

SCIENTIFIC COMMITTEE REPORT

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Vitamin D: Scientific Recommendations for 5 to 65 Year Olds Living in Ireland



Report of the Scientific Committee of the Food Safety Authority of Ireland

Vitamin D: Scientific Recommendations for 5 to 65 Year Olds Living in Ireland

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Acronyms and abbreviations

Acronym/abbreviation	Definition				
25(OH)D	25-hydroxyvitamin D				
hð	microgram				
BMD	oone mineral density				
CI	confidence interval				
COPSAC	Copenhagen Prospective Studies on Asthma in Childhood				
D2d	Vitamin D and Type 2 Diabetes				
D-VinCHI	D Vitamin in Children				
EAR	estimated average requirement				
EFSA	European Food Safety Authority				
EU	European Union				
FAO	Food and Agriculture Organization of the United Nations				
FIND	Finnish Vitamin D Trial				
FINDIET	The Finnish National Dietary Survey in Adults and Elderly				
FSAI	Food Safety Authority of Ireland				
g	grams				
GP	general practitioner				
IOM	Institute of Medicine				
IPD	individual participant data				
IQR	interquartile range				
IU	international units				
J/cm ²	joules per square centimetre				
MAVIDOS	Maternal Vitamin D Osteoporosis Study				
mg	milligram				
mL	millilitre				
MO-VITD	maternal body weight and vitamin D status				
MSL	maximum safe level				
NANS	National Adult Nutrition Survey				

NCFS II	National Children's Food Survey II				
NDNS NI	National Diet and Nutrition Survey in Northern Ireland				
nmol/L	nanomoles per litre				
NNR	Nordic Nutrition Recommendations				
NTFS II	National Teens' Food Survey II				
OR	odds ratio				
PRI	population-recommended intake				
RCT	randomised controlled trial				
RDA	recommended dietary allowance				
RECORD	Randomised Evaluation of Calcium Or vitamin D				
RTEBC	ready-to-eat breakfast cereal				
SACN	Scientific Advisory Committee on Nutrition				
SCOPE	Screening for Pregnancy Endpoints				
SES	socioeconomic status				
STURDY	Study To Understand Fall Reduction and Vitamin D in You				
TILDA	The Irish Longitudinal Study on Ageing				
UK	United Kingdom				
UL	tolerable upper intake level				
USA	United States of America				
UV	ultraviolet				
UVB	ultraviolet B				
VAT	value-added tax				
VDAART	Vitamin D Antenatal Asthma Reduction Trial				
ViDA	Vitamin D Assessment				
VITAL	VITamin D and OmegA-3 TriaL				
WHO	World Health Organization				
YH2000	Young Hearts 2000				
μg/d	micrograms per day				

Foreword

Vitamin D deficiency is common across Europe, including in Ireland. While vitamin D deficiency can have consequences for skeletal integrity at any stage of life, it can also have a negative impact on bone development and growth in key life stages, such as childhood and adolescence. Vitamin D also contributes to the normal function of the immune system and a healthy inflammatory response, as well as the maintenance of normal muscle function. It is generally agreed that the prevention of vitamin D deficiency is a public health nutrition priority.

Limited sun availability for a significant portion of the year in Ireland means that we are dependent on foods to supply vitamin D. However, because the amount of vitamin D in our food system is generally limited, low intake of vitamin D is common among Irish children, teenagers and adults. These factors contribute to the high prevalence of vitamin D deficiency observed among individuals aged 5–65 years in Ireland.

This report, aimed at policy-makers and healthcare professionals, as well as other relevant stakeholders, identifies the scientific basis for vitamin D dietary requirements for children, teenagers and adults – including pregnant women and individuals of dark-skinned ethnicity in Ireland. It benchmarks current dietary intakes among people living in Ireland against these recommended intakes for vitamin D. The report also offers key policy options for closing the gap between current and recommended dietary intakes of vitamin D. Eating vitamin D-fortified foods as well as taking vitamin D supplements, at appropriate doses, are important options in the strategy for preventing vitamin D deficiency.

This report on scientific recommendations for vitamin D for children, teenagers and adults (aged 5–65 years) complements three recent Food Safety Authority of Ireland (FSAI) reports which included vitamin D recommendations for infants (first year of life), young children (aged 1–5 years), and older adults (aged 65 years and older). This report, like the earlier ones, is underpinned by robust scientific data from researchers across the island of Ireland and beyond on various aspects of vitamin D nutrition relevant to our population. Collectively, these reports inform policy and practice and in so doing will, hopefully, enable the prevention of vitamin D deficiency in Ireland in the not-too-distant future.

Kevin Cashman

Chair, Public Health Nutrition Subcommittee September 2022

Executive summary

This report was developed by the Scientific Committee of the Food Safety Authority of Ireland (FSAI) in response to a request from the Department of Health for advice to provide an evidence base to underpin public health policy with regard to vitamin D in children, teenagers and adults (aged 5–65 years) living in Ireland.

Vitamin D plays key physiological roles in the musculoskeletal system, the functioning of the immune system, and the process of cell division. Vitamin D deficiency leads to impaired mineralisation of bone due to an inefficient absorption of dietary calcium and phosphorus, which manifests as rickets in children and osteomalacia in adults. In addition, although causation has not been proven, several studies suggest associations between vitamin D deficiency and non-skeletal health conditions, such as cardiovascular diseases; diabetes; inflammatory disorders; some infectious diseases (including COVID-19) and immune disorders; certain cancers; and higher mortality rates.

Representative studies of vitamin D status in Ireland have shown a high frequency of teenagers and adults (including pregnant women) – varying from 12% to 26% of the population – with serum 25-hydroxyvitamin D (25(OH)D) concentrations below 30 nanomoles per litre (nmol/L), which is representative of an increased risk of vitamin D deficiency, as it relates to bone health. This deficiency was more pronounced in the winter months. Although not nationally representative, data from cross-sectional studies of 4–11-year-old children in Ireland suggest that 15–16% have serum 25(OH)D concentrations below 30 nmol/L. In addition, a cross-sectional study of adults aged 18–50 years showed that the prevalence of serum 25(OH)D levels below 30 nmol/L among adults from a dark-skinned ethnic minority group (e.g. Irish Asian) is much higher (70%) than that in the Caucasian population (12%).

Vitamin D is obtained from the diet (via natural foods, fortified foods, and food supplements) and unprotected skin exposure to sunlight (during the months of April through October in Ireland). A review of the available evidence, including studies in Ireland, shows that the dietary vitamin D requirement for maintaining serum 25(OH)D at or above 30 nmol/L (and thus preventing risk of deficiency for most people) is 10 micrograms (μ g) daily for healthy children aged 5–11 years in Ireland, and 15 μ g daily for healthy teenagers and adults (aged 12–65 years, including pregnant women) of all ethnicities.

In Ireland, the national nutrition surveys covering the period 2008–2020 (depending on the survey) showed that the mean daily intakes of vitamin D from diet and supplements were 4.2 μ g, 3.7 μ g, and 4.3 μ g for children (5–12 years), teenagers (13–18 years), and adults (18–64 years), respectively, and that 19%, 8%, and 17%, respectively, of those surveyed regularly consumed a

food supplement containing vitamin D. Mean daily intakes of vitamin D in children, teenagers and adults in Ireland who did not consume vitamin D-containing supplements were only around 2–3 μ g per day (μ g/d), compared with current dietary requirements of 10–15 μ g/d.

The World Health Organization (WHO) together with the Food and Agriculture Organization of the United Nations (FAO) have suggested that there are three possible strategies that can be considered in terms of addressing inadequate intakes of micronutrients: i) increasing the diversity of foods consumed, ii) supplementation, and iii) food fortification.

Increasing dietary diversity means increasing both the quantity and the range of micronutrient-rich foods consumed. However, in the context of vitamin D, this is particularly challenging because the range of foods naturally rich in vitamin D is very limited, with the majority of them being of animal origin with low environmental sustainability ratings. In Ireland, fish, eggs and meats have been key natural food sources of vitamin D – in addition to vitamin D-fortified foods, such as ready-to-eat breakfast cereals, milk, yogurt, butters and spreading fats – across all age groups. In recent years, however, there has been a growing trend of people opting to consume less dairy and meat to achieve a more sustainable, plant-based diet. Thus, improving intakes, as well as the diversity, of foods naturally rich in vitamin D would arguably be the strategy least likely to work, at least in the short to medium term. Thus, while natural vitamin D food sources as well as foods voluntarily fortified with vitamin D will continue to play a role towards individuals meeting their vitamin D dietary requirements, they will also need additional vitamin D supply in the range of 8–12 μ g/d.

The use of vitamin D-containing supplements and vitamin D-fortified foods, as suggested by the WHO and FAO, is likely to be a more feasible strategy to help close the gap between individuals' current intakes and recommended dietary intakes. Taking daily supplements containing 10 μ g of vitamin D for children and 15 μ g for teenagers/adults would facilitate achieving the recommended intakes. These are considered safe levels of supplemental vitamin D, even when combined with typical vitamin D intakes from natural and fortified foods.

Greater consumption of vitamin D-fortified foods as a means of increasing vitamin D intakes could also facilitate improved intake of vitamin D in Ireland. Key stakeholders should consider the merits of mandatory versus voluntary fortification of foods with vitamin D to achieve improved vitamin D intakes across the population. Consumption of a combination of vitamin D-fortified foods may also be considered safe for children, teenagers and adults in Ireland, even for those taking daily supplements containing 10 or 15 μ g of vitamin D. Of note, people should not have total vitamin D intakes (i.e. from all sources, including foods and supplements) greater than their age-appropriate tolerable upper intake level (50 μ g for 5–10-year-olds and 100 μ g for those aged 11 years and older) because it could be harmful. The FSAI has recently published guidance for food business operators regarding the maximum safe levels (MSLs) of vitamins and minerals that can be added

to food supplements in Ireland. The vitamin D content of food supplements should not exceed these MSLs in order to help ensure that people do not exceed safe intake levels.

A key challenge in applying what we know about vitamin D requirements, and the options available for meeting those requirements at population level, is how best to achieve equitable intakes across the population, including in disadvantaged subgroups, in a way that is sustainable and acceptable to the public.

Scientific recommendations on vitamin D nutrition for the population aged between 5 and 65 years in Ireland

The following total daily intakes of vitamin D would minimise the risk of vitamin D deficiency for children, teenagers and adults in Ireland:

- 10 µg for healthy children (aged 5–11 years)
- 15 µg for healthy teenagers and adults (aged 12–65 years, including pregnant women) of all ethnicities.

Regarding vitamin D food supplements for children, teenagers and adults in Ireland, the key points are as follows:

- For healthy children (aged 5–11 years) who get sunlight exposure during summer:
 - For those of fair-skinned ethnicity, a daily vitamin D supplement containing 10 µg (400 international units (IU)) taken during the extended winter months (end of October to March) is expected to meet their requirements.
 - For those of darker-skinned ethnicity a daily vitamin D supplement containing 10 µg (400 IU) taken throughout the full year is expected to meet their requirements.
- For healthy teenagers and adults (aged 12–65 years) who get sunlight exposure during summer:
 - For those of fair-skinned ethnicity, a daily vitamin D supplement containing 15 µg (600 IU) taken during the extended winter months (end of October to March) is expected to meet their requirements.
 - For those of darker-skinned ethnicity and for individuals of all ethnic groups who are pregnant, a daily vitamin D supplement containing 15 μg (600 IU) taken throughout the full year is expected to meet their requirements.

A daily vitamin D supplement of 10 μ g for children and 15 μ g for teenagers and adults in Ireland is considered safe.

Issues of cost and acceptability of, and access and adherence to, supplementation must be addressed in order to achieve equitable benefit from vitamin D supplementation at population level.

Regarding food sources of vitamin D for children, teenagers and adults in Ireland, the key points are as follows:

- Diets that include regular intake of natural sources of vitamin D such as oily fish, eggs, and meats – help to meet vitamin D requirements.
- Diets that include regular intake of vitamin D-fortified foods help to meet vitamin D requirements. This report provides examples of the types of vitamin D-fortified foods which can make meaningful contributions towards recommended intakes.
- Fortification of foods with vitamin D may be mandatory or voluntary for manufacturers. An appropriately implemented programme of mandatory fortification of a staple food(s) would offer the major advantage of widespread access to vitamin D at no extra cost to consumers. This may be of particular importance for those who have limited exposure to sunlight and have difficulty in consistent access to an adequate supply of foods naturally rich in vitamin D, as well as those for whom accessing and adhering to a supplemental regimen is difficult. Guidance should be provided to food manufacturers to support the effectiveness of the chosen approach.
- Consumption of a combination of vitamin D-fortified foods is safe for children, teenagers and adults in Ireland, even for those taking daily supplements containing 10 or 15 µg of vitamin D.

Consideration should be given as to how best to communicate with the public and key stakeholders in order to raise awareness of the issues around dietary intake, status and sources of vitamin D, and how to achieve the necessary behavioural changes that result in improved intakes and status.

The role of food businesses in relation to vitamin D

This report also includes industry-specific details relating to adherence to the MSLs in terms of the amount of vitamin D in food supplements placed on the Irish market and the use of μ g for measuring vitamin D in these supplements.

1. Background and scope

Vitamin D plays a key physiological role in the musculoskeletal system, the functioning of the immune system, and the process of cell division (EFSA Panel on Dietetic Products, Nutrition and Allergies, 2016; Scientific Advisory Committee on Nutrition, 2016; Nordic Council of Ministers, 2014; Institute of Medicine, 2011). Vitamin D deficiency leads to impaired mineralisation of bone due to inefficient absorption of dietary calcium and phosphorus, which manifests as rickets in children and osteomalacia in adults (EFSA Panel on Dietetic Products, Nutrition and Allergies, 2016). In addition, although causation has not been proven, association studies suggest a link between vitamin D deficiency and non-skeletal health conditions, such as cardiovascular diseases; diabetes; inflammatory disorders; some infectious diseases (including COVID-19) and immune disorders; certain cancers; and higher mortality rates (Lanham-New *et al.*, 2020; Lips *et al.*, 2019).

Two separate sources contribute to vitamin D supply in Ireland: dietary sources (including natural foods, fortified foods, and food supplements),¹ and unprotected skin exposure to ambient ultraviolet B (UVB) radiation from sunlight during the months of April through October. However, Ireland experiences a 'vitamin D winter' through the remaining 5 months of the year, when lack of sufficient UVB radiation limits the potential for synthesis of vitamin D in the skin (O'Neill *et al.*, 2016; Kilbane *et al.*, 2014). In the absence of sufficient exposure to UVB to enable synthesis in the skin, it is critical for the population to take in extra vitamin D through food as well as supplements, in order to meet requirements and prevent vitamin D deficiency. However, typical vitamin D intakes in populations within the European Union (EU) are generally low and, in the majority of cases, inadequate (Cashman, 2022).

The Scientific Committee of the Food Safety Authority of Ireland (FSAI), as part of its support for national policy and food-based dietary guidelines, has previously developed scientific recommendations for vitamin D supplementation for infants (birth to 12 months) (Food Safety Authority of Ireland, 2020d), young children (1–5 years) (Food Safety Authority of Ireland, 2020b) and older adults (≥65 years) (Food Safety Authority of Ireland, 2020e). However, the population group that has yet to be considered in this context for vitamin D intake is those aged 5–65 years. International evidence has shown that, across the population, teenagers, young adults, pregnant women, and dark-skinned ethnic subgroups are those with the highest prevalence of vitamin D

¹ Food supplements are small amounts of concentrated sources of micronutrients or other substances with a nutritional or physiological effect whose purpose is to supplement the normal diet (Directive 2002/46/EC). These are sometimes referred to as nutritional supplements or nutrient-specific supplements, e.g. 'vitamin D supplement'.

deficiency (Cashman, 2022; Kiely *et al.*, 2020). Therefore, the purpose of this current report is to address the issue of vitamin D nutrition for children, teenagers and adults living in Ireland, with specific reference to those who are pregnant and those who are dark-skinned (see <u>Appendix 1</u>).

This report will outline current information on vitamin D status in Irish children, teenagers and adults (including seasonal variations); possible health consequences of low status; and dietary vitamin D requirements and whether these are being met by Irish children, teenagers and adults, and, if not, how this might be addressed through dietary means. Finally, it will present a number of key options with regard to meeting vitamin D requirements for children, teenagers and adults in Ireland.

Key issues relating to population-based guidance on vitamin D for those aged between 5 and 65 years in Ireland

2.1 Vitamin D status and deficiency

Defining vitamin D deficiency and other degrees of low vitamin D status

While there is consensus that serum 25-hydroxyvitamin D (25(OH)D) concentration should be used to assess vitamin D status because it reflects the contribution from both diet and dermal synthesis, there has been considerable debate on suggested thresholds (cut-offs) of serum 25(OH)D for defining low vitamin D status (Cashman, 2020). This is despite the fact that most of the proposed serum 25(OH)D thresholds relate primarily to musculoskeletal health outcomes.

With regard to vitamin D deficiency as it relates to nutritional rickets and osteomalacia, the majority of expert bodies (such as the Institute of Medicine (IOM; renamed as the National Academy of Medicine in 2015) in the United States of America (USA); the European Food Safety Authority (EFSA); the Scientific Advisory Committee on Nutrition (SACN) in the United Kingdom (UK); and the Nordic Council of Ministers' Nordic Nutrition Recommendations (NNR)) have suggested that serum 25(OH)D concentrations of <25 or <30 nanomoles per litre (nmol/L) are indicative of increased/high risk of vitamin D deficiency (EFSA Panel on Dietetic Products, Nutrition and Allergies, 2016; Scientific Advisory Committee on Nutrition, 2016; Nordic Council of Ministers, 2014; Institute of Medicine, 2011).

In the context of establishing dietary recommendations for vitamin D, in 2011 the IOM used bone health indicators – such as risk of rickets in children and risk of osteomalacia in adults, calcium absorption, and bone mineral density (BMD) – for which it believed the evidence was sufficiently strong for the development of recommendations (Institute of Medicine, 2011). In addition to selecting a serum 25(OH)D threshold of <30 nmol/L as indicative of increased risk of vitamin D deficiency, the IOM proposed 50 nmol/L as the concentration of serum 25(OH)D that would ensure 'adequacy' of vitamin D status for nearly all individuals. In 2016, the EFSA (EFSA Panel on Dietetic Products, Nutrition and Allergies, 2016) took a very similar approach, again using musculoskeletal health outcomes as the primary basis. Also, within the framework of vitamin D recommendations, serum 25(OH)D concentrations greater than 30 but less than 50 nmol/L risk being inadequate for some members of the population, whereas concentrations greater than 50 nmol/L represent 'sufficiency' for nearly everyone on the basis of musculoskeletal health (Nordic Council of Ministers, 2014; Institute of Medicine, 2011).

The SACN in the UK (Scientific Advisory Committee on Nutrition, 2016) also selected musculoskeletal health (rickets, osteomalacia, falls, and muscle strength and function, depending on the age group) as a basis for the development of vitamin D recommendations, but it considered that the evidence overall suggested that the risk of poor musculoskeletal health was increased at serum 25(OH)D concentrations of less than about 20–30 nmol/L. On this basis, the SACN used a serum 25(OH)D target of 25 nmol/L to represent a 'population protective level' that individuals in the UK should stay above throughout the year in order to protect musculoskeletal health.

Non-skeletal health effects of vitamin D deficiency – including infection, cancer, diabetes, cardiovascular disease, and detrimental perinatal health outcomes, among others – are the subject of global research efforts. In its 2011 report, the IOM expert committee suggested that purported health benefits beyond bone came from studies that provided often mixed and inconclusive results and could not be considered reliable at that time to establish trusted dietary recommendations for the population (Institute of Medicine, 2011). Since then, other vitamin D guidelines have also generally been based on beneficial effects of vitamin D on musculoskeletal health (e.g. preventing rickets, osteomalacia, fractures, muscle weakness, falls, etc.) and occasionally on extra-skeletal health, such as pregnancy-related health outcomes (EFSA Panel on Dietetic Products, Nutrition and Allergies, 2016) or mortality (Nordic Council of Ministers, 2014).

A number of the above-mentioned expert agencies referenced the potential importance of up to eight mega-trials (with more than 2,000 participants in each) in which higher doses of vitamin D supplementation were given than had previously been used. These trials would finish after publication of their vitamin D reports, but nevertheless they may demonstrate evidence for non-skeletal health effects of higher circulating 25(OH)D (in excess of the 50 nmol/L required for good bone health). To date, five of these trials have published their findings and have shown that vitamin D supplementation does not prevent hard disease endpoints – such as cardiovascular disease, cancer, type 2 diabetes, fractures, or falls – aside from a possible beneficial effect on cancer mortality and a reduced risk of an autoimmune disease as a secondary outcome in one trial (Scragg and Sluyter, 2021; Pittas *et al.*, 2019).

It should be noted that baseline mean serum 25(OH)D in these five trials was in the range of 56– 82 nmol/L, and thus the trials tested the effect of increasing vitamin D status beyond what is considered adequate by many and reported average increases of 30–69 nmol/L in the vitamin D intervention groups at the trial endpoints. In contrast, subgroup analyses showed that beneficial effects were seen for intermediate outcomes, such as BMD of the spine and hips (in all participants, but especially so in those with baseline serum 25(OH)D <30 nmol/L) as well as arterial function and lung function (in those with baseline serum 25(OH)D <50 nmol/L) (Hahn *et al.*, 2022; Scragg and Sluyter, 2021). Details of these mega-trials, as well as other relevant

randomised controlled trials (RCTs) of vitamin D supplementation since 2005 with a focus on both non-skeletal and skeletal health outcomes, are provided in <u>Appendix 2</u>.

Thus, while universal agreement on the various definitions of vitamin D status is yet to be reached, overall, it is generally agreed that prevention of such vitamin D deficiency is a public health priority, and that all individuals should have circulating concentrations of 25(OH)D equal to or greater than 25–30 nmol/L (Cashman, 2020).

For this report, the following definitions relating to different degrees of vitamin D status, as proposed by the IOM (Institute of Medicine, 2011), will be used:

- Persons are at risk of deficiency at serum 25(OH)D concentrations below 30 nmol/L.
- Some, but not all, persons are potentially at risk for inadequacy at serum 25(OH)D concentrations between 30 and 50 nmol/L.
- Practically all persons are sufficient at serum 25(OH)D concentrations of at least 50 nmol/L.
- There may be reason for concern at serum 25(OH)D concentrations of above 125 nmol/L, especially when these concentrations are sustained.

In particular, at risk of vitamin D deficiency (<30 nmol/L) and at risk of inadequacy (30–50 nmol/L) are relevant in relation to vitamin D dietary requirements (see <u>Section 2.2</u>).

Vitamin D status and its determinants in those aged between 5 and 65 years in Ireland

Nationally representative studies

Several nationally representative studies in Ireland have evaluated vitamin D status in children, teenagers and adults, and have explored its determinants. Such studies include the National Adult Nutrition Survey (NANS) (Cashman *et al.*, 2013a), the National Teens' Food Survey II (NTFS II) (Cashman *et al.*, 2022a), the Young Hearts 2000 (YH2000) study in Northern Ireland (Carson *et al.*, 2015), the SCOPE (Screening for Pregnancy Endpoints) Ireland prospective pregnancy cohort study (Hemmingway *et al.*, 2018a; Kiely *et al.*, 2016). All studies reported a high prevalence of individuals with serum 25(OH)D concentrations <30 nmol/L (at risk of vitamin D deficiency, as per Institute of Medicine, 2011). The prevalence of individuals with serum 25(OH)D concentrative studies ranged from 12% to 26% (Table 1). The NTFS II reported that 14% of teenagers, and the NANS reported that 7% of adults (aged 18–65 years), had serum 25(OH)D concentrations <30 nmol/L during summer months, with prevalence estimates of these low concentrations becoming more pronounced in the winter months (Table 1). There was also a clear seasonal divide in the prevalence of being at risk of inadequate vitamin D status (Table 1).

Table 1 Frequency of being at risk of vitamin D deficiency and inadequacy* in childhood, teenage

 and adult cohorts in nationally representative studies in Ireland

Study**	Year of study	Sample size	Age (years)	% with 25(OH)D <30 nmol/L***	% with 25(OH)D 30–50 nmol/L***
NANS	2008– 2010	986	18–65	12 [S: 7; W: 20]	34 [S: 27; W: 43]
NTFS II	2019– 2020	245	13–18	22 [S: 14; W: 27]	33 [S: 30; W: 36]
YH2000	2000	1015	12 and 15	26	40
SCOPE Ireland	2008– 2011	1768	30 [15 weeks' gestation]	17 [S: 7; W: 25]	26.8 [S: 19; W: 32]

*Serum 25(OH)D of <30 and 30–50 nmol/L, representing being at risk of vitamin D deficiency and inadequacy, respectively. **The serum 25(OH)D data in these studies were standardised according to the Vitamin D Standardization Program protocols (Sempos *et al.*, 2012).

***Prevalence data presented as year-round estimates and/or as summer (S) and winter (W) estimates in brackets, where available.

Predictors of risk of serum 25(OH)D <30 nmol/L within the NTFS II sample of teenagers (aged 13– 18 years) in Ireland included being sampled in extended winter (November to March), being in the 16–18-year-old age group, having low vitamin D intake, having overweight/obesity, and having a skin colour other than white (Cashman *et al.*, 2022a). Winter sampling time and low vitamin D intake were also significant predictors of serum 25(OH)D <50 nmol/L in the YH2000 teenagers (Hill *et al.*, 2008).

In terms of determinants of vitamin D status in adults, vitamin D supplement use, together with sunnier season, sun exposure preference, and dietary vitamin D intake, were significant positive determinants of serum 25(OH)D concentrations in adults in the NANS (Cashman *et al.*, 2014), even when the sample was limited to those aged 18–65 years.

SCOPE Ireland showed that the main predictors of sufficient 25(OH)D concentrations in pregnant women were use of vitamin D-containing supplements and summer sampling, while non-Caucasian ethnicity and smoking were predictors of insufficient 25(OH)D concentrations (Hemmingway *et al.*, 2018a; Kiely *et al.*, 2016).

Additional studies

Although not nationally representative, a cross-sectional prospective study of 252 Irish children and adolescents (Carroll *et al.*, 2014), conducted between March 2010 and March 2011, reported mean serum 25(OH)D concentrations of 46, 48, and 44 nmol/L among 4–7-, 8–11-, and 12–17year-olds, respectively. The mean 25(OH)D concentrations across the entire sample during January–March, April–June, July–September, and October–December were 37.6, 52.4, 61.5, and 49.2 nmol/L, respectively (Carroll *et al.*, 2014). A majority (83%) of the children and adolescents in

this study (Carroll *et al.*, 2014) had serum 25(OH)D concentrations <50 nmol/L in January–March. Taking vitamin D supplements and consuming vitamin D-fortified milk were behaviours significantly associated with higher serum 25(OH)D concentrations (Carroll *et al.*, 2014). The D Vitamin in Children (D-VinCHI) Study reported the mean plasma 25(OH)D concentration of primary school children (n=47) aged 4–11 years in Northern Ireland. The mean plasma 25(OH)D concentration was 49.2 nmol/L, with 14.9% and 55.3% of participating children having plasma 25(OH)D concentration was 49.2 nmol/L, with 14.9% and 55.3% of participating children having plasma 25(OH)D concentrations <30 nmol/L and <50 nmol/L, respectively, at the time of recruitment (November–March 2020). Dietary intake of vitamin D (all sources) and time spent outdoors were associated with higher vitamin D status, whereas increased weekly screen time was associated with lower vitamin D status (Glatt *et al.*, 2022). The control groups in two Dublin-based case-control studies of children (one focused on vitamin D and fracture, and the other on vitamin D and admission to paediatric intensive care units with sepsis) showed that mean baseline serum 25(OH)D was 62.5 nmol/L (n=58; mean age: 8.9 years) and 66.0 nmol/L (n=3; <12 years old; mean age: 3.2 years), respectively (Moore *et al.*, 2022; Onwuneme *et al.*, 2015).

In a retrospective analysis of general practitioner (GP)-requested 25(OH)D tests at St James's Hospital for 1,226 community-dwelling children aged 1–17 years, 23% had levels <30 nmol/L and 51% had levels <50 nmol/L (Scully *et al.*, 2022). Serum 25(OH)D concentration <30 nmol/L was more common in disadvantaged areas (34%) and among those aged over 12 years versus 12 years and under (24% vs. 16%; *p*=0.033). The greatest predictor was socioeconomic status (SES; assessed via mapping of postal addresses and deprivation index) (disadvantaged versus affluent, odds ratio (OR): 2.18; confidence interval (CI): 1.34–3.53; *p*=0.002), followed by female sex (OR: 1.57; CI: 1.15–2.14; *p*=0.005), and winter season (October–February, OR: 1.40; CI: 1.07–1.84; *p*=0.015) (Scully *et al.*, 2022). A recent laboratory-based 25(OH)D trend analysis from St Vincent's University Hospital reported that, of samples analysed between April 2019 and March 2021, 15.4% and 32.3% of those from children and adolescents (aged 5–19 years; n=5524) had 25(OH)D concentrations <30 nmol/L and between 30 and 50 nmol/L, respectively (McKenna *et al.*, 2022).

High rates of being at risk of vitamin D deficiency and inadequacy have also been observed in younger adults in large observational studies. In a retrospective analysis of GP-requested 25(OH)D tests at St James's Hospital for 11,319 community-dwelling adults aged 18–39 years, 21% had levels <30 nmol/L and 47% had levels <50 nmol/L, with higher rates in men compared with women (Scully *et al.*, 2020). Almost all (97%) of the adults in the study were residing in Dublin or Kildare at the time that their 25(OH)D test was requested. Season was the strongest predictor of having serum 25(OH)D <30 nmol/L, followed by location, where specific urban areas were identified as having a higher risk of deficiency (Scully *et al.*, 2020). In the nationally representative The Irish Longitudinal Study on Ageing (TILDA), 5.0% and 18.4% of those aged 55–59 years had

serum 25(OH)D concentrations <30 nmol/L during the summer and winter periods, respectively (Laird and Kenny, 2020). Only 5.6% reported taking vitamin D supplements (Laird and Kenny, 2020). The previously mentioned laboratory-based 25(OH)D trend analysis also reported that, of samples analysed between April 2019 and March 2021, 13.3% and 29.2% of those from younger adults (aged 20–64 years, n=63290) had 25(OH)D concentrations <30 nmol/L and between 30 and 50 nmol/L, respectively (McKenna *et al.*, 2022).

It should be noted that the three previously mentioned studies are based on convenience samples, which limits the generalisability of their findings to a wider population. In particular, there may be selection bias of study participants who may have conditions predisposing them to serum 25(OH)D concentrations <30 nmol/L that underlie the reason for their testing.

The maternal body weight and vitamin D status (MO-VITD) study of pregnant women (n=240; mean age: 29.6 years) in Northern Ireland reported that 45.2% of participants had 25(OH)D concentrations <50 nmol/L at 12 weeks' gestation (Alhomaid *et al.*, 2021).

Looking specifically to ethnic minority groups in Ireland, a recent study (Laird *et al.*, 2020) reported high rates of vitamin D deficiency (serum 25(OH)D concentration <30 nmol/L) in an Irish Asian population (n=186). The average 25(OH)D concentration for those aged under 18 years was only 20.0 nmol/L, and more than 70% of those aged 18–50 years were deficient in vitamin D during both winter and summer (Laird *et al.*, 2020).

2.2 Vitamin D dietary requirements

Health authorities in the EU through the EFSA (EFSA Panel on Dietetic Products, Nutrition and Allergies, 2016), in the UK through the SACN (Scientific Advisory Committee on Nutrition, 2016), in Nordic countries through the NNR (Nordic Council of Ministers, 2014), and in the USA through the IOM (Institute of Medicine, 2011) have all established dietary vitamin D requirements for all ages, including children, adolescents and adults, including pregnant and lactating women. These dietary requirements are based on specified health outcomes (largely musculoskeletal health outcomes, as mentioned in <u>Section 2.1</u> and below) and the associated serum 25(OH)D concentration. A vitamin D intake requirement value, aligned to that target serum 25(OH)D concentration, is established using vitamin D intake-status response data from vitamin D RCTs. The vitamin D RCTs informing these recommendations are typically winter based so as to allow for the assumed absence of vitamin D supply derived from UVB radiation in establishing the dietary requirement estimates. This reflects a paucity of data and resulting uncertainty concerning individuals' sun exposure – which confounds the interpretation of dose–response data – as well as concerns about skin cancer risk, which precluded factoring the effects of sun exposure into the vitamin D dietary

requirement exercises internationally. While various health authorities have adopted this approach of deriving dietary requirement estimates for vitamin D under conditions of assumed minimal endogenous vitamin D synthesis, they do highlight that this is a markedly cautious approach, given that the vast majority of individuals obtain at least some vitamin D from inadvertent or intentional sun exposure.

Various international dietary vitamin D requirement values for children, adolescents and adults, including pregnant and lactating women (i.e. encompassing those aged 5-65 years) are summarised in Table 2. As mentioned in Section 2.1, all agencies which have established dietary requirements for vitamin D in these age groups have based them on bone/musculoskeletal health, with some including additional health outcomes such as adverse pregnancy-related health outcomes (EFSA) and total mortality and risk of falling in older adults (aged 61-74 years) and the elderly (aged 75 years and older) (NNR). Three of the four sets of recommendations (those of the IOM, NNR and EFSA) aim to achieve adequacy of vitamin D status to support these bone health outcomes and thus based their recommendations on a serum 25(OH)D target of 50 nmol/L. The IOM and EFSA have established a dietary requirement of 15 micrograms per day (µg/d) for children, adolescents and adults, while the NNR recommends 10 µg/d for children, adolescents and adults (aged 18–74 years). This takes into account some contribution of vitamin D from sun exposure through outdoor activities during the summer season (late spring to early autumn). This is compatible with normal, everyday life and is also in line with recommendations on physical activity. For people who get little or no sun exposure, the NNR recommends an intake of 20 µg/d. The 2016 UK vitamin D recommendation of 10 µg/d for individuals aged 4 years and older seeks to provide protection to nearly all (97.5%) individuals in the population against serum 25(OH)D concentrations falling below 25 nmol/L, in order to protect musculoskeletal health (Scientific Advisory Committee on Nutrition, 2016). Following a review of the evidence on vitamin D supplementation and acute respiratory tract infection risk in 2020, the SACN suggested that consumption of 10 µg/d may also provide some additional benefit in reducing the risk of acute respiratory tract infections (Scientific Advisory Committee on Nutrition, 2020).

Table 2 International specifications on vitamin D status and recommendations for oral intake

 requirements in children, adolescents and adults with assumed minimal or no sunlight exposure

		Serum 25(OH	H)D (nmol/L)*	Population	Basis for PRI	
Report	Country/region	At risk of deficiency	Sufficiency	recommended intake (PRI) of vitamin D (µg/d)** [age group]	Health outcome Target serum 25(OH)D	
IOM (2011) (Institute of Medicine, 2011)	USA and Canada	<30	≥50	15 [1–70 years] (estimated average requirement (EAR): 10)***	Bone health ≥50 nmol/L	
NNR (2014) (Nordic Council of Ministers, 2014)	Nordic countries	<25/30	≥50	10 [2–74 years] 20 [61–74 years with little/no sun exposure]	Bone health; total mortality; risk of falling (older adults only) ≥50 nmol/L	
SACN (2016) (Scientific Advisory Committee on Nutrition, 2016)	UK	<25	Not stated	10 [≥4 years]	Musculoskeletal health; falls (older adults only) ≥25 nmol/L	
EFSA Panel on Dietetic Products, Nutrition and Allergies (2016) (EFSA, 2016)	EU	Not stated	≥50	15 [≥1 year]	Musculoskeletal health; adverse pregnancy outcomes ≥50 nmol/L	

*Representing the serum 25(OH)D thresholds at which health authorities suggested individuals were at increased/high risk of vitamin D deficiency, and at which practically all persons have sufficient vitamin D levels.

**In each report, the PRI is that which covers the needs of 97.5% of individuals at the specified serum 25(OH)D target concentration based on a defined health outcome(s); note that the EFSA's recommendation is an adequate intake, and thus covers the needs of the majority of individuals (which may be less than 97.5%).

***Using bone health as the outcome, the EAR covers the needs of 50% of individuals at a serum 25(OH)D target concentration of 40 nmol/L.

Vitamin D equivalents: 10 µg=400 IU; 15 µg=600 IU; 20 µg=800 IU.

None of these agencies (the IOM, NNR, EFSA and SACN) have indicated an increased dietary requirement for vitamin D in pregnant or lactating women over that of non-pregnant or non-lactating women, largely owing to data gaps.

The primary focus of the recommendations in this report will be on taking a population protective approach to preventing serum 25(OH)D concentrations from being at or below 30 nmol/L (reflective of being at risk of vitamin D deficiency) among those aged 5–65 years in Ireland, since recommendations in relation to achieving adequate vitamin D levels are mixed and still being debated internationally, as outlined in <u>Section 2.1</u>. This is also consistent with the approach taken in establishing the recently published *Vitamin D – Scientific Recommendations for Food-Based Dietary Guidelines for Older Adults in Ireland* (Food Safety Authority of Ireland, 2020e). The

vitamin D-related guidelines in the recent *Scientific Recommendations for Food-Based Dietary Guidelines for 1 to 5 Year-Olds in Ireland* used the IOM's EAR and recommended dietary allowance (RDA) of 10 and 15 μ g/d for vitamin D in this age group (Institute of Medicine, 2011) as its target values. In particular, the EAR of 10 μ g/d was used in the modelling of food intake patterns exercise in order to assess the adequacy of vitamin D dietary intakes and means of meeting the recommendations (Food Safety Authority of Ireland, 2020b).

It is important to note that by convention, dietary vitamin D requirement values are set assuming that intakes of interacting nutrients, such as calcium, are adequate (EFSA Panel on Dietetic Products, Nutrition and Allergies, 2016; Institute of Medicine, 2011). The national nutrition surveys conducted by the Irish Universities Nutrition Alliance have shown that 25% of adults aged 18–64 years (35% of women and 15% of men), 37% of children aged 5–12 years and 51% of teenagers aged 13–18 years in Ireland have inadequate intakes of calcium (i.e. below the EAR) (Irish Universities Nutrition Alliance, 2021; Irish Universities Nutrition Alliance, 2020; Irish Universities Nutrition Alliance, 2021; Irish Universities Nutrition Alliance, 2020; Irish Universities Nutrition Alliance, 2021; Irish Universities Nutrition D supplements also contain calcium, and vice versa.

Children, adolescents and adults

Two RCTs that were specifically designed to establish vitamin D requirements in adults in Ireland aged 20-40 years and 64 years and older (which encompasses adults aged 18-65 years in context of this report) showed that an intake of 9 µg/d would keep wintertime serum 25(OH)D >25 nmol/L in nearly all (97.5%) individuals (Cashman et al., 2009). In order to achieve 25(OH)D >30 nmol/L, the estimated required vitamin D intake would be 12.2 and 13.7 µg/d for those aged 20-40 years and 64 years and older, respectively (Cashman, 2014). The intake of vitamin D needed for 97.5% of adults to maintain serum 25(OH)D above 50 nmol/L would be 25-28 µg/d (Cashman et al., 2009). While vitamin D requirements for children and adolescents have not been established using RCTs conducted in Ireland, RCTs using the same specific design as that used in the abovementioned Irish studies of adults have been conducted in northern locations along the same latitudes bracketing Ireland (51–55 °N); these studies involved children in Denmark (55 °N), Finland (60 °N) and Sweden (55 °N and 63 °N), and involved adolescents in the UK (51 °N). These studies have shown that intakes of 6.0/8.3, 10.3, and 13.1 µg/d would keep wintertime serum 25(OH)D >30 nmol/L in nearly all (97.5%) children aged 5-7/4-8, 11, and 14-18 years, respectively (Öhlund et al., 2017; Mortensen et al., 2016; Smith et al., 2016; Cashman et al., 2011). The intake of vitamin D needed in order for 97.5% of children to maintain serum 25(OH)D above 50 nmol/L would be 19–20 µg/d (Öhlund et al., 2017; Mortensen et al., 2016; Cashman et al., 2011). The vitamin D intake requirement for maintaining serum 25(OH)D >50 nmol/L for

adolescents could not be estimated, as the serum 25(OH)D response plateaued (Smith *et al.*, 2016), but is likely to be similar to that of adults.

These estimates are also supported by two Irish-led meta-analyses using the individual participant data (IPD) of several RCTs with vitamin D supplements (Cashman *et al.*, 2017) and vitamin D-fortified foods (Cashman *et al.*, 2021). In particular, the IPD exercise in 2017 used data from all five of the above-mentioned vitamin D RCTs together with data from two additional vitamin D RCTs of Irish adults (using data from a total of 882 participants aged 4–90 years). This showed that, irrespective of age group, the vitamin D intake needed for 97.5% of individuals to maintain serum 25(OH)D above 30 nmol/L would be 13 μ g/d (Cashman *et al.*, 2017). In their vitamin D requirement analyses, the IOM, NNR and EFSA combined summary data from RCTs of children and adults, as age effects on the response of serum 25(OH)D to increased vitamin D intake were not evident. However, further analysis of the above-mentioned IPD, which were not available to other authorities when they considered this, shows that the vitamin D intake needed for 97.5% of adult individuals (n=521) to maintain serum 25(OH)D above 30 nmol/L would be 16 μ g/d, whereas for children (n=361) it was 10 μ g/d (Professor C Ritz, personal communication, 28 January 2022).

Based on data from the above-mentioned collection of studies, the estimated vitamin D intake needed for 97.5% of individuals aged 5–65 years to maintain serum 25(OH)D above 30 nmol/L is in the range of 10–16 µg/d, depending on age group (lower in children and higher in teenagers and adults). It has been stressed that the vast majority of adult bone mass is accrued throughout adolescence (Heaney *et al.*, 2000). For example, it has been estimated that during adolescence, approximately 40% of total bone mineral is acquired during the 4 years surrounding the peak in bone accretion that occurs in the early teenage years, and that 95% of adult bone mass has been acquired by 4 years following this peak (Baxter-Jones *et al.*, 2011).

As mentioned above, while there is debate on the serum 25(OH)D threshold concentration which ensures adequacy of vitamin D status in terms of bone health, there is strong agreement that maintaining serum 25(OH)D above 30 nmol/L is important to prevent increased risk of poor bone health.

The dietary vitamin D requirement to maintain serum 25(OH)D \ge 30 nmol/L in healthy individuals aged 5–11 years in Ireland is 10 µg/d.

The dietary vitamin D requirement to maintain serum 25(OH)D \ge 30 nmol/L in healthy individuals aged 12–65 years in Ireland is 15 µg/d.

These requirements were established using apparently healthy children, adolescents and adults, the majority of whom had sun exposure the previous summer. It should also be noted that the adults were living independently.

With regard to the 50 nmol/L serum 25(OH)D threshold suggested by some authorities in relation to adequacy of vitamin D status, an intake of 17 μ g/d has been estimated to allow 80% of freeliving adults in Ireland to maintain a serum 25(OH)D above this threshold during winter (Cashman *et al.*, 2008). An intake of 10 and 17 μ g/d has been estimated to allow approximately 50% and 95%, respectively, of free-living children at northern latitudes (51–61 °N, along the same latitudes bracketing Ireland) maintain a serum 25(OH)D above this threshold during winter (Mortensen *et al.*, 2016; Cashman *et al.*, 2011). Thus, the recommended vitamin D intakes of 10 and 15 μ g/d will not only protect nearly all children, adolescents and adults in Ireland against being at risk of vitamin D deficiency, it will allow a significant number of individuals within these population groups to attain serum 25(OH)D concentrations ≥50 nmol/L.

Pregnant women

Pregnancy is a life stage for which evidence of being at risk of vitamin D deficiency and inadequacy is widespread, but for which the evidence basis for setting dietary requirements for vitamin D is weakest (Institute of Medicine, 2011). As mentioned previously, dietary recommendations for pregnant and lactating women are currently the same as for non-pregnant individuals due to the unavailability of dose-response trial data on which to base pregnancyspecific guidelines at the time the recommendations were developed. Since those recommendations were developed, a three-arm, dose-response, double-blind RCT among 144 white-skinned pregnant women was conducted in Cork (51 °N) to estimate the vitamin D intake requirement (O'Callaghan *et al.*, 2018). Foetuses and newborn infants are completely dependent on maternal 25(OH)D concentrations, and it is widely accepted that at minimum 25(OH)D concentrations should exceed 25–30 nmol/L during pregnancy in order to protect foetal skeletal development (Kiely *et al.*, 2020). The O'Callaghan *et al.* study showed that a vitamin D₃ intake of 13.8 µg/d safely maintained serum 25(OH)D concentrations \geq 30 nmol/L during pregnancy among white women.

Internationally, current recommendations for vitamin D intakes during pregnancy do not consider the vitamin D requirements of newborn infants and assume the immediate availability of an adequate supply from early life (Kiely *et al.*, 2020). An alternative, pragmatic approach has been suggested in which the vitamin D requirement during pregnancy could also be considered to be the intake required to maintain maternal 25(OH)D in late gestation at concentrations of about 25–30 nmol/L, sufficient to prevent risk of neonatal deficiency. The RCT by O'Callaghan *et al.* showed that when maternal 25(OH)D was ≥50 nmol/L, 95% of umbilical cord sera were ≥30 nmol/L and 99% were >25 nmol/L (O'Callaghan *et al.*, 2018). Among white women, a total vitamin D₃ intake of 30 µg/d safely maintained serum 25(OH)D concentrations ≥50 nmol/L during pregnancy at 51 °N, thus preventing the risk of neonatal deficiency (O'Callaghan *et al.*, 2018). Whether this approach

will be accepted by health agencies internationally, and possibly feature in future iterations of vitamin D dietary requirement exercises, will be watched with interest. In the meantime, for this report the vitamin D requirement during pregnancy will be based on maintaining maternal 25(OH)D ≥30 nmol/L.

The dietary vitamin D requirement to maintain maternal serum 25(OH)D \geq 30 nmol/L during pregnancy in Ireland is 15 µg/d.

Individuals of dark-skinned ethnicity

In Europe, dark-skinned racial/ethnic groups are at a much higher risk of vitamin D deficiency compared with their white-skinned counterparts (Cashman et al., 2016). In Ireland, as mentioned in Section 2.1, a study of the Irish Asian population reported that more than 70% of those aged 18-50 years had serum 25(OH)D <30 nmol/L in both winter and summer (Laird et al., 2020). The equivalent prevalence of serum 25(OH)D <30 nmol/L in white-skinned Irish adults was 20% during winter and 7% during summer (Cashman et al., 2013a). A recent Irish-led meta-analysis using IPD from several RCTs with vitamin D supplements and vitamin D-fortified foods in dark-skinned children and adults with who were resident at high latitudes (>40 °N) has provided estimates of dietary vitamin D requirements in these individuals (Cashman et al., 2022b). To maintain serum 25(OH)D concentrations \geq 25 and \geq 30 nmol/L in 97.5% of individuals, 24 and 27 µg/d of vitamin D, respectively, were required among South Asian participants and 24 and 33 µg/d, respectively, among Black participants. It should be noted that this analysis included RCTs from Europe (generally >50 °N) as well as the USA (generally >40 °N), but none from Ireland, as such studies have yet to be conducted here. These intake estimates are higher than those recommended by the health authorities in the EU and the USA, which have not delineated their recommendations by racial/ethnic grouping (see Table 2), largely owing to data gaps. How the health agencies will consider these IPD in their future vitamin D requirement exercises will be watched with interest.

In the meantime, these latest bespoke IPD data underscore the need for darkskinned healthy individuals aged 5–65 years in Ireland to attain a minimum vitamin D intake of 15 µg/d.

It should also be noted that the IPD analyses showed that intakes of vitamin D close to this recommended 15 μ g/d (i.e. 15.5–17.0 μ g/d) allowed a majority (90%) of South Asian individuals to maintain serum 25(OH)D concentrations ≥25 nmol/L, as well as 90% and 95% of Black individuals to maintain serum 25(OH)D concentrations ≥30 nmol/L and ≥25 nmol/L, respectively, during winter (Cashman *et al.*, 2022b).

2.3 Current dietary vitamin D intakes

Estimates of the current dietary intakes of vitamin D among children, teenagers, adults and pregnant women in Ireland are shown in Table 3. For children, nationally representative data from the National Children's Food Survey II (NCFS II) (2017–2018) in the Republic of Ireland and the National Diet and Nutrition Survey in Northern Ireland (NDNS NI) (2012–2013 to 2016–2017) reported mean daily intakes of vitamin D ranging from 2.2 to 3.3 µg/d from food sources only, and of 4.2 µg/d from all sources (including food supplements) (Kehoe et al., 2022, Irish Universities Nutrition Alliance, 2020; Bates et al., 2019). In Northern Ireland, further data from a small observational study of primary-school-aged children (2019-2020) reported a mean intake of vitamin D of 6.4 µg/d from all sources (Glatt et al., 2021). For teenagers, nationally representative data from the NTFS II (2019–2020) and the NDNS NI (2012–2013 to 2016–2017) reported mean intakes of vitamin D ranging from 2.0 to 3.1 µg/d from food sources only, and of 3.7 µg/d from all sources (including food supplements) (Irish Universities Nutrition Alliance, 2021; Bates et al., 2019). For adults, nationally representative data from the NANS (2008-2010) and the NDNS NI (2012–2013 to 2016–2017) reported mean intakes of vitamin D ranging from 2.7 to 3.1 µg/d from food sources only, and of 4.3 µg/d from all sources (including food supplements) (Bates et al., 2019; Black et al., 2015; Irish Universities Nutrition Alliance, 2011). For pregnant women, baseline data from two recent RCTs in Ireland have reported mean intakes of vitamin D of 4.9 µg/d from food sources only (Alhomaid et al., 2017) and 10.7 µg/d from all sources (including food supplements) (Hemmingway et al., 2018b).

From a public health nutrition perspective, the percentage of the population/population group with a habitual daily nutrient intake lower than the EAR is taken as an estimate of the percentage of the population with probable inadequate intakes (EFSA Panel on Dietetic Products, Nutrition and Allergies, 2010). Using the IOM's EAR for vitamin D of 10 μ g/d, it can be estimated from nationally representative data that 94% of children, 94% of teenagers and 90% of adults on the island of Ireland have inadequate vitamin D intakes (Kehoe *et al.*, 2022; Irish Universities Nutrition Alliance, 2021; Black *et al.*, 2015).

Key food sources of vitamin D across all age groups include breakfast cereals (vitamin D-fortified, ready-to-eat breakfast cereals (RTEBCs)); meat and meat products; butters and spreading fats; eggs and egg dishes; fish and fish dishes; and milk and yogurt (Kehoe *et al.*, 2022; Irish Universities Nutrition Alliance, 2021; Bates *et al.*, 2019; Alhomaid *et al.*, 2017; Black *et al.*, 2015). Furthermore, food supplements have been shown to contribute 10% of vitamin D intakes in children, 5% in teenagers, and 24% in adults (Kehoe *et al.*, 2022; Irish Universities Nutrition Alliance, 2021; Black *et al.*, 2015).

Risk of excessive intakes

The tolerable upper intake level (UL) is the highest level of long-term daily intake of a nutrient, from all sources, judged to be unlikely to pose a risk of adverse health effects to humans (EFSA Panel on Dietetic Products, Nutrition and Allergies, 2010). The UL for vitamin D is 50 μ g/d for children aged 5–10 years and 100 μ g/d for all those aged 11 years and older (EFSA Panel on Dietetic Products, Nutrition and Allergies, 2012).

Daily intake of vitamin D among higher consumers (i.e. 95^{th} percentile of the population: P₉₅) in Ireland is estimated for children as 10.1 µg/d from all sources (including food supplements) (NCFS II) and 4.5–7.0 µg/d from food sources only (including fortified foods) (NCFS II and NDNS NI) (Kehoe *et al.*, 2022; Irish Universities Nutrition Alliance, 2020; Bates *et al.*, 2019). The P₉₅ for teenagers is estimated as 9.5 µg/d from all sources (NTFS II) and 4.5–7.0 µg/d from food sources only (NTFS II and NDNS NI) (Irish Universities Nutrition Alliance, 2021; Bates *et al.*, 2019), and for adults it is estimated as 13.4 µg/d from all sources (NANS) and 7.9–8.0 µg/d from food sources only (NANS and NDNS NI) (Bates *et al.*, 2019; Black *et al.*, 2015; Irish Universities Nutrition Alliance, 2011).

Furthermore, the proportion of children, teenagers and adults with intakes above the ageappropriate ULs (i.e. 50 μ g/d for those aged 5–10 years and 100 μ g/d for those aged 11 years and older) was 0% for all population groups (Kehoe *et al.*, 2022; Walsh *et al.*, 2022; Black *et al.*, 2015).

Table 3 Estimated current dietary intakes of vitamin D for children, teenagers, adults and pregnant women in Ireland

	Study type	Years of data collection	Population subgroup	Vitamin D intake		% below	
Study				Food sources (µg/d)	All sources* (µg/d)	EAR (10 µg/d)	Reference
Children							
NCFS II	Nationally representative	2017–2018	5–12 years (n=600)	3.3	4.2	94†	(Kehoe <i>et al</i> ., 2022)
NDNS NI (Years 5–9)	Nationally representative	2012–2013 to 2016– 2017	4–10 years (n=168)	2.2	-	-	(Bates <i>et al</i> ., 2019)
D-VinCHI Study	Baseline data from RCT (convenience sample)	2019–2020	Healthy children 4–11 years (n=47)	-	6.4	83	(Glatt <i>et al</i> ., 2021)
Teenagers							
NDNS NI (Years 5–9)	Nationally representative	2012–2013 to 2016– 2017	11–18 years (n=198)	2.0	-	-	(Bates <i>et al</i> ., 2019)
NTFS II	Nationally representative	2019–2020	13–18 years (n=428)	3.1	3.7	94†	(Irish Universities Nutrition Alliance, 2021)
Adults							
NANS	Nationally representative	2008–2010	18–64 years (n=1274)	3.1	4.3	90†	(Black <i>et al</i> ., 2015)
NDNS NI (Years 5–9)	Nationally representative	2012–2013 to 2016– 2017	19–64 years (n=325)	2.7	-	-	(Bates <i>et al</i> ., 2019)
Pregnant women							
ODIN DMAT RCT (Cork, Ireland)	Baseline data from RCT (convenience sample)	2014–2016	Pregnant women (healthy Caucasian) (n=142)	-	10.7	-	(Hemmingway <i>et</i> <i>al</i> ., 2018b)
MO-VITD vitamin D intervention study in pregnancy (Northern Ireland)	Baseline data from RCT (convenience sample)	2015–2017	Pregnant women ≥18 years (n=240)	4.9	-	-	(Alhomaid <i>et al</i> ., 2017)

*Including food supplements.

[†]Percentage below the EAR was estimated excluding energy under-reporters.

2.4 Approaches to addressing low vitamin D intakes

Public health concerns about skin cancer and skin damage preclude recommending increased sun exposure as a means of enhancing vitamin D status. This places increased emphasis on addressing low vitamin D intakes through dietary means. Any intervention that is aimed at improving vitamin D intake must incorporate the concept of total vitamin D intake (i.e. reflecting the combined dietary contribution from foods (including fortified foods) and supplements), not just supplemental intake (Lanham-New *et al.*, 2020; Scientific Advisory Committee on Nutrition, 2016; Institute of Medicine, 2011). The World Health Organization (WHO) and the Food and Agriculture Organization of the United Nations (FAO) have suggested that there are three possible strategies for addressing inadequate micronutrient intake (Allen *et al.*, 2006). These include:

- i) Increasing the diversity of foods consumed
- ii) Supplementation
- iii) Food fortification.

Increasing the diversity of foods consumed

Increasing dietary diversity means increasing both the quantity and the range of micronutrient-rich foods consumed. However, in the context of vitamin D consumption, this is particularly challenging because the range of foods naturally rich in vitamin D is very limited, and the majority are foods of animal origin (oily fish and eggs – see <u>Table 4</u>). It is also worth noting that, in recent years, there has been a growing trend of people opting to reduce their consumption of dairy and meat to achieve a more environmentally sustainable flexitarian-type diet (Willett *et al.*, 2019). Thus, improving intake of naturally occurring vitamin D-rich foods and increasing the diversity of vitamin D-containing foods is arguably the strategy least likely to work, at least in the short to medium term (Cashman, 2020).

Table 4 Vitamin D content of natural and vitamin D-fortified foods per typical serving

Food	Serving size (household measure)	Vitamin D content (µg)
Natural food sources of vitamin D	inclear of	(19)
Salmon* Wild salmon (raw, flesh only) Farmed salmon (raw, flesh only) Pink/red salmon, canned in brine (drained weight)	100 grams (g) (palm of hand size)**	8.6 4.7 13.6/10.9
Trout* (rainbow, raw, flesh only) (rainbow, baked, flesh only)	100 g (palm of hand size)**	7.9 8.2
Mackerel* (raw, flesh only) (smoked/grilled, flesh only)	100 g (palm of hand size)**	8.0 8.2/8.5
Tuna* (baked, flesh only) (canned in brine/oil – drained, flesh only)	100 g (palm of hand size)**	3.1 1.1/1.1
Sardines* (grilled, flesh only) (canned in brine/oil – drained)	100 g (palm of hand size)**	5.1 3.3/3.6
Chicken eggs* (raw) (boiled/poached/fried in sunflower oil)	2 eggs	3.2 3.2/3.0/2.0
Meat (beef, pork, lamb; raw, average of various cuts)***	100 g (palm of hand size)**	0.5–0.8
Vitamin D-fortified foods****		
Milk with added vitamin D	200 millilitres (mL) (a glass)	2.0-4.0
Non-dairy milk alternatives with added vitamin D	200 mL (a glass)	1.5–2.2
Cheese with added vitamin D	One cheese string	1.3
Yogurt with added vitamin D	125 g (a pot)	0.8–5.0
Breakfast cereal with added vitamin D	30–40 g (a bowl)	0.8–3.4
Bread with added vitamin D	76 g (2 slices)	0.6–1.4
Dairy/non-dairy spreads with added vitamin D	10 g (a portion pack)	0.5–0.8

*Public Health England (2021)

**The width and depth of an individual's palm (without fingers and thumb) indicates how much meat, poultry of fish is needed in a day. This is best split between two meals. Using the size of the hand helps indicate how bigger people need more and smaller people need less. 100 g is taken as an average.

***Cashman and Hayes (2017)

****Nutrition labelling must be checked, as the types of foods fortified, and the amounts of vitamin D added to such foods, change continuously. The range of vitamin D content provided reflects differences among brands.

Vitamin D supplementation

There have been calls to promote the use of vitamin D supplements as a means of correcting low vitamin D intakes and status in the population, and vitamin D supplement use has been recommended as national policy in certain countries, particularly for at-risk population groups (Public Health England, 2016; Health Council of the Netherlands, 2012), especially infants (Health Service Executive, 2018; Munns *et al.*, 2016; Braegger *et al.*, 2013). This is not surprising in light of the clear evidence that vitamin D supplementation can significantly improve vitamin D intake and status (Calvo and Whiting, 2006). The WHO and FAO suggest that of the three strategies for increasing the population's intake of micronutrients, programmes that deliver micronutrient supplements often see the fastest improvement in the micronutrient status of individuals or the targeted population (Allen *et al.*, 2006). Supplementation has the advantage of being capable of supplying an optimal amount of a specific nutrient or nutrients in a highly absorbable form, and is often the fastest way to control deficiency in individuals or population groups that have been identified as being deficient (Allen *et al.*, 2006).

There have been a number of systematic reviews and meta-analyses of vitamin D RCTs which highlight the effectiveness of vitamin D supplementation in terms of improving vitamin D status across a variety of age, race, ethnic and gender groups (Autier *et al.*, 2012; Seamans and Cashman, 2009; Cranney *et al.*, 2007). This is irrespective of whether supplementation is with vitamin D₂ or D₃, albeit the latter has proved to be modestly better (Autier *et al.*, 2012). It should be noted that, while vitamin D₂ has always been suitable for vegetarians and vegans, supplements based on vitamin D₃ derived from non-animal sources, such as lichens, are now also available for those with plant-based diets.

Meta-analysis of IPD is considered the gold standard for synthesising evidence across several studies (Riley *et al.*, 2007), and thus is highest placed within the hierarchy of evidence.

The IPD meta-analysis of seven RCTs (conducted at latitudes above 50 °N) which used vitamin D supplements (Cashman *et al.*, 2017) shows that nearly all individuals (97.5%) will maintain their serum 25(OH)D above 30 nmol/L with vitamin D intakes of 10–15 μ g/d, as recommended in Section 2.2.

This is also borne out by evidence at a population level, whereby data from the NANS show that the prevalence of serum 25(OH)D concentrations <30 nmol/L among those who take a vitamin D supplement containing at least 10 μ g/d (and an additional mean intake of 4.5 μ g/d from food sources) was only 2%, compared with 12.8% among individuals who do not take vitamin D supplements (further analysis of the data presented in Cashman *et al.*, 2013b.

Thus, while supplementation is a viable option for increasing vitamin D status, supplements are only beneficial to those who consume them. However, it is important to note that in Ireland, nationally representative nutrition survey data show that only 19%, 8%, and 17% of children, teenagers, and adults, respectively, take a vitamin D-containing supplement. In addition, data for adults aged 55–59 years from the nationally representative TILDA show that only 6% of participants reported vitamin D supplement use (Laird and Kenny, 2020). In addition, the dose of vitamin D contained within the supplement is an important consideration. Vitamin D-containing supplements used in the national nutrition surveys in Ireland (covering the period from 2008 to 2020, depending on the survey) typically contain between 0.75 and 50 μ g per dose per day. In the above example of the NANS, only 26% of supplement users consumed doses of supplemental vitamin D of \geq 10 μ g/d.

A recent analysis of socio-demographic and knowledge-related determinants of vitamin D supplementation in the context of the COVID-19 pandemic in Slovenia highlights some key independent predictors of voluntary vitamin D supplementation (Žmitek et al., 2021). The study highlighted financial status as an independent predictor of vitamin D supplementation, with those with a below-average financial status having the lowest prevalence of vitamin D supplementation. Thus, policy-makers also need to consider the financial dimensions of vitamin D supplementation in order to ensure equity of access within the population (Žmitek et al., 2021). A recent publication by the Joint Committee on Health, Report on addressing Vitamin D deficiency as a public health measure in Ireland, driven largely in response to the COVID-19 pandemic, recommended that the cost of vitamin D supplements should be reduced in order to promote their uptake (Joint Committee on Health, 2021). The Joint Committee on Health suggested that the Government should consider the current value-added tax (VAT) applied to vitamin D supplements, with a view to either reducing or eliminating it. Data regarding the UK's Healthy Start food and vitamin voucher scheme for low-income pregnant women and families, and pregnant women aged under 18 years regardless of financial circumstances, show that the uptake of Healthy Start vitamins is extremely low among eligible families (McFadden et al., 2015). Thus, issues of cost and acceptability of, and access and adherence to, supplementation are critical considerations with regard to ensuring equitable benefit from vitamin D supplementation at population level.

The Slovenian study also found vitamin D-related knowledge to be a key predictor of dietary supplementation (Žmitek *et al.*, 2021). In another study regarding knowledge of, and attitudes and perceptions towards, vitamin D in a UK adult population, O'Connor *et al.* (2018) showed that individuals with better knowledge of vitamin D were more than two times as likely to take a vitamin D supplement than those with poorer knowledge. The Joint Committee on Health's recently published *Report on addressing Vitamin D deficiency as a public health measure in Ireland*

highlighted the need for an information campaign on the importance of vitamin D (Joint Committee on Health, 2021).

Food fortification with vitamin D

The WHO and FAO suggest that while supplementation often provides the fastest improvement in the micronutrient status of individuals or a targeted population, food fortification potentially has the widest and most sustainable impact (Allen *et al.*, 2006). Furthermore, as food fortification can be a very affordable way of correcting inadequate micronutrient intakes, it could be a very cost-effective public health intervention (Allen *et al.*, 2006). In terms of evidence, there have been a number of systematic reviews and meta-analyses of vitamin D RCTs which highlight the effectiveness of vitamin D-fortified foods in relation to increasing vitamin D intakes and improving vitamin D status (Dunlop *et al.*, 2021; Black *et al.*, 2012; O'Donnell *et al.*, 2008). As mentioned in the previous section, the IPD meta-analysis approach is the gold standard for evidence synthesis across several studies (Riley *et al.*, 2007):

A recent IPD meta-analysis of seven identified RCTs (conducted at latitudes above 50 °N) which used vitamin D-fortified foods (Cashman *et al.*, 2021) shows that nearly all individuals (97.5%) will maintain their serum 25(OH)D above 30 nmol/L with vitamin D intakes of 10–15 μ g/d, as recommended in <u>Section 2.2</u>.

It should be noted, however, that vitamin D-fortified foods in Ireland are not currently providing intakes of vitamin D at the above-mentioned protective levels. While 62-89% of children, teenagers and adults in Ireland consume some sort of vitamin D-fortified food(s) (for example, 38-41%, 26–48%, and 5–17% consume fat spreads, RTEBCs, and milk, respectively, among other foods), the impact of this food fortification with vitamin D on usual intake appears modest. For example, using the NANS data, Black et al. (2015) showed that the mean intake of vitamin D among Irish adults aged 18-64 years from foods in which it is naturally occurring was 2.7 µg/d; this increased to 4.4 µg/d when vitamin D-fortified foods were accounted for. This modest impact may stem from the fact that, under EU legislation (Regulation (EC) No 1925/2006), it is not mandatory for fortified foods on the market in Ireland to be fortified with vitamin D. Whether the fortification of foods with vitamin D is mandatory or voluntary can influence its impact within a population (Pilz et al., 2018). In addition, and beyond the type of fortification policy, the WHO and FAO point out that fortified foods need to be consumed in adequate amounts by a large proportion of the target population (Allen et al., 2006). Thus, a key challenge is finding a suitable industrially manufactured food that is consumed in sufficient amounts by the at-risk population (Allen et al., 2006). The cost and choice of food vehicle are also important considerations in terms of trying to ensure equity of access to these foods within the population (Allen et al., 2006). The WHO and FAO also highlight that consumer barriers to the success of food fortification may exist (Allen et al., 2006). Some

consideration of these three aspects of fortification of foods with vitamin D is provided in the following three sections.

Mandatory versus voluntary food fortification

Countries with mandatory fortification policies have vitamin D intakes that are about 2–3 µg greater than those with voluntary food fortification policies (McCourt and O'Sullivan, 2022). Finland is a good example of a European country where fortification of fluid milk products, as well as margarine and spreads, is widespread. While fortification is voluntary, it is recommendation-based and thus very close in effect to mandatory fortification in terms of its uptake by industry. In 2003, the Finnish Government introduced regulations for the optional fortification of milks and yogurt (at a level of 0.5 μ g vitamin D₃/100 g) as well as margarine and spreads (10 μ g vitamin D₃/100 g) (Tylavsky *et al.*, 2006); these were increased to 1 and 20 μ g of vitamin D₃/100 g, respectively, in 2010. The representative Finnish National Dietary Survey in Adults and Elderly (FINDIET) 2012 shows that milk and fat spreads contribute between 25% and 40% of the mean daily vitamin D intake of adults in Finland aged 25-74 years (Helldán et al., 2013), and that, from 2002 to 2012, the mean intake increased from 5 µg/d to 17 µg/d in men and from 3 µg/d to 18 µg/d in women (Raulio et al., 2017). A comparison of standardised serum 25(OH)D data from the Finnish Health 2000 (n=6134) and Health 2011 (n=4051) surveys show that the mean serum 25(OH)D concentrations increased from 48 nmol/L to 65 nmol/L, and prevalence of serum 25(OH)D concentrations <30 nmol/L decreased from 12% to <1% (Jääskeläinen et al., 2017). Similarly, in Sweden, an extended mandatory vitamin D fortification programme includes fortification of various milks and margarine/fat spreads with about 1 and 20 µg/100g of vitamin D (Itkonen et al. (2018). Fortified fat spreads are the secondhighest contributor to vitamin D intake in Swedish adults and children (Nälsén et al., 2020). In the Netherlands, fortified butter and margarine contribute 45% to the total vitamin D intake from food sources for older Dutch adults (Vaes et al., 2017).

In other European countries where fortification of milk is voluntary and the uptake of fortification is far lower than in Finland and Sweden, the impact of vitamin D-fortified milk and dairy on vitamin D intake is understandably low. For example, data from national nutrition surveys in Ireland show that in general, the percentage contribution that milk and yogurt make to the mean daily intake of vitamin D is in the range of 9–17% for those aged 5 years and older (Irish Universities Nutrition Alliance, 2021; Irish Universities Nutrition Alliance, 2020; Irish Universities Nutrition Alliance, 2011).

While all vitamin D-fortified foods are clearly labelled with information to indicate this fortification to consumers, policies of voluntary food fortification can make it very difficult for consumers to choose foods, as the food types and brands being fortified are continuously changing and the level of fortification within these foods can vary greatly (e.g. yogurts may be fortified with anywhere from

0.8 to 5.0 µg of vitamin D). This places a burden on consumers to keep checking labels as manufacturers can change the level of fortification, or stop fortifying foods completely, at any time. Fortified foods also tend to be more expensive (e.g. €1.55 per litre for a fortified milk versus €1.29 per litre for a non-fortified milk), making them less accessible to socioeconomically disadvantaged groups. This type of fortification is also difficult for competent authorities and governments to monitor due to the wide range of foods being fortified and the varying levels of fortification.

Mandatory food fortification is undertaken by governments to address public health issues and has many advantages over voluntary food fortification. Mandatory food fortification is developed to reach as many people as possible and is carefully modelled to avoid providing excess nutrients (in this case, vitamin D) to any population subgroup. Mandatory food fortification only uses one or two food vehicle(s) and one level of fortification, thus making it much easier for competent authorities and governments to monitor. Individuals who do not consume the fortified food can be easily identified and given guidance on alternatives for how they can achieve adequate intakes.

Food vehicles for fortification with vitamin D, beyond fluid milk products and spreads

Fortified milk makes a valuable contribution to vitamin D intakes among consumers, particularly in children, and there is continued need for fortification of milk and other dairy products. Nevertheless, it has been suggested that additional strategic approaches to fortification (including biofortification) of a wider range of foods to accommodate diversity have the potential to increase vitamin D intakes in the population and minimise the prevalence of risk of vitamin D deficiency and inadequacy (Cashman and Kiely, 2016; Kiely and Black, 2012). For example, the availability of vitamin D-fortified foods beyond cow's milk is particularly important for vegans and vegetarians.

The fortification of bread with vitamin D_3 has been shown to be effective in enhancing vitamin D status in RCT participants (Natri *et al.*, 2006) and is thought to be a promising vehicle for effective fortification strategies (Souza *et al.*, 2022). McCourt *et al.* (2020) used dietary modelling analysis, based on data from the nationally representative NANS, to determine the best foods for potential vitamin D food fortification for adults in Ireland aged 50 years and older. Bread and milk, as the most frequently consumed foods across all meals, were targeted for the data modelling exercise. The modelling showed that hypothetical fortification of milk or bread with a level of vitamin D sufficient to achieve a mean daily intake of 9 and 13 µg/d resulted in 31% or 56% of individuals, respectively, meeting a target intake of 10 µg/d; however, fortifying both staple foods simultaneously resulted in 71% of individuals meeting this target intake (see Table 5). This modelling assumed that 100% of the food products were fortified.

It should be noted, however, that while traditional fortification of bread with vitamin D_3 or D_2 has been shown to improve vitamin D status in the population – thus potentially making it a good food vehicle for omnivores as well as those with plant-based diets – there is a question mark over the approach of using ultraviolet (UV)-irradiated yeast for the purposes of increasing the vitamin D_2 content of bread. For example, an 8-week RCT, which investigated the bioavailability of vitamin D_2 from UV-irradiated yeast present in bread consumed by healthy 20–37-year-old women (n=33) in Helsinki (60 °N) during winter, showed that serum 25(OH)D concentrations did not change in those consuming the vitamin D_2 -fortified bread containing UV-irradiated yeast, whereas those receiving supplemental vitamin D (either D_3 or D_2) together with regular bread had appreciable increases in serum 25(OH)D concentrations (Itkonen *et al.*, 2016). Analysis of the bread containing UVirradiated yeast following baking confirmed that it contained the expected 25 µg of vitamin D_2 , which suggests that vitamin D_2 from UV-irradiated yeast in bread, despite being present postbaking, is not currently bioavailable for humans.

Beyond milk, margarine/spreads and bread, there are several other foods which have been fortified with vitamin D and for which there is evidence of their effectiveness in raising the vitamin D status of those who consume them. For example, RTEBCs fortified with vitamin D have also been shown to result in an increase in serum 25(OH)D concentrations across all cohorts (Calame *et al.*, 2020), and orange juice has been shown to increase serum 25(OH)D concentrations in healthy adults aged 18–84 years (Biancuzzo *et al.*, 2010). There is also RCT evidence showing how vitamin D-fortified cheese (including low-fat Gouda cheese) (Manios *et al.*, 2017; Al-Khalidi *et al.*, 2015; Johnson *et al.*, 2005) and yogurt (Neyestani *et al.*, 2012; Bonjour *et al.*, 2018) can increase serum 25(OH)D concentrations.

In Ireland, as mentioned previously, the impact of voluntary fortification of a range of foods with vitamin D on usual intake appears to be modest. Importantly, however, Black *et al.* (2015), using deterministic modelling, showed that median vitamin D intake could be increased from 3 μ g/d (with current voluntary fortification practices) to 12 μ g/d with hypothetical addition of vitamin D at relatively low increments to milk/alternatives, yogurt/alternatives, cream, cheese, fat spreads, fruit juice/drinks, RTEBCs and breads/rolls (see <u>Table 5</u>). This modelling assumed that 100% of these food products were hypothetically fortified.

In addition to traditional fortification, biofortification strategies have also been shown to successfully enhance micronutrient concentrations in a range of foodstuffs (Neill *et al.*, 2021; Jha and Warkentin, 2020; Guo *et al.*, 2018; Bouis and Saltzman, 2017; Hayes and Cashman, 2017). In this biofortification approach, animal-derived food products have increased their vitamin D and/or 25(OH)D₃ content by adding vitamin D and/or 25(OH)D₃ (where permissible) to the respective fish,

livestock or poultry feeds. Similarly, the fungi, yeast, and a very limited number of plant-based foods have increased their vitamin D content through UV irradiation (Hayes and Cashman, 2017).

The most researched – and, arguably, most promising – vitamin D-biofortified food to date is eggs. There is ample evidence that the vitamin D_3 and/or $25(OH)D_3$ content of eggs can be significantly increased by adding greater amounts of vitamin D_3 and/or commercially available $25(OH)D_3$ to the feed of hens (Hayes and Cashman, 2017). Additional vitamin D and/or $25(OH)D_3$ at levels adhering to the maximum allowed by EU regulation resulted in eggs with a total vitamin D content of about 5 µg per egg. Moreover, RCT evidence shows how eggs biofortified with vitamin D₃ and $25(OH)D_3$ (at 4–5 µg per egg) were effective in preventing serum 25(OH)D concentrations falling below 30 nmol/L during winter (Hayes *et al.*, 2016).

The feasibility of producing other vitamin D-biofortified animal-based foods has also been demonstrated, with variable levels of improvement in vitamin D content over that of equivalent, non-biofortified foods (reviewed by Cashman and Kiely (2022) and Neill *et al.* (2021)). For example, biofortified beef and pork with maximum vitamin D content levels of about 1.5 and 1.3 μ g/100 g, respectively, have been reported, but these have not been tested in RCTs (Cashman and Kiely, 2022; Neill *et al.*, 2021).

Dietary modelling has also been performed to estimate the hypothetical impact that adding vitamin D to the food chain using biofortified food strategies – such as eggs, beef and pork, either alone or in combination with the fortification of milk and cheese – would have on the intake of vitamin D by adults, as well as separately by children (aged 5–12 years) and adolescents, in Ireland. While the impacts of biofortification of single foods in isolation on the distributions of vitamin D intakes were relatively small, when all three foods (eggs, beef and pork) were biofortified, together with the fortification of milk and cheese, the modelling projected that mean and median intakes close to the EAR of 10 μ g/d would be achieved without increasing the risk of excessive intakes (Buttriss *et al.*, 2022) (Professor M Kiely, personal communication, 15 March 2022).

Table 5 Dietary modelling of the impact of hypothetical addition of vitamin D to various foods on projected vitamin D intake in the adults in the NANS

Modelling exercise	Fortification scenarios: foods [and hypothetical addition of vitamin D, in $\mu g/100~g]$	Vitamin D intake achieved (5 th , 95 th percentile) [% attaining EAR of 10 μg/d]	Reference
Adults: 18–64 years old	Current fortification practices	3 µg/d* (NR) [~10%]**	Black <i>et al</i> . (2015)
	Reduced-fat milk [2], yogurt [2], fat spreads [8], orange juice [2], RTEBCs [5]	7 μg/d* (NR) [~28%]**	Black <i>et al.</i> (2015)
	Reduced-fat milk [2], yogurt [2], fat spreads [8], orange juice [2], RTEBCs [5], milk and yogurt alternatives [2], bread [2]	9 μg/d* (NR) [~37%]**	Black <i>et al.</i> (2015)
	All milk and alternatives [2], yogurt and alternatives [2], cream [2], cheese [2], fat spreads [8], all fruit juice and drinks [2], RTEBCs [5], all bread and rolls [2]	12 μg/d* (NR) [~60%]**	Black <i>et al.</i> (2015)
Older adults: ≥50 years	Current intake of milk was substituted with milk fortified with 1.5 μ g/100 mL (except for some existing milk that is fortified at 2.5 μ g/100 mL, which was retained)	9 μg/d*** (2, 25 μg/d) [31%]	McCourt <i>et al.</i> (2020)
	Current intake of bread was substituted with bread fortified with 5 μ g/100 g	13 μg/d*** (4, 29 μg/d) [56%]	McCourt <i>et al.</i> (2020)
	Current intake of milk and bread was substituted with fortified versions (as above)	15 μg/d*** (6, 31 μg/d) [71%]	McCourt <i>et al.</i> (2020)

*Representing median intakes

Estimated from Figure 1 in Black *et al.* (2015) *Mean daily intake

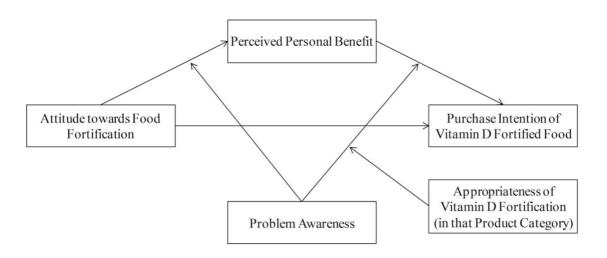
In terms of biofortification of foods beyond those which are animal-derived, UV irradiation of mushrooms, baker's yeast, and some plant foods (such as tomatoes) has been shown to stimulate their endogenous vitamin D_2 or D_3 content (Li *et al.*, 2022; Jäpelt and Jakobsen, 2013). As mentioned above, the bioavailability of vitamin D_2 in UV-irradiated baker's yeast appears to be poor (Itkonen *et al.*, 2016). A recent review of vitamin D_2 yields in different mushrooms after UV irradiation illustrated the large achievable range: $0.9-1340 \mu g/100 g$ dry weight after doses ranging from 0.2 to 379 J/cm² (Schümmer *et al.*, 2021). Thus, consuming vitamin D_2 -enriched mushrooms could be an important means by which vegans and vegetarians can increase their vitamin D intake. However, the RCT data demonstrating that the vitamin D_2 in UV-treated mushrooms can increase the vitamin D status of consumers has been quite mixed. A systematic review and meta-analysis of the impact of UV-exposed mushrooms on serum 25(OH)D response in six available RCTs showed that serum 25(OH)D was not significantly increased (*p*=0.12) by consuming UV-exposed mushrooms, but there was high heterogeneity within the analysis (*P*=87%). The effect of UV-irradiated plant foods on serum 25(OH)D has not been tested in human studies.

It should be noted that UV irradiation has also been explored as a means of increasing the vitamin D content of some animal-derived foods such as eggs, meat and cow's milk, and while increments have been reported (see review by Neill *et al.* (2021)), the wider cost-benefit analysis and other considerations around use of UV irradiation compared with adding vitamin D to animal feeds in terms of enhancing vitamin D content in foods would need to be examined.

Public attitudes towards food fortification with vitamin D

Fortification of foods with vitamin D has been shown to be technologically feasible and generally accepted by consumers from a taste/sensory perspective (Cashman and Kiely, 2022; Hayes *et al.*, 2016). However, there are a number of consumer considerations that must be taken into account for vitamin D fortification. Once fortification levels are approved and suitable foods identified, we then need to consider the complex psychological processes and influences underpinning individuals' consumption of fortified foods.

Figure 1 shows a conceptual model to understand consumers' attitudes towards vitamin D fortification that was proposed and tested by Jahn *et al.* (2019) in an adult Danish population.





Source: Jahn et al. (2019)

As seen in Figure 1, results from a large survey among Danish consumers (n=1263) indicate that purchase intention of vitamin D-fortified foods is mediated by perceived personal benefit. Therefore, if consumers are aware of the benefits and see the personal benefit of the product, then purchase intention will be high. Purchase intention will also be influenced by the level of problem awareness and whether consumers consider the food used for fortification to be appropriate. Therefore, a combination of positive attitude towards food fortification, awareness of what a vitamin D deficiency entails and the benefits of preventing it, and the perceived appropriateness of the food for vitamin D fortification are all essential considerations to take into account in order to incentivise consumers to purchase a vitamin D-fortified food. When asked about the appropriateness of foods for fortification, Danish consumers scored dairy products and bread highest, while they did not consider processed foods such as sausages and pâtés to be appropriate.

A study on vitamin D fortification in German adults (Sandmann *et al.*, 2015) showed that consumers' health awareness was an essential determinant of their acceptance of vitamin D-fortified food, and that public health campaigns to increase awareness can also increase likelihood of acceptance. Identification of appropriate communication channels is essential for any information campaign on vitamin D. Consumers' most preferred sources for nutritional information were physicians, health insurance companies and the Internet/television. In the same study (Sandmann *et al.*, 2015), approximately 18% of the population reported that they would not purchase vitamin D-fortified products if they saw them in store, with the main reasons cited as the products 'being too expensive' and 'fear of artificial additives'. Any public health campaigns on

vitamin D fortification should address these valid and important worries and concerns in a positive way.

A study of knowledge, attitudes and perceptions towards vitamin D in a UK adult population (O'Connor *et al.*, 2018) showed that perceptions of fortified foods varied among the participants (n=208): while 68% did not believe fortified foods were harmful, 24% were unsure and 8% believed they were harmful. Of the participants, 65% were willing to purchase or consume fortified foods, 24% were unsure and 11% were unwilling. The 16 participants who felt that fortified foods were harmful gave several reasons for their belief: fear of vitamin overdose (n=4), lack of choice (n=3), a desire to avoid processed food products (n=5), a belief that relying on fortified foods might eventually lead to less nutrition understanding (n=2) and a desire to achieve sufficient vitamin D status through natural sources (n=2).

A sample of non-users of supplements/fortified foods in Australia were surveyed to determine their willingness to accept a free trial of vitamin supplements or functional foods (O'Connor and White, 2010). Overall, the survey found that participants' attitudes towards the products in terms of how effective, good or healthy they were; their concern with social norms such as the behaviour or opinion of their peers; and perceptions of associated risk (such as overdose) all predicted respondents' willingness to use the products in a free trial.

The results of these four studies demonstrate the challenge policy-makers face when trying to promote food fortification as a means of increasing vitamin D intake in the population. A thorough understanding of consumer considerations – including, but not limited to, attitudes, awareness and product benefits – must be considered in all promotions to enhance awareness and acceptance of vitamin D-fortified products. Some of these challenges would be negated in the case of mandatory food fortification with vitamin D.

Should food fortification with vitamin D be considered the public health strategy with a potentially wider and more sustained impact, as per the WHO and FAO (Allen *et al.*, 2006), consideration should be given as to how to best communicate with the public and key stakeholders in order to raise awareness of the issues around vitamin D status, intakes and sources, and how to achieve behaviour change that results in improved intake. This is exemplified by the case of mandatory fortification of wheat flour in Mongolia triggered by the incidence of rickets. An initial public survey prior to fortification indicated that 55% of urban and rural Mongolians favoured fortification, but, after the population learned about the importance of vitamin D for the prevention of rickets, the percentage favouring fortification increased to 75% (Bromage *et al.*, 2019).

Conclusions

- The average vitamin D intake in children, teenagers and adults in Ireland who do not consume vitamin D-containing supplements is around 2–3 µg/d. Thus, while natural vitamin D food sources as well as (voluntarily) vitamin D-fortified foods will continue to play a role in individuals meeting the recommended vitamin D dietary intake of 10–15 µg/d, additional vitamin D supply of approximately 8–12 µg/d is needed, at least in part, in order to ensure that most people meet the dietary requirement.
- Use of vitamin D-containing supplements at appropriate doses (10–15 µg/d, depending on age group) can help close the gap between current and recommended intakes. It is important to stress, however, that supplements are only effective in those who consume them. Only 19% of children, 7% of teenagers and 16% of adults have reported taking vitamin D-containing supplements in national nutrition surveys that have been carried out in Ireland. Thus, if vitamin D supplements are to contribute more effectively to improved vitamin D intake at a population level, consideration must be given to methods of improving the cost and acceptability of, and access and adherence to, supplementation.
- Use of vitamin D-fortified foods can also help close this gap between current and • recommended intakes. While 62–89% of children, teenagers and adults consume some sort of vitamin D-fortified food(s), the average increase in vitamin D intake arising from the consumption of foods voluntarily fortified with vitamin D over that coming from natural sources only is modest (i.e. 0.7–1.7 µg/d, depending on age group). Thus, if vitamin Dfortified foods are to contribute more effectively to improved vitamin D intake at a population level, options include: 1) enhanced availability of a range of voluntarily vitamin D-fortified foods to accommodate diversity, which would represent an additional means of increasing vitamin D intakes across the population distribution of children, teenagers and adults in Ireland; and 2) consideration of mandatory fortification of some staple food(s) with vitamin D. which would likely have a greater impact. For example, countries with mandatory fortification policies have vitamin D intakes that are about $2-3 \mu g/d$ higher than in countries with voluntary food fortification policies. Mandatory fortification also has additional benefits compared with voluntary fortification in terms of increasing accessibility for those living on low incomes (voluntarily fortified foods are more expensive), and in terms of ease of public health monitoring of a fixed amount of vitamin D in a single food vehicle compared with varying amounts of vitamin D in multiple foods.

The findings from consumer-type studies highlight vitamin D-related knowledge as a key
predictor of the acceptability of vitamin D supplements and vitamin D-fortified foods to
consumers. Effective measures to improve knowledge of vitamin D supplementation and
food fortification within the population would contribute to better outcomes in relation to the
prevalence of serum 25(OH)D concentrations <30 nmol/L.

2.5 Consideration of safety issues around use of vitamin D supplements

The tolerable upper intake level (UL) is the highest level of long-term daily intake of a nutrient, from all sources, that is judged to be unlikely to pose a risk of adverse health effects to humans (EFSA Panel on Dietetic Products, Nutrition and Allergies, 2006). Following a review of ULs established by the EFSA (EFSA Panel on Dietetic Products, Nutrition and Allergies, 2012) and the IOM (Institute of Medicine, 2011) in the context of the safety of vitamins and minerals in food supplements, the Scientific Committee of the FSAI recommended that Ireland adopt the EFSA ULs for vitamin D of 50 µg (2000 international units (IU)) daily for children (aged 1–10 years) and 100 µg (4000 IU) daily for adolescents/teenagers (aged 11–17 years) and adults (aged 18 years and older) (Food Safety Authority of Ireland, 2020c). It is also important to note that the UK Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment and the UK Scientific Advisory Committee on Nutrition took account of the reviews by the EFSA and the IOM, along with other relevant research that had been published subsequently, and endorsed the vitamin D ULs of 50 µg/d for children and 100 µg/d for adolescents/teenagers and adults (Scientific Advisory Committee on Nutrition, 2016; Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment, 2014). The ULs from the USA, UK and EU authorities were established on the basis of minimising the risk of hypercalcaemia, the most well-recognised adverse effect of high vitamin D intakes, and using evidence from vitamin D supplementation studies (Food Safety Authority of Ireland, 2020c).

The vitamin D ULs of 50 and 100 μ g/d for children and adults, respectively, have been supported by recent studies that observed either no hypercalcaemia in adults aged 50 years and older who consumed 50 μ g of vitamin D per day for 5 years (Manson *et al.*, 2018), or only rare, mild, transient hypercalcaemia in adults aged 55–70 years who consumed 100 or 250 μ g of vitamin D per day for 3 years, with all cases resolved on repeat testing (Billington *et al.*, 2019; Burt *et al.*, 2019). In an RCT of children (mean age: 9.4 years) receiving 350 μ g of vitamin D weekly for 3 years, there was

one case of hypercalcaemia (Ganmaa *et al.*, 2020). In a multi-dose RCT during pregnancy (with doses of 105 μ g, 420 μ g or 700 μ g weekly), there were no episodes of confirmed hypercalcaemia during pregnancy (Roth *et al.*, 2018). Although higher vitamin D doses increased serum calcium and urinary calcium excretion postpartum, hypercalcaemia and hypercalciuria were infrequent in mothers and infants, even in the group receiving the highest dose of vitamin D (700 μ g weekly), and clinical adverse events did not differ significantly across groups (Roth *et al.*, 2018).

On the other hand, two recent RCTs in adults and older adults (\geq 55 years) have shown increased risk of hypercalcaemia/hypercalciuria at an intake of 250 µg of vitamin D daily for at least 1 year (Burt *et al.*, 2019; Aloia *et al.*, 2018a). The findings of these two RCTs suggest that the 'no observed adverse event level' is below 250 µg (10000 IU) daily and justify the adoption of an uncertainty factor by the governmental agencies in specifying the UL for vitamin D as 100 µg/d.

These governmental agencies considered the evidence for other potential adverse effects, which might occur at lower exposures, to be inconsistent (Scientific Advisory Committee on Nutrition, 2016; Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment, 2014; EFSA Panel on Dietetic Products, Nutrition and Allergies, 2012). This also seems to be the case for studies published following the establishment of the ULs by the authorities in the USA, UK and EU. For example, the evidence of adverse effects of vitamin D supplementation is inconsistent in trials of adults/older adults (with a mean age ranging from 62 to 77 years across studies), and of 1.0–4.3 years in duration, in which falls, fracture/fracture healing and/or bone mineral density (BMD) were assessed (see <u>Appendix 2</u>). The recent FSAI report, *Scientific Recommendations for Food-Based Dietary Guidelines for Older Adults in Ireland*, discussed some of these mixed findings in relation to falls and BMD and concluded that further research is needed on possible adverse effects of vitamin D at daily doses greater than 100 µg/d (Food Safety Authority of Ireland, 2021). The evidence of adverse effects of vitamin D supplementation is generally lacking in trials of adults/older adults as well as children and pregnant women which assessed outcomes other than hypercalcaemia/hypercalciuria or musculoskeletal health (see <u>Appendix 2</u>).

As mentioned previously, the UL is an estimate of the highest level of usual (long-term) intake of a nutrient which carries no appreciable risk of adverse health effects for nearly all people in a particular group. The UL is meant to apply to all groups of the general population, including sensitive individuals (such as pregnant women), throughout the life course. However, it is not meant to apply to individuals receiving the nutrient under medical supervision or to individuals with predisposing conditions that render them especially sensitive to one or more adverse effects of the nutrient, such as those with genetic predispositions or certain diseases (EFSA Panel on Dietetic Products, Nutrition and Allergies, 2006). In the case of vitamin D, these conditions include

idiopathic infantile hypercalcaemia and granulomatous conditions, such as sarcoidosis (Motlaghzadeh *et al.*, 2021; Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment, 2014; Jacobs and Bilezikian, 2005). For such individuals, intakes of micronutrients should be guided by medical advice (EFSA Panel on Dietetic Products, Nutrition and Allergies, 2006).

Use of the UL and the intake at the 95th percentile of the population (P₉₅, representing the higher consumers) can be used for risk assessment of vitamins and minerals in food supplements (Food Safety Authority of Ireland, 2020c). Accordingly, use of data from the National Children's Food Survey II (NCFS II), National Teens' Food Survey II (NTFS II) and NANS showed that daily intakes of vitamin D in higher consumers (i.e. P₉₅) among children (aged 5–12 years), teenagers (aged 13–18 years) and adults (aged 18–64 years) in Ireland are estimated at 10.1, 9.5 and 12.5 µg, respectively, from all sources (including supplements), and 7.0, 7.0, and 7.9 µg, respectively, from food sources only (including fortified foods) (Irish Universities Nutrition Alliance, 2021; Irish Universities Nutrition Alliance, 2020; Irish Universities Nutrition Alliance, 2011). Nationally representative data for vitamin D intakes in pregnant women and individuals of dark-skinned ethnicity in Ireland are not available.

Dietary modelling of these nationally representative survey samples predicts that daily consumption of a 10 or 15 μ g vitamin D supplement in addition to dietary consumption of vitamin D would increase daily vitamin D intake of high consumers (from foods) to about 15–17 μ g/d or 20–22 μ g/d, respectively, in both children and teenagers, and about 18–23 μ g/d in adults (see <u>Table</u> 6). While these total intakes are higher than the current intake of high consumers in all three age groups, all are well below the respective age-appropriate vitamin D ULs (50–100 μ g/d). Thus, a daily vitamin D supplement of 10 μ g or 15 μ g may be considered safe for children, teenagers and adults in Ireland. Daily supplementation is preferred to intermittent bolus because, in some studies, bolus doses at intermittent intervals have been associated with increased risk of fracture and falls in adults/older adults (Waterhouse *et al.*, 2021; Bischoff-Ferrari *et al.*, 2016; Sanders *et al.*, 2010; Smith *et al.*, 2007).

Table 6 Effect on total daily vitamin D intakes of adding a 10 or 15 μ g daily vitamin D supplement to intakes of high (P₉₅) vitamin D consumers from foods*

Population subgroup	P∍₅ vitamin D intake from food (µg/d)	Supplemental dose (µg/d)	Total dietary intake (µg/d)	UL (µg/d)
		10	15–17	
5–12-year-olds	5–7	15	20–22	50
		10	15–17	
13–17-year-olds	5–7	15	20–22	100
		10	18	
18–64-year-olds	8	15	23	100

*Using data from the NCFS II (5–12-year-olds) (Irish Universities Nutrition Alliance, 2020), NTFS II (13–17-year-olds) (Irish Universities Nutrition Alliance, 2021) and the NANS (18–64-year-olds) (Irish Universities Nutrition Alliance, 2011). Resulting total dietary intakes are compared with the relevant UL as per the FSAI (Food Safety Authority of Ireland, 2020c).

Dietary modelling of the Irish national food consumption data has also shown that consumption of vitamin D-fortified/biofortified foods as a means of improving vitamin D intake could be done without increasing the risk of excessive intakes in children, teenagers and adults in Ireland, even among those who are also consuming daily supplements containing 10 or 15 µg of vitamin D (Buttriss *et al.*, 2022) (Professor M Kiely, personal communication, 15 March 2022).

Thus, overall, for most children, teenagers and adults in Ireland, 10 or 15 μ g daily is a safe level of supplemental vitamin D, even when combined with vitamin D intake from base diet and fortified foods.

People should not have total vitamin D intakes (from all sources) greater than the age-appropriate UL (50 μ g/d for 5–10-year-olds and 100 μ g/d for those aged 11 years and older) because it could be harmful.

Industry-specific safety issues around vitamin D supplements

All food supplements placed on the Irish market must be notified to the competent authority, i.e. the FSAI (S.I. No. 506/2007, as amended). In addition to the UL (encompassing daily oral vitamin D intake from all sources, including base diet, fortified foods and food supplements), the FSAI has also published guidance for food business operators regarding the maximum safe levels (MSLs) of vitamins and minerals that can be added to food supplements in Ireland (Food Safety Authority of Ireland, 2020a). This guidance was based both on the relevant EU legislation and on the advice that the independent Scientific Committee provided to the FSAI in its report *The Safety of Vitamins and Minerals in Food Supplements – Establishing Tolerable Upper Intake Levels and a Risk*

Assessment Approach for Products Marketed in Ireland (Revision 2) (Food Safety Authority of Ireland, 2020c). The MSL for vitamin D is calculated using a risk assessment approach: the MSL is equal to the UL minus the estimated vitamin D intake of the highest consumers (95th percentile of intake from both base diet and fortified foods); this calculation also makes allowance for uncertainty in estimated intake, including possible future changes such as mandatory fortification of certain foods. The MSL for vitamin D in food supplements is 75 µg/d for teenagers and adults and 35 µg/d for children aged 5–10 years.

A recent assessment of vitamin D-containing food supplements (n=2689) notified to the FSAI between January 2017 and December 2021 found a year-on-year upward trend in the average daily amount of vitamin D provided by such supplements since the onset of the COVID-19 pandemic in 2020 (Figure 2), ranging from 10.6 µg/d in 2017 to 21.3 µg/d in 2021 (Lyons et al., 2022; McKenna et al., 2022). Of concern is the proportion of food supplement products notified that provide daily amounts of vitamin D exceeding the UL of 100 µg (1%, n=9) and the MSL of 75 µg (3%, n=80), the majority of which were notified during the COVID-19 pandemic (n=3 in 2017– 2019 compared with n=6 in 2020–2021 for those above the UL, and n=18 in 2017–2019 compared with n=62 in 2020-2021 for those above the MSL). Furthermore, the extent of the excess vitamin D provided has significantly increased. It was also noted that a large proportion of the notified food supplement products labelled the daily amount of vitamin D in IU (international units), not in µg (micrograms), which is the permitted unit in Ireland and the EU. The amount of vitamin D in µg can be calculated by dividing the IU by 40 (see Table 7 for some common µg and IU conversions). Use of the non-permitted IU on vitamin D products may lead to confusion for the consumer, especially as guidance on vitamin D supplementation issued by the Department of Health in Ireland uses the permitted measure of $\mu g/d$.

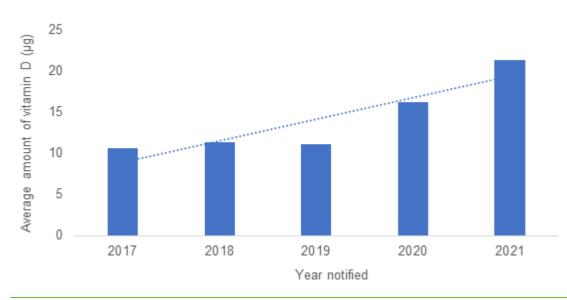


Figure 2 Average daily amount of vitamin D provided by vitamin D-containing food supplements notified to the FSAI between January 2017 and December 2021.

μg (micrograms)	IU (international units)	Alignment with Department of Health/FSAI recommendations
5 µg	200 IU	Supplemental daily amount for 1–5-year-olds (October–March)
10 µg	400 IU	Supplemental daily amount for 5–10-year-olds (October–March)
15 µg	600 IU	Supplemental daily amount for 11–65-year-olds (all year for pregnant women and people of dark-skinned ethnicity October–March for everyone else)
25 µg	1000 IU	UL* for infants aged up to 12 months
35 µg	1400 IU	MSL** for 5–10-year-olds
50 µg	2000 IU	UL for 1–10-year-olds
75 µg	3000 IU	MSL for everyone aged 11 years and older
100 µg	4000 IU	UL for everyone aged 11 years and older

Table 7 Vitamin D unit conversion table for vitamin D supplements

*Warning: The UL is not a recommended level of intake but rather the highest level of total intake deemed safe. As intake increases above the UL, the potential risk of adverse effects increases (Food Safety Authority of Ireland, 2020c). **Warning: The MSL is not a target intake but rather a guideline value for the safe maximum amount of vitamin D present in food supplements per daily dose as recommended by the manufacturer (Food Safety Authority of Ireland, 2020a).

Food businesses should follow the FSAI guidance that vitamin D supplements should not exceed the age-appropriate MSL (35 μ g for 5–10-year-olds and 75 μ g for those aged 11 years and older) in order to help ensure that people do not exceed safe intake levels.

3. Recommendations

3.1. Scientific recommendations on vitamin D nutrition for the population aged 5–65 years in Ireland

The following total daily intakes of vitamin D would minimise the risk of vitamin D deficiency for children, teenagers and adults in Ireland:

- 10 µg for healthy children (aged 5–11 years)
- 15 µg for healthy teenagers and adults (aged 12–65 years, including pregnant women) of all ethnicities.

Regarding vitamin D food supplements for children, teenagers and adults in Ireland, the key points are as follows:

- For healthy children (aged 5–11 years) who get sunlight exposure during summer:
 - For those of fair-skinned ethnicity, a daily vitamin D supplement containing 10 µg (400 IU) taken during the extended winter months (end of October to March) is expected to meet their requirements.
 - For those of darker-skinned ethnicity, a daily vitamin D supplement containing 10 μg (400 IU) taken throughout the full year is expected to meet their requirements.
- For healthy teenagers and adults (aged 12–65 years) who get sunlight exposure during summer:
 - For those of fair-skinned ethnicity, a daily vitamin D supplement containing 15 µg (600 IU) taken during the extended winter months (end of October to March) is expected to meet their requirements.
 - For those of darker-skinned ethnicity and for individuals of all ethnic groups who are pregnant, a daily vitamin D supplement containing 15 μg (600 IU) taken throughout the full year is expected to meet their requirements.

A daily vitamin D supplement of 10 μ g for children and 15 μ g for teenagers and adults in Ireland is considered safe.

Issues of cost and acceptability of, and access and adherence to, supplementation must be addressed in order to achieve equitable benefit from vitamin D supplementation at population level.

Regarding food sources of vitamin D for children, teenagers and adults in Ireland, the key points are as follows:

- Diets that include regular intake of natural sources of vitamin D such as oily fish, eggs, and meats – help to meet vitamin D requirements.
- Diets that include regular intake of vitamin D-fortified foods help to meet vitamin D requirements. This report provides examples of the types of vitamin D-fortified foods which can make meaningful contributions towards recommended intakes.
- Fortification of foods with vitamin D may be mandatory or voluntary for manufacturers. An appropriately implemented programme of mandatory fortification of a staple food(s) would offer the major advantage of widespread access to vitamin D at no extra cost to consumers. This may be of particular importance for those who have limited exposure to sunlight and have difficulty in consistent access to an adequate supply of foods naturally rich in vitamin D, as well as those for whom accessing and adhering to a supplemental regimen is difficult. Guidance should be provided to food manufacturers to support the effectiveness of the chosen approach.
- Consumption of a combination of vitamin D-fortified foods is safe for children, teenagers and adults in Ireland, even for those taking daily supplements containing 10 or 15 µg of vitamin D.

Consideration should be given as to how best to communicate with the public and key stakeholders in order to raise awareness of the issues around dietary intake, status and sources of vitamin D, and how to achieve the necessary behavioural changes that result in improved intakes and status.

3.2. The role of food businesses in relation to vitamin D

This report also includes industry-specific details relating to adherence to the MSLs in terms of the amount of vitamin D in food supplements placed on the Irish market and the use of μ g for measuring vitamin D in these supplements.

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Appendix 1 Request for Advice from the Scientific Committee

Topic Title: Scientific Recommendations for vitamin D supplementation in the population aged between 5 and 65 years²

Date Requested: 18th October 2021

Date Accepted: 18th October 2021

Target Deadline for Advice: 31st March 2022

Form of Advice required: Report with recommendations

Background/Context

The Scientific Committee, as part of its consideration of national policy and food-based dietary guidelines, has previously developed scientific recommendations for vitamin D supplementation of infants (birth–12 months) (Food Safety Authority of Ireland, 2020d), young children (1–5-year-olds) (Food Safety Authority of Ireland, 2020b) and older adults (aged 65 years and older) (Food Safety Authority of Ireland, 2020e). However, the population group that has yet to be considered regarding vitamin D supplementation is those aged 5–65 years.

It is well known that there are significant levels of low intake of vitamin D and vitamin D deficiency across this population group (Irish Universities Nutrition Alliance, 2021; Irish Universities Nutrition Alliance, 2020; Irish Universities Nutrition Alliance, 2011). Vitamin D deficiency has also been shown to be more prevalent among those living in more deprived areas (Scully *et al.*, 2020).

Vitamin D is obtained from two sources: skin synthesis from exposure to ultraviolet B (UVB) sunlight; and dietary sources, including natural food sources, fortified foods and food supplements. As Ireland experiences a 'vitamin D winter' of 5 to 6 months a year, during which lack of sufficient UVB radiation limits the potential for synthesis of vitamin D through the skin, the Irish population is at risk of vitamin D deficiency (Kilbane *et al.*, 2014). A seasonal variation in vitamin D deficiency has been shown to exist, with some studies reporting that vitamin D status is significantly lower during the winter months in young children (Ní Chaoimh *et al.*, 2018), adults (Cashman *et al.*, 2013a) and older adults (Laird *et al.*, 2018; O'Sullivan *et al.*, 2017; McCarroll *et al.*, 2015). It is

² In the course of its work the Scientific Committee adjusted the scope of the Request for Advice.

widely accepted that vitamin D has a role in bone health and immune function (Lanham-New *et al.*, 2020). There may be some benefit from daily, low-dose vitamin D supplementation (between 10 and 25 micrograms (µg) per day) in reducing risk of acute respiratory tract infections (Scientific Advisory Committee on Nutrition, 2020).

The European Food Safety Authority (EFSA) tolerable upper intake level (UL) for vitamin D from all sources is 50 µg daily for 5–10-year-olds and 100 µg daily for those aged 11 years and older (EFSA Panel on Dietetic Products, Nutrition and Allergies, 2012). While vitamin D can be obtained from a number of sources, including summer sunlight exposure (including that which is inadvertent), natural foods and fortified foods (of which the availability is ever increasing), given that vitamin D deficiency is so prevalent in this population group, a low-dose vitamin D supplement may be required. To avoid potential harm, vitamin D intakes should not exceed ULs, and high-dose vitamin D supplements should be avoided (Food Safety Authority of Ireland, 2020e; Kilbane *et al.*, 2014).

There is great confusion among the public regarding the role of vitamin D supplementation. There are many excessively high-dose vitamin D supplements available on the Irish market. Therefore, providing science-based recommendations regarding vitamin D supplementation in this age group will have significant benefits for population health.

Questions to be addressed by the Scientific Committee

The Scientific Committee is requested to deliver scientific advice for population-based guidance to the Department of Health that addresses the following questions:

- What are the current vitamin D intake levels and vitamin D status (including seasonal variation, if available) in the population aged 5–65 years in relation to dietary requirements and serum 25-hydroxyvitamin D threshold concentrations, respectively?
- 2. What, if any, are the considerations around reduced vitamin D synthesis from sun exposure in terms of vitamin D requirements in those aged 5–65 years?
- 3. How best can vitamin D requirements in those aged 5–65 years be achieved from food and, if necessary, food supplementation, taking total vitamin D intake into consideration?
- 4. What, if any, are the food safety issues?

The use of vitamin D for therapeutic purposes for treatment or prevention of specific infectious diseases is outside the scope of this Request for Advice.

Appendix 2

Summary of vitamin D randomised controlled trials regarding benefits (skeletal and extra-skeletal) and adverse effects

Study (year)	Vitamin D dose ^a	Duration	Participants	Number of participants	Baseline 25(OH)D (nmol/L)	Age (years)	Primary outcome(s)	Result(s)	Adverse effect(s)	Comment
Sanders <i>et al</i> . (2010)	12 500 micrograms (μg) (500 000 international units (IU)) yearly	3 years	Older women at risk of hip fracture	2256	49 (IQR 40-63) n=137 randomly selected for serial blood sampling for 25- hydroxycholecal ciferol and parathyroid hormone levels	76 (IQR 73-80)	Fracture	No benefit	Increased risk of fractures and falls	
Smith <i>et al.</i> (2007)	7500 µg (300 000 IU) yearly	3 years	Community- dwelling older adults	9440	Data not adequate	79 (IQR 77-83)	Fracture	No benefit	Increased fractures in women	
Randomised Evaluation of Calcium Or vitamin D (RECORD) (Grant <i>et al.</i> , 2005)	20 µg (800 IU) daily	24–62 months	Prior low- trauma fracture, aged over 70 years	5292	56±16 n=60 had blood collected for 25(OH)D measu red using straight-phase HPLC at baseline and 1 yr later	77±6	Fracture	No benefit of vitamin D, calcium, or both	None mentioned	Factorial design with calcium 1000 milligrams (mg)
Bischoff- Ferrari <i>et al.</i> (2016)	600 μg (24 000 IU), 1500 μg (60 000 IU), or 600 μg (24 000 IU) with 300 μg	12 months	Home- dwelling adults aged over 70 years with history of falls	200	48±22 ^b	78±5 ^b	Lower extremity function	No benefit	Increased risk of falls for both higher doses	

Study (year)	Vitamin D dose ^a	Duration	Participants	Number of participants	Baseline 25(OH)D (nmol/L)	Age (years)	Primary outcome(s)	Result(s)	Adverse effect(s)	Comment
	25(OH)D ₃ monthly									
Uusi-Rasi et al. (2015); Uusi-Rasi et al. (2017)	20 µg (800 IU) daily	2 years	Healthy women	409	67±18 ^b	74±3 ^b	Falls	No benefit	None	Factorial design with exercise
D-Health Trial (Waterhouse <i>et al</i> ., 2021)	1500 μg (60 000 IU) monthly	4.3 years	Healthy adults	21 315	78±25 (sample of placebo group)	60–84	Falls	No benefit	Higher risk of falls in vitamin D in those with body mass index <25.0	
Study To Understand Fall Reduction and Vitamin D in You (STURDY) Trial (Guralnik <i>et</i> <i>al.</i> , 2022; Juraschek <i>et</i> <i>al.</i> , 2022 Appel <i>et al.</i> , 2021; Wanigatunga <i>et al.</i> , 2021)	5 μg (200 IU), 25 μg (1000 IU), 50 μg (2000 IU), or 100 μg (4000 IU) daily	2 years	Older adults with high risk of falls and 25(OH)D <75 nmol/L	688	55±13	77±5	Falls, fall- related fracture, physical functioning, and orthostatic hypotension	No benefit	Higher risk of serious falls and fall-related fracture when given doses ≥25 µg per day	
Vitamin D Assessment (ViDA) Sub- Study (Reid <i>et al.</i> , 2017)	2500 μg (100 000 IU) monthly	2 years	Healthy adults	452	56±22 ^b	69±7 ^b	Lumbar bone mineral density (BMD)	No benefit	None	
Aloia <i>et al.</i> (2018a)	60 μg (2400 IU), 90 μg (3600 IU), or	3 years	Healthy Black women	260	55±17	68 (65– 73)	Femur BMD	No benefit	None	

Study (year)	Vitamin D dose ^a	Duration	Participants	Number of participants	Baseline 25(OH)D (nmol/L)	Age (years)	Primary outcome(s)	Result(s)	Adverse effect(s)	Comment
	120 μg (4800 IU) variable dose to maintain 25(OH)D >75 nmol/L				(serum 25(OH)D >20 and <65 nmol/L)					
Burt et al. (2020); Burt et al. (2019)	10 μg (400 IU), 100 μg (4000 IU), or 250 μg (10 000 IU) daily	3 years	Healthy adults	311	79±19 ^b	62±4 ^b	Volumetric BMD and bone strength at radius and tibia	No benefit	Decreased BMD at radius and tibia in women; hypercalcaemia and hypercalciuria demonstrated a significant dose- response effect	
Heyer <i>et al.</i> (2021)	750 μg (30 000 IU) or 1875 μg (75 000 IU) twice, 6 weeks apart	12 weeks	Individuals with distal radius fractures	32	60 (36–89) ^b	65 (58– 75) ^b	Fracture healing	No benefit	Detrimental to restoring bone stiffness after fracture	
Aloia <i>et al.</i> (2018b)	15 μg (600 IU) or 250 μg (10 000 IU) daily	1 year	Healthy adults	132	69±16 ^b	62 (58, 68) ^b	Hypercalciuri a	Increased risk of hypercalciuria		Calcium 1200 mg per day
VITamin D and OmegA-3 TriaL (VITAL) (Hahn et al., 2022; LeBoff et al., 2022; Albert et al., 2021; LeBoff et al., 2020a; LeBoff et al.,	50 μg (2000 IU) daily	5.3 years	Healthy adults	25 871	77 <u>±2</u> 5 n=15787	67±7	Cardiovascul ar disease, cancer, falls, atrial fibrillation, BMD, fracture and autoimmune disease	No benefit, except reduction in autoimmune disease	None	Factorial design with Omega-3

Study (year)	Vitamin D dose ^a	Duration	Participants	Number of participants	Baseline 25(OH)D (nmol/L)	Age (years)	Primary outcome(s)	Result(s)	Adverse effect(s)	Comment
2020b; Manson <i>et al.</i> , 2019)										
ViDA (Scragg <i>et al.</i> , 2017)	2500 µg (100 000 IU) monthly	3.3 years	Healthy adults	5108	56±23 ^b	50–84	Cardiovascul ar disease	No benefit	None	
DO-HEALTH (Bischoff- Ferrari <i>et al.</i> , 2020)	50 μg (2000 IU) daily	3.0 years	Healthy adults	2157	56±21 ^b	75±5 ^b	Fractures, blood pressure, physical function, infection, and cognition	No benefit	None	Factorial design with Omega-3
Finnish Vitamin D Trial (FIND) (Virtanen <i>et</i> <i>al.</i> , 2022)	35 μg (1600 IU) or 70 μg (3200 IU) daily	4.3 years	Healthy adults	2495	75±18	68±6	Cardiovascul ar disease, cancer	No benefit	None	
Lappe <i>et al</i> . (2017)	50 μg (2000 IU) daily	4 years	Healthy women	2303	82±26 ^b	65±7 ^b	Cancer	No benefit	None	Calcium 1500 mg also given to treated group
Jorde <i>et al.</i> (2016)	500 μg (20 000 IU) weekly	5 years	Individuals with pre- diabetes	511	62±9 ^b	60±22 ^b	Diabetes	No benefit	1 treated participant had hypercalcaemia	
Vitamin D and Type 2 Diabetes (D2d) trial (Pittas <i>et al.</i> , 2019)	100 µg (4000 IU) daily	2.5 years	Individuals with pre- diabetes	2423	70±25	60±10	Diabetes	No benefit	None	
Mousa <i>et al.</i> (2017)	2500 µg (100 000 IU) bolus	12 weeks	Individuals with obesity and	65	33±11 ^b	30 (25– 37) ^b	Insulin sensitivity	No benefit	Not mentioned	

Study (year)	Vitamin D dose ^a	Duration	Participants	Number of participants	Baseline 25(OH)D (nmol/L)	Age (years)	Primary outcome(s)	Result(s)	Adverse effect(s)	Comment
	followed by placebo or 100 µg (4000 IU) daily		25(OH)D concentratio n <50				and secretion			
Maternal Vitamin D Osteoporosis Study (MAVIDOS) (Cooper et al., 2016)	25 µg (1000 IU) daily	From 14– 17 weeks' gestation to term	Pregnant women	569 mothers, 737 infants	46±17 ^b	31±5 ^b	Infant whole body mineral content at 2 weeks	No benefit	None	
Vitamin D Antenatal Asthma Reduction Trial (VDAART) (Litonjua et al., 2016)	10 μg (400 IU) or 110 μg (4400 IU) daily	From 10– 18 weeks' gestation to term	Pregnant women	876 mothers; 806 mothers & infants for childhood outcome measures	67.5±15 ^b	27.3±5. 6 in the 400 IU/d group; 27.5±5. 5 in the 4400 IU/d group	Asthma in early childhood	No benefit	None	
Copenhagen Prospective Studies on Asthma in Childhood (COPSAC) (Chawes <i>et</i> <i>al.</i> , 2016)	10 µg (400 IU) or 60 µg (2400 IU) daily	From 24 weeks' gestation to term	Pregnant women	623 mothers, 581 children	Not given	32.3±4. 3	Persistent wheeze at 3 years of age	No benefit	None	
Roth <i>et al.</i> (2018)	105 µg (4200 IU), 420 µg (16800 IU) or 700 µg (28	From 17– 24 weeks' gestation to term	Pregnant and lactating women	1300 mothers, 1164 infants	27±7 ^b	23 (absolu te range: 18–40)	Infant growth	No benefit	Risk of possible maternal hypercalciuria at birth increased with dose	

Study (year)	Vitamin D dose ^a	Duration	Participants	Number of participants	Baseline 25(OH)D (nmol/L)	Age (years)	Primary outcome(s)	Result(s)	Adverse effect(s)	Comment
	000 IU) weekly up to 26 weeks postpartum									
Rajakumar <i>et</i> <i>al</i> . (2020)	15 μg (600 IU), 25 μg (1000 IU), or 50 μg (2000 IU) daily	6 months	10–18-year- olds with obesity and 25(OH)D concentratio n <50	225	36±9	14±2	Endothelial function	No benefit	None	
Ganmaa <i>et al.</i> (2020)	350 μg (14 000 IU) weekly	3.0 years	Children	8851	30±10	9.4±1.6	Preventing tuberculosis	No benefit	Hypercalcaemia in 1 child	

^a All randomised controlled trials were placebo-controlled, in which vitamin D was not administered to the control group, except the STURDY Trial (Guralnik *et al.*, 2022; Juraschek *et al.*, 2022; Appel *et al.*, 2021; Wanigatunga *et al.*, 2021) (which administered 5 µg per day to the control group), the study by Aloia *et al.* (2018b) (which administered 15 µg to the control group), VDAART (Litonjua *et al.*, 2016) (which administered 10 µg to the control group), and the study by Rajakumar *et al.* (2020) (which administered 15 µg to the control group).

^b Results are presented as approximations of either mean ± standard deviation or median (interquartile range), if baseline results are only given for groups and not the total sample. 25(OH)D: 25-hydroxyvitamin D, IQR: interquartile range, nmol/L: nanomoles per litre

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