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

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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, calciferol or vitamin D3, a hormone manufactured in the skin in response to ultraviolet B irradiation from sunlight, and ergocalciferol or vitamin D2, 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)2D). 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 D3, ergocalciferol, may be less active than calciferol, 1,25(OH)2D 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.8 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).3 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%.
Unfortunately, analytical methods for 25OHD determination show great variability, particularly immunoassays, making assessment of risk of osteomalacia based on laboratory methods difficult.\textsuperscript{12} 25OHD also falls in acute illness.\textsuperscript{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 50–100/100,000 year.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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 \textit{Cochrane} reviews which found no reduction in the risk of falls.\textsuperscript{17–19} Two recent large trials showed an increased risk of falls with higher dose, intermittent vitamin D supplementation.\textsuperscript{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 these conclusions.

\textbf{What does more recent evidence tell us?}

We updated our previous literature search\textsuperscript{22} in Medline, Embase and the Cochrane Library from 2016 to October 2019 to look for wide-ranging systematic reviews, \textit{Cochrane} reviews and health
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| Comprehensive, large,  | Cardiovascular disease, mortality, cancer incidence                        | 172 RCTs*                                                                 | ▶ No effect on disease occurrence  
▶ Small reduction in all-cause mortality (RR range 0.93–0.96)                                               |
| wide-ranging systematic | 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            |
| reviews                | Falls                                                                     | 20 RCTs*                                                                 | ▶ Supplementation with vitamin D, with or without calcium, does not reduce falls by 15% or more                 |
| Autier, 2014           | Clinical and surrogate endpoints                                         | 87 meta-analyses of RCTs*                                                                 | ▶ No consistent difference in health outcomes                                                                       |
| Bolland, 2014          | 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 |
| Bolland, 2018          | Fractures, falls, bone mineral density                                    | 81 RCTs                                                                 | ▶ Does not prevent fractures or falls or having clinically meaningful effects on bone mineral density               |
| Kahwati, 2018          | Fractures, mortality, cardiovascular events, cancer                       | 8 RCTs*                                                                 | ▶ No effect on fractures, all-cause mortality, cardiovascular disease, cancer incidence in community dwelling adults |
| Zhang, 2019            | All-cause mortality                                                       | 52 RCTs                                                                 | ▶ No effect on all-cause mortality (RR 0.98, 95% CI 0.95 to 1.02)                                                   |
| Barbarawi, 2019        | Cardiovascular disease                                                   | 21 RCTs†                                                                 | ▶ No reduction in major cardiovascular events, myocardial infarction, stroke, cardiovascular mortality, all-cause mortality |
| Rejnmark, 2017         | 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 |
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| Bolland, 2018          | Fractures, falls, bone mineral density                                    | 81 RCTs                                                                 | ▶ No effect on fractures or falls or having clinically meaningful effects on bone mineral density               |
| Kaushal, 2018          | Fractures, mortality, cardiovascular events, cancer                       | 8 RCTs*                                                                 | ▶ No effect on fractures, all-cause mortality, cardiovascular disease, cancer incidence in community dwelling adults |
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Table 2: Continued

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<tr>
<td>Soe, 2017</td>
<td>Sickle cell disease</td>
<td>1 RCT</td>
<td>▶ One low-quality study which had high risk of bias, evidence insufficient quality to guide clinical practice</td>
</tr>
<tr>
<td>Bjelakovic, 2017</td>
<td>Liver disease</td>
<td>15 RCTs†</td>
<td>▶ Uncertain whether vitamin D supplements have important effect on all-cause mortality, liver-related mortality, or adverse events because results were imprecise</td>
</tr>
<tr>
<td>Guirgis-Blake, 2017</td>
<td>Fractures by community-dwelling older adults</td>
<td>7 RCTs†</td>
<td>▶ 1 trial of annual high-dose cholecalciferol showed an increase in people experiencing a fall</td>
</tr>
<tr>
<td>Zhao, 2017</td>
<td>Fractures</td>
<td>33 RCTs°</td>
<td>▶ Not associated with lower risk of fractures in community dwelling older adults</td>
</tr>
<tr>
<td>Jagannath, 2018</td>
<td>Multiple sclerosis</td>
<td>12 RCTs°</td>
<td>▶ Very low-quality evidence suggests no benefit of vitamin D for patient-important outcomes</td>
</tr>
<tr>
<td>Martineau, 2019</td>
<td>Acute respiratory infections</td>
<td>25 RCTs</td>
<td>▶ 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 of 25OHD &lt;25 nmol/L</td>
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*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.
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.44 In the UK, enthusiasm has led some to purchase 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.45 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,46 and from 27 nmol/L to 43 nmol/L,47 but had little effect when the baseline 25OHD was 52 nmol (post-supplementation 25OHD 55 nmol/L).11 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,13 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-19.1415 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.

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

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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.

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