

Scientific Advisory Group

COVID-19 Scientific Advisory Group Rapid Evidence Brief

Vitamin D in the Treatment and Prevention of COVID-19



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Physical distancing works

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Lay Summary

Background

- Vitamin D is important for bone and muscle health. It has also been hypothesized that vitamin D may have a role in the body's immune response to respiratory viruses, including COVID-19.
- There is an overlap between groups at risk of vitamin D deficiency and groups at high risk of severe COVID-19, with a complex relationship of lower socioeconomic status and nutritional status. Low vitamin D levels may be a marker of poor health so whether low vitamin D levels are a cause of COVID-19 or a reflection of health status is a point of debate.
- We examined current scientific evidence to evaluate if vitamin D is effective in the treatment and prevention of COVID-19.

Findings

- There is no high quality evidence that suggests taking vitamin D supplements is specifically effective in the prevention or treatment of COVID-19.
- For general health, it is important to have adequate vitamin D levels regardless of the effects on COVID-19. The recommended daily intake for Canadians ranges from 400-800 IU (10-20 mcg) daily depending on stage of life, with a tolerable upper intake level of 1,000-4,000 IU (25-100 mcg) daily.
- Further research on vitamin D and COVID-19, with well-designed randomized controlled trials and appropriate follow-up time is ongoing.

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Topic: Vitamin D in the treatment and prevention of COVID-19

Key Research Questions

1. ***What is the effectiveness and safety of vitamin D supplementation for the treatment of COVID-19?***
2. ***What is the effectiveness and safety of vitamin D supplementation for the prevention of COVID-19?***
3. ***Is vitamin D status associated with susceptibility to COVID-19?***
 - ***Is there any evidence that low vitamin D levels are an independent risk for COVID-19 infection or severe COVID-19 infection?***
4. ***From the evidence selected, are there any subgroups of people who may benefit from vitamin D supplementation more than the wider population of interest?***

Context

- Vitamin D is important for bone and muscle health. It has also been hypothesized that vitamin D may have a role in the body's immune response to respiratory viruses.
- Research suggests that there is inadequate sunlight (UVB) during Alberta's winters for effective synthesis of vitamin D due to a significant impact of northern latitudes. Edmonton, at 52 degrees N, has an ineffective winter period from October through March, Boston at 42.2 degrees N from November to February, but winter photoconversion is effective south of 34 degrees N (Webb et al., 1988).
- Given the widespread interest in therapeutic potential of vitamin D, clinicians may be increasingly asked about whether vitamin D deficiency is related to increased susceptibility to or severity of COVID-19.
- Media reports are presenting vitamin D as promising in the prevention and treatment of COVID-19.
- Some media and social media reports appear to recommend supplementation well above the current vitamin D supplementation guidelines.
- This evidence summary examines the effectiveness and safety of vitamin D supplementation for the treatment and prevention of COVID-19, and explores the evidence regarding vitamin D as an independent risk factor for COVID-19 infection.
- This review summarizes and builds upon the [evidence review](#) completed by the National Institute for Health and Care Excellence (NICE) [COVID-19 Rapid Guideline: Vitamin D](#) published December 17, 2020. This review comprises an updated literature search through to December 8, 2020, compared to the NICE review where the literature search ended October 27, 2020.
- There is an overlap between groups at high risk of vitamin D deficiency and groups at high risk of severe COVID-19. Examples include people with chronic disease, older age, and people of Black and minority ethnic heritage, which makes assessment of observed associations between low vitamin D and COVID-19 infection challenging. Vitamin D levels may be indicative of co-morbidities that may themselves impact COVID-19 outcomes, so whether low vitamin D levels are a cause of disease or consequence of health disparity has remained a point of debate.

Key Messages from the Evidence Summary

- There is no high quality evidence to support taking vitamin D supplements to specifically prevent or treat COVID-19. To date, there are three RCTs assessing different formulations of vitamin D in patients hospitalized with COVID-19; however, the results have been variable and concerns with small sample size, dosing regimen, and inappropriate randomization limit the conclusions that can be drawn. The largest trial (Murai et al, 2020; n = 240) showed no benefit.
- While there have been a number of observational studies evaluating the association of vitamin D status and COVID-19, the evidence is very weak. Concerns with confounding (see description of patient population at risk overlap above), sample size, selection bias, and reverse causality limit the conclusions that can be drawn.
- Addressing vitamin D deficiency is important for general health, irrespective of the effects on COVID-19. People should continue to follow the current practice guidelines on daily vitamin D supplementation. The daily recommended intake for Canadians ranges from 400-800 IU daily by age and can be found at: <https://www.canada.ca/en/health-canada/services/food-nutrition/healthy-eating/vitamins-minerals/vitamin-calcium-updated-dietary-reference-intakes-nutrition.html#a10>.
- There may be some benefit from daily, low-dose vitamin D supplementation (between 400 to 1,000 IU/day) in reducing the risk of acute respiratory tract infections, based on a meta-analysis of randomized controlled clinical trials.

Recommendations

Recommendation 1: Vitamin D should not be offered as therapy for COVID-19 infection.
Rationale: To date, the clinical evidence is very weak with only a few small studies available. There is insufficient evidence at this time to recommend treatment of COVID-19 with high dose vitamin D supplementation, except as part of a clinical trial.

Recommendation 2: Vitamin D supplementation should not be recommended for the purpose of preventing COVID-19.
Rationale: While a number of observational studies have demonstrated an association between vitamin D status and COVID-19, the strength of the evidence remains very low and there are no RCTs evaluating vitamin D as preventive therapy.

Recommendation 3: Health Care Providers and patients are encouraged to follow current established guidelines by [Health Canada](#) which suggest appropriate supplementation of vitamin D, with all Albertans noted to be eligible for appropriate supplementation.
Rationale: Vitamin D deficiency has been established as an important risk factor for bone health, and supplementation with vitamin D may reduce the risk of acute respiratory tract infections. Testing of vitamin D levels is not required or routinely recommended prior to vitamin D supplementation.

Practical Considerations

- Given the current evidence, testing for vitamin D deficiency is not recommended in routine screening or in the setting of COVID-19 – see the guidelines from Choosing Wisely Canada ([Pathology](#) and [Family Medicine](#)) and the [Alberta Medical Association](#).
- Associations between vitamin D status and COVID-19 are not surprising as vitamin D deficiency may represent a surrogate marker for a general micronutrient deficiency, which in turn reflects the patient’s overall health status – many of the risk factors for severe COVID-19 outcomes are the same as the risk factors for low vitamin D status.
- Clinicians should encourage appropriate vitamin D supplementation (see the current [Health Canada](#) guidelines for Canadians) particularly in groups at higher risk of vitamin D deficiency.
- While there is limited evidence for an association between vitamin D and the severity of COVID-19, it is reasonable to counsel patients around appropriate vitamin D requirements and recommended supplementation for general health. This would include people at higher susceptibility for COVID-19 (e.g. those in long-term care centers) to ensure that current vitamin D supplementation is in accordance with guidelines.

Current Recommendations on Vitamin D Supplementation

Vitamin D supplements are available in two forms: vitamin D₂ (ergocalciferol) and vitamin D₃ (cholecalciferol). Both vitamin D₂ and vitamin D₃ are metabolized by the liver to form 25-hydroxycholecalciferol or 25(OH)D (calcifediol), which is then metabolized by the kidney to form calcitriol (1,25-dihydroxycholecalciferol), the most biologically active form of vitamin D (Armas, Hollis, & Heaney, 2004). Vitamin D₃ is the preferred supplementary form, with vitamin D₂ being available for large-dose preparations.

Current recommendations are based on an Institute of Medicine report (IOM, 2011) commissioned by Health Canada on the dietary reference intakes for vitamin D. The report suggests that a 25(OH)D serum level of 50 nmol/L is sufficient for most of the population to maintain bone and overall health and have based the recommended dietary allowances on this serum level and the assumption that sun exposure is minimal. However, as vitamin D supplementation for the general adult population is safe and necessary, supplements can be recommended without testing for deficiency.

Table 1: Dietary Reference Intakes (DRIs) for Vitamin D ([Health Canada](#), 2020)

Age group	Recommended Dietary Allowance (RDA) per day	Tolerable Upper Intake Level (UL) per day
Infants 0-6 months	400 IU (10 mcg)*	1000 IU (25 mcg)
Infants 7-12 months	400 IU (10 mcg)*	1500 IU (38 mcg)
Children 1-3 years	600 IU (15 mcg)	2500 IU (63 mcg)
Children 4-8 years	600 IU (15 mcg)	3000 IU (75 mcg)
Children and Adults 9-70 years	600 IU (15 mcg)	4000 IU (100 mcg)
Adults > 70 years	800 IU (20 mcg)	4000 IU (100 mcg)
Pregnancy & Lactation	600 IU (15 mcg)	4000 IU (100 mcg)

*Adequate Intake rather than Recommended Dietary Allowance.

- For adults over the age of 50 and at risk of osteoporosis, recommended supplementation doses range from 800-2,000 IU.
- There are health risks associated with excessive or toxic amounts of vitamin D. The upper limit suggested to be safe for most individuals is 4,000 IU per day, and toxic levels of vitamin D usually require much higher consumption, up to 10,000 IU per day. These risks include hypercalcemia, hypercalciuria, which can lead to nausea, vomiting, muscle weakness, neuropsychiatric disturbances, pain, loss of appetite, dehydration, polyuria, excessive thirst, and kidney stones. In extreme cases, vitamin D toxicity can cause renal failure, calcification of soft tissues throughout the body (including in coronary vessels and heart valves), cardiac arrhythmias, and even death.
- There is no clinical benefit of testing vitamin D levels in the general population regardless of common risks (such as low dietary intake and/or seasonal (sunlight) variation), as vitamin D supplementation for the general population should be recommended regardless of screening and monitoring.
- In patients with clinical conditions that may be predisposed to vitamin D deficiency such as malabsorption syndromes, chronic renal or liver failure, unexplained bone pain, unusual fractures, and other evidence of metabolic bone disorders, vitamin D testing may be warranted.

Research Gaps

As with all the COVID-19 literature, there is much we still do not know. This review and the accompanying recommendations are limited by the fact that most studies in the area of vitamin D and COVID-19 have many limitations, in particular, the potential for bias and insufficient power. It is suggested that future RCTs completed have a minimum 8-week follow up and examine all care settings (NICE, 2020, December). There should be a particular focus on subgroup analyses including, but not limited to, age (such as over 75 years), ethnicity (for example, Black, Asian and minority ethnic groups) and comorbidities (for example, obesity) that are associated with poorer outcomes in people with COVID-19. Adequately powered RCTs of a properly defined effective doses of vitamin D in prophylaxis and in therapy are needed to clarify the role of vitamin D supplementation in COVID-19, and many trials are ongoing (71 trials are registered at clinicaltrials.gov). This brief therefore may be updated in the future.

Strength of Evidence

At this time, the evidence is not strong for the use of vitamin D supplementation in the prevention or treatment of COVID-19. Much of the published evidence is observational and examines retrospective associations making it subject to potential bias and confounding. Association studies should be used to inform future research. Results from high quality, appropriately powered randomized controlled trials are needed. We identified only three RCTs. Two were small in size ($n < 80$) with serious concerns with quality and confounding. The remaining study was larger ($n = 240$) and of a stronger methodological design; this study failed to find any difference between the groups and has yet to be peer-reviewed.

Limitations of this review

Many of the populations examined here are patients who have been admitted to hospital or the ICU. Clinical decisions made with respect to admission may vary greatly by country/jurisdiction

and may change substantially over the course of the pandemic. This may limit the generalizability of these findings to the Alberta context.

Rapid turnaround time limited the ability to perform an in-depth data extraction of effects and/or meta-analysis. Databases were searched for English-language evidence published in 2020, after the period covered by the NICE evidence review, thus, evidence from other jurisdictions where English is not common has not been included in this review.

Summary of Evidence

This review summarizes and builds upon the [evidence reviews](#) completed by the National Institute for Health and Care Excellence (NICE, 2020, December) published December 17, 2020 for their [COVID-19 rapid guideline: Vitamin D](#). Their search was completed on October 27, 2020 and did not include preprints, whereas this current review had a search date of Dec 8, 2020 and does include preprints.

Our search was adapted from the initial NICE evidence review Vitamin D for COVID-19, June 29, 2020 (NICE, 2020, June). For this review, we searched the literature in a database search covering: OVID MEDLINE, LitCovid, PubMed, TRIP PRO, WHO COVID-19 Database, Centre for Evidence Based Medicine (CEBM), CADTH COVID-19 Evidence Portal, COVID-Evidence medRxiv, Cochrane Library and Google Scholar. Given the NICE systematic review, we primarily limited our search to dates beyond their search date of June 5, 2020.

A total of two writers were involved in the screening and extraction. We identified 182 articles that met our PICO criteria through title and abstract screen. The included studies were identified through two screening stages. In the first stage, we screened articles based on our inclusion/exclusion criteria (n=50). The majority of the studies excluded at this stage were commentaries or reviews that were not systematic, as well as ecological studies that used weather patterns (e.g. ultraviolet index) or geographical latitude of locations as a proxy for vitamin D alone. The second stage of screening involved a preliminary quality appraisal screen resulting in the inclusion of 16 key studies: 3 RCTs, 12 observational cohorts, and 1 systematic review. It should be noted that given interventional studies are regarded as the highest level of evidence, we did not exclude any interventional studies based on quality alone.

Evidence from secondary and grey literature

We found that any secondary and grey literature that was identified that addressed these research questions primarily included citations to primary literature or original research. In turn, this review limited its analysis and discussion to primary literature or original research (including preprints) for all the research questions.

Research Question 1

What is the effectiveness and safety of vitamin D supplementation for the treatment of COVID-19?

Evidence from the primary literature

We identified three RCTs, details of the studies are summarized in Table 2.

A pilot randomized controlled trial (Entrenas Castillo et al., 2020) among patients (n=76) hospitalised for COVID-19 infection evaluated the effectiveness of administering a high dose

(0.532 mg / 21,280 IU) of oral 25-hydroxyvitamin D₃ (calcifediol) upon admission. Patients were allocated at a 2:1 ratio for randomization and all patients received a combination of hydroxychloroquine and azithromycin in combination with the vitamin D supplementation. Outcomes included need for ICU admission and mortality. The study reported that among the 26 patients in the control group, 13 (50%) were admitted to ICU, and two died. In the intervention group, only one out of 50 (2%) required ICU admission, and none died. Multivariate risk estimate odds ratio for ICU admission after adjusting for hypertension and type 2 diabetes mellitus was 0.03 (95% CI: 0.003-0.25). Weaknesses include small number of patients, ICU admission as a subjective outcome, and the unusual dosing regimen.

A multicentre, double-blind, placebo-controlled RCT (Murai et al., 2020) in hospitalized patients (n=240) with severe COVID-19 investigated the efficacy of a single dose of 200,000 IU of vitamin D₃. Outcomes included length of stay, admission to ICU, mechanical ventilation, and mortality. The study found that length of stay was comparable between the two groups; there was also no difference in mortality, admission to ICU and use of mechanical ventilation. Vitamin D significantly increased serum 25(OH)D with no adverse reactions.

A placebo-controlled RCT (Rastogi et al., 2020) of hospitalized patients with COVID-19 examined whether a dose of 60,000 IU of vitamin D₃ for 7 days resulted in a difference in negative SARS-CoV-2 RNA tests at 21 days. Ten (62.5%) participants in the intervention group and 5 (20.8%) participants in the control arm (p<0.018) became SARS-CoV-2 RNA negative.

Table 2: Summary of identified randomized controlled trials

Study	Population	Intervention group	Control group/ Comparator	Analysis	Outcome	Main Results
(Entrenas Castillo et al., 2020) RCT Spain	N=76 admitted with confirmed COVID-19 randomised in a 2:1 ratio into intervention and comparator arms.	n=50 received calcifediol (0.532 mg) on admission, then 0.266 mg on days 3 and 7, then weekly until discharge, plus standard care	n=26 received standard care only	Univariate and multivariable logistic regressions were used to estimate the probability of admission to intensive care unit (ICU). Mortality was reported as number of event counts.	ICU admission COVID-19 mortality	Of the 26 patients in the control group, 13 (50%) were admitted to ICU, and two died. In the intervention group, only one out of 50 (2%) required ICU admission, and none died. Multivariate OR: 0.03 (95% CI: 0.003-0.25) adjusted for hypertension and diabetes.
(Murai et al., 2020) RCT Brazil <i>Preprint</i>	N=240 hospitalized patients with severe COVID-19 randomized in a 1:1 ratio into intervention and comparator arms.	n=120 received single oral dose of 200,000 IU of vitamin D ₃ dissolved in 10mL of peanut oil solution, plus standard care	n=120 received single oral dose of 10mL of peanut oil solution, plus standard care	Log-rank test was used to compare the Kaplan-Meier estimate curves for the number of days for hospital length of stay.	Hospital length of stay Mortality, admission to ICU, mechanical ventilation requirement, serum levels of 25(OH)D, creatinine, calcium, C-reactive	Hospital length of stay was comparable between the vitamin D ₃ group and the placebo group (7.0 days [95% CI: 6.1 to 7.9] and 7.0 days [95% CI: 6.2 to 7.8 days], HR, 1.12, [95% CI: 0.9 to 1.5]; P = .379; respectively). The

					protein, D-dimer	rate of mortality, admission to ICU, and mechanical ventilation requirement did not significantly differ between groups.
(Rastogi et al., 2020) RCT India	N=40 admitted with confirmed COVID-19 were randomized to the intervention arm or control arm.	n=16 received standard care plus daily dose of 60,000 IU of vitamin D ₃ for 7 days with the aim to achieve 25(OH)D level >50 ng/ml. 25(OH)D levels assessed at day-7, and vitamin D ₃ supplementation continued for those with 25(OH)D <50 ng/ml up until day-14	n=24 received standard care plus daily dose of 5mL of distilled water for 7 days	Fischer Exact (2 by 2 tailed) test to compare proportion of participants achieving SARS-CoV-2 RNA negativity	Proportion of participants who turn SARS-CoV-2 negative (confirmed twice at 24-hour interval) before week 3 and change in inflammatory markers	10 out of 16 patients could achieve 25(OH)D >50 ng/ml by day-7 and another two by day-14 (p<0.001) in intervention group. 10 (62.5%) participants in the intervention group and 5 (20.8%) participants in the control arm (p<0.018) became SARS-CoV-2 RNA negative.

Synthesis of the Information Relating to Question 1

RCTs provide the strongest level of evidence as they are less susceptible to confounding. Among the three RCTs identified, two (Entrenas Castillo et al., 2020; Rastogi et al., 2020) reported results in support of vitamin D supplementation where one (Murai et al., 2020) reported no difference between the intervention and control groups. However, issues with methodological quality warrant caution when interpreting the results.

These studies are limited by their small sample sizes thereby decreasing their statistical power and may be unrepresentative of the wider population of interest. The pilot RCT (Entrenas Castillo et al., 2020) with 2:1 allocation was not placebo controlled and the blinding was incomplete, leading to concerns with bias. In addition, patients assigned to calcifediol were slightly older, whereas the control group had a higher percentage of hypertension and diabetes mellitus. Finally, ICU admission is a somewhat subjective outcome measure which can be affected by many variables. The randomized controlled trial (Murai et al., 2020) conducted in Brazil had the largest sample size (n=240) of the 5 studies examined, and yet the sample size could still have been underpowered to detect significant changes for the secondary outcomes. As the patients had several coexisting diseases and were subjected to a diverse medication regimen, the results could have been affected by the heterogeneity of the sample and its treatment. The proportion of patients with 25-(OH)D deficiency in this study was considerably lower than those reported in other cohorts, possibly as a consequence of differences in geographic locations. The randomized controlled trial (Rastogi et al., 2020) conducted in India only included mildly symptomatic and asymptomatic individuals, which limits the generalisability of its results to symptomatic or severe cases of COVID-19. It is not clear whether the study was blinded. The placebo used in the study was not exactly matched with regards to the taste and consistency with the vitamin D₃ nano formulation leading to concerns of lack of concealment. The use of SARS-COV2 RT-PCR negativity as an outcome is both nonclinical and of limited

relevance given the wide variation in duration of RT-PCR positivity and lack of correlation with clinical disease resolution (see an upcoming Scientific Advisory Group review on this topic).

Overall, there is limited and weak evidence from randomized controlled studies available at this time. Of note, is that the larger study (Murai et al., 2020) with 240 patients and appropriate randomization, failed to find any difference in outcomes with a single bolus supplementation of vitamin D with COVID-19 diagnosis. Further research is needed in order to better evaluate if vitamin D is effective in the treatment of COVID-19.

Research Question 2

What is the effectiveness and safety of vitamin D supplementation for the prevention of COVID-19?

Evidence from the primary literature

No evidence relevant to the PICO protocol was found for this question.

Synthesis of the Information Relating to Question 2

At this time, there is no effectiveness or safety studies available on the efficacy nor the effectiveness of vitamin D supplementation for the prevention of COVID-19. All available evidence for prevention is limited to observational data as outlined below.

Note: Information and guidelines regarding the safety of vitamin D supplementation in general, not specific to COVID-19, can be found at: Health Canada; [Vitamin D and Calcium: Updated Dietary Reference Intakes](#)

Research Question 3

Is vitamin D status associated with susceptibility to COVID-19?

- i. Is there any evidence that low vitamin D levels are an independent risk factor for COVID-19 infection or severe COVID-19 infection?***

Evidence from the primary literature

We identified 46 observational studies that reported on how vitamin D status is associated with COVID-19 outcomes. Upon completing an initial quality appraisal, we identified 12 studies for inclusion in this evidence review. The main reason for the exclusion of studies (n=34) was based on quality and lack of appropriate adjustment for confounders. Among the 12 key studies included, they examined associations of vitamin D with COVID-19 cases/infections, as well as COVID-19 disease severity. Included in the severity outcomes were variables such as hospitalization, admission to ICU, length of stay, mechanical ventilation, chest CT-scans, pneumonia scoring and death. Table 3 outlines a summary of the observational studies.

Many of the studies reported on the prevalence of vitamin D deficiency in the identified COVID-19 populations compared with controls. Although there was a range (55% to 97%), many of the studies reported a statistically significant higher prevalence of vitamin D deficiency and lower mean serum levels in those diagnosed with COVID-19 and in those with more severe disease outcomes. Although several studies found no difference in vitamin D status among groups (Butler-Laporte et al., 2020; Cereda, Bogliolo, Klersy, et al., 2020; Li et al., 2020), the majority of included studies (n=7) did find a statistically significant difference with more vitamin D deficiency

in the COVID-19 or more severe COVID-19 groups. The possibility of publication bias is not excluded.

In evaluating the strength of the association between vitamin D status and COVID-19, the results are less clear. While many studies reported a significant association, with odd ratios ranging from 1.5 and as high as 3.87 in favor of vitamin D, some studies reported no association and even reported an inverse association suggesting harm. Differing statistical approaches on the adjustment/modeling for a variety of confounding variables further provided mixed results.

One systematic review and meta-analyses (Pereira, Dantas Damascena, Galvão Azevedo, de Almeida Oliveira, & da Mota Santana, 2020) was identified with a search date ending Oct 9, 2020. This systematic review found that while vitamin D deficiency was not associated with a higher chance of infection by COVID-19, they observed a positive association between vitamin D deficiency and the severity of the disease. They reported that severe cases of COVID-19 were more likely to have vitamin D deficiency than mild cases with a modest odds ratio (OR 1.62%, 95% CI=1.06-2.58). However, concerns regarding the methodology and inappropriate meta-analysis warrant caution when interpreting the results.

Table 3: Summary of observational studies included in the evidence review

Reference	N	Population	Comparisons	Outcomes	Summary of Key Results
(C. Annweiler et al., 2020) Retrospective “quasi-experimental” study France	66	Nursing home residents diagnosed with COVID-19. Residents received chronic vitamin D ₃ supplementation with regular maintenance boluses (single oral dose of 80,000 IU vitamin D ₃ every 2 to 3 months). When residents last received supplementation dictated which group they were in: n=57 received vitamin D ₃ bolus within 1 month of or a week after COVID-19 diagnosis; n=9 did not receive vitamin D ₃ bolus	Associations between predictor variables, such as vitamin D ₃ supplements, and the likelihood of COVID-19 mortality at a specific time. Comparing time to death between intervention and comparator groups. Associations between bolus vitamin D ₃ supplements and World Health Organization Ordinal Scale for Clinical Improvement (OSCI) score, taking into account factors that may affect the result.	COVID-19 mortality World Health Organization Ordinal Scale for Clinical Improvement (OSCI) score for COVID-19 in acute phase	In the intervention group, 82.5% (n=47) survived COVID-19, compared to only 44.4% (n=4) in the comparator group (P = 0.023). The adjusted model for mortality according to vitamin D ₃ supplementation was HR = 0.11 [95% CI:0.03-0.48], P = 0.003.
(G. Annweiler et al., 2020) Retrospective “quasi-	77	Patients admitted to hospital with COVID-19.	Comparisons between groups for the reported outcomes. Association between each group and 14- day	14-day COVID-19 mortality	In Group 1, 93% survived compared to 81% in Group 2 (p=0.33) and 69% in Group 3 (p=0.02). Regular bolus vitamin D ₃ supplementation pre-diagnosis was associated with

experimental” study France		n=29 received vitamin D ₃ bolus over the preceding year n=16 received a vitamin D ₃ supplement after COVID-19 diagnosis n=32 received no vitamin D ₃ supplement	mortality at a specific time, adjusting for confounders. Comparison of survival between the groups. Association between vitamin D status and severe COVID-19, adjusted for confounding variables.	OSCI score for COVID-19 in acute phase	less severe COVID-19 and better survival rate in hospitalized frail elderly. Supplementation with 80,000 IU vitamin D ₃ after the diagnosis of COVID-19 was not associated with improved COVID-19 outcomes.
(Butler-Laporte et al., 2020) Cohort study (Mendelian Randomization) <i>Preprint</i>	443,734	Genotype data from UK Biobank data from people of European descent	Mendelian randomization of genetic variants strongly associated with serum 25(OH)D from genome-wide association study (GWAS)	COVID-19 (risk of infection, hospitalization, severity, death)	Genetically increased 25(OH)D levels had no clear effect on susceptibility but tended to increase the odds ratio of hospitalization (OR = 2.34; 95% CI: 1.33, 4.11) and severe disease (OR = 2.21; 95% CI: 0.87, 5.55). Sensitivity analyses provided consistent estimates. Findings do not support a protective role of increased 25(OH)D levels on COVID-19 outcomes and may suggest harm.
(Cereda et al., 2020b) Cohort study	129	Adults hospitalized with COVID-19	25(OH)D serum levels assessed at hospital admission and categorized into: normal (≥ 30 ng/mL), insufficient ($< 30 - \geq 20$ ng/mL), moderately deficient ($< 20 - \geq 10$ ng/mL), severely deficient (< 10 ng/mL)	Severe pneumonia, admission to intensive care units [ICU] and in-hospital mortality	77% of patients were vitamin D deficient. Vitamin D deficiency (< 20 ng/mL) was not associated with COVID-19 outcomes. A significant positive association between increasing vitamin D levels and in-hospital mortality (on a continuous logarithmic scale, odds ratio = 1.73 [95% CI: 1.11 to 2.69]; P = .016) was observed.
(Chang et al., 2020) Case-control study <i>Preprint</i>	26,602	Individuals tested by PCR for SARS-CoV-2; 992 were COVID-19 positive; 72 with severe outcome	25(OH)D level within past year before PCR test.	Positive PCR test	Vitamin D deficiency found to be an independent risk factor for COVID-19 (OR 1.8 [95% CI: 1.4–2.2], $p = 5.7 \times 10^{-6}$)
(De Smet et al., 2020) Cohort study	186	Individuals hospitalized with severe SARS-CoV-2 infection	25(OH)D measurement on admission	Mortality	Of the patients with COVID-19, 59% were vitamin D deficient on admission. Death rate was 15% (n=27). Vitamin D was associated with mortality (odds ratio [OR], 3.87; 95% CI: 1.30-11.55), independent of age, chronic lung disease, and extent of lung damage expressed by chest CT severity score but not sex.

(Hernández et al., 2020) Case-control study	413	Cases (n=216): Individuals age ≥ 18 admitted to hospital with confirmed COVID-19; n=19 taking vitamin D supplements Controls: Individuals recruited from the Camargo study cohort and were sex-matched with non-vitamin D supplemented cases.	25(OH)D measurement on hospital admission (cases) or during recruitment into study (controls)	Composite severity endpoint: Admission to the ICU, requirement for mechanical ventilation, or in-hospital mortality	Vitamin D deficiency was found in 82.2% of COVID-19 cases and 47.2% of population-based controls (P < .0001). Vitamin D-deficient COVID-19 patients had a greater prevalence of hypertension and cardiovascular diseases, raised serum ferritin and troponin levels, as well as a longer length of hospital stay than those with serum 25(OH)D levels ≥20 ng/mL. No causal relationship was found between vitamin D deficiency and COVID-19 severity as a combined endpoint or as its separate components.
(Kaufman et al., 2020) Cohort study	191,779	Participant data collected from a Quest Diagnostics database that processed SARS-CoV-2 tests and matched it to data held on individual's vitamin D results from the preceding 12 months.	Patients stratified according to their serum 25(OH)D level from preceding 12 months: ≥75 nmol/L (optimal); 51-74 nmol/L (suboptimal); <50 nmol/L (deficiency)	SARS-CoV2 infection	The association between lower SARS-CoV-2 positivity rates and higher circulating 25(OH)D levels remained significant in a multivariable logistic model adjusting for all included demographic factors (adjusted odds ratio 0.984 per ng/mL increment, 95% CI 0.983–0.986; p<0.001). Other significant factors in both the adjusted and unadjusted models were male sex, northern and central latitudes, predominately Black non-Hispanic zip codes, and predominately Hispanic zip codes.
(Li et al., 2020) Cohort study (Mendelian Randomization) <i>Preprint</i>	495,780	Demographic information and genotype data from UK Biobank linked to COVID-19 test results provided by Public Health England	25(OH)D concentration (status: deficient, insufficient, sufficient), ambient UVB, and genetically predicted 25(OH)D concentrations	COVID-19 (risk of infection, hospitalisation and death)	Significant inverse associations were found between COVID-19 infection and 25(OH)D in univariable models, but these associations were non-significant after adjustment for confounders. Ambient UVB was strongly and inversely associated with hospitalization and death. Although the main Mendelian Randomization (MR) analysis showed that genetically predicted vitamin D levels were not causally associated with COVID-19 risk, MR sensitivity analysis using weighted mode method indicated a potential causal effect (p=0.041).
(Luo et al., 2020)	895	COVID-19 positive patients	25(OH)D concentrations between 2018-2019	COVID-19 incidence and	In the general linear model adjusted for age, sex,

Cross-sectional study		hospitalized (n=335) and an age- and sex-matched population (n=560)		disease severity	comorbidities, and BMI, serum 25(OH)D concentrations were significantly lower among COVID-19 patients than the 2018–2019 controls. Multivariable logistic regression showed that male sex (OR: 2.26; 95% CI: 1.06, 4.82), advanced age (≥ 65 y) (OR: 4.93; 95% CI: 1.44, 16.9), and vitamin D deficiency (< 30 nmol/L) (OR: 2.72; 95% CI: 1.23, 6.01) were significantly associated with COVID-19 severity (all $P < 0.05$).
(Meltzer et al., 2020) Cohort study	4313	Patients tested for SARS-CoV-2 infection at the university.	25(OH)D or 1,25(OH) ₂ D measurement were from the preceding 12 months. To account for changes to vitamin D status, status was estimated by taking into account changes to supplements taken. Participants were grouped as follows: likely deficient; likely sufficient; last level deficient and treatment increased; and last level not deficient and treatment decreased.	SARS-CoV-2 infection	The relative risk of testing positive for COVID-19 was 1.77 times greater for patients with likely deficient vitamin D status compared with patients with likely sufficient vitamin D status. In multivariate analysis, testing positive for COVID-19 was associated with increasing age up to age 50 years, non-White race, and likely deficient vitamin D status compared with sufficient vitamin D status, a difference that was statistically significant.
(Merzon et al., 2020) Case-control study	14,022 n=782, COVID-19 positive; n=7052, COVID-19 negative	People of the Leumit Health Services who were tested for SARS-CoV-2.	25(OH)D levels for COVID-19 positive and COVID-19 negative patient	SARS-CoV2 infection	Multivariate analysis, after controlling for the demographic variables, and psychiatric and somatic disorders, demonstrated an independent and significant association between low 25(OH)D levels and the increased likelihood of COVID-19 infection [adjusted OR of 1.50 [(95% CI: 1.13–1.98, $P < 0.001$)]. Age over 50 years, male gender, and low–medium socioeconomic status were also positively associated with the risk of COVID-19 infection; age over 50 years was positively associated with the likelihood of hospitalization due to COVID-19.

Vitamin D and COVID-19 in children

While we did not restrict our search by age, we only identified one study in our broader search that examined the association of vitamin D status and COVID-19 infections in children (Yılmaz & Şen, 2020). This study examined pediatric patients with COVID-19 and found significantly lower

vitamin D levels 13.14 µg/L (4.19–69.28) in COVID-19 diagnosed children (n=40) than in healthy controls (n=45) 34.81 µg/L (3.8–77.42) (p <.001). The symptom of fever was significantly higher in COVID-19 patients who had deficient and insufficient vitamin D levels than in patients who had sufficient vitamin D levels (p=.038). This study did not contain any predictive values and it should be noted that the analysis was not adjusted for any confounders.

Evidence for Vitamin D and acute respiratory tract infections

Evidence regarding acute respiratory tract infections (ARTIs) may be applicable to COVID-19. A systematic review and meta-analysis by Martineau et al. (2017), including 25 eligible RCTs (11,321 participants), reported that daily or weekly vitamin D supplementation reduces the risk of ARTIs, particularly among individuals with 25(OH)D concentrations <25 nmol/L but no effect was seen in those receiving bolus doses (of 30,000 IU or more). However, study settings, vitamin D supplemental doses, reporting and assessment of ARTIs, and trial results were very heterogeneous. Many of the included studies were in populations with pre-existing respiratory disease which may limit their applicability to the general population.

The same authors have now updated their meta-analysis (Jolliffe et al., 2020; preprint) with 20 more RCTs and reported an overall protective effect of vitamin D supplementation on ARTI risk (OR 0.91, 95% CI: 0.84 to 0.99), with heterogeneity across trials (I² 37.2%; p=0.014). The update did not find a protective effect of vitamin D supplementation compared to placebo in subgroups based on baseline serum 25(OH)D concentrations. The authors identified evidence of publication bias and downgraded the quality of the evidence to ‘moderate’.

A recent evidence review on this topic concluded, overall, that there may be some benefit from daily, low-dose vitamin D supplementation (between 10 and 25 µg/day; 400 to 1,000 IU/day) in reducing risk of ARTIs. However, the size of any potential benefit of vitamin D in reducing ARTI risk may be small. [For a more extensive overview of the evidence, please refer to the available rapid review: [Vitamin D and Acute Respiratory Tract Infections](#) from the Scientific Advisory Committee on Nutrition (SACN, 2020) from the UK, published Dec 17, 2020].

Synthesis of the Information Relating to Question 3

In reviewing the evidence for the association of vitamin D status with COVID-19, there appears to be support for low vitamin D status being associated with more severe outcomes from COVID-19. However, this is not surprising as vitamin D deficiency may represent a surrogate marker for a general micronutrient deficiency, which in turn reflects only the patient’s overall health status. It is not possible to confirm causality because many of the risk factors for severe COVID-19 outcomes are the same as the risk factors for low vitamin D status. Furthermore, vitamin D has been found to be a negative acute phase reactant (Waldron et al., 2013), meaning its serum concentration falls during a systemic inflammatory response, which may occur during severe COVID-19 illness. Therefore, it is difficult to know if low vitamin D status causes poorer outcomes or vice versa.

Many authors have hypothesized a variety of mechanisms in which vitamin D could improve the body’s immune response to COVID-19. It has been suggested that: a) vitamin D can normalize mitochondrial dynamics, which would improve oxidative stress, pro-inflammatory state, and cytokine production; b) vitamin D may prevent cytokine storms by decreasing the production of inflammatory cytokines; and c) vitamin D reduces renin–angiotensin–aldosterone system activation and, consequently, decreases reactive oxygen species generation and improves the prognosis of COVID-19 infection. In contrast, one study (Cereda, Bogliolo, Klersy, et al., 2020) that failed to find an association and even reported an association with potential harm, hypothesized that the disease could also be an example of “reversed causality” –that severe illnesses characterized by robust inflammatory responses, like COVID-19, may be responsible

for a reduction in vitamin binding proteins (due to shorter half-life) and an increase in total body water and volume distribution volume, which, in turn, could result in the dilution of solutes, thus low serum concentrations.

Both non-randomized “quasi-experimental” studies (C. Annweiler et al., 2020; G. Annweiler et al., 2020) were restricted to a limited number of nursing-home residents who might be unrepresentative of all older adults. The timing of administration of vitamin D supplementation in the “intervention” arms was quite broad. The studies were not able to control for residual potential confounders such as baseline serum 25(OH)D levels. There are concerns of bias in both studies with only 9 participants in the comparator group (C. Annweiler et al., 2020), and the control group consisting of patients who refused supplementation (G. Annweiler et al., 2020). These studies would support the need for additional research particularly around longer-term supplementation as “prophylaxis” rather than therapy –that is, whether being vitamin D replete is potentially protective against more severe outcomes in the event of COVID-19 infection.

Overall, many of the studies identified to date regarding vitamin D and COVID-19 are retrospective association studies which inherently have significant limitations. These include concerns with the accuracy and timeframe of vitamin D status measurements, the likelihood of confounding, the general low quality of evidence, all which contribute to a high risk of bias and in turn, a lack of generalizability to the Alberta population.

Research Question 4

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

Evidence from the primary literature

There is an overlap between groups at high risk of vitamin D deficiency and groups at high risk of severe COVID-19. Examples include people with chronic disease, older age, and people of Black and minority ethnic heritage. It has been suggested that the higher incidence of COVID-19 infection in older people and ethnic minorities could be partly explained by lower serum vitamin D, which is more common in these groups. However, infants and children are at risk of vitamin D deficiency but are not considered high-risk for severe COVID-19. In our examination of the current evidence, we did not find any studies of sufficient quality examining particular subgroups of people.

Synthesis of the Information Relating to Question 4

Although there was limited evidence that directly answered this research question, Health Canada (2020) notes that the following groups may be more at risk of vitamin D deficiency:

- Infants and children aged under four years old;
- Pregnant and breastfeeding women, particularly teenagers and young women;
- People over 65;
- People who have low or no exposure to the sun, for example those living in northern latitudes (above the 35th parallel), those who cover their skin for cultural reasons, and those who are housebound or confined indoors for long periods;
- People with darker skin, for example people of African, Caribbean, or South Asian family origin

Evolving Evidence

Research on COVID-19 is continually evolving and as such, the evidence will continue to be assessed as new information is provided. There is a growing evidence base on vitamin D as an independent risk for COVID-19 infection as researchers from the various jurisdictions publish the findings from further along the COVID-19 trajectory. There will be a need to revisit the state of the literature and understanding on the clinical effectiveness and safety of vitamin D supplementation for the prevention and treatment of COVID-19. Of note, there are currently 71 registered trials at clinicaltrials.gov related to vitamin D and COVID-19. Reassessment of the evidence may be appropriate in 6 months from now and incorporate results released from randomized controlled trials.

Appendix

List of Abbreviations

AHS: Alberta Health Services

COVID-19: Coronavirus Disease-2019

25(OH)D: serum concentrations of 25 hydroxyvitamin D

SARS-COV2 rRTPCR: severe acute respiratory syndrome coronavirus 2 real-time reverse transcriptase–polymerase chain reaction

ICU: Intensive Care Unit

KRS: Knowledge Resource Services

SAG: Scientific Advisory Group

RCT: Randomized Controlled Trial

PICO: Population, Intervention, Comparator, Outcome (framework for literature searches)

Methods

Literature Search

A literature search was conducted by Nicole Loroff from Knowledge Resources Services (KRS) within the Knowledge Management Department of Alberta Health Services. KRS searched databases for articles published from June 1, 2020 until December 8, 2020 and included: OVID MEDLINE, LitCovid, PubMed, TRIP PRO, WHO COVID-19 Database, Centre for Evidence Based Medicine (CEBM), CADTH COVID-19 Evidence Portal, COVID-Evidence medRxiv, Cochrane Library and Google Scholar. Briefly, the search strategy involved combinations of keywords and subject headings including: vitamin d, vitamin d deficiency ergocalciferol, calciferol, coronavirus, covid, covid 19, etc.

Articles identified by KRS in their search were initially screened by title against the identified PICO criteria listed in Table 1 below. 182 articles were identified by KRS with references and abstracts provided for further review. We excluded 132 articles from the review in accordance with the inclusion/exclusion criteria stated below.

Table A1: PICO Table for Literature Review

Note: This table was adapted from National Institute for Health and Care Excellence (NICE) Vitamin D for COVID-19 evidence review, (NICE, 2020, June).

Criteria	Details
P - Population and indication	Treatment or prevention of COVID-19, or the susceptibility to COVID-19 infection in adults, young people and children (or any population subgroup) For treatment: people with confirmed or suspected COVID- 19 infection For prevention: all people to prevent COVID-19 infection

I – Intervention (exposure)	Vitamin D (all strengths, formulations and route of administration) alone or in combination with other treatments Vitamin D status
C - Comparator(s)	Any other plausible strategy or comparator, including placebo or no treatment
O - Outcomes	Treatment: Critical outcomes: mortality Important outcomes: hospitalization, ventilation, complications, infection cure rates, time to clinical cure, reduction in symptoms, rate of complications, safety, tolerability and adverse events Prevention: Critical outcomes: incidence of COVID-19 infection Important outcomes: safety, tolerability, adherence, morbidity

Table A2. Inclusion and exclusion criteria for results of the literature search

Inclusion Criteria	Exclusion Criteria
<ul style="list-style-type: none"> - English Language - Human Studies Only - All ages - Patients with COVID-19 infection - Systematic reviews - Randomized controlled trials - Interventional studies - Controlled clinical trials - Observational studies including case series. - Full-text only - Preprints were included 	<ul style="list-style-type: none"> - Ecological studies which used either weather patterns (ultraviolet index) or geographical latitude of locations as a proxy for vitamin D alone (not measuring vitamin D or supplementation) will not be included - Article is not from a credible source - Article does not have a clear research question or issue - Presented data/evidence is not sufficient to address the research questions - Research question was unclear - Commentary/ non-systematic reviews

Critical Evaluation of the Evidence

Exclusion criteria for study quality were adapted from the Mixed Methods Appraisal Tool (MMAT) (Hong et al., 2018). Potential articles were evaluated on three criteria: 1) Peer reviewed or from a reputable source; 2) Clear research question or issue; 3) Whether the presented data/evidence is appropriate to address the research question. Preprints and non peer-reviewed literature (such as commentaries and letters from credible journals) are not excluded out of hand due to the novelty of COVID-19 and the speed with which new evidence is available.

Table 2 below is a narrative summary of the body of evidence included in this review. The categories, format, and suggested information for inclusion were adapted from the Oxford Centre for Evidence-Based Medicine, the Cochrane Library, and the AGREE Trust (Brouwers et al., 2010; Urwin, S., Gavinder, K., Graziadio, 2020; Viswanathan et al., 2008; Wynants et al., 2020).

Table A3. Narrative overview of the literature included in this review.

	Description
Volume	<p>The literature search retrieved 182 articles from which key studies were identified through two screening stages. The first stage involved screening the articles based on inclusion/exclusion criteria above and narrowed the results down to 50 articles. The second stage entailed evaluating the quality of these 50 studies based on the Mixed Methods Appraisal Tool (Hong et al., 2018), and identifying 16 key studies with appropriate methodological quality (3 RCTs and 12 observational) and 1 systematic review.</p> <p>Among the articles identified with appropriate methodological quality, the articles examined in this evidence review included 1 systematic review, 3 RCTs, 2 retrospective quasi-experimental studies, 2 retrospective case control study (1 was pre-review), 4 retrospective cohort studies, 1 prospective cohort study, 1 retrospective cross-sectional study, and 2 cohort studies using Mendelian Randomization (which were pre-review).</p> <p>The jurisdictional distribution of the studies was as follows: USA (n=3), France (n=2), and one each from Italy, Brazil, India, Israel, China, Belgium, UK, Spain, and an International team.</p> <p>No grey literature was included in this review.</p>
Quality	<p>The quality of the studies was assessed using the adapted MMAT (Hong et al., 2018).</p> <p>Two of the systematic reviews identified were excluded based on not being peer-reviewed (preprints) and concerns with methodological quality. The one systematic review (Pereira et al., 2020), was published in a peer-reviewed journal and was higher in quality with a clear research question and appropriate methodology following reporting guidelines. However, the meta-analysis was inappropriate with heterogenous baseline characteristics, and the use of point estimates from studies where some are adjusted (on different variables) and some are unadjusted</p> <p>We identified 3 studies that applied vitamin D as an intervention in randomized controlled trials. The quality of the studies warrants caution when interpreting the results based on inappropriate randomization, lack of blinding, lack of placebo and small sample sizes.</p> <p>We identified 46 observational studies meeting our inclusion criteria. Among these, 12 were identified as key studies through our quality appraisal. Reasons for exclusion from the final assessment were related to study quality such as lack of statistical power (e.g. inception cohort of n <100 with very small # of events), inappropriate or lack of adjustment for confounding, concerns with timing of exposure measurement (i.e. vitamin D measured >10 years earlier), and lack of clarity on methodology for vitamin D measurements. Identifying many studies of low methodological quality is consistent with findings from the systematic review (Pereira et al., 2020) where they reported that the methodological quality of the majority of the included articles (74%) was identified as “high risk of bias”.</p> <p>In our initial eligibility screen, we identified the majority of available studies to be observational in design (e.g. retrospective cohort, case-control, cross-sectional, etc.) using regression analyses to reveal relationships among variables while adjusting for confounders. In the case of vitamin D, sicker people tend to have low vitamin D and poorer COVID-19 outcomes. Regression analyses without any adjustments will not infer whether vitamin D or some other variable(s) are associated with poorer COVID-19 outcomes. Many other factors are associated both with COVID-19 outcomes and</p>

	<p>with vitamin D status, for example, obesity, ethnicity, diabetes, renal disease, socioeconomic status, household crowding and urban place of residence. For this reason, only studies that reported multivariable (adjusted) models for outcomes of interest were included because at least some confounding variables are considered in these models.</p> <p>Furthermore, it is important to note that associations demonstrated in an adjusted model do not imply that the relationships are causal. There are other factors that could be influencing the association that were not adjusted for. Association should not be confused with causality. This is especially important when many variables are studied in a complex public health scenario. In this scenario, erroneous associations can arise because the large number of factors makes it possible that an association could be discovered by chance or collinearity. Studies on associations can be used to form the basis for hypothesis testing for causality in randomized controlled trials.</p>
Applicability	<p>At the time of writing, there was no available evidence from populations in Alberta or from the broader Canadian context. Given that different countries have had very different levels of reported community transmission, this may influence the associations or findings related to vitamin D. For example, there may be a higher proportion of asymptomatic people in the comparator groups.</p> <p>Many of the samples examined here are patients who have been admitted to hospital or the ICU. Clinical decisions made with respect to admission may vary greatly by country/jurisdiction and may change substantially over the course of the pandemic. This may limit the generalizability of these findings to the context in hospitals in Alberta.</p> <p>It should also be reiterated that without high quality randomized controlled trial evidence, no causal association between vitamin D deficiency and severity/outcome of COVID-19 can be inferred.</p>
Consistency	<p>At this time, the available evidence is primarily observational in nature with only 3 RCTs available at this time. Two RCTs reported benefit, while one reported no difference. More large-scale trials are needed to be able to draw conclusions.</p> <p>Although many of the observational studies report an inverse association with vitamin D deficiency and severity/complications of COVID-19, there were several studies (Butler-Laporte et al., 2020; Cereda, Bogliolo, Klersy, et al., 2020) that found the opposite and through their analysis, even found that higher vitamin D levels could cause harm.</p>

Table A4. Identified studies based on apriori inclusion/exclusion criteria ($n=50$)

Author	Study Design	Peer-reviewed?
(Abrishami et al., 2020)	Observational cohort	Peer-reviewed
(Arvinte, Singh, & Marik, 2020)	Observational cohort	Peer-reviewed
(Baktash et al., 2020)	Observational cohort	Peer-reviewed
(Blanch-Rubio et al., 2020)	Observational cross-sectional	Peer-reviewed
(Brenner, Holleccek, & Schöttker, 2020)	Observational cohort	Peer-reviewed
(Butler-Laporte et al., 2020)	Cohort (Mendelian randomization)	Preprint
(Carpagnano et al., 2020)	Observational cohort	Peer-reviewed
(Cereda, Bogliolo, Klersy, et al., 2020)	Observational cohort	Peer-reviewed
(Cereda, Bogliolo, Lobascio, et al., 2020)	Observational cohort	Peer-reviewed
(Chang et al., 2020)	Observational case-control	Preprint

(D'avolio et al., 2020)	Observational cohort	Peer-reviewed
(Das et al., 2020)	Systematic review	Preprint
(De Smet, De Smet, Herroelen, Gryspeerdt, & Martens, 2020)	Observational cohort	Peer-reviewed
(Faniyi et al., 2020)	Observational cohort	Preprint
(Fasano et al., 2020)	Observational cohort	Peer-reviewed
(Ferrari & Locatelli, 2020)	Observational cohort	Peer-reviewed
(Ghasemian et al., 2020)	Systematic review	Preprint
(Gonçalves et al., 2020)	Observational cross-sectional	Peer-reviewed
(Hars et al., 2020)	Observational cohort	Peer-reviewed
(Hastie et al., 2020)	Observational cohort	Peer-reviewed
(Hernández et al., 2020)	Observational case-control	Peer-reviewed
(Im et al., 2020)	Observational cohort	Peer-reviewed
(Israel et al., 2020)	Observational cohort	Preprint
(Jain et al., 2020)	Observational cohort	Peer-reviewed
(Karahan & Katkat, 2020)	Observational case-control	Peer-reviewed
(Kaufman, Niles, Kroll, Bi, & Holick, 2020)	Observational cohort	Peer-reviewed
(Lau et al., 2020)	Observational cohort	Preprint
(Li et al., 2020)	Cohort (Mendelian randomization)	Preprint
(Louca et al., 2020)	Observational cross-sectional	Preprint
(Luo, Liao, Shen, Li, & Cheng, 2020)	Observational cross-sectional	Peer-reviewed
(Macaya et al., 2020)	Observational case series	Peer-reviewed
(Maghbooli et al., 2020)	Observational cross-sectional	Peer-reviewed <i>*Note: journal has issued expression of concern</i>
(Mardani et al., 2020)	Observational case-control	Peer-reviewed
(Marik, Kory, & Varon, 2020)	Observational cohort	Peer-reviewed
(Meltzer et al., 2020)	Observational cohort	Peer-reviewed
(Mendy, Apewokin, Wells, & Morrow, 2020)	Observational cohort	Preprint
(Merzon et al., 2020)	Observational case-control	Peer-reviewed
(Ohaegbulam, Swalih, Patel, Smith, & Perrin, 2020)	Observational case series	Peer-reviewed
(Padhi, Suvankar, Panda, Pati, & Panda, 2020)	Observational cohort	Peer-reviewed
(Panagiotou et al., 2020)	Observational cross-sectional	Peer-reviewed
(Pereira et al., 2020)	Systematic review & meta-analysis	Peer-reviewed
(Pizzini et al., 2020)	Observational cohort	Peer-reviewed
(Pugach & Pugach, 2020)	Observational cohort	Preprint
(Radujkovic et al., 2020)	Observational cohort	Peer-reviewed
(Raharusun, Priambada, Budiarti, Agung, & Budi, 2020)	Observational cohort	Peer-reviewed
(Raisi-Estabragh et al., 2020)	Observational cohort	Peer-reviewed
(Tomasia-Irriguible, Bielsa-Berrocal, & Laguna, 2020)	Observational cohort	Preprint
(Tomisti et al., 2020)	Observational case-control	Preprint
(Ye et al., 2020)	Observational case-control	Peer-reviewed
(Yilmaz & Şen, 2020)	Observational cross-sectional	Peer-reviewed

Search Strategy

Search strategy was partially adapted from the NICE Vitamin D for COVID-19 [evidence summary](#), June 2020.

Citation tracking of key research was conducted in Google Scholar.

Ovid MEDLINE(R) and In-Process & Other Non-Indexed Citations and Daily 1946 to December 04, 2020

Date searched: December 7, 2020

Search strategy:

1. exp Vitamin D/ or exp Vitamin D Deficiency/ (71989)
2. ((vitamin* adj5 D*2) or vitaminD*2).tw,kf,kw. (81273)
3. (ergocalciferol* or calciferol* or vs041h42xc or dihydrotachysterol* or dihydrotachysterin* or calcamine or 67-96-9 or r5lm3h112r or hydroxyvitamin D*2 or 25hydroxyvitamin D*2 or hydroxyvitaminD*2 or 25hydroxyvitaminD*2 or hydroxycalciferol* or 25hydroxycalciferol* or hydroxyergocalciferol* or 25hydroxyergocalciferol* or ercalcidiol or "25(OH)D" or 21343-40-8 or alfalcidol*).tw,kf,kw. (19975)
4. (cholecalciferol* or colescalciferol* or calciol or 67-97-0 or 1c6v77qf41 or hydroxycholecalciferol* or hydroxycolescalciferol* or 25hydroxycholecalciferol* or 25hydroxycolescalciferol* or calcifediol* or calcidiol* or "19356-17-3" or p6yz13c99q or t0wxw8f54e or dihydroxycholecalciferol* or dihydroxycolescalciferol* or 25dihydroxycholecalciferol* or 25dihydroxycolescalciferol* or dihydroxyvitamin D*2 or 25dihydroxyvitamin* or dihydroxyvitaminD*2 or calcitriol* or 32222-06-3 or 40013-87- 4 or 55721-11-4).tw,kf,kw. (21319)
5. or/1-4 (110112)
6. exp Coronavirus/ or exp Coronavirus Infections/ (54813)
7. (covid or coronaviru* or corona viru* or ncov* or n-cov* or novel cov* or COVID-19 or COVID19 or COVID-2019 or COVID2019 or SARS-CoV-2 or SARSCoV-2 or SARSCoV2 or SARSCoV19 or SARS-Cov-19 or SARSCov-19 or SARSCoV2019 or SARS-Cov-2019 or SARSCov-2019 or "severe acute respiratory syndrome cov 2" or 2019 ncov or 2019ncov or post-covid).tw,kf,kw. (69773)
8. or/6-7 (78492)
9. 5 and 8 (247)
10. limit 9 to english language (245)
11. limit 10 to dt=20200601-20211231 (192)

PubMed

Date searched: December 7, 2020

Search strategy:

1. "vitamin d"[MeSH Terms] or "vitamin d deficiency"[MeSH Terms] (71999)
2. "vitamin d"[Title/Abstract] OR "vitamind*"[Title/Abstract] OR "vit d*"[Title/Abstract] (73723)
3. "ergocalciferol*"[Title/Abstract] OR "calciferol*"[Title/Abstract] OR "dihydrotachysterol*"[Title/Abstract] OR "dihydrotachysterin*"[Title/Abstract] OR "calcamine"[Title/Abstract] OR "hydroxyvitamin d*"[Title/Abstract] OR "25hydroxyvitamin d*"[Title/Abstract] OR "hydroxyvitamind*"[Title/Abstract] OR "25hydroxyvitamind*"[Title/Abstract] OR "hydroxycalciferol*"[Title/Abstract] OR "25hydroxycalciferol*"[Title/Abstract] OR "hydroxyergocalciferol*"[Title/Abstract] OR "25hydroxyergocalciferol*"[Title/Abstract] OR "ercalcidiol"[Title/Abstract] OR "25 oh d"[Title/Abstract] OR "alfalcidol*"[Title/Abstract] (20479)
4. "cholecalciferol*"[Title/Abstract] OR "colescalciferol*"[Title/Abstract] OR "calciol"[Title/Abstract] OR "hydroxycholecalciferol*"[Title/Abstract] OR "hydroxycolescalciferol*"[Title/Abstract] OR "25hydroxycholecalciferol*"[Title/Abstract] OR "25hydroxycolescalciferol*"[Title/Abstract] OR "calcifediol*"[Title/Abstract] OR "calcidiol*"[Title/Abstract] OR "dihydroxycholecalciferol*"[Title/Abstract] OR "25dihydroxycholecalciferol*"[Title/Abstract] OR "25dihydroxycolescalciferol*"[Title/Abstract] OR "25dihydroxyvitamin*"[Title/Abstract] OR "dihydroxyvitamin d*"[Title/Abstract] OR "calcitriol*"[Title/Abstract] (21123)
5. or/1-4 (102956)

6. "coronavirus"[MeSH Terms] OR "coronavirus infections"[MeSH Terms] (54793)
7. "covid"[Title/Abstract] OR "coronaviru*"[Title/Abstract] OR "corona viru*"[Title/Abstract] OR "ncov*"[Title/Abstract] OR "n cov*"[Title/Abstract] OR "novel cov*"[Title/Abstract] OR "COVID-19"[Title/Abstract] OR "COVID19"[Title/Abstract] OR "COVID-2019"[Title/Abstract] OR "COVID2019"[Title/Abstract] OR "SARS-CoV-2"[Title/Abstract] OR "SARSCoV-2"[Title/Abstract] OR "SARSCoV2"[Title/Abstract] OR "SARSCoV19"[Title/Abstract] OR "SARS-Cov-19"[Title/Abstract] OR "SARSCoV2019"[Title/Abstract] OR "SARS-Cov-2019"[Title/Abstract] OR "severe acute respiratory syndrome cov 2"[Title/Abstract] OR "2019 ncov"[Title/Abstract] OR "2019ncov"[Title/Abstract] OR "post-covid"[Title/Abstract] (91535)
8. or/6-7 (100196)
9. 5 and 8 (336)
10. limit 9 to english language (334)
11. limit 10 from 2020/6/1-2021/21/31 (295)

Trip Pro

Date searched: December 7, 2020

(vitamin D* or vitaminD* or vit-D* or ergocalciferol* or cholecalciferol* or calciferol* or 25 hydroxyvitamin D* or 25hydroxyvitamin D* or 25OHD) AND (covid or coronaviru* OR "corona virus" OR ncov* OR n cov* OR COVID-19 OR COVID19 OR COVID-2019 OR COVID2019 OR SARS-COV-2 OR SARSCOV-2 OR SARSCOV2 OR SARSCOV19 OR SARS-COV-19 OR SARSCOV-19 OR SARSCOV2019 OR SARS-COV-2019 OR SARSCOV-2019 OR "severe acute respiratory syndrome cov 2" OR 2019 ncov OR 2019ncov OR Hcov* or post-covid) from:2020

LitCovid/WHO COVID-19 Research Database/Centre for Evidence Based Medicine (CEBM)/CADTH COVID-19 Evidence Portal/COVID-Evidence

Date searched: December 7 & 8, 2020

vitamin D or vitaminD or vit-D or ergocalciferol* or cholecalciferol* or calciferol* or 25 hydroxyvitamin D* or 25hydroxyvitamin D* or 25OHD

medRxiv/Cochrane Library

Date searched: December 7 & 8, 2020

"covid-19 vitamin D"; "coronavirus vitamin D"

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