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Vitamin D in adolescence: evidence-based dietary requirements and implications for public health policy

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Abbreviations: 25(OH)D: 25-hydroxyvitamin D; 1,25(OH)₂D: 1,25-dihydroxyvitamin D; EAR: Estimated Average Requirement; EFSA: European Food Safety Authority; ESPGHAN: European Society for Paediatric Gastroenterology, Hepatology and Nutrition; IOM: Institute of Medicine; NDNS: National Diet and Nutrition Survey; RCT: randomised controlled trial; RDA: Recommended Dietary Allowance; RNI: Recommended Nutrient Intake; SACN: Scientific Advisory Committee on Nutrition; UVB: ultraviolet B.

Abstract

Vitamin D is a unique nutrient. Firstly, it acts as a pro-hormone and secondly, the requirement for vitamin D can be met by both endogenous synthesis from sunlight and by dietary sources. This complicates the determination of dietary requirements for vitamin D, which along with the definition of optimal vitamin D status, have been highly controversial and much debated over recent years. Adolescents are a population group at high risk of low vitamin D status, which is concerning given the important role of vitamin D, and calcium, in promoting normal bone mineralisation and attainment of peak bone mass during this rapid growth phase. Dietary vitamin D recommendations are important from a public health perspective in helping to avoid deficiency and optimise vitamin D status for health. However limited experimental data from winter-based dose-response randomised trials in adolescents has hindered the development of evidence-based dietary requirements for vitamin D in this population group. This review will highlight how specifically designed randomised trials and the approach adopted for estimating such requirements can lead to improved recommendations. Such data indicates that vitamin D intakes of between 10 and ~30 µg/day may be required to avoid deficiency and ensure adequacy in adolescents, considerably greater than the current recommendations of 10-15 µg/day. Finally this review will consider the implications of this on public health policy, in terms of future refinements of vitamin D requirement recommendations and prioritisation of public health strategies to help prevent vitamin D deficiency.

Overview and Basic Biology of Vitamin D: Sources, Metabolism and Function

Diet

There are two main forms of vitamin D, namely vitamin D₂ (ergocalciferol) and vitamin D₃ (cholecalciferol), both of which are found in the diet in predominantly plant based and animal based foods respectively. While there are few foods which are a natural rich source of vitamin D, good sources include oily fish and egg yolks (vitamin D₃) and wild mushrooms (vitamin D₂)⁽¹⁾. Foods can also be fortified, on a voluntary or mandatory basis, with vitamin D₂ or D₃, although fortification policies vary quite considerably between countries, with minimal voluntary fortification found in the UK and across much of Europe (with the exception of Finland; for review see Kiely and Black⁽²⁾). Consequently, dietary vitamin D intakes among adolescents are typically low (< 3 µg/day). In the UK National Diet and Nutrition Survey (NDNS) Rolling Programme (2008/09-2011/12), mean vitamin D intakes from food sources alone were 1.9 and 2.4 µg/day in 11-18 year old females and males respectively⁽³⁾. Main food group contributors were meat and meat products (35%), fat spreads (20%) and cereal/cereal products (17%), with eggs and oily fish, both good sources of vitamin D, contributing only 9% each, emphasising the low consumption of oily fish among adolescents⁽³⁾. While supplement use can be an effective means of increasing dietary vitamin D intakes, uptake tends to be greater among infants, young children and elderly adults and low among adolescents. Indeed, in the UK NDNS only 8% of adolescents aged 11-18 years reported taking any type of supplement (compared to 16%, 22% and 41% of 4-10, 19-64 and 65+ year olds respectively) and mean vitamin D intakes increased only marginally to 2.1 and 2.6 µg/day in females and males respectively when supplements were included⁽³⁾.

Endogenous synthesis

Vitamin D is unique in that the majority of this nutrient (80-90%) is synthesised within the human body following skin exposure to sunlight, hence vitamin D's recognition as the 'sunshine nutrient'. Ultraviolet B (UVB) radiation (wavelength 290-315 nm) mediates the conversion of 7-dehydrocholesterol, a cholesterol precursor contained within the skin, to vitamin D₃. This synthesised vitamin D₃, along with dietary vitamin D₂/D₃, then undergoes a two-step hydroxylation process: first in the liver to form the biologically inactive 25-hydroxyvitamin D (25(OH)D; the main circulating and storage form of vitamin D and that measured to assess vitamin D status), and secondly in the kidneys to the active 1,25-dihydroxyvitamin D (1,25(OH)₂D) when required by the body⁽¹⁾. The amount of vitamin D₃ endogenously produced is a function of the amount of UVB radiation reaching the skin, therefore being affected by a number of environmental and individual factors, including season and latitude, skin pigmentation, concealing clothing, use of sunscreen, time spent outdoors and other individual factors such as obesity and ageing⁽⁴⁾. Season and latitude

dramatically affect vitamin D₃ synthesis and at high latitudes > 40°N during the winter-time (October-March) there are marked decreases in endogenous vitamin D₃ production, giving rise to striking seasonal variations in vitamin D status throughout the year^(3, 5, 6). This is demonstrated in the NDNS data of sex-combined 11-18 year old adolescents, whose mean plasma 25(OH)D concentrations ranged from 52.3 nmol/l when blood samples were collected during the months of July-September, down to 31.5 nmol/l when sampled during the winter months of January-March⁽³⁾.

Physiological function

The primary and well recognised function of the biologically active metabolite 1,25(OH)₂D is in the maintenance of calcium and phosphorus homeostasis via endocrine mechanisms targeting the intestine, kidneys and bone^(1, 7). This is essential for skeletal health throughout the life cycle, from bone accretion and growth in infancy, childhood and adolescence, through to maintenance of healthy bones and prevention of bone loss in later adulthood. Vitamin D, along with calcium, is important during the adolescent years when the most rapid bone accrual occurs⁽⁸⁾. Approximately 80-90% of peak bone mass is achieved by late adolescence and maximising this may help reduce age-related bone loss in later life^(9, 10).

In recent years however, more attention has been paid to the paracrine/autocrine functions of vitamin D in the facilitation of gene expression. It was previously believed that the kidneys were the only site of 1,25(OH)₂D synthesis, although it is now recognised that many extra renal tissues (e.g. colon, prostate, breast and immune cells) have the ability to locally convert 25(OH)D to 1,25(OH)₂D due to the presence of the vitamin D receptor and 1 alpha-hydroxylase enzymes^(7, 11). Epidemiological studies have therefore indicated a broader role of vitamin D in common cancers, cardiovascular disease and respiratory diseases⁽¹²⁻¹⁴⁾. Although vitamin D is emerging as a promising nutrient in many extra skeletal health outcomes, it must be borne in mind that the evidence is largely observational and thus further data from robust randomised controlled trials (RCTs) is required to help clarify the causal role of vitamin D and the underlying mechanisms.

Vitamin D Deficiency: Definitions, Prevalence and Consequences

Defining vitamin D deficiency and adequacy

Currently there is no international consensus on the optimal circulating 25(OH)D concentrations for health, with debate surrounding the cut-off thresholds to be applied to define vitamin D deficiency and adequacy. **Table 1** summarises the current cut-off thresholds proposed by various international authoritative bodies and agencies.

There is generally good agreement that populations should not have circulating 25(OH)D concentrations below 25-30 nmol/l based on an increased risk of rickets and impaired bone growth in adolescents. At present, the Institute of Medicine (IOM), European Food Safety Authority (EFSA), European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the American Academy of Pediatrics, all suggest that a serum 25(OH)D concentration > 50 nmol/l is adequate based on ensuring optimal bone health⁽¹⁵⁻¹⁸⁾, while others have proposed much greater 25(OH)D sufficiency thresholds. The Society for Adolescent Health and Medicine and the Endocrine Society for example, consider sufficiency at 25(OH)D concentrations > 75 nmol/l and that concentrations of less than 50 nmol/l are indicative of deficiency^(19, 20). It is worth noting however that the Endocrine Society guidelines target patient care of those at risk of vitamin D deficiency (e.g. obese patients, patients with malabsorption syndromes or those on medication that affects vitamin D metabolism), in contrast to the IOM, EFSA and the UK Scientific Advisory Committee on Nutrition (SACN), who propose recommendations for the general healthy population^(15, 16, 21). Regardless it may be premature to recommend circulating 25(OH)D concentrations > 75 nmol/l due to the lack of evidence from RCTs to date supporting higher serum 25(OH)D concentrations and health outcomes beyond musculoskeletal health.

Prevalence of vitamin D deficiency among adolescent populations

Adolescents are a population group with a recognised risk of low vitamin D status and several nationally representative and individual studies have highlighted the global nature of vitamin D deficiency and inadequacy among adolescent populations⁽²²⁾. Estimates of vitamin D deficiency (defined across studies as 25(OH)D < 22.5 – 27.5 nmol/l) have ranged from 4-17% in the United States and Canada⁽²³⁻²⁶⁾, 15-40% in Europe^(3, 27-31), 13-33% in Asia (Korea, India and China)⁽³²⁻³⁴⁾ and up to 81% in Saudi Arabia⁽³⁵⁾. If a cut-off of 50 nmol/l is applied, these estimates increase to 19-91% of the population as having inadequate vitamin D concentrations⁽²²⁾. Data from the UK NDNS Rolling Programme (2008/09-2011/12) demonstrated that 22% of 11-18 year old adolescents had year round plasma 25(OH)D concentrations < 25 nmol/l and this increased to 40% during the winter months (January-March)⁽³⁾.

Caution must be taken when comparing data from different studies due to variations in participant characteristics (e.g. age, ethnicity, cultural dress), latitude and season of sampling and in the analytical techniques and assays used to measure 25(OH)D (for review of the impact of different analytical techniques on 25(OH)D results see Fraser and Milan⁽³⁶⁾). A recent study, based on standardised serum 25(OH)D data from European cohorts and national surveys ($n = 55,844$), found 15-18 year old adolescents to have the highest risk of vitamin D deficiency (25(OH)D < 30 nmol/l)

in the range of 12-40%, compared to 4-7% in younger children (1-14 years), 9-24% in adults (19-60 years) and 1-8% in older adults (> 61 years) ⁽³⁷⁾. The underlying causes of this apparent increased risk and higher prevalence of vitamin D deficiency in adolescents are unclear, although negative associations between pubertal status and circulating 25(OH)D concentrations have been reported ⁽³⁸⁻⁴⁰⁾, which may be due to behavioural (e.g. reduced outdoor time, sedentary lifestyles) ⁽⁴¹⁾ and/or biological mechanisms ⁽⁴²⁾. In order to meet the increased calcium demands for skeletal growth during adolescence, the metabolism of 25(OH)D to the active 1,25(OH)₂D is increased ⁽⁴²⁾ and a concomitant decrease in circulating 25(OH)D has been reported ^(42, 43), although not consistently ⁽⁴⁴⁾.

Consequences of vitamin D deficiency and inadequacy during adolescence

This susceptibility to low vitamin D status in adolescent populations is concerning given the important role of vitamin D in promoting normal bone mineralisation and attainment of peak bone mass during periods of rapid growth and development. It is well recognised that prolonged and severe vitamin D deficiency leads to an increased risk of rickets and altered bone development in children and adolescents ⁽⁴⁵⁾, although the effects of mild vitamin D inadequacy (25(OH)D between 30 and 50 nmol/l), which has been widely reported in adolescent populations worldwide ⁽⁴⁶⁾, remains less clear. Observational studies in adolescent females have suggested adverse effects of circulating 25(OH)D concentrations less than 40-50 nmol/l on bone mass at various skeletal sites ^(29, 30, 47, 48), although the evidence is inconsistent with others reporting no association between vitamin D status and bone mass in adolescents ^(49, 50). A three year prospective study in Finnish females aged 9-15 years found a 4% difference in lumbar spine bone mineral density accrual between those with serum 25(OH)D concentrations > 37.5 nmol/l and those with concentrations < 20 nmol/l at baseline ⁽⁵¹⁾. Importantly, there is limited data available in male adolescents, a research gap recognised in the National Osteoporosis Foundation's 2016 position statement on peak bone mass development ⁽⁸⁾. Intervention studies, predominantly in white females, have failed to consistently find a beneficial effect of vitamin D supplementation on bone health indices in adolescents and a 2010 Cochrane systematic review concluded that supplementation may only benefit those with inadequate circulating 25(OH)D concentrations below 35 nmol/l ⁽⁵²⁾. There is currently no consensus on the 25(OH)D concentration that is optimal for the acquisition of bone mass in adolescents or the outcome measures that should be targeted.

As previously alluded to, there is a growing body of evidence that vitamin D may be associated with other non-musculoskeletal, chronic diseases, such as cardiovascular disease, cancer, diabetes and autoimmune diseases. However much of the evidence base for this has been derived from epidemiologic studies of adults and much less is known of the effect of low vitamin D status during

adolescence on these health outcomes in the short- and long-term⁽⁵³⁾. Cross-sectional studies in children and adolescents aged 2-19 years have found circulating 25(OH)D concentrations to be inversely associated with total and low-density lipoprotein (LDL) cholesterol concentrations^(54, 55), glucose^(56, 57) and systolic blood pressure^(54, 56, 58, 59) and positively correlated with high-density lipoprotein (HDL) cholesterol^(23, 57, 59), although not consistently^(60, 61). Furthermore, vitamin D status below 50 nmol/l has been associated with an increased prevalence of metabolic syndrome in 12-19 year old adolescents in the United States^(56, 58), however no association was found in 13 year old Portuguese adolescents⁽⁵⁵⁾. A 2013 systematic review concluded that there was no consistent association between 25(OH)D and lipid and glucose concentrations in adolescents and that systolic blood pressure was inversely associated with 25(OH)D in cross-sectional studies, but no association was found in prospective cohort studies⁽⁶²⁾.

Current Vitamin D Recommendations

From a public health perspective, dietary vitamin D recommendations are of great importance in helping to prevent vitamin D deficiency, particularly during the winter months when UVB exposure is inadequate for cutaneous synthesis. Many countries and authoritative bodies worldwide have proposed vitamin D intake recommendations and some have recently been re-evaluated and revised (**Table 2**). Due to difficulties in establishing the contribution of UVB exposure to vitamin D status, such recommendations are often set assuming minimal sun exposure and are the average daily intakes needed to meet the requirements of the majority of the population (i.e. the vitamin D intake needed to maintain serum 25(OH)D concentrations above the specified threshold in 97.5% of the population). Furthermore, these recommendations are based upon intakes that will ensure adequate vitamin D status to protect against poor musculoskeletal health and do not, at this stage, consider the prevention or reduction in risk of non-musculoskeletal health outcomes. Additionally, recommendations can vary between different life stage groups, with vitamin D supplementation specifically recommended for infants, pregnant and lactating women and the elderly, and are often determined based on evidence from white Caucasian populations. As demonstrated in Table 2, at present there is a lack of consensus on the intakes required to maintain circulating 25(OH)D concentrations above differing levels of defined adequacy.

Development and re-evaluation of the UK recommendations

In 1991 the UK Department of Health published Dietary Reference Values for most nutrients and energy⁽⁶⁸⁾. At this time it was assumed that free-living individuals aged between 4 and 64 years of age would synthesise sufficient vitamin D from summer sun exposure to ensure adequate vitamin D throughout the winter months to avoid deficiency (25(OH)D < 25 nmol/l). Thereby no Reference

Nutrient Intake (RNI) was set for these age groups, although intake recommendations were determined for population sub-groups perceived to be at risk of vitamin D deficiency, namely infants, those aged ≥ 65 years and pregnant and lactating women (Table 2). Subsequent reviews in 1998 and 2007 by the Department of Health and SACN respectively, concluded that these recommendations should remain unchanged while further evidence was generated from RCTs^(63, 69). In 2010, SACN agreed to reassess the evidence relating to vitamin D and health on the basis of new data that had become available since the previous review.

The revised dietary intake recommendations for vitamin D were released by SACN in 2016 and a daily intake of 10 μg was set for those aged ≥ 4 years to ensure a serum 25(OH)D concentration > 25 nmol/l, which was deemed protective against adverse musculoskeletal health outcomes⁽²¹⁾. This year-round recommendation also includes those of ethnic minority groups and with limited sun exposure (e.g. institutionalised individuals). A precautionary Safe Intake of 8.5-10 $\mu\text{g}/\text{day}$, rather than an RNI, was set for infants 0 - < 4 years of age due to insufficient evidence and uncertainties with specifying an intake recommendation for this age group.

Other notable recommendations

The 2011 IOM Dietary Reference Intakes was the first landmark publication of vitamin D (and calcium) requirements, based on a risk assessment framework and provided a comprehensive review of vitamin D requirements for health⁽¹⁵⁾. The risk assessment framework, which has previously been reviewed in detail^(70, 71), has since been adopted in more recent re-evaluations of vitamin D requirements by EFSA, SACN and the Nordic Nutrition Recommendations^(16, 21, 64). Briefly, the risk assessment framework involves undertaking independent systematic evidence-based reviews, which are then used by the committee to identify, describe and rate potential indicators (e.g. rickets, osteomalacia, calcium absorption and fracture risk) in order to derive population targets for 25(OH)D status. The associated dietary vitamin D intake requirements were then established by the IOM via a simulated dose-response meta-regression exercise using group mean/median 25(OH)D response data from selected RCTs (winter-based at latitudes $> 49^\circ\text{N}$)⁽¹⁵⁾. Based upon this method, the IOM committee proposed a Recommended Dietary Allowance (RDA) of 15 $\mu\text{g}/\text{day}$ for those aged 1-70 years (20 $\mu\text{g}/\text{day}$ for those > 70 years), which corresponds to a serum 25(OH)D concentration of 50 nmol/l that meets the needs of 97.5% of the population. Additionally, an Estimated Average Requirement (EAR) of 10 $\mu\text{g}/\text{day}$ for those aged ≥ 1 year was set to maintain serum 25(OH)D of 40 nmol/l in 50% of the population⁽¹⁵⁾.

228 Interestingly, using the same simulated dose-response meta-regression method, the Nordic Nutrition
229 Recommendations set a Recommended Intake (RDA equivalent) of 10 µg/day to maintain serum
230 25(OH)D > 50 nmol/l, using data from winter-based RCTs conducted at latitudes covering the
231 Nordic region (49.5-60°N) ⁽⁶⁴⁾.

232

233 Also of note are the recent EFSA vitamin D Dietary Reference Values (15 µg/day to maintain
234 serum 25(OH)D > 50 nmol/l), which defined an Adequate Intake instead of an Average
235 Requirement, based on the committee's assertion that there was insufficient evidence to allow for
236 an Average Requirement to be established for all population groups ⁽¹⁶⁾.

237

238 In contrast to the meta-regression approach adopted by the IOM, EFSA and the Nordic Nutrition
239 Recommendations as described above, SACN generated its vitamin D intake estimates by
240 modelling individual participant-level data and it has been suggested that this method may lead to
241 improved dietary requirement guidelines ^(72, 73). This may also be an underlying reason for the
242 variability in the current recommendations and is discussed in more detail below.

243

244 *Meta-regression vs. individual participant-level modelling in determining vitamin D intake*
245 *requirements*

246 The use of meta-regression and individual participant-level modelling and the impacts on dietary
247 vitamin D intake estimates has been described previously in detail ^(74, 75) and so will be reviewed
248 briefly here. The meta-regression approach used by the IOM, and more recently EFSA, in
249 establishing vitamin D requirements used group mean/median data from intervention arms of
250 selected RCTs, together with estimates of vitamin D intakes (from diet and supplements) in a
251 simulated dose-response relationship ^(15, 16). While this avoids over reliance on data from any
252 particular RCT, the disadvantage is that data are combined from different RCTs that use a variety of
253 analytical methods to measure 25(OH)D concentrations ⁽³⁶⁾. The use of group mean/median data
254 and the resulting regression line and 95% confidence intervals in the meta-regression model
255 generates average responses, and as such the intake estimates of 10 and 15 µg/day might only be
256 expected to offer protection for 50% of the population (EAR-type estimate) instead of the intended
257 97.5% (RDA-type estimate). Furthermore, the meta-regression approach does not take into
258 consideration the inter-individual variability in 25(OH)D response to increasing vitamin D intakes.
259 This can be overcome with the use of individual participant-level data and 95% prediction intervals
260 (**Figure 1**), as applied by SACN ⁽²¹⁾. Individual data from three winter-based RCTs in 11-12 year
261 old female adolescents ⁽⁷⁶⁾ and adults aged 20-40 and ≥ 64 years ^(77, 78) was modelled by SACN in
262 order to derive vitamin D intake estimates for the UK population. With this method it is possible to

estimate with more confidence the distribution of intakes required to achieve specific serum 25(OH)D concentrations.

Evidence-based dietary vitamin D requirements in adolescence: use of individual participant-level data to fill knowledge gaps

While vitamin D intake recommendations have been set for the adolescent age group (Table 2), the regulatory authorities tasked with establishing these recommendations have highlighted the significant knowledge gaps in relation to winter-based dose-response RCTs specifically designed to estimate dietary vitamin D intakes required to maintain 25(OH)D above certain cut-off thresholds in younger populations. Consequently, intake recommendations for adolescents are often extrapolated from adult data in the absence of adolescent-specific data. Of the 3 RCTs in children and adolescents included in the IOM dose-response model, one month long study was conducted in 20 participants (6-14 years)⁽⁷⁹⁾ and another was carried out in 1988 in 60 participants (8-10 years) using doses of 0 and 10 µg/day⁽⁸⁰⁾. Other under researched population sub-groups identified with a lack of dose-response experimental data also included younger children, pregnant women and ethnic minority populations. Winter-based dose-response RCTs, designed and implemented within the ODIN project (Food-based solutions for Optimal vitamin D Nutrition through the life cycle) aimed to fill these knowledge gaps by modelling individual participant-level data in order to estimate dietary requirements for vitamin D in these population sub-groups⁽⁸¹⁾.

In the ODIN adolescent study, 110 healthy white male and female 14-18 year olds were randomly allocated to receive 0, 10 or 20 µg vitamin D₃ per day for 20 weeks throughout the winter-time (October-March)⁽⁸²⁾. Via mathematical modelling of individual participant-level 25(OH)D and total vitamin D intake data, the vitamin D intakes required to maintain serum 25(OH)D concentrations above 25, 30, 40 and 50 nmol/l in 50%, 90%, 95% and 97.5% of the adolescents were estimated. Of particular note, the vitamin D intakes needed to avoid deficiency and maintain serum 25(OH)D concentrations > 25 and > 30 nmol/l in 97.5% of the population were 10.1 and 13.1 µg/day respectively⁽⁸²⁾. The 10.1 µg/day estimate supports the SACN recommendation for the UK population aged ≥ 4 years. In order to maintain serum 25(OH)D > 40 nmol/l in 50% of the population, corresponding to the EAR-type intake, 6.6 µg/day was estimated for adolescents. While lower than the 10 µg/day recommendation of the IOM, this is close agreement with the 6.3 µg/day estimate in 11-12 year old Danish and Finnish females in a similarly designed RCT⁽⁷⁶⁾. However greater discrepancies arise when considering the RDA-type intake (to maintain serum 25(OH)D > 50 nmol/l in 97.5% of the population). The intake estimate of ~30 µg/day in adolescents derived from the ODIN study is considerably higher than the IOM recommendation of 15 µg/day. The large

inter-individual variability in 25(OH)D response to vitamin D intakes and the inability of the meta-regression using aggregate data to consider this, explains, in part, the wide variation in these estimates at the 97.5th percentile ⁽⁷³⁾.

It is important to note that the adolescent trial mentioned above and many of those included by the IOM, SACN and EFSA were conducted in healthy white populations. A winter-based RCT in 8-14 year old black African American and white children and adolescents estimated that vitamin D intakes of 28 and 52 µg/day would maintain serum 25(OH)D > 30 and > 50 nmol/l respectively in 97.5% of the population ⁽⁸³⁾. Unfortunately intake estimates were not determined for the ethnic groups separately, limiting the opportunity to compare intake estimates. In a recent food-based dose-response RCT in 5-7 year old Swedish children it was estimated, using 95% prediction intervals, that vitamin D intakes of 6 and 20 µg/day would maintain 25(OH)D > 30 and > 50 nmol/l respectively in fair skinned children, while the corresponding intakes in dark skinned children were 14 and 28 µg/day respectively ⁽⁸⁴⁾. These data provide early indications that greater intakes may be required by ethnic minority populations, however this should be confirmed in further winter-based vitamin D dose-response RCTs ⁽⁸⁵⁾.

Achieving Vitamin D Intakes: Supplements vs. Food Fortification

Current recommendations, along with the new data presented here, propose that vitamin D intakes of between 10 and ~30 µg/day are required by adolescents in order to avoid vitamin D deficiency and ensure adequacy. Population-based dietary intake surveys in the UK and beyond have highlighted significant gaps between typical vitamin D intakes in adolescents and these recommendations, especially in countries with limited food fortification, which includes the UK. Current intakes in UK adolescents aged 11-18 years participating in the NDNS were around 2 µg/day ⁽³⁾. Strategies therefore need to be implemented in order to help the UK population achieve higher dietary vitamin D intakes and this becomes increasingly important during times of insufficient UVB exposure for cutaneous synthesis. While vitamin D supplements can be useful in increasing vitamin D intakes and consequently vitamin D status, relying on supplements may not be a viable public health strategy to increase intakes at the population level. Supplement use is not widespread and will only be effective in those that take them, which varies by age, sex and by individuals' health motivation and purchasing power. As previously mentioned, supplement uptake is typically low among adolescents compared to younger and older age groups and so adolescents are far less likely to acquire the same level of benefit as other population groups do from supplements. Therefore sustainable public health strategies to ensure vitamin D intakes need to be

designed and implemented to continually meet the needs of the majority, irrespective of age, sex and other individual factors.

Food fortification presents an opportunity to increase vitamin D intakes at the population level. Using data from the 2003-2006 National Health and Nutrition Examination Survey in the United States, fortification has been shown to considerably improve dietary vitamin D intakes above that obtained from the basal diet⁽⁸⁶⁾. Intakes of 1.7 µg/day were reported in 2-18 year old children and adolescents from naturally occurring food sources, with 100% having intakes below the IOM EAR of 10 µg/day. Intakes increased to 6.1 µg/day when fortified foods were included, with 86.8% having intakes below the EAR. Commonly fortified foods in the United States include milk, breakfast cereals, yoghurts, cheeses, juices and spreads. When supplement use was also considered, intakes further increased to 8.3 µg/day, with 73.2% of intakes remaining below 10 µg/day. However, dietary diversity needs to be given important consideration when developing and initiating fortification policies. While fortification of milk and other staple commodities (e.g. margarine/fat spreads, other dairy products and breakfast cereals) will be important for increasing vitamin D in the food supply, this will not be an effective strategy in non- or infrequent consumers. For example, routine fortification of milk with vitamin D in Finland had little impact on the vitamin D intakes of female adolescents (12-18 years)⁽⁸⁷⁾. Intakes increased from 4.0 µg/day prior to the introduction of the fortification policy to 5.4 µg/day following fortification introduction, with no change in serum 25(OH)D concentrations (48.3 and 48.1 nmol/l respectively)⁽⁸⁷⁾. Additionally the prevalence of serum 25(OH)D concentrations < 50 nmol/l in these adolescent females was 60.6% and 65.5% prior to and following fortification respectively. Conversely fortification of milk and fat spreads in Finland was found to have a positive impact on the dietary vitamin D intakes of adults and young children⁽⁸⁸⁻⁹¹⁾. This may be due to low and/or infrequent consumption of milk and other dairy products among adolescent females. This data from Finland demonstrates the importance of giving consideration to food consumption patterns in fortification policies and several widely consumed foods should be fortified to ensure widespread reach. Dietary diversity among different ethnic groups can also influence vitamin D intakes, with African American adolescent females reported to consume more vitamin D from meat and bean food sources compared to white females who consumed more from milk, which is routinely fortified in the United States⁽⁹²⁾. Bio-fortification of food presents a novel opportunity to increase vitamin D in the food supply through a range of foods, alongside more traditional fortification practices. The vitamin D content of animal produce (e.g. pork, beef, chicken, eggs and fish) can be increased via the fortification of livestock feeds, where permissible. RCTs conducted within the aforementioned ODIN project have initiated

investigation into the efficacy and safety of vitamin D fortification and bio-fortification of a variety of foodstuffs in different population groups and we await these findings ⁽⁸¹⁾.

Conclusions and Future Directions

Vitamin D recommendations are of great importance from a public health perspective in terms of preventing vitamin D deficiency and optimising vitamin D status for health. It is crucial therefore that recommendations are evidence-based in order to establish more accurate and precise requirements for population sub-groups. Limited experimental data continues to be an issue for certain population sub-groups, particularly those of ethnic minority populations, and further research and targeted dose-response RCTs should be undertaken to continue to fill these gaps in the evidence base. This will have important implications for public health policy as presented here: whilst the current recommendations of 10-15 µg/day may help avoid winter-time vitamin D deficiency in adolescents (circulating 25(OH)D concentrations < 25-30 nmol/l), they remain inadequate to achieve and maintain 25(OH)D concentrations above 50 nmol/l. This upper threshold of circulating 25(OH)D concentration may be optimal for health, particularly with respect to bone accretion in adolescents, although this needs to be confirmed in RCTs, along with other non-musculoskeletal health outcomes. Consideration should also be given to the model adopted for the estimation of dietary requirements for vitamin D and future refinements of these should consider the use of individual participant-level data from dose-response RCTs as more data becomes available. Understanding optimal vitamin D concentrations, clinical outcomes and vitamin D intake requirements will help prioritise and inform public health strategies to prevent vitamin D deficiency.

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Conflicts of Interest

Authors have no conflicts of interest to declare.

Authorship

TJS wrote the manuscript; LT, SAL-N and KHH assisted with manuscript editing; TJS had primary responsibility for the final content; all authors read and approved the final manuscript.

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Figure Legends

Figure 1. Relationship between serum 25 (OH)D concentration and total vitamin D intake using data from randomised controlled trials. The central thick solid line is the regression line and the two curved lines represent the 95% confidence intervals around the mean. The outer two dashed lines represent the 95% prediction intervals.

25(OH)D, 25-hydroxyvitamin D; IU, international units (to convert IU to $\mu\text{g/day}$ divide by 40).

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Tables

Table 1. Circulating 25(OH)D deficiency and adequacy cut-off thresholds currently proposed by various international agencies

Agency	Deficiency cut-off threshold (nmol/l)	Adequacy cut-off threshold (nmol/l)
Scientific Advisory Committee on Nutrition ⁽²¹⁾	< 25	
Institute of Medicine ⁽¹⁵⁾	< 30	> 50
European Food Safety Authority ⁽¹⁶⁾	< 30	> 50
ESPGHAN ⁽¹⁷⁾	< 25	> 50
American Academy of Pediatrics ⁽¹⁸⁾		> 50
The Society for Adolescent Health and Medicine ⁽¹⁹⁾	< 50	75 – 125
Endocrine Society ⁽²⁰⁾	< 50	> 75

25(OH)D, 25-hydroxyvitamin D; ESPGHAN, European Society for Paediatric Gastroenterology, Hepatology and Nutrition.

Table 2. Dietary reference values for vitamin D ($\mu\text{g/day}$) by life stage as proposed by various international agencies to maintain adequate circulating 25(OH)D concentrations

Agency	Year	Country/ Countries	Recommended Dietary Vitamin D Intake (µg/d)						25(OH)D
			0-12 months	1-<4 yrs	4-18 yrs	19-69 yrs	> 70 yrs	Pregnancy/Lactation	Threshold (nmol/l)
United Kingdom									
Department of Health ⁽⁶³⁾	1998	United Kingdom	8.5-7	7	-- ^a	-- ^a	10	10	25
SACN ⁽²¹⁾	2016	United Kingdom	8.5-10	10	10	10	10	10	25
Europe									
EFSA ⁽¹⁶⁾	2016	Europe	10	15 ^b	15 ^b	15 ^b	15 ^b	15 ^b	50
Nordic Nutrition Recommendations ⁽⁶⁴⁾	2012	Denmark, Finland, Iceland, Norway, Sweden	10	10	10	10	20	10	50
Health Council of the Netherlands ⁽⁶⁵⁾	2012	The Netherlands	10	10	10	10	20	10	30 ^c
German Nutrition Society ⁽⁶⁶⁾	2012	Germany, Austria, Switzerland	10	20 ^d	20 ^d	20 ^d	20 ^d	20	50
Other									
IOM ⁽¹⁵⁾	2011	North America and Canada	10	15	15	15	20	15	50
The Endocrine Society ^e ⁽²⁰⁾	2011	Worldwide	25	25	25	37.5-50	37.5-50	37.5-50	75
WHO/FAO Joint Expert Consultation ⁽⁶⁷⁾	2004	Worldwide	5	5	5	5-10	15	5	27

25(OH)D, 25-hydroxyvitamin D; SACN, Scientific Advisory Committee on Nutrition; EFSA, European Food Safety Authority; IOM, Institute of Medicine; WHO/FAO, World Health Organization/Food and Agriculture Organization.

^a For those aged 4-64 years it was assumed that sun exposure during the summer months would ensure an adequate vitamin D status year round so no intake was set.

^b Requirements set under conditions of minimal cutaneous synthesis and in the presence of cutaneous vitamin D₃ synthesis the requirement for dietary vitamin D is lower or may even be zero.

^c Target concentration of 50 nmol/l for those aged > 70 years.

^d Estimated value of adequate vitamin D intake without cutaneous synthesis.

^e Recommendations for populations at risk of vitamin D deficiency.

Figure 1. Relationship between serum 25 (OH)D concentration and total vitamin D intake using data from randomised controlled trials. The central thick solid line is the regression line and the two curved lines represent the 95% confidence intervals around the mean. The outer two dashed lines represent the 95% prediction intervals.

25(OH)D, 25-hydroxyvitamin D; IU, international units (to convert IU to $\mu\text{g}/\text{day}$ divide by 40).
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