



## Should Vitamin D supplements be used in the prevention or treatment of COVID-19?

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*This rapid review summarizes the available evidence on the efficacy and safety of Vitamin D supplements in treating patients with COVID-19. This may change as new evidence emerges.*

### KEY FINDINGS

There is no clinical evidence that Vitamin D supplements should be used in the prevention or treatment of COVID-19.

- Vitamin D plays a significant role in bone health and supports the induction of antimicrobial peptides in response to both viral and bacterial stimuli by inducing innate antimicrobial effector mechanisms. Vitamin D supplementation is associated with preservation of alveolar barrier function, reduction of alveolar lung injury, and proinflammatory cytokines (1,2).
- There are no completed clinical trials assessing the efficacy of vitamin D supplementation in the prevention or treatment of COVID-19. Excessive intake of vitamin D supplements has been associated with anorexia, weight loss, polyuria, and heart arrhythmias, vascular and tissue calcification that lead to cardiovascular and kidney damage (3).
- We found 8 registered clinical trials investigating the efficacy of vitamin D supplements alone or in combination with other drugs or supplements in the prevention or treatment of COVID-19.
- British Dietetic Association recommends a daily intake of 10mg vitamin D supplements and vitamin D-rich food if one is undergoing self-isolation or unable to go outside for sun exposure (4). There are no recommendations regarding vitamin D supplementation from CDC, WHO, and the Infectious Diseases Society of America.

**Disclaimer:** The aim of these rapid reviews is to retrieve, appraise, summarize and update the available evidence on COVID-related health technology. The reviews have not been externally peer-reviewed; they should not replace individual clinical judgement and the sources cited should be checked. The views expressed represent the views of the authors and not necessarily those of their host institutions. The views are not a substitute for professional medical advice.

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## RESULTS

We did not find clinical trials or observational studies on vitamin D supplementation for COVID-19.

A recently published rapid review (May 1, 2020) on vitamin D and COVID-19 did not find completed clinical trials or observational studies on vitamin D supplementation for COVID-19. (8).

We found indirect evidence on vitamin D supplementation for non-COVID respiratory infections and critically ill patients. Vitamin D deficiency has been associated with an increased risk of lower respiratory viral infections caused by the influenza virus, RSV, and rhinovirus but *in vitro* vitamin D supplementation did not show any protective effect (9). An umbrella review on the role of vitamin D in prevention or treatment of extra-skeletal conditions included a meta-analysis analyzing 25 RCTs (N=11,321) and showed that vitamin D supplementation reduced the risk of at least one ARI (adjusted odds ratio of 0.88; 95% CI: 0.81 to 0.96) among critically-ill patients. The overall number needed to treat was 33 (95% CI: 20 to 101) and was lower at 8 (95% CI: 5 to 21) in individuals with low baseline vitamin D serum levels (10 ng/mL) (10,11).

This review found eight registered randomized controlled trials were found with one trial as prophylaxis. For details, refer to Appendix 1 Characteristics of Registered Clinical Trials.

### Recommendations from Other Guidelines

The British Dietetic Association recommendations in its “COVID-19 Advise to the General Public” are: a daily intake of 10mg vitamin D supplements and Vitamin D-rich food if one is undergoing self-isolation or unable to go outside for sun exposure (4). There are no recommendations from CDC, WHO, and the Infectious Diseases Society of America regarding vitamin D supplementation for COVID-19 patients.

## CONCLUSION

Despite indirect evidence on the benefit of Vitamin D supplementation among critically ill patients with acute respiratory illnesses, there is still no direct evidence supporting the efficacy and safety of vitamin D supplementation for COVID-19 prevention or treatment. Clinical trials are still being planned or have just begun recruiting participants.

### Declaration of Conflict of Interest

No conflict of interest

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## Appendix 1. Characteristics of registered clinical trials

No.	Clinical Trial ID/ Title	Status	Start & estimated primary completion date	Study design	Country	Population	Intervention	Comparison Group(s)	Outcomes
1	Vitamin D on Prevention and Treatment of COVID-19 (COVITD-19)  NCT04334005	Not yet recruiting	April 10, 2020; June 30, 2020	Double-blind, randomized placebo-controlled trial (N=300)  Treatment	Spain	40-70 y/o non-severe COVID-19 patients	25000 IU of vitamin D supplement in addition to drug recommendations in usual care	Usual care:  NSAIDs, ACE2 inhibitor, ARB or thiazolidinediones	Composite of cumulative death (i.e. mortality) for all causes and for specific causes  (10 weeks)
2	Covid-19 and Vitamin D Supplementation: a Multicenter Randomized Controlled Trial of High Dose Versus Standard Dose Vitamin D3 in High-risk COVID-19 Patients (CoVitTrial)	Recruiting	April 15, 2020 - July 2020	Multi-center open-label randomized controlled trial (N=260)  Treatment	France	70 y/o and older with COVID-19 or CT scan suggesting viral pneumonia; diagnosed past 24 hours	ZYMAD® high dose Vit. D3 400,000 IU (2 vials of 200,000 IU) single oral dose	Standard dose Vit. D3 50,000 IU (1 vial of 50,000 IU) single oral dose	Number of deaths of any cause, [ Time Frame: Day 14 ]

	NCT04344041								
3	Impact of Zinc and Vitamin D3 Supplementation on the Survival of Aged Patients Infected With COVID-19 (ZnD3-CoVici)  NCT04351490	Not yet recruiting	April to July 2020	open-label, randomized controlled trial (N=3140)  Treatment	France	60 y/o and older  institutionalized	Zinc gluconate capsule 15 mg twice daily for 2 months	Dietary Supplement: 25-OH cholecalciferol  25-OH cholecalciferol drinkable solution 10 drops (2000 IU) per day for 2 months	Survival rate in asymptomatic subjects [ Time Frame: Two months after inclusion ]
4	Oral 25-hydroxyvitamin D3 and COVID-19  NCT04386850	Recruiting	April 14 to Nov 14 2020	Quadruple blinded RCT (N=1500)  Treatment phase	Iran	Patients with confirmed COVID-19	25 mcg of 25(OH)D3 once daily at bedtime for 2 months	placebo daily for 2 month	COVID-19 (SARS-Cov-2) infection  Severity of COVID-19 (SARS-Cov-2) infection  Hospitalization  Disease duration  Death  Oxygen support
5	Vitamin D and COVID-19 Management  NCT04385940	Not yet recruiting	May to Aug 2020	Quadruple blinded RCT (N=64)	Canada	17 y/o; Patients with COVID-19	High-dose vitamin D  Ergocalciferol 1.25 MG (50,000 IU)	Low-dose vitamin D  Vitamin D3 1,000 IU	Symptoms recovery  Secondary outcomes:

									Hospitalization [ Time Frame: Between diagnosis and day 21 ]  Number of patients who required hospitalization
6	NCT04334005 Vitamin D on Prevention and Treatment of COVID-19 (COVITD-19)	Not yet recruiting	April 1 to June 30 2020	Double blind Parallel RCT (N=200)  Treatment	Spain	40-70 y/o; Non-severe symptomatic patients who present cough, fever, nasal congestion, gastrointestinal symptoms, fatigue, anosmia, ageusia or alternative signs of respiratory infections.	25000 UI of vitamin D supplement in addition to the above-mentioned drug recommendations.	Usual care  Prescription of NSAIDs, ACE2 inhibitor, ARB or thiazolidinediones, according to clinician criteria, based on the current recommendations.	Primary: Composite of cumulative death (i.e. mortality) for all causes and for specific causes  Necessity of invasive assisted ventilation
7	NCT04363840 The LEAD COVID-19 Trial: Low-risk, Early Aspirin and Vitamin D to Reduce COVID-19 Hospitalizations (LEAD COVID-19)	Not yet recruiting	May to Dec 2020	Open label Parallel RCT (N=1080)  Treatment	US	18 y/o; New (within 24 hours) COVID-19 diagnosis	Aspirin  Aspirin + Vit D	No intervention	Hospitalization
8	NCT04372017 Hydroxychloroquine as Post-Exposure Prophylaxis Against COVID-19 Infection	Recruiting	May 14, 2020 to April 20, 2022	Double blind Parallel RCT (N=1739)  Prevention	US	18 y/o and above  <u>Cohort A Healthcare worker</u>  Employee of healthcare organization with exposure to a person	Experimental: Hydroxychloroquine	Placebo:  Vitamin D IU1600 on day 1 and IU 800 on days 2-5.	Positive COVID test

					<p>with COVID-19 within the last 5 days</p> <p>Occupational of community exposure</p> <p>No current symptoms attributable to COVID-19, per HCW report</p> <p>No prior COVID-19 positive diagnosis</p>			
					<p><u>Cohort B</u></p> <p>High-risk person who had close contact with a COVID-19 positive person within the last 5 days</p> <p>No current symptoms attributable to COVID-19</p> <p>No prior COVID-19 positive diagnosis</p>	<p>Experimental: Hydroxychloroquine</p>	<p>Placebo: Vitamin D IU1600 on day 1 and IU 800 on days 2-5.</p>	<p>Positive COVID test</p>