Population vitamin D supplementation in UK adults: too much of nothing?

Alison Avenell,[1] Mark J Bolland,[2] Andrew Grey[2]
[1]Health Services Research Unit, University of Aberdeen, Aberdeen, UK
[2]Department of Medicine, University of Auckland, Auckland, New Zealand

Correspondence to Professor Alison Avenell; a.avenell@abdn.ac.uk

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Key learning points

- Current systematic reviews of randomised controlled trials do not provide evidence that vitamin D supplementation reduces cardiovascular disease, cancer or premature mortality, as has been suggested by observational studies.
- Recent research has been unable to show that vitamin D supplementation is effective in preventing falls or fractures, so it appears that supplementation is unnecessary for most people to protect musculoskeletal health, except people from high risk populations with no sunlight exposure at high risk of rickets and osteomalacia.
- Adult populations in the UK whose skin has little or no exposure to the sun or people who always cover their skin when outside may be at higher risk, but we do not have good evidence that universal supplementation of these groups is beneficial for their health.

Introduction

In 2016, Public Health England advised for everyone aged ≥5 years that "Since it is difficult for people to meet the 10 microgram (400 IU) recommendation from consuming foods naturally containing or fortified with vitamin D, people should consider taking a daily supplement containing 10 micrograms of vitamin D in autumn and winter".[1] This guidance was subsequently adopted in Scotland, Wales and Northern Ireland. Supplementation guidance was extended beyond previous recommendations for those who cover most of their skin when outside, or ethnic groups with dark skin and for people at high risk of little or no sun exposure such as people in care homes. The rationale for this advice was to improve bone and muscle health. All forms of vitamin D prescription dispensed in primary care cost the NHS in England in the 12 months to July 2020 over £95 million (openprescribing.net), and there have been concomitant dramatic increases in laboratory testing for 25-hydroxyvitamin D (25OHD), which is used to assess vitamin D status.[2–4] Is this an effective use of NHS resources?

Public Health England's guidance was derived from the findings of the 2016 Scientific Advisory Committee on Nutrition (SACN)'s report on Vitamin D and Health.[5] What were the findings of that report? How reliable are the findings and has newer research meant that those findings should be revisited? Here we discuss the evidence for the general adult population, but do not cover questions of vitamin D supplementation in pregnancy or for the prevention of rickets in children.

What is vitamin D?

Vitamin D has two forms, colecalciferol or vitamin D_3, a hormone manufactured in the skin in response to ultraviolet B irradiation from sunlight, and ergocalciferol or vitamin D_2 often found in supplements. Both are metabolised to 25-hydroxyvitamin D (25OHD) by the liver and kidneys to its most active form 1,25-dihydroxyvitamin D (1,25$(OH)_2$D). Vitamin D is stored long term in adipose tissue and liver. Few dietary sources exist, mainly oily fish, eggs, liver, butter and meat. People who are housebound or those with very limited sun exposure and/or dark skins or malabsorption are at increased risk of vitamin D deficiency diseases—rickets in children and osteomalacia in adults. Vitamin D_2, ergocalciferol, may be less active than colecalciferol. 1,25$(OH)_2$D facilitates intestinal calcium and phosphate absorption to maintain bone mineralisation. Adults who have prolonged severe vitamin D deficiency develop osteomalacia, a clinical syndrome characterised by impaired bone mineralisation, bone fragility and myopathy.

What did the Scientific Advisory Committee on Nutrition (SACN) find?

The SACN took the US Institute of Medicine's 2011 report on dietary reference intakes for calcium and vitamin D, supplemented by a 2014 US Agency for Healthcare Research and Quality update, as their starting point.[6 7] SACN updated searches to 2016, but no search strategy was described or search results reported. A series of position papers that have not been published were prepared to summarise the evidence for the Committee's discussion.[5] There is no description in the report or its appendices of an assessment of the quality of that newer evidence, nor attempts to judge the quality of the evidence in making recommendations, for example, by using GRADE (Grading of Recommendations, Assessment, Development and Evaluations).[8] No economic evaluation of the anticipated changes in prescribing or laboratory testing was undertaken.

SACN's recommendations on vitamin D supplementation for adults were stated to be based on musculoskeletal health outcomes (including osteomalacia, falls, muscle strength and function), since data on other outcomes were considered insufficient for the development of guidance. Table 1 lists SACN's findings, taken from their summary. The risk of osteomalacia increased with 25OHD <15–20 nmol/L. SACN emphasised that these thresholds are not diagnostic of disease. Two cited cross-sectional reports from 1975 and 2011 in osteomalacia showed that groups of patients had very low 25OHD status of <7.5 nmol/L or a mean of 15 nmol/L, respectively. The analytical method used in 1975 is known to overestimate 25OHD by about 50%.

Table 1 Summary of Scientific Advisory Committee on Nutrition's findings for musculoskeletal health outcomes reviewed up until 2014

Rickets	▶ A distinct threshold 25OHD concentration above which there is no risk of rickets could not be identified. Data suggested risk increased <25 nmol/L ▶ <25nmol/L is not diagnostic of the disease ▶ Evidence was mainly from cross-sectional observational studies and case reports and may have been influenced by confounding ▶ It was not clear whether the cause of rickets was vitamin D deficiency and/or calcium deficiency
Osteomalacia	▶ No clear serum 25OHD threshold concentration below which risk of osteomalacia increased but <20 nmol/L and ≤15 nmol/L in cross-sectional analyses
Bone health indices (bone mineral content, bone mineral density, biochemical markers of bone turnover)	▶ Evidence suggested beneficial effects of vitamin D supplementation on bone health indices in adults aged ≥50 years. The evidence base for adults aged <50 years was insufficient to draw conclusions
Fracture prevention	▶ Data in adults aged ≥50 years were mixed but suggested vitamin D supplementation did not reduce fracture risk ▶ The effect of vitamin D supplementation on stress fracture risk in adults aged <50 years was insufficient to draw conclusions
Muscle strength and function	▶ Limited evidence suggested a beneficial effect of vitamin D supplementation on muscle strength and function in adults aged <50 years with 25OHD <30 nmol/L ▶ For adults aged ≥50 years with a range of 25OHD concentrations, evidence was mixed but overall suggested vitamin D supplementation improved muscle strength and function
Falls	▶ Evidence mixed but suggested vitamin D supplementation reduced fall risk in community dwelling adults aged ≥50 years with mean baseline serum 25OHD concentrations across a range of values ▶ Two studies reported increased fall risk with vitamin D supplementation; however, doses were very high and administered annually or monthly which may produce different effects from daily supplementation at lower doses

25OHD, 25-hydroxyvitamin D.

Unfortunately, analytical methods for 25OHD determination show great variability, particularly immunoassays, making assessment of risk of osteomalacia based on laboratory methods difficult.[9 10] 25OHD also falls in acute illness.[11] Much more reliable methods for 25OHD determination by liquid chromatography-tandem mass spectrometry are expensive and time-consuming, but in response to huge escalations in demand for 25OHD testing, they are increasingly being replaced in the UK by immunoassays, which are cheaper but have greater variability at low concentrations.

SACN reported 25OHD status taken from the UK National Diet and Nutrition Surveys, where 25OHD was measured by immunoassay. The proportions with 25OHD concentration <25 nmol/L in winter were 39% of adults aged 19–64 years and 29% of adults aged ≥65 years. In summer, the proportions with 25OHD concentration <25 nmol/L were 8% of adults aged 19–64 years and 4% of adults aged ≥65 years. As expected, the proportions of the population with a concentration <25 nmol/L increased with latitude, and in populations who were housebound, had dark skin or little sun exposure. SACN indicated that 10 micrograms/day (400 IU/day) of vitamin D from diet, fortified food or supplements was needed to keep 25OHD ≥25 nmol/L to maintain optimum musculoskeletal outcomes in the autumn and winter. As UK diets do not provide sufficient vitamin D, supplements were advised for these periods. Public Health England therefore made recommendations for adults to "consider taking a daily supplement containing 10 micrograms of vitamin D in autumn and winter".

Given the frequency of 25OHD <25 nmol/L in the adult population, it might be expected that substantial numbers of adults would develop osteomalacia. Yet hospital admissions for osteomalacia in England are only 50–100/year.[12]

In its review, SACN reported beneficial effects from vitamin D on bone mineral density, a predictor of fracture risk in adults aged ≥50 years. This conclusion was drawn despite citing a recent comprehensive systematic review that reported no clinically relevant effects of vitamin D on bone density.[13] SACN did not find evidence to support an effect of vitamin D on fracture prevention.

SACN considered that four recent systematic reviews of trials of vitamin D (25OHD group means approximately 30 nmol/L, 24–66 nmol/L, <30 nmol/L and <25 nmol/L before supplementation) showed some limited evidence of benefit on muscle strength and function. The quality of these systematic reviews was not considered, but close examination raises important concerns about the validity of their conclusions. One review inappropriately included multiple related outcomes as if they were independent.[14] When correctly analysed, there is no effect of vitamin D on muscle strength (see online supplemental appendix). The other three reviews were heavily influenced by small trials with mean 25OHD <25 nmol/L, which have subsequently been retracted or have unresolved data irregularities.[15 16] When these trials are removed from analyses, again the meta-analyses show no effect of vitamin D (see online supplemental appendix).

For falls, SACN concluded that vitamin D reduced the risk of falls, despite citing the most recent and most comprehensive review at that time reporting no effect, and two *Cochrane* reviews which found no reduction in the risk of falls.[17–19] Two recent large trials showed an increased risk of falls with higher dose, intermittent vitamin D supplementation.[20 21]

In summary, while SACN reported beneficial effects for vitamin D supplements on several musculoskeletal outcomes, close examination of the underpinning evidence does not support those conclusions.

What does more recent evidence tell us?

We updated our previous literature search[22] in Medline, Embase and the Cochrane Library from 2016 to October 2019 to look for wide-ranging systematic reviews, *Cochrane* reviews and health

Table 2 Wide-ranging systematic reviews, *Cochrane* reviews and health technology assessments of RCTs of vitamin D supplementation since the SACN report search completed

Review	Endpoint	Description	Findings
Comprehensive, large, wide-ranging systematic reviews			
Autier, 2014[23]	Cardiovascular disease, mortality, cancer incidence	172 RCTs*	► No effect on disease occurrence ► Small reduction in all-cause mortality (RR range 0.93–0.96)
Bolland, 2014[24]	Stroke, myocardial infarction, cancer, fractures, mortality	Trial sequential analysis of RCTs*	► Does not reduce skeletal or non-skeletal outcomes by >15% in unselected community dwelling individuals
Bolland, 2014[17]	Falls	20 RCTs*	► Supplementation with vitamin D, with or without calcium, does not reduce falls by 15% or more
Theodoratou, 2014[25]	Clinical and surrogate endpoints	87 meta-analyses of RCTs†	► No consistent difference in health outcomes
Rejnmark, 2017[26]	Cardiovascular disease, type 2 diabetes, cancer, respiratory tract infections, mortality, depression, blood pressure	54 meta-analyses of RCTs*†	► Most meta-analyses reported null findings on cardiovascular disease, type 2 diabetes, cancer ► 1 of 4 meta-analyses on depression, 2 of 9 on blood pressure, 3 of 7 on respiratory tract infection, 8 of 12 on mortality reported beneficial effects
Autier, 2017[27]	Non-skeletal disorders	35 recent good quality meta-analyses*	► Most meta-analyses and trials have found no evidence of an effect on preventing or treating acute and chronic conditions. No evidence for effect on cardiovascular disease or colorectal adenomas ► Can reduce all-cause mortality, mainly in hospital or an institution, and cancer mortality ► Might help to prevent upper respiratory tract infections and asthma exacerbations
Bolland, 2018[28]	Fractures, falls, bone mineral density	81 RCTs	► Does not prevent fractures or falls or having clinically meaningful effects on bone mineral density
Kahwati, 2018[29]	Fractures, mortality, cardiovascular events, cancer	8 RCTs*	► No effect on fractures, all-cause mortality, cardiovascular disease, cancer incidence in community dwelling adults
Zhang, 2019[30]	All-cause mortality	52 RCTs	► No effect on all-cause mortality (RR 0.98, 95% CI 0.95 to 1.02)
Barbarawi,2019[31]	Cardiovascular disease	21 RCTs*†	► No reduction in major cardiovascular events, myocardial infarction, stroke, cardiovascular mortality, all-cause mortality
Recent *Cochrane* reviews or health technology assessments			
Bjelakovic 2014[32]	Cancer	18 RCTs*†	► No effect on cancer incidence ► Reduced cancer mortality in 4 trials of vitamin D alone (RR 0.88, 95% CI 0.78 to 0.98), rated low quality evidence
Bjelakovic, 2014[33]	All-cause mortality	56 RCTs*†	► Reduced mortality by small amount (RR 0.97, 95% CI 0.94 to 0.99) ► Authors state that risks of attrition bias, outcome reporting bias and other weaknesses warrant further placebo-controlled RCTs
Ferguson, 2014[34]	Cystic fibrosis	3 RCTs*†	► Insufficient evidence to draw reliable conclusions
LeBlanc, 2015[35]	Benefits of screening, mortality, fractures, falls	17 RCTs or case-control studies*	► No RCTs of screening vs. not screened ► Vitamin D with or without calcium reduced mortality in institutionalised older people in 3 RCTs ► No effect on risk of fall, but decreased falls per person ► No effect on fractures
Straube, 2015[36] (CD007771)	Chronic pain	10 RCTs†	► Insufficient evidence to draw reliable conclusions but large effect unlikely
Martineau, 2016[37]	Asthma	7 RCTs (2 in adults)	► In each trial, vitamin D had no effect on the primary or secondary clinical endpoints ► Reduced rate of exacerbations requiring corticosteroids or hospital visit. These were not the primary or secondary endpoints of the RCTs ► Authors state caution warranted applying evidence to practice because results come from relatively few trials

Continued

Table 2 Continued

Review	Endpoint	Description	Findings
Soe, 2017[38] (CD010858)	Sickle cell disease	1 RCT	▸ One low-quality study which had high risk of bias, evidence insufficient quality to guide clinical practice
Bjelakovic, 2017[39]	Liver disease	15 RCTs*†	▸ Uncertain whether vitamin D supplements have important effect on all-cause mortality, liver-related mortality, or adverse events because results were imprecise ▸ No evidence on effect of vitamin D supplementation on liver-related morbidity or health-related quality of life ▸ Overall quality of evidence is very low
Guirguis-Blake, 2017[40]	Falls by community-dwelling older adults	7 RCTs*†	▸ 1 trial of annual high-dose cholecalciferol showed an increase in people experiencing a fall ▸ 1 trial of calcitriol showed a reduction in people experiencing a fall ▸ 5 trials showed no significant difference in people experiencing a fall
Zhao, 2017[41]	Fractures	33 RCTs*	▸ Not associated with lower risk of fractures in community dwelling older adults
Jagannath, 2018[42]	Multiple sclerosis	12 RCTs*	▸ Very low-quality evidence suggests no benefit of vitamin D for patient-important outcomes
Martineau, 2019[43]	Acute respiratory infections	25 RCTs	▸ Adjusted OR 0.88 (95% CI 0.81 to 0.96) representing 2% reduction in participants experiencing at least one infection with vitamin D. Most benefits if 25OH <25 nmol/L

*Results include some RCTs examining calcium in addition to vitamin D.
†Results include some RCTs examining activated forms of vitamin D.
CI, confidence interval; 25OHD, 25-hydroxyvitamin D; OR, odds ratio; RCT, randomised controlled trial; RR, risk ratio.

technology assessments of randomised controlled trials (RCTs) of vitamin D supplementation on clinical outcomes for the general adult population, published since the end of the search conducted by SACN. We did not include evidence for supplementation before or during pregnancy or for children. The findings of these publications are provided in table 2.[23–43]

Notable are the large number of trials and systematic reviews published. Different systematic reviews included widely ranging numbers of RCTs for the same outcome (eg, seven RCTs for falls from a 2017 review[40] compared with 20 RCTs in an earlier review from 2014).[17] Differences in criteria for inclusion of trials, including those with calcium co-supplementation, those with vitamin D analogues and those with specific populations make comparisons challenging. Systematic reviews have consistently shown no effect from vitamin D supplementation on the incidence of cardiovascular disease or cancer. Earlier small reductions in all-cause mortality[23 33] were reported with caution because of the low quality of the included trials, and the most recent largest systematic review did not find an effect on all-cause mortality.[30]

If, as determined by SACN, vitamin D improves surrogate musculoskeletal outcomes, then it would be expected that fractures and falls would also be reduced. Recent systematic reviews have consistently shown that vitamin D given alone is unable to prevent fractures (see table 2). Our 2018 systematic review also showed no meaningful effect on all fractures (36 trials, 44 790 participants; risk ratio [RR] 1.00, 95% CI 0.93 to 1.07), hip fracture (20 trials, 36 655 participants; RR 1.11, 95% CI 0.97 to 1.26) or bone density.[28] Two systematic reviews with small numbers of trials showed contradictory evidence for prevention of falls.[35 40] Our more recent review was unable to demonstrate an effect on falls (37 trials, 34 144 participants; RR 0.97, 95% CI 0.93 to 1.02).[28]

Our systematic review included only four trials in participants with 25OHD <25 nmol/L, and large trials in progress will not evaluate supplementation in this higher risk population.[28 44] Benefits on fracture prevention might be seen in populations which are very vitamin D deficient and given calcium supplements, as shown by one old trial in very elderly women in French nursing homes, who appeared to be profoundly vitamin D deficient.[45] One recent large trial from Norway, which particularly investigated supplementation in participants with low 25OHD, reported no effect on four indicators of muscle strength in participants with 25OHD <25 nmol/L, despite supplementation achieving serum 25OHD of 89 nmol/L.[46] One systematic review reported a very small reduction in respiratory infections, predominantly in those with 25OHD <25 nmol/L and in children.[43]

When should vitamin D status be measured?

Given the caveats around the utility of vitamin D supplementation and problems with assay reliability, when is measurement justified? There is little reason for measurement in osteoporosis, where vitamin D supplementation does not reduce fracture risk, nor for high-risk individuals (sunlight-deprived) who require supplementation. Measurement for investigation of unexplained disorders of bone, calcium or phosphate metabolism may be required, but common symptoms such as tiredness, weakness and musculoskeletal pain are extremely unlikely to be due to vitamin D deficiency. The classical biochemical picture of osteomalacia with low serum calcium, low serum phosphate and raised alkaline phosphatase in the absence of liver disease is rarely seen by laboratories.

What about supplementation?

Vitamin D supplements regularly feature among the top 20 prescription costs for the NHS. There is no convincing evidence that community dwelling individuals, who are not at risk of

osteomalacia, benefit from vitamin D supplements. They should not take supplements unless benefits have been proven.

Prolonged high dose vitamin D supplementation is not risk free, and doses ≥700 micrograms/day (2800 IU/day) taken for a year or longer are associated with a risk of hypercalcaemia.[47] In the UK, enthusiasm has led some to purchase over the counter preparations and consume daily intakes greatly in excess of this. For example, 2.5% (n=372) of members of the public accessing NHS 25OHD laboratory measurements in Birmingham had 25OHD >220 nmol/L, a cut-off thought to indicate risk of hypercalcaemia.[48]

In fact, if the goal is to raise 25OHD to >25 nmol/L to prevent osteomalacia, low doses of vitamin D supplements are likely to be adequate because change in 25OHD following supplementation is dependent on baseline 25OHD. For example, in different RCTs 400 IU/day increased 25OHD from 27 nmol/L to 54 nmol/L,[49] and from 27 nmol/L to 43 nmol/L,[50] but had little effect when the baseline 25OHD was 52 nmol (post-supplementation 25OHD 55 nmol/L).[51]

Rates of osteomalacia have not decreased since the 2016 SACN report.[12] This suggests that public health policies have not had a major impact. Present NHS expenditure on vitamin D might be better spent on more effective targeted supplementation for those at very high risk and/or by food fortification appropriate for the at-risk population successfully adopted by other countries,[52] which would be more effective and less costly.

SACN and the National Institute for Health and Care Excellence (NICE) have recently reviewed evidence for an effect of vitamin D supplementation on COVID-19.[53,54] NICE concluded that "There is no evidence to support taking vitamin D supplements to specifically prevent or treat COVID-19. However, all people should continue to follow UK Government advice on daily vitamin D supplementation to maintain bone and muscle health during the COVID-19 pandemic."

At present it is uncertain if adults with 25OHD <25 nmol/L in winter, who are not at high risk of osteomalacia, derive any clinical benefit from supplementation. This is an important question for future research.

Information for patients

- Vitamin D regulates the amount of calcium and phosphate in the body; both are needed for healthy bones, teeth and muscles.
- Vitamin D is made in the skin by the action of sunlight and this is the main source of vitamin D for most people.
- Vitamin D is found naturally in a small number of foods including oily fish, red meat, liver and egg yolks and in fortified food like breakfast cereals and fat spreads.
- Diseases caused by a deficiency of vitamin D are called rickets in children and osteomalacia in adults. They are both very uncommon diseases.
- People at increased risk of vitamin D deficiency in the UK whose skin has little or no exposure to the sun (eg, people in care homes or those who always cover their skin when outside) might need to take a supplement throughout the year. But we do not have good evidence that universal supplementation of these groups is beneficial for their health.
- Based on maintaining musculoskeletal health, official UK advice is that, in spring and summer, the majority of the population get enough vitamin D through sunlight on the skin and through a healthy balanced diet, and that during autumn and winter everyone will need to rely on dietary sources of vitamin D.
- UK Public Health guidance states that it is difficult for people to achieve the recommended intake of 10 micrograms/day from consuming foods naturally containing or fortified with vitamin D, so people should consider taking a daily supplement containing 10 micrograms of vitamin D in autumn and winter.
- The daily safe upper limit for oral vitamin D recommended by the European Food Safety Authority is 100 micrograms/day (4000 IU/day).
- Recent research has been unable to show that vitamin D supplementation is effective in preventing falls or fractures, so it appears that supplementation during the autumn and winter is not necessary for most people, except those from high-risk populations.

Competing interests None declared. Refer to the online supplementary files to view the ICMJE form(s).

Provenance and peer review Commissioned; externally peer reviewed.

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DOI: 10.1136/dtb.2020.000060