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FACTS BEHIND THE HEADLINES

Nutrition Bulletin

Vitamin D: What's new a year on from the COVID-19 outbreak?

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When COVID-19 hit the UK in early 2020, few would have envisaged that this catastrophic public health crisis would still be posing an unprecedented threat to human health, healthcare systems, public life and the economy a year on. Saving lives and slowing the worldwide pandemic remains an urgent priority. A great deal has been learnt but COVID-19 is still a relatively new disease and research into preventative measures and treatments continues to evolve. During the pandemic, there has been an increased clinical and public interest in the role of diet and health, particularly in supporting immunity, sparking media stories suggesting that certain food components and supplements are capable of 'boosting' the immune system (BBC, 2020; Mirror, 2020).

No specific food or supplement can simply 'boost' immunity. To support normal immune function, the body requires adequate energy and nutrition (Calder, 2020), and specific roles have been demonstrated for a number of vitamins, trace elements, amino acids and fatty acids, which together contribute to the body's immune defences, including ability to reduce risk of infections (Calder, 2020). For example, the European Commission has approved health claims for vitamin A, vitamin B6, folate, vitamin B12, vitamin C, vitamin D, zinc, selenium, iron and copper recognising their contribution to the normal function of the immune system (EC, 2021) (see Lockyer, 2020 for more details on these nutrients and their role in immunity). However, early on in the pandemic, the spotlight landed on vitamin D presumably because vitamin D status is typically lowest in late winter when respiratory tract infections peak (Berry et al., 2011; Lanham-New et al., 2020). Whilst this is purely an association rather than indicative of causation, interest continued to grow once it was realised that severe COVID-19 outcomes were particularly common in those population groups known to be at greater risk of low vitamin D status, including people living with obesity and those from ethnic minorities (discussed in more detail later on) (PHE, 2020). Therefore, a potential beneficial effect of vitamin D in protecting against COVID-19 infection and disease severity was considered plausible and has stimulated much research to investigate whether this is actually the case.

Vitamin D is a generic name for two different secosteroid compounds, ergocalciferol (vitamin D2) and cholecalciferol (vitamin D3) (Buttriss et al., 2021). Vitamin D3 is found in a limited number of foods such as oil-rich fish, eggs, red meat and vitamin D-fortified products, but the main source results from synthesis in the skin following exposure to sunlight (UVB radiation at 290–315 nm), which converts 7-dehydrocholesterol to vitamin D3. In contrast, vitamin D2 production is not triggered by sunlight in humans but can be obtained from fungi (*e.g.* wild mushrooms or UVB treated cultivated mushrooms) and yeasts (Lanham-New et al., 2020). In 1940, a mandatory requirement of vitamin D (and vitamin A) fortification of margarines was introduced, which was removed in 2013, although many fat spreads still contain vitamin D, added on a voluntary basis (Defra, 2014).

Vitamin D status is usually measured by the level of the circulating metabolite 25-hydroxyvitaminD [25(OH)D], produced by hepatic hydroxylation of vitamin D sourced from either skin or the gut via oral intake (SACN, 2016). 25(OH)D is the most commonly used marker of vitamin D status because it has a relatively long half-life (several weeks) and its concentration in serum/plasma reflects dietary intakes, UVB exposure and biological reserves of vitamin D (Buttriss et al., 2021). In the UK,

a plasma or serum 25(OH)D concentration of 25 nmol/l (10 ng/ml) is considered as the minimum necessary for protecting musculoskeletal health and lowering the risk of osteomalacia (adults) and nutritional rickets (children). These conditions are characterised by pain, deformities, fractures and poor bone mineralisation, and are caused by low calcium intakes and/or vitamin D deficiency and are corrected by nutritional intervention (Buttriss et al., 2021; SACN, 2016). However, it is noteworthy that different thresholds are used to indicate risk; for example, the US Institute of Medicine set a minimum threshold of 30 nmol/l to define increased risk of deficiency and 50 nmol/l as the minimum threshold for 'sufficiency' (Institute of Medicine, 2011).

The angle of the sun determines whether skin synthesis of vitamin D is possible. So, during the winter months in areas further away from the equator (between October to March in the UK), there is insufficient solar UVB to support adequate vitamin D synthesis (Schoenmakers et al., 2016). During the winter months in countries such as the UK, the body is reliant on tissue stores of vitamin D as dietary intake typically does not meet the recommended vitamin D requirements [the *National Diet and Nutrition Survey (NDNS)* (years 2016/2017–2018/2019) suggests average vitamin D intakes from food sources only for adults aged 19–64 years is 2.9 μg/day] (PHE & FSA, 2020), and vitamin D status usually declines. Interestingly, the *NDNS* (years 2008/2009–2011/2012) that compared data for the devolved nations shows a larger proportion of individuals living in Scotland and Northern Ireland with a plasma 25(OH)D concentration below 25 nmol/l than that of the UK as a whole, and it is assumed this is because of the lower availability of UVB for vitamin D synthesis at higher latitudes (Bates et al., 2017a; Bates et al., 2017b). Globally, low vitamin D status is prevalent in a wide range of population groups, including those in low latitude areas (*i.e.* closer to the equator) with an abundance of sunlight (Bouillon, 2019), and not necessarily confined to winter (Mendes et al., 2020). This may be due to environmental factors, such as air pollution, as well as cultural factors where skin is covered up and therefore not exposed to sunlight (Al-Yatama et al., 2019). Older, housebound adults and individuals with dark skin pigment are at particular risk of vitamin D deficiency in the UK. The latter is associated with lower efficiency of cutaneous vitamin D synthesis due to the higher concentration of melanin in darker skin, but can also be exacerbated by sun avoidance and by culturally defined dress codes that require skin to be covered when outdoors (SACN, 2016).

In 2016, the Science Advisory Committee on Nutrition (SACN) published its *Vitamin D and Health* report, which reviewed the totality of the evidence at the time, and new dietary reference values were set based on protecting musculoskeletal health (*i.e.* rickets, osteomalacia, falls, risk of falling and muscle strength) (SACN, 2016). Insufficient evidence was found for vitamin D in relation to non-musculoskeletal outcomes (Buttriss et al., 2021; SACN, 2016). The reference nutrient intake (RNI) established for vitamin D was modelled on the basis of maintaining population protective 25(OH)D concentrations of ≥25 nmol/l, at the individual level, throughout the year; below this concentration, the risk of poor musculoskeletal health increases (Buttriss et al., 2021; SACN, 2016). The RNI was set at 10 μg/day [400 international units (IU)/day] for everyone over 4 years of age. For infants and younger children, data were insufficient to set a RNI, so instead, as a precaution, a 'Safe Intake' of 8.5–10 μg/day (340–400 IU) was recommended (SACN, 2016) (see Table 1 for a summary of recent official advice in the UK on vitamin D). Prior to this in the UK, an RNI for vitamin D was set only for population groups at high risk of deficiency, for example young children, pregnant and lactating women, adults aged over 65 years and some ethnic minorities (DH, 1991). It was assumed that, for most people, the amount of vitamin D produced by exposure to sunlight containing UVB in the summer months would be adequate for achieving serum 25(OH)D concentrations ≥25 nmol/l during winter, but the new report recognised that this was now not the case.

Since SACN's report in 2016, standard government advice has been to consider taking a daily vitamin D supplement of 10 μg [400 IU] in the winter months (between October and March in the UK), since it is difficult for people to get enough vitamin D from food alone (NHS, 2020; SACN, 2016). However, in April 2020 Public Health England (PHE) reissued advice that whilst people are following recommendations to stay at home due to lockdown rules they may not be getting enough vitamin D from sunlight exposure, so everyone should additionally consider taking a daily vitamin D supplement of 10 μg in spring and summer (NHS, 2020). At the time, PHE emphasised that this advice was specifically to underpin musculoskeletal health, and that there was no evidence vitamin D supplementation would help to prevent COVID-19 infection as a media story at the time had suggested (heart.co.uk, 2020).

Since then, more research has been published and there have been several rapid reviews on the available evidence on acute respiratory tract infections, but they have concluded that there is still insufficient reliable evidence to support taking vitamin D supplements in order to prevent or treat COVID-19, and that more well-designed studies are needed, particularly high-quality randomised controlled trials (NICE, 2020a; SACN, 2020a; SACN, 2020b). However, some experts argue that whilst results of clinical trials are pending, there is little to lose in recommending higher dose vitamin D supplements amidst this public health emergency, as a low-risk nutritional intervention that is inexpensive and safe, and may have potential gains for some individuals (Lewis, 2020). The topic remains controversial

TABLE 1 Recent UK official advice on vitamin D supplements

Date	Source	Advice
July 2016	Science Advisory Committee on Nutrition (SACN) – Vitamin D and Health report	Infants and Young Children - As a precaution all breastfed infants aged 0–1 years, whether exclusively or partially breastfed, should be given 8.5–10 µg/day (340–400 IU/day) of vitamin D - Infants fed infant formula should not be given a vitamin D supplement unless they are receiving <500 ml of formula a day - All children aged 1–4 years should be given 10 µg/day (400 IU/day) of vitamin D Children aged over the age of 4 years and adults (including pregnant and lactating women, and adults aged over 65 years) - Everyone should consider taking 10 µg/day of vitamin D from October to March People at risk of vitamin D deficiency (e.g. for people who are not often outdoors, are in an institution like a care home, usually wear clothes that cover up most of their skin when outdoors or have darker skin) - Should take 10 µg/day of vitamin D throughout the year
Advice since the pandemic		
April 2020	Public Health England (PHE)	- During the COVID-19 pandemic, everyone should consider supplementation (10 µg/day), even during the summer months, if time outdoors is limited
June 2020	SACN – Rapid review: Vitamin D and acute respiratory tract infections (ARTIs)	- Overall, the evidence at this time does not support recommending vitamin D supplementation to prevent ARTIs in the general UK population - No reason to change the current recommendation on vitamin D supplements in order to protect bone and muscle health
November 2020	Department of Health and Social Care (DHSC)	- Free vitamin D supplements offered to those who were clinically extremely vulnerable and for care home residents for the winter months to support general health, in particular bone and muscle health
December 2020	SACN – Update of rapid review: Vitamin D and acute respiratory tract infections	- Overall, there may be some benefit from daily, low-dose vitamin D supplementation (between 10–25 µg/day; 400–1000 IU/day) in reducing risk of ARTIs. The size of any potential benefit of vitamin D in reducing ARTI risk may be small - No reason to change current recommendation on vitamin D supplements in order to protect bone and muscle health - This topic should be kept under urgent review
December 2020	National Institute for Health and Care Excellence (NICE) – COVID-19 rapid guideline: vitamin D – NICE guideline NG187	- Encourage people to follow UK government advice on taking a vitamin D supplement to maintain bone and muscle health - Do not offer a vitamin D supplement to people solely to prevent or treat COVID-19, except as part of a clinical trial
December 2020	National Institute for Health and Care Excellence (NICE) – Vitamin D deficiency in adults – treatment and prevention	- All adults living in the UK, including people at increased risk of vitamin D deficiency, should take a daily supplement containing 400 international units (IU [10 µg]) of vitamin D throughout the year, including in the winter months

Source: SACN (2016), NHS (2020), DHSC (2020), SACN (2020a), SACN (2020b), NICE (2020a), NICE (2020b).

and continues to attract media headlines (ITV News, 2021; The Guardian, 2021a; The Guardian, 2021b). This article aims to explore some of the aspects in the scientific debate on vitamin D supplementation and COVID-19 and the public health implications, as well as providing some background on vitamin D's role in immunity.

VITAMIN D AND IMMUNITY

The immune system is complex and involves a network of cells, tissues and organs that work together to defend the body against a variety of assaults, including attacks from pathogens. Vitamin D has been shown to have immunoregulatory and anti-inflammatory properties

(Calder, 2020). Vitamin D receptors have been identified in most immune cells, including in activated T cells, antigen-presenting cells, macrophages, monocytes and cytotoxic T cells, and some cells of the immune system (*e.g.* macrophages and monocytes) can synthesise the active form of vitamin D from its precursor (Calder, 2020; Di Rosa et al., 2011). Data from in vitro studies suggest that vitamin D can increase the ability of the innate immune system to fight against viruses and defend against respiratory pathogens, as well as inhibit pulmonary inflammatory responses (Hughes & Norton, 2009; Sassi et al., 2018; Zdrenghea et al., 2017) and other evidence suggests vitamin D might also exert an inhibitory effect on the adaptive immune system by retarding the differentiation of B cell precursors into plasma cells and reducing the inflammatory response of T helper 1 cells (EFSA, 2010). Furthermore, population-based studies have shown that serum 25(OH)D concentration is associated with improved lung function markers (Craveiro et al., 2018; Ganji et al., 2020).

VITAMIN D AND COVID-19: A BRIEF LOOK AT THE EVIDENCE SO FAR

In the spring of 2020, the available evidence linking vitamin D with upper respiratory tract infections (URTIs) was reviewed by Lanham-New and colleagues (Lanham-New et al., 2020). The authors concluded that there were plausible mechanisms linking vitamin D and protection against URTI, but whether these mechanisms apply with COVID-19 is not currently known. One of the studies discussed was a systematic review and meta-analysis of individual participant data from vitamin D supplementation randomised controlled trials (RCTs), which reported that vitamin D supplementation can reduce the incidence of acute URTIs, especially in those with vitamin D deficiency at baseline (Martineau et al., 2017). However, study settings, vitamin D supplemental doses, reporting and assessment of ARTIs and trial results were very heterogenous. Many of the included studies were in populations with pre-existing respiratory disease, and the overall statistically significant result in the meta-analysis of the 24 included trials was dependent on the inclusion of two studies undertaken in developing countries (Mongolia and Afghanistan), which may limit their applicability to the general population in the UK (Lanham-New et al., 2020). Lanham-New and colleagues recommended a need for appropriate vitamin D RCTs to evaluate the effects of vitamin D supplementation on COVID-19 infections. However, until there is more robust scientific evidence for vitamin D, they strongly cautioned against the use of high vitamin D supplementation [greater than the upper limit of 4000 IU/day (100 μg/day)], and strongly endorsed avoidance of vitamin D deficiency in the population and following government advice on supplementation (10 μg/day) (Lanham-New et al., 2020).

Observational evidence indicates that, in general, groups such as some ethnic minorities, older adults and people living with obesity, who are at greater risk of hospitalisation and mortality risk from COVID-19 infection, also have lower vitamin D status (Lanham-New et al., 2020). According to a PHE report looking at disparities in the risk and outcomes of COVID-19, among those diagnosed with COVID-19, the mortality risk (not taking into account underlying health issues) is greater in males, people aged 80 years or over, those living in deprived areas and those in Black, Asian and Minority Ethnic (BAME) population groups (PHE, 2020). In England up to 8 May 2020, 27% of deaths from COVID-19 were reported among people in care homes, and obesity has also been linked to COVID-19 infection and poorer outcomes among those infected (*i.e.* hospitalisation and/or death) (PHE, 2020). Observational data have also shown an association between patients who have low vitamin D status and an increased risk of severe COVID-19 infection (Liu et al., 2021; Panagiotou et al., 2020). Data from an initial analysis of the first-reported UK Biobank COVID-19-positive cases [n = 580 (included those who have been treated as a hospital inpatient as well as those who have not)] compared with negative controls (n = 723) found, on average, serum 25(OH)D status was almost identical in those who tested positive (43.3 nmol/l) compared to those who tested negative (44.1 nmol/l) for COVID-19. Similarly, a more recent study on the UK Biobank cohort (656 had inpatient confirmed COVID-19 infection and 203 died of COVID-19 infection) did not demonstrate a link between 25(OH)D concentrations and risk of severe COVID-19 infection and mortality (Hastie et al., 2021). Notably, vitamin D status was assessed in the Biobank cohort a decade before the pandemic, in 2006–2010 and so may have since changed.

In June 2020, SACN published a rapid review which included the systematic review and meta-analysis by Martineau et al. (2017) (mentioned earlier) that had reported some benefit. SACN concluded there was insufficient evidence to determine whether vitamin D supplementation could have a role in preventing respiratory tract infections (SACN, 2020a). Subsequently, the National Institute for Health and Care Excellence (NICE), PHE and SACN convened an expert panel and published rapid guidelines in December 2020 on vitamin D for COVID-19, under the auspices of NICE (NICE, 2020a; see Table 1). The panel agreed that although low vitamin D status has been associated with more severe outcomes from COVID-19, it was not possible to confirm causality because many of the risk factors for severe COVID-19 outcomes are the same as the risk factors for low vitamin D status. They added that since vitamin D is a negative acute phase reactant, its

serum concentration falls during a systemic inflammation such as severe COVID-19 illness and it is difficult to know if low vitamin D levels, measured after the onset of infection, cause poor outcomes or are a result of the infection (NICE, 2020a; SACN, 2020b; Wise, 2020). It could also be possible, however, that vitamin D requirements increase as a result of infection, causing serum levels to fall, since it has been reported, for example, that epithelial cells in the lungs activate vitamin D in response to infection, leading to increased levels of the anti-microbial peptide, cathelicidin (Laaksi, 2012).

Included in the NICE review was discussion of a recent systematic review and meta-analysis by Jolliffe et al. (2021). This study reported that vitamin D supplementation reduced the risk of acute respiratory infections and that protection was associated with administration of daily doses of 10–25 µg (400–1000 IU) of vitamin D for up to 12 months, compared with placebo, despite evidence of significant heterogeneity across trials (Jolliffe et al., 2021). NICE highlighted a number of notable limitations with the sub-group analyses. Protection was only seen in children (aged 1–16 years), yet poorer outcomes of COVID-19 are generally far more common in older adults (NICE, 2020a). Beneficial effects on acute respiratory tract infection prevention in children were associated with daily doses of 10–25 µg (400–1000 IU) of vitamin D, but not with higher doses [over 25 µg (1000 IU) daily or more], when supplementation was weekly or monthly, or in adults (NICE, 2020a). In addition, the panel highlighted substantive limitations in the included studies with inconsistency between study results and differences in study populations and methodologies including country, latitude, age ranges, comorbidities, dosing frequency, percentage of participants with low vitamin D status (<25 nmol/l) and definitions of outcomes (including type of respiratory infection), making it difficult to draw conclusions relevant to the general population (NICE, 2020a).

When the panel considered the evidence for treating COVID-19 using vitamin D supplements, they were presented with evidence from the NICE evidence review of vitamin D for COVID-19 (NICE, 2020a), which comprised one small, very low quality, RCT in secondary care from Spain (Entrenas Castillo et al., 2020). The trial used a very high dose of oral calcifediol [25(OH)D], the circulating metabolite of vitamin D produced from vitamin D in the liver, which is not commonly used as a supplement in the UK. This dose was estimated to be considerably higher than UK vitamin D recommendations, equivalent to around 5000 µg (200 000 IU) of vitamin D in the first week [about 700 µg vitamin D (28 000 IU) daily] falling to 1300 µg (52 000 IU) in subsequent weeks for the duration of the study [about 200 µg vitamin D (8000 IU) daily]. The panel also had concerns about differences in comorbidities between the two comparator groups and a lack of blinding which could have resulted in biased estimates (NICE, 2020a; Wise, 2020).

In relation to COVID-19, the NICE guidance recognises that there is currently no robust evidence to recommend vitamin D supplementation specifically to prevent or treat COVID-19 (unless as part of a clinical trial). The panel also recognised the pressing need for good quality, relevant data to ensure that guidance can be updated if necessary (*i.e.* definitive large-scale RCTs, including population groups who have higher risk of low vitamin D status and/or are disproportionally affected by COVID-19, such as BAME groups and people living with obesity). Whilst awaiting results of such trials, the panel agreed that the UK population should be encouraged to adhere to current government guidance, that is to take a daily supplement containing 10 µg of vitamin D especially between October and early March, and all year round for those at particular risk of low vitamin D status (*e.g.* those who are frail, housebound or in a care home, or those who usually wear concealing clothes outdoors). These recommendations are to support good musculoskeletal health, and the panel was aware of the updated SACN recommendation that a vitamin D intake of 10 µg/day may also provide some additional benefit in reducing the risk of acute respiratory tract infections (NICE, 2020a). At the end of November 2020, the government announced free vitamin D supplements for those who are clinically extremely vulnerable and for care home residents for the winter months to support general health, in particular bone and muscle health (DHSC 2020). This topic is being kept under review and the panel agreed that the recommendations for COVID-19 prevention and treatment should be considered for an update as additional evidence from trials becomes available (NICE, 2020a). The panel acknowledged that a number of RCTs considering vitamin D supplementation in prevention and treatment COVID-19 are known to be in progress and many of these are listed in NICE guideline NG187 (NICE, 2020a), some of which are outlined on the next section.

Since the publication of the NICE review, and at the time of writing this article, results from some studies and trials on vitamin and COVID-19 have become available, and mostly have demonstrated that vitamin D is not related to COVID-19 outcomes. An RCT in Brazil aimed to investigate the effect of a single high dose of vitamin D3 on hospital length of stay in patients with COVID-19 (Murai et al., 2021). The study included 240 hospitalised patients with COVID-19 who were moderately to severely ill at the time of enrolment and were randomly assigned to receive a single oral dose of 200 000 IU (5000 µg) of vitamin D3 (n = 120) or placebo (n = 120). Results indicated that length of hospital stay was not significantly different between the vitamin D3 group and the placebo group, nor was in-hospital mortality, admission to the intensive care unit or need for mechanical ventilation. The authors

concluded that their findings do not support the use of a high dose of vitamin D3 for treatment of moderate to severe COVID-19 (Murai et al., 2021). Several limitations have been highlighted. Firstly, the relatively low sample size means it could have been underpowered to detect small, but clinically meaningful, differences between the groups (Murai et al., 2021). Secondly, patients who required invasive mechanical ventilation and those admitted to the intensive care unit, in other words those who were critically ill, were excluded; therefore, the results cannot be generalised to critically ill patients. Thirdly, only 115 participants had vitamin D deficiency [25(OH)D <20 ng/ml]. Lastly, the patients were given vitamin D3 after a relatively long time from symptom onset to randomisation (mean of 10.3 days) (Murai et al., 2021).

An accompanying editorial stated that if this clinical trial is taken in isolation, the findings may appear ambiguous; for example, the findings do not exclude clinically important benefit (or harm) from high-dose vitamin D3 administration in hospitalised patients with moderate to severe COVID-19. In addition, the study did not look at use of vitamin D in patients with mild (outpatient) COVID-19 who are early in their symptom course (Leaf & Ginde, 2021). Leaf and Ginde emphasised that, based on experience in the pandemic, it is likely many of the other trials currently running will also be underpowered or will not achieve target enrolment. Therefore, given the lack of highly effective therapies against COVID-19, Leaf and Ginde conclude that it is important to remain open-minded to emerging results from rigorously conducted studies of vitamin D, despite smaller sample sizes and important limitations of some studies (Leaf & Ginde, 2021). Also worthy of consideration is that differences in participants, type, dose, initial vitamin status and duration of vitamin D supplementation, study endpoints and risk of bias make interpretation of the trial evidence difficult (Vimaleswaran et al., 2021).

A study, yet to be peer-reviewed at the time of writing, made headlines in *The Guardian* and found no evidence that vitamin D sufficiency could protect against COVID-19 (The Guardian, 2021c). Butler-Laporte and colleagues used two-sample Mendelian randomisation (MR) to assess evidence supporting a causal effect of circulating 25(OH)D levels on COVID-19 susceptibility and severity (Butler-Laporte et al., 2021). MR is a genetic epidemiological method that uses genetic variants as instrumental variables to infer the causal effect of an exposure [in this case 25(OH)D level] on an outcome (in this case, COVID-19 susceptibility and severity) in observational data (Butler-Laporte et al., 2021; Davies et al., 2018). The researchers used the genetic variants obtained from the largest consortium of COVID-19 cases and controls (The COVID-19 Host Genetics Initiative, 2020), and the largest study on genetic determinants of vitamin D levels from UK Biobank data (Manousaki et al., 2020), and used MR to estimate the effect of increased vitamin D on COVID-19 outcomes, whilst limiting confounding. In multiple analyses, results showed no evidence for an association between genetically predicted vitamin D levels and COVID-19 susceptibility, hospitalisation or severe disease. The researchers conclude that their findings suggest that other therapies should be prioritised over vitamin D for COVID-19 trials (Butler-Laporte et al., 2021).

CLINICAL TRIALS ON VITAMIN D AND COVID-19 AND THE IMPACT OF VACCINATION PROGRAMMES

A number of clinical trials, looking at either the prevention or treatment of COVID-19 with vitamin D, are currently under way, and the main results are anticipated some time in 2021. One trial looking at whether vitamin D can prevent COVID-19 is the *CORONAVIT* trial, an open-label, phase 3, RCT conducted in the UK, investigating whether implementation of a test-and-treat approach to correct sub-optimal vitamin D status results in reduced risk and/or severity of COVID-19 and other acute respiratory infections (Clinicaltrials.gov, 2020a). The trial is designed to recruit 6200 healthy individuals aged 16 years or older, and participants in the intervention group with low vitamin D status will be offered either 20 μg/day (800 IU/day) or 80 μg/day (3200 IU/day) of vitamin D3, whilst the control group receives standard care [national recommendation of 10 μg/day (400 IU/day) vitamin D]. The primary endpoint is the proportion of participants experiencing at least one doctor-diagnosed or laboratory-confirmed acute respiratory infection of any cause over 6 months. The secondary endpoints include a number of COVID-19-related endpoints, such as requiring hospitalisation due to COVID-19, hospitalised for COVID-19 requiring ventilatory support, and dying of COVID-19, as well as other endpoints such as the proportion of participants who experience influenza requiring hospitalisation, dying of any cause, dying of influenza and dying of any acute respiratory infection (Clinicaltrials.gov, 2020a).

Other trials are looking at the therapeutic benefit of high doses of vitamin D in people with COVID-19. The *CoVitTrial* is a multicentre randomised trial of high dose versus standard dose vitamin D3 in high-risk COVID-19 patients based in France. It is recruiting 260 patients aged 65 years or older, diagnosed with COVID-19 infection within the preceding 3 days and seen in a hospital, clinical consultation or nursing home setting (Clinicaltrials.gov, 2020b). The trial compares a single high oral dose of 10 000 μg (400 000 IU) of vitamin D3 with a single lower oral dose of 1250 μg (50 000 IU) of vitamin D3. The primary endpoint is death from any cause during the first 14 days; secondary endpoints include death from any cause during the first 28 days and

clinical evolution over 14 days and 28 days based on the World Health Organization (WHO) Ordinal Scale for Clinical Improvement for COVID-19 (Clinicaltrials.gov, 2020b).

The first *COVIDIOL* trial in Cordoba, Spain (Castillo et al., 2020), included in the recent rapid review mentioned earlier, is being followed by a trial involving 1008 patients aged 18–90 years diagnosed with either COVID-19 and radiological image compatible with inflammatory pleuropulmonary exudate or with onset of symptoms in the last 7 days and an uncomplicated respiratory infection for outpatient follow-up (Clinicaltrials.gov, 2020c). The intervention group will receive the best available treatment (which will include any combination of drugs included in the current protocol of the Ministry of Health and/or complementary notes issued by the Spanish Agency of Medicines and Health Products) plus oral calcifediol [25(OH)D] [2 capsules (532 µg/21 280 IU) on day 1 and 1 capsule (266 µg/10 640 IU) on days 3, 7, 14, 21 and 28], whereas the control group will receive the best available treatment only as described earlier (Clinicaltrials.gov, 2020c). The primary endpoints are intensive care unit (ICU) admission and death within 28 days; secondary endpoints include time until admission to ICU with mechanical ventilation, time from onset of symptoms to discharge of patients in conventional hospitalisation, and time until mechanical ventilation is removed (Clinicaltrials.gov, 2020c).

A trial investigating both the prevention and treatment of COVID-19 with vitamin D is the *Vitamin D for COVID-19 (VIVID)* trial in the US. This is recruiting 1500 newly diagnosed individuals with COVID-19 infection, together with up to one close household contact for each COVID-19 patient (~1200 contacts), randomised to either vitamin D3 [loading dose of 240 µg/day (9600 IU/day) for day 1 and day 2, then 80 µg/day (3200 IU/day] or placebo in a 1:1 ratio and a household cluster design (study duration of 4 weeks) (Wang et al., 2021). The primary outcome is the occurrence of hospitalisation and/or mortality; key secondary outcomes include symptom severity scores among cases and changes in the infection (seroconversion) status (to help identify infection rates) for their close household contacts. Changes in vitamin D 25(OH)D levels will be assessed, and their relation to study outcomes will be investigated (Wang et al., 2021).

Worthy of consideration is that, since these trials were initiated, there has been a roll out of a large-scale vaccination programme, especially in the UK in older and middle-aged adults, and front-line workers (NHS, 2021), which could potentially decrease the power of the trials by reducing the event rate (Proteomics & Metabolomics, 2021). However, vitamin D status has also been suggested to influence the effectiveness of vaccinations. A systematic review and meta-analysis of nine studies (involving 2367 participants) found that individuals with low vitamin D status were less protected against two strains of influenza after having been vaccinated compared to those who had adequate vitamin D levels (Lee et al., 2018). Professor Adrian Martineau, Queen Mary University of London, the lead researcher of the *CORONAVIT* trial has said that he hopes vitamin D might improve the immune response to the COVID-19 vaccination making it more effective, and that his team are investigating that possibility as a sub-study within the trial (Proteomics & Metabolomics, 2021).

PUBLIC HEALTH IMPLICATIONS OF WIDESPREAD LOW VITAMIN D STATUS

Low vitamin D status is widespread in many countries and could be preventable by supplementation, especially in the winter months (Brenner, 2021; Griffin et al., 2020). In the UK, prior to SACN's advice in 2016, the government's advice was that only vulnerable groups (*e.g.* young children, pregnant and lactating women, adults aged over 65 years and some ethnic minorities) should take vitamin D supplements to meet the recommended intakes set by COMA in 1991. Yet, the re-emergence of nutritional rickets in young children in some groups of the population, as well as widespread low vitamin D status in the population as a whole, suggests that these recommendations were not being widely implemented (Buttriss, 2020). The most recent data published from the *NDNS* include the period following the new advice on vitamin D introduced in 2016 [years 9–11 of the rolling programme (2016/2017–2018/2019)]. Results show that mean vitamin D intakes from all sources (including supplements) were below the recommendations for all age groups (except for women aged 65–74 years), and that 19% of children aged 11–18 years, 16% of adults aged 19–64 years and 13% of adults aged 65 years and over, had low vitamin D status (PHE & FSA, 2020). However, there is some evidence of improvement in vitamin D status in children. Compared with years 7 and 8 (combined), the mean 25(OH)D concentration was 6.2 nmol/l higher in children aged 4–10 years in years 9–11 (combined). Consistent with this, the prevalence of deficiency in children aged 4–10 years was lower in years 9–11 (combined) (2%) compared with years 7 and 8 (combined) (10%), although this difference was not tested for statistical significance. There were no significant changes in mean 25(OH)D in the other age groups (PHE & FSA, 2020). Interestingly, women aged 65–74 years had the highest vitamin D supplement use, with 40% taking supplements compared to just 9% of children aged 11–18 years, 17% of adults aged 19–64 years and 32% of adults aged 65 years and over (PHE & FSA, 2020). These data suggest that people are still insufficiently aware of government advice on

vitamin D supplementation and/or how to implement it (Buttriss, 2020).

The sample size of the *NDNS* is not large enough to explore sub-group differences. However, the UK Biobank has been used to study regional, BMI-related and ethnic minority differences in vitamin D status (Lin et al., 2021). The authors report that Asian (n = 4297/8000, 53.7%) and Black (n = 2459/7046, 34.9%) participants had a higher prevalence of vitamin D deficiency than White participants (n = 50 920/422 907, 12%). Male sex, abnormal BMI (underweight/overweight/obese), non-white ethnic backgrounds (Mixed/Asian/Black/Chinese/Other ethnicity), smoking, living in Scotland (*i.e*. a more northerly latitude) and being more socioeconomically deprived were associated with higher risk of vitamin D deficiency (defined as <25 nmol/l) (Lin et al., 2021).

Although there are signs of improvement from the *NDNS*, compliance with current advice is far from widespread. This highlights the importance of healthcare professionals routinely raising awareness of the need for supplementation at every point of contact, especially in at-risk groups. It has also been suggested that the need for somewhat complex and nuanced advice seems to have led to an oversimplified interpretation by some healthcare professionals, which may be leading to confusion about the detail of the government's recommendations (Buttriss, 2020; Buttriss et al., 2021). Over the past year, advice from government has become more streamlined (Table 1) and this may be of help going forward. NICE's guidance on *Vitamin D deficiency in adults – treatment and prevention* has recently been updated which recommends that all adults living in the UK, including people at increased risk of vitamin D deficiency (NICE, 2020b), should take a daily supplement containing 400 IU (10 µg) of vitamin D throughout the year, including in the winter months, but it is unclear if this advice is routinely given. Whilst the government has supplementation policies in place, a recent workshop concluded that there has been a lack of implementation strategies (Buttriss et al., 2021). Therefore, as part of a multi-pronged approach to ensure that the government's vitamin D recommendations are actioned, it has been suggested that a fortification strategy to improve dietary intakes might be a consideration, especially if uptake of supplements remains low (Buttriss, 2020).

With regards to COVID-19, some experts argue that the lack of good randomised trial data, particularly with respect to vitamin D supplementation and disease prevention, does not necessarily indicate that vitamin D supplementation should not be advised based on the precautionary principle that it does no harm, may be beneficial and improves bone health (Griffin et al., 2020; Vimaleswaran et al., 2021). An evidence synthesis report by The Royal Society on recommendations for vitamin D supplementation for the prevention of COVID-19 suggests that vitamin D supplementation could be recommended based on indirect evidence just as the recommendations for social distancing and the wearing of masks have been (Griffin et al., 2020). Furthermore, even a small effect on protection from infection that may lower the COVID-19 effective Reproduction number (R) from just above one (as estimated for many countries shortly before or during lockdown measures of varying intensity during most of the second half of 2020) to just below one could make the difference between further exponential growth or regression of the pandemic (Brenner, 2021). A position statement from the Spanish Society of Geriatrics and Gerontology on vitamin D supplementation for the prevention and treatment of COVID-19 also recommends that its use should be standardised in clinical practice, despite the lack of evidence on specific doses of vitamin D to treat COVID-19 in older adults. They argue that '*…in an ideal world, health decisions must be made based on overwhelming evidence, but a time of crisis such as the current one may require a slightly different set of rules*' (Tarazona-Santabalbina et al., 2021).

Experts agree that regardless of whether vitamin D protects against COVID-19, adequate levels are important for musculoskeletal health so current recommendations on taking vitamin D supplements should be widely promoted (Brenner, 2021; Griffin et al., 2020; NICE, 2020a, 2020b). However, regarding safety, SACN reiterates the upper limits for vitamin D recommended by the European Food Safety Authority (EFSA), of 100 µg/day (4000 IU/day) for adults and children aged 11–17 years, 50 µg/day (2000 IU/day) for children aged 1–10 years and 25 µg/day (1000 IU) for infants (SACN, 2016).

CONCLUSION

Low vitamin D status particularly during the winter months remains commonplace around the world. This situation could be alleviated if supplementation policies designed to support musculoskeletal health were followed. It remains unclear whether vitamin D can protect against COVID-19 although studies are exploring this hypothesis. Despite some media headlines, it is important that vitamin D (or any other nutrient, food or supplement) is never positioned as a 'magic bullet' against COVID-19. During this unprecedented time, when people are constantly bombarded with information from the internet and social media and may be highly vulnerable to misinformation, it is vital that robust evidence-based messaging is disseminated to avoid a scenario where people may be misled into believing that taking vitamin D supplements will prevent or treat COVID-19 infection. Even if robust evidence emerges for vitamin D (or another nutrient), it should be considered in the context of the other established approaches

to combat the disease, such as vaccines, social distancing, wearing of masks, keeping windows open and hygiene measures. The communication of nuanced messages, where the evidence-base is less certain, is complex as it involves making a distinction between telling people that they should do something because it will make a difference versus telling people that they could do something that might help.

As the vaccination programme continues to be rolled out to more population groups, and is seen as a reliable action to bring an end to the pandemic, its effects could be maximised by ensuring the population has adequate nutrition and is taking vitamin D supplements as recommended, particularly those in at-risk groups. Although, no one food or single nutrient can combat infections or support the immune system, following a healthy, dietary pattern that includes foods rich in vitamin D and other nutrients known to support the immune system, maintaining a healthy weight, as well as having a healthy lifestyle including regular physical activity, safe exposure to sunlight, stress management and adequate amounts of sleep are all important.

CONFLICT OF INTEREST

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