EVIDENCE SYNTHESIS BRIEFING NOTE

> **TOPIC**: ASSOCIATION BETWEEN COVID-19 AND VITAMIN D LEVELS

Information finalized as of December 9, 2020.[a]

This Briefing Note was completed by the Research, Analysis, and Evaluation Branch (Ministry of Health) in collaboration with McMaster Health Forum, a member of the COVID-19 Evidence Synthesis Network.
Please refer to the Methods section for further information.

Purpose: This note summarizes research evidence on the association between COVID-19 and individuals' Vitamin D levels.

Key Findings:
- Twenty-three systematic reviews, reviews, or studies were identified that suggested that Vitamin D supplementation may help boost the immune system and reduce COVID-19 incidence, symptoms, and/or severity, particularly among vulnerable populations (e.g., older adults, obese individuals, individuals living at high latitudes and experiencing lower daily light exposure during the dark months of the year, individuals with dark skin tones or with greater levels of skin pigmentation), although definitive randomized controlled trials are needed. Since Vitamin D has multiple cellular and intracellular targets, it is recommended to be administered with caution and monitoring to avoid stimulating or inhibiting some cellular functions that could induce infectious tolerance.
- Ten systematic reviews, reviews, or studies were identified that suggested there is not enough evidence regarding the association between Vitamin D levels and COVID-19 severity and mortality.

Analysis for Ontario: No findings identified.

Implementation Implications: The current status of research supports the role of Vitamin D supplementation in preventing or ameliorating the severity of COVID-19, but further clinical studies are needed.

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[a] This briefing note includes current available evidence as of the noted date. It is not intended to be an exhaustive analysis, and other relevant findings may have been reported since completion.

Supporting Evidence

Table 1 lists and describes scientific evidence (systematic reviews, reviews, or single studies) identified on the association between COVID-19 and Vitamin D levels. The majority of the information presented is taken directly from the original articles.

- Some of the information contains clinical guidance (e.g., Vitamin D supplementation dosages); these recommendations are those of the authors of the original studies and the Research, Analysis, and Evaluation Branch does not have the expertise to evaluate such recommendations.
- The methodological quality of some of the identified literature was rated using AMSTAR[b] by McMaster Health Forum. These ratings are included where available. The methodological quality of all other sources identified are unclear as they have not been assessed.

In the Appendix, Table 2 lists the systematic reviews and rapid reviews identified by McMaster Health Forum, along with their AMSTAR methodological quality rating. Table 3 lists the key primary studies (and related editorials that contained primary data) and primary-study protocols cited from the identified systematic reviews and rapid reviews.

Table 1: Overview of Research Findings on the Association between COVID-19 and Vitamin D Levels

Reference	Description of Findings	Methodological Quality (AMSTAR)
Evidence Supporting the Role of Vitamin D Status in the Pathogenesis of COVID-19		
Beiter, K., Lau, F.H., & Danos, D. (preprint). Ecological association between COVID-19 deaths and vitamin D deficiency among older adults: An international country-level systematic review and analysis. BMC Nutrition.	• **Objective**: The objective of this study was to evaluate Vitamin D deficiency (VDD) and COVID-19 mortality worldwide during the first 50 days of the pandemic as experienced by various countries. • **Methods**: Country-specific VDD prevalence among older adults was evaluated according to a systematic literature search of PubMed, CINAHL, EMBASE, and SCOPUS during April 2020. Data were obtained from the public Our World in Data database which reports COVID-19 mortality from European Centre for Disease Prevention and Control and country population characteristics, size and proportion of the population greater than 65 years, from the United Nations Department of Economic and Social Affairs. Country-specific cumulative mortality was modeled via negative binomial random coefficient growth curve models. • **Results**: Among 29 countries included in this analysis, VDD prevalence among older adults ranged from 6.9% in Canada to 69% in France. Cumulative COVID-19 deaths up to day 50 within each country, modeled via exponential growth curves, demonstrated an association with country-level VDD (p = 0.0538). However, the association was not robust when controlling for proportion of older adults in each country (p = 0.2135). • **Conclusion**: This ecological analysis is further evidence for VDD correction as a component of COVID-19 treatment, especially among older individuals. Inclusion of data cross-culturally (i.e., collected from countries worldwide) supports the theory that VDD is a universal mechanism contributing to COVID-19 mortality. Though	4/11

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[b] The methodological quality of some of the identified literature was rated using AMSTAR by McMaster Health Forum in their evidence product. These ratings are included where available. AMSTAR rates overall quality on a scale of 0 to 11, where 11/11 represents a review of the highest quality. It is important to note that the AMSTAR tool was developed to assess reviews focused on clinical interventions.

Reference	Summary	Quality
	definitive randomized controlled trials are still needed, the current study provides support for VDD screening and correction as the influenza season rapidly approaches in the Northern hemisphere.	
Kumar, R., Himani, Haq, A., Wimalawansa, S. J., & Sharma, A. (Nov 21, 2020). Putative Roles of Vitamin D in Modulating Immune Response and Immunopathology Associated With COVID-19. Virus research, 292, 198235.	• **Background**: This review focuses on the pathogenesis of SARS-CoV-2, especially on the dysfunctional immune responses following a cytokine storm in severely affected persons. Older persons with weaker immune systems and associated co-morbidities are more vulnerable to experiencing dysfunctional immune responses, as most of them concomitantly have severe hypovitaminosis D (i.e., VDD). Consequently, such patients can suffer severe damage to key organs of the body including lungs and the cardiovascular system. The authors note that since the vast majority of persons entering the intensive care units and who died had severe vitamin D deficiency, this area must be investigated seriously. In addition, this article assesses the role of vitamin D in reducing the risk of COVID-19. • **Conclusion**: There is a strong association between vitamin D deficiency and severe viral infections including COVID-19. The potential role of vitamin D in modulating the immune response in viral infection further substantiated its importance in the current pandemic situation. In addition, the potential role of dexamethasone has been highlighted as an anti-inflammatory drug in severe or critically ill COVID-19 patients. Lastly, large-scale population-based randomized controlled clinical trials are required to unveil the potential of vitamin D alone or in combination with dexamethasone in mitigating the viral infection.	No information identified.
Pereira M, Dantas Damascena A, Galvão Azevedo LM, de Almeida Oliveira T, da Mota Santana J. (Nov 4, 2020). Vitamin D deficiency aggravates COVID-19: systematic review and meta-analysis. Crit Rev Food Sci Nutr.:1-9.	• **Objective**: In this systematic review and meta-analysis, the association between vitamin D deficiency and COVID-19 severity is analyzed, via an analysis of the prevalence of vitamin D deficiency and insufficiency in people with the disease. • **Methods**: Five online databases (Embase, PubMed, Scopus, Web of Science, ScienceDirect and pre-print Medrevix) were searched. The inclusion criteria were observational studies measuring serum vitamin D in adult and elderly subjects with COVID-19. The main outcome was the prevalence of vitamin D deficiency in severe cases of COVID-19. A meta-analysis with random effect measures was conducted. • **Results**: The review identified 1,542 articles and selected 27. Vitamin D deficiency was not associated with a higher chance of infection by COVID-19 (OR = 1.35; 95% CI = 0.80–1.88), but severe cases of COVID-19 presented 64% (OR = 1.64; 95% CI = 1.30–2.09) more vitamin D deficiency compared with mild cases. A vitamin D concentration insufficiency increased hospitalization (OR = 1.81, 95% CI = 1.41–2.21) and mortality from COVID-19 (OR = 1.82, 95% CI = 1.06–2.58). • **Conclusion**: The review observed a positive association between vitamin D deficiency and the severity of the disease.	7/11
Ferrari D, Locatelli M, Briguglio M, Lombardi G. (Nov 2, 2020). Is there a link between vitamin D status, SARS-CoV-2 infection risk and COVID-19 severity? Cell Biochem Funct.	• **Objective**: This narrative review aims at collecting the literature available on the involvement of the vitamin D status in the pathogenesis of COVID-19 and the putative utility of vitamin D supplementation in the therapeutics. • **Conclusion**: It emerges that a poor vitamin D status seems to be associated with an increased risk of infection whereas age, gender, and comorbidities seem to play a more important role in COVID-19 severity and mortality. While randomized control trials are needed to better inquire into this topic, vitamin D supplementation may be useful beside its potential effects on SARS-CoV-2 infection and COVID-19.	No information identified.
Bae, M., & Kim, H. (Nov 2020). Mini-Review on the Roles of Vitamin C, Vitamin D, and Selenium in the Immune System against COVID-19. Molecules (Basel, Switzerland), 25(22), 5346.	• **Objective**: In this mini-review, the roles of vitamin C, vitamin D, and selenium in the immune system are discussed in relation to COVID-19. • **Results**: Studies have found that the immunomodulatory properties of Vitamin D may include: improving the physical barriers of the body by regulating the production of proteins for tight junctions, adherens junctions, and gap junctions; stimulating the production of antimicrobial peptides, such as cathelicidin and defensins; modulating T helper (Th) cell responses to induce a shift from Th1 to Th2 responses; and preventing cytokine storms by decreasing inflammatory cytokines and nuclear factor κB (NF-κB) activation. Studies have suggested that consequences of deficiency/effects of supplementation in infectious diseases,	No information identified.

including COVID-19, include: inverse correlation between vitamin D level and viral respiratory tract infection; vitamin D deficiency/insufficiency observed in patients with COVID-19; inverse correlation between COVID-19 mortality and sunlight exposure or vitamin D level; and worse prognosis in COVID-19 patients with a low level of vitamin D.

- **Conclusion**: The study indicates that nutritional therapy should be a part of patient care for survival of COVID-19, as well as for better and shorter recovery. Patients with malnutrition are more likely to be from lower socioeconomic groups; thus, nutrition supplementation is important for the risk group as well as older adults who have a relatively weak immune system. Since severely ill COVID-19 patients were reported to be deficient in more than one nutrient, this review suggests that nutritional deficiencies may favor the onset of COVID-19 and increase the severity of the disease. Combination of some of these micronutrients (vitamin C, vitamin D, and selenium) may help to boost the immune system, prevent virus spread, and reduce the disease progressing to severe stages.

De Smet D, De Smet K, Herroelen P, Gryspeerdt S, Martens GA. (Nov 25, 2020). Serum 25(OH)D Level on Hospital Admission Associated With COVID-19 Stage and Mortality. Am J Clin Pathol. Online ahead of print.	**Objective**: Vitamin D deficiency was previously correlated with incidence and severity of coronavirus disease 2019 (COVID-19). We investigated the association between serum 25-hydroxyvitamin D (25(OH)D) level on admission and radiologic stage and outcome of COVID-19 pneumonia. **Methods**: A retrospective observational trial was done on 186 severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-infected individuals hospitalized from March 1, 2020, to April 7, 2020, with combined chest computed tomography (CT) and 25(OH)D measurement on admission. Multivariate regression analysis was performed to study if vitamin D deficiency (25(OH)D <20 ng/mL) correlates with survival independently of confounding comorbidities. **Results**: Of the patients with COVID-19, 59% were vitamin D deficient on admission: 47% of females and 67% of males. In particular, male patients with COVID-19 showed progressively lower 25(OH)D with advancing radiologic stage, with deficiency rates increasing from 55% in stage 1 to 74% in stage 3. Vitamin D deficiency on admission was not confounded by age, ethnicity, chronic lung disease, coronary artery disease/hypertension, or diabetes and was associated with mortality (odds ratio [OR], 3.87; 95% confidence interval [CI], 1.30-11.55), independent of age (OR, 1.09; 95% CI, 1.03-1.14), chronic lung disease (OR, 3.61; 95% CI, 1.18-11.09), and extent of lung damage expressed by chest CT severity score (OR, 1.12; 95% CI, 1.01-1.25). **Conclusion**: Low 25(OH)D levels on admission are associated with COVID-19 disease stage and mortality.	No information identified.
Malaguarnera, L. (Nov 2020). Vitamin D3 as Potential Treatment Adjuncts for COVID-19. Nutrients, 12(11), 3512.	**Objective**: This review compared the mechanisms of the host immune response to SARS-CoV2 infection and the immunomodulatory actions that vitamin D exerts in order to consider the preventive effect of vitamin D supplementation on SARS-CoV2 viral infection. **Conclusion**: There is emerging evidence revealing the promising role of vitamin D in preventing cytokine storm and, consequently, determining outcomes of SARS-Cov2. Vitamin D insufficiency has been shown to be related to latitude, obesity, diabetes, hypertension, ethnicity, and sex, and it is a condition associated with the increased susceptibility for SARS-Cov2 infection and mortality. It has also been suggested that the different gender-related susceptibilities involve testosterone levels associated with vitamin deficiency in men. Some clinical trials revealed that vitamin D supplementation was effective to prevent infection both in the early and in the hyperinflammatory stage of the disease, since it modulated efficaciously the immune response against SARS-COV2. However, following an in-depth analysis of the mechanisms involved in the immune response conducted in this review, it can be noted that vitamin D, in severe SARS-CoV2 stage, should be administered with caution because it could stimulate or inhibit some cellular functions that could induce infectious tolerance. The proposed guidelines for the treatment of COVD19 recommended the use of glucocorticoids. Therefore, the suggested treatment with glucocorticoids in combination with vitamin D supplementation could be an interesting	1/9

	perspective to be taken into account. Since vitamin D has multiple cellular and intracellular targets, additional studies are needed to determine the consequences of the interaction of vitamin D in the immune-response against SARS-CoV2 in order to achieve a significant vision into prophylactic and therapeutic strategy for the prevention of this viral infection.	
Tan CW, Ho LP, Kalimuddin S, Cherng BPZ, Teh YE, Thien SY, Wong HM, Tern PJW, Chandran M, Chay JWM, Nagarajan C, Sultana R, Low JGH, Ng HJ. (2020 Nov-Dec). Cohort study to evaluate the effect of vitamin D, magnesium, and vitamin B12 in combination on progression to severe outcomes in older patients with coronavirus (COVID-19). Nutrition; 79-80:111017.	• **Objectives**: The aim of this study was to determine clinical outcomes of older patients with coronavirus (COVID-19) who received a combination of vitamin D, magnesium, and vitamin B12 (DMB) compared with those who did not. The study hypothesized that fewer patients administered this combination would require oxygen therapy, intensive care support, or a combination of both than those who did not. • **Methods**: This was a cohort observational study of all consecutive hospitalized patients ≥50 y of age with COVID-19 in a tertiary academic hospital. Before April 6, 2020, no patients received the (DMB) combination. After this date, patients were administered 1000 IU/d oral vitamin D3, 150 mg/d oral magnesium, and 500 mcg/d oral vitamin B12 upon admission if they did not require oxygen therapy. The primary outcome was deterioration leading to any form of oxygen therapy, intensive care support, or both. • **Results**: Between January 15 and April 15, 2020, the study identified 43 consecutive patients ≥50 y of age with COVID-19. Seventeen patients received DMB before onset of primary outcome and 26 patients did not. Baseline demographic characteristics between the two groups were significantly different by age. In univariate analysis, age and hypertension had a significant influence on outcome. After adjusting for age or hypertension separately in a multivariate analysis, the intervention group retained protective significance. Fewer treated patients than controls required initiation of oxygen therapy during hospitalization (17.6 vs 61.5%, P = 0.006). DMB exposure was associated with odds ratios of 0.13 (95% confidence interval [CI], 0.03–0.59) and 0.20 (95% CI, 0.04–0.93) for oxygen therapy, intensive care support, or both on univariate and multivariate analyses, respectively. • **Conclusions**: A vitamin D/magnesium/vitamin B12 combination in older COVID-19 patients was associated with a significant reduction in the proportion of patients with clinical deterioration requiring oxygen support, intensive care support, or both. This study supports further larger randomized controlled trials to ascertain the full benefit of this combination in ameliorating the severity of COVID-19.	No information identified.
Mercola J, Grant WB, Wagner CL. (Oct 31, 2020). Evidence Regarding Vitamin D and Risk of COVID-19 and Its Severity. Nutrients;12(11):3361.	• **Objective**: Vitamin D deficiency co-exists in patients with COVID-19. At this time, darker skin colour, increased age, the presence of pre-existing illnesses and vitamin D deficiency are features of severe COVID disease. Of these, only vitamin D deficiency is modifiable. Through its interactions with a multitude of cells, vitamin D may have several ways to reduce the risk of acute respiratory tract infections and COVID-19: reducing the survival and replication of viruses, reducing risk of inflammatory cytokine production, increasing angiotensin-converting enzyme 2 concentrations, and maintaining endothelial integrity. • **Results**: Fourteen observational studies offer evidence that serum 25-hydroxyvitamin D concentrations are inversely correlated with the incidence or severity of COVID-19. The evidence to date generally satisfies Hill's criteria for causality in a biological system, namely, strength of association, consistency, temporality, biological gradient, plausibility (e.g., mechanisms), and coherence, although experimental verification is lacking. • **Conclusion**: The evidence seems strong enough that people and physicians can use or recommend vitamin D supplements to prevent or treat COVID-19 in light of their safety and wide therapeutic window. In view of public health policy, however, results of large-scale vitamin D randomized controlled trials are required and are currently in progress.	No information identified.

Chen, J., Xie, L., Yuan, P., et al. (Oct 27, 2020). Low serum vitamin D level and COVID-19 infection and outcomes, a multivariate meta-analysis. medRxiv (preprint).	• **Objective**: This study aimed to determine whether serum vitamin D is independently associated with COVID-19 infection and outcomes in patients with COVID-19. • **Methods**: We identified relevant studies by searching the PubMed, Embase, and medRxiv databases from December 2019 to October 1, 2020. Odds ratios (ORs) were pooled using random-effects models. Only reports with multivariate adjusted results were included to avoid the impact of potential confounding factors. • **Results**: A total of six studies with 377,265 patients were identified. Overall, in the categorical analysis, a low serum vitamin D level was associated with an increased risk of COVID-19 infection (OR: 1.47, 95% CI: 1.09- 1.97, I2=81%), hospitalization (OR: 1.83, 95% CI: 1.22-2.74, I2=0%), but not in-hospital death (OR: 2.73, 95% CI: 0.27-27.61). Notably, when vitamin D level was analyzed as a continuous variable, each 5 ng/ml increase in vitamin D level was not associated with any increased risk of COVID-19 infection (OR: 1.04, 95% CI: 0.96-1.12, I2=74%) or in-hospital death (OR: 1.02, 95% CI: 0.93-1.12). • **Conclusion**: Low serum vitamin D is associated with an increased risk of COVID-19 infection and hospitalization. In-hospital death showed a tendency to be increased in COVID-19 patients with low vitamin D levels. The ongoing clinical trials for evaluation of vitamin D supplementation will be key to the validation of this adjunctive treatment for COVID-19 patients.	9/11
Ghasemian, R., Shamshirian, A., Heydari, K., Malekan, M. et al. (Oct 26, 2020). The Role of Vitamin D in The Age of COVID-19: A Systematic Review and Meta-Analysis. MedRxiv (preprint).	• **Objective**: Evidence recommends that vitamin D might be a crucial supportive agent for the immune system, mainly in cytokine response regulation against COVID-19. A systematic review and meta-analysis was carried out in order to maximize the use of everything that exists about the role of vitamin D in the COVID-19. • **Methods**: A systematic search was performed in PubMed, Scopus, Embase, Cochrane Library, Web of Science, and Google Scholar (intitle) as well as preprint database of medRxiv, bioRxiv, Research Square, preprints.org, and search engine of ScienceDirect up to October 10, 2020. Studies focused on the role of vitamin D in confirmed COVID-19 patients were entered into the systematic review. • **Results**: Sixteen studies containing 4,922 participants entered into the meta-analysis. The meta-analysis indicated that 48% of COVID-19 patients were suffering from vitamin D deficiency (95% CI, 29%-67%), and in 41% of patients, levels of vitamin D were insufficient (95% CI, 10%-82%). The serum 25-hydroxyvitamin D concentration was 18 ng/mL among all COVID-19 patients (95% CI, 13-24). Co-morbidities frequency in COVID-19 patients were as follows: 7.4% cancer, 27.1% chronic kidney disease, 30.4% cardiovascular diseases, 5.1% dementia, 14.5% depression/anxiety, 32.1% diabetes, 47.4% hypertension, 22.0% obesity and 17.5% respiratory diseases. Reported ethnic groups in studies were 1.0% Afro-Caribbean, 10.3% Asian, and 92.1% Caucasian. • **Conclusion**: This study found that the mean serum 25-hydroxyvitamin D level was low in all COVID-19 patients, and most of them were suffering from vitamin D deficiency/insufficiency. The Caucasian was the dominant ethnic group, and the most frequent co-morbidities in COVID-19 patients were hypertension, cardiovascular diseases, chronic kidney disease, diabetes, obesity, and respiratory diseases, which might be affected by vitamin D deficiency directly or indirectly.	9/11
Zhang, J. McCullough, P.A., Tecson, KM. (Sept 30, 2020). Vitamin D deficiency in association with endothelial dysfunction: Implications for patients with COVID-19. Reviews in	• **Objective**: This review provides a summary of the literature on vitamin D deficiency as it pertains to COVID-19. • **Results**: This review hypothesizes that endothelial dysfunction relevant to vitamin D deficiency results from decreased binding of the vitamin D receptor with its ligand on the vascular endothelium and that it may be immune-mediated via increased interferon 1 α. A possible sequence of events may be described as (1) angiotensin II converting enzyme-related initial endothelial injury followed by vitamin D receptor-related endothelial dysfunction, (2) endothelial lesions deteriorating to endothelialitis, coagulopathy and thrombosis, and (3) vascular damage	No information identified.

Cardiovascular Medicine, 21(3): 339-344.	exacerbating pulmonary pathology and making patients with vitamin D deficiency vulnerable to death. • **Conclusion**: The current status of research in vitamin D deficiency may support the role of vitamin D supplementation in prevention of COVID-19 infection-induced pulmonary pathology and vascular damage, although controversy remains.	
Allegra A, Tonacci A, Pioggia G, Musolino C, Gangemi S. (Sept 2020). [Vitamin deficiency as risk factor for SARS-CoV-2 infection: correlation with susceptibility and prognosis](#). Eur Rev Med Pharmacol Sci.;24(18):9721-9738.	• **Objective**: In 2019, an infection provoked by SARS-CoV-2 virus arose in Wuhan, China. Currently, there is still no definite and efficacious therapy for SARS-CoV-2 infection. Moreover, the understanding of the physiopathology of the infection, and risk elements for severity and mortality, is incomplete. • **Methods**: One largely neglected element that could affect prognosis of SARS-CoV-2 infection is the vitamin status of population. The purpose of this review is to evaluate whether a vitamin insufficiency could provoke an augmented risk of SARS-CoV-2 infection or the appearance of major complications. In particular, the study evaluated the presence of studies related to the state and effects of vitamin D, C, B, and A in subjects with SARS-CoV-2 disease. • **Results**: Although, actually, the interest in a possible use for vitamin supplementation in SARS-CoV-2 patients is essentially based on indirect data, the study tried to examine the evidence about a favorable effect of vitamin supplementation in the therapy of the infection and its complications. • **Conclusion**: Supplements with vitamin A, B, C, D, and E could represent an inexpensive and sufficiently safe approach, and a useful therapeutic complement. However, solid clinical research data are expected to support such claims.	No information identified.
de Las Heras, N., Martín Giménez, V. M., Ferder, L., Manucha, W., & Lahera, V. (Sept 9, 2020). [Implications of Oxidative Stress and Potential Role of Mitochondrial Dysfunction in COVID-19: Therapeutic Effects of Vitamin D](#). Antioxidants (Basel, Switzerland), 9(9), 897.	• **Objective**: Recent evidence suggests the mechanistic role of mitochondria and vitamin D in the development of COVID-19. Indeed, mitochondrial dynamics contribute to the maintenance of cellular homeostasis, and its uncoupling involves pathological situations. SARS-CoV-2 infection is associated with altered mitochondrial dynamics with consequent oxidative stress, pro-inflammatory state, cytokine production, and cell death. Furthermore, vitamin D deficiency seems to be associated with increased COVID-19 risk. In contrast, vitamin D can normalize mitochondrial dynamics, which would improve oxidative stress, pro-inflammatory state, and cytokine production. Vitamin D reduces renin–angiotensin–aldosterone system activation and, consequently, decreases reactive oxygen species (ROS) generation and improves the prognosis of SARS-CoV-2 infection. Thus, the purpose of this review is to deepen the knowledge about the role of mitochondria and vitamin D directly involved in the regulation of oxidative stress and the inflammatory state in SARS-CoV-2 infection. • **Conclusion**: As future prospects, evidence suggests enhancing the vitamin D levels of the world population, especially of those individuals with additional risk factors that predispose to the lethal consequences of SARS-CoV-2 infection.	No information identified.
Meltzer DO, Best TJ, Zhang H, Vokes T, Arora V, Solway J. (Sept 2020). [Association of Vitamin D Status and Other Clinical Characteristics With COVID-19 Test Results](#). JAMA Netw Open. 1;3(9):e2019722.	• **Objective**: To examine whether the last vitamin D status before COVID-19 testing is associated with COVID-19 test results. • **Methods**: This retrospective cohort study at an urban academic medical center included patients with a 25-hydroxycholecalciferol or 1,25-dihydroxycholecalciferol level measured within one year before being tested for COVID-19 from March 3 to April 10, 2020. Vitamin D deficiency was defined by the last measurement of 25-hydroxycholecalciferol less than 20 ng/mL or 1,25-dihydroxycholecalciferol less than 18 pg/mL before COVID-19 testing. Treatment changes were defined by changes in vitamin D type and dose between the date of the last vitamin D level measurement and the date of COVID-19 testing. Vitamin D deficiency and treatment changes were combined to categorize the most recent vitamin D status before COVID-19 testing as likely deficient (last level deficient and treatment not increased), likely sufficient (last level not deficient and treatment not decreased), and 2 groups with uncertain deficiency (last level deficient and treatment increased, and last level not deficient and treatment decreased). The outcome was a positive COVID-19 polymerase chain reaction test result. Multivariable analysis tested	No information identified.

	whether vitamin D status before COVID-19 testing was associated with testing positive for COVID-19, controlling for demographic and comorbidity indicators. • **Results**: A total of 489 patients (mean [SD] age, 49.2 [18.4] years; 366 [75%] women; and 331 [68%] race other than White) had a vitamin D level measured in the year before COVID-19 testing. Vitamin D status before COVID-19 testing was categorized as likely deficient for 124 participants (25%), likely sufficient for 287 (59%), and uncertain for 78 (16%). Overall, 71 participants (15%) tested positive for COVID-19. In multivariate analysis, testing positive for COVID-19 was associated with increasing age up to age 50 years (relative risk, 1.06; 95% CI, 1.01-1.09; P = .02); non-White race (relative risk, 2.54; 95% CI, 1.26-5.12; P = .009), and likely deficient vitamin D status (relative risk, 1.77; 95% CI, 1.12-2.81; P = .02) compared with likely sufficient vitamin D status. Predicted COVID-19 rates in the deficient group were 21.6% (95% CI, 14.0%-29.2%) vs 12.2% (95% CI, 8.9%-15.4%) in the sufficient group. • **Conclusion**: In this single-centre, retrospective cohort study, likely deficient vitamin D status was associated with increased COVID-19 risk, a finding that suggests that randomized trials may be needed to determine whether vitamin D affects COVID-19 risk.	
Xu, Y., Baylink, D. J., Chen, C. S., Reeves, M. E., Xiao, J., Lacy, C., Lau, E., & Cao, H. (Aug 2020). The importance of vitamin d metabolism as a potential prophylactic, immunoregulatory and neuroprotective treatment for COVID-19. Journal of translational medicine, 18(1), 322.	• **Objective**: This review summarizes the potential role of vitamin D extra-renal metabolism in the prevention and treatment of the SARS-CoV-2 infection, with a focus on how: 1) Vitamin D might aid in preventing SARS-CoV-2 infection; 2) Vitamin D might act as a strong immunosuppressant inhibiting cytokine release syndrome in COVID-19; and 3) Vitamin D might prevent loss of neural sensation in COVID-19 by stimulating expression of neurotrophins like Nerve Growth Factor (NGF). • **Conclusion**: The review hypothesizes that vitamin D supplementation can reduce the risk of COVID-19 incidence, symptoms, and severity. It should be investigated in a well-designed clinical trial as vitamin D is in general safe and there is a large body of data supporting the use of higher doses of Vitamin D3 in the setting of vitamin D deficiency. While there are various outcomes regarding the benefit of vitamin D supplementation in the clinical research, the clear association between low levels of 25(OH)D or 1,25(OH)2D3 and pathogenesis of a wide variety of infectious and autoimmune diseases is warranted for further investigation of vitamin D supplementation as a potential agent to prevent viral infection and improve the survival outcome. The review hypothesizes that vitamin D supplementation will help COVID-19 patients maintain sufficient serum levels of vitamin D as guideline recommended. Serum calcium level should be monitored and if significantly elevated, it can be mitigated by hydration or a dose adjustment of the vitamin D supplement.	No information identified.
Tan SHS, Hong CC, Saha S, Murphy D, Hui JH. (Aug 2020). Medications in COVID-19 patients: summarizing the current literature from an orthopaedic perspective. Int Orthop.;44(8):1599-1603.	• **Objective**: The review aims to provide a summary of the current literature regarding common medications prescribed in orthopaedic surgery and their potential implications in COVID-19 patients. • **Methods**: A systematic review was performed using the PRISMA guidelines. All clinical studies, reviews, consensus and guidelines related to the above medications and COVID-19 were included. • **Results**: A total of 18 articles were included. The use of analgesia, anti-inflammatories, steroids, anticoagulants, antibiotics, vitamin B, vitamin C and vitamin D and their potential impact on COVID-19 patients were reported. • **Conclusion**: Eight main recommendations were derived from the review. Firstly, paracetamol remains the first line of analgesia and antipyretic. Secondly, there is no need to avoid NSAIDs for COVID-19 patients. Thirdly, opioids have the potential for immunosuppression in addition to respiratory depression and, therefore, should be prescribed with care in COVID-19 patients. Fourthly, patients with conditions where steroids are proven to be efficacious can continue to receive their steroids; otherwise, systemic steroids are not recommended for COVID-19 patients. Fifthly,	2/9

	orthopaedic surgeons following up on COVID-19 patients who are using steroids should continue to follow them up for possible avascular necrosis. Sixthly, whenever possible, oral anticoagulation should be converted to parental heparin. Seventhly, common orthopaedic antibiotics including penicillin and clindamycin are safe to continue for COVID-19 patients. However, for COVID-19 patients, the antibiotics can potentially be switched to macrolides and tetracyclines if the organisms are sensitive. Lastly, prescription for vitamins B, C and D should continue as per usual clinical practice.	
Munshi R, Hussein MH, Toraih EA, Elshazli RM, Jardak C, Sultana N, Youssef MR, Omar M, Attia AS, Fawzy MS, Killackey M, Kandil E, Duchesne J. (July 27, 2020). Vitamin D insufficiency as a potential culprit in critical COVID-19 patients. J Med Virol.	• **Objective**: As an immune modulator, vitamin D has been implicated in the coronavirus disease-2019 (COVID-19) outcome. This review aims to systematically explore the association of vitamin D serum levels with COVID-19 severity and prognosis. • **Methods**: The standardized mean difference (SMD) or odds ratio and 95% confidence interval (CI) were applied to estimate pooled results from six studies. The prognostic performance of vitamin D serum levels for predicting adverse outcomes with detection of the best cut-off threshold was determined by receiver operating characteristic curve analysis. Decision tree analysis by combining vitamin D levels and clinical features was applied to predict severity in COVID-19 patients. • **Results**: Mean vitamin D serum level of 376 patients, was 21.9 nmol/L (95% CI = 15.36–28.45). Significant heterogeneity was found (I2 = 99.1%, p < .001). Patients with poor prognosis (N = 150) had significantly lower serum levels of vitamin D compared with those with good prognosis (N = 161), representing an adjusted standardized mean difference of −0.58 (95% CI = −0.83 to −0.34, p < .001). • **Conclusion**: Serum vitamin D levels could be implicated in the COVID-19 prognosis. Diagnosis of vitamin D deficiency could be a helpful adjunct in assessing patients' potential of developing severe COVID-19. Appropriate preventative and/or therapeutic intervention may improve COVID-19 outcomes.	No information identified.
Lanham-New, S. A., Webb, A. R., Cashman, K. D., Buttriss, J. L., Fallowfield, J. L., Masud, T., Hewison, M., Mathers, J. C., Kiely, M., Welch, A. A., Ward, K. A., Magee, P., Darling, A. L., Hill, T. R., Greig, C., Smith, C. P., Murphy, R., Leyland, S., Bouillon, R., Ray, S., … Kohlmeier, M. (May 2020). Vitamin D and SARS-CoV-2 virus/COVID-19 disease. BMJ nutrition, prevention & health, 3(1), 106–110.	• **Objective**: This article aims to provide a balanced scientific view on vitamin D and SARS-CoV-2 virus/COVID-19 disease. It provides a succinct summary of the current scientific evidence of associations between vitamin D, influenza, upper respiratory tract infections (URTIs), and immune health. • **Results**: The article concludes with lifestyle strategies for avoiding vitamin D deficiency and ensuring a healthy balanced diet at any time, including during the current pandemic. The overarching messages are as follows: (1) Vitamin D is essential for good health. (2) Many people, particularly those living in northern latitudes (such as the UK, Ireland, Northern Europe, Canada and the northern parts of the USA, northern India and China), have poor vitamin D status, especially in winter or if confined indoors. (3) Low vitamin D status may be exacerbated during this COVID-19 crisis (e.g., due to indoor living and hence reduced sun exposure), and anyone who is self-isolating with limited access to sunlight is advised to take a vitamin D supplement according to their government's recommendations for the general population (i.e., 400 IU/day for the UK and 600 IU/day for the USA (800 IU for >70 years)) and the European Union (EU). (4) There is no strong scientific evidence to show that very high intakes (i.e., mega supplements) of vitamin D will be beneficial in preventing or treating COVID-19. (5) There are evidenced health risks with excessive vitamin D intakes especially for those with other health issues such as a reduced kidney function. • **Conclusion**: The authors recommend appropriate vitamin D RCTs to evaluate the effects of vitamin D supplementation on COVID-19 infections. Until there is more robust scientific evidence for vitamin D, the authors strongly caution against the use of high vitamin D supplementation (greater than the upper limit of 4,000 IU/day (100 µg/day)). Rather, they strongly endorse avoidance of vitamin D deficiency in the population and complete adherence to government's advice worldwide on the prevention of the spread of COVID-19.	No information identified.

Ebadi, M., & Montano-Loza, A. J. (May 2020). Perspective: improving vitamin D status in the management of COVID-19. European journal of clinical nutrition, 74(6), 856–859.	• **Objective**: This review examines improving Vitamin D status in the management of COVID-19. • **Conclusion**: Given the high prevalence of vitamin D deficiency and in order to rapidly, safely, and significantly raise serum concentrations, high-dose vitamin D intervention with potential benefit in decreasing risk of COVID-19 severity and mortality is suggested, which is a safe and non-invasive treatment. Patients would take large doses of vitamin D for a week, followed by several thousand IU/d vitamin D for a period of 2 weeks. This will provide a quick and sustainable restoration of serum vitamin D levels, thus, potentially triggering an improvement in clinical status and prognosis. However, prospective clinical studies are required to address this speculation and overcome the obstacles in the current understanding of vitamin D's role as an adjuvant therapy in patients with COVID-19.	No information identified.
Kohlmeier M. (May 2020). Avoidance of vitamin D deficiency to slow the COVID-19 pandemic. BMJ nutrition, prevention & health, 3(1), 67–73.	• **Objective**: This article explores key factors that make it more likely, particularly in combination, that individuals are vitamin D deficient. These factors include old age, obesity, darker skin tone, and common genetic variants that impede vitamin D status. • **Results:** In regard to avoiding vitamin D deficiency, people with excess body fat, a darker skin tone or older age usually need to use a moderately dosed daily vitamin D supplement, particularly those living in a high-latitude region, getting little ultraviolet B exposure due to air pollution or staying mostly indoors. Carriers of the GC (group-specific component) rs4588 AA genotype also are more likely to become deficient. Very high-dosed supplements with more than 4000 IU vitamin D are rarely needed or justified. A state-by-state Mendelian randomisation analysis of excess COVID-19 mortality of African-Americans in the USA shows a greater disparity in northern states than in southern states. It is conceivable that vitamin D adequacy denies the virus easy footholds and thereby slows spreading of the contagion. • **Conclusion**: It is known that 25(OH)D concentrations of people living at high latitudes drop due to the lower daily UV-B light exposure during the dark months of the year. And still, not enough is done to offset the typical seasonal drop in 25(OH)D concentrations at higher latitudes by using appropriately dosed vitamin D supplements. Now in the context of the current COVID-19 pandemic, renewed attention to the very high prevalence of severe vitamin D deficiency there and elsewhere is in order. Advanced age, obesity, darker skin tone and risk-related genotypes, particularly in combination, are alarm signs that should prompt corrective action, typically with a moderate, individually tailored dose of supplemental vitamin D. While the preventive potential of supplemental vitamin D should not be exaggerated and the dose kept within recommended ranges (typically well under 4,000 IU per day), preventing vitamin D deficiency should be a widely shared goal.	No information identified.
Grant WB, Lahore H, McDonnell SL, Baggerly CA, French CB, Aliano JL, Bhattoa HP. (April 2, 2020). Evidence that Vitamin D Supplementation Could Reduce Risk of Influenza and COVID-19 Infections and Deaths. Nutrients;12(4):988.	• **Objective**: This article reviews the roles of vitamin D in reducing the risk of respiratory tract infections, knowledge about the epidemiology of influenza and COVID-19, and how vitamin D supplementation might be a useful measure to reduce risk. • **Results**: Through several mechanisms, vitamin D can reduce risk of infections. Those mechanisms include inducing cathelicidins and defensins that can lower viral replication rates and reducing concentrations of pro-inflammatory cytokines that produce the inflammation that injures the lining of the lungs, leading to pneumonia, as well as increasing concentrations of anti-inflammatory cytokines. Several observational studies and clinical trials reported that vitamin D supplementation reduced the risk of influenza, whereas others did not. Evidence supporting the role of vitamin D in reducing risk of COVID-19 includes that the outbreak occurred in winter, a time when 25-hydroxyvitamin D (25(OH)D) concentrations are lowest; that the number of cases in the Southern Hemisphere near the end of summer are low; that vitamin D deficiency has been found to contribute to acute respiratory distress	No information identified.

	syndrome; and that case-fatality rates increase with age and with chronic disease comorbidity, both of which are associated with lower 25(OH)D concentration. • **Conclusion**: To reduce the risk of infection, it is recommended that people at risk of influenza and/or COVID-19 consider taking 10,000 IU/d of vitamin D3 for a few weeks to rapidly raise 25(OH)D concentrations, followed by 5,000 IU/d. The goal should be to raise 25(OH)D concentrations above 40-60 ng/mL (100-150 nmol/L). For treatment of people who become infected with COVID-19, higher vitamin D3 doses might be useful. Randomized controlled trials and large population studies should be conducted to evaluate these recommendations.	
Insufficient or Low-Quality Evidence on the Role of Vitamin D Status in the Pathogenesis of COVID-19		
Jolliffe DA, Camargo CA, Sluyter JD, Aglipay M, Aloia JF, Ganmaa D, Bergman P, Borzutzky A, Damsgaard CT, Dubnov-Raz G, Esposito S, Gilham C, Ginde AA, Golan-Tripto I, Goodall EC, Grant CC, Griffiths CJ, Hibbs AM, Janssens W, Khadilkar AV, Laaksi I, Lee MT, Loeb M, Maguire JL, Majak P, Mauger DT, Manaseki-Holland S, Murdoch DR, Nakashima A, Neale RE, Pham H, Rake C, Rees JR, Rosendahl J, Scragg R, Shah D, Shimizu Y, Simpson-Yap S, Kumar GT, Urashima M, Martineau AR. (Nov 25, 2020). Vitamin D supplementation to prevent acute respiratory infections: systematic review and meta-analysis of aggregate data from randomised controlled trials. medRxiv [Preprint].	• **Objective**: A 2017 meta-analysis of data from 25 randomized controlled trials of vitamin D supplementation for the prevention of acute respiratory infections (ARI) revealed a protective effect of the intervention. Since then, 20 new RCTs have been completed. • **Methods**: Systematic review and meta-analysis of data from randomised controlled trials (RCTs) of vitamin D for ARI prevention using a random effects model. Pre-specified sub-group analyses were done to determine whether effects of vitamin D on risk of ARI varied according to baseline 25-hydroxyvitamin D (25[OH]D) concentration or dosing regimen. The researchers searched MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science and the ClinicalTrials.gov registry from inception to 1st May 2020. Double-blind RCTs of supplementation with vitamin D or calcidiol, of any duration, were eligible if they were approved by a Research Ethics Committee and if ARI incidence was collected prospectively and pre-specified as an efficacy outcome. Aggregate data, stratified by baseline 25(OH)D concentration, were obtained from study authors. The study was registered with PROSPERO (no. CRD42020190633). • **Results**: The analysis identified 45 eligible RCTs (total 73,384 participants). Data were obtained for 46,331 (98.0%) of 47,262 participants in 42 studies, aged 0 to 95 years. For the primary comparison of vitamin D supplementation vs. placebo, the intervention reduced risk of ARI overall (Odds Ratio [OR] 0.91, 95% CI 0.84 to 0.99; P for heterogeneity 0.01). No statistically significant effect of vitamin D was seen for any of the sub-groups defined by baseline 25(OH)D concentration. However, protective effects were seen for trials in which vitamin D was given using a daily dosing regimen (OR 0.75, 95% CI 0.61 to 0.93); at daily dose equivalents of 400–1000 IU (OR 0.70, 95% CI 0.55 to 0.89); and for a duration of ≤12 months (OR 0.82, 95% CI 0.72 to 0.93). No significant interaction was seen between allocation to vitamin D vs. placebo and dose frequency, dose size, or study duration. Vitamin D did not influence the proportion of participants experiencing at least one serious adverse event (OR 0.97, 95% CI 0.86 to 1.09). Risk of bias within individual studies was assessed as being low for all but three trials. A funnel plot showed left-sided asymmetry (P=0.008, Egger's test). • **Conclusion**: Vitamin D supplementation was safe and reduced risk of ARI, despite evidence of significant heterogeneity across trials. Protection was associated with administration of daily doses of 400–1,000 IU vitamin D for up to 12 months. The relevance of these findings to COVID-19 is not known and requires investigation.	No information identified.
Bilezikian JP, Bikle D, Hewison M, Lazaretti-Castro M, Formenti AM, Gupta A, Madhavan MV, Nair N, Babalyan V, Hutchings N, Napoli N, Accili D, Binkley N, Landry DW, Giustina A. (Nov 2020). Mechanisms in Endocrinology: Vitamin D	• **Objective**: This review applies the current understanding of vitamin D as a facilitator of immunocompetence both with regard to innate and adaptive immunity and considers how this may relate to COVID-19 disease. There are also intriguing potential links to vitamin D as a factor in the cytokine storm that portends some of the most serious consequences of SARS-CoV-2 infection, such as the acute respiratory distress syndrome. Moreover, cardiac and coagulopathic features of COVID-19 disease deserve attention as they may also be related to vitamin D. Finally, the review examines the current clinical data associating vitamin D with SARS-CoV-2 infection, a putative clinical link that at this time must still be considered hypothetical.	No information identified.

and COVID-19. Eur J Endocrinol.; 183(5):R133-R147.	• **Conclusion**: The pervasive actions of vitamin D on many organ systems have raised many possible interactions between it and the mechanisms by which the SARS-CoV-2 virus infects human beings. While the data are far from conclusive in attributing a role for vitamin D in influencing the risk and outcome of this disease, it is nevertheless also clear that more research would be timely and revealing.	
Ali N. (October 2020). Role of vitamin D in preventing of COVID-19 infection, progression and severity. Journal of infection and public health, 13(10), 1373–1380.	• **Objective**: This review discussed the possible roles of vitamin D in reducing the risk of COVID-19 and other acute respiratory tract infections and severity. Moreover, this study determined the correlation of vitamin D levels with COVID-19 cases and deaths in 20 European countries as of 20 May 2020. • **Methods**: This study evaluated the correlation of vitamin D concentrations with COVID-19 cases and deaths per one million of the population in 20 European countries using data from the COVID-19 pandemic data portal for 20 May 2020 (most countries after peak). PubMed, Google Scholar, Web of Science, Scopus, Cochrane Central Register of Controlled Trials, and medRXiv were searched for relevant literature about the role of vitamin D in COVID-19 infection, severity, and mortality. • **Results**: A significant negative correlation (p = 0.033) has been observed between mean vitamin D levels and COVID-19 cases per one million population in European countries. However, the correlation of vitamin D with COVID-19 deaths of these countries was not significant. Some retrospective studies demonstrated a correlation between vitamin D status and COVID-19 severity and mortality, while other studies did not find the correlation when confounding variables are adjusted. Several studies demonstrated the role of vitamin D in reducing the risk of acute viral respiratory tract infections and pneumonia. These include direct inhibition with viral replication or with anti-inflammatory or immunomodulatory ways. In the meta-analysis, vitamin D supplementation has been shown as safe and effective against acute respiratory tract infections. • **Conclusion**: People who are at higher risk of vitamin D deficiency during this global pandemic should consider taking vitamin D supplements to maintain the circulating 25(OH)D in the optimal levels (75–125 nmol/L). There is not enough evidence on the association between vitamin D levels and COVID-19 severity and mortality. Therefore, randomized control trials and cohort studies are necessary to test this hypothesis.	3/10
Singh SK, Jain R, Singh S. (Sept-Oct 2020). Vitamin D deficiency in patients with diabetes and COVID-19 infection. Diabetes Metab Syndr.;14(5):1033-1035.	• **Objective**: Data show that vitamin D deficiency may play a role in patients with diabetes mellitus and COVID-19 infection. The evidence of vitamin D deficiency and COVID-19 infection in context of diabetes mellitus is reviewed. • **Methods**: A literature search was carried out by using the key term 'COVID 19' combined with 'Diabetes', 'Vitamin D', 'Extra skeletal effects', 'immunity', 'infection', 'India' from Pub Med (National Library of Medicine, Bethesda, MD and Google Scholar from December 2019 to May 2020. A manual search of the references was also carried out. • **Results**: Vitamin D deficiency has been linked to increased morbidity and mortality in COVID-19 infections, but convincing data on diabetic subgroup of patients in particular is still awaited. • **Conclusion**: Robust studies are required to ascertain if Vitamin D supplementation could be beneficial in patients with diabetes and COVID-19.	No information identified.
Siddiqui, M., Manansala, J. S., Abdulrahman, H. A., Nasrallah, G. K., Smatti, M. K., Younes, N., Althani, A. A., & Yassine, H. M. (Sept 2020). Immune Modulatory Effects of Vitamin D on Viral	• **Objective:** This review summarizes the recent mechanisms by which vitamin D regulates the immune system, both innate and adaptive systems, and reflects on the link between serum vitamin D levels and viral infections. • **Conclusion**: Vitamin D has immuno-modulating properties that affect both innate and adaptive immunity. As vitamin D plays an integral role in regulating the immune system, researchers have been studying the role of vitamin D disease mechanisms. The review found that only few viruses have been studied in relation to the effect vitamin D has on them. While most of the work has been done on chronic infections such as HCV and HIV, there is some substantial research done	No information identified.

Reference	Summary	Score
[Infections](link). Nutrients, 12(9), 2879.	on the influenza and other viruses. Until now, there has been no direct correlation made to vitamin D levels and Covid-19 outcome. Other viruses have not been studied in depth. However, as this paper shows that vitamin D affects the immune system in various ways, future studies are needed to understand the role of vitamin D in preventing infections caused by various viruses as well as how re- stabilizing the vitamin D levels in diseased patients can improve the outcome of the disease. Some of the works mentioned above have shown some promising results and if experimentation with other viruses shows similar results, vitamin D can be used as a readily available and inexpensive form of adjunct therapy. This can help improve the outcome of the disease and the quality of life of patients.	
Mohan, M., Cherian, J. J., & Sharma, A. (Sept 2020). [Exploring links between vitamin D deficiency and COVID-19](link). PLoS pathogens, 16(9), e1008874.	• **Objective:** This review examined whether there is an association between vitamin D deficiency and susceptibility to COVID-19, and whether vitamin D administration to deficient individuals can prevent infection or alter the course of disease severity. • **Conclusion:** The authors of the review do not endorse the use of vitamin D for treatment or prevention of COVID-19 infections but instead stress the need for more robust research that can address the early correlations noted above. The review's hypothesis could be explored by a case control study (such as the COVIDENCE UK study) to observe the frequency of vitamin D deficiency amongst patients with poor COVID-19 outcomes. Case reports on the compassionate use of vitamin D may also help probe vitamin D's therapeutic effects. Randomised controlled trials such as those initiated in Spain ([NCT04334005](link)), Argentina ([NCT04411446](link)), France ([NCT04344041](link)), and Iran (IRCT20200324046850N1) would bring forth superior evidence to link healthy levels of vitamin D with better outcomes in COVID-19.	No information identified.
Jovic TH, Ali SR, Ibrahim N, Jessop ZM, Tarassoli SP, Dobbs TD, Holford P, Thornton CA, Whitaker IS. (August 2020). [Could Vitamins Help in the Fight Against COVID-19?](link) Nutrients;12(9):2550.	• **Objective**: There are limited proven therapeutic options for the prevention and treatment of COVID-19. The role of vitamin and mineral supplementation or "immunonutrition" has previously been explored in a number of clinical trials in intensive care settings, and there are several hypotheses to support their routine use. The aim of this narrative review was to investigate whether vitamin supplementation is beneficial in COVID-19. • **Methods**: A systematic search strategy with a narrative literature summary was designed, using the Medline, EMBASE, Cochrane Trials Register, WHO International Clinical Trial Registry, and Nexis media databases. The immune-mediating, antioxidant and antimicrobial roles of vitamins A to E were explored and their potential role in the fight against COVID-19 was evaluated. The major topics extracted for narrative synthesis were physiological and immunological roles of each vitamin, their role in respiratory infections, acute respiratory distress syndrome (ARDS), and COVID-19. • **Results**: Vitamins A to E highlighted potentially beneficial roles in the fight against COVID-19 via antioxidant effects, immunomodulation, enhancing natural barriers, and local paracrine signaling. Level 1 and 2 evidence supports the use of thiamine, vitamin C, and vitamin D in COVID-like respiratory diseases, ARDS, and sepsis. • **Conclusion**: Although there are currently no published clinical trials due to the novelty of SARS-CoV-2 infection, there is pathophysiologic rationale for exploring the use of vitamins in this global pandemic, supported by early anecdotal reports from international groups. The final outcomes of ongoing trials of vitamin supplementation are awaited with interest.	4/9
BourBour F, Mirzaei Dahka S, Gholamalizadeh M, Akbari ME, Shadnoush M, Haghighi M, Taghvaye-Masoumi H, Ashoori N, Doaei S. (July 9, 2020). [Nutrients in prevention, treatment, and](link)	• **Background**: The coronavirus disease 2019 (COVID-19) is a pandemic caused by coronavirus with mild to severe respiratory symptoms. This paper aimed to investigate the effect of nutrients on the immune system and their possible roles in the prevention, treatment, and management of COVID-19 in adults. • **Methods**: This Systematic review was designed based on the guideline of the Preferred Reporting for Systematic Reviews (PRISMA). The articles that focussed on nutrition, immune system, viral infection, and coronaviruses were collected by searching databases for both published papers and accepted manuscripts from	4/9

[management of viral infections; special focus on Coronavirus](). Arch Physiol Biochem.:1-10.	1990 to 2020. Irrelevant papers and articles without English abstract were excluded from the review process. • **Results**: Some nutrients are actively involved in the proper functioning and strengthening of the human immune system against viral infections including dietary protein, omega-3 fatty acids, vitamin A, vitamin D, vitamin E, vitamin B1, vitamin B6, vitamin B12, vitamin C, iron, zinc, and selenium. Few studies were done on the effect of dietary components on prevention of COVID-19, but supplementation with these nutrients may be effective in improving the health status of patients with viral infections. • **Conclusion**: Following a balanced diet and supplementation with proper nutrients may play a vital role in prevention, treatment, and management of COVID-19. However, further clinical trials are needed to confirm these findings and presenting the strong recommendations against this pandemic.	
• Infusino F, Marazzato M, Mancone M, Fedele F, Mastroianni CM, Severino P, Ceccarelli G, Santinelli L, Cavarretta E, Marullo AGM, Miraldi F, Carnevale R, Nocella C, Biondi-Zoccai G, Pagnini C, Schiavon S, Pugliese F, Frati G, d'Ettorre G. (June 2020). [Diet Supplementation, Probiotics, and Nutraceuticals in SARS-CoV-2 Infection: A Scoping Review](). Nutrients; 12(6):1718.	• **Objective**: This scoping review analyzed the possible role of non-pharmacological substances such as supplements, probiotics, and nutraceuticals in reducing the risk of Sars-CoV-2 infection or mitigating the symptoms of COVID-19. • **Conclusion:** During the pandemic, as in all other circumstances, it is reasonable to recommend a proper nutrition rich in antioxidant nutrients. Vitamin C and D play a well-proven role in the immune system. However, it is not known whether a supplemental dose of these vitamins administered to patients without their deficiency would result in a benefit. Specific clinical studies are underway on the intra-venous administration of vitamin C in hospitalized COVID-19 patients. Vitamin D deficiency has been associated with increased susceptibility to respiratory infections, therefore it is reasonable, even in the absence of specific data, to administer vitamin D to healthy individuals and COVID-19 patients. While diet, nutritional supplements, and similar interventions show great promise for preventing and managing COVID-19, it is also true that strong clinical research data are required to support any such claim.	3/10
Lee, J., van Hecke, O., and Roberts, N. (May 1, 2020). [Vitamin D: A rapid review of the evidence for treatment or prevention in COVID-19](). Oxford COVID-19 Evidence Service Team, Centre for Evidence-Based Medicine, Nuffield Department of Primary Care Health Sciences, University of Oxford.	• **Objective:** This rapid review examined the evidence relating to a role for vitamin D in COVID-19. • **Conclusion:** No clinical evidence was identified on vitamin D in COVID-19. There was no evidence related to vitamin D deficiency predisposing to COVID-19, nor were there studies of supplementation for preventing or treating COVID-19 (Search date up to 4th of April 2020, clinicaltrials.gov searched up to on 23rd April). There is some evidence that daily vitamin D3 supplementation over weeks to months may prevent other acute respiratory infections, particularly in people with low or very low vitamin D status. This evidence has limitations, including heterogeneity in study populations, interventions, and definitions of respiratory infections that include upper and lower respiratory tract involvement. The current advice is that the whole population of the UK should take vitamin D supplements to prevent vitamin D deficiency. This advice applies irrespective of any possible link with respiratory infection. Clinicians should treat patients with vitamin D deficiency irrespective of any link with respiratory infection. Policymakers should attend to public health measures to ensure the population has adequate vitamin D intake.	3/9

Methods

The COVID-19 Evidence Synthesis Network is comprised of groups specializing in evidence synthesis and knowledge translation. The group has committed to provide their expertise to provide high-quality, relevant, and timely synthesized research evidence about COVID-19 to inform decision-makers as the pandemic continues. The following member of the Network provided an evidence synthesis product that was used to develop this Evidence Synthesis Briefing Note:

- Wilson MG, Mansilla C, Lavis JN. COVID-19 rapid query response #4: What's known about vitamin D deficiency as a prognostic factor for COVID-19? Hamilton: McMaster Health Forum, 7 December 2020.

For more information, please contact the [Research, Analysis and Evaluation Branch (Ministry of Health)](#).

APPENDIX

The following tables are from an evidence synthesis product produced by a member of the COVID-19 Evidence Synthesis Network:

- Wilson MG, Mansilla C, Lavis JN. COVID-19 rapid query response #4: What's known about vitamin D deficiency as a prognostic factor for COVID-19? Hamilton: McMaster Health Forum, 7 December 2020.

McMaster Health Forum searched the COVID-END database of evidence syntheses for 'vitamin D' to identify systematic reviews and rapid reviews relevant to the question. The Forum identified nine full systematic reviews and two rapid reviews that were relevant, which are listed in Table 2. Each systematic review and rapid review are listed with a hyperlinked title, date of last search, and the methodological quality (rated using AMSTAR). The reviews ordered from the most recent and highest quality to the least recent and lowest quality. McMaster Health Forum also extracted from these reviews the key primary studies (and related editorials that contained primary data) and primary-study protocols cited in the reviews, which are listed in Table 3 (in alphabetical order by name of first author).

Table 2: Reviews of studies about vitamin D deficiency as a prognostic factor for COVID-19

Type of document	Title	Date of last search	Methodological quality (AMSTAR)
Full systematic reviews	Vitamin D deficiency aggravates COVID-19: Systematic review and meta-analysis	9 October 2020	7/11
	Low serum vitamin D level and COVID-19 infection and outcomes, a multivariate meta-analysis	1 October 2020	9/11
	Vitamin D3 as potential treatment adjuncts for COVID-19	Not specified (published 14 November 2020)	1/9
	Could vitamins help in the fight against COVID-19?	Not specified (published 23 August 2020)	4/9
	Nutrients in prevention, treatment, and management of viral infections: Special focus on coronavirus	Not specified (published 9 July 2020)	4/9
	Role of vitamin D in preventing of COVID-19 infection, progression and severity	Not specified (published 16 June 2020)	3/10
	Medications in COVID-19 patients: Summarizing the current literature from an orthopaedic perspective	19 April 2020	2/9
	Diet supplementation, probiotics, and nutraceuticals in SARS-CoV-2 infection: A scoping review	8 April 2020	3/10
	Ecological association between COVID-19 deaths and vitamin D deficiency among older adults: An international country-level systematic review and analysis	6 March 2020	4/11
Rapid reviews	The role of vitamin D in the age of COVID-19: A systematic review and meta-analysis	10 October 2020	9/11
	Vitamin D: A rapid review of the evidence for treatment or prevention in COVID-19	Not specified (published 1 May 2020)	3/9

Table 3: Studies and study protocols about vitamin D deficiency as a prognostic factor for COVID-19 that were included in the reviews cited in Table 2

Type of document	Title
Primary studies (and related editorials)	Alipio M. 2020. Vitamin D supplementation could possibly improve clinical outcomes of patients infected with coronavirus-2019 (COVID-2019). SSRN Electronic Journal . doi: 10.2139/ssrn.3571484
	Baktash V, Hosack T, Patel N, Shah S, Kandiah P, Van Den Abbeele K, Mandal AKJ, and Missouris CG. 2020. Vitamin D status and outcomes for hospitalised older patients with COVID-19. Postgraduate Medical Journal
	Carpagnano GE, Di Lecce V, Quaranta VN, Zito A, Buonamico E, Capozza E, Palumbo A, Di Gioia G, Valerio VN, and Resta O. 2020. Vitamin D deficiency as a predictor of poor prognosis in patients with acute respiratory failure due to COVID-19. Journal of Endocrinological Investigation
	Chang TS, Ding Y, Freund MK, Johnson R, Schwarz T, Yabu JM, et al. 2020. Prior diagnoses and medications as risk factors for COVID-19 in a Los Angeles Health System. medRxiv
	Cuñat T, Ojeda A and Calvo A. 2020. Vitamin D deficiency in critically ill patients diagnosed with COVID-19: Are we doing enough? A retrospective analysis of 226 patients
	D'Avolio A, Avataneo V, Manca A, Cusato J, De Nicolo A, Lucchini R, Keller F, and Cantu M. 2020. 25-Hydroxyvitamin D concentrations are lower in patients with positive PCR for SARS-CoV-2. Nutrients 12 (5):1359
	Daneshkhah A, Agrawal V, Eshein A, Subramanian H, Roy HK, Backman V. 2020. The possible role of vitamin D in suppressing cytokine storm and associated mortality in COVID-19 patients [preprint] Infect Dis (except HIV/AIDS)
	Darling AL, Ahmadi KR, Ward KA, Harvey NC, Alves AC, Dunn-Waters DK, Lanham-New SA, Cooper C, and Blackbourn DJ. 2020. Vitamin D status, body mass index, ethnicity and COVID-19: Initial analysis of the first-reported UK biobank COVID-19 positive cases (n 580) compared with negative controls (n 723). MedRxiv
	De Smet D, De Smet K, Herroelen P, Gryspeerdt S, Martens GA. 2020. Vitamin D deficiency as risk factor for severe COVID-19: A convergence of two pandemics [preprint] Infect Dis (except HIV/AIDS)
	Faniyi AA, Lugg ST, Faustini SE, Webster C, .Duffy JE, Hewison M, Shields A, Nightingale P, Richter AG, and Thickett DR. 2020. Vitamin D status and seroconversion for COVID-19 in UK healthcare workers who isolated for COVID-19 like symptoms during the 2020 pandemic
	Faul J , Kerley C, Love B, O'neill E, Cody C, Tormey W, Hutchinson K, Cormican L, and Burke C. 2020. Vitamin D deficiency and ARDS after SARS-CoV-2 infection. Irish Medical Journal 113 (5):84
	Glicio EJ. 2020. Vitamin D level of mild and severe elderly cases of COVID-19: A preliminary report
	Hastie, CE , Mackay DF, Ho F, Celis-Morales CA, Katikireddi SV, Niedzwiedz CL, Jani BD, Welsh P, Mair FS, Gray SR, et al. 2020. Corrigendum to "Vitamin D concentrations and COVID-19 infection in UK Biobank" [Diabetes Metabol Syndr: Clin Res Rev 2020 14 (4) 561-5]. Diabetes & Metabolic Syndrome 14 (5):1315–6 Hastie, CE, Pell JP, and Sattar N. 2020. Vitamin D and COVID-19 infection and mortality in UK Biobank. European Journal of Nutrition 26:1–4
	Ilie PC, Stefanescu S, Smith L 2020. The role of vitamin D in the prevention of coronavirus disease 2019 infection and mortality. Aging Clin. Exp. Res.
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