☐ time until admission to the ICU;
	  ☐ time until mechanical ventilation is removed;
	  ☐ ICU registration.
	  * Collection of clinical evolution data in all patients (“Check list of the disease”) on days 0, 3, 7, 14 and 21 and 28.

EUCTR2020-001717-20-ES *(Continued)*

- Blood analytics
  - * Collection of hematimetry and biochemistry data ("Check list of the disease") in all patients, including RCT and Ca / Cr analysis on days 0, 3, 7, 14, 21 and 28
  - * [SUB-STUDY] 50 aliquots of 2 cc for quantification will be collected in 50 patients (25 randomised from each group) for quantification on days 0, 3, 7, 14, 21 and 28 days:
    - ☐ disease-related inflammation markers IL 1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-12, IL118, 1L32, tumor necrosis factor (TNF) α, interferon -γ, macrophage granulocyte colony stimulating factor- (GMCSF) and chemokines: CCL2, CCL3, CCL5, CXCL8, CXCL9;
    - ☐ vitamin D metabolites (25 OHD, 1,25 (OH) D and 24,25 (OH) 2D3 ratio of 25OHD / 24,25 (OH) 2D, [system catabolism marker];
    - ☐ evolution of viral load.
- Respiratory parameters, oxygen therapy and respiratory support
  - * Respiratory rate and SatO2, evaluated at baseline and on days 3, 7, 14, 21 and 28
  - * O2 / FiO2 saturation ratio: the average of three evaluations of said ratio will be taken into account with a time interval of at least 6 hours, before and after the administration of calcifediol at 24 hours, at 3 days, at 7 days, at 14 days and at 28 days.
  - * Evaluate degree of dyspnoea at 0 3, 7, 14 days with the Borg analog scale.
  - * Level of consciousness, assessed at baseline and on days 3, 7, 14, 21 and 28
  - * Applied oxygen (FiO2) evaluated at baseline and on days 3, 7, 14, 21 and 28
    - ☐ Time until the absence of oxygen need, at least for 48 hours to maintain a saturation at room air ≥ 93%.
    - ☐ Number of days in need of supplemental oxygen.
    - ☐ Average time in the duration of high flow nasal oxygen and Invasive mechanical ventilation
  - * Collect patients who require invasive mechanical ventilation, at baseline and on days 3, 7, 14, 21 and 28.
  - * Collect radiological evolution established by baseline radiological evaluator, day 14 and day 28.
  - * Collection of thromboembolic events.
- Security variables
  - * Collection of adverse events potentially related to the medication and its administration.
  - * Vital signs and physical exploration
  - * Blood biochemistry
  - * Hematological parameters

Starting date	20/04/2020
Contact information	Antonio Luque Edificio IMIBIC. Avenida Menéndez Pidal s/n 14004 Córdoba Spain 0034671596070 0034957736571 uicec@imibic.org
Notes	• Recruitment status: ongoing • Prospective completion date: NI • Date last update was posted: NI • Sponsor/funding: Fundación para la Investigación Biomédica de Córdoba

EUCTR2020-001960-28-ES

Study name	Efficacy of vitamin D treatment in patients diagnosed with pneumonia who require hospital admission and have vitamin D deficiency and a positive diagnosis for SARS-Cov-2 (COVID-19)
Methods	• Trial design: double-blind RCT • Sample size: 108 • Setting: inpatient • Language: English / Spanish (Spain) • Number of centres: 1 • Type of intervention (treatment/prevention): treatment

Participants	• Inclusion criteria
	  * Older patients of both sexes
	  * Admitted to the Respiratory and / or Internal Medicine Unit of the Hospital De Santiago, the OSI Araba HUA is walking due to pneumonia
	  * Possibility for observation during the treatment period
	  * Signature of written and, exceptionally oral, informed consent
	  * Have requested the test for SARS-CoV-2 (nasopharyngeal exudate PCR) and obtain positive results
	  * Having a deficiency of vitamin D (25 (OH) vitamin D), defined by blood levels below 30 mg/mL
	• Exclusion criteria
	  * Patients taking any type of vitamin D supplement
	  * Patients with hypoparathyroidism
	  * Pregnant or lactating women
	  * Patients in whom vitamin D administration is formally contraindicated
	  * Patients who cannot take vitamin D orally at the time of enrolment

Interventions	• Details of intervention: Vitamin D supplement (Hydroferol)
	  * Dose: 0.266 mg soft capsules
	  * Route of administration: oral
	• Treatment details of control group (e.g dose, route of administration): placebo
	• Concomitant therapy: none

Outcomes	Primary study outcome
	• Evolution of respiratory syndrome compared to patients who do not receive a supplement, in terms of mortality and ICU admission
	Review outcomes
	• All-cause mortality at day 28, day 60, time-to-event, and at hospital discharge - probably reported
	• Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale (WHO 2020e), WHO Ordinal Scale for Clinical Improvement (WHO 2020f)) at day 28, day 60, and up to longest follow-up); including:
	  * Improvement of clinical status:
	  ☐ weaning or liberation from invasive mechanical ventilation in surviving patients i.e. WHO ≤ 6, if ≥ 7 at baseline;
	  ☐ ventilator-free days; ventilato- free defined as WHO ≤ 6;
	  ☐ Duration to liberation from invasive mechanical ventilation;
	  ☐ Liberation from supplemental oxygen in surviving patients i.e. WHO ≤ 4, if ≥ 5 at baseline;
	  ☐ Duration to liberation from supplemental oxygen.
	  * Worsening of clinical status:
	  ☐ need for invasive mechanical ventilation i.e. WHO 7-9, if ≤n6 at baseline;
	  ☐ need for non-invasive mechanical ventilation or high flow i.e. WHnO = 6, if ≤ 5 at baseline;
	  ☐ need for oxygen by mask or nasal prongs i.e. WHO = 5, if ≤ 4 at baseline
	  * probably reported

EUCTR2020-001960-28-ES *(Continued)*

- Need for dialysis (at up to 28 days) - NP
- Quality of life, including fatigue and neurological status, assessed with standardised scales (e.g. WHOQOL-100) at up to seven days; up to 30 days, and longest follow-up available - NP
- Admission to ICU - probably reported
- Duration of hospitalisation - reported
- Time to discharge from hospital - probably reported
- Viral clearance, assessed with reverse transcription polymerase chain reaction (RT-PCR) test for SARS-CoV-2 at baseline, up to 3, 7, and 15 days - NP
- Vitamin D serum levels - reported
- Serious adverse events, defined as number of participants with event - NP
- Adverse events (any grade, grade 1-2, grade 3-4), defined as number of participants with event - NP

Additional study outcomes

- Diagnosis (SARS-CoV-2 positive / negative)
- Disease severity determined based on the categories established according to the clinic presented by the patients included in the study
- Blood vitamin D concentration
- Clinical symptoms
- Days in ICU / hospital
- Discharge date
- Drug use (specify drugs and doses)
- Death (Yes /No)
- Income costs

Starting date	26/05/2020
Contact information	Investigation Institute Bioaraba Inés Pérez Francisco c/José Atxotegui s/n Vitoria-Gasteiz 01009 Spain INES.PEREZFRANCISCO@osakidetza.eus
Notes	• Recruitment status: ongoing • Prospective completion date: NI • Date last update was posted: NI • Sponsor/funding: Investigation Institute Bioaraba

EUCTR2020-002274-28-ES

Study name	Usefulness of vitamin D on morbidity and mortality of SARS-COV-2 virus infection (Covid-19) at the Central University Hospital of Asturias
Methods	• Trial design: RCT, non-controlled • Sample size: 60 • Setting: inpatient • Language: English / Spanish (Spain) • Number of centres: NI

EUCTR2020-002274-28-ES *(Continued)*

	• Type of intervention (treatment/prevention): treatment
Participants	• Inclusion criteria * Patients treated in the ER or admitted to the HUCA Hospitalisation unit * Diagnosis of COVID19 demonstrated by positive PCR for SARS COV2 prior to randomisation * Age> = 18 years * That they have accepted to participate in the study through informed consent • Exclusion criteria * When discharge or a fatal outcome is expected within the next 48 hours * Obvious cognitive impairment (inability to communicate) * PCR for SARS-COV 2 negative despite radiological, analytical and clinical findings compatible with this type of infection * Allergy to vitamin D * Patients who are receiving, or have received in the past 3 months, any form of vitamin D * Pregnant women
Interventions	• Details of intervention * Dose: 100,000 IU of native Vitamin D3 (calcifediol) (1 dose) * Route of administration: oral solution in sachet • Treatment details of control group (e.g. dose, route of administration): NR • Concomitant therapy: none
Outcomes	Primary study outcome: (14 and 21 days or until a negative SARS-CoV-2 test every 7 days) • Percentage and time of patients who have a negative SARS-CoV-2 viral load • Clinical symptoms and time during hospitalisations • Improvement of biochemical and molecular parameters of inflammation • Overall mean hospital stay • Percentage of patients requiring transfer to the ICU • Average stay in ICU • Mortality during follow-up Review outcomes • All-cause mortality at day 28, day 60, time-to-event, and at hospital discharge: reported at day 21 • Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale (WHO 2020e), WHO Ordinal Scale for Clinical Improvement (WHO 2020f)) at day 28, day 60, and up to longest follow-up); including: NP * Improvement of clinical status: ☐ weaning or liberation from invasive mechanical ventilation in surviving patients i.e. WHO ≤ 6, if ≥7 at baseline; ☐ ventilator-free days; ventilator-free defined as WHO ≤ 6; ☐ duration to liberation from invasive mechanical ventilation; ☐ liberation from supplemental oxygen in surviving patients i.e. WHO ≤4, if ≥5 at baseline; ☐ duration to liberation from supplemental oxygen * Worsening of clinical status: ☐ need for invasive mechanical ventilation i.e. WHO 7-9, if ≤ 6 at baseline; ☐ need for non-invasive mechanical ventilation or high flow i.e. WHO = 6, if ≤ 5 at baseline; ☐ need for oxygen by mask or nasal prongs i.e. WHO = 5, if ≤ 4 at baseline • Need for dialysis (at up to 28 days): NP • Quality of life, including fatigue and neurological status, assessed with standardised scales (e.g. WHOQOL-100) at up to seven days; up to 30 days, and longest follow-up available: NP • Admission to ICU: reported • Duration of hospitalisation: reported • Time to discharge from hospital: reported

EUCTR2020-002274-28-ES *(Continued)*

	• Viral clearance, assessed with reverse transcription polymerase chain reaction (RT-PCR) test for SARS-CoV-2 at baseline, up to 3, 7, and 15 days: reported • Vitamin D serum levels: reported • Serious adverse events, defined as number of participants with event: NP • Adverse events (any grade, grade 1-2, grade 3-4), defined as number of participants with event: NP Additional study outcomes:
Starting date	2020-05-21
Contact information	Avenida Hospital Universitario s/n: enrique.caso@gmail.com
Notes	• Recruitment status: ongoing • Prospective completion date: NR • Date last update was posted: NR • Sponsor/funding: Fundación para la Investigación y la Innovación Biosanitaria del Principado de Asturias (FINBA)

EUCTRCT2020-002312-43-ES

Study name	Clinical trial, PHASE III, randomized, open-label, to evaluate the efficacy of administering high-dose cholecalciferol orally alongside standard therapy in patients with COVID-19 pneumonia (COVID-19 HUSO).
Methods	• Trial design: open-label, phase III RCT • Sample size: 82 • Setting: inpatient • Language: English (Spain) • Number of centres: 1 • Type of intervention (treatment/prevention): treatment

Participants	• Inclusion criteria
	  * 25-hydroxyvitamin D3 levels < 30 ng/mL
	  * Agree to participate in the study by signing the informed consent
	  * Men and women aged ≥ 18 and ≤ 85
	  * Patients admitted with a diagnosis of pneumonia based on clinical-radiological criteria or confirmed by COVID-19 microbiology, who have had > 7 days of symptoms (cough or fever) and whose oxygen saturation is less than 94%
	  * Men and women with reproductive capacity should agree to use contraceptives in the study and within 30 days of the last visit
	  * women in the study with reproductive capacity should have a negative pregnancy test at the time of inclusion

EUCTRCT2020-002312-43-ES *(Continued)*

- Exclusion criteria
  * Patients participating in any other clinical trials with drugs with potential antiviral action for COVID-19
  * They are already being treated with vitamin D
  * Evidence of multiorgan failure
  * Patients requiring mechanical ventilation at the time of inclusion
  * Patients with hypersensitivity to the active ingredient cholecalciferol or to refined olive oil excipient
  * Patients with hypercalcemia or hypercalciuria
  * Kidney stones (nephrolithiasis, nephrocalcinosis) in patients with chronic hypercalcemia
  * Patients with severe renal failure. (stage 4, eGF < 30)
  * Patients being treated with digoxin.
  * Patients with a diagnosis of hereditary fructose intolerance, malabsorption of glucose-galactose or sucrose insufficiency.
  * Gestation or lactation
  * Sarcoidosis
  * Hyperparathyroidism
  * Patients who for any reason should not be included in the study according to evaluation of the investigation team
  * Patients who are not capable of understanding the information sheet and unable to sign the informed consent
  * Patients who are expected to be transferred to another facility within 96 hours
  * Patients who are expected to die within the next 24-48 hours

Interventions

- Details of intervention
  * Dose: increased levels of 25-hydroxyvitamin D3 on days 7 and 14 after high-dose vitamin D treatment (10. 000 IU/day) Thorens@ 25,000 IU single-dose vials (maximum 14 days)
  * Route of administration:oral 2.5 mL = 1mL/day on admission
- Treatment details of control group (e.g. dose, route of administration): conventional dosing (2,000 IU/day) Thorens@ 25,000 IU single-dose vials oral solution 2.5 mL = 0.2 mL/day on admission (maximum 14 days)
- Concomitant therapy: none

Outcomes

Primary study outcome

- Increased levels of 25-hydroxyvitamin D3 will be determined on days 7, and 14 after initiation of treatment

Review outcomes

- All-cause mortality at day 28, day 60, time-to-event, and at hospital discharge - probably reported
- Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale (WHO 2020e), WHO Ordinal Scale for Clinical Improvement (WHO 2020f)) at day 28, day 60, and up to longest follow-up); including:
  * Improvement of clinical status:
    - ☐ weaning or liberation from invasive mechanical ventilation in surviving patients i.e. WHO ≤ 6, if ≥7 at baseline;
    - ☐ Ventilator-free days; ventilator free defined as WHO ≤ 6;
    - ☐ duration to liberation from invasive mechanical ventilation;
    - ☐ liberation from supplemental oxygen in surviving patients i.e. WHO ≤ 4, if ≥ 5 at baseline;
    - ☐ duration to liberation from supplemental oxygen
  * Worsening of clinical status:
    - ☐ need for invasive mechanical ventilation i.e. WHO 7-9, if ≤ 6 at baseline;
    - ☐ need for non-invasive mechanical ventilation or high flow i.e. WHO = 6, if ≤ 5 at baseline;
    - ☐ need for oxygen by mask or nasal prongs i.e. WHO = 5, if ≤ 4 at baseline
  * Probably reported

EUCTRCT2020-002312-43-ES *(Continued)*

- Need for dialysis (at up to 28 days) - probably reported
- Quality of life, including fatigue and neurological status, assessed with standardised scales (e.g. WHOQOL-100) at up to seven days; up to 30 days, and longest follow-up available - NP
- Admission to ICU - reported
- Duration of hospitalisation - NP
- Time to discharge from hospital - NP
- Viral clearance, assessed with reverse transcription polymerase chain reaction (RT-PCR) test for SARS-CoV-2 at baseline, up to 3, 7, and 15 days - probably reported
- Vitamin D serum levels - probably reported
- Serious adverse events, defined as number of participants with event -probably reported
- Adverse events (any grade, grade 1-2, grade 3-4), defined as number of participants with event - probably reported

Additional study outcomes

- Safety and tolerability of both treatment guidelines
- Secondary efficacy parameters between the two treatment guidelines on days 7 and 14 of treatment initiation: no progression to respiratory failure, no Increased oxygen requirements; need for mechanical ventilation; reduction of analytical parameters associated with poor prognosis; radiological progression of the disease; average hospital stay; intensification treatments such as steroid boluses, Tocilizumab or Anakinra, ICU admission, % mortality at end of follow-up
- Evolution of the analytical parameters on the 7th and 14th days of treatment
  * Haematological: haemogram, differential count, D-dimer, coagulation study, fibrinogen
  * Biochemicals: renal function (creatinine, urea, and electrolytes), liver function (AST, ALT, total and fractionated bilirubin, GGT, LDH), C-reactive protein (PCR), procalcitonin (PCT), troponin, pro-BNP, CPK, albumin, total proteins, uric acid, cholesterol, triglycerides, and glucose
  * Phospho-calcium metabolism: calcium, PTHi, phosphorus and magnesium
- Immunological study: immunological parameters on days 7 and 14 of the beginning of the treatment of IL1b, IL2r, IL6, IL8, IL10, TNF alpha, MIP-1 alpha, MIP-1 beta, CD14, GM-CSF, IFN alpha, IFN beta y IFN gamma
- Viral load evolution, if available

Starting date	31/05/2020
Contact information	Miguel Cervero Avenida Orellana S/N Leganés 28911 Spain 00349148180008338 mcerveroj@gmail.com
Notes	• Recruitment status: ongoing • Prospective completion date: NI • Date last update was posted: NI • Sponsor/funding: Miguel Cervero Jiménez, servicio de Medicina Interna, Hospital Universitario Severo Ochoa

NCT04334005

Study name	Vitamin D on prevention and treatment of COVID-19 (COVITD-19)

NCT04334005 *(Continued)*

Methods	• Trial design: RCT • Sample size: 200 • Setting: outpatient • Language: English (Spain) • Number of centres: NA • Type of intervention (treatment/prevention): treatment

Participants	• Inclusion criteria
	  * Age 40-70 years
	  * Non-severe symptomatic patients who present cough, fever, nasal congestion, gastrointestinal symptoms, fatigue, anosmia, ageusia or alternative signs of respiratory infections
	• Exclusion criteria
	  * Patients presenting severe respiratory and/or multisystemic symptoms compatible with advanced COVID-19 and intercurrent acute or severe chronic diseases (i.e. active cancer)

Interventions	• Details of intervention
	  * Dose: 25,000 IU of vitamin D supplement + standard of care
	  * Route of administration: taken in the morning together with a toast with olive oil to facilitate its absorption
	• Treatment details of control group (e.g dose, route of administration): standard of care: prescription of NSAIDs, ACE2 inhibitor, ARB or thiazolidinediones, according to clinician criteria, based on the current recommendations
	• Concomitant therapy: none

Outcomes	Primary study outcome
	• Composite of cumulative death (i.e. mortality) for all causes and for specific causes. [Time Frame: through study completion, an average of 10 weeks]
	Review outcomes
	• All-cause mortality at day 28, day 60, time-to-event, and up to longest follow-up - reported
	• Admission to hospital (WHO≥ 4) - reported
	• Development of moderate to severe clinical COVID-19 symptoms, defined as WHO Clinical Progression Scale ≥ 6 (WHO 2020e), up to longest follow-up
	  * Need for invasive mechanical ventilation, non-invasive mechanical ventilation or high flow i.e. WHO ≥6, severe disease:
	  ☐ need for invasive mechanical ventilation i.e. WHO 7-9;
	  ☐ need for non-invasive mechanical ventilation or high flow i.e. WHO = 6;
	  * need for hospitalisation with or without supplemental oxygen i.e. WHO = 4-5, moderate disease;
	  ☐ need for oxygen by mask or nasal prongs i.e. WHO = 5;
	  ☐ need for hospitalisation without oxygen therapy i.e. WHO = 4.
	  * reported
	• Quality of life, including fatigue and neurological status, assessed with standardised scales (e.g. WHOQOL-100) at up to 7 days, up to 30 days, and longest follow-up available - NP
	• Duration of hospitalisation, for subgroup of participants hospitalised during course of disease - NP
	• Time to hospital discharge, for subgroup of participants hospitalised during course of disease - NP
	• Vitamin D serum levels - NP
	• Serious adverse events, defined as number of participants with event - NP
	• Adverse events (any grade, grade 1-2, grade 3-4), defined as number of participants with event- NP
	Additional study outcomes
	• Necessity of invasive assisted ventilation
	• Necessity of non-invasive assisted ventilation

NCT04334005 *(Continued)*

	• Intensive care unit admission • Post-anesthesia care unit admission • Hospital admission • Medical consultation • Home care and isolation time • Bed rest time • symptoms' duration (i.e. cough, fever, nasal congestion, gastrointestinal symptoms, fatigue, anosmia, ageusia, diarrhea or alternative signs of COVID-19) • Subjective perception of recovery Time Frame: through study completion, an average of 10 weeks
Starting date	10/04/2020
Contact information	Manuel J Castillo, MD, PhD +34 649440850 mcgarzon@ugr.es
Notes	• Recruitment status: not yet recruiting • Prospective completion date: 30/06/2020 • Date last update was posted: 07/04/2020 • Sponsor/funding: Universidad de Granada

NCT04344041

Study name	COvid-19 and Vitamin D supplementation: a multicenter randomizedcControlled trial of high dose versus standard dose vitamin D3 in high-risk COVID-19 Patients (CoVitTrial)
Methods	• Trial design: RCT • Sample size: 260 • Setting: mixed (Patient seen in hospitalisation or consultation or in nursing home) • Language: English (France) • Number of centres: 10 • Type of intervention (treatment/prevention): treatment
Participants	• Inclusion criteria * Age ≥ 65 years old * Infection with COVID-19 diagnosed with RT-PCR SARS-CoV-2 or withCT-scan of the chest suggesting viral pneumonia of peripheral predominance in a clinically relevant context * Patient seen in hospitalisation or consultation or in nursing home * Diagnosed within the preceding 3 days * Having at least one of the following two risk factors for complications: ☐ age ≥75 years; ☐ Peripheral capillary oxygen saturation (SpO2) ≤ 94% ambient air, or a partial oxygen pressure (PaO2) to fraction of inspired oxygen (FiO2) ratio ≤ 300 mmHg. * Patients affiliated with or benefitting from a social security scheme * Written and signed consent of the patient or a relative or, if not possible, emergency inclusion procedure

NCT04344041 *(Continued)*

- Exclusion criteria
  * Organ failure requiring admission to a resuscitation or high dependency unit
  * Comorbidity that is life-threatening in the short term (life expectancy <3 months)
  * Any reason that makes follow-up at day 28 impossible
  * Vitamin D supplementation in the previous month, with the exception of treatment providing less than 800 IU of vitamin D per day
  * Contraindication for vitamin D supplementation: active granulomatosis (sarcoidosis, tuberculosis, lymphoma), history of calcic lithiasis, known hypervitaminosis D or hypercalcaemia, known intolerance to vitamin D
  * Participation in another simultaneous trial
  * Persons deprived of their liberty by administrative or judicial decision, persons under psychiatric care under duress, adults subject to a legal protection measure
  * Peripheral capillary oxygen saturation (SpO2) ≤ 92% in spite of an oxygen therapy > 5L/minuter

Interventions

- Details of intervention
  * Dose: vitamin D supplementation of 400,000 IU
  * Route of administration: single dose orally
- Treatment details of control group (e.g dose, route of administration): Vitamin D supplementation of 50,000 IU in a single dose orally
- Concomitant therapy: none

Outcomes

Primary study outcome

- Number of death of any cause, during the 14 days following the inclusion and intervention

Review outcomes

Inpatient setting

- All-cause mortality at day 28, day 60, time-to-event, and at hospital discharge - reported
- Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale (WHO 2020e), WHO Ordinal Scale for Clinical Improvement (WHO 2020f)) at day 28, day 60, and up to longest follow-up); including:
  * Improvement of clinical status:
    - ☐ weaning or liberation from invasive mechanical ventilation in surviving patients i.e. WHO ≤ 6, if ≥ 7 at baseline;
    - ☐ ventilator-free days; ventilator-free defined as WHO ≤ 6;
    - ☐ duration to liberation from invasive mechanical ventilation;
    - ☐ liberation from supplemental oxygen in surviving patients i.e. WHO ≤ 4, if ≥ 5 at baseline;
    - ☐ duration to liberation from supplemental oxygen.
  * Worsening of clinical status:
    - ☐ Need for invasive mechanical ventilation i.e. WHO 7-9, if ≤6 at baseline;
    - ☐ Need for non-invasive mechanical ventilation or high flow i.e. WHO = 6, if ≤ 5 at baseline;
    - ☐ Need for oxygen by mask or nasal prongs i.e. WHO = 5, if ≤4 at baseline
  * reported
- Need for dialysis (at up to 28 days) - NP
- Quality of life, including fatigue and neurological status, assessed with standardised scales (e.g. WHOQOL-100) at up to seven days; up to 30 days, and longest follow-up available - NP
- Admission to ICU - NP
- Duration of hospitalisation - NP
- Time to discharge from hospital - NP
- Viral clearance, assessed with reverse transcription polymerase chain reaction (RT-PCR) test for SARS-CoV-2 at baseline, up to 3, 7, and 15 days - NP
- Vitamin D serum levels - reported
- Serious adverse events, defined as number of participants with event - reported

NCT04344041 *(Continued)*

- Adverse events (any grade, grade 1-2, grade 3-4), defined as number of participants with event - probably reported

Outpatient setting

- All-cause mortality at day 28, day 60, time-to-event, and up to longest follow-up - reported
- Admission to hospital (WHO≥ 4) - reported
- Development of moderate to severe clinical COVID-19 symptoms, defined as WHO Clinical Progression Scale ≥ 6 (WHO 2020e), up to longest follow-up
  * need for invasive mechanical ventilation, non-invasive mechanical ventilation or high flow i.e. WHO ≥ 6, severe disease;
    ☐ need for invasive mechanical ventilation i.e. WHO 7-9;
    ☐ need for non-invasive mechanical ventilation or high flow i.e. WHO = 6.
  * Need for hospitalisation with or without supplemental oxygen i.e. WHO = 4-5, moderate disease;
    ☐ need for oxygen by mask or nasal prongs i.e. WHO = 5;
    ☐ need for hospitalisation without oxygen therapy i.e. WHO = 4.
  * reported
- Quality of life, including fatigue and neurological status, assessed with standardised scales (e.g. WHOQOL-100) at up to 7 days, up to 30 days, and longest follow-up available - NP
- Duration of hospitalisation, for subgroup of participants hospitalised during course of disease - NP
- Time to hospital discharge, for subgroup of participants hospitalised during course of disease - NP
- Vitamin D serum levels - reported
- Serious adverse events, defined as number of participants with event - reported
- Adverse events (any grade, grade 1-2, grade 3-4), defined as number of participants with event - probably reported

Additional study outcomes:

- Number of death of any cause, during the 28 days following the inclusion and intervention.
- Clinical evolution between day 0 and day 14 based on the change of the WHO Ordinal Scale for Clinical Improvement (OSCI) for COVID-19
- Clinical evolution between day 0 and day 28 based on the change of the OSCI for COVID-19
- Rate of patients with at least one severe adverse event at day 28, according to the regulations
- Number of death of any cause during the 14 days following the inclusion and intervention, in patients with severe hypovitaminosis D (25-OHD <25nmol/L) at baseline
- Number of death of any cause during the 28 days following the inclusion and intervention, in patients with severe hypovitaminosis D (25-OHD <25nmol/L) at baseline
- Clinical evolution between day 0 and day 14 based on the change of the OSCI for COVID-19, in patients with severe hypovitaminosis D (25-OHD <25nmol/L) at baseline
- Clinical evolution between day 0 and day 28 based on the change of the OSCI for COVID-19, in patients with severe hypovitaminosis D (25-OHD<25nmol/L) at baseline
- Number of death of any cause during the 14 days following the inclusion and intervention, depending on serum vitamin D concentration achieved at day 7 (25-OHD<75nmol/L or 25-OHD≥75nmol/L)
- Number of death of any cause during the 28 days following the inclusion and intervention, depending on serum vitamin D concentration achieved at day 7 (25-OHD<75nmol/L or 25-OHD≥75nmol/L)
- Clinical evolution between day 0 and day 14 based on the change of the OSCI for COVID-19, depending on serum vitamin D concentration achieved at day 7 (25-OHD<75nmol/L or 25-OHD≥75nmol/L)
- Clinical evolution between day 0 and day 28 based on the change of the OSCI for COVID-19, depending on serum vitamin D concentration achieved at day 7 (25-OHD<75nmol/L or 25-OHD≥75nmol/L)
- Number of death of any cause during the 14 days following the inclusion and intervention, in patients with severe hypovitaminosis D (25-OHD<25nmol/L) at day 0, depending on serum vitamin D concentration achieved at day 7 (<75nmol/L or ≥75nmol/L)

NCT04344041 *(Continued)*

	• Number of death of any cause during the 28 days following the inclusion and intervention, in patients with severe hypovitaminosis D (25-OHD<25nmol/L) at day 0, depending on serum vitamin D concentration achieved at day 7 (<75nmol/L or ≥75nmol/L) • Clinical evolution between day 0 and day 14 based on the change of the OSCI for COVID-19, in patients with severe hypovitaminosis D (25-OHD<25nmol/L) at day 0, depending on serum vitamin D concentration achieved at day 7 (<75nmol/L or ≥75nmol/L) • Clinical evolution between day 0 and day 28 based on the change of the OSCI for COVID-19, in patients with severe hypovitaminosis D (25-OHD<25nmol/L) at day 0, depending on serum vitamin D concentration achieved at day 7 (<75nmol/L or ≥75nmol/L) • Number of death of any cause during the 14 days following the inclusion and intervention, depending on evolution of serum vitamin D concentration between day 0 and day 7 • Number of death of any cause during the 28 days following the inclusion and intervention, depending on evolution of serum vitamin D concentration between day 0 and day 7 • Clinical evolution between day 0 and day 14 based on the change of the OSCI for COVID-19, depending on evolution of serum vitamin D concentration between day 0 and day 7 • Clinical evolution between day 0 and day 28 based on the change of the OSCI for COVID-19, depending on evolution of serum vitamin D concentration between day 0 and day 7 • Number of death of any cause during the 14 days following the inclusion and intervention, compared to mortality data in French hospital geriatric units from the current national survey by the French Society of Geriatrics and Gerontology
Starting date	15/04/2020
Contact information	Cédric ANNWEILER 241354725 ext +33 cedric.annweiler@chu-angers.fr

Notes	• Recruitment status:
	  * Recruiting (according to clinical tials.gov)
	  * Completed (according to EU Clinical Trials Register)
	• Prospective completion date: 05/2021
	• Date last update was posted: 05/10/2020
	• Sponsor/funding: University Hospital, Angers

NCT04363840

Study name	The LEAD COVID-19 Trial: Low-risk, Early Aspirin and vitamin D to reduce COVID-19 hospitalizations (LEAD COVID-19)
Methods	• Trial design: RCT • Sample size: 1080 • Setting: outpatient • Language: English (USA) • Number of centres: NA • Type of intervention (treatment/prevention): treatment

Participants	• Inclusion criteria
	  * Patients > 18 years
	  * Written informed consent
	  * New (within 24 hours) COVID-19 diagnosis

NCT04363840 *(Continued)*

- Exclusion criteria
  * Pregnant patients or prisoners
  * History of GI bleeding or peptic ulcer disease, or spontaneous bleeding from other sites; history of thrombocytopenia; history of chronic kidney disease; concurrent use of nonsteroidal anti-inflammatory drugs, or steroids.
  * Hypervitaminosis D and associated risk factors: renal failure, liver failure, hyperparathyroidism, sarcoidosis, histoplasmosis

Interventions	• Details of intervention * Dose: aspirin 81 mg and vitamin D 50,000 IU * Route of administration: p.o. daily for 2 weeks • Treatment details of control group (e.g dose, route of administration): Aspirin only vs. no intervention • Concomitant therapy: none
Outcomes	Primary study outcome • Hospitalisation for COVID-19 symptoms Review outcomes • All-cause mortality at day 28, day 60, time-to-event, and up to longest follow-up - NP • Admission to hospital (WHO≥ 4) - reported • Development of moderate to severe clinical COVID-19 symptoms, defined as WHO Clinical Progression Scale ≥ 6 (WHO 2020e), up to longest follow-up * Need for invasive mechanical ventilation, non-invasive mechanical ventilation or high flow i.e. WHO ≥6, severe disease; ☐ need for invasive mechanical ventilation i.e. WHO 7-9; ☐ need for non-invasive mechanical ventilation or high flow i.e. WHO = 6. * need for hospitalisation with or without supplemental oxygen i.e. WHO = 4-5, moderate disease; ☐ need for oxygen by mask or nasal prongs i.e. WHO = 5; ☐ need for hospitalisation without oxygen therapy i.e. WHO=4. * NP • Quality of life, including fatigue and neurological status, assessed with standardised scales (e.g. WHOQOL-100) at up to 7 days, up to 30 days, and longest follow-up available - NP • Duration of hospitalisation, for subgroup of participants hospitalised during course of disease - NP • Time to hospital discharge, for subgroup of participants hospitalised during course of disease - NP • Vitamin D serum levels - NP • Serious adverse events, defined as number of participants with event - NP • Adverse events (any grade, grade 1-2, grade 3-4), defined as number of participants with event - NP Additional study outcomes: • None
Starting date	05/2020
Contact information	Frank H Lau, MD 504 412 1240 flau@lsuhsc.edu
Notes	• Recruitment status: not yet recruiting • Prospective completion date: 12/2020 • Date last update was posted: 27/04/2020

NCT04363840 *(Continued)*

	• Sponsor/funding: Louisiana State University Health Sciences Center in New Orleans

NCT04385940

Study name	Vitamin D and COVID-19 management
Methods	• Trial design: RCT • Sample size: 64 • Setting: Mixed (inpatient and outpatient) • Language: English (USA) • Number of centres: NR • Type of intervention (treatment/prevention): treatment

Participants	• Inclusion criteria
	  * Patients with COVID-19
	  * ≥ 17 years old
	  * Both sexes
	• Exclusion criteria
	  * Patients with dementia, learning disability, mental health needs and alcohol or drug dependency, pregnant women
	  * Patients with sarcoidosis, hypercalcemia, known vitamin D intolerance

Interventions	• Details of intervention
	  * Dose: Ddrops® product Vitamin D3 50,000 IU
	  * Route of administration: oral
	• Treatment details of control group (e.g dose, route of administration): Vitamin D3 1000 IU
	• Concomitant therapy: none

Outcomes	Primary study outcome
	• Symptoms recovery
	Review outcomes
	Outpatient setting
	• All-cause mortality at day 28, day 60, time-to-event, and up to longest follow-up - NP
	• Admission to hospital (WHO≥ 4) - reported
	• Development of moderate to severe clinical COVID-19 symptoms, defined as WHO Clinical Progression Scale ≥ 6 (WHO 2020e), up to longest follow-up
	  * Need for invasive mechanical ventilation, non-invasive mechanical ventilation or high flow i.e. WHO ≥ 6, severe disease;
	  ☐ need for invasive mechanical ventilation i.e. WHO 7-9;
	  ☐ need for non-invasive mechanical ventilation or high flow i.e. WHO = 6.
	  * Need for hospitalisation with or without supplemental oxygen i.e. WHO = 4-5, moderate disease;
	  ☐ need for oxygen by mask or nasal prongs i.e. WHO = 5;
	  ☐ need for hospitalisation without oxygen therapy i.e. WHO = 4.
	  * NP
	• Quality of life, including fatigue and neurological status, assessed with standardised scales (e.g. WHOQOL-100) at up to 7 days, up to 30 days, and longest follow-up available - NP
	• Duration of hospitalisation, for subgroup of participants hospitalised during course of disease - reported
	• Time to hospital discharge, for subgroup of participants hospitalised during course of disease - probably reported

NCT04385940 *(Continued)*

- Vitamin D serum levels - NP
- Serious adverse events, defined as number of participants with event - NP
- Adverse events (any grade, grade 1-2, grade 3-4), defined as number of participants with event - NP

Inpatient setting

- All-cause mortality at day 28, day 60, time-to-event, and at hospital discharge - NP
- Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale (WHO 2020e), WHO Ordinal Scale for Clinical Improvement (WHO 2020f)) at day 28, day 60, and up to longest follow-up); including:
  * Improvement of clinical status:
    - ☐ weaning or liberation from invasive mechanical ventilation in surviving patients i.e. WHO ≤ 6, if ≥7 at baseline;
    - ☐ ventilator-free days; ventilator-free defined as WHO ≤ 6;
    - ☐ duration to liberation from invasive mechanical ventilation;
    - ☐ liberation from supplemental oxygen in surviving patients i.e. WHO ≤ 4, if ≥ 5 at baseline;
    - ☐ duration to liberation from supplemental oxygen
  * Worsening of clinical status:
    - ☐ need for invasive mechanical ventilation i.e. WHO 7-9, if ≤ 6 at baseline;
    - ☐ need for non-invasive mechanical ventilation or high flow i.e. WHO = 6, if ≤ 5 at baseline;
    - ☐ need for oxygen by mask or nasal prongs i.e. WHO = 5, if ≤4 at baseline
  * NP
- Need for dialysis (at up to 28 days) - NP
- Quality of life, including fatigue and neurological status, assessed with standardised scales (e.g. WHOQOL-100) at up to seven days; up to 30 days, and longest follow-up available - NP
- Admission to ICU - probably reported
- Duration of hospitalisation - reported
- Time to discharge from hospital - probably reported
- Viral clearance, assessed with reverse transcription polymerase chain reaction (RT-PCR) test for SARS-CoV-2 at baseline, up to 3, 7, and 15 days -
- Vitamin D serum levels - NP
- Serious adverse events, defined as number of participants with event - NP
- Adverse events (any grade, grade 1-2, grade 3-4), defined as number of participants with event - NP

Additional study outcomes

- Hospitalisation
- Blood white blood cell count (WBC)
- Duration of mechanical ventilation
- Duration of hospitalisation
- Intensive care unit (ICU) admission
- Duration of ICU stay
- Blood C-reactive protein (CRP)
- Blood Lymphocyte count
- Blood Ferritin
- Blood platelet count
- Blood interleukin-6 (IL-6)
- Blood Tumor Necrosis Factor alpha (TNF)

Starting date	06/2020
Contact information	Aldo Montano-Loza Associate Professor of Medicine, Program Director of Hepatology

NCT04385940 *(Continued)*

	University of Alberta
Notes	• Recruitment status: not yet recruiting • Prospective completion date: 12/2020 • Date last update was posted: 05/06/2020 • Sponsor/funding: University of Alberta

NCT04386850

Study name	Oral 25-hydroxyvitamin D3 and COVID-19
Methods	• Trial design: RCT • Sample size: 1500 • Setting: outpatient • Language: English (USA) • Number of centres: NA • Type of intervention (treatment/prevention): 2 groups, one for treatment, one for prevention
Participants	• Inclusion criteria * Older than 18 years old and younger than 75 years old for all study groups * Meet the diagnostic criteria of COVID-19 for different types (including ordinary type, heavy type and critical type) in infected patients * No medications or disorders that would affect vitamin D metabolism * Women must be on birth control and not pregnant * Ability and willingness to give informed consent and comply with protocol requirements • Exclusion criteria * Ongoing treatment with pharmacologic doses of vitamin D, vitamin D metabolites or analogues * Pregnant or lactating women * Severe underlying diseases, such as advanced malignant tumors, endstage lung disease, etc * History of elevated serum calcium >10.6 mg/dl; that is corrected for albumin concentration or subjects with a history of hypercalciuria and kidney stones * Chronic hepatic dysfunction, chronic kidney disease or intestinal malabsorption syndromes including inflammatory bowel disease * Supplementation with over the counter formulations of vitamin D2 or vitamin D3 * Use of tanning bed or artificial UV exposure within the last two weeks * Consuming medication affecting vitamin D metabolism or absorption (anticonvulsants, anti-tuberculosis medication glucocorticoids, HIV medications and cholestyramine) * Participants with a history of an adverse reaction to orally administered vitamin D, vitamin D metabolites or analogues. * Participants with a history of conditions that can lead to high serum calcium levels such as sarcoidosis, tuberculosis and some lymphomas associated with activated macrophages which increase the production of 1,25(OH)2D. * Inability to give informed consent
Interventions	• Details of intervention * Dose: 25-Hydroxyvitamin D3 25 mcg once * Route of administration: p.o. daily at bedtime for 2 months • Details of control * Placebo daily for 2 months

NCT04386850 *(Continued)*

- Treatment details of prevention group (e.g dose, route of administration)
  - * includes the health care providers and hospital workers with a negative test for COVID-19 and a close patient relative with a negative test for COVID-19 who lives with the infected patients
  - * Dose: 25-Hydroxyvitamin D3 25 mcg once
  - * Route of administration: orally daily at bedtime for 2 months
  - * Control group: placebo daily for 2 months
- Concomitant therapy: none

Outcomes	Primary study outcome
	• COVID-19 (SARA-Cov-2) infection
	• Severity of COVID-19 (SARA-Cov-2) infection
	• Hospitalisation
	• Disease duration
	• Death due to COVID-19
	• Oxygen support
	
	Review outcomes
	• All-cause mortality at day 28, day 60, time-to-event, and up to longest follow-up - NP
	• Admission to hospital (WHO≥ 4) - reported
	• Development of moderate to severe clinical COVID-19 symptoms, defined as WHO Clinical Progression Scale ≥ 6 (WHO 2020e), up to longest follow-up
	  * Need for invasive mechanical ventilation, non-invasive mechanical ventilation or high flow i.e. WHO ≥6, severe disease;
	  ☐ need for invasive mechanical ventilation i.e. WHO 7-9;
	  ☐ need for non-invasive mechanical ventilation or high flow i.e. WHO = 6.
	  * Need for hospitalisation with or without supplemental oxygen i.e. WHO = 4-5, moderate disease;
	  ☐ need for oxygen by mask or nasal prongs i.e. WHO = 5;
	  ☐ need for hospitalisation without oxygen therapy i.e. WHO = 4.
	  * Probably reported
	• Quality of life, including fatigue and neurological status, assessed with standardised scales (e.g. WHOQOL-100) at up to 7 days, up to 30 days, and longest follow-up available - NP
	• Duration of hospitalisation, for subgroup of participants hospitalised during course of disease - NP
	• Time to hospital discharge, for subgroup of participants hospitalised during course of disease - NP
	• Vitamin D serum levels - reported
	• Serious adverse events, defined as number of participants with event - NP
	• Adverse events (any grade, grade 1-2, grade 3-4), defined as number of participants with event - NP
	
	Additional study outcomes:
	• Type of oxygen support
	• Symptoms of COVID-19
	• Serum Levels of 25-hydroxyvitamin D3
	• Serum levels of calcium
	• Serum levels of phosphorus
	• Serum levels of creatinine
	• Serum levels of albumin
	• Serum levels of the blood urea nitrogen (BUN)
	• Serum levels of the parathyroid hormone (PTH)

Starting date	14/04/2020
Contact information	Zhila Maghbooli, PhD

NCT04386850 *(Continued)*

	+98 21 6670 6142 zhilayas@gmail.com
Notes	• Recruitment status: recruiting • Prospective completion date: 15/03/2021 • Date last update was posted: 12/06/2020 • Sponsor/funding: Tehran University of Medical Sciences

NCT04411446

Study name	Randomized controlled trial of high dose of vitamin D as compared with placebo to prevent complications among COVID-19 patients
Methods	• Trial design: RCT • Sample size: 1264 • Setting: inpatient • Language: English (Argentina) • Number of centres: 1 • Type of intervention (treatment/prevention): treatment
Participants	• Inclusion criteria * SARS-CoV-2 confirmed infection * Admission to a hospital * Expected hospitalisation in the centre for at least for 24 hours * Oxygen Saturation > 90% breathing without oxygen supplement * Age at least 45 years or the presence of one of the followings risk factors * Hypertension * Diabetes (type I o II) * At least moderate COPD or Asthma * Cardiovascular disease (history of myocardial infarction, coronary angioplasty, coronary artery bypass grafting or valve replacement surgery) * Body Mass Index >=30 * Signed Written consent • Exclusion criteria * < 18 years old * Women in childbearing age * >= 72 hours since current admission * Requirement for high dose of oxygen (>5 liters/minute) or mechanical ventilation (non-invasive or invasive) * History of Chronic kidney disease requiring hemodialysis or chronic liver failure * Inability for oral intake * Previous treatment with pharmacological vitamin D * History of: ☐ previous treatment with anticonvulsants; ☐ sarcoidosis; ☐ malabsorption syndrome; * Known hypercalcemia * Life expectancy less than 6 months * Known allergy to the study medication * Any condition impeding to bring informed consent

NCT04411446 *(Continued)*

Interventions	• Details of intervention
	  * Dose: 5 capsules of 100,000 IU Vitamin D given all at once. One dose.
	  * Route of administration: oral
	• Treatment details of control group (e.g dose, route of administration): 5 capsules of containing placebo given all at once (p.o.). One dose.
	• Concomitant therapy: none

Outcomes	Primary study outcome
	
	• Respiratory SOFA score
	• Need of high dose oxygen or medical ventilation
	
	Review outcomes
	
	• All-cause mortality at day 28, day 60, time-to-event, and at hospital discharge - reported
	• Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale (WHO 2020e), WHO Ordinal Scale for Clinical Improvement (WHO 2020f)) at day 28, day 60, and up to longest follow-up); including:
	  * Improvement of clinical status:
	  ☐ weaning or liberation from invasive mechanical ventilation in surviving patients i.e. WHO ≤6, if ≥7 at baseline;
	  ☐ ventilator free days; ventilator free defined as WHO ≤6;
	  ☐ duration to liberation from invasive mechanical ventilation;
	  ☐ liberation from supplemental oxygen in surviving patients i.e. WHO ≤4, if ≥5 at baseline;
	  ☐ duration to liberation from supplemental oxygen.
	  * Worsening of clinical status:
	  ☐ need for invasive mechanical ventilation i.e. WHO 7-9, if ≤6 at baseline;
	  ☐ need for non-invasive mechanical ventilation or high flow i.e. WHO=6, if ≤5 at baseline;
	  ☐ need for oxygen by mask or nasal prongs i.e. WHO=5, if ≤4 at baseline.
	  * Probably reported
	• Need for dialysis (at up to 28 days) - probably reported
	• Quality of life, including fatigue and neurological status, assessed with standardised scales (e.g. WHOQOL-100) at up to seven days; up to 30 days, and longest follow-up available - NP
	• Admission to ICU - reported
	• Duration of hospitalisation - reported
	• Time to discharge from hospital - NP
	• Viral clearance, assessed with reverse transcription polymerase chain reaction (RT-PCR) test for SARS-CoV-2 at baseline, up to 3, 7, and 15 days - NP
	• Vitamin D serum levels - NP
	• Serious adverse events, defined as number of participants with event - NP
	• Adverse events (any grade, grade 1-2, grade 3-4), defined as number of participants with event - NP
	
	Additional study outcomes
	
	• Change in oxygen saturation
	• Oxygen desaturation
	• Change in Quick SOFA score
	• Myocardial infarction
	• Stroke
	• Acute kidney injury
	• Pulmonary thromboembolism
	• Combined endpoint (stroke, myocardial infarct, acute kidney injury, pulmonary thromboembolism)
	• Admission to ICU
	• Invasive mechanical ventilation

NCT04411446 *(Continued)*

	• Hospital length of stay • ICU length of stay • Death (30 days or discharge)
Starting date	11/08/2020
Contact information	Javier Mariani, MD +541142109000 ext 1523 ja_mariani@hotmail.com
Notes	• Recruitment status: recruiting • Prospective completion date: 28/12/2020 • Protocol published: 1 February 2021 * Anticipated recruitment completion for the first stage in mid-February, 2021, and in August, 2021 for the second stage • Sponsor/funding: Vitamin D study group

NCT04482673

Study name	The role of vitamin D in mitigating COVID-19 infection severity: focusing on reducing health disparities in South Carolina
Methods	• Trial design: RCT • Sample size: 140 • Setting: outpatient • Language: English (USA) • Number of centres: NA • Type of intervention (treatment/prevention): prevention

Participants	• Inclusion criteria
	  * Adults aged 50 years of age or older who presents to MUSC or its affiliate hospitals (or associated testing centres) for COVID-19 testing during the recruitment period is eligible for participation
	• Exclusion criteria
	  * Hospitalisation at the time of study recruitment.
	  * Any individual less than 50 years of age. The reason that the participants ≥ 50 years are being excluded from this study is because those who are ≥ 50 years have a higher risk of being symptomatic with COVID-19 and have the potential for the greatest benefit. The disease appears to manifest differently in children and its occurrence is quite rare.
	  * Only those patients tested for COVID-19 initially will be eligible to participate; therefore, anyone wanting to participate in the trial must have had a COVID-19 test prior to enrolment/participation in the study.
	  * Any individual who is not capable of making independent decisions and who is considered cognitively impaired.

Interventions	• Details of intervention
	  * Dose:
	  ☐ COVID-19 Negative Active Treatment: 6000 IU vitamin D3 daily
	  ☐ COVID-19 Positive Active Treatment: 6000 IU vitamin D3 daily + Bolus 20,000 IU vitamin D3 daily for 3 days
	  * Route of administration: NI

NCT04482673 *(Continued)*

- Treatment details of control group (e.g dose, route of administration):
  * COVID-19 Negative Placebo: placebo daily
  * COVID-19 Positive Placebo: placebo daily + Bolus placebo daily for 3 days
- Concomitant therapy: All participants will receive a multivitamin containing 800 IU vitamin D3/day.

Outcomes	Primary study outcome
	• Change in total circulating 25(OH)D concentration
	• Change in total circulating 25(OH)D concentration in COVID-19 positives
	• Change in SARS-CoV-2 antibody titres
	Review outcomes
	• All-cause mortality at day 28, day 60, time-to-event, and up to longest follow-up - NP
	• Admission to hospital (WHO≥ 4) - NP
	• Development of moderate to severe clinical COVID-19 symptoms, defined as WHO Clinical Progression Scale ≥ 6 (WHO 2020e), up to longest follow-up
	  * Need for invasive mechanical ventilation, non-invasive mechanical ventilation or high flow i.e. WHO ≥6, severe disease;
	  ☐ need for invasive mechanical ventilation i.e. WHO 7-9;
	  ☐ need for non-invasive mechanical ventilation or high flow i.e. WHO = 6.
	  * Need for hospitalisation with or without supplemental oxygen i.e. WHO=4-5, moderate disease;
	  ☐ need for oxygen by mask or nasal prongs i.e. WHO = 5;
	  ☐ need for hospitalisation without oxygen therapy i.e. WHO = 4.
	  * NP
	• Quality of life, including fatigue and neurological status, assessed with standardised scales (e.g. WHOQOL-100) at up to 7 days, up to 30 days, and longest follow-up available - NP
	• Duration of hospitalisation, for subgroup of participants hospitalised during course of disease - NP
	• Time to hospital discharge, for subgroup of participants hospitalised during course of disease - NP
	• Vitamin D serum levels - probably reported
	• Serious adverse events, defined as number of participants with event - NP
	• Adverse events (any grade, grade 1-2, grade 3-4), defined as number of participants with event - NP
	Additional study outcomes
	• Change in inflammatory cytokine concentration
	• Respiratory symptoms
	• Signs and symptoms of rhino/sinusitis
	• NCI Dietary Intake
	• Charlson Comorbidity survey
	• Paffenberger Physical Activity Assessment
	• Perceived stress
	• Pandemic stress
	• NEO-Personality Inventory
	• GrassrootsHealth Monthly Health assessment

Starting date	31/07/2020
Contact information	Carol L Wagner, MD 843-792-8829 washinro@musc.edu Medical University of South Carolina

NCT04482673 *(Continued)*

Notes	• Recruitment status: recruiting • Prospective completion date: 31/12/2021 • Date last update was posted: 04/08/2020 • Sponsor/funding: Medical University of South Carolina

NCT04489628

Study name	Tele-health enabled clinical trial for COVID-19: vitamin D as aniImmunomodulator to prevent complications and reduce resource utilization in Ootpatients
Methods	• Trial design: RCT • Sample size: 110 • Setting: outpatient • Language: English (USA) • Number of centres: NA • Type of intervention (treatment/prevention): treatment

Participants	• Inclusion criteria
	  * ≥ 18 years of age
	  * Laboratory confirmed SARS-CoV-2 infection < 4 days before randomisation
	  * Report of symptoms consistent with SARS-CoV-2 infection (including but not limited to fever, cough, muscle aches, joint pain, change in taste, change in smell, or shortness of breath) <4 days before admission
	  * Asymptomatic or mild symptoms (not requiring hospital admission)
	  * Access to and ability to use a mobile phone with telehealth capability
	• Exclusion criteria
	  * Unable to provide informed consent or comply with study directions
	  * Admitted to an acute care bed
	  * Baseline serum calcium < 8.8 mg/dL or > 10.2 mg/dL (as evaluated by labs taken in the ER/urgent care)
	  * Women who are currently breastfeeding
	  * History of kidney stone in the past year or h/o multiple (>1) previous kidney stones
	  * Does not have a smart phone that can download apps from Google Play or App Store.
	  * No way to keep the phone charged consistently
	  * The smartphone is shared with another individual.
	  * Required laboratory data is unavailable (eg calcium levels)
	  * No new oxygen requirement (see remote monitoring document)
	  * Pregnant and lactating mothers.
	  * Vitamin D level of 80ng/mL and above
	  * No lab work for calcium or vitamin D completed in ED

Interventions	• Details of intervention
	  * Dose: 8 capsules of cholecalciferol 50,000 IU
	  * Route of administration: 4 capsules on receipt of the treatment package (Day 0), 2 capsules on Day 5, 1 capsule on Day 10, and 1 capsule on Day 15 (orally)
	• Treatment details of control group (e.g dose, route of administration): 8 capsules of placebo (orally.)
	• Concomitant therapy: Doctella telehealth monitoring, phone and text reminder to take the capsules

Outcomes	Primary study outcome

NCT04489628 *(Continued)*

	1. Patients requiring admission to the hospital or experiencing death Review outcomes • All-cause mortality at day 28, day 60, time-to-event, and up to longest follow-up - probably reported • Admission to hospital (WHO ≥ 4) - reported • Development of moderate to severe clinical COVID-19 symptoms, defined as WHO Clinical Progression Scale ≥ 6 (WHO 2020e), up to longest follow-up * need for invasive mechanical ventilation, non-invasive mechanical ventilation or high flow i.e. WHO ≥ 6, severe disease; ☐ need for invasive mechanical ventilation i.e. WHO 7-9; ☐ need for non-invasive mechanical ventilation or high flow i.e. WHOn = n6. * need for hospitalisation with or without supplemental oxygen i.e. WHO = 4-5, moderate disease; ☐ need for oxygen by mask or nasal prongs i.e. WH O = 5; ☐ need for hospitalisation without oxygen therapy i.e. WHO = 4. * NP • Quality of life, including fatigue and neurological status, assessed with standardised scales (e.g. WHOQOL-100) at up to 7 days, up to 30 days, and longest follow-up available - NP • Duration of hospitalisation, for subgroup of participants hospitalised during course of disease - NP • Time to hospital discharge, for subgroup of participants hospitalised during course of disease - NP • Vitamin D serum levels - NP • Serious adverse events, defined as number of participants with event - NP • Adverse events (any grade, grade 1-2, grade 3-4), defined as number of participants with event - NP Additional study outcomes: none
Starting date	01/08/2020
Contact information	Kevin Cooper, MD 216-844-5197 UHDermatologyClinicalTrials@UHhospitals.org
Notes	• Recruitment status: not yet recruiting • Prospective completion date: 01/08/2021 • Date last update was posted: 31/07/2020 • Sponsor/funding: University Hospitals Cleveland Medical Center

NCT04502667

Study name	Efficacy of vitamin D treatment in pediatric Patients hospitalized by COVID-19: open controlled clinical trial
Methods	• Trial design: RCT • Sample size: 40 • Setting: inpatient • Language: English (Mexico) • Number of centres: 1 • Type of intervention (treatment/prevention): treatment

NCT04502667 *(Continued)*

Participants	• Inclusion criteria
	  * Age over 1 month and under 17 years (children)
	  * Confirmed diagnosis of COVID-19 infection with the results of real-time PCR
	  * That they agreed to participate in the study
	  * That the patient tolerates the enteral route
	• Exclusion criteria
	  * Have received vitamin D in the four weeks prior to hospitalisation

Interventions	• Details of intervention
	  * Dose: Children under 12 months they will be given 1000 U of Vitamin D and in children over 12 months they will be given 2000 U of Vitamin D
	  * Route of administration: every 24 hours orally during hospitalisation
	• Treatment details of control group (e.g dose, route of administration): no intervention
	• Concomitant therapy: none

Outcomes	Primary study outcome
	• Interleukins
	• Ferritin
	• Dimder-D
	Review outcomes
	• All-cause mortality at day 28, day 60, time-to-event, and at hospital discharge - NP
	• Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale (WHO 2020e), WHO Ordinal Scale for Clinical Improvement (WHO 2020f)) at day 28, day 60, and up to longest follow-up); including:
	  * Improvement of clinical status:
	  ☐ weaning or liberation from invasive mechanical ventilation in surviving patients i.e. WHO ≤ 6, if ≥7 at baseline;
	  ☐ ventilator-free days; ventilator-free defined as WHO ≤ 6;
	  ☐ duration to liberation from invasive mechanical ventilation;
	  ☐ liberation from supplemental oxygen in surviving patients i.e. WHO ≤4, if ≥ 5 at baseline;
	  ☐ duration to liberation from supplemental oxygen.
	  * Worsening of clinical status:
	  ☐ need for invasive mechanical ventilation i.e. WHO 7-9, if ≤ 6 at baseline;
	  ☐ need for non-invasive mechanical ventilation or high flow i.e. WHO = 6, if ≤ 5 at baseline;
	  ☐ need for oxygen by mask or nasal prongs i.e. WHO = 5, if ≤ 4 at baseline
	  * NP
	• Need for dialysis (at up to 28 days) - NP
	• Quality of life, including fatigue and neurological status, assessed with standardised scales (e.g. WHOQOL-100) at up to seven days; up to 30 days, and longest follow-up available - NP
	• Admission to ICU - NP
	• Duration of hospitalisation - NP
	• Time to discharge from hospital - NP
	• Viral clearance, assessed with reverse transcription polymerase chain reaction (RT-PCR) test for SARS-CoV-2 at baseline, up to 3, 7, and 15 days - NP
	• Vitamin D serum levels - reported
	• Serious adverse events, defined as number of participants with event - NP
	• Adverse events (any grade, grade 1-2, grade 3-4), defined as number of participants with event - NP
	Additional study outcomes:
	• Vitamin D serum levels

NCT04502667 *(Continued)*

Starting date	15/07/2020
Contact information	Hospital Centro Medico Nacional Siglo XXI Carla Castuera Martinez 56276900 ext 21218 carla_martinez@imss.gob.mx
Notes	• Recruitment status: recruiting • Prospective completion date: 04/2021 • Date last update was posted: 06/08/2020 • Sponsor/funding: Coordinación de Investigación en Salud, Mexico

NCT04525820

Study name	High dose vitamin-D substitution in patients With COVID-19: a randomized controlled, multicCenter study (VitCov)
Methods	• Trial design: RCT • Sample size: 80 • Setting: inpatient • Language: English (Switzerland) • Number of centres: 3 • Type of intervention (treatment/prevention): treatment

Participants	• Inclusion criteria
	  * Informed Consent as documented by signature
	  * Hospitalised Patient
	  * Ongoing COVID-19 infection
	  * Vitamin D deficiency defined as a serum 25-hydroxyvitamin D concentration ≤ 50 nmol/L(≤ 20 ng/mL)
	  * > 18 years of age
	• Exclusion criteria:
	  * Known hypersensitivity to one of the used products of vitamin D or indigents in the drug's composition
	  * Active malignancy
	  * Hypercalcaemia
	  * Granulomatous disease such as sarcoidosis
	  * History of renal stones within the past year
	  * Pregnancy/breastfeeding, as evaluated through screening,
	  * Previous enrolment into the current study,
	  * Enrolment of the investigator, his/her family members, employees and other dependent persons

Interventions	• Details of intervention
	  * Dose: one dose of 140,000 IU (7 mL) Vitamin D
	  * Route of administration: oral
	• Treatment details of control group (e.g dose, route of administration): placebo
	• Concomitant therapy: all patients receive daily 800 IU of vitamin D, orally administered additionally to TAU

NCT04525820 *(Continued)*

Outcomes	Primary study outcome • Length of hospitalisation Review outcomes • All-cause mortality at day 28, day 60, time-to-event, and at hospital discharge -probably reported • Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale (WHO 2020e), WHO Ordinal Scale for Clinical Improvement (WHO 2020f)) at day 28, day 60, and up to longest follow-up); including: * Improvement of clinical status: ☐ weaning or liberation from invasive mechanical ventilation in surviving patients i.e. WHO ≤ 6, if ≥ 7 at baseline; ☐ ventilator-free days; ventilator-free defined as WHO ≤ 6; ☐ duration to liberation from invasive mechanical ventilation; ☐ liberation from supplemental oxygen in surviving patients i.e. WHO ≤ 4, if ≥ 5 at baseline; ☐ duration to liberation from supplemental oxygen. * Worsening of clinical status: ☐ need for invasive mechanical ventilation i.e. WHO 7-9, if ≤ 6 at baseline; ☐ need for non-invasive mechanical ventilation or high flow i.e. WHO = 6, if ≤ 5 at baseline; ☐ need for oxygen by mask or nasal prongs i.e. WHO = 5, if ≤ 4 at baseline * NP • Need for dialysis (at up to 28 days) - NP • Quality of life, including fatigue and neurological status, assessed with standardised scales (e.g. WHOQOL-100) at up to 7 days; up to 30 days, and longest follow-up available - NP • Admission to ICU - probably reported • Duration of hospitalisation - reported • Time to discharge from hospital - NP • Viral clearance, assessed with reverse transcription polymerase chain reaction (RT-PCR) test for SARS-CoV-2 at baseline, up to 3, 7, and 15 days - NP • Vitamin D serum levels - reported • Serious adverse events, defined as number of participants with event - NP • Adverse events (any grade, grade 1-2, grade 3-4), defined as number of participants with event - NP Additional study outcomes • Need of intensive care • Length of the intensive care treatment • Overall mortality • Development of vitamin D levels • Development of sepsis • Complications due to COVID-19 • Blood pressure • Heart rate • Peripheral oxygen saturation (SpO2) • Percentage of patients who require oxygen • Breathing frequency • Glasgow Coma Scale (GCS) • Percentage of patients are smokers, former smokers or lifelong non-smokers • Current Symptoms • Temperature
Starting date	15/12/2020
Contact information	Jörg D Leuppi, Professor

NCT04525820 *(Continued)*

	+41 61 925 2181 joerg.leuppi@ksbl.ch
Notes	• Recruitment status: recruiting • Prospective completion date: 30/06/2021 • Date last update was posted: 22/12/2020 • Sponsor/funding: Prof. Dr. Jörg Leuppi

NCT04536298

Study name	A cluster-randomized, double-blind, placebo-controlled study to evaluate the efficacy of vitamin D3 supplementation to reduce disease severity in persons with newly diagnosed COVID-19 infection and to prevent infection in household members
Methods	• Trial design: RCT, parallel assignment • Sample size: 2700 • Setting: outpatient • Language: English (UK) • Number of centres: NR • Type of intervention (treatment/prevention): treatment

Participants	Inclusion/exclusion criteria for INDEX CASES
	
	• Inclusion criteria
	  * Adults aged 30 years or older who are newly diagnosed with COVID-19 infection within 72 hours of testing *AND* no more than 5 days from the onset of COVID-19-related symptoms.
	  * Age-specific criteria: Age 30 to 49 years with 2 or more co-morbidities (diabetes; hypertension; BMI of 30 or greater; chronic obstructive pulmonary disease or emphysema: history of heart attack, stroke, coronary bypass surgery, coronary angioplasty or stent, hospitalisation for heart failure; diagnosed sleep apnoea) and/or risk factors (smoking; African American, Hispanic, Native American) *OR* Age 50 to 59 years with 1 or more co-morbidities or risk factors *OR* Age 60 or older regardless of co-morbidity or risk factor status.
	  * Ability and willingness to understand and provide informed consent.
	• Exclusion criteria
	  * Known current pregnancy
	  * Current hospitalisation
	  * Unable to complete online questionnaires or adhere to study requirements
	  * Consume more than 400 IU per day of vitamin D from all supplemental sources combined (individual vitamin D supplements, calcium plus vitamin D supplements, medications with vitamin D [e.g., Fosamax Plus D], and multivitamins) in the past 4 weeks
	  * Known diagnosis of hypercalcemia or a condition associated with vitamin D hypersensitivity
	  * Prior diagnosis of cancer *AND* currently undergoing radiation, chemotherapy, or immunotherapy
	  * Kidney failure or dialysis; severe liver disease or cirrhosis.
	  * Unstable, transient, or group (6 or more adults) living arrangement
	  * Participation in other COVID-19 trials
	
	Inclusion/exclusion criteria for HOUSEHOLD CONTACTS
	
	• Inclusion criteria
	  * Persons aged 18 years or older who live in the same household as the index case and have been identified as the closest contact within that household.
	  * Ability and willingness to understand and provide informed consent

NCT04536298 *(Continued)*

- Exclusion criteria
  * Known current pregnancy
  * History of SARS-CoV-2 infection with onset of symptoms more than 6 days before study entry
  * Receipt of a SARS-CoV-2 vaccination or monoclonal antibody
  * Unable to complete online questionnaires or adhere to study requirements
  * Consume more than 400 IU per day of vitamin D from all supplemental sources combined (individual vitamin D supplements, calcium plus vitamin D supplements, medications with vitamin D [e.g., Fosamax Plus D], and multivitamins) in the past 4 weeks
  * Known diagnosis of hypercalcemia or a condition associated with vitamin D hypersensitivity
  * Prior diagnosis of cancer *AND* currently undergoing radiation, chemotherapy or immunotherapy
  * Kidney failure or dialysis; severe liver disease or cirrhosis
  * Unstable, transient, or group (6 or more adults) living arrangement
  * Participation in other COVID-19 trials

Interventions

- Details of intervention:
  * Dose: 9600 IU of Vitamin D3/cholecalciferol
  * Route of administration: Daily for 28 days (days 1 and 2; 3200 IU/day on days 3 through 28)
- Treatment details of control group (e.g dose, route of administration): Placebo softgel capsules
- Concomitant therapy: none

Outcomes

- Primary study outcome: hospitalisation or death in index cases
- Review outcomes
  * All-cause mortality at day 28, day 60, and up to longest follow-up - reported
  * Admission to hospital (WHO≥ 4) - NP
  * Development of severe clinical COVID-19 symptoms, defined as WHO Clinical Progression Scale ≥ 6, up to longest follow-up: Self-reported disease severity in index cases (Severity: 1=no COVID-19 illness; 2=COVID-19 illness with no hospitalisation; 3 = COVID-19 illness with hospitalisation or death)
  * Quality of life, assessed with standardised scales (e.g. WHOQOL-100) at up to 7 days, up to 30 days, and longest follow-up available: NP
  * Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale (WHO 2020e), WHO Ordinal Scale for Clinical Improvement (WHO 2020f)) at day 28, day 60, and up to longest follow-up; including:
    ☐ mean status according to WHO score: NR;
    ☐ increase of WHO score (10-point WHO clinical progression scale (WHO 2020e)), for subgroup of patients without the respective need for respiratory support at baseline: NR;
      ○ need for invasive ventilation i.e. WHO 7-9;
      ○ need for non-invasive ventilation or high flow i.e. WHOn=n6;
      ○ need for oxygen by mask or nasal prongs i.e. WHOn=n5;
      ○ need for hospitalisation without oxygen therapy i.e. WHOn=n4.
    ☐ NP
  * Duration of hospitalisation, for subgroup of participants hospitalised during course of disease - NP
  * Time to hospital discharge, for subgroup of participants hospitalised during course of disease - NP
  * Serious adverse events, defined as number of participants with event - NP
  * Adverse events (any grade, grade 1-2, grade 3-4), defined as number of participants with events - NP
- Additional review outcomes
  * Time to hospitalisation or death in index cases
  * ICU admission/ventilation support in index cases
  * SARS-CoV-2 infection in close household contacts
  * Self-reported disease severity in close household contacts

NCT04536298 *(Continued)*

Starting date	28/12/2020
Contact information	Trisha Copeland, MS, RD1-877-517-2555 pcopeland2@bwh.harvard.edu
Notes	• Recruitment status: recruiting • Prospective completion date: 30/04/2021 • Sponsor/funding: Brigham and Women's Hospital

NCT04552951

Study name	Effect of vitamin D on morbidity and mortality of the COVID-19 (COVID-VIT-D)
Methods	• Trial design: RCT • Sample size: 80 • Setting: inpatient • Language: English (Spain) • Number of centres: 1 • Type of intervention (treatment/prevention): treatment

Participants	• Inclusion criteria
	  * > 18 years
	  * Diagnosis of COVID-19
	  * Accept to participate in the study (consent)
	• Exclusion criteria
	  * Pregnancy
	  * Allergy to vitamin D
	  * Consumption of any form of vitamin D during the last 3 months
	  * Expected fatal outcome in the next 24 hours
	  * Cognitive deterioration

Interventions	• Details of intervention
	  * Dose: Single dose of 100,000 IU
	  * Route of administration: NI
	• Treatment details of control group (e.g dose, route of administration): no vitamin D (on top of the current medication used to treat COVID 19).
	• Concomitant therapy: none

Outcomes	Primary study outcome • Mortality [Time Frame: time to death or hospital discharge] Review outcomes • All-cause mortality at day 28, day 60, time-to-event, and at hospital discharge - reported

NCT04552951 *(Continued)*

- Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale (WHO 2020e), WHO Ordinal Scale for Clinical Improvement (WHO 2020f)) at day 28, day 60, and up to longest follow-up); including:
  * Improvement of clinical status:
    - ☐ weaning or liberation from invasive mechanical ventilation in surviving patients i.e. WHO ≤ 6, if ≥7 at baseline;
    - ☐ ventilator-free days; ventilator-free defined as WHO ≤ 6;
    - ☐ duration to liberation from invasive mechanical ventilation;
    - ☐ liberation from supplemental oxygen in surviving patients i.e. WHO ≤ 4, if ≥ 5 at baseline;
    - ☐ duration to liberation from supplemental oxygen;
  * Worsening of clinical status:
    - ☐ need for invasive mechanical ventilation i.e. WHO 7-9, if ≤ 6 at baseline;
    - ☐ need for non-invasive mechanical ventilation or high flow i.e. WHO = 6, if ≤ 5 at baseline;
    - ☐ need for oxygen by mask or nasal prongs i.e. WHO = 5, if ≤4 at baseline
  * NP
- Need for dialysis (at up to 28 days) - NP
- Quality of life, including fatigue and neurological status, assessed with standardised scales (e.g. WHOQOL-100) at up to seven days; up to 30 days, and longest follow-up available - NP
- Admission to ICU - reported
- Duration of hospitalisation - reported
- Time to discharge from hospital - probably reported
- Viral clearance, assessed with reverse transcription polymerase chain reaction (RT-PCR) test for SARS-CoV-2 at baseline, up to 3, 7, and 15 days - NP
- Vitamin D serum levels - NP
- Serious adverse events, defined as number of participants with event - NP
- Adverse events (any grade, grade 1-2, grade 3-4), defined as number of participants with event - NP

Additional study outcomes

- Admission to Intensive Care Unit (ICU)
- Time of hospitalisation
- Clinical changes (Cough, fever, headache, weakness, dyspnoea, anosmia, diarrhoea, ageusia, others)
- Radiological changes (pneumonia and severity)
- Inflammation markers changes (C-reactive protein)
- Inflammation markers changes (Interleukin-6)
- Inflammation markers changes (Leucocytes)
- Inflammation markers changes (D-dimer)
- General biochemical parameters changes (Creatinine)
- General biochemical parameters changes (Ferritin)
- General biochemical parameters changes (Bilirubin)
- General biochemical parameters changes (Albumin)
- General biochemical parameters changes (Haemoglobin)
- General biochemical parameters changes (HDL cholesterol)
- General biochemical parameters changes (Procalcitonin)
- General biochemical parameters changes (Protonin)
- General biochemical parameters changes (Calcium)
- General biochemical parameters changes (Phosphate)
- General biochemical parameters changes (pO2)

Starting date	04/04/2020
Contact information	Jorge B Cannata-Andía, MD PhD Hospital Universitario Central de Asturias

NCT04552951 *(Continued)*

	*34 985 106137 cannata@hca.es
Notes	• Recruitment status: recruiting • Prospective completion date: 30/12/2020 • Date last update was posted: 17/09/2020 • Sponsor/funding: Fundación para la Investigación Biosanitaria del Principado de Asturias

NCT04621058

Study name	Efficacy of vitamin D treatment in mortality reduction due to COVID-19
Methods	• Trial design: RCT • Sample size: 108 • Setting: inpatient • Language: English (Spain) • Number of centres: 1 • Type of intervention (treatment/prevention): treatment

Participants	• Inclusion criteria
	  * Admitted to the Respiratory or Internal medicine Units of Santiago hospital (HUA) due to pneumonia
	  * Vitamin D deficiency (25(OH) defined by blood levels below 30 mg/mL
	  * Possibility for observation during the treatment period
	  * Signing of written consent (oral informed consent exceptionally)
	  * Positive PCR for diagnosis of SARS-COV2 infection
	• Exclusion criteria
	  * Patients taking any type of vitamin D supplement
	  * Patients with hypoparathyroidism
	  * Pregnant or lactating women
	  * Patients in whom the administration of vitamin D is formally contraindicated
	  * Patients who at time of inclusion, cannot take vitamin D orally

Interventions	• Details of intervention: in case of Vitamin D levels < 30 ng/mLor 40 ng/mL (deficiency) patients will take vitamin D supplements (soft capsules)
	  * Dose: 1 or 2 capsules 0.266 mg depending on deficiency
	  * Route of administration: oral
	• Treatment details of control group (e.g dose, route of administration): placebo capsules
	• Concomitant therapy: none

Outcomes	• Primary study outcome * Mortality (21 days)

NCT04621058 *(Continued)*

- Review outcomes
  * All-cause mortality at day 28, day 60, time-to-event, and at hospital discharge - probably reported
  * Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale (WHO 2020e), WHO Ordinal Scale for Clinical Improvement (WHO 2020f)) at day 28, day 60, and up to longest follow-up); including:
    - ☐ Improvement of clinical status:
      - ○ weaning or liberation from invasive mechanical ventilation in surviving patients i.e. WHO ≤ 6, if ≥ 7 at baseline;
      - ○ ventilator-free days; ventilator-free defined as WHO ≤ 6;
      - ○ duration to liberation from invasive mechanical ventilation;
      - ○ liberation from supplemental oxygen in surviving patients i.e. WHO ≤ 4, if ≥5 at baseline;
      - ○ duration to liberation from supplemental oxygen
    - ☐ Worsening of clinical status:
      - ○ need for invasive mechanical ventilation i.e. WHO 7-9, if ≤ 6 at baseline;
      - ○ need for non-invasive mechanical ventilation or high flow i.e. WHO = 6, if ≤ 5 at baseline;
      - ○ need for oxygen by mask or nasal prongs i.e. WHO = 5, if ≤ 4 at baseline
    - ☐ NP
  * Need for dialysis (at up to 28 days) - NP
  * Quality of life, including fatigue and neurological status, assessed with standardised scales (e.g. WHOQOL-100) at up to 7 days; up to 30 days, and longest follow-up available - NP
  * Admission to ICU - reported
  * Duration of hospitalisation - reported
  * Time to discharge from hospital - NP
  * Viral clearance, assessed with reverse transcription polymerase chain reaction (RT-PCR) test for SARS-CoV-2 at baseline, up to 3, 7, and 15 days - NP
  * Vitamin D serum levels - NP
  * Serious adverse events, defined as number of participants with event - NP
  * Adverse events (any grade, grade 1-2, grade 3-4), defined as number of participants with event - NP
- Additional review outcomes
  * ICU admissions
  * Length of hospital stay
  * Prevalence of vitamin D deficiency (at baseline)
  * Incremental cost effectiveness ratio (ICER)

Starting date	09/11/2020
Contact information	Joaquín Durán Cantolla Vitoria-Gasteiz, Alava, Spain, 01002 +34945207925 joaquin.durancantolla@gmail.com
Notes	• Recruitment status: recruiting • Prospective completion date: 30/11/2021 • Date last update was posted: 23/12/2020 • Sponsor/funding: Bioaraba Health Research Institute

NCT04636086

Study name	Vitamin D supplementation and Covid-19: a randomised, double- blind, controlled study
Methods	• Trial design: RCT • Sample size: 100 • Setting: inpatient • Language: English (Belgium) • Number of centres: 1 • Type of intervention (treatment/prevention): treatment

Participants	• Inclusion criteria
	  * Male and female over 18 years old (18 years inclusive)
	  * Has laboratory-confirmed SARS-CoV-2 infection as determined by PCR, or other commercial or public health assay in any specimen as diagnosed within 72 hours prior to randomisation
	  * Expected to survive for at least 96 hours after study entry
	  * If patient is a female of childbearing potential, patient must use an effective means of birth control (oral, intravaginal or transdermal oestrogen-progestogen combined hormonal contraceptives or intrauterine devices or sexual abstinence)
	  * Subject or legally authorised representative understands and agrees to comply with planned study procedures
	  * Subject or legally authorised representative provides informed consent prior to initiation of any study procedures
	• Exclusion criteria
	  * Women currently pregnant or breast-feeding
	  * Patients presenting acute impairment of renal function or nephrolithiasis
	  * Patients presenting hypercalcaemia and/or hypercalciuria
	  * Patients presenting pseudohypoparathyroidism
	  * Use of any vitamin D supplementation alone or in association at screening visit
	  * Use of any prohibited medication as detailed in the concomitant medication section
	  * Patients with any sensitivity or allergy to any of the products used within this clinical trial
	  * Presence of any other condition or illness, which, in the opinion of the investigator, would interfere with optimal participation in the study

Interventions	• Details of intervention
	  * Dose: 9 doses of 25,000 IU/mL
	  * Route of administration: one ampoule on Day 1, Day 2, Day 3, Day 4, Day 8, Day 15, Day 22, Day 29 and Day 36 (orally)
	• Treatment details of control group (e.g dose, route of administration): placebo, same scheme
	• Concomitant therapy: none

Outcomes	Primary study outcome
	• vitamin D serum concentration
	Review outcomes
	• All-cause mortality at day 28, day 60, and up to longest follow-up - reported
	• Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale (WHO 2020e), WHO Ordinal Scale for Clinical Improvement (WHO 2020f)) at up to 7 days, 8 to 15 days, 16 to 30 days; including: yes, reported with ordinal scale for clinical improvement as recommended by WHO
	  * Ventilator-free days and need for intubation or IV (at day 28, day 60, and up to longest follow-up)
	  * Weaning/liberation from mechanical ventilation

NCT04636086 *(Continued)*

  * Increase of WHO score (WHO clinical progression scale), for subgroup of patients without the respective need for respiratory support at baseline: reported
    ☐ need for invasive ventilation i.e. WHO 7-9;
    ☐ need for non-invasive ventilation or high flow i.e. WHO = 6;
    ☐ need for oxygen by mask or nasal prongs i.e. WHO = 5;
    ☐ need for hospitalisation without oxygen therapy i.e. WHO = 4
- Need for dialysis (at up to 28 days) - NP
- Quality of life, including fatigue and neurological status, assessed with standardised scales (e.g. WHOQOL-100) at up to seven days; up to 30 days, and longest follow-up available - NP
- Admission to ICU - NP
- Duration of hospitalisation - NP
- Time to discharge from hospital - NP
- Time to symptom resolution (defined as no need for oxygen support; WHO Scale <=4) - NP
- Viral clearance (at day 3, 7 or 15) - NP
- Serious adverse events, defined as number of participants with event - NR
- Adverse events (any grade, grade 1-2, grade 3-4), defined as number of participants with event - NR
- Vitamin D serum levels - reported
- Additional review outcomes
  * Duration of supplemental oxygen, non-invasive or invasive ventilation or organ support
  * Absence of fever
  * Intensive care unit length of stay
  * Time until negative laboratory SARS-CoV-2 test
  * Mortality related to Covid-19
  * Blood levels of C-reactive protein, interleukin 6 and 10, cathelicidin, white blood cells, creatinine and 1,25(OH)2-D3

Starting date	November 12, 2020
Contact information	Contact: Anne-Françoise Rousseau, MD, PhD +3243667495 afrousseau@chuliege.be
Notes	• Recruitment status: recruiting • Prospective completion date: 28/02/2021 • Date last update was posted: 19/11/2020 • Sponsor/funding: University of Liege

NCT04641195

Study name	Vitamin D and zinc supplementation for improving treatment outcomes among COVID-19 patients in India
Methods	• Trial design: factorial design RCT • Sample size: 700 • Setting: inpatient • Language: English (India) • Number of centres: 2 • Type of intervention (treatment/prevention): treatment

NCT04641195 *(Continued)*

Participants	• Inclusion criteria * Aged >=18 years old * Polymerase chain reaction (PCR)-confirmed infection with SARS-COV2 * Oxygen saturation level of 90 or above * Provide informed consent • Exclusion criteria * Pregnancy * Enrolment in other clinical trials * Daily use of multivitamins for the past 1 month
Interventions	• Details of intervention: 4 groups (factorial design) * 1: Vitamin D and zinc ☐ Dose: 180,000 IU of vitamin D3 at enrolment, followed by 2000 IU of vitamin D3 and 40 mg of zinc gluconate once per day from enrolment to 8 weeks ☐ Route of administration: oral * 2: Placebo and zinc ☐ Dose: 40 mg of zinc gluconate taken once per day from enrolment to 8 weeks ☐ Route of administration: oral * 3: Vitamin D and placebo ☐ Dose: 180,000 international units (IU) of vitamin D3 at enrolment, followed by 2000 IU once per day from enrolment to 8 weeks ☐ Route of administration: oral * 4: Placebo and placebo ☐ Placebo vitamin D bolus at enrolment followed by placebo daily vitamin D maintenance doses and placebo daily zinc supplements. • Concomitant therapy: all groups receive a vitamin D bolus at the hospital
Outcomes	• Primary study outcome * Time to recovery

NCT04641195 *(Continued)*

- Review outcomes
  - All-cause mortality at day 28, day 60, and up to longest follow-up - reported
  - Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale (WHO 2020e), WHO Ordinal Scale for Clinical Improvement (WHO 2020f)) at up to 7 days, 8 to 15 days, 16 to 30 days; including:
    - ☐ ventilator-free days and need for intubation or IV (at day 28, day 60, and up to longest follow-up);
    - ☐ weaning/liberation from mechanical ventilation.
    - ☐ increase of WHO score (WHO clinical progression scale), for subgroup of patients without the respective need for respiratory support at baseline:
      - ○ need for invasive ventilation i.e. WHO 7-9;
      - ○ need for non-invasive ventilation or high flow i.e. WHO = 6;
      - ○ need for oxygen by mask or nasal prongs i.e. WHO = 5;
      - ○ need for hospitalisation without oxygen therapy i.e. WHO = 4
    - ☐ Probably reported
  - Need for dialysis (at up to 28 days) for subgroup of severely ill patients - NP
  - Quality of life, including fatigue and neurological status, assessed with standardised scales (e.g. WHOQOL-100) at up to 7 days; up to 30 days, and longest follow-up available - NP
  - Admission to ICU - NP
  - Duration of hospitalisation - NP
  - Time to discharge from hospital - NP
  - Time to symptom resolution (defined as no need for oxygen support; WHO Scale <=4) - probably reported
  - Viral clearance (at day 3, 7 or 15) - NP
  - Serious adverse events, defined as number of participants with event - NP
  - Adverse events (any grade, grade 1-2, grade 3-4), defined as number of participants with event - NP
  - Vitamin D serum levels - reported
- Additional review outcomes
  - All-cause mortality
  - Necessity for assisted ventilation
  - Individual symptoms duration
  - Vitamin D
  - Zinc
  - Interleukin 6 (IL-6)
  - Angiopoietin-2
  - sTREM-1
  - Immunoglobulin M (IgM)
  - Immunoglobulin (IgG)

Starting date	01/03/2021
Contact information	Wafaie W Fawzi, MBBS, MPH, MS, DrPH 617 432 2086 mina@hsph.harvard.edu
Notes	• Recruitment status: not yet recruiting • Prospective completion date: 31/03/2022 • Date last update was posted: 10/02/2021 • Sponsor/funding: Harvard School of Public Health

CRP: C-reactive protein; HDL: high-density lipoprotein; ICU: intensive care unit; IV: intravenous; LDL: low-density lipoprotein; NA: not applicable; NI: no information; NP: not planned; NR: not reported; TAU: treatment as usual

RISK OF BIAS

Legend: Low risk of bias | High risk of bias | Some concerns

Risk of bias for analysis 1.1 All-cause mortality

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Entrenas Castillo 2020	~	✓	✓	✓	~	~
Murai 2021	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 1.2 Worsening of clinical status: need for mechanical ventilation

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Murai 2021	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 1.6 Adverse events (any grade)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Murai 2021	✓	✓	✓	✓	~	~

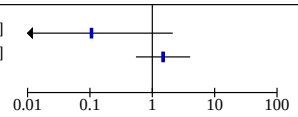
DATA AND ANALYSES

Comparison 1. Vitamin D supplementation vs. placebo or standard care alone for individuals with moderate to severe disease

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 All-cause mortality	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.2 Worsening of clinical status: need for mechanical ventilation	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.3 Duration of hospitalisation	1	237	Hazard Ratio (IV, Fixed, 95% CI)	1.07 [0.81, 1.41]
1.4 Vitamin D serum levels	1	237	Mean Difference (IV, Fixed, 95% CI)	24.70 [21.41, 27.99]
1.5 Admission to intensive care unit	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.6 Adverse events (any grade)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1: Vitamin D supplementation vs. placebo or standard care alone for individuals with moderate to severe disease, Outcome 1: All-cause mortality

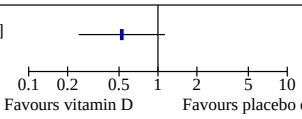
Study or Subgroup	Vitamin D Events	Vitamin D Total	Placebo or standard care alone Events	Placebo or standard care alone Total	Risk Ratio M-H, Random, 95% CI	Risk of Bias A	B	C	D	E	F
Entrenas Castillo 2020	0	50	2	26	0.11 [0.01 , 2.13]	?	+	+	+	?	?
Murai 2021	9	119	6	118	1.49 [0.55 , 4.05]	+	+	+	+	+	+



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: All-cause mortality
(C) Bias due to missing outcome data: All-cause mortality
(D) Bias in measurement of the outcome: All-cause mortality
(E) Bias in selection of the reported result: All-cause mortality
(F) Overall bias: All-cause mortality

Analysis 1.2. Comparison 1: Vitamin D supplementation vs. placebo or standard care alone for individuals with moderate to severe disease, Outcome 2: Worsening of clinical status: need for mechanical ventilation

Study or Subgroup	Vitamin D Events	Vitamin D Total	Placebo or standard care alone Events	Placebo or standard care alone Total	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A	B	C	D	E	F
Murai 2021	9	119	17	118	0.52 [0.24 , 1.13]	+	+	+	+	+	+

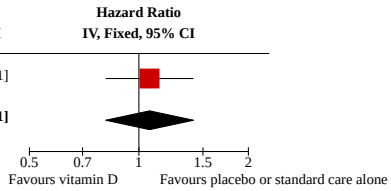


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Worsening of clinical status: need for mechanical ventilation
(C) Bias due to missing outcome data: Worsening of clinical status: need for mechanical ventilation
(D) Bias in measurement of the outcome: Worsening of clinical status: need for mechanical ventilation
(E) Bias in selection of the reported result: Worsening of clinical status: need for mechanical ventilation
(F) Overall bias: Worsening of clinical status: need for mechanical ventilation

Analysis 1.3. Comparison 1: Vitamin D supplementation vs. placebo or standard care alone for individuals with moderate to severe disease, Outcome 3: Duration of hospitalisation

Study or Subgroup	log[Hazard Ratio]	SE	Vitamin D Total	Placebo or standard care alone Total	Weight	Hazard Ratio IV, Fixed, 95% CI
Murai 2021	0.067659	0.141826	119	118	100.0%	1.07 [0.81 , 1.41]
Total (95% CI)			**119**	**118**	**100.0%**	**1.07 [0.81 , 1.41]**

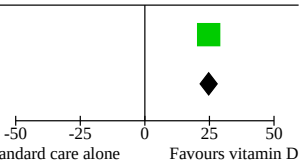
Heterogeneity: Not applicable
Test for overall effect: Z = 0.48 (P = 0.63)
Test for subgroup differences: Not applicable



Analysis 1.4. Comparison 1: Vitamin D supplementation vs. placebo or standard care alone for individuals with moderate to severe disease, Outcome 4: Vitamin D serum levels

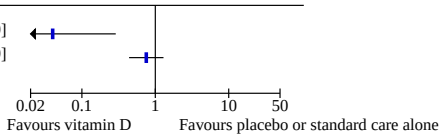
Study or Subgroup	Vitamin D Mean	SD	Total	Placebo or standard care alone Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Murai 2021	44.5	15	119	19.8	10.5	118	100.0%	24.70 [21.41 , 27.99]
Total (95% CI)			**119**			**118**	**100.0%**	**24.70 [21.41 , 27.99]**

Heterogeneity: Not applicable
Test for overall effect: Z = 14.70 (P < 0.00001)
Test for subgroup differences: Not applicable



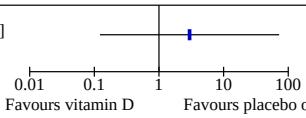
Analysis 1.5. Comparison 1: Vitamin D supplementation vs. placebo or standard care alone for individuals with moderate to severe disease, Outcome 5: Admission to intensive care unit

Study or Subgroup	Vitamin D Events	Total	Placebo or standard care alone Events	Total	Risk Ratio M-H, Random, 95% CI
Entrenas Castillo 2020	1	50	13	26	0.04 [0.01 , 0.29]
Murai 2021	19	119	25	118	0.75 [0.44 , 1.29]



Analysis 1.6. Comparison 1: Vitamin D supplementation vs. placebo or standard care alone for individuals with moderate to severe disease, Outcome 6: Adverse events (any grade)

Study or Subgroup	Vitamin D Events	Total	Placebo or standard care alone Events	Total	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A	B	C	D	E	F
Murai 2021	1	119	0	118	2.98 [0.12 , 72.30]	+	+	+	+	?	?

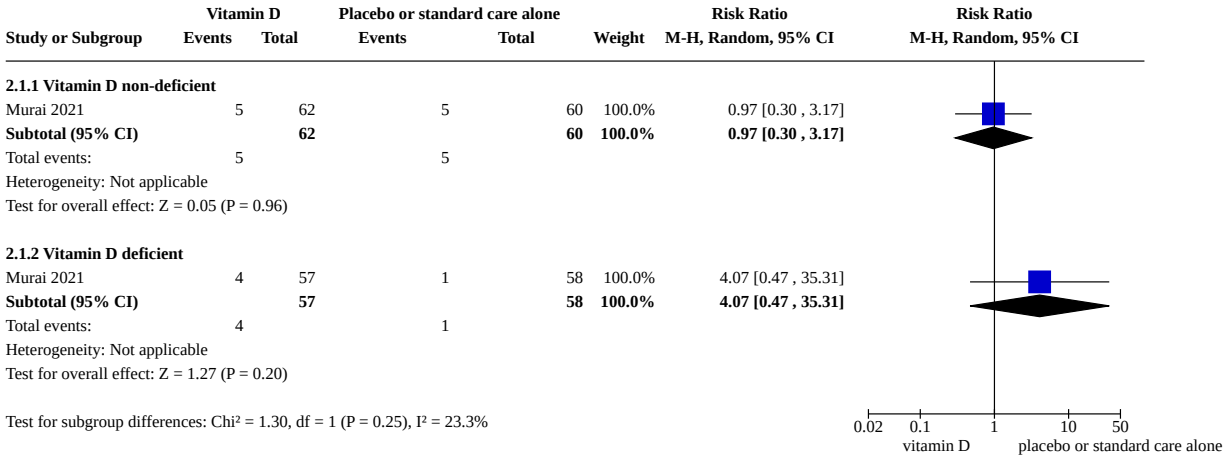


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Adverse events (any grade)
(C) Bias due to missing outcome data: Adverse events (any grade)
(D) Bias in measurement of the outcome: Adverse events (any grade)
(E) Bias in selection of the reported result: Adverse events (any grade)
(F) Overall bias: Adverse events (any grade)

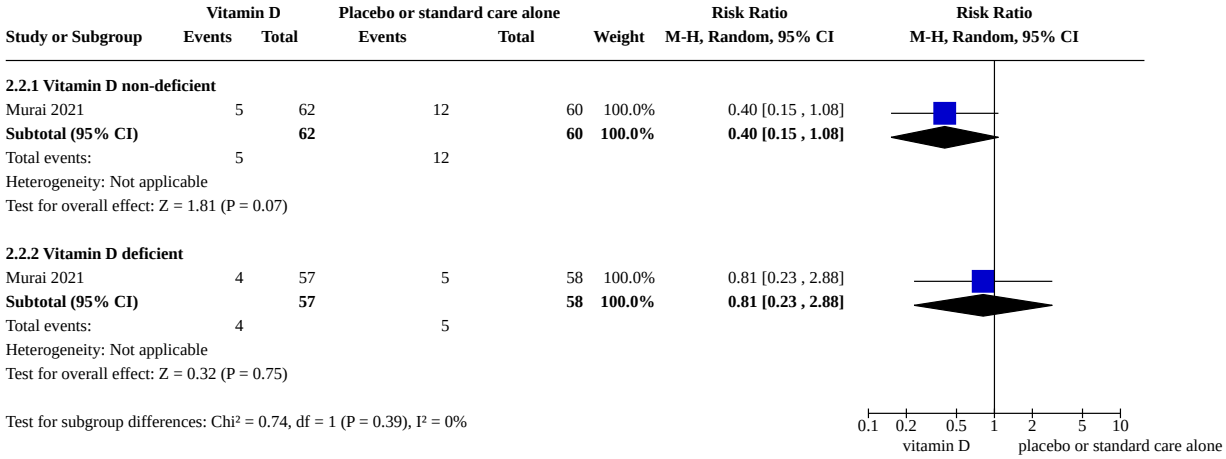
Comparison 2. Subgroup analysis (vitamin D baseline status): Vitamin D supplementation vs. placebo or standard care alone in individuals with moderate to severe disease

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 All-cause mortality	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1.1 Vitamin D non-deficient	1	122	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.30, 3.17]
2.1.2 Vitamin D deficient	1	115	Risk Ratio (M-H, Random, 95% CI)	4.07 [0.47, 35.31]
2.2 Need for mechanical ventilation	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.2.1 Vitamin D non-deficient	1	122	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.15, 1.08]
2.2.2 Vitamin D deficient	1	115	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.23, 2.88]
2.3 Admission to intensive care unit	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.3.1 Vitamin D non-deficient	1	122	Risk Ratio (M-H, Random, 95% CI)	1.29 [0.48, 3.50]
2.3.2 Vitamin D deficient	1	115	Risk Ratio (M-H, Random, 95% CI)	1.24 [0.56, 2.77]

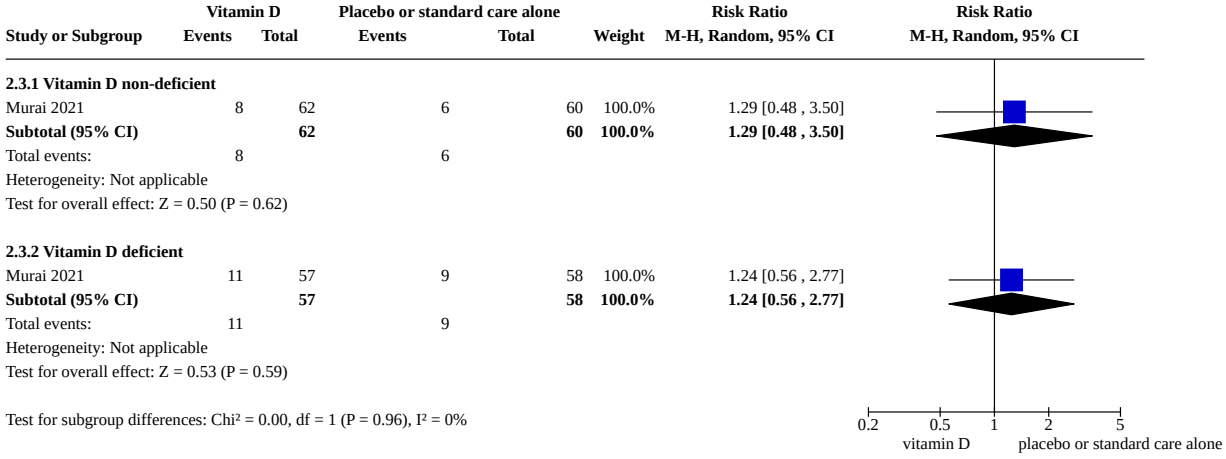
Analysis 2.1. Comparison 2: Subgroup analysis (vitamin D baseline status): Vitamin D supplementation vs. placebo or standard care alone in individuals with moderate to severe disease, Outcome 1: All-cause mortality



Analysis 2.2. Comparison 2: Subgroup analysis (vitamin D baseline status): Vitamin D supplementation vs. placebo or standard care alone in individuals with moderate to severe disease, Outcome 2: Need for mechanical ventilation



Analysis 2.3. Comparison 2: Subgroup analysis (vitamin D baseline status): Vitamin D supplementation vs. placebo or standard care alone in individuals with moderate to severe disease, Outcome 3: Admission to intensive care unit



ADDITIONAL TABLES

Table 1. WHO clinical progression scale

Patient State	Descriptor	Score
Uninfected	Uninfected; no viral RNA detected	0
Ambulatory mild disease	Asymptomatic; viral RNA detected	1
	Symptomatic; independent	2
	Symptomatic; assistance needed	3

Table 1. WHO clinical progression scale *(Continued)*

Hospitalised: moderate disease	Hospitalised; no oxygen therapy[a]	4
	Hospitalised; oxygen by mask or nasal prongs	5
Hospitalised: severe disease	Hospitalised; oxygen by non-invasive mechanical ventilation or high flow	6
	Intubation and mechanical ventilation, $pO_2/FiO_2 \geq 150$ or $SpO_2/FiO_2 \geq 200$	7
	Invasive mechanical ventilation $pO_2/FiO_2 < 150$ ($SpO_2/FiO_2 < 200$) or vasopressors	8
	Invasive mechanical ventilation $pO_2/FiO_2 < 150$ and vasopressors, dialysis or ECMO	9
Dead	Dead	10

WHO clinical progression scale from: WHO 2020e
[a]If hospitalised for isolation only, record status as for ambulatory patient
ECMO: extracorporeal membrane oxygenation
FiO_2: fraction of inspired oxygen
pO_2: partial pressure of oxygen
SpO_2: oxygen saturation

APPENDICES

Appendix 1. Search strategies

Cochrane COVID-19 Study Register

Search string: "vitamin d" OR "vitamind" OR "vitamin d3" OR "vitamin d2" OR "hydroxyvitamin d" OR "dihydroxyvitamin d" OR cholecalciferol* OR colecalcifer* OR calciferol* OR calciol* OR calcidiol* OR calcitriol* OR calcifediol* OR calciferol* OR ercalcidiol* OR ercalcitriol* OR ergocalciferol* OR doxercalciferol* OR colecalciferol* OR paricalcitol* OR alphacalcidol* OR dihydrotachysterol*

Study characteristics:
1) "Intervention assignment": “Randomised” OR
2) "Study type": "Interventional" AND "Study design": "Parallel/Crossover" OR "Unclear" OR "Other"

= 62 studies (75 references)

Web of Science Core Collection (Advanced search)

#1

TI=("vitamin d" OR "vitamind" OR "vitamin d3" OR "vitamin d2" OR "hydroxyvitamin d" OR "dihydroxyvitamin d" OR cholecalciferol* OR colecalcifer* OR calciferol* OR calciol* OR calcidiol* OR calcitriol* OR calcifediol* OR calciferol* OR ercalcidiol* OR ercalcitriol* OR ergocalciferol* OR doxercalciferol* OR colecalciferol* OR paricalcitol* OR alphacalcidol* OR dihydrotachysterol*) OR AB=("vitamin d" OR "vitamind" OR "vitamin d3" OR "vitamin d2" OR "hydroxyvitamin d" OR "dihydroxyvitamin d" OR cholecalciferol* OR colecalcifer* OR calciferol* OR calciol* OR calcidiol* OR calcitriol* OR calcifediol* OR calciferol* OR ercalcidiol* OR ercalcitriol* OR ergocalciferol* OR doxercalciferol* OR colecalciferol* OR paricalcitol* OR alphacalcidol* OR dihydrotachysterol*)

#2

TI=(COVID OR COVID19 OR "SARS-CoV-2" OR "SARS-CoV2" OR SARSCoV2 OR "SARSCoV-2" OR "SARS coronavirus 2" OR "2019 nCoV" OR "2019nCoV" OR "2019-novel CoV" OR "nCov 2019" OR "nCov 19" OR "severe acute respiratory syndrome coronavirus 2" OR "novel coronavirus disease" OR "novel corona virus disease" OR "corona virus disease 2019" OR "coronavirus disease 2019" OR "novel coronavirus pneumonia" OR "novel corona virus pneumonia" OR "severe acute respiratory syndrome coronavirus 2") OR AB=(COVID OR COVID19 OR

"SARS-CoV-2" OR "SARS-CoV2" OR SARSCoV2 OR "SARSCoV-2" OR "SARS coronavirus 2" OR "2019 nCoV" OR "2019nCoV" OR "2019-novel CoV" OR "nCov 2019" OR "nCov 19" OR "severe acute respiratory syndrome coronavirus 2" OR "novel coronavirus disease" OR "novel corona virus disease" OR "corona virus disease 2019" OR "coronavirus disease 2019" OR "novel coronavirus pneumonia" OR "novel corona virus pneumonia" OR "severe acute respiratory syndrome coronavirus 2")

#3

#1 AND #2

#4

TI=(random* OR placebo OR trial OR groups OR "phase 3" or "phase3" or p3 or "pIII") OR AB=(random* OR placebo OR trial OR groups OR "phase 3" or "phase3" or p3 or "pIII")

#5

#3 AND #4
Indexes=SCI-EXPANDED, ESCI Timespan=2020-2021

= 100

WHO COVID-19 Global literature on coronavirus disease

("vitamin d" OR "vitamind" OR "vitamin d3" OR "vitamin d2" OR "hydroxyvitamin d" OR "dihydroxyvitamin d" OR cholecalciferol* OR colecalcifer* OR calciferol* OR calciol* OR calcidiol* OR calcitriol* OR calcifediol* OR calciferol* OR ercalcidiol* OR ercalcitriol* OR ergocalciferol* OR doxercalciferol* OR colecalciferol* OR paricalcitol* OR alphacalcidol* OR dihydrotachysterol*) AND (random* OR placebo OR trial OR groups OR "phase 3" or "phase3" or p3 or "pIII")
- without MEDLINE and PubMed = 106

CONTRIBUTIONS OF AUTHORS

JS: methodological expertise, study selection, data extraction and assessment, conception and writing of the manuscript

JW: clinical expertise, conception and writing of the manuscript

CI: methodological expertise, study selection, data extraction and assessment, writing of the manuscript

AM: clinical expertise, conception and writing of the manuscript

MS: clinical expertise, conception and writing of the manuscript

CB: methodological expertise, conception and writing of the manuscript

MIM: information specialist, development of the search strategy, writing of the manuscript

PM: clinical expertise and advice, proof-reading of the manuscript

MB: data extraction

NS: methodological expertise and advice, study selection, conception, writing and proof-reading of the manuscript

VP: methodological expertise and advice, data extraction and assessment, conception, writing and proof-reading of the manuscript

DECLARATIONS OF INTEREST

JS: is funded by the Federal Ministry of Education and Research, Germany (NaFoUniMedCovid19, funding number: 01KX2021; part of the project "CEOSys", which was paid to the institution).

JW: none known

CI: is funded by the Federal Ministry of Education and Research, Germany (NaFoUniMedCovid19, funding number: 01KX2021; part of the project "CEOSys", which was paid to the institution).

AM: none known

CB: none known

MIM: is member of the CEOsys project funded by the Network of University Medicine (Nationales Forschungsnetzwerk der Universitätsmedizin (NUM)) by the Federal Ministry of Education and Research of Germany (Bundesministerium für Bildung und Forschung (BMBF)), grant number 01KX2021, paid to the institution.

PM: institution received grants by the Federal Ministry of Education and Research of Germany (Bundesministerium für Bildung und Forschung (BMBF), grant number 01KG1815, for the VITDALIZE-Study.

MB: none known

NS: none known

MS: none known

VP: is funded by the Federal Ministry of Education and Research, Germany (NaFoUniMedCovid19, funding number: 01KX2021; part of the project "CEOSys", which was paid to the institution).

SOURCES OF SUPPORT

Internal sources

- University Hospital of Cologne, Germany

  Cochrane Cancer, Department I of Internal Medicine

External sources

- Federal Ministry of Education and Research, Germany

  This review is part of the CEOsys project funded by the Network of University Medicine (Nationales Forschungsnetzwerk der Universitätsmedizin (NUM)) by the Federal Ministry of Education and Research of Germany (Bundesministerium für Bildung und Forschung (BMBF)), grant number 01KX2021.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The following differences exist between protocol (Stroehlein 2021a) and review:

Objectives

We also included studies with an active comparator, such as another treatment, if these were comparable between groups.

Types of outcome measures

We specified outcomes regarding effectiveness and safety of vitamin D supplementation for individuals with COVID-19 and either moderate to severe or mild to asymptomatic disease after a guideline consortium (CEOSys) that took place after protocol registration. We created outcome categories and added/specified the following outcomes for hospitalised participants with moderate or severe COVID-19:

- All-cause mortality at day 60, time-to-event, and at hospital discharge
- Need for dialysis (at up to 28 days)
- Quality of life, including fatigue and neurological status, assessed with standardised scales (e.g. WHOQOL-100) at up to seven days; up to 30 days, and longest follow-up available
- Admission to ICU
- Duration of hospitalisation
- Time to discharge from hospital
- Adverse events (any grade, grade 1-2, grade 3-4), defined as number of participants with event

For ambulatory managed individuals with mild to asymptomatic disease, we added and specified the following outcomes:

- All-cause mortality at day 60, time-to-event, and up to longest follow-up
- Admission to hospital (WHO≥ 4)
- Need for hospitalisation with or without supplemental oxygen i.e. WHO=4-5, moderate disease;
  - Need for hospitalisation without oxygen therapy i.e. WHO=4.
  - Need for oxygen by mask or nasal prongs i.e. WHO=5;
- Quality of life, including fatigue and neurological status, assessed with standardised scales (e.g. WHOQOL-100) at up to 7 days, up to 30 days, and longest follow-up available
- Adverse events (any grade, grade 1-2, grade 3-4), defined as number of participants with event

- Vitamin D serum levels

Types of subgroup analyses

We expanded subgroup analysis and additionally plan to conduct separate analysis in the next updates of this review for

- age (< 18 years, 18-65 years, and > 65 years)
- pre-existing conditions
- duration since symptom onset (below or above seven days)
- formulation of vitamin D (active, non-active)
- doses of vitamin D (single or multiple)
- administration of vitamin D
- co-treatments

Summary of findings and assessment of the certainty of the evidence

After guideline consortium (CEOSys), we prioritised the following outcome categories for hospitalised individuals with COVID-19 and moderate or severe disease:

- All-cause mortality
- Improvement of clinical status, assessed with liberation from supplemental oxygen support or invasive mechanical ventilation, in accordance with WHO Clinical Progression Scale (WHO 2020c) at longest follow-up available
  * Liberation from supplemental oxygen
  * Liberation from invasive mechanical ventilation
- Worsening of clinical status assessed by need for invasive mechanical ventilation
- Quality of life
- Adverse events
- Serious adverse events

For ambulatory managed individuals with COVID-19 and mild or asymptomatic disease, we prioritised the outcome categories:

- All-cause mortality
- Development of severe clinical COVID-19 symptoms
- Quality of life
- Adverse events
- Serious adverse events

NOTES

Parts of the review's methods section is adopted from templates of Cochrane Haematology and a similar protocol published by Piechotta 2020, and the corresponding reviews (Chai 2020).