Abstract. Subramanian S, Griffin G, Hewison M, Hopkin J, Kenny RA, Laird E, et al. Vitamin D and COVID-19—Revisited. J Intern Med. 2022;292:604–626.

Vitamin D, when activated to 1,25-dihydroxyvitamin D, is a steroid hormone that induces responses in several hundred genes, including many involved in immune responses to infection. Without supplementation, people living in temperate zones commonly become deficient in the precursor form of vitamin D, 25-hydroxyvitamin D, during winter, as do people who receive less sunlight exposure or those with darker skin pigmentation. Studies performed pre-COVID-19 have shown significant but modest reduction in upper respiratory infections in people receiving regular daily vitamin D supplementation. Vitamin D deficiency, like the risk of severe COVID-19, is linked with darker skin colour and also with obesity. Greater risk from COVID-19 has been associated with reduced ultraviolet exposure. Various studies have examined serum 25-hydroxyvitamin D levels, either historical or current, in patients with COVID-19. The results of these studies have varied but the majority have shown an association between vitamin D deficiency and increased risk of COVID-19 illness or severity. Interventional studies of vitamin D supplementation have so far been inconclusive. Trial protocols commonly allow control groups to receive low-dose supplementation that may be adequate for many. The effects of vitamin D supplementation on disease severity in patients with existing COVID-19 are further complicated by the frequent use of large bolus dose vitamin D to achieve rapid effects, even though this approach has been shown to be ineffective in other settings. As the pandemic passes into its third year, a substantial role of vitamin D deficiency in determining the risk from COVID-19 remains possible but unproven.

Keywords: COVID-19, vitamin D

Introduction

It was recognised early during the COVID-19 pandemic that many of the phenotypic markers of poor prognosis were also known correlates of vitamin D deficiency [1]. Obesity and darker skin colour both associate with increased risk of vitamin D deficiency. Old age is the strongest risk factor for poor COVID-19 prognosis, to a much greater extent than seen with other viral pandemics such as influenza. Although old age is not itself consistently associated with increased risk of vitamin D deficiency, living in a care home certainly is, unless the residents get out in the summer sunshine—which is almost never the case in UK care settings—or receive regular vitamin D supplements. Similarly, incarceration in prison is also associated with increased risk for vitamin D deficiency, although the England & Wales Prison Service did begin offering daily vitamin D 25 micrograms to its inmates from September 2020. It is almost impossible to obtain sufficient vitamin D from dietary sources alone, and most vitamin D is derived from synthesis in the skin by the action of ultraviolet B (UVB; wavelength 315–280 nm), which breaks a carbon-to-carbon bond in the 7-hydroxycholesterol precursor. UVB is largely removed during passage through the earth’s ozone layer, and also by particulate air pollution, so vitamin D can only be synthesised when the sun is high in the sky. In the Northern Hemisphere at more than 35 degrees
latitude, sufficient UVB for vitamin D synthesis can only be obtained under cloudless skies during the late morning and early afternoon from March to September, and deficiency becomes increasingly common as winter progresses.

After synthesis in the skin, vitamin D undergoes two metabolic conversions. The first, which occurs mainly in the liver, produces 25-hydroxyvitamin D (25[OH]D), the main circulating form of vitamin D and the metabolite of vitamin D that is most commonly measured in laboratories around the world. However, 25[OH]D is an inactive form of vitamin D that requires further metabolism to produce 1,25-dihydroxyvitamin D (1,25[OH]2D), a secosteroid hormone that acts by binding to ubiquitous nuclear vitamin D receptors (VDR) that regulate gene transcription. Gene promoter vitamin D response elements for the 1,25[OH]2D-VDR complex are found in around 5% of genes in the human genome. There is extensive in vitro and in vivo evidence for a role of 1,25[OH]2D in the regulation of both innate and adaptive immune responses to bacterial and viral infection [2]. Circulating levels of 1,25[OH]2D are dependent on the metabolism of 25[OH]D by the kidney, but within the immune system 1,25[OH]2D can be synthesised by cells such as macrophages and dendritic cells. Localised vitamin D metabolism is then able to drive antimicrobial innate immunity in an intracrine fashion depending on the availability of 25[OH]D for conversion to 1,25[OH]2D and may thus be compromised in the setting of vitamin D deficiency [3]. Beyond antimicrobial actions, 1,25[OH]2D also promotes potent anti-inflammatory effects on T lymphocytes (T cells) that protect against possible tissue damage following infection. This was initially thought to involve a paracrine effect via 1,25[OH]2D synthesised by macrophages or dendritic cells but recent studies of T cells from patients with COVID-19 have shown that T cells themselves are able to convert 25[OH]D to 1,25[OH]2D [4]. As a result, it now appears that anti-inflammatory adaptive immunity is also dependent on 25[OH]D availability and will therefore be compromised under conditions of vitamin D deficiency.

A causal association between vitamin D deficiency and the risk or severity of COVID-19 is therefore entirely plausible. It has, however, been pointed out by government advisory bodies such as the UK National Institute for Health and Care Excellence (NICE) that the evidence supporting a role of vitamin D is mainly circumstantial and lacks the high-quality randomised control trial evidence nowadays regarded as essential to justify therapeutic interventions. NICE has concluded that clinicians should not ‘offer a vitamin D supplement to people solely to prevent COVID-19, except as part of a clinical trial’ and that ‘Randomised controlled trials in all care settings with a minimum 8-week follow up are recommended’ [5]. Consequently, governmental messaging advocating avoidance of vitamin D deficiency in winter has been muted. However, at the time of writing, we are well over 24 months into the pandemic and large, high-quality randomised trials of vitamin D supplementation have yet to be published. There are several reasons for this. Randomised controlled trials (RCTs) of vitamins or hormones are very hard to perform, partly because supplementation is unlikely to have any benefit in people who are already replete. The ‘ideal’ study would recruit people with known vitamin deficiency and then ask them to be randomised to vitamin supplement or placebo, but this is unethical as anyone with vitamin D deficiency should routinely be supplemented. Studies are therefore comparing high-dose vitamin D with a low dose as a control, but there is good evidence that a regular daily low-dose supplement, up to 1000 IU or 25 micrograms per day, may be at least as effective and possibly more effective than a higher dose at reducing risk for respiratory infection [6]. Perhaps because nutrition research is currently less ‘fashionable’ than other research areas such as genetic engineering or systems biology, it has also proven difficult to obtain funding for trials of vitamins. The Wellcome Trust/Bill Gates/Mastercard COVID-19 Therapeutics Accelerator fund, which has generated around 125 million US dollars towards COVID research, expressly excluded vitamin research as ‘out of scope’ from funding [7]. Consequently, it is quite likely that we will never obtain high-quality RCT evidence to support or refute the role of vitamin D in determining COVID-19 outcomes. This does not mean though that there is no evidence worth considering, particularly given that vitamin D deficiency is very common and easily preventable and that vitamin D supplementation is extremely cheap, very safe unless taken in great excess and anyway likely to have beneficial effects on bone health in many individuals.

The associations between vitamin D status and COVID-19 prognostic factors were reviewed previously in this journal [1] and the interactions of vitamin D with the immune system have also been.
thoroughly reviewed elsewhere [8]. The present review, therefore, focuses on evidence published since the start of the pandemic for/against an effect of vitamin D status in determining the infection risk and severity of COVID-19.

**Methods**

This is a narrative review but informed by a PubMed literature search that included as search terms ‘COVID-19 and vitamin D’ and with emphasis on reports published since January 2021.

**Seasonality, associations between latitude, UV exposure and COVID-19 outcomes**

SARS-CoV-2, the causative organism of COVID-19, is a coronavirus and coronaviruses, like other respiratory viruses such as influenza and respiratory syncytial virus, tend to be seasonal [9]. Although COVID-19 infections have been prevalent throughout the year, there is good evidence for an impact of seasonality on the risk for infection and severity [10]. The mechanisms underlying seasonality are not clearly understood but one possible factor is UV light exposure, acting either via vitamin D synthesis or by some other effect such as direct viral killing on sun-exposed surfaces. In contrast, changes in temperature and humidity do not appear to have an impact consistently.

It was noticed early in the pandemic that there was an association between latitude and COVID-19 mortality. Although much of this could be accounted for by the relatively low average age of populations living close to the equator, a significant association between latitude and COVID-19 mortality per head of population remained after adjustment for this [11]. Further studies have looked in more detail at the impact of UV exposure on COVID-19 risk. Most, but not all, studies have shown a significant negative association [12].

A study of 417,342 participants from the UK Biobank cohort found that ambient UVB, measured over the previous 135 days, although not associated with COVID-19 infection risk, was strongly and inversely associated with hospitalisation (p < 2 x 10^-16) and death (p < 2 x 10^-16) in a multivariable analysis that adjusted for various factors including age, gender and BMI. Median UVB (kJ/m²) in those who died (43.09, interquartile range [IQR] 31.89–74.10) was less than half that in those with COVID-19 not requiring hospital admission (90.89, IQR 67.43–98.95) [13].

A study based on the large US Nurses Health cohort had similar findings. Data from 39,315 participants in periodic studies within Nurses Health II from May 2020 to March 2021 showed that participants in the highest quartile for annual UVB exposure based on the state of residency had a lower risk of SARS-CoV-2 infection compared with the lowest quartile (multivariable-adjusted odds ratio [OR] 0.76, 95% confidence intervals [CI] 0.66, 0.87; p-trend 0.002) [14] (Fig. 1). Winter-time UVA (400–315 nm) exposure, which would not induce vitamin D synthesis, also showed a similar size effect (OR 0.76, 95% CI 0.66, 0.88; p-trend <0.001), but this was not adjusted for annual UVB exposure, with which it was likely associated. A separate study, also performed in the United States, has, however, also shown an association between winter UVA exposure and reduced COVID-19 mortality, thought possibly to be mediated via cutaneous release of nitric oxide [15].

Nationwide and global studies have also investigated associations between UV exposure and COVID-19 infection rates. A study of SARS-CoV-2 transmission from March to December 2020 across 2669 US counties calculated that the fractions of the SARS-CoV-2 reproduction number (R_t) attributable to cold temperature, reduced specific humidity and lower UV radiation were 3.73%, 9.35% and 4.44%, respectively. UVB and UVA were not separately measured [16].

A global analysis conducted up until late April 2020 estimated the daily reproduction number at 3739 global locations and found a significant negative association with higher temperature (>27.5°C) and a U-shaped relationship with outdoor UV exposure [17]. Another study performed over approximately the same time period included data from 3235 regions across 173 countries [18]. No association was found between COVID-19 growth rates and either temperature or humidity but there was again a significant negative association with UV radiation. A one standard deviation (SD) increase in ambient UV was accompanied by approximately a one percentage point reduction in daily growth rate over the subsequent 2.5 weeks compared with an average growth rate of 13.2%. A direct effect of UV on the virus in the environment is likely but the time scale of the response, peaking in magnitude after 9–11 days, is also compatible with vitamin D synthesis and subsequent activation in response to dermal UV exposure.
Vitamin D status as a possible explanation for differing national mortalities from COVID-19

There are marked differences in COVID-19 mortality between countries and many of these cannot be accounted for by latitude or the age of the population. There are of course many other possible determinants of COVID-19 outcome including vaccine availability and uptake, government responses affecting social distancing and mask wearing, ethnicity, deprivation and population density. Moreover, latitude is not the only determinant of vitamin D status. Cloud cover, atmospheric pollution, supplementation, fortification, clothing and social customs and occupations impacting on sunlight exposure will all have an impact. It was noted early in the pandemic that there was some correlation between COVID-19 mortality by country and
historical vitamin D status [19]. A more recent study across 47 European and Asian countries has confirmed this association (r = 0.35; p = 0.016) [20].

Several of the Nordic countries have impressively low COVID-19 mortalities and a recent estimation of overall excess mortality rates during the pandemic supports this [21]—in Iceland, excess mortality per 100,000 is (minus)47.8 (95% uncertainty intervals −107.1 to 1.6), Norway 7.2 (−0.0 to 15.9) and Finland 80.8 (66.2–94.0) in comparison with the much higher excess mortalities seen in the UK, 126.8 (122.3–130.9), and across Western Europe as a whole, 140.0 (133.5–146.3). Even before the pandemic, Norwegians maintained healthy vitamin D levels through a high intake of vitamin D, either through regular daily consumption of a teaspoonful of cod liver oil, other vitamin D supplements, fortification of dairy products or frequent consumption of oily fish. Blood levels of vitamin D in Norwegians consequently have been shown to vary relatively little from the end of winter (average 58 nmol/L) to the end of summer (average 69 nmol/L) [22] whereas in the UK, average blood levels in White men fall by about 50% from their peak (average 70 nmol/L) in September to a low point in February at an average of around 35 nmol/L—well below the 50 nmol/L ‘sufficiency’ level and dangerously close to the 25 nmol/L ‘severe deficiency’ level [23]. Icelanders, like Norwegians, have a strong tradition of supplementing vitamin D to prevent deficiency in winter [24] and have an even lower COVID-19 mortality. In Finland, an active policy of food fortification with vitamin D has led to a massive improvement in vitamin D status in recent years [25].

Some countries close to the Equator have suffered high COVID-19 mortalities. These include, particularly, countries in central and southern America such as Peru, with an estimated excess mortality of 528.6 (497.5–556.4), Brazil 186.9 (172.2–199.8), and Ecuador 333.4 (315.1–348.0) [21]. Perhaps surprisingly, these countries do, however, have quite high rates of vitamin D deficiency (defined here as <50 nmol/L). A study of teenagers in Peru found that 28% were vitamin D deficient and a smaller study in Peruvian adults performed in June 2016 reported deficiency in 46% of 144 adults from an impoverished community [26]. A study of 2374 older adults living in Ecuador showed that 22% were vitamin D deficient, particularly those living in mountainous regions [27]. Similarly, a study of 39,004 Brazilians of all ages found deficiency in 34% with marked seasonal variation [28].

Relevance of vitamin D status to immune function—Evidence from COVID-19

As outlined earlier in this review, studies published before the pandemic have extensively documented interactions between vitamin D and the immune system. These are reviewed at length elsewhere [1, 8]. VDR are ubiquitously expressed by immune cells and their effects include downregulation of inflammatory cytokines, induction in macrophages and epithelial cells of the antimicrobial peptide cathelicidin and promotion of differentiation of regulatory T cells. Vitamin D also induces expression of angiotensin-converting enzyme 2 (ACE2), the SARS-CoV-2 receptor. This is particularly relevant since ACE2, by hydrolysing angiotensin II, has a protective effect against the development of acute respiratory distress syndrome. In experimental mouse models of lung damage, vitamin D deficiency or VDR knockout both result in greatly increased lung damage in response to intratracheal bacterial lipopolysaccharide [1].

A set of key experiments performed on bronchoalveolar lavage T cells from patients with severe COVID-19 has provided direct evidence for the relevance of vitamin D to immune defence against SARS-CoV-2 [4]. In these studies, single-cell RNA sequencing of COVID-19 pulmonary T-helper T cells showed upregulation of genes that regulate type 1 T helper (T H1) cells that are likely to be pro-inflammatory and also showed derepression of genes normally downregulated by vitamin D. Addition of either 1,25(OH)2D or 25(OH)D repressed interferon gamma production and induced the anti-inflammatory cytokine IL-10. The efficacy of 25(OH)D, as well as 1,25(OH)2D, in achieving this confirmed the ability of the activated T cells to synthesise their own 1,25(OH)2D from 25(OH)D and suggested that this effect is likely to be impaired in subjects with vitamin D (25(OH)D) deficiency. The authors also noted that corticosteroids such as dexamethasone could induce expression of VDR and speculated that there could be a beneficial synergistic interaction between dexamethasone and vitamin D.

Recent studies have also examined the relationship between the immune response to SARS-CoV-2 vaccination and serum 25(OH)D levels with contradictory results. In a cohort of healthy German adults,
SARS-CoV-2 IgG antibody responses and neutralisation potency along with 25(OH)D concentrations were analysed for 24 weeks from the time of vaccination [29]. No significant differences were found in the dynamic increase or decrease of SARS-CoV-2 IgG as a function of 25(OH)D status. In contrast, a study of UK healthcare workers reported that antibody response to immunisation was significantly affected by vitamin D status with a 29.3% greater peak antibody response in individuals with 25(OH)D >50 nmol/L [30].

Identifying the optimal blood concentrations and supplement dosing strategy for vitamin D

Before considering the evidence linking vitamin D status with COVID-19 outcomes, it is necessary to understand what constitutes a healthy vitamin D status and what is likely to be an effective form of supplementation to prevent the consequences of deficiency. Regrettably, these questions do not have unequivocal answers.

Vitamin D status is usually assessed by measuring blood levels of 25(OH)D. This is because blood levels of the fully activated 1,25(OH)2D are too low to be easily measured; moreover, many cells, including most immune cells, express the 1α-hydroxylase (1α-hydroxylase) enzyme that produces 1,25(OH)2D and are therefore able to complete activation of vitamin D independent of the circulating levels of 1,25(OH)2D. It is important to remember that 1,25(OH)2D is a steroid hormone. It follows that too much vitamin D, as well as too little, is likely to be harmful and, whilst hypercalcaemia is an easily diagnosed and well-recognised consequence of extreme vitamin D toxicity, there might be other much subtler consequences of too much vitamin D. It is frustrating that a 100 years on from the discovery of vitamin D, there is still disagreement about both the lower and higher limits of a healthy blood 25(OH)D concentration. There is a reasonably strong consensus that 50 nmol/L is an appropriate lower limit. This is supported by the US Institute of Medicine and by the European Union Food Safety Authority [31]. The UK Scientific Advisory Committee on Nutrition has set a lower limit of 25 nmol/L, albeit without clearly documented evidence to support this and there are many published cases of the bone disease rickets with blood 25(OH)D levels between 25 and 50 nmol/L [32]. The US Endocrine Society has set a higher threshold of 75 nmol/L for sufficiency, by which standard a majority of the world’s population would be judged insufficient. This higher level is based partly on the relationship between 25(OH)D levels and parathyroid hormone concentration as well as calcium absorption, and also on post-mortem studies of relationships between 25(OH)D and the presence of uncalcified osteoid suggesting that plateauing of its effect may not occur until 25(OH)D concentration reaches at least >75 nmol/L [33, 34]. The US Institute of Medicine concluded that there was insufficient clinical evidence of benefit above 75 nmol/L. It also set an upper level of 125 nmol/L, above which there was ‘reason for concern’ [31], although levels in excess of this are regularly achieved in populations having high sunlight exposure to bare skin such as beach lifeguards and traditional herders.

There is also controversial literature (pre-COVID-19) suggesting a possible ‘U-shaped’ (or ‘reverse-J’) curve for the relationship between blood 25(OH)D levels and clinical outcomes, most importantly all-cause mortality. A Danish community-based study of 247,574 subjects found a reverse J-shaped association between blood 25(OH)D and all-cause mortality, with the lowest mortality for those at 50–60 nmol/L, although arguably their data could be interpreted as showing low mortality across a broader optimal range of 50–75 nmol/L [35] (Fig. 2). A study of 24,094 hospital in-patients from Boston, United States, showed a U-shaped relationship between prehospitalization 25(OH)D and 90-day all-cause mortality but inferred a much broader optimal range of 25(OH)D 50–150 nmol/L [36]. An individual participant data meta-analysis across 26,916 individuals from eight European prospective studies also showed increased all-cause mortality below 50 nmol/L but no significant increase at high levels up to 125 nmol/L [37]. Similarly, a study of 365,530 participants in the UK Biobank cohort showed no evidence of a U-shaped curve for serum 25(OH)D and all-cause mortality [38].

Optimum dosing regimens for vitamin D supplementation will depend on the target 25(OH)D blood level. The UK SACN recommendation of 400 IU/day for adults in the winter months aims to ensure that at least 97.5% of the population receiving this will attain a blood level of at least 25 nmol/L [39]. If, however, the more widely accepted target level of at least 50 nmol/L is chosen, then a higher daily dose, for example, 600–800 (for the elderly) IU/day as recommended by the US Institute of Medicine [31], is needed and some data
would suggest a slightly higher dose still, around 1000 IU/day [40]. This assumes a ‘one dose fits all’ policy, which would be much cheaper than tailored dosing according to blood 25(OH)D measurements, although it has been pointed out that it might imply reaching an average 25(OH)D level of 90 nmol/L to ensure that almost all supplemented people achieve >50 nmol/L [31]. Obesity is a major factor determining the need for a higher regular dose to achieve sufficiency. The mechanisms behind obesity negatively affecting serum 25(OH)D are not well defined but both sequestration of vitamin D in fat stores and reduced hepatic 25-hydroxylation have been suggested as possible explanations [1].

An even more important issue than the size of dose is that of daily dosing versus intermittent ‘bolus’ dosing. In recent years, intermittent high-dose bolus supplementation of vitamin D, without intervening maintenance dosing, has gained traction, both in routine clinical practice and in RCTs. Bolus replacement achieves satisfactory blood levels of 25(OH)D without obvious toxicity [41]. There is, however, growing evidence, now substantial, that this strategy is probably ineffective or even
Vitamin D and COVID-19 / S. Subramanian et al.

Vitamin D status and COVID-19 outcomes—Hospital studies

There has been much interest in the possible benefits of vitamin D supplementation and normalisation of serum 25(OH)D levels with respect to its antimicrobial effects and risk of COVID-19 infection. In this context, vitamin D can be viewed as a nutritional factor for improving ‘immune health’ in the general population. However, vitamin D supplementation may also have therapeutic applications that are more consistent with its use as a drug rather than a nutrient. Several studies have examined the association between serum 25(OH)D concentrations and COVID-19 outcomes in hospitalised patients. There is wide heterogeneity among these studies in various aspects, including study design, time of sample draw, definition of end points and sample size. Among studies with ≥200 subjects and with in-hospital mortality as the endpoint, a majority show an association between low serum 25(OH)D and increased mortality from COVID-19 (Table 1). This is in keeping with the result of a recent systematic review that included 13 observational studies [49].

Serum 25(OH)D has been reported to be a negative acute phase reactant and thus a low 25(OH)D might be more likely in a severe disease of any etiology. Controlled studies in calves infected with bovine diarrhoea virus showed that serum 25(OH)D levels fell by 57% during the acute phase response to illness [81] and similar falls, albeit of lower magnitude, have been documented in humans although generally in the context of invasive procedures, for example, following orthopaedic surgery and acute pancreatitis [82]. There is a biological explanation as the majority of 25(OH)D is bound to serum vitamin D binding protein (DBP) and albumin, both of which fall in acute illnesses. Measurement of unbound or free 25(OH)D has been suggested as a more accurate marker of 25(OH)D status, analogous to free thyroid hormones (although it remains contentious whether free testosterone is physiologically more relevant than total concentration). Two recent studies from the UK investigated the correlation between free 25(OH)D and mortality. In a multicentre study of 295 hospitalised patients from the UK, a correlation was noted between both total and directly measured free 25(OH)D and receipt of in-hospital mechanical ventilation [72]. However, in a larger study from two acute hospitals, performed by some of the authors of the present review, we did not find a correlation between computed free 25(OH)D and in-hospital mortality [80]. However, a total serum 25(OH)D of <25 nmol/L was associated with in-hospital mortality when assessed by quartiles. An increase in mortality was also seen in those with high levels (>100 nmol/L), suggesting a possible U-shaped relationship; however, this was not significant when 25(OH)D was analysed as a continuous variable (Fig. 3). In this study, the negative acute phase effect seemed modest as mean serum 25(OH)D concentration was approximately 50 nmol/L at CRP <5 mg/L compared with approximately 40 nmol/L at a median CRP of 200 mg/L.

Definitions of vitamin D deficiency and the validity of supplementation dosing regimens therefore need to be taken carefully into account when assessing the results of studies investigating a role of vitamin D in determining COVID-19 outcomes. The case can be made for excluding from meta-analysis all studies reporting a pure intermittent bolus regimen (rather than single bolus for rapid normalisation of serum levels followed by daily maintenance).

© 2022 The Association for the Publication of the Journal of Internal Medicine.
Journal of Internal Medicine, 2022, 292; 604–626

Some evidence comes from a negative RCT of bolus vitamin D (100,000 IU every 3 months) to prevent rickets in children [43]. A recent RCT of 6-weekly bolus vitamin D also showed no benefit in healing radius fractures in post-menopausal women and some evidence of a detrimental effect on bone stiffness in those receiving the higher bolus dose of 75,000 IU every 6 weeks [44]. This adds to negative trials of bolus vitamin D supplementation in tuberculosis [45], and, most relevantly, in acute respiratory infections [46]. The most recent meta-analysis of vitamin D supplementation in the prevention of acute respiratory infections has not only shown that intermittent bolus, whether weekly or less frequently, is ineffective but that daily doses of >1000 IU/day are also ineffective [6]. There is a plausible biological explanation for why bolus and/or high dose vitamin D may not be effective: not only will transiently high levels of 25(OH)D induce the inhibitory, catabolic enzyme vitamin D-24-hydroxylase CYP24A1, which may persist for several weeks after the 25(OH)D has fallen, but they are also likely to induce fibroblast growth factor 23 (FGF23), which can then suppress the activating enzyme 1α-hydroxylase in both renal [46] and extrarenal tissues [47]. Blood 25(OH)D levels of >100 nmol/L are likely to result in significant increase in FGF23 [48].
| Author and year | Location | Study design | N  | Direction of association | Key findings                                                                 |
|----------------|----------|--------------|----|--------------------------|-------------------------------------------------------------------------------|
| Maghbooli et al., 2020 [50] | Iran | Cross-sectional study | 235 | ↑ | Serum 25(OH)D (>30 ng/ml or 75 nmol/L) associated with decreased severity and mortality from COVID-19 |
| Luo et al., 2021 [51] | China | Retrospective cohort study | 335 | ↑ | Low serum 25(OH)D (<30 nmol/L) associated with increased severity of COVID-19 |
| Alguwaihes et al., 2020 [52] | Saudi Arabia | Cross-sectional study | 439 | ↑↑ | Low serum 25(OH)D (<12.5 nmol/L) associated with increased mortality |
| Hutchings et al., 2021 [53] | Armenia | Cross-sectional study | 330 | ↔ | No association between serum 25(OH)D and COVID-19 severity or mortality |
| Gavioli et al., 2021 [54] | USA | Retrospective cohort study | 437 | ↑ | Low serum 25(OH)D (<20 ng/ml or 50 nmol/L) associated with increased need for oxygen support but not mortality from COVID-19 |
| Basaran et al., 2021 [55] | Turkey | Retrospective cohort study | 204 | ↑ | Low serum 25(OH)D associated (<20 ng/ml) with increased severity of COVID-19 |
| Mazzioti et al., 2021 [56] | Italy | Retrospective cohort study | 348 | ↔ | Low serum 25(OH)D (<12 ng/ml or 30 nmol/L) associated with increased hypoxic respiratory failure, but not mortality |
| Charoenngam et al., 2021 [57] | USA | Retrospective cohort study | 287 | ↑↑ | Serum 25(OH)D >30 ng/ml or 75 nmol/L associated with decreased mortality in patients >65 or those with Body Mass Index (BMI) <30 kg/m² |
| Jevalikar et al., 2021 [58] | India | Cross-sectional study | 410 | ↔ | No association between serum 25(OH)D and COVID-19 severity or mortality |
| Tehrani et al., 2021 [59] | Iran | Cross-sectional study | 205 | ↑ | No association between serum 25(OH)D and COVID-19 mortality except in severe disease |
| Osman et al., 2021 [60] | Oman | Cross-sectional study | 329 | ↔ | No association between serum 25(OH)D and COVID-19 mortality |
| Nasiri et al., 2021 [61] | Iran | Retrospective cohort study | 329 | ↑ | Insufficient serum 25(OH)D (20–30 ng/ml) associated with increased length of stay, but not mortality |

(Continued)
| Author and year                  | Location | Study design          | N   | Direction of association | Key findings                                                                                                                                                                                                 |
|---------------------------------|----------|-----------------------|-----|--------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Reis et al., 2021 [62]          | Brazil   | Retrospective cohort study | 220 | ↔                        | No association between serum 25(OH)D and length of stay, COVID-19 severity or mortality                                                                                                                       |
| AlSafar et al., 2021 [63]       | UAE      | Cross-sectional study | 464 | ↑↑                       | Low serum 25(OH)D (<12 ng/ml) associated with increased COVID-19 severity, Intensive Therapy Unit (ITU) admission and mortality                                                                                     |
| Diaz-Curiel et al., 2021 [64]   | Spain    | Cross-sectional study | 1549| ↑                        | Serum 25(OH)D as a continuous variable was independently associated with ITU admission but not mortality                                                                                                     |
| Al-Jarallah et al., 2021 [65]   | Kuwait   | Cross-sectional study | 231 | ↔                        | No association between serum 25(OH)D and increased COVID-19 mortality                                                                                                                                       |
| Guven and Gultekin, 2021 [66]   | Turkey   | Retrospective cohort study | 520 | ↔                        | No association between serum 25(OH)D and COVID-19 mortality                                                                                                                                             |
| Bianconi et al., 2021 [67]      | Italy    | Cross-sectional study | 200 | ↔                        | No association between serum 25(OH)D COVID-19 severity or mortality                                                                                                                                       |
| Shakeri et al., 2022 [68]       | Iran     | Cross-sectional study | 293 | ↔                        | No association between serum 25(OH)D and mortality                                                                                                                                                    |
| Vasheghani et al., 2021 [69]    | Iran     | Retrospective cohort study | 508 | ↑↑                       | Low serum 25(OH)D associated with increased COVID-19 severity, ITU admission and mortality                                                                                                               |
| Afaghi et al., 2021 [70]        | Iran     | Retrospective cohort study | 646 | ↑↑                       | Low serum 25(OH)D associated with increased mortality                                                                                                                                                    |
| Freitas et al., 2021 [71]       | Portugal | Cross-sectional study | 491 | ↑↑                       | Low serum 25(OH)D (<20 ng/ml) associated with increased COVID-19 severity and mortality                                                                                                                   |
| Hurat et al., 2021 [72]         | UK       | Cross-sectional study | 295 | ↑↑                       | Low serum 25(OH)D associated with invasive mechanical ventilation (19.6 vs. 31.9 nmol/L) and increased mortality (23.2 vs. 29.5 nmol/L)                                                                         |
| Ramirez-Sandoval et al., 2021 [73] | Mexico | Retrospective cohort study | 290 | ↑↑                       | Low serum 25(OH)D (<12.5 ng/ml) associated with increased in-hospital mortality                                                                                                                         |
| Derakhshanian et al., 2021 [74] | Iran     | Retrospective cohort study | 290 | ↑↑                       | Serum 25(OH)D levels (<20 ng/ml) associated with increased death and ITU admission rates but not mechanical ventilation                                                                                  |

(Continued)
### Table 1. Continued

| Author and year                      | Location | Study design         | N    | Direction of association | Key findings                                                                                       |
|--------------------------------------|----------|----------------------|------|--------------------------|---------------------------------------------------------------------------------------------------|
| Seven et al., 2021 [75]              | Turkey   | Retrospective cohort study | 403  | ↑                        | Serum 25(OH)D levels (<14.5 ng/ml) independently associated with increased severity in pregnant COVID-19 patients |
| Apaydin et al., 2021 [76]            | Turkey   | Retrospective cohort study | 219  | ↔                        | No association between serum 25(OH)D levels and COVID-19 severity, Intensive Care Unit (ICU) admission or mortality |
| Hernandez et al., 2021 [77]          | Spain    | Case-control study    | 216  | ↔                        | No association between categorical or continuous 25(OH)D levels and COVID-19 mortality             |
| Jenei et al., 2022 [78]              | Hungary  | Retrospective cohort study | 257  | ↑↑                       | Serum 25(OH)D levels independently associated with increased mortality in >60-year olds (30 ± 12 in the deceased compared to 21 ± 13 nmol/L in the recovered group) |
| Juraj et al., 2022 [79]              | Slovakia | Retrospective cohort study | 357  | ↑↑                       | Serum 25(OH)D levels (<12 ng/ml or 30 nmol/L) independently associated with increased mortality |
| Subramanian et al., 2022 [80]        | UK       | Retrospective cohort study | 472  | ↑↑                       | Serum 25(OH)D <25 nmol/L and >100 nmol/L associated with increased mortality (when assessed by quartiles but not significant as continuous variable) |

**Note:** We included studies with a sample size of more than 200 subjects and an outcome of in-hospital mortality. Studies with a sample size lesser than 200 or not including mortality as endpoint were excluded. ↑ represents increased severity of COVID-19 in patients with low serum 25(OH)D, ↑↑ represents increased mortality from COVID-19 in patients with low serum 25(OH)D and ↔ represents no association between serum 25(OH)D and COVID-19 mortality. Conversion of 25(OH)D ng/ml to nmol/ml is approximately ×2.5, that is, 20 ng/ml = 50 nmol/L.

In summary, several hospital studies show an association between low serum 25(OH)D levels and in-hospital mortality from COVID-19 and the putative negative acute phase effect seems insufficient to explain this association.

**Vitamin D status and COVID-19 outcomes—Community studies**

Many large studies have examined the association between serum 25(OH)D levels measured prior to illness in the community and subsequent SARS-CoV-2 infection risk as well as risk of severe COVID-19 and mortality (Table 2). Several of these studies are limited by a long delay, sometimes many years, between the measurement of serum levels and subsequent COVID-19 positivity. Notwithstanding this limitation, the majority of studies report an association between low pre-illness levels of 25(OH)D and subsequent increased risk of SARS-CoV-2 infection and hospitalisation from COVID-19. These include a large study from Israel [88], a US veterans affairs study [87] as well as the Nurses Health study [14]. Conversely, the association was lost after multivariate analysis in a UK Biobank study but this was significantly limited by the extremely long duration (median 11 years) between the measurement of 25(OH)D levels and the COVID-19
Few published studies have included dose response data but two studies that have recorded it again reveal a mixed picture: (a) Relationship between 25(OH)D concentration on admission and 28-day mortality in 472 hospital patients admitted for COVID-19 in the UK. Log odds ratio for mortality compared with mean 25(OH)D (47.4 nmol/L) as reference with adjustment for age and sex and cubic spline smoothing. This analysis, with 25(OH)D as a continuous variable, was not significant, although a separate multivariable analysis with 25(OH)D by quartiles did show significant increased mortality if 25(OH)D < 25 nmol/L or > 100 nmol/L (from Subramanian et al. [80] with permission). (b) Relationships between serum 25(OH)D concentrations and COVID-19 severity in patients admitted to a single medical centre in Israel. Severity of illness was defined as per WHO/2019-nCoV/clinical/2020.5. Historical 25(OH)D concentrations measured 14–730 days prior to infection were available for 253 of 1176 admitted patients. No U-shaped curve was noted (from Dror et al. [117] with permission).

Interactions between race and vitamin D status also appear to modulate the risk of SARS-CoV-2 infection but findings are inconsistent. In a large cohort study from the United States, low serum 25(OH)D levels were associated with SARS-CoV-2 positivity among White but not Black individuals [86]. However, another study among US Black women reported an association between low serum 25(OH)D levels and infection risk [90] and similarly, a higher proportion of vitamin D deficient ethnic minority subjects had evidence of SARS-CoV-2 infection among UK healthcare workers [83]. This is further supported by another UK Biobank cohort study, which used structural equation modelling and reported that serum vitamin D levels mediate Asian and Black ethnic disparities in COVID-19 severity [91].

Mendelian randomisation studies

The perceived difficulty in interpreting serum 25(OH)D levels during illness and the lack of immediate pre-illness serum 25(OH)D levels have led investigators to consider alternative methods of association such as Mendelian randomisation. This uses gene polymorphisms that predict vitamin D status as a surrogate for vitamin D deficiency. Six studies to date have used this approach to test the association between genetically determined vitamin D levels and COVID-19 infection risk and/or severity and all of them report no association (Table 3).

However, there are obvious limitations to these studies: (i) all the studies used data from the UK Biobank, which limits the generalisability to a non-European population and (ii) serum
25(OH)D levels are overwhelmingly an expression of environmental factors, with the heritability of serum 25(OH)D levels estimated to be less than 10%, thereby necessitating an extremely large sample size in order to detect any effect. Thus, whilst Mendelian randomization has the potential to interpret the impact of inherited variations in serum 25(OH)D concentration over the lifetime of an individual, these effects are very small and likely to be even less relevant for populations with
Table 2. Association between vitamin D status and risk of SARS-CoV-2 infection

| Author and year       | Location | Study design       | N     | Key findings                                                                 |
|-----------------------|----------|--------------------|-------|-------------------------------------------------------------------------------|
| Faniyi et al., 2021 [83] | UK       | Cross-sectional study | 392   | Healthcare workers with serum 25(OH)D levels <30 nmol/L independently associated with COVID-19 seroconversion |
| Li et al., 2021 [84]   | USA      | Cohort study       | 18,148 | No association between serum 25(OH)D and SARS-CoV-2 infection risk              |
| Jude et al., 2021 [85]  | UK       | Retrospective cohort study | 80,670 | Low serum 25(OH)D (<50 nmol/L) associated with increased risk of COVID-19 hospitalisation but not mortality |
| Cozier et al., 2021 [90] | USA      | Retrospective cohort study | 5081  | Low serum 25(OH)D (<29 ng/ml) associated with increased SARS-CoV-2 infection risk among Black women |
| Crandell et al., 2021 [86] | USA      | Retrospective cohort study | 21,629 | A 10 ng/ml increase in 25(OH)D lowered the odds of having a positive COVID-19 test overall and among White but not Black individuals |
| Li et al., 2021 [13]   | UK       | Retrospective cohort study | 417,342 | No association between 25(OH)D levels and SARS-CoV-2 infection risk* |
| Ma et al., 2021 [14]   | USA      | Retrospective cohort study | 39,315 | Higher predicted 25(OH)D levels associated with lower risk of SARS-CoV-2 infection (highest quintile median 34.7 ng/ml vs. lowest quintile 25.2 ng/ml) Vitamin D supplement intake >400 IU/d associated with lower hospitalisation risk |
| Seal et al., 2022 [87]  | USA      | Retrospective cohort study | 4599  | Independent inverse dose–response relationship between increasing continuous 25(OH)D concentrations (from 15 to 60 ng/ml) and decreasing the probability of COVID-19-related hospitalization and mortality |
| Israel et al., 2022 [88] | Israel   | Retrospective cohort study | 41,575 | Higher risk of infection among low serum 25(OH)D levels (<30 nmol/L) and SARS-CoV-2 positivity |
|                        |          |                    |       | Low serum 25(OH)D associated with increased severity of COVID-19               |

*Number of patients with positive SARS-CoV-2 polymerase chain reaction (PCR) tests.
**Number of patients hospitalised for severe COVID-19.
*Median duration of 11 years between 25(OH)D measurement and COVID-19 pandemic.

inherently low vitamin D status, as is characteristic of countries such as the UK. Perhaps more importantly, much of the genetic effect on 25(OH)D concentration is mediated by polymorphisms in the DBP and although reduced DBP concentration or activity will reduce 25(OH)D concentration, it will simultaneously tend to increase free 25(OH)D and arguably has little or no impact on the biological effects of vitamin D [1]. Finally, Mendelian randomization is a useful tool for assessing the potential impact of factors such as vitamin D on diseases where long-term exposure may be important. A good example of this is the strong link between genetic determinants of vitamin D and the
autoimmune disease multiple sclerosis [97]. However, it is unclear whether this approach is relevant to acute respiratory infections, where a transient, rather than sustained, rise in serum 25(OH)D may be sufficient to achieve a biological effect.

Community supplementation studies

More compelling evidence for a causal role of vitamin D status in determining SARS-CoV-2 infection risk and its severity could be inferred if pre-illness supplementation among deficient individuals were shown to attenuate the subsequent risk of infection or its severity compared with nonsupplemented subjects. However, this would require a very large sample size, especially if the study were performed on a population with a high vaccination rate since vaccines are now shown to be very effective in preventing serious illness. This is exemplified in an RCT from the UK recently reported as a non-peer-reviewed preprint [98]. This open-label study randomly assigned 6200 adults to ‘test and treat’ high dose vitamin D (3200 IU/day, \( N = 1550 \)) or low dose (800 IU/day, \( N = 1550 \)) to those with blood 25(OH)D concentration <75 nmol/L compared to a control group (\( N = 3100 \)) who were not offered testing or additional supplementation but who were allowed to take the government recommended supplement of 400 IU vitamin D per day. Neither the primary outcome of the proportion of all participants developing at least one acute respiratory infection nor the secondary outcome of proportion of patients developing swab-confirmed COVID-19 were significantly different among the three groups. A number of other outcomes such as hospitalisation and mortality from COVID-19 were not significantly different between the groups. However, whereas on entry to the study, only 2.5% had received one or more vaccine doses, 89.1% had received at least one dose of the vaccine by the end of the study. Likely as a result of this, plus other public health measures, the proportion of people in the control group who became infected with SARS-CoV-2 was only 4.6% compared with 20% predicted in the sample size calculation. Consequently, the rate of COVID-19 infections makes even this relatively large study underpowered; moreover, it was not designed to study the severity, and mortality was 0% in all three groups. Furthermore, the control group had a mean serum 25(OH)D level of 66.6 nmol/L at the end of the study as roughly 50% of this group reported taking vitamin D supplements. There are further trials still in progress but most trial protocols continue to allow substantial albeit lower-dose supplementation in the control group, which makes it difficult to interpret the beneficial effect of supplementation.

Contrary to evidence from the single randomised trial, indirect evidence from nonrandomised community-based studies seems to suggest a protective effect of vitamin D supplementation on infection risk and adverse COVID-19 outcomes (Table 4).

### Table 3. Mendelian randomisation studies of genetically predicted vitamin D deficiency and COVID-19

| Author and year         | Population | N       | Key findings                                                                 |
|-------------------------|------------|---------|-------------------------------------------------------------------------------|
| Cui and Tian, 2021 [92] | European   | 1,683,768 | No association between genetically determined 25(OH)D levels and COVID-19 susceptibility or severity |
| Liu et al., 2021 [93]   |            | 1,079,768 | No association between genetically determined 25(OH)D levels and COVID-19 susceptibility or severity |
| Amin and Drenos, 2021 [94] | European   | 127,637  | No association between genetically determined 25(OH)D levels and COVID-19 susceptibility or severity |
| Patchen et al., 2021 [95] | European   | 1,388,512 | No association between genetically determined 25(OH)D levels and COVID-19 susceptibility |
| Li et al., 2021 [13]    | European   | 417,343  | No association between genetically determined 25(OH)D levels and COVID-19 susceptibility |
| Butler-Laporte et al., 2021 [96] | European | 443,774  | No association between genetically determined 25(OH)D levels and COVID-19 susceptibility, severity or mortality |
Table 4. Community vitamin D supplementation and clinical outcomes

| Author and year | Location | Study design | N      | Vitamin D dose | Key findings                                                                 |
|----------------|----------|--------------|--------|----------------|------------------------------------------------------------------------------|
| Jolliffe, 2022 [98] | UK       | Randomised controlled trial (RCT) | 6200   | 3200 IU/d (N = 1550) 800 IU/d (N = 1550) No testing or supplementation (N = 3200) | No difference in acute respiratory infection or COVID-19 incidence rates across the three groups |
| Ma et al., 2021 [99] | UK       | observational studies | 8297   | Not specified | Intake of supplements ≥400 IU/d associated with a lower risk of COVID-19 hospitalisation |
| Ma et al., 2021 [14] | USA       | observational studies | 39,315 (1768) | Varying doses, 0 to ≥2000 IU/d | Intake of supplements ≥400 IU/d associated with a lower risk of COVID-19 hospitalisation |
| Oristrell et al., 2022 [100] | Spain     | observational studies | 4.6 m (30,557) | Cholecalciferol or calcifediol-varying doses | Patients supplemented with cholecalciferol or calcifediol achieving serum 25OHD levels ≥30 ng/ml associated with better COVID-19 outcomes |

(Continued)
Amongst the larger studies, in the UK Biobank cohort, habitual use of vitamin D supplements was associated with a lower risk of COVID-19 infection [99]. In a US veterans cohort of 26,508 SARS-CoV-2-positive individuals, the benefit of vitamin D supplementation on mortality within 2 weeks of COVID-19 diagnosis was estimated using electronic prescription records [104]. Among hospitalised patients, a significantly decreased mortality rate was observed for the use of vitamin D in the absence of corticosteroids relative to patients who received steroids but not vitamin D. Among patients receiving systemic steroids such as dexamethasone, the use of vitamin D was associated with significantly fewer deaths in hospitalised patients compared with nonhospitalised patients. Similarly, in the Nurses Health study, subjects with a ‘high’ intake of vitamin D supplements (≥400 IU/day) had a lower risk of hospitalisation after adjusting for other factors [14]. In keeping with this, a recent systematic review concluded that vitamin D supplementation was associated with better clinical outcomes, although curiously this was only significant when vitamin D was administered after the diagnosis of COVID-19 [106].

### Table 4. Continued

| Author and year | Location | Study design | N      | Vitamin D dose | Key findings |
|----------------|----------|--------------|--------|----------------|--------------|
| Louca et al., 2021 [101] | UK, USA and Sweden | Community survey | 445,850 (30,746)a | Not specified but frequency >3 times/week for at least 3 months | Lower risk of SARS-CoV-2 infection among vitamin D supplement users |
| Annweiler et al., 2021 [102] | France | Quasi-experimental study | 95 | 50,000 IU/month, or 80,000 IU or 100,000 IU or 200,000 IU every 2–3 months or 800 IU/d | Lower adjusted mortality among the supplemented group |
| Arroyo-Diaz et al., 2021 [103] | Spain | Cross-sectional study | 1267 | Not specified | No association between vitamin D supplementation and death |
| Efird et al., 2021 [104] | USA | Retrospective cohort study | 26,508 | Not specified—daily ‘low’ dose | Use of vitamin D in conjunction with steroids reduced mortality |
| Nimer et al., 2022 [105] | Jordan | Cross-sectional survey | 2148 | Not specified | Use of vitamin D supplements was independently associated with low risk of hospitalisation and severe COVID-19 |

*aNumbers in brackets represent number of COVID-19-positive individuals.*
Impact of vitamin D supplementation on COVID-19 outcomes—Hospital studies

It is also disappointing that there have been so few studies of vitamin D supplementation in hospitalised patients with COVID-19 (Table 5). A Cochrane systematic review published in June 2021 noted two RCTs that evaluated supplementation in hospitalised patients with moderate to severe disease [110]. The trials were too heterogeneous to allow meta-analysis. One was a pilot study performed in Cordoba, Spain [107]. Seventy-six consecutive hospitalised patients were randomised in a ratio of 2:1 to receive oral calcifediol (25(OH)D) in a substantial dose (0.532 mg on admission followed by 0.266 mg on days 3 and 7, then weekly till discharge) compared with no added vitamin D, in addition to standard care, which, at that time, included hydroxychloroquine and azithromycin. The choice of calcifediol is interesting and likely to be relevant as a previous trial showed that calcifediol raised 25(OH)D levels more rapidly and in a greater proportion of patients than cholecalciferol [111]. The trial was, however, seriously underpowered to look at mortality—only two of the 76 patients died. Moreover, the treatment groups were not well matched for diabetes or hypertension and baseline 25(OH)D levels were not measured. Patients treated with calcifediol were less likely to be admitted to intensive care (OR after adjustment for diabetes and hypertension 0.03 [95% CI 0.003–0.25]). A larger study has been planned (NCT04366908) but has yet to report (estimated completion 31 December 2021).

The second RCT was performed in Sao Paulo, Brazil. This was conducted in 240 hospitalised patients with moderate to severe COVID-19 who were randomised 1:1 to receive a single oral dose of 200,000 IU cholecalciferol or placebo [108]. No significant difference was seen in vitamin D versus placebo groups for mortality (7.6% vs. 5.1%, p 0.43) or length of hospital stay. Patients in this study did not receive vitamin D until an average of 10 days from symptom onset but more importantly, as previously discussed, high dose bolus vitamin D supplementation is already known to be ineffective for various clinical conditions, including rickets. A further larger recent open-label RCT of moderate to severe COVID-19 patients randomised to a single oral bolus of cholecalciferol (100,000 IU) likewise showed no difference in the length of stay, Intensive Care Unit (ICU) admission or mortality between the treatment and control arms [109].

Several further systematic reviews have been published since the Cochrane review but although they have tended to set broader criteria for study inclusion, they have not noted any further prospective RCTs [89, 106, 112–115]. Several cohort observational studies have been reported but these can only provide relatively low quality evidence.
They include a large retrospective study looking at calcifediol (25(OH)D) and cholecalciferol use 15–30 days before hospital admission with COVID-19 across Andalucia, Spain [116]. This included all 15,968 patients hospitalised between January and November 2020, within which propensity score matching was conducted with adjustment for known variables associated with poor prognosis to yield 1269 individuals in each matched group. This showed reduced 30-day mortality in those receiving vitamin D within the previous 30 days with a larger effect for calcifediol (Hazard Ratio [HR] = 0.73, with 95% CI 0.57–0.95) than for cholecalciferol (HR = 0.88, with 95% CI 0.75, 1.03).

Conclusions

The impact of vitamin D deficiency on the risk of COVID-19 infection and perhaps particularly on the risk of its severity remains plausible but evidence to substantiate this is indirect, coming largely from association studies. There is growing evidence from studies performed prepandemic that intermittent high-dose bolus vitamin D supplementation is ineffective for various endpoints. Future studies should carefully consider the dose and formulation of vitamin D. For acute respiratory infection, calcifediol may be a better choice for both disease prevention and treatment due to its ability to raise serum 25(OH)D more rapidly compared to conventional vitamin D (cholecalciferol). Better quality evidence for an impact of vitamin D status on COVID-19 outcomes might still come from randomised trials of regular daily supplementation. Meanwhile, avoidance of vitamin D deficiency by regular low-dose daily supplementation, particularly in winter months, should be encouraged.

Acknowledgements

This was a commissioned review.

Conflict of interest

M. H. has received speaking honoraria from DSM and Danone. R. Q. has participated in the Data Monitoring Committee for the Coronavit study of vitamin D in COVID-19 (NCT04579640). D. T. receives funding from the Health Technology Assessment/National Institute for Health Research for the ‘Vitalize’ study of vitamin D replacement in ITU patients. S. S. has received speaking honoraria and consultancy fees from several companies but none in relation to vitamin D. G. G., J. H., R. A. K., E. L. and J. M. R. have no conflict of interest to declare.

Author contributions

Sreedhar Subramanian: Conceptualization; Data curation; Writing – original draft; Writing – review and editing. George Griffin: Conceptualization; Data curation; Writing – original draft; Writing – review and editing. Martin Hewison: Conceptualization; Data curation; Writing – original draft; Writing – review and editing. Julian Hopkin: Conceptualization; Data curation; Writing – original draft; Writing – review and editing. Eamon Laird: Conceptualization; Data curation; Writing – original draft; Writing – review and editing. Rose Anne Kenny: Conceptualization; Data curation; Writing - original draft; Writing - review and editing. David Thickett: Conceptualization; Data curation; Writing – original draft; Writing – review and editing. Richard Quinton: Conceptualization; Data curation; Writing – original draft; Writing – review and editing. Jonathan M. Rhodes: Conceptualization; Data curation; Writing – original draft; Writing – review and editing.

References

1 Rhodes JM, Subramanian S, Laird E, Griffin G, Kenny RA. Perspective: vitamin D deficiency and COVID-19 severity—plausibly linked by latitude, ethnicity, impacts on cytokines, ACE2 and thrombosis. J Intern Med. 2021;289:97–115.
2 Bishop E, Ismailova A, Dimento SK, Hewison M, White JH. Vitamin D and immune regulation: antibacterial, antiviral, anti-inflammatory. JBMR Plus. 2020;5:e10405.
3 Adams JS, Hewison M. Extrarenal expression of the 25-hydroxyvitamin D-1-hydroxylase. Arch Biochem Biophys. 2012;523:95–102.
4 Chauss D, Freiwald T, McGregor R, Yan B, Wang L, Nova-Lamerti E, et al. Autocrine vitamin D signaling switches off pro-inflammatory programs of TH1 cells. Nat Immunol. 2022;23:62–74.
5 NICE. COVID-19 rapid guideline: vitamin D NICE guideline [NG187]. https://www.nice.org.uk/guidance/ng187 (2020). Accessed 16 March 2022.
6 Jolliffe DA, Camargo CA Jr, Shyter JD, Aglipay M, Aloria JF, Gammal D, et al. Vitamin D supplementation to prevent acute respiratory infections: a systematic review and meta-analysis of aggregate data from randomised controlled trials. Lancet Diabetes Endocrinol. 2021;9:276–92.
7 COVID-19 Therapeutics Accelerator, Wellcome Trust/Gates Foundation/Mastercard. Propose a treatment or study. https://www.therapeuticsaccelerator.org/propose-a-treatment-or-study/ (2020). Accessed 16 March 2022.
8 Bouillon R, Quesada-Gomez JM. Vitamin D endocrine system and COVID-19. JBMR Plus. 2021;5:e10576.
Vitamin D and COVID-19 / S. Subramanian et al.

9 Moriyaama Y, Hugentobler WJ, Iwasaki A. Seasonality of respiratory viral infections. *Ann Rev Virol.* 2020;7:83–101.

10 Liu X, Huang J, Li C, Zhao Y, Wang D, Huang Z, et al. The role of seasonality in the spread of COVID-19 pandemic. *Environ Res.* 2021;195:110874.

11 Rhodes J, Dunstan F, Laird E, Subramanian S, Kenny RA. COVID-19 mortality increases with northerly latitude after adjustment for age suggesting a link with ultraviolet and vitamin D. *BMJ Nutr Prev Health.* 2020;3:118–20.

12 Gorman S, Weller RB. Investigating the potential for ultraviolet light to modulate morbidity and mortality from COVID-19: a narrative review and update. *Front Cardiovasc Med.* 2020;7:616527.

13 Li X, van Geffen J, van Weele M, Zhang X, He Y, Meng X, et al. An observational and Mendelian randomisation study on vitamin D and COVID-19 risk in UK Biobank. *Sci Rep.* 2021;11:18262.

14 Ma W, Nguyen LH, Yue Y, Yang D, Hu Z, Wang M, et al. Associations between predicted vitamin D status, vitamin D intake, and risk of SARS-CoV-2 infection and coronavirus disease 2019 severity. *Am J Clin Nutr.* 2021;101(26):e29795. https://doi.org/10.1093/ajcn/nqab389

15 Cherrie M, Clemens T, Colandrea C, Feng Z, Webb DJ, Weller RB, et al. Ultraviolet A radiation and COVID-19 deaths in the USA with replication studies in England and Italy. *Br J Dermatol.* 2021;185:363–70.

16 Ma Y, Pei S, Shamon J, Dubrow R, Chen K. Role of meteorological factors in the transmission of SARS-CoV-2 in the United States. *Nat Commun.* 2021;12:3602.

17 Xu R, Rahmandad H, Gupta M, DiGennaro C, Ghaffarzadegan N, Amini H, et al. Weather, air pollution, and SARS-CoV-2 transmission: a global analysis. *Lancet Planet Health.* 2021;5:e671–80.

18 Carleton T, Cornetet J, Huybers P, Meng KC, Proctor J. Global evidence for ultraviolet radiation decreasing COVID-19 growth rates. *Proc Natl Acad Sci U S A.* 2021;118:e202370118.

19 Laird E, Rhodes J, Kenny RA. Vitamin D and inflammation: potential implications for severity of covid-19. *Ir Med J.* 2020;113:81.

20 Sooriyaarachchi P, Jeyakumari DT, King N, Jayawardena R. Impact of vitamin D deficiency on COVID-19. *Clin Nutr ESPEN.* 2021;44:372–8.

21 COVID-19 Excess Mortality Collaborators. Estimating excess mortality due to the COVID-19 pandemic: a systematic analysis of COVID-19-related mortality, 2020–21. *Lancet.* 2022;399(10334):1513–36.

22 Petrenya N, Lambreg-Allardt C, Melhus M, Broderstad AR, Brustad M. Vitamin D status in a multi-ethnic population of northern Norway: the SAMINOR 2 Clinical Survey. *Public Health Nutr.* 2020;23:1186–209.

23 Hyponen E, Power C. Hypovitaminosis D in British adults at age 45 y: nationwide cohort study of dietary and lifestyle predictors. *Am J Clin Nutr.* 2007;85:860–8.

24 O’Neill CM, Kazantzidis A, Ryan MJ, Barber N, SMPos CT, Durazo-Arvizu RA, et al. Seasonal changes in Vitamin D-Effective UVB availability in europe and associations with population serum 25-hydroxyvitamin D. *Nutrients.* 2016;8:533.

25 Jaakkola J, J. Zh., Chvatal J, Ilonen ST, Lundvqvist A, Erkkola M, Koskela T, Lakkola K, et al. The positive impact of general vitamin D food fortification policy on vitamin D status in a representative adult Finnish population: evidence from an 11-y follow-up based on standardized 25-hydroxyvitamin D data. *Am J Clin Nutr.* 2017;105:1512–20.

26 Kramer AS, Thomas M, Makowski A, Drozek D. The prevalence of Vitamin D deficiency in impoverished communities in northern Lima, Peru. *Int J Dis Reversal Prev.* 2021;3(2):10.

27 Orces CH. Vitamin D status among older adults residing in the Littoral and Andes mountains in Ecuador. *Scientific WorldJournal.* 2015;2015:545297.

28 Elo I, Horvath DV, Szejnfeld VL, Ortega JC, Rocha DA, Szejnfeld J, et al. Vitamin D deficiency and seasonal variation over the years in Sao Paulo, Brazil. *Osteoporos Int.* 2016;27:3449–56.

29 Chillon TS, Demircan K, Heller RA, Hirschblil-Bremmer IM, Diegmann J, Bachmann M, et al. Relationship between vitamin D status and antibody response to COVID-19 mRNA vaccination in healthy adults. *Biomedicines.* 2021;9(11):1714.

30 Piec I, Cook L, Dervisievic S, Fraser WD, Ruetten S, Berman M, et al. Age and vitamin D affect the magnitude of the antibody response to the first dose of the SARS-Cov-2 BNT162b2 vaccine. *Curr Res Transl Med.* 2022;70(3):103344.

31 Roth DE, Abrams SA, Aloia J, Bergeron G, Bourassa MW, Brown KH, et al. Global prevalence and disease burden of vitamin D deficiency: a roadmap for action in low- and middle-income countries. *Ann NY Acad Sci.* 2018;1430:44–79.

32 Griffin G, Hewison M, Hopkin J, Kenny RA, Quinton R, Rhodes J, et al. Preventing vitamin D deficiency during the COVID-19 pandemic: UK definitions of vitamin D sufficiency and recommended supplement dose are set too low. *Clin Med (Lond).* 2021;21:e48–51.

33 Holck MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, et al. Guidelines for preventing and treating vitamin D deficiency and insufficiency revisited. *J Clin Endocrinol Metab.* 2012;97:1153–8.

34 Holck MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab.* 2011;96:1911–30.

35 Durup D, Jorgensen HL, Christensen J, Schwarz P, Heegaard AM, Lind B. A reverse J-shaped association of all-cause mortality with serum 25-hydroxyvitamin D in general practice: the CopD study. *J Clin Endocrinol Metab.* 2012;97:2644–52.

36 Amrein K, Quareshi SA, Litonjua AA, Gibbons FK, Pieber TR, Camargo CA Jr, et al. Evidence for a U-shaped relationship between prehospital vitamin D status and mortality: a cohort study. *J Clin Endocrinol Metab.* 2014;99:1461–9.

37 Gaksh M, Jorde R, Grimmes G, Joakimsen R, Schirmer H, Wilsgaard T, et al. Vitamin D and mortality: individual participant data meta-analysis of standardized 25-hydroxyvitamin D in 26916 individuals from a European consortium. *PLos One.* 2017;12:e0170791.

38 Fan X, Wang J, Song M, Giovannucci EL, Ma H, Jin G, et al. Vitamin D status and risk of all-cause and cause-specific mortality in large cohort: results from the UK Biobank. *J Clin Endocrinol Metab.* 2020;105:dgaa432.
39 Scientific Advisory Committee on Nutrition. Vitamin D and health. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/537616/SACN_Vitamin_D_and_Health_report.pdf (2016). Accessed 16 March 2022.

40 Cashman KD, Ritz C, Kiely M, Odin C. Improved dietary guidelines for vitamin D: application of individual participant data (IPD)-level meta-regression analyses. *Nutrients.* 2017;9:469.

41 Ataide FL, Carvalho Bastos LM, Vicente Matias MF, Skare TL, Freire de Carvalho J. Safety and effectiveness of vitamin D mega-dose: a systematic review. *Clin Nutr ESPEN.* 2021;46:115–20.

42 Mazess RB, Bischoff-Ferrari HA, Dawson-Hughes B. Vitamin D: bolus is bogus—a narrative review. *JBMR Plus.* 2021;5:e10567.

43 Crowe FL, Mughal MZ, Maroof Z, Berry J, Kaleem M, Abburu TL, Freire de Carvalho J. Safety and effectiveness of vitamin D supplementation on distal radius fracture healing: a randomized controlled trial using HR-pQCT. *J Bone Miner Res.* 2021;36:1492–501.

44 Gammna D, Uyangya B, Zhou X, Gantsetseg G, Delgerke B, Enkhmaa D, et al. Vitamin D supplements for prevention of tuberculosis infection and disease. *N Engl J Med.* 2020;383:359–68.

45 Griffin G, Hewison M, Hopkin J, Kenny RA, Quinton R, Rhodes J, et al. Perspective: vitamin D supplementation prevents rickets and acute respiratory infections when given as daily maintenance but not as intermittent bolus: implications for COVID-19. *Clin Med (Lond).* 2021;21:e144–9.

46 Bacchetta J, Sea JL, Chun RF, Lisse TS, Wesseling-Perry K, Zittermann A, Berthold HK, Pilz S. The effect of vitamin D3 supplementation with parathyroidism and respiratory insufficiency in hospitalized patients with COVID-19. *J Endocrinol Invest.* 2021;44:2285–93.

47 Charoengnag N, Shrivani A, Reddy N, Vodopivec DM, Apovian CM, Holick MF. Association of vitamin D status with hospital morbidity and mortality in adult hospitalized patients with COVID-19. *Endocr Pract.* 2021;27:271–8.

48 Jevalikar G, Mital H, Singh A, Sharma R, Farooqui KJ, Mahendru S, et al. Lack of association of baseline 25-hydroxyvitamin D levels with disease severity and mortality in Indian patients hospitalized for COVID-19. *Sci Rep.* 2021;11:6258.

49 Tehrani S, Khabiri N, Moradi H, Mosavat MS, Khabiri SS. Evaluation of vitamin D levels in COVID-19 patients referred to Labafinejad Hospital in Tehran and its relationship with disease severity and mortality. *Clin Nutr ESPEN.* 2021;42:313–7.

50 Osman W, Al Fahdi F, Al Salmi I, Al Khalili H, Gokhale A, Khamis F. Serum calcium and vitamin D levels: correlation to vitamin D status among SARS-CoV-2-positive UAE residents. *Nutrients.* 2021;13(5):1714.

51 Diaz-Curiel M, Cabello A, Arboirro-Pinel R, Mansur JL, Heili-Frades S, Mahillo-Fernandez I, et al. The relationship between 25(OH) vitamin D levels and COVID-19 onset and disease course in Spanish patients. *J Steroid Biochem Mol Biol.* 2021;212:105928.

52 Al-Jarallah M, Rajan R, Dashit R, Al Saber A, Pan J, Zhanna KD, et al. In-hospital mortality in SARS-CoV-2 stratified by serum 25-hydroxy-vitamin D levels: a retrospective study. *J Med Virol.* 2021;93:5880–5.

53 Guven M, Gultekin H. Association of 25-hydroxyvitamin D level with COVID-19-related in-hospital mortality: a retrospective cohort study. *J Am Coll Nutr.* 2021;1–10. https://doi.org/10.1080/07315724.2021.1935361.

54 Bianconi V, Mannarino MR, Figorilli F, Cosentini E, Batori G, Marinii E, et al. Prevalence of vitamin D deficiency and its prognostic impact on patients hospitalized with COVID-19. *Nutrition.* 2021;91–92:11408.
Shakeri H, Azimian A, Ghasemzadeh-Moghaddam H, Safdari M, Hareshabadi M, Daneshmand T, et al. Evaluation of the relationship between serum levels of zinc, vitamin B12, vitamin D, and clinical outcomes in patients with COVID-19. *J Med Virol.* 2022;94:141–6.

Vasheghani M, Jannati N, Baghaei P, Rezaei M, Aliyari R, Marjani M. The relationship between serum 25-hydroxyvitamin D levels and the severity of COVID-19 disease and its mortality. *Sci Rep.* 2021;11:17594.

Aflaghi S, Esmeeiil Tarki F, Sadat Rahimi F, Besharat S, Mirhaidari S, Karimi A, et al. Prevalence and clinical outcomes of vitamin D deficiency in COVID-19 hospitalized patients: a retrospective single-center analysis. *Tohoku J Exp Med.* 2021;255:127–34.

Freitas AT, Calhau C, Antunes G, Araújo B, Bandeira M, Hurst EA, Mellanby RJ, Handel I, Griffith DM, Rossi AG, Derakhshanian H, Rastad H, Ghosh S, Zeinali M, Ziaee M, Ramirez-Sandoval JC, Castillos-Avalos VJ, Paz-Cortes A, Apaydin T, Polat H, Dincer Yazan C, Ilgin C, Elbasan Seven B, Gunduz O, Ozgu-Erdinc AS, Sahin D, Moraloglu Jenei T, Jenei S, Tamas LT, García-Unzueta M, Hernández-Jimenez S, Mehta R, et al. Very low vitamin D levels are a strong independent predictor of mortality in hospitalized patients with severe COVID-19. *Arch Med Res.* 2021;53:215–22.

Derakhshanian H, Rastad H, Ghosh S, Zeinali M, Ziaee M, Khoeini T, et al. The predictive power of serum vitamin D for poor outcomes in COVID-19 patients. *Food Sci Nutr.* 2021;9:6307–13.

Farhat OA, Haresabadi M, Daneshmand T, et al. Evaluation of the relationship between serum 25-hydroxyvitamin D levels and the severity of COVID-19 disease and its mortality. *Sci Rep.* 2021;11:20837.

Hurst EA, Mellanby RJ, Handel I, Griffith DM, Rossi AG, Walsh TS, et al. Vitamin D insufficiency in COVID-19 and influenza A, and critical illness survivors: a cross-sectional study. *BMJ Open.* 2021;11:e055435.

Ramirez-Sandoval JC, Castillo-Alvarez VJ, Paz-Cortes A, Santillan-Ceron A, Hernández-Jimenez S, Mehta R, et al. Very low vitamin D levels are a strong independent predictor of mortality in hospitalized patients with severe COVID-19. *Clin Endocrinol (Oxf).* 2021;85:2083–41.

Faniyi AA, Lugg ST, Faustini SE, Webster C, Duffy JE, Hewison M, et al. Vitamin D status and COVID-19 severity in pregnant women: a cross-sectional study. *BMJ Nutr Prev Health.* 2021;5:91–6.

Israel A, Cicurel A, Feldhammer I, Stern DF, Dror DY, Giveon DS, et al. Vitamin D deficiency is associated with higher risks for SARS-CoV-2 infection and COVID-19 severity: a retrospective case-control study. *Intern Emerg Med.* 2022;17:1053–63. https://doi.org/10.1007/s11739-021-02902-w

Dissanayake HA, de Silva NL, Sumanatileke M, de Silva SDN, Gamage KKK, Dematapitiya C, et al. Prognostic and therapeutic role of vitamin D in COVID-19: a systematic review and meta-analysis. *J Clin Endocrinol Metab.* 2022;107:1484–502. https://doi.org/10.1210/clinem-dgab892

Cozier YC, Castro-Webb N, Hochberg NS, Rosenberg L, Albert MA, Palmer JR. Lower serum 25(OH)D levels associated with higher risk of COVID-19 infection in U.S. Black women. *PLoS One.* 2021;16:e0255132.

Marino-Ramirez L, Ahmad M, Rishishwar L, Nagar SD, Lee KK, Norris ET, et al. Vitamin D and socioeconomic deprivation mediate COVID-19 ethnic health disparities. *medRxiv.* 2021. https://doi.org/10.1101/2021.09.20.21263865

Cui Z, Tian Y. Using genetic variants to evaluate the causal effect of serum vitamin D concentration on COVID-19 susceptibility, severity and hospitalization traits: a Mendelian randomization study. *J Transl Med.* 2021;19:300.

Liu D, Tian QY, Zhang J, Hou HF, Li Y, Wang W, et al. Association between 25 hydroxyvitamin D concentrations and the risk of COVID-19: a Mendelian randomization study. *Biomed Environ Sci.* 2021;34:750–4.

Amin HA, Drenos F. No evidence that vitamin D is able to prevent or affect the severity of COVID-19 in individuals with European ancestry: a Mendelian randomisation study of open data. *BMJ Nutr Prev Health.* 2021;4:42–8.

Patchen BK, Clark AG, Gaddis N, Hancock DB, Cassano PA. Genetically predicted serum vitamin D and COVID-19: a Mendelian randomisation study. *BMJ Nutr Prev Health.* 2021;4:213–25.
Vitamin D and COVID-19 / S. Subramanian et al.

96 Butler-Laporte G, Nakanishi T, Mooser V, Morrison DR, Abdullah T, Adeleye O, et al. Vitamin D and COVID-19 susceptibility and severity in the COVID-19 Host Genetics Initiative: a Mendelian randomization study. PLoS Med. 2021;18:e1003605.

97 Mokry LE, Ross S, Ahmad OS, Forgetta V, Smith GD, Goltzman D, et al. Vitamin D and risk of multiple sclerosis: a Mendelian randomization study. PLoS Med. 2015;12:e1001866.

98 Jolliffe DA. Vitamin D supplements for prevention of COVID-19 or other acute respiratory infections: a phase 3 randomized controlled trial (CORONAVIT). medRxiv. 2022. https://doi.org/10.1101/2022.03.22.22271707

99 Ma H, Zhou T, Heianza Y, Qi L. Habitual use of vitamin D supplements and risk of coronavirus disease 2019 (COVID-19) infection: a prospective study in UK Biobank. Am J Clin Nutr. 2021;113:1275–81.

100 Oritrell J, Oliva JC, Casado E, Subirana I, Dominguez D, Toloba A, et al. Vitamin D supplementation and COVID-19 risk: a population-based, cohort study. J Endocrinol Invest. 2022;45:167–79.

101 Louca P, Murray B, Klaser K, Graham MS, Mazidi M, Leeming ER, et al. Modest effects of dietary supplements during the COVID-19 pandemic: insights from 445,850 users of the COVID-19 Symptom Study app. BMJ Nutr Prev Health. 2021;4:149–57.

102 Annweiler C, Beaudenon M, Simon R, Guenet M, Otekpo M, Célarier T, et al. Vitamin D supplementation prior to or during COVID-19 associated with better 3-month survival in geriatric patients: expansion phase of the GERIA-COVID study. J Steroid Biochem Mol Biol. 2021;213:105958.

103 Arroyo-Díaz JA, Julve J, Vlacho B, Corcory R, Ponte P, Román E, et al. Previous Vitamin D supplementation and morbidity and mortality outcomes in people hospitalized for COVID-19: a cross-sectional study. Front Public Health. 2021;9:758347.

104 Efird JT, Anderson EJ, Jindal C, Redding TS, Thompson AD, Press AM, et al. The interaction of vitamin D and corticosteroids: a mortality analysis of 26,508 veterans who tested positive for SARS-CoV-2. Int J Environ Res Public Health. 2021;19:447.

105 Nimer R, Khabour O, Swedan S, Kofahi H. The impact of vitamin and mineral supplements usage prior to COVID-19 infection on disease severity and hospitalization. Bosn J Basic Med Sci. 2022. https://doi.org/10.17305/bjms.2021.7009

106 Pal R, Banerjee M, Bhadada SK, Shetty AJ, Singh B, Vyas A. Vitamin D supplementation and clinical outcomes in COVID-19: a systematic review and meta-analysis. J Endocrinol Invest. 2022;45:53–68.

107 Entrenas Castillo M, Entrenas Costa LM, Vaquero Barrios JM, Alcalá Díaz JF, Lopez Miranda J, Bouillon R, et al. “Effect of calcifediol treatment and best available therapy versus best available therapy on intensive care unit admission and mortality among patients hospitalized for COVID-19: a pilot randomized clinical study”. J Steroid Biochem Mol Biol. 2020;203:105751.

108 Murali IH, Fernandes AL, Sales LP, Pinto AJ, Goessler KF, Duran CSC, et al. Effect of a single high dose of vitamin D3 on hospital length of stay in patients with moderate to severe COVID-19: a randomized clinical trial. JAMA. 2021;325:1053–60.

109 Cannata-Andia JB, Diaz-Sottolano A, Fernandez P, Palomo-Antequera C, Herrero-Puente P, Mouzo R, et al. A single oral bolus of 100,000 IU of cholecalciferol at hospital admission did not improve outcomes in the COVID-19 disease: the COVID-VIT-D-a randomised multicentre international clinical trial. BMC Med. 2022;20:83.

110 Stroehlein JK, Wallqvist J, Iannizzi C, Mikolajewska A, Metzendorf M-I, Benstoem C, et al. Vitamin D supplementation for the treatment of COVID-19: a living systematic review. Cochrane Database Syst Rev. 2021;5:CD015043.

111 Shieh A, Ma C, Chun RF, Witzel S, Rafijson B, CoSntreras HTM, et al. Effects of cholecalciferol vs calcifediol on total and free 25-hydroxyvitamin D and parathyroid hormone. J Clin Endocrinol Metab. 2017;102:1133–40.

112 Rawat D, Roy A, Maltra S, Shankar V, Khanna P, Badiya DK. Vitamin D supplementation and COVID-19 treatment: a systematic review and meta-analysis. Diabetes Metab Syndr. 2021;15:102189.

113 Tentolouris N, Samakidou G, Eleftheriadou I, Tentolouris A, Jude EB. The effect of vitamin D supplementation on mortality and intensive care unit admission of COVID-19 patients. A systematic review, meta-analysis and meta-regression. Diabetes Metab Res Rev. 2022;38:e3517.

114 Szarpak L, Filipiak KJ, Gasecka A, Gawel W, Koziel D, Jaguszkewicz MJ, et al. Vitamin D supplementation to treat SARS-CoV-2 positive patients. Evidence from meta-analysis. Cardiol J. 2021;29(2):188–96.

115 Chen J, Mei K, Xie L, Yuan P, Ma J, Yu P, et al. Low vitamin D levels do not aggravate COVID-19 risk or death, and vitamin D supplementation does not improve outcomes in hospitalized patients with COVID-19: a meta-analysis and GRADE assessment of cohort studies and RCTs. Nutr J. 2021;20:89.

116 Loucera C, Pena-Chalet M, Esteban-Medina M, Muñoz-Juárez-Díaz D, Villegas R, Lopez-Miranda J, et al. Real world evidence of calcifediol or vitamin D prescription and mortality rate of COVID-19 in a retrospective cohort of hospitalized Andalusian patients. Sci Rep. 2021;11:23380.

117 Dror AA, Morozov N, Daoud A, Namir Y, Yakir O, Schachar Y, et al. Pre-infection 25-hydroxyvitamin D3 levels and association with severity of COVID-19 illness. PLoS One. 2022;17:e0263069.

Correspondence: Jonathan Rhodes, Molecular Physiology and Cell Signalling, Institute of Systems, Molecular and Integrative Biology, University of Liverpool, The Henry Wellcome Laboratory, Nuffield Building, Crown St., Liverpool, L69 3GE, UK. Email: rhodesjm@liverpool.ac.uk