Does vitamin D supplementation prevent SARS-CoV-2 infection in military personnel? Review of the evidence

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ABSTRACT
For most individuals residing in Northwestern Europe, maintaining replete vitamin D status throughout the year is unlikely without vitamin D supplementation and deficiency remains common. Military studies have investigated the association with vitamin D status, and subsequent supplementation, with the risk of stress fractures particularly during recruit training. The expression of nuclear vitamin D receptors and vitamin D metabolic enzymes in immune cells additionally provides a rationale for the potential role of vitamin D in maintaining immune homeostasis. One particular area of interest has been in the prevention of acute respiratory tract infections (ARTIs). The aims of this review were to consider the evidence of vitamin D supplementation in military populations in the prevention of ARTIs, including SARS-CoV-2 infection and consequent COVID-19 illness. The occupational/organisational importance of reducing transmission of SARS-CoV-2, especially where infected young adults may be asymptomatic, presymptomatic or paucisymptomatic, is also discussed.

Key messages

► Vitamin D insufficiency and deficiency are common in military cohorts and there is good evidence for supplementation in the prevention of musculoskeletal disease.
► Vitamin D status may influence the risk of acute respiratory tract infection particularly in a military cohort, although further research is under way.
► There is mechanistic and observational data in vitamin D repletion and in the reduction of the severity of COVID-19, although more interventional data are required.
► More research is required to ascertain the effect of vitamin D status/supplementation on asymptomatic/mildly symptomatic SARS-CoV-2 infection, COVID-19 and associated transmission risks.

INTRODUCTION

Vitamin D is synthesised in the skin on exposure to ultraviolet (UV) radiation, such that vitamin D concentrations are influenced by season[1] and geographical location.[2] Vitamin D is also present in certain foods, naturally in oily fish and, to a lesser extent, meat, fortified spreads and cereals (Table 1). For most individuals residing in Northwestern Europe and other northern latitudes, maintaining adequate (replete) vitamin D status throughout the year is unlikely without vitamin D supplementation[3] and deficiency remains common.[4] Vitamin D deficiency has also been recognised in military cohorts,[1] with the role of sunlight and vitamin D sufficiency recognised prior to World War II.[5] Servicemen used UV lights when underground for prolonged periods of time while defending the Maginot line[6] (Figure 1), although it is unknown if this was specifically for the purpose of treating vitamin D deficiency.

Vitamin D is converted to its active metabolite calcitriol $(1,25(OH)_2D3)$ in two hydroxylation steps. The first intermediary metabolite (calcidiol, 25(OH)D3) is generated in the liver and is the most widely used marker of vitamin D status. In the kidney, 25(OH)D3 is then converted to calcitriol $(1,25(OH)_2D3)$, which, reflecting vitamin D stores less well than 1,25(OH)D3, is not measured routinely in clinical practice. Vitamin D deficiency is defined by the UK Scientific Advisory Committee on Nutrition (SACN)[4] as circulating serum concentration of 25(OH)D<25 nmol/L (immunoassay value). Relative insufficiency and sufficiency of vitamin D are taken as concentrations up to 49.9 and ≥50 nmol/L, respectively.[7] Of the UK adult population (19–64 years of age), 39% are vitamin D deficient in winter compared with 8% in summer.[4] As well as those residing at northern latitudes, vitamin D deficiency is more common in the elderly, pregnant, obese, persons of colour, as well as those hospitalised or residing in institutions.[4]

Vitamin D's primary role is in the regulation of calcium and phosphate metabolism, where it plays an essential role in bone health; however, vitamin D may regulate many other cellular functions with receptors for vitamin D universally expressed in nucleated cells. Epidemiological studies have implicated vitamin D deficiency in increasing the risk of numerous extraskeletal disease processes, including cancer and autoimmune, cardiovascular and infections.[8]

One recent potential application of vitamin D is in the prevention of infection by SARS-CoV-2 and/or the prevention or attenuation of the clinical manifestation of SARS-CoV-2 infection, COVID-19. Given the current absence of a proven safe, effective vaccine against SARS-CoV-2, prevention of new infections and their onward transmission is

Table 1 Dietary sources of vitamin D

Food	Vitamin D content (µg per 100 g/100 mL)
Fish and shellfish	
Grilled herring	16.1
Canned pink salmon in brine	13.6
Grilled salmon	7.8
Smoked mackerel	8.2
Tinned sardines in tomato sauce	3.3
Milk and milk products	
Build up powdered sachet (shake)	1.7
Fortified soy milk	0.8
Skimmed milk, dried	0.8
Horlicks, powder	18.5
Animal products	
Lamb leg, roast	0.7
Beef, roast	0.8
Corned beef, canned	1.3
Grilled back bacon rashers	0.8
Grilled pork sausage	1.1
Cereals and spreads	
Fortified, low-fat spread, polyunsaturated	8.4
Baking fat/margarine	8.8
Bran-type cereal, fortified	3.9
Breakfast cereal, cornflakes, fortified	4.7

Adapted from x.

of critical importance to public health and the ability of individuals, organisations and nation states to meet the challenges presented by the pandemic.

The aims of this review were to consider the evidence of vitamin D supplementation in military populations in the prevention of acute respiratory tract infections (ARTIs), including SARS-CoV-2 infection, transmission and hospitalisation with COVID-19. There are multiple other factors, physiological, anthropological and psychological, which influence SARS-CoV-2 infection and transmission. While these are beyond the scope of this paper, the role of vitamin D in defence populations would need to be studied comprehensively with these considerations.

SEARCH STRATEGY
Studies were identified through a systematic search of the following electronic databases: MEDLINE (Ovid), Embase (Ovid) and CINHAL (Ebsco). The search strategy included vocabulary (Medical Subject Headings) and natural language terms: (('vitamin D' OR 'vit D' OR 25-(OH)D OR '25-OH-D3'
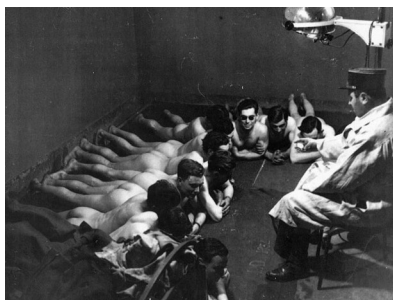

Figure 1 Soldiers receiving ultralight light, presumably to prevent vitamin D deficiency, while defending the Maginot line during World War II.

OR '25-hydroxyvitamin D') AND (COVID-19 OR COVID-19 OR (respiratory AND infection))). This yielded over 700 abstracts, which were manually reviewed for relevancy, and then original manuscripts were reviewed. Due to the lack of observational or interventional research, no systematic review could be performed with regard to vitamin D and COVID-19.

VITAMIN D IN THE MILITARY: DEFICIENCY STATES AND MUSCULOSKELETAL HEALTH
Several studies have shown a predominantly seasonal vitamin D deficiency in multiple different military populations. In a prospective study of serum 25-(OH)D3 concentrations in 220 Finnish military recruits over the course of a year, 0.9% had vitamin D deficiency increasing to 38.9% in the winter.[2] A study of Royal Navy submariners investigated three cohorts: one deployed in winter, one deployed in summer and a non-deployed cohort. Vitamin D supplementation was available for deployed cohorts only. The predeployment winter cohort had a mean serum 25-(OH)D3 concentration of 38 ± 16 nmol/L in comparison to the predeployment summer cohort (53 ± 20 nmol/L, $p<0.001$), which improved significantly with 2400 IU of daily supplementation (mean increase of 47 ± 4 nmol/L, $p<0.001$) in comparison to participants who did not supplement.[9] A small randomised study in US submariners reported similar reductions in vitamin D levels, with elevation of bone turnover biomarkers on submergence, but supplementation with 400 IU was insufficient to maintain serum vitamin D levels.[10] This is of particular interest as 400 IU is the supplementation dose advised by SACN.[4] In a subsequent Israeli study, in addition to the significant reduction in vitamin D levels, there was a detrimental effect on bone strength and metabolism, which took 6 months to return to baseline levels on return to shore.[11]

An initial observational study in 74 female US Army recruits over an 8-week period showed a significant decrease in 25(OH)D3 and a significant rise in parathyroid hormone (PTH) from August to October.[12] A further observational study of vitamin D status in Caucasian female participants during US Army basic training showed a decrease in 25(OH)D3 levels over the 10-week course of training. While black female participants showed an increase in vitamin D levels during basic training, the serum 25(OH)D3 levels were significantly lower than Caucasian participants at all time points.[13]

Vitamin D promotes gastrointestinal calcium and phosphate absorption, allows mineralisation of type II collagen matrix in bone and also plays a role in muscle function. While protracted deficiency in adults is manifested as osteomalacia or secondary hyperparathyroidism, more modest deficiency is associated with increased risk of musculoskeletal injuries. Predominantly, military studies have investigated the association with vitamin D status (and subsequent supplementation) in relation to the risk of stress fractures, particularly during recruit training. In a prospective study of Finnish military recruits, stress fractures were associated with a higher PTH but not with lower 25(OH)D3 levels, although the authors concluded that given the poor vitamin D status of young Finnish men, intervention studies of vitamin D supplementation to lower serum PTH were warranted.[14] A further study of 800 randomly selected healthy Finnish military recruits had below median vitamin D levels (75.8 nmol/L) associated with an increased risk of stress fracture.[15] These findings were replicated in UK Armed Forces cohorts, where a study on Royal Marine recruits who had a baseline serum 25(OH)D3 concentration below 50 nmol/L had a significantly higher incidence of stress fracture (OR 1.6, 95% CI 1.0 to 2.6; $p<0.05$).[16]

Vitamin D supplementation appears to modify the stress fracture risk. In a large randomised double blind trial of female naval recruits randomised to 2000 mg of calcium and 800 IU of vitamin D or placebo, there was a 20% reduction in stress fractures in the treatment arm.[17] A further US Army study in military recruits again showed the benefit of vitamin D and calcium supplementation in terms of bone mineral density and cortical bone mineral content.[18] There is therefore good evidence for the supplementation of vitamin D for the prevention of musculoskeletal injury, such as stress fractures, particularly in recruit populations or in military cohorts undergoing periods of high musculoskeletal load, such as special forces selection or promotion cadres.

VITAMIN D STATUS AND SUPPLEMENTATION TO REDUCE THE RISK OF ARTIS

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 homeostasis. One area of interest has been in the prevention of ARTIs. In the respiratory tract, 1-alpha hydroxylase (CYP27B1), which is required for final activation of 25(OH)D3, is highly expressed in epithelial cells, suggesting vitamin D may play a role in preventing pulmonary infections.[19] In the respiratory tract, vitamin D has been found to attenuate viral and bacterial infection.[20] Potential mechanisms include down-regulation of intercellular adhesion molecule 1 and platelet activating factor receptor.[21]

A systematic review and meta-analysis that included 11 randomised controlled trials (RCTs; n=5660, mean age, 16y) indicated that vitamin D supplementation significantly reduced the risk of respiratory tract infection (RTI) (OR 0.64, 95% CI 0.49 to 0.84; p=0.001), though these results should be interpreted in the context of only four of the studies involving patient groups, significant heterogeneity and evidence of significant publication bias.[22] The protective effect was significant in trials with daily vitamin D supplementation (OR 0.51, 95% CI 0.39 to 0.67) but not in those that administered vitamin D in bolus doses once per month or less (OR 0.86, 95% CI 0.60 to 1.20). There was no effect of baseline serum 25(OH)D3 concentration on supplementation outcome. A further meta-analysis of the same seven RCTs, without the addition of the trials in patient groups, reported no difference in ARTI between supplemented and controlled groups (RR=0.98, 95% CI 0.93 to 1.03; p=0.45).[23] A 2013 systematic review of 39 studies (14 RCTs, 13 cohort, 8 case–control and 4 cross-sectional studies)[4] reported overall significant associations between low vitamin D status and increased risk of ARTIs for observational studies. Interventional trials in the systematic review provided conflicting evidence, possibly due to significant heterogeneity in dosing regimens and baseline vitamin D status. Several RCTs subsequent to this systematic review have reported that vitamin D supplementation did not reduce ARTI risk.[24–28] In a further study comparing high and low bolus dosing of vitamin D in predominantly deficient sheltered accommodation residents showed an increased risk of upper ARTI with the high bolus dose (HR=1.48, 95% CI 1.02 to 2.16; p=0.039).[29] At the present time, there is insufficient evidence to support recommending vitamin D supplementation to prevent ARTIs in the general UK population. The SACN 'Rapid review: Vitamin D and acute respiratory tract infections'[30] issued a statement (June 2020) cautiously concluding this, unless data from interventional studies suggest otherwise.

ARTI, along with skin and soft tissue infections, represent a significant clinical burden during recruit training which leads to morbidity, loss of training time and additional training costs[31 32] as well as the potential for febrile illness to potentiate exertional heat illness.[33 34] While skin and soft tissue infections have been managed with topical antimicrobials and decolonisation protocols,[35] the role of vitamin D may been considered due to its integral role in innate immunity.[36] Hypothetically military cohorts most benefiting from vitamin D for ARTIs are those who would most benefit from the musculoskeletal effects; phase I and phase II recruit training, promotion cadres and special forces selection, as well as operational deployment in temperate settings. Thus, a rationale exists for examining any benefits of vitamin D supplementation specific to military units.

VITAMIN D STATUS IN COVID-19 INFECTION

SARS-CoV-2 appears to interact with human dipeptidyl peptidase 4 receptor (CD26), which is downregulated in vivo after correction of vitamin D insufficiency, hypothetically reducing propensity for infection.[37 38] Vitamin D may also modulate the immune response to increase production of antimicrobial peptides, including cathelicidin and defensins that destroy enveloped viruses, like SARS-CoV-2.[36 39] Vitamin D sufficiency may reduce the viral infection-associated cytokine storm[40] and lipopolysaccharide-induced upregulation of the renin–angiotensin system,[41] which are thought to be key components of the maladaptive host response leading to lung injury in COVID-19, but this concept again has not been definitively proven.[42] Increasing vitamin D status (to a state of vitamin D repletion) may also influence infection rates by promoting effective endothelial barrier function in the gut.[43] In the respiratory tract, 1-alpha hydroxylase (CYP27B1), which is required for final activation of 25-OH-D3, is highly expressed in bronchial epithelial cells, suggesting vitamin D plays an important role in preventing pulmonary infections.[44] Vitamin D also appears to modulate the activity of the cytokine interleukin-6. This might reduce the acute-phase response associated with greater pulmonary damage and complications such as ARDS or sepsis in a similar fashion to the monocloncal antibody tocilizumab, which has shown promise in cohort studies.[45 46]

It has been speculated that the distribution and chronicity of severe COVID-19 infections relate to seasonal variation in vitamin D status through sunshine exposure.[47] Black, Asian and minority ethnic groups may be at increased risk of developing severe manifestations of COVID-19[48–50] and have been shown to be at increased risk of vitamin D deficiency. While it has not been established independently or conclusively, increased melanin production may block synthesis of vitamin D in the skin, and hence, this may play a role in this risk of vitamin D deficiency. The endemic seasonal vitamin D deficiency may be exacerbated further secondary to government policy enforcing social distancing, self-isolation, lockdown and/or home working to reduce the transmission of COVID-19 during prior and successive waves. In addition, a high body mass index is strongly associated with lower serum 25-(OH)D3 status due to reduced synthetic capacity and sequestration of vitamin D in adipose tissue potentially rendering a significant fraction metabolically 'inert'. Ethnicity and obesity have both been identified as key risk factors for COVID-19 in the UK Biobank analysis, but, although 25(OH)D3 concentration was associated with severe COVID-19 infection and mortality univariately (mortality per 10 nmol/L 25(OH)D3 HR 0.92, 95% CI 0.86 to 0.98; p=0.016), this was no longer significant after adjustment for confounders (mortality per 10 nmol/L 25(OH)D3 HR 0.98, 95% CI 0.91 to 1.06; p=0.7). Vitamin D insufficiency or deficiency was also not

independently associated with either COVID-19 infection or linked mortality.[51]

However, several observational studies have indicated a protective effect of vitamin D sufficiency.[51 52] In 14 000 health service members who were tested for COVID-19 from 1 February to 30 April 2020, the mean plasma vitamin D level was significantly lower among those who tested positive than negative for COVID-19. Univariate analysis demonstrated an association between the low plasma 25(OH)D3 nmol.l^{-1} level and increased likelihood of COVID-19 infection [crude OR of 1.58 (95% CI: 1.24 to 2.01, p<0.001)], and of hospitalisation due to the SARS-CoV-2 virus [crude OR of 2.09 (95% CI: 1.01 to 4.30, p<0.05)]. In multivariate analyses that controlled for demographic variables, and psychiatric and somatic disorders, the adjusted OR of COVID-19 infection (1.45, 95% CI 1.08 to 1.95; p<0.001)) and of hospitalisation due to the SARS-CoV-2 virus (adjusted OR 1.95, 95% CI 0.98 to 4.845; p=0.061) with low vitamin D status remained significant.[53] A further observational study examined vitamin D status and hospitalisation outcomes in 212 COVID-19 patients. Of 49 patients with mild clinical outcomes, 47 had vitamin D>75 nmol/L. In contrast, only 2 of the 48 critical patients had vitamin D>75 nmol/L. For each SD increase in vitamin D, the odds of having a mild clinical outcome rather than a severe outcome were increased approximately 7.94 times. For the same increment, the odds of having a mild clinical outcome rather than a critical outcome were increased 19.61 times approximately.[54]

The National Institute for Health and Care Excellence (NICE) Evidence Summary 28 published as 'COVID-19 rapid evidence summary: vitamin D for COVID-19' (June 2020)[55] reviewed five studies published to date that have looked retrospectively at the association between vitamin D status and development of COVID-19. While four studies found an association or correlation with lower vitamin D status and subsequent development of COVID-19, confounding factors were not accounted for. Overall, NICE acknowledged that all studies assessed were at risk of bias due to the non-interventional study design. While we agree that studies have shown association rather than causation, these data are important to note and lend further support to the growing call for RCTs both in the treatment and prevention of COVID-19.[56–58]

Role of vitamin D supplementation in asymptomatic/mildly symptomatic SARS-CoV-2 infection and COVID-19

Presently, there is widespread interest in interventional studies into vitamin D with multiple randomised trials registered (Table 2). Predominantly, these are researching the effect of vitamin D supplementation in COVID-19; however, NCT 04386850 is also assessing the effect of vitamin D supplementation in preventing COVID-19 in healthcare workers. Several other trials (involving multiple interventions so not listed in Table 2) are assessing the role of vitamin D alongside other medications or vitamins, including hydroxychloroquine, aspirin, N-acetylcysteine, azithromycin, zinc, vitamin C and vitamin B$_{12}$. Additionally, there are numerous observational or non-controlled studies registered.

A public health application of vitamin D which could have a profound impact would be if vitamin D supplementation/sufficiency reduced asymptomatic spread of SAR-CoV-2. There is evidence for asymptomatic and presymptomatic infection playing a significant role in the rapid spread of COVID-19 around the globe.[59] Factors that may have contributed to the increased transmissibility of SARS-CoV-2 include (1) high levels of viral shedding in the upper respiratory tract, even before patients become symptomatic of COVID-19[60]; (2) reduced efficacy of symptom-based detection due to relatively early peaking of viral loads, such that false-negative results are more likely by the time patients present for testing[61]; and (3) the potential for higher viral loads in upper respiratory tract secretions and an extended period of shedding in asymptomatic persons, relative to other viruses such as influenza.[62]

Estimates for the proportion of individuals infected with SARS-CoV-2 who remain asymptomatic vary widely, with figures ranging between 5% and 80%. Perhaps the highest profile instance of asymptomatic case detection occurred with the outbreak of COVID-19 on the Princess Diamond cruise ship, with 18% of 634 cases lacking symptoms at the time of testing.[63] Although some cases identified as asymptomatic COVID-19 may in fact represent presymptomatic disease and go on to develop recognisable SARS-CoV-2 infection, cases that do not manifest features on serial follow-up have been identified in the literature. These include 4 of 13 infected Japanese evacuees from the initial outbreak in Wuhan,[64] 4 of 97 COVID-19 cases in a call centre in South Korea and 3 of 48 affected residents in a nursing home setting.[59] Importantly, 1 of 18 cases in two familial clusters of disease in China was asymptomatic yet had comparable viral load at the time of testing, indicating 'silent' transmission potential,[65] and similar infection rates have been attributed to asymptomatic and symptomatic COVID-19 (4.4% vs 6.3% of close contacts infected).[66 67] A cross-sectional study screened 215 pregnant women being admitted to a New York hospital for delivery for symptoms of COVID-19.[68] Four women (1.9%) had symptoms suggestive of COVID-19 and tested positive. Nasopharyngeal swabs were obtained from 210 women without symptoms of COVID-19 and 29 (13.7%) were positive for SARS-CoV-2. As such, 29 of the 33 patients (87.9%) who were positive for SARS-CoV-2 on admission were asymptomatic. As the immune system is relatively downregulated in pregnancy, meaning that symptoms may potentially be blunted or quiescent versus non-gravid women, this high prevalence of asymptomatic infection should be extrapolated with caution. The Office for National Statistics 28 May report shows that of those people that tested positive for COVID-19 between 11 and 24 May 2020, only 21% (95%CI 13% to 31%) reported experiencing one or more of the various symptoms at the time of their test.[69] The proportion increased to only 30% (95% CI 20% to 43%) experiencing symptoms at any time point over the course of the study period. Particularly relevant to the military is the outbreak on the USS Theodore Roosevelt, where there was widespread transmission among the 4800 crew members. Of the 736 sailors who had a positive diagnosis of SARS-CoV-2, 146 sailors were asymptomatic (19.8%).[70] In a further sample of 382 sailors of the ship's company, of which 238 participants had a previous or current SARS-CoV-2 infection, 18.5% were asymptomatic.[71]

Asymptomatic infection may be a particular issue in the younger population. The immune systems of younger individuals are perhaps less likely to mount clinically identifiable disease responses that ultimately could exacerbate transmission in communities as a whole. Children, adolescents and younger adults may be less likely to develop symptomatic infection with SARS-CoV-2, with 56% of 728 laboratory-confirmed cases in children showing only mild or no symptoms.[72] However, transmission with high infectivity has been reported in young people, with an attack rate of 40%.[73] Such 'cryptic cases' of SARS-CoV-2 infection might act as important sources in the propagation of the pandemic. Surveying the available evidence, some authorities have considered a proportion of asymptomatic infection of

Table 2 Summary of registered interventional randomised controlled clinical trials of vitamin D (only) in COVID-19

Trial ID	Scientific title	Nations	Size	Status	Completion date	Aim/description	Primary outcome measures (summarised)
NCT 04386850	Preventive and Therapeutic Effects of Oral 25-Hydroxyvitamin D3 on Coronavirus (COVID-19) in Adults	Iran and USA	1500	Recruiting	March 2021	Two-armed study looking at the effect of 1000 IU of vitamin D in the prevention of COVID-19 in healthcare workers and their families as well as in patients with a COVID-19 diagnosis and treatment of patients with COVID-19	COVID19 diagnosis, severity, hospitalisation, disease duration, death, oxygen support
NCT 04411446	Randomised Controlled Trial of High Dose of Vitamin D as Compared With Placebo to Prevent Complications Among COVID-19 Patients	Argentina	1265	Recruiting	December 2020	An RCT comparing one dose of 500 000 IU of vitamin D versus placebo in SARS-CoV-confirmed patients requiring hospitalisation for COVID-19 but not critical care at the time of admission.	▶ Respiratory SOFA score (200 patients). ▶ Need of a high dose of oxygen or mechanical ventilation (1265 patients).
NCT 04385940	Improving Vitamin D Status in the Management of COVID-19	USA	64	Not yet recruiting	December 2020	A double-blind RCT assessing the efficacy of vitamin D (1000 IU daily vs 50 000 IU two times per week for the first week then once weekly) in COVID-19 patients	Symptom recovery over 3-week time period
IRCT20200401046909N2	Investigating Preventive Effects of Oral 25-Hydroxyvitamin D3 on COVID-19 in Adults: a Randomised, Controlled Double-Blind Clinical Trial	Iran	540	Recruiting	Not stated	A double-blind RCT on adult participants without COVID-19 to determine the effect of vitamin D supplementation (1000 IU/day) on serum levels of 25(OH)D and relate this to decreased incidence of COVID-19	Affected by COVID-19 during study (symptoms, CT findings, PCR)
NCT 04344041 / EUCTR2020001602-34-FR	COVID-19 and Vitamin D Supplementation: a Multicenter Randomised Controlled Trial of High Dose vs Standard Dose Vitamin D3 in High-risk COVID-19 Patients (CoVitTrial)	France	260	Recruiting	May 2021	Open-labelled randomised study of 400 000 IU of vitamin D as a single dose compared with 50 000 IU of vitamin D in confirmed COVID-19	Number of death of any cause, during the 14 days following the inclusion and intervention
NCT 04334005	Effect of Vitamin D Administration on Prevention and Treatment of Mild Forms of Suspected COVID-19	Spain	200	Not yet recruiting	June 2020	An RCT assessing the addition of 25 000 IU of vitamin D in 40–70 year olds who have non-severe symptomatic COVID-19 and who are taking NSAIDs, ACE2 inhibitor, ARB or thiazolidinediones, according to clinician criteria, based on the current recommendations.	Composite of cumulative death (ie, mortality) for all causes and for specific causes
EUCTR2020002312-43-ES	Clinical Trial, PHASE III, Randomised, Open-Label, to Evaluate the Efficacy of Administering High-Dose Cholecalciferol Orally Alongside Standard Therapy in Patients with COVID-19 Pneumonia (COVID-19 HUSO) - Efficacy of High Dose Vitamin D in COVID-19 Pneumonia	Spain	82	Unknown	Not stated	RCT in vitamin D-deficient (<30ng/mL) COVID-19 patients with the aim to provide estimates of increased levels of vitamin D levels on days 7 and 14 after high-dose vitamin D treatment (10 000 IU/day) compared with conventional dosing (2000 IU/day)	Increased levels of vitamin D will be determined on days 7 and 14 after initiation of treatment
EUCTR2020001960-28-ES	Efficacy of Vitamin D Treatment in Patients Diagnosed with Pneumonia Who Require Hospital Admission and Have Vitamin D Deficiency and a Positive Diagnosis for SARS-CoV-2 (COVID-19)	Spain	108	Unknown	Not stated	Randomised controlled blinded trial of vitamin D in COVID-19-positive patients with vitamin D deficiency	Less serious evolution of respiratory syndrome in terms of mortality and ICU admission

ARB, angiotensin receptor blocker; ICU, intensive care unit; NSAID, non-steroidal anti-inflammatory drug; RCT, randomised controlled trial; SOFA, sequential organ failure assessment.

40%–50% in the community, and it is conceivable that this could be higher in young healthy adults. The true extent of asymptomatic COVID-19 will only be understood with further widespread serial systematic population-based antibody testing. The study of vitamin D sufficiency/supplementation in the prevention of asymptomatic spread is therefore highly relevant to the military, where the predominant concern is the control of transmission and force preservation, but where the implementation of control measures, such as social distancing and the use of masks, is challenging due to the nature of military training.

Risks of vitamin D supplementation in the prevention of SARS-CoV-2 infection and COVID-19

The main risk of vitamin D supplementation is overdosing, although relatively high doses, exceeding the Public Health England dose of 10 mcg (400 IU), can be safely taken. The upper daily limit of vitamin D dose given by the Endocrine Society is 10 000 IU.[74] The SACN, the Institute of Medicine, the European Food and Safety Authority[75] and the Institute of Medicine[7] recommend staying below 4000 IU/day (100 μg). Vitamin D intoxication (hypervitaminosis D) can occur in large doses[76] with subsequent symptoms secondary to hypercalcaemia (confusion, polyuria, polydipsia, anorexia, vomiting and muscle weakness). As vitamin D is not prescribed but supplemented, there is the potential that users could accidentally overdose. Given the effect of the pandemic on buying behaviours, there is the potential that individuals could stockpile supplements, leaving a shortage for those in need such as pregnant mothers. Furthermore, any potential beneficial effect of vitamin D reducing the transmission of SARS-CoV-2 needs to be studied in the context of other measures to reduce spread, namely, mask wearing, social distancing, hand hygiene and avoiding contact, crowds and public gathering.

CONCLUSION

Vitamin D insufficiency and deficiency is common in military cohorts. There are mechanistic reasons why vitamin D status may influence the risk of ARTI, although trial data are lacking presently. Work is currently under way within Defence to retrospectively ascertain the risk of ARTI in a large cohort previously supplemented with vitamin D versus a control group. There are mechanistic as well as observational data suggesting the positive benefits of being vitamin D replete in reducing the severity of COVID-19, although interventional data are needed in support of this approach. Research is required to ascertain the effect of vitamin D status/supplementation on asymptomatic/mildly symptomatic SARS-CoV-2 infection, the fuller clinical syndrome of COVID-19 and associated transmission risks. This would be of particular relevance to the Armed Forces as well, as other populations engaged in congregate living and working.

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