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Review Article

Vitamin D: The Challenge of Bridging the Gap and the Rationale for Supplementation

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Introduction

Vitamin D is classified amongst nutrients as a fat-soluble vitamin, which is consumed from food, including fortified food or supplements. It can also be synthesized by exposure of the skin to sunlight. Vitamin D facilitates absorption and retention of calcium and phosphorus both of which are critical for bone and teeth formation. Many organs and tissues have vitamin D receptors, which suggest important roles in the body beyond bone and research has shown that vitamin D regulates inflammation and immune function with potentially beneficial effects on the health of the brain, the cardiovascular system, the endocrine system, and other metabolic pathways. Few foods contain vitamin D. Oily fish, butter, liver, eggs, milk, and fortified foods including some breakfast cereals and spreads are the main dietary sources. Whilst most of the requirement for vitamin D is considered to come from casual exposure to sunlight, there is considerable debate on the sufficiency of sunlight to achieve acceptable blood levels of vitamin D because a significant proportion of the population does not achieve adequate skin exposure. Studies from many countries, including those in sunnier regions, such as Southern Europe, the Middle East and Australia demonstrate low vitamin D levels in a high proportion of the populations. Because so few foods contain vitamin D, supplementation with vitamin D should be recommended to bridge this gap.

In this paper we consider the magnitude of the vitamin D gap and its impacts on health and disease. We also outline how the gap can be bridged, discussing the role of foods, sunshine and supplements, explaining why supplements are the most achievable way forwards.

What is the vitamin D gap?

Many countries and organisations globally make recommendations for vitamin D intake for infants and children, adults, older people and in pregnancy and breastfeeding (see Table 1).

Country or region	Organisation	Target population	Age (years)	Conditions	Threshold 25(OH)D (nmol/litre	Oral daily vitamin D recommendation	TUL
UK	SACN (2016) [1]	General population	Birth to 1 year 1-4 years >4 years Pregnancy and lactation	Bone health	<25nmol/litre (deficiency)	8.5-10 mcg 10mcg 10 mcg 10 mcg	As EFSA (below)
Ireland [2]	Food Safety Authority of Ireland (2020) [2]	Healthy older adults		Bone health	>30nmol/litre	15 mcg 20mcg (if little or no sun exposure)	
Nordic Countries [3]	Nordic Council of Ministers (2014) [3]	General population	6 months-74 years >74 years	Bone health	<25/30 nmol/ litre (deficiency) >50nmol/litre (adequacy	10mcg 20mcg (If little or no sun exposure) 20mcg	
European Union	EFSA (2016) [4]	General population	< 1year >1 year	Bone health	>50nmol/litre (adequacy)	10 mcg 15 mcg	25mcg < 1 year 50 mcg (1-10 years) 100mcg (>11 years)
	EMAS (2023) [5]	Postmenopausal women		General Health	>75nmol/litre	20-50mcg (after repletion with higher weekly or daily doses + calcium 1200mcg daily)	
	ESPGHAN (2013) [6]	Infants		General Health	>50nmol/litre	10mcg	
	ESCEO (2013) [7]	Postmenopausal and older women Fragile elderly		Bone health	>50nmol/litre >75mmol/litre	20-25 mcg	
DACH countries (Austria, Germany, Switzer-land)	German Nutrition Society (2012) [8]	General population	<1 year >1 year	Bone health	>50nmol/litre	10 mcg 20 mcg	

Central Europe	Polish Multidisciplinary Group (2023) [9]	General population	0-6 months 6-12 months 1-18 years >18 years Pregnant and breast-feeding women	General health	Vitamin D deficiency < 50nmol/litre; Suboptimal 50-75nmol/litre; Target concentration 75-125nmol/litre	10mcg 10-15mcg 15-25mcg 20-50mcg 37.5-50mcg	
		Groups at risk of deficiency	Premature infants Obese children and adolescents (>90th percentile) Obese adults and older people Night workers and people with dark skins			10-20 mcg 30-50mcg 40-100mcg 25-50mcg	
Australia and New Zealand	Eat for health (2006) [10]	General population	1-50 years 51-70 years >70 years Pregnant and breastfeeding women	Bone health	>50nmol/litre	5 mcg 10 mcg 15 mcg 5 mcg	25 mcg (0-12 months) 80 mcg (1 year – all adults)
Canada	Health Canada (2022) [11]	General population	0-1 years 1-70 years 70+ years	Bone health	>50 mmol/litre	10 mcg 15 mcg 20 mcg	25-38 mcg 63 mcg (1-9 years) 100 mcg (9-70+ year)

US	Institute of Medicine (IOM) (2010) [12]	General population	< 1 year 1-70 years 70+ years	Bone health	>50nmol/litre	10mcg 15mcg 20mcg	25-38 mcg 63 mcg (1-9 years) 100 mcg (9-70+ years)
	Endocrine Society (2011) [13]	General population	<1 year 1-18 years Adults Obese children and obese adults Patients on steroids, antifungals, AIDS medications, anticonvulsants	Bone health	100-150nmol/litre	10-25mcg 15-25mcg 37.5-50mcg 2-3 times the dose for age 2-3 times the dose for age	25 mcg (< 6 months) 37.5 mcg (6 months – 1 year) 63 mcg (1-3 years) 75 mcg (4-8 years) 100cg (> 8 years)
	American Geriatric Society [14]	Older people		Falls and fracture reduction	>75nmol/litre	25mcg	
	National Osteoporosis Foundation [15]	Adults	< 50 years 50+ years	Bone health		10-20 mcg 20-25 mcg	
	AADMD [16]		People with neurodevelopmental disorders and intellectual disabilities	General health	75-125 mmol/litre	20-100 mcg	
Brazil	SBEM [17]	People with osteoporosis	Prevention of falls, fragility fractures and other conditions		>75 mmol/litre	25-50 mcg	

United Arab Emirates and the GULF	[18]	General population	0 – 6 months 6-12 months 1-18 years Adults > 18 years >65 years Pregnant and breastfeeding women Obesity and metabolic syndrome Dark skins and night workers		75-125 mmol/ litre	10 mcg 10-15 mcg 15-25 mcg 25-50mcg 50 mcg 50mcg 50mcg 25-50mcg	
Global	FAO/WHO (2001) [19]	General population	0-18 years 19-50 years 51-65 years >65 years	Risk of vitamin D deficiency	>50 nmol/litre	5 mcg 5 mcg 10 mcg 10 mcg	

AADMD: the American Academy of Developmental Medicine and Dentistry (AADMD)

ESCEO: European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis

ESPGHAN: European Society for Paediatric Gastroenterology and Hepatic Nutrition

FAO/WHO: Food and Agricultural Organisation/World Health Organisation

SACN: Scientific Advisory Committee on Nutrition

SBEM: Brazilian Society of Clinical Pathology/Laboratory Medicine

Table 1: Current selected vitamin D supplementation guidelines.

Recommendations for intake are based on achieving specific serum concentrations of 25 hydroxyvitamin D (25(OH) D), which is considered to be the best marker of vitamin D status. Most guidelines unanimously agree that serum concentrations of 25(OH)D of <25nmol/litre should be avoided at all ages across a population. However, there is no consensus globally on the concentrations of serum 25(OH)D concentrations reflecting vitamin D sufficiency. Recommendations from different countries and even organisations in the same country for sufficiency of vitamin D vary for serum 25(OH)D from 25 to > 100 nmol/litre. The recommended daily dose considered to be required to achieve these specific serum concentrations also varies.

The UK recommends a dose of 10 mcg daily to achieve a serum concentration of 25(OH)D of at least 25nmol/litre [1]. The European Food Safety Authority (EFSA) [4], the United States Institute of Medicine (IOM) [12] and Health Canada [11] recommend a dose of 15mcg for adults to achieve a serum concentration of 50nmol/litre. Higher doses are often recommended for older people e.g. 20mcg daily for adults > 70 years in the US and Canada.

Organisations with a specific health remit for example the European Menopause and Andropause Society (EMAS) [5] and the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) [7] recommend 20-50mcg and 20-25mcg respectively for postmenopausal women. The National Osteoporosis Foundation (NOF) [15] recommends a daily dose of 20-25mcg, whilst the US Endocrine Society [13] recommend that obese children and adults take 2-3 times the dose recommended for their healthy weight peers. In one recent trial the effect of vitamin D in terms of vitamin D biomarkers was blunted in obese patients [20]

Whatever the recommendations for vitamin D intake, it is clear that vitamin D deficiency is prevalent throughout the world even in sunnier countries, including Australia, where it was once assumed that sunlight was sufficient to prevent this deficiency [21] A pooled analysis of 7.9 million people globally found that, 15.7%, 47.9% and 76·6% of participants had serum 25-hydroxyvitamin D levels less than 30, 50, and 75 nmol/l, respectively [22]. With regards to the UK the Scientific Advisory Committee on Nutrition (SACN) [1] set a Reference Nutrient Intake (RNI) of 10 mcg daily

to achieve a vitamin D serum concentration above 25 nmol/litre in those aged 4 years and upwards.

The UK National Diet and Nutrition Survey (NDNS) time trend analysis show that intakes have changed little over the past decade with average daily intakes of 2-3 mcg from food alone [23] showing a substantial gap in actual vs recommended intakes. In 2016 the UK government changed its advice to recommend that everyone considers taking a 10mcg daily vitamin D supplement.

The latest NDNS data (years 2016-2019) show that one in five people in the UK are deficient in vitamin D [23] This applies to 10% of children aged 4-10 years (boys 8% girls 13%); 26% of 11–18-year-olds (boys 15%; girls 39%); 17% of adults aged 19-64 years (men 16%, women 19% and 13% of adults > 65 years (men 13%, women, 13%). In addition, a study in UK primary care found that amongst 210,502 patients who had a vitamin D test, one third were deficient (with deficiency identified as a blood level below 30nmol/litre). Deficiency among ethnic minority groups ranged from 43% among those of mixed ethnicity to 66% in Asians [24].

Studies of the UK Biobank Cohort looking at ethnic minorities have confirmed the huge differences in vitamin D status with Black and Asian populations more at risk of a vitamin D status < 25nmol/litre than white populations [25,26]. In addition, South Asian populations have less seasonal variation in vitamin D status as they have all year-round low vitamin D status [27]. Looking at the European perspective where the target level of 25(OH)D is >50nmol/litre, data suggest that 10mcg daily of vitamin D would allow only approximately 50% of the UK population to achieve the higher level, if that level were to be recommended, and that 25mcg vitamin D daily would be required to achieve the target level of > 50nmol/litre in 97.5% of the population.

In Ireland a similar picture emerges. An Irish epidemiological study [28] found that 10-40% of the Irish population had vitamin D levels below the US threshold of 25(OH)D of <30nmol/litre, which was more pronounced in the winter months.

Vitamin D deficiency (<30nmol/litre) is common in Europe and the Middle East. It occurs in <20% of the population in Northern Europe, in 30–60% in Western, Southern and Eastern Europe and up to 80% in Middle East countries. Severe deficiency (serum 25(OH)D <30 nmol/L)) is found in >10% of Europeans [29]. A systematic review of 107 studies representing 633,093 individuals in Southern Europe found that of one-third of the studies reported mean 25(OH)D concentrations below 50 nmol/L and approximately 10% reported mean serum 25(OH)D concentrations below 25 nmol/L. Women, infants and adolescents had a higher prevalence of low vitamin D status [30].

A survey of a representative population in Australia found that 20 % of participants (19 % men; 21 % women) were classified as vitamin D deficient (<25nmol/litre 25(OH)D), with a further 43 % classified as insufficient (45 % men; 42 % women) (50-75nmol/litre) [31].

Why does the vitamin D gap matter?

Health risks from low vitamin D status

Vitamin D is essential for calcium absorption and bone mineralisation which is positively associated with bone mineral density. However, vitamin D has actions on bone independent of its ability to absorb calcium. It is a major bone regulatory hormone, whose renal metabolite, 1,25(OH)2D3 has effects on bone through facilitating the development and differentiation of the osteoblasts [32].

Good bone health is essential for consolidation of bone mass in adulthood and reduction in risk of osteoporosis later life. Many of the vitamin D guidelines globally (e.g., the UK, wider Europe, Australia and New Zealand, Canada and the US) are based on vitamin D (sometimes with additional calcium) requirements for bone health. (see Table 1). For adults, recommendations for bone health range for adults under 70 years vary from 10 mcg (e.g., UK, Nordic Countries, Australia and New Zealand) 15mcg (e.g., EFSA, Canada, the US) and 20mcg (e.g., Germany, Austria and Switzerland). For adults > 70 years, Australia and New Zealand recommends 15 mcg, Canada and the US, 20mcg and the Nordic Countries recommend 20mcg for people of >74 years. Ireland recommends 15mcg daily for healthy older adults and 20mcg daily where there is no or limited exposure to sunlight. For bone health, some authorities recommend higher doses for people who are obese (e.g., the US Endocrine Society recommends 2-3 times the dose of vitamin D for people of healthy weight).

Nutritional rickets and osteomalacia represent the most serious sequelae of vitamin D deficiency. The risk of developing rickets/osteomalacia is increased at a 25(OH)D concentration of ≤ 30 nmol/L. This threshold may vary depending on other conditions such as calcium and phosphate nutrition, parathyroid hormone (PTH) levels, and season. Nutritional rickets remains a global problem, particularly in the Middle East and African countries. However, rickets occurs in the UK, albeit with a low incidence, but with serious complications and deaths especially amongst Black and South Asian children under 5 years [33]. Nutritional rickets also persists in Canada [34], Australia [35], New Zealand [36] and the United States [37].

However, low vitamin D status has other far-reaching impacts on bone health. Low vitamin D status (<50nmol/litre) accelerates bone turnover, bone loss and osteoporotic fracture [38]. A systematic review of 28 studies in 61,744 people found that the risk of hip fractures was 1.8 times as high in those with low vs high 25(OH)D levels. The risk of hip fracture was 2.16

(1.49-3.11, P ≤ 0.001) in case-control studies; 1.52 (1.29-1.79, P = 0.001) in cohort studies; and 1.1 (1.18-1.70, P ≤ 0.001) in case-cohort studies [39].

Low vitamin D status is also associated with fracture in younger people. A recent study in US military personnel (mean age 20 years) showed that lower 25(OH)D status was associated with higher risk of stress fracture [40]. A cross-sectional US study including 165 participants (83 men, 82 women, 18-30y) who self-identified as Asian, Black, or White measured bone microarchitecture and strength of the distal radius and tibia. In this study 43.6% of participants had low 25(OH) D (< 50nmol/ml) with greater prevalence in Asian (38.9%) and Black (43.1%) compared with White (18.0%) participants (p<0.001). Lower 25(OH) D was associated with worse bone outcomes at the distal radius and tibia at the time of peak bone mass, warranting paying further attention to vitamin D status in young adults [41].

Both skeletal muscle atrophy and poor muscle function are consequences of low vitamin D status [42] This is likely because vitamin D deficiency reduces oxygen consumption and causes disruption of mitochondrial function [43]. Hand grip strength is higher in those with 25(OH)D levels from 30 to <50 nmol/L and ≥50 to ≤125 nmol/L than in people who are deficient [44]. Poor muscle function increases the risk of falls and low vitamin D status has been linked with poor gait and balance in older people [45] as well as falls [46]. Vitamin D deficiency is also associated and with poor sports/athletic function [47,48].

Vitamin D has key roles in immune function [49,50]. Low vitamin D (<25nmol/litre) reduces the number of lymphocytes and the immune capability of macrophages lowering their ability to kill pathogens**,** altering integrity of the respiratory and gastrointestinal epithelium, and impairing T and B cell (T & B Cells are a types of white blood cells that protect immune function) movements in the intestine with a reduced number and activity of NK (natural killer) cells and impaired innate immunity. Low vitamin D status is linked with various autoimmune conditions such as type 1 diabetes, systemic lupus erythematosus (SLE) and rheumatoid arthritis [51].

Vitamin D also appears to influence the gut microbiota. This is likely one mechanism by which vitamin D affects immune function and hence its extra-skeletal functions. Evidence from a recent systematic review of 25 studies (14 interventional (1511 subjects) and 11 observational (4618 subjects) found that vitamin D supplementation significantly changed the gut microbial population particularly *Firmicutes*, *Actinobacteria* and *Bacteroidetes* phyla. *Firmicutes* were correlated with serum 25(OH)D. Dietary vitamin D also appears to induce a shift in bacterial composition and/or affects the species' richness. *Veillonellaceae* and *Oscillospiraceae* families, in the *Firmicutes* phylum, more frequently decreased with both increasing levels of 25(OH)D and vitamin D supplementation [52].

Low serum vitamin D levels are associated with increased risk of respiratory tract infection in several studies. Cross-sectional data from 6,789 participants in the nationwide 1958 British birth cohort [53] indicated that the prevalence of respiratory infections had a strong seasonal pattern in the opposite direction to the pattern for 25(OH)D concentrations. Each 10 nmol/l increase in 25(OH) D was associated with a 7 % lower risk of infection (95 % CI 3, 11 %) and improved lung function. A 2019 systematic review [54] of epidemiological studies also found an increased risk of upper and lower respiratory tract infections with low serum vitamin D levels.

Low serum vitamin D has been linked with increased risk from COVID-19. A meta-analysis of 31 peer-reviewed observational studies (14262 subjects) identified a positive trend between serum 25(OH)D level <50 nmol/litre and an increased risk of mortality, ICU admission, invasive ventilation, non-invasive ventilation or SARS-CoV-2 positivity. However, these associations were not statistically significant [55]. A retrospective study involving 1226 participants across two East Sussex NHS Trust hospitals suggests a similar mortality from COVID-19 irrespective of 25(OH)D levels [56]. However, low vitamin D levels have been associated with Long COVID in COVID-19 survivors [57].

Vitamin D status is linked with cardiometabolic disease. In a 2018 cohort study higher vitamin D was associated with a lower risk of type 2 diabetes [58]. In the UK Biobank study, a similar inverse association was more prominent in people with healthier sleep patterns (i.e., less frequent day time sleeping) [59]. Low plasma vitamin D is linked with insulin resistance [60]. Serum 25(OH)D levels are inversely associated with an increased risk of coronary heart disease (CHD) and the association was more evident in people with poor sleep patterns [61]. In a meta-analysis of 40 studies, serum 25(OH)D concentrations was not only associated with increased total cardiovascular events and cardiovascular mortality, but also with increased risk of heart failure, myocardial infarction and CHD [62]. A meta-analysis of four prospective studies found that in people with one stroke, low vitamin D levels were associated with a higher risk of recurrent stroke [63]. Other non-skeletal conditions with which low vitamin D status is associated include depression [64] and poor sleep [65].

Supplementation studies

Given the links between low vitamin D status and both musculo-skeletal and non-skeletal conditions, it is important to clarify the impact of vitamin D supplementation on these same conditions. Table 2 presents summary data by health condition from key randomised controlled trials (RCTs) and meta-analyses over the past 10 years. Whilst findings from RCTs are often used to infer causation, it is important to consider that epidemiological studies evaluate links across longer time frames, without such large differences in vitamin D intake and can better represent a

real-life context. With supplementation studies both the starting 25-hydroxyvitamin D [25(OH)D] level and the dose of vitamin D administered are important. Where studies show limited effect of supplementation, it is possible that participants were vitamin D replete at the start of the study, suggesting that the key requirement with vitamin D supplementation is to avoid vitamin D deficiency.

With regards to bone health and bone density, many studies indicate a positive effect of vitamin D supplementation on bone density [66-68] but inconsistencies exist across a few studies [69]. Again, findings with regards to falls and fractures are inconsistent, but vitamin D supplementation in doses of 800-1000 IU (20-25mcg) daily with adequate calcium intake can decrease the incidence of fractures in elderly, vitamin D deficient subjects [70,71]. In terms of falls, vitamin D supplementation is most effective with moderate doses of vitamin D given to older people who are vitamin D deficient [72,73]. In summary, older adults with serum 25(OH)D levels <50nmol/L are likely to have fewer falls if supplemented with 800-1000 IU (20-25mcg) per day of vitamin D. Similarly, older adults with poor muscle function, including sarcopenia, improve their muscle function with supplementation, but with moderate doses of 800-1000 IU (20-25mcg daily). Improved hand grip strength was demonstrated in one study [74]. Vitamin D supplementation has been shown to reduce joint pain in osteoarthritis of the knee but without impact on progression of the condition [75-77].

Turning to extra-skeletal conditions, vitamin D supplementation has been shown to reduce risk of acute respiratory tract infection in daily doses of 400-1000 IU(10-25mcg) in people who are deficient in vitamin D [78-80].Vitamin D supplementation also showed efficacy in treatment of respiratory tract infection in a meta-analysis of 18 studies (3648 participants) and although the analysis was restricted to the highest quality studies, just a small benefit was found. As a result, further research is needed.

With regards to COVID-19 the UK CORONAVIT study showed no benefit of vitamin D supplementation on risk of COVID-19 [81]. Some studies have shown a benefit of vitamin D supplementation in patients who already have COVID-19. A meta-analysis of five clinical trials including 1400 patients found that vitamin D administration in large daily or weekly doses resulted in reduced risk of death and admission to intensive care unit (ICU) [82].

Supplementation studies evaluating vitamin D in cardiometabolic conditions have shown inconsistent findings, but as the number of clinical trials have increased, more recent meta-analyses have demonstrated positive findings particularly in terms of blood lipids and insulin parameters and in reducing the risk of type 2 diabetes [83-90].

Studies evaluating vitamin D supplementation in depression [91,92] and sleep [93] have shown promising findings with research required to confirm these outcomes. Evidence also exists that vitamin D supplementation can significantly shift the gut microbiota [94] which may have a beneficial effect on immune function and contribute to the emerging positive findings for vitamin D in cardiovascular and metabolic health and brain health.

Bone Health and Fracture					
Reference	**Type of Study**	**Dose of vitamin D**	**Study group**	**Outcome measures**	**Observed effects**
Reid, et al. (2014)[66]	Meta-analysis	Various doses	28 studies; 4082 participants	BMD	Benefit of vitamin D at the femoral neck
Overton, et al. (2015) [67]	48-week RCT	Vitamin D (4000 IU (10mcg) daily) and calcium (1000 mg daily) supplementation	167 subjects taking antiretroviral therapy	BMD	Vitamin D and calcium mitigated BMD loss particularly at hip
Zhao, et al. (2017) [95]	Systematic review and meta-analysis; 33 RCTs	Various doses of vitamin D, calcium or both	51 145 community-dwelling adults >50 years	Hip fracture, non-vertebral fracture, vertebral fracture, total fracture	Vitamin D, calcium or both had limited impact on risk of fracture
Segheto, et al (2021) [68]	Meta-analysis	Various	35 RCTs in adults	Bone health	Vitamin D supplementation positively linked with bone health
Kong, et al. (2022) [70]	Meta-analysis	Various	32 RCTs	Daily vitamin D dose to prevent fractures and falls	Daily vitamin D dose of 800 to 1,000 IU (20-25mcg) was the most probable way to reduce the fracture and fall risk.
LeBoff, et al.(2022) [96]	RCT Ancillary study of the Vitamin D and onega-3 trial	Vitamin D_3 (2000 IU (50mcg) per day), n-3 fatty acids (1 g per day) or both	25,871 participants. Men > 50 years; women > 55 years	Total, non-vertebral and hip fractures	Vitamin D had limited impact on risk of fractures
Luo, et al. (2022) [97]	Meta-analysis	Various	23 studies (5390 pregnant women)	Bone development and offspring growth during pregnancy	Vitamin D supplementation during pregnancy may be associated with increased humeral length (HL) in the uterus, increased body length at birth and higher cord blood 25(OH)D concentration.
Kazemian, et al. (2023) [69]	Meta-analysis	Various	39 RCTs	Bone health (BMD)	Vitamin D3 supplementation had limited impact on whole-body or total hip BMD was observed.
Manoj, et al. (2023) [71]	Meta-analysis	Various	7 RCTs (calcium and vitamin D)	Hip fracture	Daily oral supplementation 800 IU (20mcg) of vitamin D3 plus 1200 mg of calcium reduces hip fracture and non-vertebral fracture in older people. No effect on femoral neck BMD

Mendez-Sanchez, et al. (2023) [98]	Meta-analysis	Vitamin D (n= 110) or vitamin D + calcium (n=271) or calcium (n=138); placebo (n=422)	7 RCTs (941 participants) in pre-menopausal women	Hip fracture, BMD	Vitamin D had limited impact on BMD and hip fracture
Falls					
Bolland, et al. (2014) [72]	Meta-analysis	Vitamin D various doses	20 RCTs (29 535 subjects)	16% risk reduction of falls	Supplementation with vitamin D, with or without Ca, had some impact on falls but did not reduce falls by 15% or more
Zheng, et al. (2015)[99]	Meta-analysis	Vitamin D intermittent high doses	9 RCTs	Fall prevention, fracture and overall mortality	Limited impact of vitamin D on fall prevention, fracture and overall mortality
Appell, et al. (2021)[100]	RCT	200 IU (5mcg), 1000 IU (25mcg), 2000 IU (50mcg) or 4000 IU (100mcg)	688 patients (>70 years) at high risk of falls and with 25(OH)D_3 25–72.5 nmol/l	Fall prevention	Doses of vitamin D ≥1000 IU (25mcg) daily did not reduce falls compared with 200 IU (5mcg) daily
Ling, et al. (2021)[101]	Meta-analysis	Various	31 RCTs (21 vitamin D alone; 10 vitamin D and calcium)	Fall prevention	Vitamin D reduces risk of falls with 25(OH) D levels <50nmol/litre; vitamin D and calcium reduces risk of falls in older adults
Joint Health					
Jin, et al. (2016) [102]	2-year RCT	Oral vitamin D_3 (50 000 IU (1250mcg) monthly; n = 209) or an identical placebo (n = 204)	413 subjects with symptomatic knee osteoarthritis (340 completed the study)	Change in tibial cartilage volume and pain score on the Western Ontario and McMaster Universities Arthritis Index	Changes in these parameters were not statistically significant
Gao, et al. (2017) [75]	Meta-analysis	Various	Four RCTs; 1136 patients	WOMAC pain, function, stiffness, tibial cartilage volume	Vitamin D was effective in reducing pain and function; limited effect on tibial cartilage volume
Diao, et al. (2017) [76]	Systematic review and meta-analysis	Various	Four RCTs; 1130 subjects	Knee OA	Small to moderate effect on pain; limited effect on tibial volume and progression of OA
Zhao, et al. (2021) [77]	Systematic review and meta-analysis	Various	Six RCTs; 1599 subjects	WOMAC pain and function; cartilage volume	Vitamin D improved pain and function.
Muscle Function					

Shea, et al. (2019) [103]	12-month RCT	Vitamin D_3 20 mcg daily	100 community dwelling older adults	Lower extremity power and function	No effects on lower extremity power or function or lean body mass
Tabrizi, et al. (2019) [104]	Meta-analysis	Various	12 RCTs	Muscle function	No effect on markers of muscle function in post-menopausal women
Abshirini, et al. (2020) [105]	Meta-analysis	Various	29 RCTs	Muscle power and function	Vitamin D supplementation resulted in small improvements in muscle strength compared to control in postmenopausal women.
Propokidis, et al. (2022) [106]	Meta-analysis	Various	10 RCTs	Indices of sarcopenia in older adults > 50 years	Limited effect on hand grip strength, general muscle strength and general physical performance
Zhang, et al. (2022) [107]	Meta-analysis	Various	13 RCTs	Muscle strength	Vitamin D improved hand grip strength in post-menopausal women.
Respiratory Tract Infection					
Martineau, et al. (2019) [79]	Meta-analysis	Various	25 RCTs (11,321 participants)	Risk of acute respiratory tract infections (ARIs)	Reduced risk of ARIs. Largest protective effects seen in those receiving daily or weekly doses and who were deficient (<25nmol/litre)
Jolliffe, et al. (2021) [108]	Meta-analysis	Various	46 RCTs	Risk of acute respiratory tract infections (ARIs)	Daily dose of 400-1000IU (10-25mcg) vitamin D for 12 months reduced risk of ARIs
Anitua, et al. (2022) [80]	Meta-analysis	Various	65 RCTs (50,554 participants)	Risk of acute respiratory tract infections (ARIs)	Significant reduction in incidence of respiratory tract infections with vitamin D when given on a daily basis
Cho, et al. (2022) [109]	Meta-analysis	Various	18 RCTs (3648 participants)	Treatment of respiratory tract infections	Beneficial effect of vitamin D in treatment of RTIs from whole meta-analysis; analysis of high quality trials showed less benefit.
Jolliffe, et al. (2022) [81]	Phase 3 open label RCT (Corona VIT)	800IU (20mcg), 3200IU (80mcg) or placebo	6,200 participants not taking vitamin D at baseline with plasma 25(OH)D < 75nmol/litre	Risk of all cause RTI including COVID 19	No reduced risk of all-cause RTI or COVID 19

Jolliffe, et al. (2022) [110]	Three sub-studies of CORONAVIT	800iu (20mcg), 3200IU (80mcg) or placebo	Study 1 n = 2808, Study 2 n= 1853, Study 3 n= 100	1.Risk of breakthrough SARS-Cov-2 infection after vaccination 2.Titres of Ig antibodies 3.Antibody and cellular responses to vaccination	No effect of vitamin D supplementation on SARS-2-Cov vaccine efficacy
Argano, et al. (2023) [82]	Meta-analysis	Various (daily or weekly doses)	5 RCTs (1400 patients with COVID-19)	Risk of death and admission to ICU	Risk of death and admission to ICU reduced with vitamin D
Cardiometabolic health					
Ford, et al. (2014) [83]	Analysis of RECORD trial, systematic review and meta-analysis	Various	RECORD trial: 5292 participants; systematic review of 21 trials	CVD	Vitamin D might protect against heart failure in older people but does not protect against myocardial infarction or stroke
Kampmann, et al. (2014) [84]	12-week RCT	Colecalciferol 280 mcg/day for 2 weeks then 140 mcg daily for 10 weeks	16 patients with type 2 diabetes and low vitamin D	Insulin sensitivity, insulin secretion, inflammatory markers	Vitamin D may improve insulin sensitivity.
Nader, et al. (2014) [111]	12-week RCT	Vitamin D_3 (2000 IU (50mcg)/day)	58 obese adolescents (12–18 years)	Fasting plasma, glucose, insulin and lipid profile	No effect of vitamin D on insulin, glucose and lipids
Ryu, et al. (2014) [112]	24-week RCT	Vitamin D 2000 IU (50mcg)/day + Ca 200 mg/day versus Ca 200 mg/day	62 patients with type 2 diabetes	CVD risk	No benefit of vitamin D on CVD risk including insulin resistance and arterial stiffness
Seida, et al. (2014) [113]	Meta-analysis	Various	35 trials	Insulin resistance, diabetes risk	No effect of vitamin D_3 supplementation on glucose homeostasis or diabetes prevention

Arora, et al. (2015 [114])	6-month, multicentre RCT	Vitamin D high (4000 IU (100mcg)/ day) vs low (400 IU (10mcg)/day) dose	534 individuals (18–50 years) with low vitamin D status and systolic blood pressure 120–159 mmHg	Blood pressure	Vitamin D did not reduce blood pressure in people with pre-hypertension or hypertension with vitamin D deficiency
Lee, et al. (2016) [85]	Meta-analysis	Various	15 trials (1134 patients with diabetes)	Change in blood pressure	Vitamin D supplementation may result in a reduction in diastolic blood pressure in patients with type 2 diabetes
Mirhosseini, et al. (2017) [86]	Meta-analysis	Various	24 RCTs (1528 patients with type 2 diabetes)	HbA1c, serum fasting plasma glucose, HOMA-IR insulin resistance,	A minimum dose of 100 mcg/day (4000 IU/ day), may significantly reduce serum fasting plasma glucose, HbA1c, and HOMA-IR index; helps to control glycaemic response and improve insulin sensitivity
Wu, et al. (2017) [87]	Meta-analysis	Various	24 studies evaluated HbA1c; 18 studies evaluated full blood glucose	HbA1c and full blood glucose	Vitamin D supplements reduced HbA1c
Tabrizi, et al. (2018) [115]	Meta-analysis	Various	22 trials involving people with metabolic syndrome	Endothelial function	Vitamin D increased flow-mediated dilatation in patients with metabolic syndrome
Upreti, et al. (2018) [116]	RCT	Oral vitamin D	60 patients with type 2 diabetes and low vitamin D	Glycaemic control	Improved glycaemic cand blood pressure control with vitamin D
Cefalo, et al. (2018) [117]	RCT	Hypocaloric diet + oral vitamin D 22 000 IU (550mcg) each week or placebo	18 non-diabetic volunteers deficient in vitamin D and BMI >25	Insulin sensitivity	Insulin sensitivity improved with vitamin D
Beveridge, et al. (2018) [118]	Systematic review	Various	31 RCTs	Vascular function	No significant effect on markers of vascular function
Li, et al. (2018) [119]	Systematic review	Various	20 studies (2703 diabetic participants)	Glycaemic control	Increase in insulin sensitivity with vitamin D, especially if given in large doses over short time period, or in Middle Eastern people, or in those deficient in vitamin D

Barbarawi, et al (2019) [120]	Meta-analysis	Various	21 RCTs; 83,291 participants	CVD events and all-cause mortality	No impact on major adverse cardiovascular events, individual CVD end points (myocardial infarction, stroke, CVD mortality), or all-cause mortality.
Wenclewska, et al. (2019) [121]	3-month RCT	Vitamin D 2000 IU (50mcg) /day	92 vitamin D-deficient people with metabolic disorders	Markers of oxidative stress and insulin resistance	Vitamin D reduced markers of oxidative stress and insulin resistance in people with and without diabetes
Lemieux, et al. (2019) [122]	6-month RCT	Vitamin D 5000 IU (125mcg) /day	96 patients at high risk of diabetes or newly diagnosed with diabetes	Insulin sensitivity	Increased insulin sensitivity and beta-cell function
Pincombe, et al. (2019) [123]	Systematic review	Various	26 studies (42% of participants vitamin D deficient)	Endothelial function	No improvement in endothelial function
Bahrami, et al. (2020) [124]	Meta-analysis	Various	4 RCTs; 299 patients	Coronary artery disease	Improvements in diastolic blood pressure; no effects on lipids
Barbarawi, et al. (2020) [125]	Meta-analysis	Various	9 RCTs; 43 559 participants (mean age, 63.5 years)	Risk of type 2 diabetes	In patients with prediabetes, doses of >1000 IU vitamin D reduced risk of diabetes
Zhang, et al. (2020) [88]	Meta-analysis	Various	8 RCTs; 4896 participants	Risk of type 2 diabetes in patients with pre-diabetes	Vitamin D reduced the risk of type 2 diabetes Benefit in non-obese subjects (not obese) Reversion of prediabetes to normoglycaemia was greater in vitamin D group than placebo. Vitamin D increased reversion rate to normoglycaemia
Qorbani, et al. (2022) [90]	Meta-analysis	Various	12 RCTs	Effect of vitamin D on cardio-metabolic risk factors in older people	Significant reduction in total cholesterol and triglyceride; significant reduction in triglyceride in people with diabetes and vitamin D deficiency; short term intervention (< 6 months) induced significantly lower triglyceride and insulin than longer term studies (> 6 months)
Zhang, et al. (2022) [74]	Meta-analysis	Various	RCTs	Lipid profile	Reduces triglycerides; negligible effects on LDL-C, HDL-C and total cholesterol

Hu, et al. (2023) [91]	RCT	800IU (20mcg)	270 patients with type 2 diabetes	Metabolic profile	Vitamin D reduced fasting insulin, HOMA-IR, and serum concentrations of non-HDL-C, hs-CRP, and uric acid
Depression					
Hansen, et al. (2019) [126]	RCT	70mcg	60 patients (18-65 years) with mild to moderate depression	Depression symptoms score	No reduction in symptom scores
Omidian, et al. (2020) [92]	12-week RCT	100mcg or placebo	68 subjects with type 2 diabetes and mild to moderate depression	Depressive symptoms	Reduction in depression scores
Penckofer, et al. (2022) [127]	6-month RCT	Weekly 50,000IU(1250mcg) for 6 months or 5,000IU (125mcg) for 6 months	129 women with type 2 diabetes and depressive symptoms	Effect on depression	Mood improved over time regardless of dose
Xie, et al. (2022) [128]	Meta-analysis		29 studies;4504 subjects	Depression	Vitamin D with a daily supplementary dose of >2,800 IU (70mcg) and intervention duration of ≥8 weeks were considered significant in both prevention and treatment analyses. Intervention duration ≤8 weeks was recognised as effective in the treatment group
Guzek, et al. (2023) [93]	Systematic review	1500IU (37.5mcg) 1600IU (40mcg) or 2800IU (70mcg) daily OR 50,000IU (1250mcg) weekly	6 RCTs	Effect on depression	Four studies support a benefit of vitamin D on depression, two studies did not
Sleep					
Mirzaei-Azandaryani, et al. (2022) [94]	Meta-analysis	Various	5 RCTs	Sleep	Significant improvement in sleep quality with vitamin D vs placebo
Abboud (2022) [129]	Meta-analysis	Various	13 intervention studies	Sleep	Pre-post studies showed a significant increase in sleep quality with vitamin D. Effect on sleep-related impairment, difficulty, and disorders, as well as sleepiness and restless legs syndrome, were not unanimous.
Gut microbiota					

Bellerba, et al. (2021) [52]	Systematic review	Studies evaluated vitamin D supplementation, vitamin D from diet and 25(OH)D levels	14 RCTs, 11 observational	Gut microbiota	Vutamin D supplementation associated with significant change in microbiome composition, in particular of *Firmicutes*, *Actinobacteria* and *Bacteroidetes* phyla. Firmicutes correlated with 25(OH)D *Veillonellaceae* and *Oscillospiraceae* families, in the *Firmicutes* phylum, more frequently decreased with both increasing levels of 25(OH)D and vitamin D supplementation.
BMC: Bone Mineral Content; BMD: Bone Mineral Density; BMI: Body Mass Index; Ca: Calcium; HbA1c: Glycated Haemoglobin; HOMA-IR: Homeostatic Model Assessment of Insulin Resistance; PTH: Parathyroid Hormone.					

Table 2: Vitamin D randomized controlled trials and meta-analyses.

How to bridge the vitamin D gap

Measures to increase intake of vitamin D to meet recommendation and to achieve target levels for 25(OH)D are, food, including food fortified with vitamin D, and vitamin D-containing supplements. To achieve the UK recommended daily intake of 10 mcg vitamin D, which aims to achieve a serum vitamin D level of > 25nmol/litre to avoid deficiency, from food alone is highly challenging. Very few foods contain vitamin D (see Table 3) and oily fish such as salmon and mackerel would need to be consumed several times a week if not daily to meet the daily 10 mcg recommendation. Oily fish is not universally enjoyed in the UK. In the UK only a few foods are fortified with vitamin D including some breakfast cereals, some fat spreads and some dairy alternative products.

It is therefore not surprising that vitamin D intakes fall short of the UK RNI of 10 micrograms daily. Years 9-11 combined of the UK National Diet and Nutrition Survey (NDNS) [23] revealed that mean vitamin D intakes from food sources were below the RNI of 10 micrograms per day in all age groups, at around a fifth to a quarter of the RNI in children and a quarter to a third in adults. When intakes of vitamin D from supplements were taken into account mean intakes increased to around 29-40% of the RNI for children and 54% for adults 19 to 64 years, 91% for 65- to 74-year-olds and 60% for adults aged 75 years and over. Mean vitamin D intake from food and supplements for women aged 65 to 74 years met the RNI (101%).

Food	Portion size	Vitamin D (mcg)
Fish		
Salmon, baked	140g	10.2
Salmon, red canned	140g	15.3
Sardines, canned	140g	4.6
Mackerel, grilled	140g	11.9
Mackerel, canned	140g	9.2
Tuna, canned	140g	1.5
Meat		
Lamb roast	90g	0.5
Pork roast	90g	0.9
Chicken breast stir fried	100g	0.2
Lamb's liver fried	100g	0.3
Beef mince, lean, stewed	100g	0.6
Eggs		
Boiled	1 egg (50g)	1.6
Fried	1 egg (60g)	1.1
Scrambled	2 eggs (120g)	3.4

Poached	2 eggs (100g)	2.9
Omelette	2 eggs (120g)	3.4
Fortified breakfast cereals	30g	1.4
Vitamin D enriched mushrooms	80g	3.2
Fats		
Fat spreads	10g	0.8
Butter	10g	0.1

- Some fortified breakfast cereals are fortified with vitamin D. This is the average amount for fortified bran flakes. Check packs for specific amounts
- Some mushrooms are enriched with vitamin D in varying amounts. Check the pack for details. This is the average for two brands.
- Vitamin D content is taken from McCance & Widdowson's. The Composition of Foods. Seventh Edition.

Table 3: Food sources of vitamin D.

A proportion of the vitamin D requirement is obtained through sun exposure [130]. However, sun exposure is also the cause of sunburn and a risk for skin cancer. Seasons, time of day, length of day, cloud cover, air pollution, skin melanin content, and sunscreen are among the factors that affect UV radiation exposure and vitamin D skin synthesis. Sunscreen appears to block vitamin D synthesis but people usually do not apply sufficient amounts of sunscreen, cover all sun-exposed skin, or reapply sunscreen regularly so some synthesis will occur but there has been little agreement on how much [130].

Recent research has evaluated how much exposure to the sun can be safely achieved to achieve target vitamin D levels in the UK. In white people, around 9 minutes of daily sunlight at lunch time from March to September would sustain serum OH(D) levels of 25nmol/litre throughout the year whilst being skin protective. This assumes that forearms and lower legs are exposed from June to August but exposing hands and face throughout the summer would not meet requirements for adequate vitamin D levels throughout the winter [130].

The impact of sunlight on 25(OH)D levels in people with different skin types is unknown. Previous research has shown that South Asians may need 25 minutes daily of skin exposure compared with 9 minutes for white people to achieve the target serum concentration for vitamin D [130] Older people too are also less able to produce vitamin D from sunlight. UVB radiation does not penetrate glass, so exposure to sunshine indoors through a window does not produce vitamin D.

Long hours spent in offices may also preclude people getting adequate and safe skin exposure to sunlight.

The practicalities of obtaining enough vitamin D through skin exposure to sunlight are therefore unknown. Not enough is known about the exposure required and whether it is practical for urban dwelling people and those who either spend a lot of time indoor or cover their skins.

Supplementation would therefore appear to be the way the best way to achieve recommended 25(OH)D levels. Facilitating the whole UK population to take the 10mcg recommended daily dose is important. This dose would allow the UK population to achieve 25(OH)D levels of 25nmol/litre. However, other countries recommend higher 25(OH)D levels and an intake of 10micrograms daily would not for example achieve the serum levels of >50nmol/litre recommended in Europe and the US. This lack of consensus on recommended intakes and levels of 25(OH)D to achieve sufficiency of vitamin D is challenging, but in the UK getting the whole population to take the government recommended 10 microgram daily supplement would reduce the risk of deficiency considerably.

There is a challenge in getting people to take a supplement. Lack of understanding that dietary intake of vitamin D will not achieve recommended intakes and the practicalities and risks of skin exposure to sunlight are difficult to shift. In the latest NDNS data, only 17% of adults aged 19 to 64 years, 34% aged 65 to 74 years and 28% aged 75 years and over reported taking vitamin D supplements during the 4-day dietary recording period. It is particularly hard to reach low-income groups. A study carried out in Scotland during the COVID pandemic showed that when HM Government offered free vitamin D to vulnerable groups there was only a 40% uptake [131].

Labelling is challenging for individuals. There are discrepancies with food labelling and consumer confusion with the recommended amount of vitamin D (e.g., SACN 10mcg/day; EU 15mcg/day and 5 mcg/day on EU guidance for food labelling. European labelling guidance for food and hence supplement labelling (5mcg/day) was based on Adequate Intakes rather than an RNI for vitamin D.

This creates confusion, not just with consumers, but with scientists as well, reiterating the need for consensus on recommended intakes which would have a huge impact when trying to clearly communicate the message to consumers.

Conclusion

Closing the gap between vitamin D intakes and recommendations is an imperative to prevent deficiency, and maintain bone and muscle health, particularly to prevent nutritional rickets and osteomalacia. Research on the impact of vitamin D supplementation on extra-skeletal functions such as gut, cardiometabolic and respiratory health has generated positive findings. Further research may elucidate further links between vitamin D supplementation and other aspects of extra-skeletal function. In any case it is crucial to prevent deficiency and ensure that 25(OH)D levels are at least 25nmol/litre possibly 50nmol/litre. This can be achieved reliably only by vitamin D supplementation across the population.

Vitamin D is cost effective, easy to take, plus supplementation offers potential cost savings to the NHS. Healthcare professionals are in a position to routinely advise patients to take a 10mcg daily supplement and to increase their intake of vitamin D containing foods. Advice needs also to be reinforced through care homes, local parenting and community groups and via faith groups.

Competing Interests Statement

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