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DOI:
10.1136/ bmjnph-2020-000089

Document Version
Publisher's PDF, also known as Version of record

Citation for published version (Harvard):
Lanham-New, S, Webb, A, Cashman, K, Buttriss, J, Fallowfield, J, Masud, T, Hewison, M, Mathers, JC, Kiely, M, Welch, A, Ward, K, Magee, P, Darling, A, Hill, TR, Greig, C, Smith, CP, Murphy, RJ, Leyland, S, Bouillon, R, Ray, S & Kohlmeier, M 2020, 'Vitamin D and SARS-CoV-2 virus/COVID-19 disease', *BMJ Nutrition, Prevention & Health*. https://doi.org/10.1136/ bmjnph-2020-000089

BMJ Nutrition, Prevention & Health

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To cite: Lanham-New SA, Webb AR, Cashman KD, *et al*. Vitamin D and SARS-CoV-2 virus/COVID-19 disease. *BMJ Nutrition, Prevention & Health* 2020;**0**. doi:10.1136/bmjnph-2020-000089

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Received 16 April 2020
Revised 29 April 2020
Accepted 30 April 2020

BACKGROUND AND AIM

The spread of novel SARS-CoV-2 virus, and the disease COVID-19 that is caused by SARS-CoV-2, continues apace. Saving lives and slowing the worldwide pandemic remain of utmost importance to everyone: the public, healthcare professionals, scientists, industry and governments.

It is absolutely essential that advice given to the public is evidence-based, accurate and timely; anything less would mislead and has the potential to cause harm. Popular information channels, such as social media platforms, have been rife with misinformation that has been perpetuated by fear and uncertainty. This has been the case particularly for diet and lifestyle advice. There are recommendations for the prevention of the spread of COVID-19 from the WHO,[1] the UK,[2] Irish[3] and USA[4] governments and the European Commission,[5] as well as public health and healthcare agencies, including key direction on self-isolation.[6]

This short original report aims to provide a balanced scientific view on vitamin D and SARS-CoV-2 virus/COVID-19 disease. It provides a succinct summary of the current scientific evidence of associations between vitamin D, influenza, upper respiratory tract infections (URTIs) and immune health. Importantly, the paper concludes with lifestyle strategies for avoiding vitamin D deficiency and ensuring a healthy balanced diet at any time, including during the current pandemic. The overarching messages are as follows: (1) Vitamin D is essential for good health. (2) Many people, particularly those living in northern latitudes (such as the UK, Ireland, Northern Europe, Canada and the northern parts of the USA, northern India and China), have poor vitamin D status, especially in winter or if confined indoors. (3) Low vitamin D status may be exacerbated during this COVID-19 crisis (eg, due to indoor living and hence reduced sun exposure), and anyone who is self-isolating with limited access to sunlight is advised to take a vitamin D supplement according to their government's recommendations for the general population (ie, 400 IU/day for the UK[7] and 600 IU/day for the USA (800 IU for >70 years))[8] and the European Union (EU).[9] (4) There is no strong scientific evidence to show that very high intakes (ie, mega supplements) of vitamin D will be beneficial in preventing or treating COVID-19. (5) There are evidenced health risks with excessive vitamin D intakes especially for those with other health issues such as a reduced kidney function.

NUTRITION, VITAMIN D AND IMMUNITY

Good nutrition and lifestyle factors (such as physical activity) have a positive impact on immune function, promoting biological and physiological systems and processes that enable humans to resist infection. In light of the current COVID-19 pandemic, and given the importance of diet to overall health and well-being, nutrients (macro and micro) deserve special attention.[10] As a key micronutrient, vitamin D should be given particular focus—not as a 'magic bullet' to beat COVID-19, as the scientific evidence base is severely lacking at this time—but rather as part of a healthy lifestyle strategy to ensure that populations are nutritionally in the best possible place.[11]

Vitamin D is unique: it is a prohormone which is produced in the skin during exposure to sunlight (UVB radiation at 290–315 nm) with, usually, smaller amounts obtained from food. During the winter months in areas of middle-high latitude, the solar elevation

remains low throughout the short daylight period, and there is insufficient solar UVB to support appreciable vitamin D synthesis.[12] For most people, dietary intake does not fully supply the body's vitamin D needs and so vitamin D status declines during the winter. For example, in Manchester, UK (53.5N) the nadir of seasonal vitamin D status occurs in February, with sunlight exposure once again becoming effective for vitamin D synthesis in the skin only from March onwards.[13] Relatively high prevalence of low vitamin D status globally has been reported over recent decades in a wide range of population groups,[14] including those in low latitude areas (despite the abundance of sunlight) and not necessarily confined to winter.[15] This may be due to environmental factors, such as air pollution, as well as cultural factors that lead to skin being covered and not subject to sunlight exposure.[16] Older, housebound individuals are at particularly high risk of vitamin D deficiency.[17]

Vitamin D status is reflected by the level of the circulating metabolite 25-hydroxyvitamin D (25OHD), which is produced by hepatic hydroxylation of vitamin D coming from either skin or the gut from oral intake.[18] If the 25OHD concentration is low (as defined in the UK by a 25OHD concentration of <25 nmol/L[7] and in the USA and some other countries by a 25OHD concentration of <30 nmol/L),[8 9] such as observed commonly during and towards the end of the winter, this indicates that stores are depleted and vitamin D-requiring functions may be impaired. The association between low vitamin D status and increased risk of rickets in children and poor musculoskeletal health in adults is well documented. In addition, vitamin D, via its active metabolites, regulates more than 200 genes including those genes that are responsible for cellular proliferation, differentiation and apoptosis.[19] The discovery of the expression of nuclear vitamin D receptors and vitamin D metabolic enzymes in immune cells provides a scientific rationale for the potential role of vitamin D in maintaining immune homoeostasis and in preventing the development of autoimmune processes.[20] The field of vitamin D research has grown exponentially in recent years with a much improved understanding of its biological importance. Recent meta-analyses of randomised controlled trials (RCTs) concluded that the use of vitamin D supplements was associated with lower total mortality in elderly, mostly vitamin D-deficient participants.[21 22] However, the most recent Vitamin D Assessment Study and the Vitamin D and Omega-3 Fatty Acid Study did not show a mortality effect in vitamin D-replete adults.[23 24]

VITAMIN D AND RESPIRATORY HEALTH

It has been hypothesised that there is an association between seasonal URTIs and low vitamin D status because both occur in the winter months. However, controversy remains as to whether there is a direct link between the seasonality of influenza and vitamin D deficiency. Higher influenza incidence in winter may be due to behavioural reasons including the greater time spent indoors, which increases individuals' proximity and hence likely interpersonal transmission. Nonetheless, vitamin D appears to inhibit pulmonary inflammatory responses[25] while enhancing innate defence mechanisms against respiratory pathogens.[26] Moreover, population-based studies show positive associations between circulating 25OHD concentration and lung function.[27] Nevertheless, formal systematic reviews/meta-analyses of these associations are urgently required.

URTIs, or 'common colds', are the most widespread of infectious diseases, with more than 200 viruses contributing to the clinical symptoms. Epidemiological studies in children have found a strong association between URTI and rickets.[28] A large cross-sectional study of the US population reported that URTI infections were higher in those with lower vitamin D status, with the association being stronger in those with respiratory diseases such as asthma and chronic obstructive pulmonary disease.[29] There is evidence that lower vitamin D status is associated with acute respiratory tract infections (ARTIs).[30] In a recent systematic review and meta-analysis of individual participant data from vitamin D supplementation RCTs, vitamin D supplementation reduced the risk of ARTI, with the greatest benefit in those with vitamin D deficiency at baseline.[31] However, it is important to note the limitations to this systematic review/meta-analysis;[32 33] there was a high level of heterogeneity in the findings and concomitantly, the overall significant results in the meta-analysis of the 24 included trials was dependent on the inclusion of the two studies undertaken in developing countries: Mongolia and Afghanistan. These two trials had specific participants and the findings should not be extrapolated to populations from more developed countries. This is particularly important as Panagiotou *et al* (2013) demonstrated that the efficacy of many treatments was substantially greater in less developed compared with more developed countries.[34] Furthermore, the specific clinical definitions of ARTI were varied across included studies, with many research participants with ARTI being self-diagnosed.

VITAMIN D, SARS-COV-2 VIRUS AND COVID-19 DISEASE

The continued spread of the novel SARS-CoV-2 virus, and the disease COVID-19 that is caused by SARS-CoV-2, has led to calls for widespread high-dose vitamin D supplementation.[35–39] These calls are without support from pertinent studies in humans at this time, but rather based on speculations about *presumed* mechanisms. There have been two key studies published to support this presumption: (1) An unbiased screen of repurposed drugs for treatment of avian influenza A H5N1 virus using appropriate cell lines and mice, which highlighted calcitriol (the active hormone of vitamin D) as a potential therapy.[40] (2) A recent analysis of vitamin D and viral infections.[41] However, whether these mechanisms apply with SARS-CoV-2 is not known. Studies investigating

vitamin D and COVID-19 are currently underway,[42 43] and more are likely to follow. Given that ethnic minorities are disproportionately affected with Covid-19—and this appears to be the case principally in the UK, the USA and other European countries—further research is justified, especially given that there is clear evidence that vitamin D deficiency is particularly common in these ethnic groups.[44 45]

However, we strongly caution against doses higher than the upper limit (4000 IU/day; 100 µg/day);[7 8] and certainly of very high doses of vitamin D (in some reports, 10 000 IU/day (250 µg/day) of vitamin D are being promoted) unless under personal medical advice/clinical advice by a qualified health professional. Instead, we advocate the following lifestyle strategies for avoiding vitamin D deficiency and ensuring a healthy, balanced diet.

VITAMIN D ADVICE

Current evidence-based advice for the prevention of vitamin D deficiency includes:

1. *Supplementation with vitamin D according to Government guidelines* (eg, 400 IU/day (10 µg/day) for the UK;[7] 600 IU/day (15 µg/day) for the USA[8] (800 IU/day (20 µg/day) for >70 years) and Europe.[9] These recommendations were established to ensure that 25OHD concentrations in the majority of the population are above 25 nmol/L (UK) in order to protect musculoskeletal health or above 30 nmol/L (USA) to minimise the risk of vitamin D deficiency (the USA recommendation was also established to optimise musculoskeletal health in the population using a 25OHD concentration of 50 nmol/L). Supplementation with vitamin D is particularly important during times of self-isolation associated with limited sunlight exposure. This is in line with the UK Scientific Advisory Committee on Nutrition (SACN)[7] recommendations for vitamin D, and the US Institute of Medicine (IOM) recommendations for vitamin D,[8] both of which were established under the assumption of minimal exposure to sunlight. Thus, re-emphasis of advice on safe sun exposure (below) and reinforcing government advice on supplements especially when sunlight exposure is low would further boost vitamin D status. The UK SACN, US IOM and EU European Food Safety Agency recommend that vitamin D intake (total from both foods and dietary supplements) should be limited to 4000 IU/day (100 µg/day) for adults, and there is broad international consensus that the general public should avoid higher dose supplements that risk total intake from all sources exceeding this level.
2. *Consumption of a nutritionally balanced diet*, for example, according to the UK Eatwell Guide[46] and US Food Pyramid[47] including vitamin D rich foods, that is, oily fish, red meat, egg yolk and fortified foods,[48] such as breakfast cereals in the UK, as well as fortified milk in the USA and Canada.[49 50]
3. *Safe sunlight exposure to boost vitamin D status*. Safe sunlight exposure will enable vitamin D production in skin from March through September in the UK, and at most northern latitudes. Dermal synthesis of vitamin D is most efficient with short, regular (daily) exposures when the sun is at its strongest (in the middle of the day).[51] The efficiency of vitamin D synthesis declines well before the threshold for sunburn is reached[12] but the desirable dose is skin-type dependent and so exposure times required differ for different skin types.[52] For the UK about 10 min of exposure at around lunchtime, in-season appropriate clothing, can meet vitamin D needs for white-skinned people; this increases to about 25 min for those of skin type V (ie, South Asian, brown skin tones).[53 54] What is key is to try to achieve the sunlight exposure without leaving home (eg, in the garden/balcony); and if that is not possible ensure that social distancing is maintained at all times. Increasing the unprotected skin area (skin not protected by clothing or sunscreen) will increase the vitamin D supply from skin while keeping exposure times short and suberythemal. Exposing as much skin as temperature and social comfort allow will maximise vitamin D supply through this route. For those of skin type V and VI (brown or black skin) the exposure requirements in UK sunlight are more challenging to achieve than for white-skinned people and oral vitamin D intake is especially important.
4. *Appropriate diet and lifestyle measures*, as emphasised by the WHO at this time, including adequate nutrition to protect the immune system.[55]
5. *Targeted nutritional advice*, for example, for UK Military personnel as advised by the Defence Nutrition Advisory Service, with specific reference to COVID-19.[56]
6. *Vitamin D—advice for bone health*. The Royal Osteoporosis Society provides specific guidelines on the management of vitamin D deficiency in adults with, or at risk of developing, bone disease.[57]

In conclusion, we recommend appropriate vitamin D RCTs to evaluate the effects of vitamin D supplementation on COVID-19 infections. Until there is more robust scientific evidence for vitamin D, we strongly caution against the use of high vitamin D supplementation (greater than the upper limit of 4000 IU/day (100 µg/day)). Rather, we strongly endorse avoidance of vitamin D deficiency[58] in the population (as per the six points above) and complete adherence to government's advice worldwide on the *prevention of the spread of COVID-19*.

SUMMARY FOR SOCIAL MEDIA

Vitamin D is essential for good health, especially bone and muscle health. Many people have low blood levels of vitamin D, especially in winter or if confined indoors, because summer sunshine is the main source of vitamin D for most people. Government vitamin D intake recommendations for the general population are 400 IU (10 µg) per day for the UK[7] and 600 IU (15 µg) per day for the

USA[8] (800 IU (20 µg) per day for >70 years) and the EU.[9] Taking a daily supplement (400 IU /day (10 µg/day) in the UK) and eating foods that provide vitamin D is particularly important for those self-isolating[59] with limited exposure to sunlight. Vitamin D intakes greater than the upper limit of 4000 IU (100 µg) per day may be harmful and should be avoided unless under personal medical/clinical advice by a qualified health professional.

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Contributors All authors drafted and amended the vitamin D and SARS-CoV-2 virus/COVID-19 disease report and all were in agreement with the wording. SAL-N, ARW and KDC are collective lead authors.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None

Patient consent for publication Not required.

Ethics approval Not required

Provenance and peer review Not commissioned; externally peer reviewed.

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