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”. 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.1-4 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) 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 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 colecalciferol. 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.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%.

...
Unfortunately, analytical methods for 25OHD determination show great variability, particularly immunoassays, making assessment of risk of osteomalacia based on laboratory methods difficult.12,13 25OHD also falls in acute illness.14 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”.

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.17,18 Two recent large trials showed an increased risk of falls with higher dose, intermittent vitamin D supplementation.19,20 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.

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

<table>
<thead>
<tr>
<th>Condition</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rickets</td>
<td>▶ A distinct threshold 25OHD concentration above which there is no risk of rickets could not be identified. Data suggested risk increased &lt;25 nmol/L</td>
</tr>
<tr>
<td></td>
<td>▶ &lt;25 nmol/L is not diagnostic of the disease</td>
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<tr>
<td></td>
<td>▶ Evidence was mainly from cross-sectional observational studies and case reports and may have been influenced by confounding</td>
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<tr>
<td></td>
<td>▶ It was not clear whether the cause of rickets was vitamin D deficiency and/or calcium deficiency</td>
</tr>
<tr>
<td>Osteomalacia</td>
<td>▶ No clear serum 25OHD threshold concentration below which risk of osteomalacia increased but &lt;20 nmol/L and ≥15 nmol/L in cross-sectional analyses</td>
</tr>
<tr>
<td>Bone health indices</td>
<td>▶ Evidence suggested beneficial effects of vitamin D supplementation on bone health indices in adults aged ≥50 years. The evidence base for adults aged &lt;50 years was insufficient to draw conclusions</td>
</tr>
<tr>
<td>Fracture prevention</td>
<td>▶ Data in adults aged ≥50 years were mixed but suggested vitamin D supplementation did not reduce fracture risk</td>
</tr>
<tr>
<td></td>
<td>▶ The effect of vitamin D supplementation on stress fracture risk in adults aged &lt;50 years was insufficient to draw conclusions</td>
</tr>
<tr>
<td>Muscle strength and function</td>
<td>▶ Limited evidence suggested a beneficial effect of vitamin D supplementation on muscle strength and function in adults aged &lt;50 years with 25OHD &lt;30 nmol/L</td>
</tr>
<tr>
<td></td>
<td>▶ 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</td>
</tr>
<tr>
<td>Falls</td>
<td>▶ 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</td>
</tr>
<tr>
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<td>▶ 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</td>
</tr>
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25OHD, 25-hydroxyvitamin D.

### What does more recent evidence tell us?

We updated our previous literature search in Medline, Embase and the Cochrane Library from 2016 to October 2019 to look for wide-ranging systematic reviews, Cochrane reviews and health
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<th>Review</th>
<th>Endpoint Description</th>
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| Autier, 2014 | 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 | 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 | Falls | 20 RCTs*  
Supplementation with vitamin D, with or without calcium, does not reduce falls by 15% or more |
| Theodoratou, 2014 | Clinical and surrogate endpoints | 87 meta-analyses of RCTs†  
No consistent difference in health outcomes |
| Rejnmark, 2017 | 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 | 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 | Fractures, falls, bone mineral density | 81 RCTs  
Does not prevent fractures or falls or having clinically meaningful effects on bone mineral density |
| Kalwati, 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 |
| Autier, 2017 | 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 | 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 | Cystic fibrosis | 3 RCTs†  
Insufficient evidence to draw reliable conclusions |
| LeBlanc, 2015 | 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 | Chronic pain | 10 RCTs†  
Insufficient evidence to draw reliable conclusions but large effect unlikely |
| Martineau, 2016 | 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 |

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<td>Bjelakovic, 2017</td>
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<td>Guirguis-Blake, 2017</td>
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<td>Zhao, 2017</td>
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<td>Jagannath, 2018</td>
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<td>Acute respiratory infections</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.

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**Table 2 Continued**

What should vitamin D status be measured for?

1. **Risk of osteoporosis**
   - Vitamin D deficiency is common in people with osteoporosis.
   - Vitamin D supplementation can improve bone density and reduce fracture risk.

2. **Risk of falls**
   - Falls are a common complication of vitamin D deficiency, especially in older adults.
   - Vitamin D supplementation can reduce the risk of falls.

3. **Risk of fractures**
   - Fractures are a major complication of vitamin D deficiency, especially in postmenopausal women.
   - Vitamin D supplementation can reduce the risk of fractures.

4. **Risk of muscle weakness**
   - Vitamin D deficiency is common in people with muscle weakness, especially in older adults.
   - Vitamin D supplementation can improve muscle strength and reduce the risk of falls.

5. **Risk of respiratory infections**
   - Vitamin D deficiency is common in people with respiratory infections, especially in children.
   - Vitamin D supplementation can reduce the risk of respiratory infections.

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**Table 3**

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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.46 In the UK, enthusiasm has led some to purchase 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.46

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,19 and from 27 nmol/L to 43 nmol/L,20 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,12 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-19.14,15 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 ICMEJ form(s).

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