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Vitamin D in the prevention or treatment of COVID-19

Adrian R. Martineau
Centre for Immunobiology, Blizard Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, 4 Newark St, London E1 2AT, UK

This review summarises evidence relating to a potential role for vitamin D supplementation in the prevention or treatment of coronavirus disease 2019 (COVID-19). Laboratory studies show that the active vitamin D metabolite 1,25-dihydroxyvitamin D induces innate antiviral responses and regulates immunopathological inflammation with potentially favourable implications for the host response to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Meta-analyses of cross-sectional, case-control and longitudinal studies report consistent protective associations between higher circulating 25-hydroxyvitamin D [25(OH)D] concentrations or vitamin D supplement use and reduced risk and severity of COVID-19. However, Mendelian randomisation studies testing for associations between genetically predicted circulating 25(OH)D concentrations and COVID-19 outcomes have yielded consistently null results. Positive findings from observational epidemiological studies may therefore have arisen as a result of residual or unmeasured confounding or reverse causality. Randomised controlled trials of prophylactic or therapeutic vitamin D supplementation to reduce risk or severity of COVID-19 reporting to date have yielded inconsistent findings. Results of further intervention studies are pending, but current evidence is insufficient to support routine use of vitamin D supplements as a therapeutic or prophylactic agent for COVID-19, or as an adjunct to augment immunogenicity of SARS-CoV-2 vaccination. Accordingly, national and international bodies have not made any recommendations regarding a role for vitamin D in the prevention or treatment of COVID-19.

Key words: Severe acute respiratory syndrome coronavirus 2: Vitamin D: Vaccination: Innate immunity

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is estimated to have caused more than 18 million deaths worldwide until the end of 2021[1]. Early in the pandemic, the striking overlap between risk factors for severe disease and those for vitamin D deficiency – older age, obesity and South Asian or Black ethnic origin – gave rise to speculation that vitamin D supplementation might have a role in the prevention or treatment of COVID-19[2,3]. This hypothesis was supported by mechanistic data relating to favourable immunomodulatory actions of vitamin D in the context of other viral respiratory infections[4–6], and by findings from meta-analyses of data from randomised controlled trials (RCTs), which demonstrated protective effects of vitamin D supplementation against acute respiratory infections caused by pathogens other than SARS-CoV-2[7,8].

Abbreviations: 1, 25$(OH)_2$D, 1, 25-dihydroxyvitamin D; 25(OH)D, 25-hydroxyvitamin D; ACE, angiotensin converting enzyme; COVID-19, coronavirus disease 2019; RCT, randomised controlled trial; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Corresponding author: Adrian R. Martineau, email a.martineau@qmul.ac.uk

- Therapeutic administration of vitamin D to reduce severity of COVID-19 in patients with existing disease.
- Prophylactic administration of vitamin D to reduce risk or severity of COVID-19.
- Pre- or peri-vaccination administration of vitamin D to augment vaccine immunogenicity and efficacy.

Fig. 1. Potential clinical applications of vitamin D supplementation for coronavirus disease 2019 (COVID-19).

Since that time, a large body of evidence from laboratory studies, epidemiological investigations, RCTs and meta-analyses has accumulated in this field. This review describes the mechanisms by which hydroxylated metabolites of vitamin D may modulate host responses to SARS-CoV-2 infection and vaccination, before going on to discuss findings of observational and intervention studies that have been conducted to establish whether vitamin D supplementation is clinically indicated (1) for the treatment of COVID-19; (2) for the prevention of COVID-19 and/or (3) as an adjunct to vaccination against SARS-CoV-2 (Fig. 1).

Mechanism of action

Vitamin D is a group of fat-soluble vitamins: vitamin D_3 (cholecalciferol) is the major form in human subjects: its primary source is via cutaneous synthesis in response to sunlight, but it can also be ingested orally, from dietary sources (such as oily fish) or in supplements[9]. Fig. 2 illustrates mechanisms by which vitamin D may modulate host immune responses to SARS-CoV-2 infection. Vitamin D from cutaneous synthesis or oral intake is converted to 25-hydroxyvitamin D [25(OH)D, the major circulating metabolite and measure of vitamin D status], primarily by the liver. Respiratory viruses ligate pattern recognition receptors to induce expression of the 25(OH)D hydroxylase *CYP27B1* in pulmonary epithelium and leucocytes. This enzyme catalyses conversion of 25(OH)D to its active vitamin D metabolite 1,25-dihydroxyvitamin D [1,25$(OH)_2$D]. 1,25$(OH)_2D_3$ ligates the vitamin D receptor to regulate gene expression profiles, resulting in upregulation of antiviral effector mechanisms (expression of antimicrobial peptides including cathelicidin LL-37 and human β defensin 2, interferon-stimulated genes and generation of reactive oxygen and nitrogen intermediates) with potential to reduce susceptibility to infection and severity of disease. It also regulates inflammation by modulating innate immune responses (regulating NF-κB and mitogen-activated protein kinase pathways to reduce expression and secretion of pro-inflammatory cytokines and increasing the ratio of angiotensin converting enzyme 2 [ACE2] to ACE)[10] and by regulating adaptive responses to inhibit differentiation of null T helper cells towards

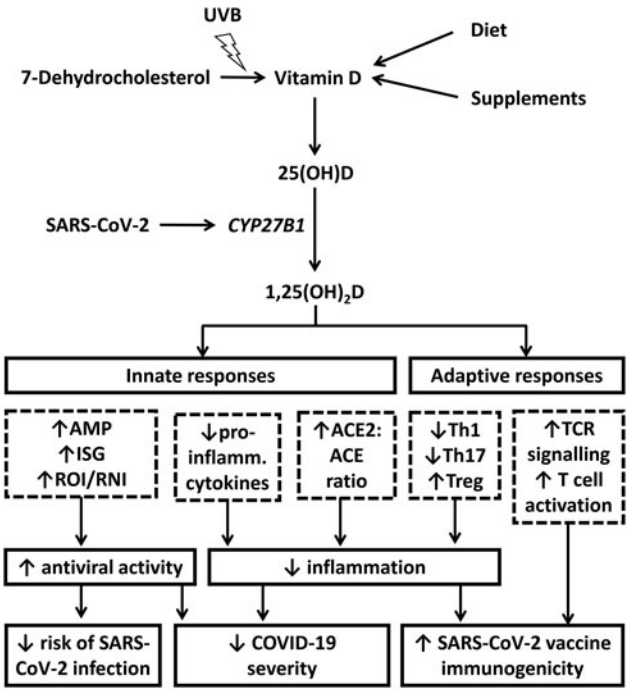

Fig. 2. Putative immunomodulatory actions of vitamin D in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Cutaneous synthesis of vitamin D from 7-dehydrocholesterol is stimulated following exposure to ultraviolet B (UVB) radiation in sunshine; alternative sources are from oral intake of foods or supplements containing vitamin D. 'Parent' vitamin D from any of these sources is converted to 25-hydroxyvitamin D [25(OH)D, the major circulating metabolite and measure of vitamin D status], primarily by the liver. SARS-CoV-2 ligates pattern recognition receptors to induce expression of the 25(OH)D hydroxylase *CYP27B1* in pulmonary epithelium and leucocytes, which catalyses conversion of 25(OH)D to the active vitamin D metabolite 1,25-dihydroxyvitamin D [1,25$(OH)_2$D]. 1,25$(OH)_2D_3$ upregulates antiviral effector mechanisms (expression of antimicrobial peptides [AMP], interferon-stimulated genes [ISG] and generation of reactive oxygen and nitrogen intermediates [ROI, RNI]) with potential to reduce susceptibility to infection and severity of disease. It also exerts anti-inflammatory actions by regulating NF-κB and mitogen-activated protein kinase (MAPK) pathways to reduce expression and secretion of pro-inflammatory cytokines; by increasing the ratio of angiotensin converting enzyme 2 [ACE2] to ACE); and by regulating adaptive responses to inhibit differentiation of null T helper (Th) cells towards type 1 or type 17 phenotypes and to promote their differentiation towards a T regulatory (Treg) phenotype. In the context of active coronavirus disease 2019 (COVID-19), these anti-inflammatory actions have potential to reduce disease severity associated with cytokine storms. In the context of vaccination, they may augment development of antigen-specific immunity. Finally, 1,25$(OH)_2$D may also support classical T cell receptor (TCR) signalling and T cell activation by inducing phospholipase C-gamma 1 (PLC-γ1) in naïve T cells. These actions would also be expected to support development of antigen-specific immunity following vaccination.

type 1 or type 17 phenotypes and to promote their differentiation towards a T regulatory phenotype[11]. In the context of active COVID-19, these anti-inflammatory actions have potential to reduce disease severity associated with 'cytokine storms'[12]. In the context of vaccination, they may serve to augment development of

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antigen-specific immunity[13]. Finally, $1,25(OH)_2D$ may also support classical T cell receptor signalling and T cell activation by inducing phospholipase C-gamma 1 in naïve T cells[14]. These actions would also be expected to support development of antigen-specific immunity following vaccination.

Findings from a number of recent mechanistic studies support the relevance of these actions for host responses to SARS-CoV-2[15]. First, in keeping with predictions from an *in silico* study[16], the vitamin D-inducible antimicrobial peptide cathelicidin LL-37 has been shown to inhibit SARS-CoV-2 attachment by blocking both the receptor-binding domain of S1 and the ligand-binding domain of ACE2[17]. Secondly, a study in transgenic mice expressing human ACE2 has shown that SARS-CoV-2 induces expression of both *CYP27B1* and *CYP24A1*, with potential implications both for conversion of 25(OH)D to $1,25(OH)_2D$ and for catabolism of 25(OH)D and $1,25(OH)_2D$ via 24-hydroxylation[18]. In this study, prophylactic administration of high-dose vitamin D_3 increased expression of type I interferons and reduced inflammation in the lung following SARS-CoV-2 infection, although this was not associated with a survival benefit[18]. Potential relevance of these findings for human disease is supported by the observation that SARS-CoV-2-infected human bronchial epithelial cells express pro-inflammatory genes predicted to be vitamin D-modifiable[19]. Studies of leucocytes isolated from patients with COVID-19 also report higher expression of vitamin D-repressible genes encoding T helper 1 cytokines than those of controls, associated with reduced vitamin D receptor expression[20–22]. However, a case study of COVID-19 arising in a family lacking functioning vitamin D receptor reported a mild disease course and normal development of antigen-specific cellular and humoral immune responses to SARS-CoV-2[23]. Taken together, these observations suggest that vitamin D signalling may have a role in regulating SARS-CoV-2-induced inflammation, but that it may not be a pre-requisite for averting severe outcomes or mounting effective adaptive immune responses.

Observational epidemiological studies

Observational studies in this field can be classified into three groups, according to whether they investigate outcomes relating to (1) COVID-19 severity, (2) susceptibility to SARS-CoV-2 infection or (3) immunogenicity of vaccination against SARS-CoV-2. Each will be considered in turn.

Observational studies investigating coronavirus disease 2019 severity

Numerous hospital-based cross-sectional, case-control and longitudinal studies have investigated potential associations between low circulating 25(OH)D concentrations and severity of COVID-19. Although some have yielded null results, the majority show positive associations, and meta-analyses of their findings consistently report statistically significant associations between

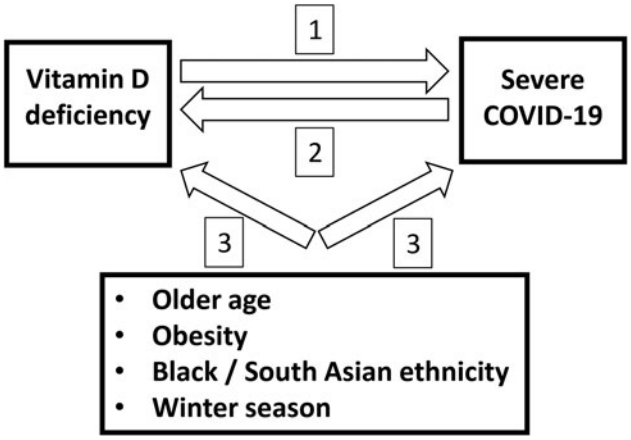

Fig. 3. Potential explanations for observed associations between vitamin D deficiency and severe coronavirus disease 2019 (COVID-19). (1) Causation: vitamin D deficiency may increase susceptibility to severe COVID-19 via attenuation of antiviral and anti-inflammatory responses to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). (2) Reverse causation: severe COVID-19 may reduce circulating 25-hydroxyvitamin D [25(OH)D] concentrations, via upregulation of vitamin D catabolism and/or reduction in concentrations of plasma proteins that bind 25(OH)D in the circulation. (3) Confounding: factors including older age, obesity, Black or South Asian ethnicity and winter season may independently associate with increased susceptibility to both vitamin D deficiency and severe COVID-19.

vitamin D deficiency at hospital admission and increased risk of adverse outcomes including mortality and requirement for intensive care unit admission and ventilatory support[24–29]. While such associations may be causal, two alternative explanations should be considered, as illustrated in Fig. 3. In one scenario, reverse causality may operate, such that reduced 25(OH)D concentrations arise as a consequence of severe COVID-19. This may arise via dysregulated vitamin D metabolism, since SARS-CoV-2 is recognised to induce expression of CYP24A1, the major catabolic enzyme that may 24-hydroxylate 25(OH)D or $1,25(OH)_2D$ to biologically inactive metabolites[18]. Alternatively, such associations may arise as a result of residual or unmeasured confounding by factors associating both with increased risk of vitamin D deficiency and with increased risk of severe COVID-19; these may include older age, Black or South Asian ethnicity, obesity or winter season. Mendelian randomisation studies are less open to confounding or reverse causality than other observational study designs[30]. Accordingly, the fact that these have consistently shown no association between adverse clinical outcomes of COVID-19 and lower genetically predicted 25(OH)D levels[31–34] raises the possibility that the associations reported in cross-sectional, case-control and longitudinal studies may not be causal.

Observational studies investigating susceptibility to severe acute respiratory syndrome coronavirus 2 infection or coronavirus disease 2019

Several population-based cross-sectional and longitudinal studies have investigated potential associations

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between circulating 25(OH)D concentrations or vitamin D supplement use and risk of incident SARS-CoV-2 infection or COVID-19. Their findings are heterogeneous, with some reporting associations between lower vitamin D status and increased susceptibility to infection[35], and others reporting null results[36]. As for studies investigating disease severity, meta-analyses of susceptibility studies have yielded consistent protective associations between higher baseline vitamin D status and reduced risk of incident disease[26,27], but Mendelian randomisation studies have yielded null results[31–34].

Observational studies investigating severe acute respiratory syndrome coronavirus 2 vaccine immunogenicity

Four observational studies have investigated associations between vitamin D status and SARS-CoV-2 vaccine immunogenicity. These have yielded conflicting results: two report higher post-vaccination titres of anti-spike antibodies in individuals using vitamin D supplements or having higher circulating 25(OH)D concentrations[37,38], but two others have yielded null findings[39,40].

Randomised controlled trials

RCTs in this field can be classified into three groups, according to whether they investigate (1) effects of therapeutic vitamin D in patients with established COVID-19; (2) effects of prophylactic vitamin D to reduce risk or severity of incident COVID-19 in healthy subjects or (3) effects of adjunctive vitamin D administered prior to SARS-CoV-2 vaccination to boost vaccine immunogenicity and efficacy (Fig. 1). Each is considered in turn next.

Randomised controlled trials of therapeutic vitamin D to reduce severity of coronavirus disease 2019

Table 1 summarises findings of twelve RCTs investigating therapeutic effects of vitamin D in patients with COVID-19 that have reported to date. They are diverse with respect to study design (five are placebo-controlled, seven are open-label or single-blind), sample size (ranging from 30 to 543 participants), the nature of the intervention [nine investigate vitamin D_3, two investigate 25(OH)D_3 and one investigates 1,25$(OH)_2D_3$] and primary outcomes (mortality, duration of hospital stay, intensive care requirement, resolution of symptoms and viral clearance). Their findings are also heterogeneous: eight trials report null results, while four report favourable effects of the intervention on a primary or co-primary outcome. Perhaps the most striking positive result comes from an open-label trial of oral 25(OH)D administration conducted in seventy-six adults hospitalised for treatment of COVID-19 in Spain, which reported that just 2 % of participants randomised to intervention were admitted to intensive care, as compared with 50 % of those randomised to control[41]. However, this study was at high risk of bias, due to imbalance in baseline characteristics and its open label design, since knowledge of allocation could have influenced physicians' decision to admit participants to intensive care. Moreover, background therapy (azithromycin and hydroxychloroquine) was unconventional, compromising generalisability of results to patients receiving current standards of care. The majority of larger well-conducted RCTs have not demonstrated sustained or consistent benefits of vitamin D on mortality, intensive care requirement or duration of hospital stay[42–45].

Randomised controlled trials of prophylactic vitamin D to reduce risk of incident coronavirus disease 2019

Two RCTs investigating effects of prophylactic vitamin D have also reported, with contrasting results. A phase 2 placebo-controlled RCT in 321 healthcare workers in Mexico, conducted before roll-out of SARS-CoV-2 vaccination, reported a strong protective effect of daily oral administration of 100 µg vitamin D_3 for 1 month against incident SARS-CoV-2 infection[46]. This finding surprised many, given that the duration of the intervention (1 month) was insufficient for participants in the intervention arm to experience a large increase in circulating 25(OH)D concentrations. By contrast, an open-label pragmatic phase 3 RCT in 6200 UK adults conducted during SARS-CoV-2 vaccine roll-out showed no effect of implementing a test-and-treat approach to correction of sub-optimal vitamin D status via daily oral administration of either 20 or 80 µg vitamin D_3 over 6 months[47]. Interpretation of this result is complicated by the pragmatic nature of this trial, which allowed for consumption of vitamin D supplements among participants randomised to its control arm; however, a sensitivity analysis excluding data from control arm participants who took off-trial supplements also yielded a null finding. Results from placebo-controlled phase 3 trials of prophylactic vitamin D and cod liver oil (clinicaltrials.gov refs NCT04609423, NCT04483635 and NCT04536298) are pending, and these should clarify whether vitamin D supplements can influence risk or severity of COVID-19.

Randomised controlled trials of pre- or peri-vaccination vitamin D to augment immunogenicity of severe acute respiratory syndrome coronavirus 2 vaccines

Three sub-studies nested within the CORONAVIT trial have investigated potential effects of vitamin D supplementation on SARS-CoV-2 vaccine efficacy and immunogenicity[48]. The first (*n* 2823) investigated effects of vitamin D supplementation on risk of breakthrough SARS-CoV-2 infection following two doses of SARS-CoV-2 vaccine. The second (*n* 1864) investigated effects of vitamin D supplementation on titres of combined immunoglobulin G, immunoglobulin A and immunoglobulin M anti-spike antibodies in eluates of dried blood spots collected after SARS-CoV-2 vaccination. The third (*n* 101) investigated effects of vitamin D supplementation on neutralising antibody and cellular responses in venous blood samples collected after SARS-CoV-2 vaccination. All yielded null results.

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Table 1. Randomised controlled trials of vitamin D_3 or its hydroxylated metabolites in the treatment of coronavirus disease 2019 (COVID-19)

Reference	Participants, setting	Intervention	Control (blinding)	Outcomes
Entrenas Castillo, J Ster, *Biochem Mol Biol*, 2020[41]	50 adults hospitalised with COVID-19, Spain	532 μg 25(OH)D_3 at d 0, then 236 μg at d 3, 7 and weekly thereafter	Nil (open label)	Proportion of participants requiring ICU: 2·0% *v.* 50·0% in intervention *v.* control arms ($P < 0·001$)
Rastogi, *Postgrad Med J*, 2020[49]	40 adults with mild COVID-19, India	1500 μg vitamin D_3 daily for 7 d	Placebo (double-blind)	Proportion of participants RT-PCR-negative for SARS-CoV-2 by week 3: 62·5% *v.* 20·8% in intervention *v.* control arms ($P = 0·018$)
Caballero-García, *Medicina*, 2021[50]	30 adults recovering from COVID-19, Spain	50 μg vitamin D_3 daily for 6 weeks	Placebo (double-blind)	Spirometric lung volumes, 6-min walk test: no difference between intervention *v.* control arms
Maghbooli, *Endocrine Pract*, 2021[51]	106 adults hospitalised with COVID-19, Iran	25 μg 25(OH)D_3 daily for 60 d	Placebo (double-blind)	Median length of hospital stay: 5 *v.* 6 d in intervention *v.* control arms ($P = 0·10$)
Murai, *JAMA*, 2021[42]/Fernandes, *AJCN*, 2022[52]/Murai, *Clinics Sao Paolo*, 2021[53]	240 adults hospitalised with COVID-19, Brazil	Single dose of 5000 μg vitamin D_3	Placebo (double-blind)	Median length of hospital stay: 7·0 *v.* 7·0 d in intervention *v.* control arms ($P = 0·59$). No influence of intervention on circulating cytokine concentrations
Sabico, *Nutrients*, 2021[54]	69 adults hospitalised with mild/moderate COVID-19, Saudi Arabia	125 μg vitamin D_3 daily for 2 weeks	25 μg daily for 2 weeks (open label)	Resolution of 11 symptoms: more rapid resolution of cough and ageusia in intervention *v.* control arms ($P \leq 0·035$); no difference for other nine symptoms investigated
Sanchez-Zuno, *J Clin Med*, 2021[55]	42 adults with mild COVID-19, Mexico	250 μg vitamin D_3 daily for 14 d	Nil (open label)	Proportion reporting symptoms at 7- and 14-d follow-up: no difference between intervention *v.* control arms ($P \geq 0·22$)
Annweiler, *PLoS Med*, 2022[43]	254 older adults with moderate/severe COVID-19, France	Single dose of 10 000 μg vitamin D_3	Single dose of 1250 μg vitamin D_3 (open label)	Mortality: reduced in intervention *v.* control arm at 14-d follow-up (aHR 0·39, 95% CI 0·16, 0·99), no different at 28-d follow-up (aHR 0·70, 95% CI 0·36, 1·36)
Cannata-Andia, *BMC Med*, 2022[44]	543 adults hospitalised with moderate/severe COVID-19, Spain	Single dose of 2500 μg vitamin D_3	Nil (open label)	Median length of hospital stay: 10·0 *v.* 9·5 d in intervention *v.* control arms ($P = 0·19$)
Elamir, *Bone*, 2022[56]	50 adults hospitalised with COVID-19, USA	0·5 μg 1,25(OH)$_2D_3$ daily during hospital admission (up to 14 d)	Nil (open label)	Median length of hospital stay: 5·5 *v.* 9·2 d in intervention *v.* control arms ($P = 0·14$)
Mariani, *PLoS One*, 2022[45]	218 adults hospitalised with mild/moderate COVID-19, Argentina	Single dose of 12 500 μg vitamin D_3	Placebo (double-blind)	Median change in respiratory sepsis-related organ failure assessment score between baseline and d 7: 0·0 *v.* 0·0. in intervention *v.* control arms ($P = 0·93$)
Torres, *Biomed Pharm*, 2022[57]	85 adults hospitalised with COVID-19, Spain	250 μg vitamin D_3 daily for 14 d	50 μg vitamin D_3 daily for 14 d (single-blind)	Median length of hospital stay: 6·4 *v.* 9·4 d in intervention *v.* control arms ($P > 0·05$)

1,25(OH)$_2D_3$, calcitriol; 25(OH)D_3, calcidiol; aHR, adjusted hazard ratio; ICU, intensive care unit; RT-PCR, reverse transcription PCR.

Conclusions

A substantial body of evidence relating to potential effects of vitamin D on risk and severity of COVID-19 has accumulated since the start of the COVID-19 pandemic. Laboratory investigations have demonstrated potential mechanisms by which $1,25(OH)_2D$ may favourably modulate host responses to SARS-CoV-2, and meta-analyses of data from cross-sectional, case-control and longitudinal studies have reported consistent associations between lower vitamin D status and increased risk or severity of COVID-19. By contrast, Mendelian randomisation studies testing for associations between genetically predicted circulating 25(OH)D concentrations and COVID-19 outcomes have yielded null results, raising the possibility that positive findings from observational epidemiological studies may have arisen because of reverse causality or confounding. RCTs of vitamin D for the treatment or prevention of COVID-19 reporting to date have not yielded consistent evidence of benefit. Results of further trials are awaited, but current evidence is insufficient to support the use of vitamin D supplements for prevention or treatment of COVID-19.

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Conflicts of Interest

A. R. M. declares receipt of funding in the past 36 months to support vitamin D research from companies that manufacture or sell vitamin D supplements (Pharma Nord Ltd, DSM Nutritional Products Ltd, Thornton & Ross Ltd and Hyphens Pharma Ltd); receipt of vitamin D capsules for clinical trial use from Pharma Nord Ltd, Synergy Biologics Ltd and Cytoplan Ltd; support for attending meetings from companies that manufacture or sell vitamin D supplements (Pharma Nord Ltd and Abiogen Pharma Ltd); receipt of a consultancy fee from DSM Nutritional Products Ltd; receipt of a speaker fee from the Linus Pauling Institute; participation on Data and Safety Monitoring Boards for the VITALITY trial (Vitamin D for Adolescents with HIV to reduce musculoskeletal morbidity and immunopathology, Pan African Clinical Trials Registry ref PACTR20200989766029) and the Trial of Vitamin D and Zinc Supplementation for Improving Treatment Outcomes Among COVID-19 Patients in India (Clinical-Trials.gov ref NCT04641195); and unpaid work as a Programme Committee member for the Vitamin D Workshop.

Authorship

The author had sole responsibility for all aspects of preparation of the present paper.

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