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ORIGINAL CONTRIBUTION

Individual participant data (IPD)-level meta-analysis of randomised controlled trials with vitamin D-fortified foods to estimate Dietary Reference Values for vitamin D

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Abstract

Context and purpose Individual participant data-level meta-regression (IPD) analysis is superior to meta-regression based on aggregate data in determining Dietary Reference Values (DRV) for vitamin D. Using data from randomized controlled trials (RCTs) with vitamin D_3-fortified foods, we undertook an IPD analysis of the response of winter serum 25-hydroxyvitamin (25(OH)D) to total vitamin D intake among children and adults and derived DRV for vitamin D.

Methods IPD analysis using data from 1429 participants (ages 2–89 years) in 11 RCTs with vitamin D-fortified foods identified via a systematic review and predefined eligibility criteria. Outcome measures were vitamin D DRV estimates across a range of serum 25(OH)D thresholds using unadjusted and adjusted models.

Results Our IPD-derived estimates of vitamin D intakes required to maintain 97.5% of winter 25(OH)D concentrations ≥ 25 and ≥ 30 nmol/L are 6 and 12 µg/day, respectively (unadjusted model). The intake estimates to maintain 90%, 95% and 97.5% of concentrations ≥ 50 nmol/L are 33.4, 57.5 and 92.3 µg/day, respectively (unadjusted) and 17.0, 28.1 and 43.6 µg/day, respectively (adjusted for mean values for baseline serum 25(OH)D, age and BMI).

Conclusions IPD-derived vitamin D intakes required to maintain 90%, 95% and 97.5% of winter 25(OH)D concentrations ≥ 50 nmol/L are much higher than those derived from standard meta-regression based on aggregate data, due to the inability of the latter to capture between person-variability. Our IPD provides further evidence that using food-based approaches to achieve an intake of 12 µg/day could prevent vitamin D deficiency (i.e., serum 25(OH)D < 30 nmol/L) in the general population.

Keywords Vitamin D recommendations · Dietary reference values · Recommended dietary allowance · Individual participant data-level meta-regression analyses · Vitamin D-fortified foods

Abbreviations

25(OH)D	25-Hydroxyvitamin D
AI	Adequate intake
DRI	Dietary reference intake
DRV	Dietary reference values
EAR	Estimated average requirement
EFSA	The European Food Safety Authority
FFQ	Food frequency questionnaire
IOM	Institute of Medicine
IPD	Individual participant data
NNR	The Nordic Council of Ministers' Nordic Nutrition Recommendations
RCT	Randomized controlled trial
RDA	Recommended dietary allowance
RI	Recommended intake
RNI	Reference nutrient intake
SACN	The Scientific Advisory Committee on Nutrition
UVB	Ultraviolet B

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WHO-FAO	World Health Organisation–Food and Agriculture Organization
SR-MA	Systematic reviews and meta-analyses

Introduction

There is widespread acknowledgement of the presence of vitamin D deficiency in the general population [1–3]. A serum 25-hydroxyvitamin D (25(OH)D) concentration of 30 nmol/L represents a cut-off below which the risk of clinical vitamin D deficiency increases, manifesting as nutritional rickets in children and osteomalacia in adults [4]. The prevalence of serum 25(OH)D < 30 nmol/L has been recently reported as 13%, 8.8% and 5.0% for representative population samples in Europe, Canada and the US, respectively [2, 5, 6]. These population-wide prevalence estimates, when coupled with current population size data, crudely suggest 20 and 97 million individuals in the US plus Canada and Europe, respectively, are at increased risk of clinical vitamin D deficiency. Thus, the first key priority from a public health perspective is to ensure that this risk is minimized [1, 2]. It should be noted also that beyond deficiency, several [4, 7, 8], but not all [9], expert bodies briefed with development of dietary recommendations for vitamin D, using musculoskeletal health as the primary basis and some extra-skeletal health outcomes to a much lesser extent, proposed 50 nmol/L as the concentration of serum 25(OH)D that would meet the physiological vitamin D requirement of nearly all 'normal healthy persons'. While it has also been suggested that in terms of extra-skeletal health, serum 25(OH)D concentration should exceed 75 nmol/L [10], a number of recent umbrella reviews in the area [11–13] as well as the findings of some expert bodies [7, 8], do not support the assertion that circulating 25(OH)D concentrations above 50 nmol/L are needed by all individuals for the prevention of non-skeletal diseases.

In the absence of sufficient ultraviolet B (UVB) radiation availability and/or exposure to enable vitamin D synthesis in the skin, dietary supply of vitamin D is critical to meeting population requirements and prevention of deficiency [14]. The median of average vitamin D intakes from various national nutrition surveys in Europe was ~ 3 µg/day [15, 16] and ~ 7 µg/day in Canada and the US [17, 18], highlighting how the majority of individuals in these regions, with the exception of some Nordic countries, are considered to have inadequate intakes [15, 17, 18]. This widespread dietary inadequacy is because there are very few rich natural food sources of vitamin D, the major ones being oily fish, egg yolks, and vitamin D-fortified products in some countries [14, 15, 18, 19]. In terms of potential strategies for addressing inadequate micronutrient intake, the World Health Organisation–Food and Agriculture Organization (WHO–FAO) have suggested that food fortification has the widest and most sustained impact, and thus represents a very cost-effective public health intervention [20].

Importantly, two systematic reviews and meta-analyses (SR-MA) have provided a key evidence-base for the efficacy of food fortification in adults in the form of data from up to 16 separate randomized controlled trials (RCTs) from around the world [21, 22]. While these provide evidence at the highest level that food fortification increases serum 25(OH)D in a RCT setting, 12 of the 16 RCTs used dairy products as a food vehicle and 9 of these were milk/milk powder-based [21]. The valuable contribution vitamin D-fortified milk makes to vitamin D intakes, particularly in children, and the continued need for vitamin D fortification of milk and other dairy products is widely acknowledged [23, 24]. However, it has been suggested that vitamin D fortification of a wider range of foods, which accommodate diversity, is likely to have the potential to increase vitamin D intakes across the population distribution and minimize the prevalence of low serum 25(OH)D [21, 23]. Since the publication of the two SR-MA (7 and 12 years ago [21, 22]), and particularly considering the diversification of food vitamin D fortification beyond milk, several new RCTs of vitamin D-fortified foods have been published (reviewed in 14,25). A recent SR-MA of vitamin D RCTs in children (ages 2–18 years) reported a significantly greater response of serum 25(OH)D per 2.5 µg vitamin D_3 increment/day in trials using fortified foods compared to those with daily vitamin D supplements [26]. While the reason for this finding is not known, it is of note, as internationally the Dietary Reference Values (DRV) or equivalents for vitamin D have for the most part been established using dose–response data from RCTs with vitamin D_3 supplements [4, 7–9]. Increasingly, the use of individual participant data (IPD)-level meta-regression analysis is recognized as best practice [27], as it avoids some of the limitations intrinsic to standard meta-regression based on aggregate data [28, 29]. None of the three SR-MA [21, 22, 26] had access to individual data from the included RCTs so they were unable to undertake IPD-level meta-regression. Similarly, most recent DRV for vitamin D were based on standard meta-regression of aggregate data [4, 7, 8], mainly from supplementation trials.

Thus, the aims of the present work were firstly, through the process of a systematic review, to identify RCTs with vitamin D_3-fortified foods and subsequently use their individual data to undertake a priority IPD meta-regression analyses of the response of winter serum 25(OH)D to total vitamin D_3 intake in both children and adults. Secondly, to compare our IPD-derived vitamin DRV estimates based on vitamin D_3-fortified food RCTs with international DRV which were largely based on vitamin D_3-supplement RCTs; as well as comparing these estimates with those from our previous IPD (also based on vitamin D_3-supplement RCTs).

Materials and methods, including scientific approach

The methodology in the present work follows the general methodology for systematic reviews as well as the more specialized IPD meta-regression analysis in the area of the vitamin D intake-serum 25(OH)D response applied previously [19, 28, 30–32], with brief details as follows:

Adherence to IPD guidelines and registration

The present IPD meta-regression analysis of data from food-based vitamin D RCTs follows the guidance provided as part of the PRISMA (*Preferred Reporting Items for Systematic Reviews and Meta-Analyses)*-IPD statement [33]. The overall process can be considered a set of sequential steps starting with a systematic review to identify the appropriate vitamin D RCTs and culminating in statistical analyses that estimates the dose–response relationship, and hence the DRV for vitamin D, utilizing the pooled data of individual participants from all included RCTs [28, 29, 34].

The IPD meta-regression analysis was registered with the PROSPERO International Prospective Register of Systematic Reviews (registration number: CRD42018097260; https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=97260).

Ethics approval

Approval by a research ethics committee to conduct this meta-analysis was not required because the aim of this secondary analysis was consistent with the ethical approval received for the individual studies. The current analysis was conducted on anonymized data.

Systematic review to identify eligible papers

Eligibility criteria

The following outlines eligibility criteria for the food-based vitamin D RCTs for inclusion in the IPD-level meta-regression analysis to estimate the DRV for vitamin D. As with our previous IPD [28], the current IPD followed an approach that prioritized the identification of the vitamin D intake values to maintain serum 25(OH)D concentrations above chosen cut-offs when UVB-induced skin synthesis of vitamin D is absent or markedly diminished. This is closely aligned with the predefined criteria used by the Institute of Medicine (IOM) in their 2011 *Vitamin D and Calcium Dietary Reference Intake* (DRI) exercise [4] to select RCTs considered most appropriate to address the specific question of setting dietary requirements for vitamin D to meet prespecified 25(OH)D thresholds and is similar to that taken by the Nordic Council of Ministers' *Nordic Nutrition Recommendations* (NNR) [8], the Scientific Advisory Committee on Nutrition (SACN) in the UK [9], and the European Food Safety Authority (EFSA) [7].

Within the Population Intervention Comparison Outcome (PICO) framework [35], the *populations* of interest in this study were specified as male and female children and adults, but excluding studies in infants (0–12 months) and young toddlers (12–23.9 months), pregnant or lactating women, and dark-skinned individuals (defined as those with a Fitzpatrick skin type of V or VI [34]). These excluded population subgroups have physiological considerations in relation to vitamin D [28] which require dedicated IPD meta-regression analyses [29, 34]. Studies on animals and patient groups with diseases that are assumed to affect vitamin D metabolism and/or response to vitamin D_3 supplementation (see Supplemental Table 1 in 'Online Resource', as per [28, 35]) were excluded. Relevant food-based vitamin D RCTs were defined as those fulfilling the following characteristics:

(1) *Intervention*: vitamin D_3 consumed orally as a fortified/enhanced/enriched food(s) and taken daily or weekly. RCTs which supplied vitamin D_3-fortified/enhanced/enriched food(s) less frequently than weekly (e.g., monthly, quarterly, annually) were excluded. The foods were to be consumed as part of a diet and not oral supplements, supplement sachets for addition to foods, or be fortified/enhanced/enriched food(s) supplying ≤ 100 IU/day (2.5 µg/day; 1 µg = 40 IU). Inclusion of RCT arms was limited to those with a maximum added vitamin D_3 dose of 4000 IU (100 µg)/day (or daily equivalent, in case of doses provided less frequently than daily). This selection of upper maximum dose takes account of the Tolerable Upper Intake Level (UL) for vitamin D of 4000 IU/day for those upwards of 9 and 11 y, set by EFSA [36] and IOM [4]. The selection of upper maximum dose of 4000 IU/day also allows for a trend amongst adults for increasing use of higher dose vitamin D supplements [37].

RCTs needed to use vitamin D_3, not vitamin D_2, on the basis that (i) the IOM DRI committee and EFSA used studies with vitamin D_3 in their regression analyses, to set DRV [4, 7], and (ii) there is evidence that the relative potency of vitamin D_2 to increase serum total 25(OH)D is lower than vitamin D_3 [38, 39]. While the IOM only selected studies that provided vitamin D alone and not with co-administration of calcium [4], both the NNR [8] and EFSA [9] allowed studies which co-administered calcium to be included. We have provided RCT data to suggest that calcium intake does not influence the response of serum 25(OH)D to vitamin

D_3 supplementation [40] and DRV for vitamin D are established under the assumption that calcium intake is adequate [4, 7–9]. Thus, we allowed food-based RCTs that provided vitamin D alone or in combination with calcium to be included. As foods were the delivery vehicle as opposed to supplements, we also allowed other micronutrients (e.g., vitamin K, B-vitamins, iron) to be included in addition to vitamin D and calcium.

(2) RCTs using a food derived from a 'vitamin D-biofortification' approach, in which 25(OH)D_3 alone or in combination with vitamin D_3 was included in the feedstuffs for poultry, livestock or farmed fish, which was then incorporated into their tissues and thus in food for human consumption [25, 41], were allowed. Otherwise, RCTs with vitamin D metabolites (25(OH)D and 1,25$(OH)_2$D) and analogues (e.g., alfacalcidol) as the human food fortificant were excluded.

(3) *Outcome* and *comparator/comparison*: reported serum or plasma 25(OH)D concentration following supplementation in at least one vitamin D intervention group and one control/placebo group needed to be available. A conversion factor of 2.496 nmol/L = 1 ng/mL was used to standardise all serum or plasma concentrations to nmol/L. Studies with no data on measured serum or plasma 25(OH)D were excluded.

(4) Only studies conducted at latitudes ≥40° N during, or at least incorporating, winter, to ensure minimal impact of UVB on the vitamin D intake–25(OH)D dose-response, and thus the calculated vitamin D_3 intake requirements to achieve serum 25(OH)D thresholds, were included. EFSA in their recent vitamin D DRV analyses defined a period of assumed minimal endogenous vitamin D synthesis at latitudes ≥40° N (covering much of Europe) as October through April [7]. The IOM and NNR selected RCTs performed in northern latitudes >49.5/50° N in Europe during winter-time as the dataset upon which to explore the vitamin D dose response relationship and establish their DRI [4, 8]. Thus, we only included data from an RCT if it took place at a latitude greater than at least 40° N and entirely within the window of October and April, or had an intermediate sampling point within this winter period and of at least 6 weeks of vitamin D supplementation.

(5) The study duration needed to be at least 6 weeks as serum 25(OH)D concentrations in adult and elderly subjects only reach equilibrium after 6–8 weeks of vitamin D supplementation [42]. Studies of a duration less than 6 weeks were excluded.

(6) Assessment of vitamin D intakes, on which to base the dose-response calculations, was based on food frequency questionnaire (FFQ), dietary history, 24-hour recall for ≥ 3 days, or a food record or diary for ≥ 3 days, as per [35]. We used 'total vitamin D intake', which is the total vitamin D intake from the diet (including personal vitamin D supplements, where permitted within a RCT) as well as that from any supplemental vitamin D dose provided in the RCT [43, 44]. The use of total vitamin D intake to derive DRV has been prioritized by expert agencies and bodies [4, 7–9]. Thus, RCTs that had not assessed habitual vitamin D intake in study participants were excluded.

Identification of studies: information sources and search strategy

During May–July 2018, electronic searches were performed in the following three online databases (PubMed, Ovid Medline and Embase) as well as three trial registries (ClinicalTrials.gov, Cochrane Central Register of Controlled Trials (CENTRAL), and the International Standard Randomized Controlled Trials Number (ISRCTN) registry) from inception to July 31st 2018 (date of the final screen) using structured electronic search strategies which accounted for the inclusion/exclusion criteria outlined above. The search strategies were based closely on that used by us previously for identification of vitamin D RCTs that could inform establishment of dietary requirements [30, 31], and an exemplar search strategy specifically adapted for PubMed is shown in Supplemental Table 2 in 'Online Resource'. The methods used in the present systematic review follow the PRISMA statement [45].

Study selection and inclusion

Study selection was independently conducted by two prespecified investigators (KDC and MEK), first by a screen of the titles and abstracts, followed by a review of the full text of potentially relevant studies. The same two investigators separately determined which RCTs met the eligibility criteria and were included. In addition, the searches were supplemented by searches of review/systematic review articles and reference lists of trial publications as well as from the key international vitamin D DRV reports over the last 9 years [4, 7–9]. Duplicates were removed in EndNote (X7.0.1, Clarivate Analytics, Philadelphia, Pennsylvania, United States). Studies that fulfilled the inclusion criteria and were not collected on the basis of the database search were added. Information on the combined number of records identified, abstracts and full-text articles screened, and articles excluded and included in the review are shown in Fig. 1.

Data collection processes, data items, IPD integrity, and data protection

For each eligible RCT, collaboration was requested and negotiated with the principal investigator [46]. For willing

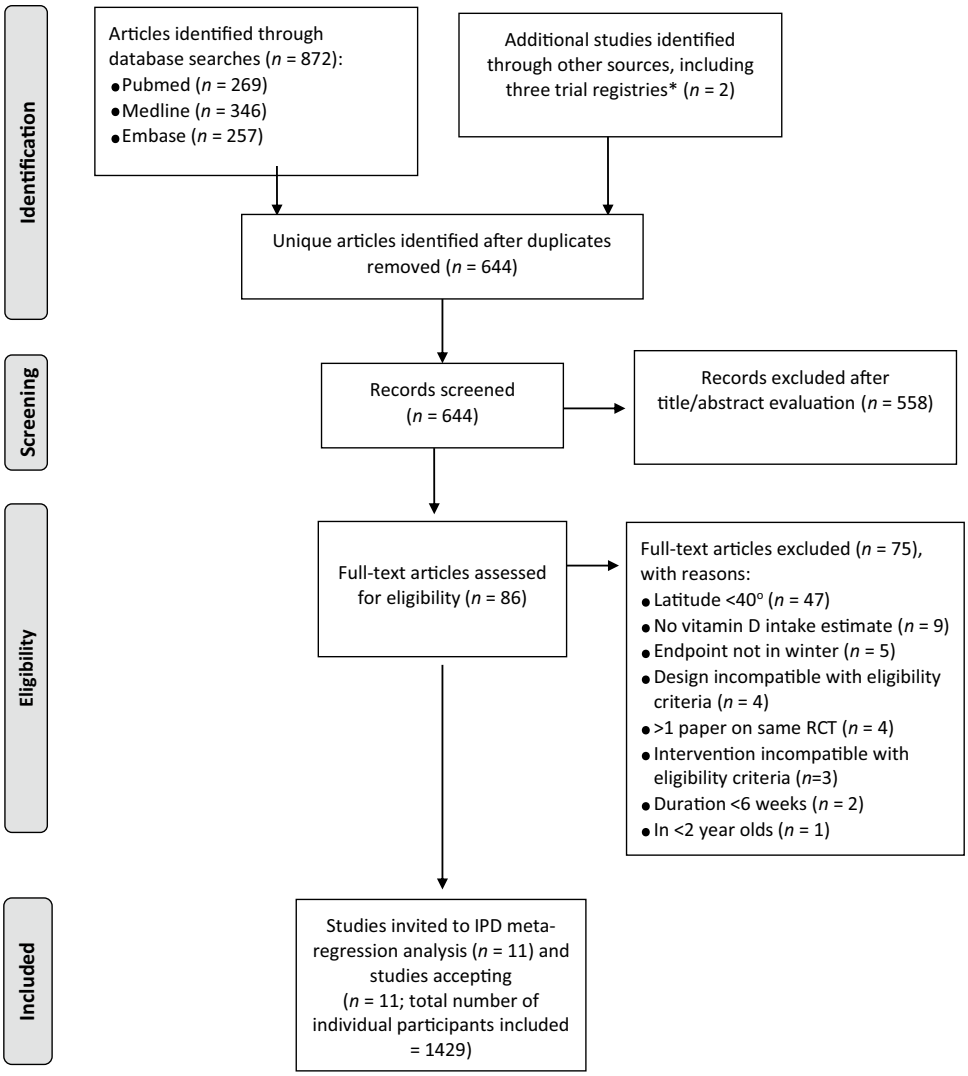

Fig. 1 PRISMA (*Preferred Reporting Items for Systematic Reviews and Meta-Analyses)* flow diagram for study selection procedure. *ClinicalTrials.gov, Cochrane Central Register of Controlled Trials, and the International Standard Randomized Controlled Trials Number registries.

collaborators, the terms of collaboration were specified in a data transfer agreement, signed by representatives of the data provider and of the recipient(s) (University College Cork and University of Copenhagen). Data were initially de-identified at source before encryption and transfer by e-mail. On receipt, a pre-specified investigator (KDC) assessed the data integrity by performing internal consistency checks and by attempting to replicate results of the analysis for group mean/median serum 25(OH)D response to supplemental vitamin D_3, as published in the original RCT report. If required, study authors were contacted to provide missing data and to resolve queries arising from these integrity checks. In line with recently published principles and recommendations in relation to the sharing and reuse of IPD [47], once queries were resolved, clean data within the individual datafiles were used to establish an overall anonymized data file, as follows: only data on the prioritized IPD variables within the transferred files were included, there were no personal identifiers included, the identity of included RCTs was also de-identified by use of a random assignment number. This was based on pseudo-random numbers generated via R version 3.6.2 (R Core Team, Vienna, Austria), using a pre-specified seed, by a researcher with no involvement in the IPD process or analysis. The anonymized data file was held in Excel® V15.30 (Microsoft Corporation, USA). The originally transferred data files from participating RCT groups were fully deleted from the lead PI's (KDC) files, and in advance of the synthesis and statistical analyses by the project biostatistician (CR).

Specification of outcomes and effect measures

Serum 25(OH)D concentration was the sole outcome considered in the IPD meta-regression analysis. Likewise, total vitamin D intake was the only predictor considered.

Quality assessment and risk of bias assessment for individual studies

The Jadad scale was used to assess the quality of the included RCTs [48], and an assessment of the risk of bias in these RCTs was performed using the Cochrane Collaboration's tool for assessing risk of bias [49]. Two pre-specified investigators (KDC and LT) independently assessed study quality and risk of bias in the RCTs. If required, a 3rd assessor (MEK) finalised Jadad score.

Statistics

Choice of model

A one-stage IPD meta-analysis was carried out [50, 51]. Initially, both linear and non-linear regression models for describing the relationship between serum 25(OH)D and total vitamin D_3 intake were fitted [4, 28, 31] and, based on model diagnostics (residual and QQ plots), results from the most appropriate model were reported. When assuming a linear trend, the one-stage IPD meta-analysis corresponded to fitting a linear regression model with vitamin D intake as the fixed effect and study-specific random intercept and slope effects. When assuming a non-linear trend, the one-stage IPD meta-analysis was carried out by fitting a linear regression model with logarithm-transformed vitamin D intakes and serum 25(OH)D concentrations, corresponding to a non-linear power model on the original scales; this model provided an operational and reasonable approximation to the exponential models previously used (as no levelling off at high intakes was observed). Both models without covariate adjustment and models including adjustment for baseline serum 25(OH)D concentrations, which were also logarithm-transformed in cases where the outcome was logarithm-transformed, age, and BMI were fitted. These were pre-specified covariates commonly used in this type of modelling exercise [7, 28]. In sensitivity analyses we also carried out the adjusted analyses replacing BMI by body weight and *z*-scores for body weight or BMI (one at a time). Child age- and sex-specific weight and BMI standard deviation scores (*z*-scores) were generated using LMS growth software and the UK-WHO 0 to 4-year and UK 4 to 20-year growth reference data [52]. Likewise, additional adjustments for methods of vitamin D intake estimation or serum 25(OH)D measurement were also performed. All models included study-specific random intercepts, implying that linear mixed models were fitted (using restricted maximum likelihood estimation). Intake and covariate adjustment (if included) constituted the fixed effects in the models. The model which adjusted for baseline 25(OH)D, age and BMI will be referred to as the 'adjusted model' throughout the remainder of the paper, and where a model used alternate or additional adjustments these will be highlighted.

To inform safety considerations around each of the various vitamin D intake requirement estimates generated from the present IPD analysis, these were compared to the ULs for vitamin D from children (50–75 µg/day, depending on age group and agency) and adults (100 µg/day) [4, 36]. In addition, the present unadjusted and adjusted models were used to predict the upper 97.5th percentile of serum 25(OH)D concentration achieved. While the serum 25(OH)D concentration representing the vitamin D toxicity threshold in humans is not readily defined [4], EFSA recently concluded that a serum 25(OH)D concentration of 200 nmol/L or below is unlikely to pose a risk of adverse health outcomes in healthy infants [53], a sensitive group within the population. The IOM, in setting their ULs for vitamin D, also considered if the intakes were likely to lead to serum 25(OH)D concentration in excess of approximately 125 to 150 nmol/L, which they considered might be of concern based on some observed U-shaped or reverse-J-shaped relationships between serum 25(OH)D and mortality as well as other health outcomes [4]. However, EFSA considered that studies reporting on an association between 25(OH)D concentration and all-cause mortality or cancer were inconsistent and they did not raise this concern [7, 36]. Thus, we benchmarked the upper 97.5th percentile of serum 25(OH)D concentrations against serum 25(OH)D concentrations of 150 and 200 nmol/L.

Derivation of vitamin D DRV estimates

Lower boundaries of the prediction intervals of the fitted (mean) regression line, corresponding to vitamin D intakes needed to maintain 50, 90, 95, and 97.5% of the participants above serum 25(OH)D thresholds of 25, 30, and 50 nmol/L (where appropriate and feasible) were estimated by means of inverse regression. While SACN's *Reference Nutrient Intake* (RNI) [9], NNR's *Recommended Intake* (RI) [8] and IOM's *Recommended Dietary Allowance* (RDA) [4] are all intended to meet the requirements of 97.5% of the individuals in the population, EFSA's *Adequate Intake* (AI) is intended as an intake at which most of the population will achieve the target serum 25(OH)D concentration [7]. Thus, the AI may not cover 97.5%, but 95% or some other majority percentage. Standard errors and 95% confidence intervals on these estimated lower boundaries were obtained using a parametric bootstrap procedure with 1000 replications, as described previously [28]. In order to achieve comparable fitted regression lines for unadjusted and adjusted model fits, we fixed covariates at their overall mean value (except for intake) in adjusted models.

Leave-one-out sensitivity analysis To assess if there were any overly influential RCTs, the derivation of vitamin D DRV estimates (as described above) based on an unadjusted model based on data from all RCTs was repeated leaving out one RCT at a time. Absolute and relative changes in estimates as compared to the full analysis were reported.

Subgroup analyses A number of specific subgroups had been considered previously [4, 7, 28]. Therefore we also carried out these subgroup analyses. Specifically, we fitted separate models for subgroups of children (< 18 years) and adults (≥ 18 years) and for subgroups of participants whose baseline serum 25(OH)D was < or ≥ 50 nmol/L. We also fitted separate models for the subgroup of RCTs of children and adults which were ≥ 50° N; only models including adjustment for baseline serum 25(OH)D level, age, and BMI were fitted. Furthermore, we fitted separate models for the subgroup of RCTs of adults which provided vitamin D at a dose ≤ 30 µg/day, above which the rise in serum 25(OH)D to additional vitamin D is less steep [31]. We also fitted separate models for a subgroup consisting of adult participants with BMI < 25 kg/m^2. Lastly, we did subgroup analysis for RCTs where compliance data were available and for participants showing compliance above 80%, and separately above 95%. The subgroup analyses were pre-specified rendering testing for interaction unnecessary.

Estimation of rate constants for included RCTs

It has been suggested that the bioavailability of vitamin D from food could potentially be influenced by the complexity of the food matrix [54]. However, data from the limited number of RCTs which compared vitamin D_3-fortified foods (regular and low-fat cheese, orange juice, various breads) with vitamin D_3 supplements demonstrate equal bioavailability [55–58]. Use of the 'rate constant' (i.e. the change in 25(OH)D in nmol/L per µg vitamin D administered [59]) would allow a comparison of vitamin D status improvement per dose of vitamin D from fortified foods and supplements across RCTs among individuals of different ages within the present IPD and equivalent winter-based RCTs with vitamin D supplements included in the IOM's DRI exercise [4], respectively. Rate constants were calculated as described by Whiting et al. [59], namely, for both the control (placebo) group and the treatment group(s), the net change from baseline to endpoint 25(OH)D determined by subtraction. The rise (or fall) in 25(OH)D of the control group is subtracted (or added) to the net change of 25(OH)D in the treatment group(s). The resulting nmol/L is divided by the dose (in µg) of vitamin D_3 administered [59].

Statistical software

All analyses were conducted using R version 3.6.2 (R Core Team, Vienna, Austria) and the R extension packages "boot" for bootstrapping; "medrc", "lme4" [60] and "nlme" [61] for fitting linear mixed models. The R code for fitting linear and nonlinear models is presented elsewhere [34].

Results

Study selection and IPD obtained

Our search identified 644 unique articles, the titles and abstracts of which were screened and ultimately 86 full-text articles were assessed for eligibility. Of these 86 articles, 11 studies [55, 62–71] fulfilled the eligibility criteria (Fig. 1). IPD were sought and obtained for all 11 studies, with a total of 1429 randomized participants that fulfilled the eligibility criteria. A number of the studies had additional participants that did not meet the eligibility criteria (e.g., were dark-skinned (in 5 RCTs), sampled outside the specified winter period (in 1 RCT), below the age threshold of 24 months (in 1 RCT), or had missing data on a required variable (in 4 RCTs), and the data on these additional participants were not included in the present analysis.

Study and participant characteristics

Table 1 shows the characteristics of the 11 eligible studies and their participants. The RCTs were conducted in 8 countries within North America and Europe. Seven studies were conducted in adults, 3 in children, and 1 in both age-groups. Three studies were conducted in adult females only, the rest were conducted in studies with a mixture of males and females.

Among the 11 RCTs, mean baseline serum 25(OH)D concentrations ranged from 45.9 to 75.0 nmol/L; 2 studies had mean baseline concentrations in the range of 40–49.9 nmol/L, 4 studies each were within the range of 50–59.9 nmol/L and 60–69.9 nmol/L, respectively, and 1 study had a mean baseline concentration > 70 nmol/L (Table 1). Five of the 11 RCTs had a requirement that participants would not travel to a sunny locale and/or use tanning beds during the study. Four and 7 RCTs were conducted within latitude bands of 40 to 49.9° N and 50 to 63° N, respectively. A range of assay types were used to measure serum 25(OH)D, including RIA (in 3 studies), LC–MS/MS (in 5 studies) and one study each used HPLC, ELISA, or chemiluminescence immunoassay (Table 1).

Table 1 Selected design parameters of the 11 randomized controlled trials with vitamin D-fortified food, conducted in winter and ≥ 40°N, as well as baseline and vitamin D-related outcome characteristics of white subjects who completed the intervention studies and were included in data analyses*

Study	Johnson et al. (2005)	Wagner et al. (2008)	Madsen et al. (2013)	Toxqui et al. (2014)
(Reference Number)	[62]	[55]	[64]	[65]
Trial registry ID	NR	NR	NCT01184716	NCT01739907
Design parameters:				
Location (°N)	USA (~44° N)	Canada (43° N)	Denmark (56° N)	Spain (40.2° N)
Year of study	2004	2007	2010–2011	2012
Duration (and Months)	2 months (within Dec–Apr)	8 weeks (within Jan–Apr)	6 months (Sep–Apr)	8 weeks (within Jan–Mar)**
Food interventions [supplemental vitamin D_3 dose]	Vit D-fortified cheese [15 µg/day] vs Non-fortified cheese vs No cheese	Fortified [700 µg/week] vs Low fat-fortified [700 µg/week] vs Placebo cheese	Vit D-fortified 0.5% milk + bread (wheat/rye) [6.8 µg/day, on average] vs Non-fortified milk and bread	Fe and Vit D-fortified skimmed cow's milk [5 µg/day] vs Fe-fortified skimmed cow's milk
Subject characteristics:				
Baseline *N*	90	50	682	107
Sex (Male:Female)	34:56	25:25	330:352	0:107
Age (year)	73.5 ± 7.2[1]	27.8 ± 9.6	27.2 ± 16.3	24.9 ± 4.4
Weight (kg)	79.8 ± 15.8	68.2 ± 14.6	60.6 ± 24.8	59.5 ± 8.9
BMI (kg/m^2)	28.3 ± 5.2	23.8 ± 4.2	21.9 ± 5.4	21.7 ± 3.0
Dietary vitamin D (µg/day)[2]	11.1 ± 7.8[d]	3.2 ± 2.3[a]	2.8 ± 1.7[a]	2.9 ± 2.8[b]
Serum 25(OH)D (nmol/L)[3]	51.8 ± 19.3[e]	53.8 ± 21.4[e]	74.8 ± 19.9[f]	61.7 ± 19.6[i]
Endpoint				
Dietary vitamin D (µg/day)[4]				
Control group(s) (*n*)	10.9 ± 8.1 (61)	3.9 ± 3.0 (20)	4.2 ± 3.8 (353)	2.9 ± 2.5 (52)
Vit D intervention group(s) (*n*)	26.0 ± 7.1 (29)	103.9 ± 3.3 (30)	13.5 ± 6.9 (329)	7.3 ± 3.3 (55)
Serum 25(OH)D (nmol/L)[3,4]				
Control group(s) (*n*)	51.0 ± 16.3 (61)	50.7 ± 24.2 (20)	45.1 ± 20.2 (353)	58.1 ± 17.5 (52)
Vit D intervention group(s) (*n*)	53.2 ± 19.9 (29)	120.0 ± 28.2 (30)	70.0 ± 19.0 (329)	65.7 ± 16.6 (55)

Study	Trautvetter et al. (2014)	Hayes et al. (2016)	Tripkovic et al. (2017)	Grønborg et al. (2019)
(Reference Number)	[66]	[68]	[70]	[71]
Trial registry ID	NCT01297023	NCT02678364	ISRCTN23421591	NCT02631629
Design parameters:				
Location (°N)	Germany (51° N)	Ireland (51.9° N)	UK (51.3° N)	Denmark (56° N)
Year of study	2011	2015	2011–2012 and 2012–2013	2016
Duration (and Months)	8 weeks (within Jan–Apr)	8 weeks (within Jan–Mar)	12 weeks (within Oct–Mar)	3 month (Jan–Mar)
Food interventions [supplemental vitamin D_3 dose]	CaP vs Vit D vs CaP + Vit D [10 µg/day]—fortified bread	Vit D [3.5 µg/day]- vs 25-(OH)D [4.5 µg/day]—fortified eggs vs Control eggs	Vit D_3-fortified Orange Juice [15 µg/day] vs Vit D_3-fortified Biscuit [15 µg/day] vs Placebo	Vitamin D-fortified low-fat cheese, yoghurt, eggs and crisp bread (supplying 30 µg/day in total) vs non-fortified equivalents
Subject characteristics:				
Baseline				
n	55	50	133	60
Sex (Male:Female)	23:32	26:24	0:133	0:60
Age (year)	42.8 ± 12.1	54.9 ± 6.4	46.2 ± 12.1	33.3 ± 11.3

Table 1 (continued)

Study	Trautvetter et al. (2014)	Hayes et al. (2016)	Tripkovic et al. (2017)	Grønborg et al. (2019)
Weight (kg)	72.9 ± 14.3	73.7 ± 15.1	65.5 ± 10.8	67.8 ± 12.0
BMI (kg/m^2)	24.8 ± 3.9	25.4 ± 4.1	23.8 ± 3.5	24.1 ± 4.1
Dietary vitamin D (µg/day)[2]	3.6 ± 4.1[d]	6.6 ± 3.8[a]	2.9 ± 2.4[c]	1.5 ± 0.8[a]
Serum 25(OH)D (nmol/L)[3]	50.8 ± 21.8[h]	45.9 ± 16.4[f]	60.2 ± 24.7[f]	48.6 ± 16.3[f]
Endpoint				
Dietary vitamin D (µg/day)[4]				
Control group(s) (*n*)	6.6 ± 0.5 (18)	6.0 ± 2.7 (16)	2.5 ± 2.3 (43)	1.5 ± 0.7 (31)
Vit D intervention group(s) (*n*)	15.0 ± 0.8 (37)	10.0 ± 3.8 (34)	8.1 ± 2.5 (90)	28.7 ± 8.8 (29)
Serum 25(OH)D (nmol/L)[3,4]:				
Control group(s) (*n*)	47.4 ± 30.3 (18)	35.1 ± 11.0 (16)	44.1 ± 17.8 (43)	44.0 ± 16.7 (31)
Vit D intervention group(s) (*n*)	67.7 ± 13.9 (37)	48.5 ± 18.7 (34)	90.7 ± 24.0 (90)	77.8 ± 14.4 (29)

Study	Hower et al. (2013)	Brett et al. (2016)	Öhlund et al. (2017)
(Reference Number)	[63]	[67]	[69]
Trial registry ID	NR	NCT02097160	NCT01741324
Design parameters:			
Location (°N)	Germany (51° N)	Canada (45.5° N)	Sweden (55 and 63° N)
Year of study	2010–2011	2014	2012–2013
Duration (and Months)	4 months (Nov–Feb)**	12 weeks (Jan–Apr)	3 months (within Nov–Mar)
Food interventions [supplemental vitamin D_3 dose]	Vit D-fortified growing up milk [10 µg/day] vs Semi-skimmed cow's milk with no added vitamin D	Vit D-fortified drinkable yogurt + cheese (providing 10 or 15 µg/day) *vs* non-fortified yogurt + cheese	Vit D-fortified lactose-free, UHT milk [12 or 22 µg/day] vs non-fortified lactose-free, UHT milk
Subject characteristics:			
Baseline			
n	62	43	97
Sex (Male:Female)	32:30	22:21	45:52
Age (year)	3.7 ± 1.2	5.5 ± 1.8	6.3 ± 0.6
Weight (kg)	16.3 ± 3.4	21.4 ± 5.9	23.1 ± 3.6
BMI (kg/m^2) [z score]	15.9 ± 1.5 [0.16 ± 1.0]	16.4 ± 1.4 [0.43 ± 0.81]	15.8 ± 1.5 [0.04 ± 1.0]
Dietary vitamin D (µg/day)[2]	2.2 ± 1.4[a]	5.2 ± 2.6[a]	5.5 ± 2.7[a]
Serum 25(OH)D (nmol/L)[3]	54.7 ± 18.8[i]	60.9 ± 12.5[e]	63.9 ± 16.9[f]
Endpoint			
Dietary vitamin D (µg/day)[4]			
Control group(s) (*n*)	2.5 ± 1.5 (23)	6.2 ± 1.8 (15)	6.3 ± 2.4 (18)
Vit D intervention group(s) (*n*)	8.7 ± 2.8 (39)	12.8 ± 3.8 (28)	22.4 ± 6.0 (79)
Serum 25(OH)D (nmol/L) [3,4]			
Control group(s) (*n*)	37.4 ± 16.6 (23)	58.6 ± 13.1 (15)	59.2 ± 14.5 (18)
Vit D intervention group(s) (*n*)	64.2 ± 22.9 (39)	63.6 ± 12.0 (28)	80.5 ± 16.6 (79)

*In some cases, additional participants in the study were not included in the analyses as they did not meet with the inclusion criteria (total *n* = 489).

**Not study endpoint but sampling point which fit with sampling months as specified by inclusion criteria

[1]Mean ± SD (all such values).

[2]Habitual dietary vitamin D intake assessed via semi-quantitative FFQ[a], 72-h detailed dietary intake report[b], 4-day diet diary[c], or 3-day diet records[d].

[3]Serum 25(OH)D measured by RIA[e], LC–MS/MS[f], HPLC[g], ELISA[h], or chemiluminescence immunoassay[i].

[4]In studies where there were more than one control and/or vitamin D intervention groups, reported values are for all control or vitamin D intervention subjects.

BMI, body mass index; 25(OH)D, 25-hydroxyvitamin D; NR, not registered.

All RCTs administered vitamin D-fortified/enhanced/enriched food(s) to participants in the intervention arms: given daily (10 RCTs) or weekly (1 RCT). The daily (or daily equivalent) dose of vitamin D provided by consumption of the assigned amount/serving size of the vitamin D-fortified/enhanced/enriched food(s) ranged from 3.5 to 100 µg/day: 5 studies used ≤ 10 µg/day, 1 study used 10 and 15 µg/day, 4 studies used ≥ 12–30 µg/day, and 1 study used 100 µg/day equivalent (Table 1). Six studies used dairy-based foods (of which 5 used a single source (cheese or a cow's milk-based beverage) and 1 used yoghurt and cheese), 1 RCT each used bread; eggs; orange juice or biscuits; or milk plus bread; or a combination of 4 foods (vitamin D-fortified low-fat cheese, yoghurt, eggs and crisp bread) (Table 1). The RCTs had a variety of consumption patterns for the study foods ranging from being consumed once per week, once per day, to participants being allowed to freely plan how they distributed the provided foods over a day or week as long as they consumed the designated amount (data not shown). Study duration ranged from 8 weeks to 6 months. A range of dietary instruments were used to assess vitamin D intake, including 72-h detailed dietary intake report (1 study), 4-day diet diary (1 study), 3-day diet records (2 studies), and semi-quantitative FFQ (7 studies; with 5 reporting their FFQ as validated for habitual vitamin D intake).

Study quality of included RCTs

All 11 studies achieved a Jadad score of ≥ 3 (18% and 55% with scores of 4 and 5, respectively). In terms of contributing to these scores, method of randomization was reported in nine studies. Two studies were reported as blinded, but methods for blinding were unclear based on the information presented within the papers, upon which the Jadad scores are adjudged (this information was attained after the fact from the PIs for use in the *Risk of bias* assessment). Ten of the 11 RCTs reported analytical verification of the vitamin D content of the vitamin D-fortified/enhanced/enriched food(s). All 11 studies reported data on dropouts. There was a relatively low percentage of participant dropouts (0–18.5% within a study arm) and only one study had a dropout rate of > 15%. It should be noted that the Jadad scale does not assess compliance, which is an important factor in food-based interventions. Compliance rates were reported in 9 studies (range of means: 79–98% with 7 RCTs > 90%), one study did not assess compliance, and another study failed to report on compliance rate even though it was assessed.

Risk of bias within studies

The summary assessments of risk of bias across domains and across the 11 RCTs are shown in Supplemental Table 3 in 'Online Resource'. The majority of RCTs had either a low or unclear risk of selection bias (low risk of random sequence generation and allocation concealment for 9 and 8 RCTs, respectively, and the remainder had unclear risk). In relation to performance and detection bias, a majority of RCTs (*n* 9–10) had low risk of bias for blinding of participants, personnel and of outcome assessment, with 1–2 RCTs having unclear risk in these domains. In relation to attrition bias, risk of bias in relation to incomplete outcome data was low for 10 RCTs and unclear for the remaining study. Risk of bias for selective reporting was low in all 11 RCTs. Overall, most of the information used in the present meta-regression analysis is from studies at low, or to a lesser extent, unclear risk of bias.

Rate constants of included vitamin D-fortified food RCTs versus those of vitamin D supplement RCTs

The rate constants (nmol/L per µg additional vitamin D intake) for the vitamin D-fortified food RCTs [55, 62–71] and appropriate vitamin D supplement RCTs as part of the IOM DRI exercise [4] plus a few published since [40, 72–74], stratified by age-group and latitude band in which they were conducted, are shown in Supplemental Table 4. The median rate constant for all RCTs, irrespective of age, in the present IPD (excluding one RCT with the negative rate constant in older adults, see below) and the updated IOM collection were similar at 1.7 and 1.6, respectively. The median rate constant from the collection of RCTs in children (at ≥ 50° N) in the present IPD was similar (1.9) to that of the updated IOM RCT collection (2.1). For adults, the median rate constants were 2.6 and 1.9 for ≥ 50° N RCTs in the IPD and IOM analyses, respectively; and 0.8 and 0.9 for 40–49.5° N RCTs in the IPD and IOM analyses, respectively. There was only one RCT of older adults (> 60 years) in the present IPD collection and that showed a negative rate constant (i.e., no response) [62] compared to the 1.3 nmol/L per µg additional vitamin D intake for the one RCT in the IOM collection [42]. In the present IPD, the median rate constant of RCTs in children (at ≥ 50° N) was lower (1.9) than that of RCTs in adults (2.6). In the updated IOM collection of RCTs, the median rate constant of RCTs in children (at ≥ 50° N) was similar (2.1) to that of RCTs in adults (1.9).

The IPD meta-analysis model and vitamin D DRV estimates based on the 1-stage IPD meta-analyses, including subgroup analyses

Following an assessment of the 1-stage IPD meta-analysis models, a log–log model was judged to be the best fit. The analyses included an unadjusted model (Fig. 2a) as per IOM, NNR and SACN [4, 8, 9], as well as a model adjusted for

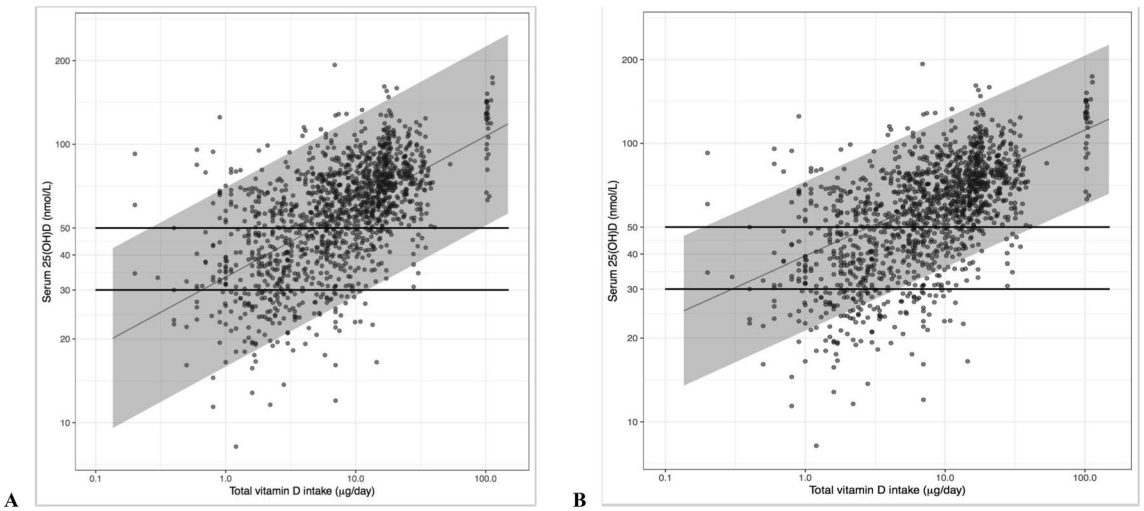

Fig. 2 The relation between serum 25-hydroxyvitamin D (25(OH)D) concentrations (in extended winter) and total vitamin D intake in healthy individuals aged 2–89 years living between 40 and 63° N based on individual participant data (IPD) ($n=1429$ individuals). The solid central diagonal lines correspond to the fitted regression lines based on one-stage IPD meta-analysis [unadjusted model (Panel A) and model adjusted for age, BMI and baseline 25(OH)D (Panel B)] and the corresponding 95% prediction bands are shown in grey. The fitted curve and the 95% confidence band were back-transformed but are displayed in the graphs using logarithmic axes in keeping with the log–log model. The black horizontal lines in each panel represent the serum 25(OH)D thresholds of 30 and 50 nmol/L relating to risk of vitamin D deficiency and inadequacy, respectively. Overlapping dots make some appear more darkly coloured

Table 2 Individual Participant Data (IPD) meta-analysis-derived dietary requirements for vitamin D (µg/day) for allowing 97.5% of individuals to maintain serum 25(OH)D at or above three recommended thresholds

Serum 25(OH)D[a]	Model 1 ≥40° N; No adjustments[b]	Model 2 ≥40° N; Adjusted[c]	Model 3 ≥50° N; No adjustments[d]	Model 4 ≥50° N; Adjusted[e]
All	$n=1429$	$n=1429$	$n=1139$	$n=1139$
≥25 nmol/L	5.9 (3.9, 9.0)	2.0 (1.3, 3.4)	6.3 (4.0, 9.7)	2.5 (1.5, 4.3)
≥30 nmol/L	12.2 (8.2, 18.4)	4.5 (2.8, 7.5)	12.1 (7.9, 19.2)	5.1 (3.1, 8.5)
≥50 nmol/L	92.3 (60.3, 146.0)	43.6 (27.7, 70.5)	75.1 (48.1, 123.5)	37.9 (23.3, 69.7)
Adults (aged 18–89)	$n=911$	$n=911$	$n=911$	$n=665$
≥25 nmol/L	8.4 (4.2, 18.2)	2.2 (1.0, 4.4)	9.6 (4.7, 21.4)	3.0 (1.3, 7.5)
≥30 nmol/L	18.0 (9.5, 39.7)	5.2 (2.7, 10.9)	18.9 (9.4, 42.7)	6.4 (2.8, 15.3)
≥50 nmol/L	156.4 (76.7, 280.8)	60.2 (31.2, 120.4)	127.9 (63.9, 271.0)	52.0 (23.6, 135.9)
Children (aged 2–17)	$n=518$	$n=518$	$n=518$	$n=474$
≥25 nmol/L	3.4 (2.9, 4.0)	1.9 (1.3, 2.9)	3.6 (3.0, 4.2)	2.1 (1.3, 3.7)
≥30 nmol/L	6.3 (5.3, 7.2)	3.7 (2.5, 5.6)	6.5 (5.6, 7.6)	4.1 (2.5, 7.0)
≥50 nmol/L	33.8 (28.5, 42.0)	24.4 (16.8, 38.2)	34.3 (28.4, 43.3)	26.1 (16.4, 45.4)

Based on a 1-stage IPD log–log model using data from RCTs performed during winter (at either ≥40° N or ≥50° N) and which related serum 25(OH)D concentration as a function of vitamin D intake (with or without adjustment). 95% CIs for the lower prediction limits were obtained using bias-corrected bootstrap based on 1000 replications

[a]Cut-off of ≥25 nmol/L used by UK Scientific Advisory Committee on Nutrition [9]; cut-off of ≥30 nmol/L used by Institute of Medicine [IOM] [4], Nordic Nutrition Recommendations [NNR] [8] and European Food Safety Authority [EFSA] [7] to define deficiency, and cut-off of ≥50 nmol/L used by IOM, NNR and EFSA to define threshold of adequacy

[b]Model 1: RCTs performed in the latitude band of 40–63° N; no adjustments to model

[c]Model 2: RCTs performed in the latitude band of 40–63° N; adjustment in model for baseline serum 25(OH)D, age and BMI

[d]Model 3: RCTs performed in the latitude band of 51–63° N; no adjustments to model

[e]Model 4: RCTs performed in the latitude band of 51–63° N adjustment in model for baseline serum 25(OH)D, age and BMI

covariates (mean values for baseline 25(OH)D, age and BMI) (Fig. 2b) similar to EFSA which adjusted for baseline 25(OH)D and other covariates [7]. Based on these 1-stage IPD meta-analysis models, the estimated vitamin D intakes needed to maintain 97.5% of individuals at latitudes ≥ 40° N and ≥ 50° N at pre-determined serum 25(OH)D thresholds as per agencies [4, 7–9], assuming minimal UVB exposure, are shown in Table 2. As the increase in vitamin D intake estimates moving from the 90th to the 97.5th percentile of requirements were very large, especially at the 50 nmol/L serum 25(OH)D threshold, it is important to also emphasize intake estimates at the 90th and 95th percentiles, as shown in Table 3.

Using the UK SACN 25(OH)D cut-off of ≥ 25 nmol/L [9], we estimated the vitamin D intake needed to maintain 97.5% of individuals above this threshold to be 5.9 µg/day based on the unadjusted model of RCTs ≥ 40° N; this decreased to 2.0 µg/day with adjustment for covariates (Table 2). The IOM, NNR and EFSA used 30 nmol/L to indicate an increased risk of vitamin D deficiency [4, 7, 8], but they did not derive a vitamin D intake for this threshold. We estimated a vitamin D intake of 12.2 µg/day to maintain 97.5% of individuals ≥ 30 nmol/L using the unadjusted model and 4.5 µg/day using the adjusted model. The vitamin D intake estimate allowing 97.5% of individuals to maintain serum 25(OH)D ≥ 50 nmol/L (the threshold of adequacy as selected by IOM [4], NNR [8] and EFSA [7]) was 92.3 µg/day and 43.6 µg/day using the unadjusted and adjusted models, respectively (Table 2). The vitamin D intake estimate required to maintain 90%

Table 3 Individual Participant Data (IPD) meta-analysis-derived dietary requirements for vitamin D (µg/day) to maintain stated percentage of the population (percentile) at a serum 25(OH)D level at or above selected concentrations in participants residing between 40 and 63° N during winter

Serum 25(OH)D	50th Percentile[a]	90th Percentile	95th Percentile	97.5th Percentile[b]
No adjustments				
All (n = 1429)				
≥ 25 nmol/L	–	2.2 (1.4, 3.2)	3.7 (2.5, 5.7)	5.9 (3.9, 9.0)
≥ 30 nmol/L	–	4.4 (3.0, 6.5)	7.6 (5.1, 10.8)	12.2 (8.2, 18.4)
≥ 50 nmol/L	4.9 (3.5, 7.0)	33.4 (23.0, 50.5)	57.5 (38.8, 87.3)	92.3 (60.3, 146.0)
Adults (n = 991)				
≥ 25 nmol/L	–	2.6 (1.3, 4.7)	4.8 (2.4, 9.5)	8.4 (4.2, 18.2)
≥ 30 nmol/L	–	5.5 (3.0, 9.9)	10.4 (5.4, 20.7)	18.0 (9.5, 39.7)
≥ 50 nmol/L	5.0 (2.8, 8.4)	47.2 (25.3, 91.4)	89.6 (46.7, 183.7)	156.4 (76.7, 280.8)
Children (n = 518)				
≥ 25 nmol/L	–	1.8 (1.5, 2.1)	2.5 (2.1, 3.0)	3.4 (2.9, 4.0)
≥ 30 nmol/L	–	3.3 (2.8, 3.8)	4.6 (4.0, 5.3)	6.3 (5.3, 7.2)
≥ 50 nmol/L	5.1 (4.6, 5.6)	17.5 (15.3, 20.1)	24.9 (21.2, 29.7)	33.8 (28.5, 42.0)
Adjusted model				
All (n = 1429)				
≥ 25 nmol/L	–	0.8 (0.5, 1.2)	1.3 (0.8, 2.1)	2.0 (1.3, 3.4)
≥ 30 nmol/L	–	1.8 (1.1, 2.8)	2.9 (1.9, 4.5)	4.5 (2.8, 7.5)
≥ 50 nmol/L	2.9 (1.9, 4.1)	17.0 (11.3, 27.0)	28.1 (18.1, 45.9)	43.6 (27.7, 70.5)
Adults (n = 911)				
≥ 25 nmol/L	–	0.7 (0.4, 1.4)	1.3 (0.6, 2.4)	2.2 (1.0, 4.4)
≥ 30 nmol/L	–	1.8 (0.9, 3.2)	3.1 (1.6, 6.3)	5.2 (2.7, 10.9)
≥ 50 nmol/L	2.6 (1.4, 4.5)	20.2 (10.9, 39.6)	36.2 (19.8, 76.0)	60.2 (31.2, 120.4)
Children (n = 518)				
≥ 25 nmol/L	–	1.0 (0.7, 1.4)	1.4 (0.9, 2.1)	1.9 (1.3, 2.9)
≥ 30 nmol/L	–	2.0 (1.4, 2.7)	2.8 (1.9, 4.0)	3.7 (2.5, 5.6)
≥ 50 nmol/L	3.8 (2.7, 5.1)	12.8 (9.1, 17.7)	18.0 (12.3, 27.1)	24.4 (16.8, 38.2)

Results based on a 1-stage IPD log–log model which related serum 25(OH)D concentration as a function of vitamin D_3 intake both unadjusted and adjusted for baseline serum 25(OH)D (mean), age (mean) and BMI (mean). 95% CIs for the lower prediction limits were obtained using bias-corrected bootstrap based on 1000 replications

[a]The vitamin D intake that will maintain serum 25(OH)D concentrations in 50% of individuals above 50 nmol/L during winter, representing an EAR at that threshold; this is not appropriate to do at the 25 and 30 nmol/L thresholds

[b]The vitamin D_3 intake that will maintain serum 25(OH)D concentrations in 97.5% of individuals above the indicated cut-off concentration during winter, representing a Recommended dietary allowance (RDA)

and 95% of individuals ≥ 50 nmol/L was 33.4 µg/day and 57.5 µg/day, respectively using the adjusted model, and 17.0 µg/day and 28.1 µg/day, respectively using the unadjusted model (Table 3). Excluding the Wagner et al. RCT [55] data (which provided additional vitamin D as a once-weekly dose of 700 µg) from the IPD analysis led to slightly higher DRV estimates than the full RCT dataset (range: 0.1–0.5 µg/day higher at the 25 and 30 nmol/L thresholds and 2.9–4.3 µg/day higher at the 50 nmol/L threshold, depending on the model) (data not shown).

By age-group, the intake estimates allowing 90%, 95% and 97.5% of children (2–17.9 years) to maintain serum 25(OH)D ≥ 50 nmol/L were two to five times lower than those of adults (≥ 18 years), depending on whether they were derived from the unadjusted or adjusted model (Table 3). When the 25 or 30 nmol/L serum 25(OH)D thresholds were applied, the intake estimates at the 90th, 95th and 97.5th percentiles were also lower for children compared to adults from the unadjusted model only (Table 3). For those studies that reported compliance, there was no statistical difference ($P = 0.11$) in median compliance between adults and children (at 98.2% and 95.6%, respectively).

The median requirement (i.e. EAR) at the 50 nmol/L serum 25(OH)D threshold was similar for adults and children (5.0 and 5.1 µg/day, respectively) based on the unadjusted model, but was higher for children than adults (3.8 versus 2.6 µg/day, respectively) based on the adjusted model (Table 3). Using a model which adjusted for baseline 25(OH)D only (not including BMI and age as additional covariates) showed that the EAR at 50 nmol/L was 3.6 and 2.5 µg/day for children and adults, respectively (data not shown).

Seven of the 11 RCTs from which the IPD were drawn were conducted ≥ 50° N, a cut-off used by the IOM [4] and NNR [8], as well as being consistent with the three RCTs used by the SACN [9]. Results of the subgroup analysis of data from these 7 RCTs in unadjusted and adjusted models conducted under the same conditions were broadly similar to the equivalent estimates from the full RCT dataset (i.e., 40–63° N), for all ages and for adults or children only (Table 2 for the 97.5th percentile, data not shown for the 90th and 95th percentiles).

Sensitivity analyses

A leave-one-out sensitivity analysis showed modest changes (maximum 17.6%, 16.2 µg/day) and there were no overly influential RCTs (Supplemental Table 5 in 'Online Resource').

The vitamin D intake requirement estimates at the 97.5th percentile based on regression models adjusted for baseline 25(OH)D alone versus baseline 25(OH)D, age and BMI were almost identical (maximum difference between estimates, 0.4 µg/day; data not shown).

Changing the anthropometry covariate had a negligible effect on the DRV estimates. Supplemental Table 6 in 'Online Resource' provides the vitamin D intake estimates for 97.5% to maintain serum 25(OH)D above the predefined thresholds based on regression models adjusted for baseline 25(OH)D, age and BMI and substituted by weight, *z*-scores of weights and *z*-scores of BMI. Using adult RCT data only, limiting the analysis to those whose BMI was less than 25 kg/m^2 showed that the 97.5th percentile vitamin D estimates at the 25 and 30 nmol/L thresholds were slightly lower (range 0.3–1.4 µg/day lower, depending on the model) than those from analysis of all adults. For the 50 nmol/L threshold, shown in Supplemental Table 7 in 'Online Resource', 97.5th percentile estimates were 5.2 and 14.5 µg/day lower for the adults with BMI < 25 compared to the full adult dataset, using unadjusted and adjusted models, respectively.

Baseline serum 25(OH)D had a major effect on estimates. Subgroup analysis, using the unadjusted regression model, showed that the vitamin D intake requirement estimates at the 97.5th percentile at each of the three serum 25(OH)D thresholds were 3- to 6-times higher in subjects whose baseline 25(OH)D concentrations was < 50 nmol/L compared to those with baseline concentrations ≥ 50 nmol/L. At the 25 and 30 nmol/L thresholds, the respective RDA estimates (95% CI) were 11.8 (7.0, 19.8) µg/day and 23.4 (14.6, 37.0) µg/day for those with baseline 25(OH)D < 50 nmol/L, and 2.1 (1.4, 3.3) µg/day and 4.8 (3.1, 7.4) µg/day for those with baseline 25(OH)D ≥ 50 nmol/L (data not shown). At the 50 nmol/L serum 25(OH)D threshold, the respective 90th, 95th and 97.5th percentile requirement estimates (95% CI) were 63.8 (41.2, 104.7) µg/day, 105.0 (64.5, 179.2) µg/day and 162 (94.1, 270.9) µg/day for those with baseline 25(OH)D < 50 nmol/L, and 17.1 (11.6, 24.8) µg/day, 29.7 (19.7, 45.5) µg/day and 47.8 (31.3, 81.5) µg/day for those with baseline 25(OH)D ≥ 50 nmol/L (data not shown).

Addition of the method of vitamin D intake assessment as an additional covariate to the model (also adjusted for baseline 25(OH)D, age and BMI) yielded vitamin D estimates at the 97.5th percentile that were higher (by 0.7, 1.4 and 10 µg/day at the 25, 30 and 50 nmol/L serum 25(OH)D thresholds, respectively) than those from analysis of all adults, irrespective of intake assessment method (data not shown). In the leave-one-out sensitivity analysis, variability in the range of change in RDA estimates at the 50 nmol/L serum 25(OH)D threshold on omission of individual RCTs was evident in those which estimated vitamin D intake by FFQ (− 17.6–22.2%) and non-FFQ assessment methods (− 16.7–12.8%) (Supplemental Table 4 in 'Online Resource').

Likewise, addition of method of serum 25(OH)D measurement as an additional covariate within the model yielded 97.5th percentile vitamin D estimates that were higher (by 1.1, 2.2 and 16.7 µg/day at the 25, 30 and 50 nmol/L serum

25(OH)D thresholds, respectively) than those from analysis of all adults, irrespective of 25(OH)D measurement method (data not shown). In the leave-one-out sensitivity analysis, variability in the range of change in RDA estimates at the 50 nmol/L serum 25(OH)D threshold on omission of individual RCTs was evident in those which measured serum 25(OH)D by chromatographic (− 17.6–22.2%) and non-chromatographic methods (− 16.7–4.7%) (Supplemental Table 4 in 'Online Resource').

Seven of the 11 RCTs from which the IPD were drawn had available individual-level data on compliance of consumption of the intervention food(s). An analysis of the estimates from a 1-step IPD meta-analysis model using data from this subset of 7 RCTs showed that percentage compliance with the food product had a relatively minor impact on the intake estimates at the 25 and 30 nmol/L serum 25(OH)D thresholds, i.e., estimates being 0–0.9 µg/day lower, depending on the intake requirement percentiles (90th to 97.5th) and whether 80% or 95% compliance threshold (Supplemental Table 8 in 'Online Resource'). At the 50 nmol/L serum 25(OH)D threshold, estimates were 2.5–10.1 µg/day lower than those from models not accounting for compliance, going from the 90th to 97.5th percentile, depending on whether 80% or 95% compliance threshold applied (Supplemental Table 7). The age-group specific differences in estimates in the full dataset from these 7 RCTs were also evident when the dataset excluded subjects with compliance < 80% or < 95% (Supplemental Table 7). This was also the case when unadjusted models were used (data not shown).

Safety considerations of the IPD-derived vitamin D intake requirement estimates

None of the vitamin D intake requirement estimates, derived from the adjusted models, exceeded the age-specific UL

Table 4 Projected upper 97.5th percentile serum 25(OH)D concentrations achieved at vitamin D intake requirement estimates from the unadjusted and adjusted models

Requirement percentile (at specified threshold)	Vitamin D intake requirement (µg/d)[a]	Projected upper 97.5th percentile serum 25(OH)D concentrations (nmol/L)
Unadjusted model		
≥ 25 nmol/L		
90th Percentile	2.2	85.4
95th Percentile	3.7	97.4
97.5th Percentile	5.9	109.6
≥ 30 nmol/L		
90th Percentile	4.4	101.8
95th Percentile	7.6	116.9
97.5th Percentile	12.2	131.8
≥ 50 nmol/L		
90th Percentile	33.4	170.1
95th Percentile	57.5	195.2
97.5th Percentile	92.3	220.2
Adjusted model		
≥ 25 nmol/L		
90th Percentile	0.8	69.4
95th Percentile	1.3	77.4
97.5th Percentile	2.0	85.3
≥ 30 nmol/L		
90th Percentile	1.8	83.3
95th Percentile	2.9	92.8
97.5th Percentile	4.5	102.5
≥ 50 nmol/L		
90th Percentile	17.0	138.4
95th Percentile	28.1	155.1
97.5th Percentile	43.6	171.3

Projected upper 97.5th percentile serum 25(OH)D results based on the 1-stage IPD log–log models which related serum 25(OH)D concentration as a function of vitamin D_3 intake both unadjusted and adjusted for baseline serum 25(OH)D (mean), age (mean) and BMI (mean)

[a]Vitamin D intake estimates as per Table 3

for vitamin D (Table 3). Using the intake estimates from the unadjusted models, none of the estimates for children exceeded the minimum specified UL for children (50 µg/day [36]). While the intake estimates covering 90% or 95% of adults did not, the 97.5% estimate for adults did exceed the UL (Table 3).

The projected upper 97.5th percentile serum 25(OH)D concentrations achieved at vitamin D intake requirement estimates, derived from the unadjusted and adjusted models, are shown in Table 4. None of the vitamin D intake requirement estimates at the 25 and 30 nmol/L serum 25(OH)D thresholds, from either the unadjusted or adjusted models, and whether covering 90, 95 or 97.5 percent of individuals, led to predicted upper 97.5th percentiles of serum 25(OH)D concentrations exceeding 150 nmol/L (maximum of 132 nmol/L at 12 µg/day intake, corresponding to the intake needed to maintain 97.5% of individuals with serum 25(OH)D ≥ 30 nmol/L). Using the vitamin D intake requirement estimates at the 50 nmol/L threshold, and based on the adjusted model, none of the three predicted upper 97.5th percentiles of serum 25(OH)D concentrations exceeded 200 nmol/L; with the vitamin D intakes covering 95% and 97.5% of individuals leading to 97.5th percentile serum 25(OH)D of 155 and 171 nmol/L, respectively (Table 4). Using on the unadjusted model, all three predicted upper 97.5th percentiles of serum 25(OH)D concentrations exceeded 150 nmol/L, and the vitamin D intake to cover the needs of 97.5% of individuals (92.3 µg/day) at 50 nmol/L threshold yielded a predicted upper 97.5th percentile serum 25(OH)D concentration of 220 nmol/L (Table 4). The vitamin D intakes corresponding to the EAR (50th percentile) at the 50 nmol/L threshold yielded a predicted upper 97.5th percentile serum 25(OH)D concentration of 105 and 93 nmol/L, based on unadjusted and adjusted models, respectively (data not shown).

Discussion

Since 2010, most expert agencies tasked with updating their vitamin D DRV have employed a standard meta-analysis approach based on aggregate data from RCTs, mostly with vitamin D supplements [4, 7, 8]. The present IPD analyses, based on pooled individual data from 11 winter-based RCTs using vitamin D-fortified foods provides new estimates for the vitamin D intakes needed to maintain individual winter-time serum 25(OH)D concentrations above commonly used thresholds. The approach used for data analysis, including the model and adjustments included, had a profound impact on the DRV estimates generated. For example, using data from RCTs conducted ≥ 50° N in an unadjusted curvilinear model, we estimated that the vitamin D intakes required to maintain 97.5% of serum 25(OH)D concentrations ≥ 25 nmol/L [9] and ≥ 30 nmol/L were 6 µg/day and 12 µg/day, respectively. Adjustment for mean values of baseline 25(OH)D, age and BMI reduced these estimates to 2.5 and 5.1 µg/day, respectively. Staying with studies ≥ 50° N and switching to the 50 nmol/L threshold [4, 8], the vitamin D intake required to maintain 90%, 95% and 97.5% of serum 25(OH)D concentrations ≥ 50 nmol/L was estimated to be 30, 49 and 75 µg/day, respectively. Adjustment for mean baseline 25(OH)D, age and BMI derived lower estimates of 16.1 and 25.5 µg/day at the 90th and 95th percentiles and 38 µg/day at the 97.5th percentile. Emphasis on the estimates at the 90th and 95th percentiles in the present work is of importance as the estimates at the 97.5th were very high and need to considered with caution.

The striking differences between the estimates at the 90th and 95th, as well as the 97.5th, percentiles for adults at the 50 nmol/L threshold from the present food trial-based and previous supplement trial-based IPD analyses [28] and the recommended 10 µg/day by NNR [8] and 15 µg/day by IOM (for those aged 1–70 years) [4] and EFSA [7] relate to the fact that the standard meta-analysis, as applied by these agencies, is not able to add the two required standard deviations to the median serum 25(OH)D response to cover the 97.5th percentile of individuals, as information on the between-individual variability is not accessible [29]. The IPD approach is highly relevant and applicable in this regard as between-participant variability is crucial for estimating individual-based DRV, such as the RDA, RNI, RI, and the EU's *Population Reference Intake* (PRI) [29]. SACN's RNI of 10 µg/day was based on regression analysis of individual data, but only from one RCT each in children, adults and older adults [9], unlike the present IPD which used pooled individual data from 11 RCTs.

The present vitamin D intake estimates at the 90th, 95th and 97.5th percentiles using all three serum 25(OH)D thresholds (25, 30 and 50 nmol/L) from the unadjusted models were 2- to fivefold higher for adults than for children. Likewise, the 90th, 95th and 97.5th percentile estimates at the 50 nmol/L serum 25(OH)D threshold from the adjusted model were ~ 2-times higher for adults than children; even though estimates were broadly similar for adults and children at the two lower thresholds. In contrast, IOM, NNR and EFSA, who combined data from RCTs in children and in adults (up to 60 years in the case of NNR) in their respective analyses [4, 7, 8], established the same vitamin D DRV for children and adults. SACN used data from a RCT in 11-year-old girls as well as one RCT each in adults and older adults [9]. Brett et al. [26] in a subgroup analysis within their recent meta-analysis based on aggregate data of vitamin D RCTs in children aged 2–18 years, reported the mean change in serum 25(OH)D per 2.5 µg vitamin D/day supplied as fortified food (9.3 nmol/L), and highlighted that this was about 3-times higher than that reported in either of the two equivalent meta-analyses of adults (~ 3 nmol/L;

[21, 22]). Lower requirements for vitamin D in children have been suggested to be possibly linked to body size [26, 72, 75], with children being, on average, smaller than adults and their tissue stores taking up a smaller amount of vitamin D from the circulation [26]. A greater volumetric dilution of ingested vitamin D within adults compared to children, is akin to that suggested to explain the lower vitamin D status among obese versus healthy weight adults [76]. The two-fold difference in vitamin D requirement estimates at the 50 nmol/L serum 25(OH)D threshold between children and adults in the present IPD remained even when body weight or *z*-scores for weight or BMI were substituted for BMI as a covariate within the analyses. There may be other factors contributing to the lower variability in serum 25(OH)D response to a specific vitamin D intake in children compared to that seen in adults. There were no significant differences in compliance between children and adults for those RCTs which had data available, suggesting this was likely not a key contributory factor. It should be noted, however, that some studies in children have compliance reported by the parent rather than the child.

That the extra vitamin D supplied in the RCTs included in the present IPD was by means of food vehicles is both timely and important as much of the analysis to-date has focussed on data from vitamin D supplement RCTs [4, 7–9]. Only EFSA included limited data from RCTs with vitamin D-fortified foods in their analyses (e.g., 18 RCT arms out of total of 83) [7]. It is worth considering that estimates arising from food-based studies may be highly relevant as the WHO–FAO [20] and others [3, 14, 19, 25, 77] have highlighted the advantages of a fortified food-based approach over supplements as a more effective public health strategy for increasing vitamin D in the food chain. While acknowledging the WHO–FAO's suggestion that increasing dietary diversity may be the most preferred way of addressing micronutrient malnutrition [20], this is not feasible for vitamin D, because there are very few naturally rich food sources [14]. However, increasing diversity in the context of types of foods fortified with vitamin D has been emphasised [14, 21, 23, 25, 77], as a wider suite of foods, in addition to milk/other dairy-based products (such as cheese and yoghurts), has the potential to increase vitamin D intakes in the population, especially among non- or low-dairy consumers. In this regard, the overall findings of this IPD highlight how vitamin D fortification of breads, biscuits, orange juice, and eggs, as well as milk/dairy products, alone or in some combination(s), can increase vitamin D status in children and adults.

While, the response of serum 25(OH)D to increased vitamin D intake from fortified cheese (i.e., the rate constant) was unexplainably low in one RCT [62], the rate constants from the other 10 RCTs with vitamin D-fortified foods and from RCTs with vitamin D supplements were comparable, suggesting similar bioavailability across a range of food products. The present IPD's finding that 12 µg/day of vitamin D, supplied by fortified foods together with habitual intake, can prevent wintertime vitamin D deficiency (serum 25(OH)D < 30 nmol/L) in the vast majority of individuals is broadly in line with nationally representative data from Finland, who have one of the most progressive vitamin D food fortification programmes in Europe. For example, the representative National *FINDIET 2012* survey in Finland has shown that the mean daily vitamin D intake has increased from 3 and 5 µg/day for women and men, respectively, in 2002 (prior to instigation of food fortification a year later) to 18 and 17 µg/day for women and men, respectively, in 2012 [78]. Such increases in vitamin D intakes have been mirrored by notable improvements in status over the same period. Data from the *Finnish Health* surveys in 2000 and 2011 show that the mean standardized serum 25(OH)D increased from 48 nmol/L to 65 nmol/L, and prevalence of serum 25(OH)D < 30 nmol/L decreased from 13% to < 1% [79]. From a safety perspective, the present IPD suggested a vitamin intake of 12 µg/day yielded an upper 97.5th percentile serum 25(OH)D of 132 nmol/L and the 2011 *Finnish Health* survey only reported 0.2% of its 4051 participants with serum 25(OH)D > 125 nmol/L [79].

Limitations of the present IPD analysis are exemplified in the variation in the 97.5th percentile estimates at the 50 nmol/L 25(OH)D threshold, much of which was attributable to less than 10% of the population (i.e., moving from the 90th to 97.5th percentile). Sensitivity analyses were used to explore the potential sources of this variability, as the 92 µg vitamin D/day required to maintain 97.5% of individuals with serum 25(OH)D > 50 nmol/L, based on the unadjusted model, predicted an upper 97.5th percentile serum 25(OH)D of 220 nmol/L, which is well in excess of the upper serum thresholds. Sub-group analysis for RCTs where compliance data were available showed that at the 50 nmol/L serum 25(OH)D threshold, intake estimates at the 97.5th percentile were 8.4 and 10.1 µg/day lower when a minimum compliance threshold of 80% and 95%, respectively, were applied compared to estimates from the model not accounting for compliance. In terms of other potential sources of variability, there can be substantial variability associated with laboratory measurement of serum 25(OH)D [80]. The use of standardized serum 25(OH)D data has many merits in overcoming some of this method-related differences in estimates [81], but this is not always feasible, particularly for RCTs. In addition, the estimates of total vitamin D intake used in the analyses are subject to measurement errors arising from the variety of different dietary assessment techniques used by the various RCTs. To estimate habitual vitamin D intakes, a time frame of sufficient duration to capture infrequent

food consumption (e.g. liver, fatty fish) is required (e.g. a month is reasonable) [82], which is why many authors used validated FFQ methods to avoid underreporting. On the other hand, it has been suggested that FFQ often tend to overestimate nutrient intakes compared to food record-based approaches [82], however this has not been verified for vitamin D. Differences in the coverage of vitamin D in foods within different food compositional databases [1, 25] used to estimate vitamin D intake, as well as the vitamin D compounds included, may also have introduced variability into our analysis. Our sensitivity analyses showed that adjusting for method of vitamin D assessment and for method of serum 25(OH)D measurement increased the intake estimates at the 97.5th percentile by 0.7, 1.4 and 10 µg/day, and 1.1, 2.2 and 16.7 µg/day, respectively, at the respective ≥ 25, ≥ 30 and ≥ 50 serum 25(OH)D thresholds. In addition, the leave-one-out sensitivity analysis did not highlight use of chromatographic versus non-chromatographic or FFQ versus non-FFQ methods of vitamin D status and intake assessment in RCTs, respectively, as key factors in driving the high RDA estimates at the 50 nmol/L threshold. While this sensitivity analysis also suggested there were no overly influential RCTs, it is possible that there was a conflation of the variability in compliance, intake estimates and 25(OH)D analytical data, which when combined with between-individual variability in dose–response, contributed to the very high DRV estimates at the 50 nmol/L threshold in the unadjusted analysis.

The strengths of the present work include the application of the IPD approach to the data from 11 vitamin D-fortified food-based RCTs in both children and adults which met or exceed the eligibility criteria of IOM and/or EFSA, and which were identified through a systematic review thus increasing the external validity of our findings. Study quality was generally high and the majority of data are recent, with 9 of 11 of trials published in the last 7 years. The majority of studies had a low risk of bias across the 7 categories.

In conclusion, this IPD analyses of food-based vitamin D RCTs has provided new DRV estimates for vitamin D using models both adjusted and unadjusted for baseline serum 25(OH)D and other covariates. The approach used for data analysis, including model and adjustments included, had a profound impact on the DRV estimates generated. The work highlights the importance of being able to capture between-participant variability, crucial for estimating individual-based DRV recommendations. The DRV estimates for the 50 nmol/L 25(OH)D threshold both here and from our previous supplement trial-based IPD analysis are higher than the recommendations from NNR, IOM and EFSA, which used standard meta-regression based on aggregate data from vitamin D supplement RCTs. The present IPD also shows that the RNI and RI/RDA estimates at the 25 and 50 nmol/L serum 25(OH)D threshold, respectively, for children are ≥ 2 times lower than those for adults, which differs from agency reports to date. Finally, the IPD work also further informs and adds to the evidence-base around implementation of food-based approaches to tackle inadequate vitamin D intake and status. For example, the present findings provide evidence on how using food-based approaches in attaining an intake of ~ 12 µg/day could prevent very low vitamin D status (i.e., serum 25(OH)D < 30 nmol/L), with significant potential for public health benefit.

Author contributions KDC, MEK and CR designed the research; KDC and MEK defined the eligibility criteria for the food-based vitamin D randomized controlled trials (RCTs) for inclusion in the individual participant data (IPD)-level meta-regression analysis; KDC conducted the electronic searches; Study selection and decision on which met the eligibility criteria and we included was conducted by KDC and MEK; KDC, LT and MEK performed the quality assessment of eligible studies; KDC, RA, IMG, KHM, JN, IT, LT, SAL-N, LT, MPV, UT, GJ, VVM, BLS, JH, AK, DW, RV, IO, PKA, NRB, HAW accessed, formatted and supplied the IPD from their 11 included RCTs which formed the core pooled dataset upon which this work was based; An assessment of the risk of bias in the included RCTs was performed by KDC and LT; CR performed the statistical analyses and derivation of vitamin D dietary reference value estimates; KDC and CR wrote the first draft of the paper, with all authors providing input and comment on subsequent versions; All authors read and approved the final manuscript.

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Code availability The R code for fitting linear and nonlinear models is presented in Cashman KD, Ritz C (2019). Individual participant data (IPD)-level meta-analysis of randomised controlled trials among dark-skinned populations to estimate the dietary requirement for vitamin D [34].

Compliance with ethical standards

Conflicts of interest The following authors had no conflicts of interest: Kevin D. Cashman, Mairead E. Kiely, Rikke Andersen, Ida M. Grønborg, Katja H. Madsen, Janna Nissen, Inge Tetens, Laura Tripkovic, Laura Toxqui, M. Pilar Vaquero, Ulrike Trautvetter, Gerhard Jahreis, Vikram V. Mistry, Bonny L. Specker, Jürgen Hower, Anette Knoll, Dennis Wagner, Reinhold Vieth, Inger Öhlund, Pia Karlsland Åkeson, Neil R. Brett, Christian Ritz. Hope A. Weiler at the time of the trial received a small speaker's honoraria for presenting at the annual conferences organized by Dairy Farmers of Canada [Weiler H. Role of dairy in body composition and health. Dairy Research Symposium, Dairy Farmers of Canada and Agriculture Canada, Ottawa, Feb 5, 2016]. Susan A. Lanham-New is Research Director of D3Tex Ltd which holds the UK and Gulf Corporation Council (GCC) Patents for the use of UVB material in preventing vitamin D deficiency in women who dress for cultural style. SLN also received a small speaker's honoraria for presentations at two conferences on Vitamin D organised by Solaris.

Ethics standards Approval by a research ethics committee to conduct this meta-analysis was not required because the aim of this secondary analysis was consistent with the ethical approval received for the individual studies. The current analysis was conducted on anonymized data.

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