ORIGINAL CONTRIBUTION

Individual participant data (IPD)-level meta-analysis of randomised controlled trials to estimate the vitamin D dietary requirements in dark-skinned individuals resident at high latitude

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Abstract

Context and purpose There is an urgent need to develop vitamin D dietary recommendations for dark-skinned populations resident at high latitude. Using data from randomised controlled trials (RCTs) with vitamin D_3-supplements/fortified foods, we undertook an individual participant data-level meta-regression (IPD) analysis of the response of wintertime serum 25-hydroxyvitamin (25(OH)D) to total vitamin D intake among dark-skinned children and adults residing at $\geq 40°$ N and derived dietary requirement values for vitamin D.

Methods IPD analysis using data from 677 dark-skinned participants (of Black or South Asian descent; ages 5–86 years) in 10 RCTs with vitamin D supplements/fortified foods identified via a systematic review and predefined eligibility criteria. Outcome measures were vitamin D intake estimates across a range of 25(OH)D thresholds.

Results To maintain serum 25(OH)D concentrations ≥ 25 and 30 nmol/L in 97.5% of individuals, 23.9 and 27.3 µg/day of vitamin D, respectively, were required among South Asian and 24.1 and 33.2 µg/day, respectively, among Black participants. Overall, our age-stratified intake estimates did not exceed age-specific Tolerable Upper Intake Levels for vitamin D. The vitamin D intake required by dark-skinned individuals to maintain 97.5% of winter 25(OH)D concentrations ≥ 50 nmol/L was 66.8 µg/day. This intake predicted that the upper 2.5% of individuals could potentially achieve serum 25(OH)D concentrations ≥ 158 nmol/L, which has been linked to potential adverse effects in older adults in supplementation studies.

Conclusions Our IPD-derived vitamin D intakes required to maintain 97.5% of winter 25(OH)D concentrations ≥ 25, 30 and 50 nmol/L are substantially higher than the equivalent estimates for White individuals. These requirement estimates are also higher than those currently recommended internationally by several agencies, which are based predominantly on data from Whites and derived from standard meta-regression based on aggregate data. Much more work is needed in dark-skinned populations both in the dose–response relationship and risk characterisation for health outcomes.

Trail registration PROSPERO International Prospective Register of SystematicReviews (Registration Number: CRD42018097260)

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

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

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NNR	The Nordic Council of Ministers' Nordic Nutrition Recommendations
RCT	Randomized controlled trial
RDA	Recommended dietary allowance
SACN	The Scientific Advisory Committee on Nutrition
UL	Tolerable upper intake level
UVB	Ultraviolet B
WHO–FAO	World Health Organisation–Food and Agriculture Organization
SR-MA	Systematic reviews and meta-analyses

Introduction

Vitamin D deficiency has significant implications for human health throughout life [1]. Most worldwide expert bodies agree that serum 25-hydroxyvitamin D [25(OH)D] concentrations below 25/30 nmol/L indicate an increased risk of clinical vitamin D deficiency implicated in the development of childhood nutritional rickets and adult osteomalacia [2–6]. In North America and Europe, dark-skinned racial/ethnic subgroups are at a much higher risk of low vitamin D status in comparison to their White counterparts. For example, across racial/ethnic groups in the National Health and Nutrition Examination Survey 2011–2014 in the US, the prevalence of serum $25(OH)D < 30$ nmol/L (vitamin D deficiency) in Non-Hispanic white, Hispanic, Non-Hispanic Asian and Non-Hispanic black participants have been reported as 2.1%, 5.9%, 7.6% and 17.5%, respectively [7]. Within the Canadian Health Measures Surveys Cycles 1–3 (covering 2007–2013), the prevalence of vitamin D deficiency was 6% in White versus 20% among participants of ethnic minority [8]. Dark-skinned ethnic groups within Europe are also worryingly at much increased risk of vitamin D deficiency compared to their White counterparts [9, 10]. Recent data from the UK Biobank show that the prevalence of serum $25(OH)D < 25$ nmol/L among adult participants of South Asian and Black ethnicity was much higher than in Caucasians (57.3% and 36.3% v. 11.7%, respectively) [11]. Within the UK-dwelling South Asian population, those of Pakistani ethnicity had the highest risk of serum $25(OH)D < 25$ nmol/L (66% v. 54% and 44% for Indian and Bangladeshi, respectively) [12]. Recent data from a population-based health survey among immigrant adults in Finland show that the prevalence of vitamin D deficiency in Somali and Kurdish participants was much higher than that of the general Finnish population (24.1% and 48.8% v. 0.9%, respectively) [13]. In Sweden, there was also a much higher prevalence of vitamin D deficiency after summer in dark-skinned compared to fair-skinned 5–7-year-old children (17% and 3.7%, respectively) [14].

Dietary Reference Values (DRVs), as estimates of the vitamin D dietary requirements, provide a framework for prevention of vitamin D deficiency among almost all individuals in the population [15]. Despite the fact that DRVs for vitamin D have been re-evaluated by several authorities in the past decade (see [16–18], for reviews), recommendations have been, by and large, based predominantly on an assumption that the dietary requirements between racial groups do not differ. Not from neglect or a lack of consideration of the issues, this assumption is largely due to an absence of data on which to base decisions for vitamin D requirements and the dietary recommendations to achieve them—a key knowledge gap identified by a number of authorities [2–4]. A small number of suitable vitamin D randomized controlled trials (RCTs) of dark-skinned children and adults existed around the time of the recent DRV reviews, ranging from one to five RCTs depending on the review year [19–23] and since then, additional RCTs have been published [24–29]. Of particular note, a number of trials compared White versus Black or fair versus dark skinned, and several, but not all [19], reported higher dietary vitamin D requirements for Black and dark-skinned participants compared with their White counterparts [20, 24, 30].

Increasingly, the use of individual participant data (IPD)-level meta-regression analysis is recognized as best practice [31], as it avoids some of the limitations intrinsic to standard meta-regression based on aggregate data [18, 32]. Thus, pooling of the individual data from suitable RCTs using an IPD approach offers a novel opportunity to investigate DRV for dark-skinned individuals residing at higher latitudes, while also ensuring greater representation, by considering data from several studies in different contexts, instead of relying on specific data from one specific study undertaken in a particular context [4].

The aims of the present work were firstly, to identify RCTs with vitamin D_3 supplements or fortified foods in dark-skinned participants residing at $> 40°$ N using a systematic review process and to undertake an 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 these IPD-derived vitamin D dietary requirement estimates (i.e., estimates of the daily dietary vitamin D needed in achieving 25(OH)D concentrations above recommended thresholds) for dark-skinned individuals with international DRV, which were largely based on vitamin D_3-supplement RCTs of White individuals; as well as comparing these estimates with those from our previous IPDs of White children and adults (based on vitamin D_3-supplement and/or -fortified food RCTs [32, 33]). Lastly, to inform safety considerations, each of the vitamin D intake requirement estimates generated were compared to the current age-appropriate Tolerable upper intake levels (ULs) for vitamin D [2, 34] and the estimates were also used to predict the upper 97.5th percentiles of serum

25(OH)D concentration achieved. These predicted concentrations were bench-marked against those suggested as high serum 25(OH)D concentrations by the Institute of Medicine (IOM) [2] and the European Food Safety Authority (EFSA) [35] as well as in two high-dose vitamin D supplementation trials in older adults with evidence of increased risk of falls and/or factures [36, 37].

Materials and methods

The description of the scientific approach and methodology used in the present work has been outlined in a detailed study protocol [38], and aligns very closely with our recent similar IPD of White children and adults [33]. Therefore, only an overview is presented here to provide context and to update on any amendments since the publication of the study protocol.

Adherence to guidelines, registration and ethics approval

The present IPD meta-regression analysis of data from vitamin D RCTs follows the guidance provided as part of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)-IPD statement [39]. The IPD meta-regression analysis was registered with the PROS-PERO International Prospective Register of Systematic Reviews (registration number: CRD42018092343; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=92343). 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 IPD analysis was conducted on anonymized data.

Systematic review to identify eligible papers

Within the Population Intervention Comparison Outcome (PICO) framework for systematic reviews [40], the populations of interest in this study were specified as dark-skinned male and female children and adults, excluding studies in infants (0–12 months) and young children (12–23.9 months), pregnant or lactating women [32]. While dark-skinned individuals were defined as those with a Fitzpatrick skin type of V or VI [38], we were aware that it is not always measured or reported within studies. Should Fitzpatrick skin type not be reported in the identified studies of dark-skinned individuals in the present work, particular emphasis was placed on studies performed on individuals who identify as of Black or South Asian descent, as these are the population groups most studied to-date in terms of vitamin D dietary requirements. The full details of inclusion and exclusion criteria for the vitamin D RCTs considered for eligibility are outlined in the study protocol and elsewhere [32, 33, 38]. In addition, participants with missing vitamin D supplement adherence data or with a vitamin D supplement adherence of < 70% were excluded from the primary analysis as total vitamin D intake estimates could be considered insecure.

Identification of studies: information sources and search strategy

During May–July 2018, electronic searches were performed in PubMed, Ovid Medline and Embase online databases 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, based closely on those used by us previously [33, 38, 41, 42] and which accounted for the inclusion/exclusion criteria outlined above. An exemplar search strategy specifically adapted for PubMed is shown in Supplemental Table 1 in the 'Online Resource'. The methods used in the present systematic review per se follow the PRISMA statement [43].

Study selection and inclusion

Study selection was independently conducted by two pre-specified 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 for inclusion. 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 decade [2–5]. 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

Full details of the data collection processes, including data transfer agreement, as well as IPD integrity checks and data protection are presented in the study protocol [38]. In brief, for each eligible RCT, collaboration was requested and negotiated with the principal investigator [44]. 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, as described previously [33, 38]. In line with recently published principles and recommendations in relation to the sharing and reuse of IPD [45], data within the individual data files were used to establish an

Table 1 Selected design parameters of the 10 vitamin D_3 randomized controlled trials, conducted in winter and ≥40° N, as well as baseline and vitamin D-related outcome characteristics of dark-skinned subjects who completed the intervention studies and were included in data analyses*

Study	Andersen et al. 2008	Gallagher et al. 2013	Gallagher et al. 2014	Ng et al. 2014
(Reference number)	[23]	[19]	[20]	[21]
Trial registry ID	NR	NCT00472823	NCT00472823	NCT00585637
Design parameters:				
Location (° N)	Denmark (56°N)	USA (41° N)	USA (41° N)	USA (42° N)
Year of study	2007	2008–2010	2010–2011	2007–2010
Duration (and Months)	12 months	12 months	12 months	3 months (within Oct–March)**
Vitamin D_3 intervention(s) [supplemental dose]	Vit D_3 supplement [10 or 20 µg/d] v. placebo	Vit D_3 supplement [10, 20, 40, 60, 80 or 100 µg/d] v. placebo	Vit D_3 supplement [10, 20, 40 or 60 µg/d] v. placebo	Vit D_3 supplement [25, 50 or 100 µg/d] v. placebo
Subject characteristics:				
Baseline N	140	19	27	190
Racial/ethnic group	South Asian	Black/African American	Black/African American	Black/African American
Sex (Male:Female)	63:77	0:19	0:27	40:150
Age (year)	35.3±13.2[1]	64.9±6.6	35.9±6.9	52.6±11.7
Weight (kg)	70.1±15.5	88.2±16.3	89.0±21.4	90.1±21.2
BMI (kg/m²)	26.0±4.7	34.2±5.3	31.2±5.9	32.4±7.7
Dietary vitamin D (µg/day)[2]	2.5±2.0[a]	3.2±2.4[b]	2.1±1.1[b]	5.1±4.6[a]
Serum/plasma 25(OH)D (nmol/L)[3]	17.9±18.9[a]	33.4±10.9[b]	36.3±18.9[b]	42.8±21.6[b]
Endpoint				
Total vitamin D intake (µg/day)[4]	12.4 (11.5, 0.5–29.0)	51.2 (42.8, 0.9–112.3)	22.8 (12.0, 0.5–63.2)	49.2, (47.9, 0.2–124.0)
Serum/plasma 25(OH)D (nmol/L)[5]	38.5 (3.8–76.4)	85.0 (22.5–140.0)	67.5 (15.0–135.0)	78.6 (8.5–245.6)
% (n) <25 nmol/L	36.4 (51)	5.3 (1)	11.1 (3)	12.6 (24)
% (n) <30 nmol/L	40.7 (57)	5.3 (1)	14.8 (4)	14.2 (27)
% (n) <50 nmol/L	74.3 (104)	5.3 (1)	33.3 (9)	24.7 (47)

Study	Adebayo et al. 2018	Tripkovic et al. 2017	Grønborg et al. 2019
(Reference number)	[25]	[28]	[29]
Trial registry ID	NCT02212223	ISRCTN23421591	NCT02631629
Design parameters:			
Location (°N)	Finland (60°N)	UK (51.3°N)	Denmark (56°N)
Year of study	2014–2015	2011–2012 and 2012–2013	2016
Duration (and Months)	5 months (within Dec–May)	12 weeks (within Oct–March)	3 months (Jan–March)
Vitamin D_3 intervention(s) [supplemental dose]	Vit D_3 supplement [10 or 20 µg/d] v. placebo	Vit D_3-fortified Orange Juice [15 µg/d] v. Vit D_3-fortified Biscuit [15 µg/d] v. Placebo	Vitamin D-fortified low-fat cheese, yoghurt, eggs and crisp bread (supplying 30 µg/d in total) v. non-fortified equivalents
Subject characteristics:			
Baseline N	47	26	50

Table 1 (continued)

Study	Adebayo et al. 2018	Tripkovic et al. 2017	Grønborg et al. 2019
(Reference number)	[25]	[28]	[29]
Racial/ethnic group	Black/East African	South Asian	South Asian
Sex (Male:Female)	0:47	0:26	0:50
Age (year)	41.2±8.0	40.3±9.8	36.8±8.7
Weight (kg)	78.2±13.3	63.6±9.9	69.3±12.9
BMI (kg/m^2)	29.4±4.8	24.9±4.1	27.6±4.8
Dietary vitamin D (μg/day)[2]	11.3±5.1[a]	1.5±1.1[c]	1.3±0.8[a]
Serum 25(OH)D (nmol/L)[3]	52.2±14.0[c]	25.7±18.6[c]	48.6±25.0[c]
Endpoint			
Total vitamin D intake (μg/day)[4]	30.0 (27.5, 9.1–94.2)	12.1 (15.1, 0.2–19.3)	11.4 (1.4, 0.3–33.6)
Serum/plasma 25(OH)D (nmol/L)[5]	55.5 (26.3–127.1)	56.1 (10.0–89.6)	41.6 (13.5–137.0)
% (n) <25 nmol/L	0 (0)	23.1 (6)	20.0 (10)
% (n) <30 nmol/L	2.1 (1)	23.1 (6)	24.0 (12)
% (n) <50 nmol/L	31.9 (15)	42.3 (11)	64.0 (32)

Study	Rajakumar et al. 2015	Sacheck et al. 2017	Öhlund et al. 2017
(Reference Number)	[22]	[27]	[24]
Trial registry ID	NCT00732758	NCT01537809	NCT01741324
Design parameters:			
Location (°N)	USA (40.4 and 40.8°N)	USA (42°N)	Sweden (55 and 63°N)
Year of study	2008–2011	2011–2013	2012–2013
Duration (and Months)	6 months (enrolled Oct-March)	6 months (baseline Oct to Dec)	3 months (within Nov–March)
Vitamin D$_3$ intervention(s) [supplemental dose]	Vit D$_3$ supplement [25 μg/d] v. placebo	Vit D$_3$ supplement [25 or 50 μg/d v. recommended 15 μg/d***]	Vit D-fortified lactose-free, UHT milk [12 or 22 μg/d] v. non-fortified lactose-free, UHT milk
Subject characteristics:			
Baseline			
N	44	53	81
Racial/ethnic group	Black	Black/African American	Dark-skinned (Multiple)
Sex (Male:Female)	25:19	26:27	38:43
Age (year)	12.0±1.9	11.6±1.4	6.3±0.7

Table 1 (continued)

Study	Rajakumar et al. 2015	Sacheck et al. 2017	Öhlund et al. 2017
(Reference Number)	[22]	[27]	[24]
Weight (kg)	53.9 ± 20.8	51.6 ± 16.7	23.2 ± 4.8
BMI (kg/m²)	23.6 ± 6.8	22.2 ± 5.2	15.8 ± 2.1
Dietary vitamin D (µg/day)²	6.3 ± 3.9ᵃ	3.1 ± 2.8ᵃ	5.5 ± 2.5ᵃ
Serum 25(OH)D (nmol/L)³	42.4 ± 18.5ᶜ	44.6 ± 18.1ᶜ	47.4 ± 17.6ᶜ
Endpoint			
Total vitamin D intake (µg/day)⁴	17.2, (14.9, 1.5–38.0)	34.7 (28.7, 13.2–60.4)	19.6 (19.9, 3.3, 33.9)
Serum/plasma 25(OH)D (nmol/L)⁵	46.3 (13.9–104.9)	69.3 (20.3–152.0)	69.0 (24.0–130.0)
% (n) <25 nmol/L	11.4 (5)	3.8 (2)	1.2 (1)
% (n) <30 nmol/L	20.5 (9)	5.7 (3)	2.5 (2)
% (n) <50 nmol/L	61.4 (27)	15.1 (8)	19.8 (16)

*In some cases, additional dark-skinned participants in the study were not included in the analyses as they did not meet with the inclusion criteria (total $n = 753$)

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

***Study did not include a placebo group for ethical reasons, instead they used a standard care dose of 15 µg/d

¹Mean ± SD (all such values)

²Habitual dietary vitamin D intake assessed via semi-quantitative FFQᵃ, 7-day food diariesᵇ, or 4-day food/diet diariesᵇ

³Serum 25(OH)D measured by HPLCᵃ, RIAᵇ, or LC–MS/MSᶜ

⁴Mean (median, min–max) (all such values)

⁵Median (min–max) (all such values)

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

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

Identification

Articles identified through database searches (*n* = 242):
- Pubmed (*n* = 122)
- Medline (*n* = 39)
- Embase (*n* = 81)

Additional studies identified through other sources, including three trial registries* (*n* = 2)

Unique articles identified after duplicates removed (*n* = 76)

Screening

Records screened (*n* = 76)

Records excluded after title/abstract evaluation (*n* = 53)

Eligibility

Full-text articles assessed for eligibility (*n* = 23)

Full-text articles excluded (*n* = 12), with reasons:
- Latitude <40° (*n* = 4)
- No vitamin D intake estimate (*n* = 9)
- Endpoint not in winter (*n* = 5)
- Design incompatible with eligibility criteria (*n* = 4)
- >1 paper on same RCT (*n* = 4)
- Intervention incompatible with eligibility criteria (*n*=3)
- Duration <6 weeks (*n* = 2)
- In <2 year olds (*n* = 1)

Included

Studies invited to IPD meta-regression analysis (*n* = 11) and studies accepting (*n* = 10; total number of individual participants included = 677)

- Studies not accepting (*n*=1)

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 in advance of the synthesis and statistical analyses by the project biostatistician (CR).

Specification of outcomes and effect measures

Serum 25(OH)D concentration [in nmol/L (2.5 nmol/L = 1 ng/mL)] was the sole outcome considered in the IPD meta-regression analysis. Likewise, total vitamin D intake {µg [1 µg = 40 international units (IU)]} was the only predictor considered. Total vitamin D intake was defined as that from the diet (including personal vitamin D supplements, where permitted within an RCT) as well as that from any supplemental vitamin D dose provided in the RCT after accounting for adherence [46–48].

Quality assessment and risk of bias assessment for individual studies

The Jadad scale was used to assess the quality of the included RCTs [49], and an assessment of the risk of bias in these RCTs was performed using the Cochrane Collaboration's tool for assessing risk of bias [50]. Two pre-specified investigators (KDC and LT) independently assessed study quality and risk of bias in the RCTs.

Statistical analysis

Choice of model

A one-stage IPD meta-analysis [51, 52] was carried out using a model which approximated the curvilinear intake-serum concentration relationship over a wide vitamin D intake distribution [2, 4]. Specifically, a linear mixed regression model with vitamin D intake as the independent variable (a fixed effect) and square root-transformed serum 25(OH)D concentration as the dependent variable, corresponding to a quadratic regression model on the original scales. Study-specific random intercepts were also included to accommodate between-study variation typically exhibited in IPD analyses. Both unadjusted models and adjusted models including fixed-effect adjustments for baseline serum 25(OH)D concentrations, age and BMI were fitted. These adjustments, which are commonly used [4, 32, 33], were pre-specified [38]. Models with additional adjustments for methods of vitamin D intake estimation or serum 25(OH)D measurement were also fitted. To inform safety considerations around the various vitamin D intake estimates generated (see below), the present unadjusted and adjusted models were also used to predict the upper 97.5th percentiles of serum 25(OH)D concentration achieved.

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 [32]. Corresponding 95% confidence intervals on these estimated lower boundaries were obtained using a parametric bootstrap procedure with 1000 replications, as described previously [32, 33].

Leave-one-out sensitivity analysis To assess if there were any overly influential RCTs, the derivation of vitamin D intake estimates at the 97.5th percentile using the 50 nmol/L threshold based on an unadjusted model (as described above) was repeated leaving out one RCT at a time [33]. The impact of omission of each RCT individually is reported as change, both as µg/day and %, from the vitamin D intake estimate derived using all studies.

Subgroup analyses A number of specific subgroups had been considered previously [2, 4, 32, 33]. We fitted separate models for subgroups of children (< 18 years) and adults (≥ 18 years) and for subgroups of participants of South Asian and African ethnicity. We also fitted separate models for a subgroup consisting of adult participants with

BMI < and ≥ 30 kg/m^2. The present work had individual total vitamin D intake estimates which accounted for adherence to vitamin D supplements/fortified foods by participants (i.e., for all those with vitamin D supplement adherence of ≥ 70%, as those below this threshold were excluded from the analysis), whereas our previous IPD of White individuals did not build adherence into the estimation of total vitamin D intakes but rather applied a minimum fortified food compliance threshold of 80% for inclusion of participants in the analyses [33]. Therefore, to better facilitate a comparison of the vitamin D DRV estimates from both IPDs, we calculated the total vitamin D intake estimates for Black individuals (children and adults) without accounting for adherence to vitamin D supplements/fortified foods, and fitted separate adjusted models after applying a minimum compliance threshold of 80%, as per our previous IPD of White individuals [33]. The present work allowed for up to 100 µg/day of supplemental vitamin D which led to a maximum individual total vitamin D intake estimate of 124 µg/day, whereas our previous IPD of White individuals had a 50 µg/day total vitamin D intake threshold [32]. Therefore, as an additional subgroup analysis, only those individuals with total vitamin D intake estimates < 50 µg/day (applying a minimum compliance threshold of 80%) in the current population were included. The subgroup analyses were pre-specified rendering testing for interaction unnecessary.

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

To inform safety considerations, each of the various vitamin D intake requirement estimates generated for children and adults, both separately and pooled, were compared to the current ULs for vitamin D for children (50–75 µg/day, depending on age group and agency) and adults (100 µg/day), respectively [2, 34]. Furthermore, and in line with our recent IPD analyses of vitamin D requirements in White individuals [33], we benchmarked the upper 97.5th percentile of serum 25(OH)D concentrations arising from the various vitamin D intake estimates from the present work against serum 25(OH)D concentrations of 150 and 200 nmol/L, as per IOM [2] and EFSA [35], respectively. In addition, the following serum 25(OH)D concentrations achieved in two high-dose vitamin D supplementation trials in older adults with evidence of increased risk of falls and/or factures [36, 37] were used as a guide. Following an annual bolus dose of 12,500 µg vitamin D$_3$ [36], median serum 25(OH)D concentrations of older women were 120 and 90 nmol/L at 1 and 3 months, respectively, which is the time frame in which most falls occurred in the trial. At 1 month, 82% of older women were at serum 25(OH)D concentrations of 100 nmol/L, and 24% at 150 nmol/L or higher [36]. Observational analyses within a study of older men

and women provided with monthly bolus doses of vitamin D_3 and/or $25(OH)D_3$ showed that those in the highest quartile of serum $25(OH)D$ at the 12-month follow-up (range: 112–247 nmol/L) had the greatest odds of falling and the most falls compared with those who reached the lowest quartile (range: 53–76 nmol/L) [37].

Results

Study selection and IPD obtained

Our search identified 242 unique articles. Following screening of titles and abstracts, 23 full-text articles were assessed for eligibility, of which 11 studies [19–25, 27–29, 53] fulfilled the eligibility criteria (Fig. 1). IPD were sought and obtained for ten studies, with a total of 677 randomized participants that fulfilled the eligibility criteria. In the case of one RCT for which IPD was sought [53], the data could not be shared due to a lack of agreeable jurisdiction that both institutions could work with in terms of interpretation of the data transfer agreement. A number of the studies had additional participants that did not meet the eligibility criteria (e.g., were White-skinned (in six RCTs), sampled outside the specified winter period (in four RCTs), were given vitamin D_2-containing fortified foods (one RCT), were given vitamin D_3 supplements at a dose above our threshold of 4000 IU/day (one RCT), or had missing data on either adherence or total vitamin D intake (in four 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 ten accepted studies and their participants. The RCTs were conducted in the USA and in four countries within Europe. Six studies were conducted in Blacks, three in South Asians and one in a mixed group of dark-skinned individuals. Six studies were conducted in adults, three in children, and one in both age-groups. Five studies were conducted in adult females only, the rest were conducted in studies with a mixture of males and females.

Mean baseline serum/plasma $25(OH)D$ concentrations among the ten RCTs ranged from 17.9 to 52.2 nmol/L, and were between 17–30 nmol/L in two RCTs, 30–39.9 nmol/L in two RCTs, 40–49.9 nmol/L in five RCTs, and 50–59.9 nmol/L in one RCT, respectively (Table 1). The ten RCTs were conducted in latitudes of 40° N or higher, locations of five sites were within 40–49.9° N and another five sites were within 50–63° N, respectively. Assays for measuring serum $25(OH)D$ varied widely amongst the studies and included radioimmunoassay in three RCTs, liquid

chromatography tandem mass spectrophotometry in six RCTs, and high-performance liquid chromatography in 1 RCT, respectively (Table 1).

The daily vitamin D interventions were either vitamin D_3 supplementation in seven RCTs or vitamin D_3-fortified food(s) in three RCTs. Of the three studies that used vitamin D-fortified food(s), one RCT each used milk; orange juice or biscuits; or a combination of four foods (vitamin D-fortified low-fat cheese, yoghurt, eggs and crisp bread) (Table 1). The daily dose of vitamin D provided by consumption of the assigned study vitamin D supplement or amount/serving size of the vitamin D-fortified food(s) ranged from 10 to 100 µg/day: four studies used ~ 10–20 µg/day, one study each used 25 or 30 µg/day, and one study each used 10–60, 15–50, 10–60, 10–100 µg/day (Table 1); one RCT [19] had an additional group which received 120 µg/day, but these subjects were excluded as this dose was above our upper threshold. Study duration ranged from 2 to 12 months. A range of dietary instruments was used to assess vitamin D intake, including 4-day diet diary (one study), 7-day food diaries (two studies) and semi-quantitative FFQ (seven studies; with five reporting their FFQ as validated for habitual vitamin D intake).

Study quality of included RCTs

All ten studies achieved a Jadad score of ≥ 3 (10% and 80% with scores of 4 and 5, respectively). In terms of contributing to these scores, method of randomization was reported in nine studies. One study was reported as blinded, but the method for blinding was unclear based on the information presented within the paper. All ten studies reported data on dropouts. Participant dropout ranged from 0 to 45.2% within a study arm and 12 study arms out of a total of 39 had a dropout rate of > 20%. It should be noted that the Jadad scale does not assess compliance, which is an important factor in vitamin D intervention studies. Compliance rates were reported in all ten studies (range of means: 73–96%, with 7 RCTs > 85%).

Risk of bias within studies

The summary assessments of risk of bias across domains and across the 10 RCTs are shown in Supplemental Table 2 in 'Online Resource'. All ten RCTs had either a low or unclear risk of selection bias (low risk of random sequence generation and allocation concealment for nine and eight RCTs, respectively, and the remainder had unclear risk). In relation to performance and detection bias, a majority of RCTs ($n = 6$–10) had low risk of bias for blinding of participants, personnel and of outcome assessment, with 2–4 RCTs having unclear risk in these domains. In relation to attrition bias, risk of bias in relation to incomplete outcome data was

low for six RCTs and unclear for four RCTs. Risk of bias for selective reporting was low in all ten 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.

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

Vitamin D intake estimates using the 50 nmol/L serum 25(OH)D threshold

The vitamin D intake estimate allowing 90%, 95% and 97.5% of dark-skinned individuals (adults and children) at latitudes $\geq 40°$ N to maintain serum 25(OH)D ≥ 50 nmol/L (the threshold of adequacy as selected by IOM [2], Nordic Council of Ministers' Nordic Nutrition Recommendations (NNR) [5] and EFSA [4]), assuming minimal UVB exposure, was 51.6, 61.0 and 69.1 μg/day, respectively, using the unadjusted model ($n = 677$) (Table 2, and see Fig. 2A). Adjusting for baseline 25(OH)D, age and BMI ($n = 675$), the vitamin D intake estimate allowing 90%, 95% and 97.5% of dark-skinned individuals to maintain serum 25(OH)D ≥ 50 nmol/L was 50.2, 59.1 and 66.8 μg/day, respectively (Table 2 and see Fig. 2B).

Vitamin D intake estimates using the 25 and 30 nmol/L serum 25(OH)D thresholds

Using the UK's Scientific Advisory Committee on Nutrition (SACN) 25(OH)D cut-off of ≥ 25 nmol/L [3], we estimated the vitamin D intake needed to maintain 90%, 95% and 97.5% of dark-skinned individuals (adults and children) above this threshold to be 17.5, 26.8 and 34.9 μg/day, respectively, based on the unadjusted model ($n = 677$); this decreased to 14.3, 23.1 and 30.8 μg/day, respectively, with adjustment for covariates ($n = 675$) (Table 2). The IOM, NNR and EFSA used serum 25(OH)D < 30 nmol/L to indicate an increased risk of vitamin D deficiency [2, 4, 5], but they did not derive a vitamin D intake for this threshold. We estimated a vitamin D intake of 25.4, 34.7 and 42.8 μg/day to maintain 90%, 95% and 97.5% of individuals ≥ 30 nmol/L, respectively, using the unadjusted model ($n = 677$), and 22.5, 31.4, and 39.0 μg/day, respectively, using the adjusted model ($n = 675$). As the increases in vitamin D intake estimates moving from the 90th to the 97.5th percentile of requirements were large at these lower thresholds, it is important to also emphasize intake estimates at the 90th and 95th percentiles.

Subgroup analysis based on ethnic grouping The estimated vitamin D intakes needed to maintain 90%, 95% and 97.5% of South Asian and Black individuals at the 25 and 30 nmol/L serum 25(OH)D thresholds are shown in Table 3. We estimated a vitamin D intake of 25.7 and 23.9 μg/day to maintain 97.5% of South Asians ≥ 25 nmol/L, using the unadjusted ($n = 216$) and adjusted models ($n = 215$), respectively. At the 30 nmol/L serum 25(OH)D threshold, the equivalent vitamin D intake estimates were 29.1 and 27.3 μg/day, respectively. In a subgroup analysis in which only Black individuals (children and adults) with a total vitamin D intake < 50 μg/day ($n = 265$) were included, we estimated a vitamin D intake of 21.3 and 27.2 μg/day was needed to maintain 97.5% of individuals ≥ 25 and 30 nmol/L, respectively, using the adjusted model (see Supplemental Table 3 in 'Online Resource'). While presented for Black individuals (Table 3), the estimated vitamin D intakes needed to maintain the higher percentiles of South Asian individuals with the serum 25(OH)D ≥ 50 nmol/L were not reported as their total vitamin D intakes were below such estimates (maximum intake 33.6 μg/day), and thus, the estimates would be extrapolations.

Additional subgroup and sensitivity analyses The outcomes of additional subgroup and sensitivity analyses, set at each of the three serum 25(OH)D thresholds, are provided in the Supplemental Material in 'Online Resource'. In brief, leave-one-out sensitivity analysis showed that there were no overly influential RCTs (Supplemental Table 4 in 'Online Resource'). Using adult RCT data only, limiting the unadjusted analysis to those with a BMI < 30 kg/m^2 ($n = 265$) reduced the 97.5th percentile vitamin D estimates by 4.3 to 8.0 μg/day, dependent on serum 25(OH)D threshold, compared to those with BMI ≥ 30 kg/m^2 ($n = 213$) (Supplemental Table 5 in 'Online Resource'). Using data from Black individuals only, vitamin D intake estimates at the 97.5th percentile were very similar irrespective of whether based on subjects whose total vitamin D intake estimates accounting for adherence to vitamin D supplements/fortified foods or where a minimum of 80% compliance was applied for subject inclusion in the analysis per se rather than applying it in the calculation of total intake estimates (Supplemental Table 3 in 'Online Resource'). Additional adjustment for methods of serum 25(OH)D and vitamin D intake assessment yielded estimates which were marginally to modestly higher, respectively, than that from analysis of all individuals irrespective of method (see Supplemental Material in 'Online Resource').

Table 2 Individual Participant Data (IPD) meta-analysis-derived vitamin D intake estimates (μg/day) to maintain stated percentage of the population (percentile) at a serum 25(OH)D level at or above selected concentrations in dark-skinned participants residing between 40-63°N during winter[1]

Serum 25(OH)D	50th Percentile[2]	90th Percentile	95th Percentile	97.5th Percentile[3]
No adjustments				
All participants (*n*=677)				
≥25 nmol/L	–	17.5 (10.2, 23.8)	26.8 (19.3, 33.8)	34.9 (27.2, 42.1)
≥30 nmol/L	–	25.4 (18.1, 31.7)	34.7 (26.1, 41.6)	42.8 (35.2, 49.7)
≥50 nmol/L	18.8 (12.6, 25.1)	51.6 (44.5, 58.6)	61.0 (53.1, 68.2)	69.1 (60.2, 77.1)
Adjusted model				
All participants (*n*=675)				
≥25 nmol/L	–	14.3 (7.8, 20.0)	23.1 (16.1, 29.0)	30.8 (23.5, 37.1)
≥30 nmol/L	–	22.5 (16.1, 28.8)	31.4 (24.1, 37.5)	39.0 (31.4, 45.5)
≥50 nmol/L	19.0 (13.4, 24.6)	50.2 (43.7, 56.4)	59.1 (52.1, 65.7)	66.8 (58.6, 73.8)

[1]Results based on a 1-stage IPD quadratic 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

[2]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

[3]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)

Fig. 2 The relation between serum 25-hydroxyvitamin D (25(OH)D) concentrations (in extended winter) and total vitamin D intake in healthy dark-skinned individuals aged 5–86 years living between 40 and 63°N based on individual participant data (IPD). The solid central lines correspond to the fitted regression lines based on one-stage IPD meta-analysis (unadjusted model ($n = 677$ individuals) (Panel A) and model adjusted for age, BMI and baseline 25(OH)D ($n = 675$ individuals) (Panel B)) and the corresponding 95% prediction bands are shown in gray. *Note*: the fitted curve and the 95% confidence band are displayed using logarithmic axes. Overlapping dots make some appear more darkly coloured

Safety considerations of the IPD-derived dietary vitamin requirement estimates

Using the age-stratified dietary vitamin D requirement estimates from the unadjusted and adjusted models (Table 4), none of the estimates for children or adults at the 25 or 30 nmol/L serum 25(OH)D threshold exceeded the minimum age-specific UL for vitamin D (50 and 100 μg/day for children or adults, respectively [34]). At the 50 nmol/L serum 25(OH)D threshold, none of the estimates for adults or those covering 90 or 95% in children exceeded the UL. The intake estimates covering 97.5% of children at the 50 nmol/L serum 25(OH)D threshold were at or marginally exceeded the UL (50 and 56 μg/day from the adjusted and unadjusted models, respectively).

The predicted upper 97.5th percentile serum 25(OH)D concentrations achieved at vitamin D intake estimates for all participants, derived from the unadjusted and adjusted models, are shown in Table 4. None of the vitamin D intake estimates at the 25 or 30 nmol/L serum 25(OH)D threshold, from either the unadjusted or adjusted model, and whether covering 90, 95 or 97.5% of individuals, led to predicted upper 97.5th percentiles of serum 25(OH)D concentrations exceeding 150 or 200 nmol/L. At the 50 nmol/L threshold, while the vitamin D intake estimates covering 90% (either model) or 95% (adjusted model) of individuals predicted upper 97.5th percentiles of serum 25(OH)D

concentrations less than 150 nmol/L, those intakes covering 95% (unadjusted) and 97.5% (both models) of individuals yielded serum 25(OH)D concentrations in the range 158–174 nmol/L. 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 102.3 and 96.4 nmol/L, based on the unadjusted and adjusted models, respectively (data not shown).

Discussion

Recent data highlighting the increased risk of vitamin D deficiency and low vitamin D status among dark-skinned populations resident at high latitudes [7–12, 54], which has been referred to as a latitude-skin colour mismatch [55], has emphasized the need to develop targeted dietary recommendations for vitamin D for people of colour resident at high latitude. The present IPD analyses, based on pooled individual data from ten winter-based RCTs using vitamin D supplements or fortified foods, provides estimates for vitamin D_3 intakes needed to maintain serum 25(OH)D concentrations of dark-skinned individuals above commonly used thresholds for defining risk of vitamin D deficiency (25 and 30 nmol/L) and adequacy (50 nmol/L) [2–5]. We estimated that the vitamin D intake required to maintain 97.5% of serum 25(OH)D concentrations ≥ 50 nmol/L in

Table 3 Individual Participant Data (IPD) meta-analysis-derived vitamin D intake estimates (μg/day) to maintain stated percentage of the population (percentile) at a serum 25(OH)D level at or above selected concentrations in South Asian (A) and Black participants (B) during winter[1]

A. South Asian Serum 25(OH)D	50th Percentile[2]	90th Percentile	95th Percentile	97.5th Percentile[3]
No adjustments				
All participants (n=216)				
≥25 nmol/L	–	17.9 (10.4, 25.4)	22.1 (14.6, 31.0)	25.7 (18.4, 35.7)
≥30 nmol/L	–	21.2 (14.0, 29.3)	25.5 (17.6, 34.8)	29.1 (21.3, 39.1)
Adjusted model				
All participants (n=215)				
≥25 nmol/L	–	17.0 (12.0, 22.7)	20.7 (15.3, 27.0)	23.9 (18.4, 31.2)
≥30 nmol/L	–	20.4 (15.3, 26.8)	24.1 (18.8, 30.0)	27.3 (21.8, 34.7)
B. Black Serum 25(OH)D	50th Percentile[2]	90th Percentile	95th Percentile	97.5th Percentile[3]
No adjustments				
All participants (n=430)				
≥25 nmol/L	–	10.7 (3.3, 18.5)	20.3 (12.0, 28.8)	28.7 (20.6, 37.3)
≥30 nmol/L	–	19.4 (12.4, 26.8)	29.0 (21.5, 37.8)	37.3 (29.4, 46.3)
≥50 nmol/L	14.4 (7.4, 21.3)	48.3 (41.1, 56.3)	58.0 (50.0, 66.4)	66.4 (58.2, 76.5)
Adjusted model				
All participants (n=429)				
≥25 nmol/L	–	6.4 (0.5, 16.0)	15.9 (6.0, 25.4)	24.1 (13.6, 35.6)
≥30 nmol/L	–	15.5 (5.8, 25.5)	25.0 (15.1, 35.4)	33.2 (23.7, 44.2)
≥50 nmol/L	12.6 (3.9, 20.6)	46.0 (36.6, 55.5)	55.5 (45.7, 65.6)	63.8 (53.2, 75.0)

[1]Results based on a 1-stage IPD quadratic 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

[2]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

[3]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)

Table 4 Estimates of dietary requirement for vitamin D (µg/day) for all and by age grouping, using different serum 25(OH)D thresholds and percentiles, and projected upper 97.5th percentile serum 25(OH)D concentrations achieved at these intake estimates for all participants

Requirement percentile (at specified threshold)	Vitamin D intake requirement (µg/d)			Projected upper 97.5th percentile serum 25(OH)D concentrations (nmol/L)[1]
	Children	Adults	All	
Unadjusted model				
≥25 nmol/L:				
90th Percentile	18.4	21.8	17.5	100.8
95th Percentile	25.0	31.8	26.8	112.5
97.5th Percentile	30.8	40.5	34.9	123.2
≥30 nmol/L:				
90th Percentile	24.1	29.9	25.4	110.7
95th Percentile	30.7	39.9	34.7	122.9
97.5th Percentile	36.5	48.6	42.8	134.1
≥50 nmol/L:				
90th Percentile	43.0	56.9	51.6	146.8
95th Percentile	49.8	67.0	61.0	161.0
97.5th Percentile	55.7	75.7	69.1	173.9
Adjusted model[2]				
≥25 nmol/L:				
90th Percentile	10.2	19.0	14.3	91.2
95th Percentile	16.2	28.7	23.1	101.1
97.5th Percentile	21.5	37.1	30.8	110.3
≥30 nmol/L:				
90th Percentile	16.7	27.4	22.5	100.4
95th Percentile	22.7	37.1	31.4	111.0
97.5th Percentile	28.0	45.6	39.0	120.4
≥50 nmol/L:				
90th Percentile	38.4	55.7	50.2	135.0
95th Percentile	44.6	65.5	59.1	147.3
97.5th Percentile	50.1	74.0	66.8	158.3

[1] Projected upper 97.5th percentile serum 25(OH)D results based on the 1-stage IPD quadratic unadjusted and adjusted models for 'All' participants

[2] Adjusted for baseline serum 25(OH)D (mean), age (mean) and BMI (mean)

dark-skinned children and adults residing at > 40°N during extended winter to be 67 μg/day, using the adjusted model.

These estimates are much higher than current recommendations and our previous IPD estimates among White-skinned groups. For example, using data from our recent IPD of White individuals [33] and applying the same model as used in the present work to best capture the curvature in the intake-status relationship, the vitamin D intake required to maintain 97.5% of serum 25(OH)D concentrations ≥ 50 nmol/L was 1.3- to 1.7-times greater for dark-skinned individuals than that for White individuals (depending on unadjusted or adjusted model estimates and method for accounting for participants' adherence). While BMI and baseline 25(OH)D were on average higher and lower, respectively, in the dark-skinned compared to the White IPD datasets, the adjusted model included these covariates. Our first IPD of White individuals applied an upper total vitamin D intake threshold of 50 μg/day [32], compared to 100 μg/day used in the present IPD. Limiting the present dataset to include Black individuals with total vitamin D intakes < 50 μg/day only, showed that the 97.5th percentile vitamin D intake requirement estimate at the 50 nmol/L serum 25(OH)D threshold, based on an adjusted model, was 46.9 μg/day compared to 26.1 μg/day for White individuals [32].

The present analyses also highlights striking differences between the estimates at the 97.5th (as well as the 90th and 95th) percentiles for dark-skinned individuals at the 50 nmol/L threshold and the recommended 10 μg/day by NNR [5] and 15 μg/day by IOM (for those aged 1–70 years) [2] and EFSA [4]. These relate not only to the fact that these Agencies predominantly based their analyses on data from White participants [2, 4, 5] available at that time, but also, importantly, 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 [18]. 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 Recommended Dietary Allowance (RDA) and its European equivalents [18]. From a safety perspective, the present IPD suggested that the vitamin D intake required to meet or exceed the 50 nmol/L serum 25(OH)D threshold (i.e., 66.8 μg/day from the adjusted model) yielded an upper 97.5th percentile serum 25(OH)D of 158 nmol/L, below EFSA's 200 nmol/L threshold [35] but marginally higher than the 125–150 nmol/L, as suggested by IOM [2]. However, older individuals at the very top of the serum 25(OH)D distribution arising from an intake of 66.8 μg/day would be attaining concentrations associated with increased risk of falls and factures in monthly/yearly high-dose vitamin

D supplementation trials [36, 37]. The intake estimates for adults in the present work did not exceed the age-specific UL for vitamin D intake of 100 μg/day, established in 2011 for the US [2] and 2012 for Europe [34]. A 2016 systematic review and meta-analysis of hypercalcaemia, hypercalciuria, and kidney stones in long-term studies of vitamin D supplementation in adults (n = 17,801), showed an increased risk of hypercalcemia in vitamin D supplementation groups within 37 studies [56]. Subgroup analyses showed that the risk was not modified by vitamin D dose [≤ 20 (n = 3 studies) or > 20 μg/day (n = 33 studies)] and meta-regression showed no association between vitamin D dose and risk of hypercalcemia [56]. The EFSA will update their ULs for vitamin D in the next year or so, which will be important in terms of latest guidance on safety of vitamin D intakes. In relation to children, using the current age-specific UL of 50 μg/day [34], the intake estimates at the 90th and 95th percentiles were below, whereas the estimate at the 97.5th percentile (based on the adjusted model) just reached the UL.

We estimated that the vitamin D intakes required to maintain 97.5% of serum 25(OH)D concentrations ≥ 25 nmol/L [3] and ≥ 30 nmol/L in dark-skinned children and adults residing at > 40° N during extended winter were 31 μg/day and 39 μg/day, respectively, based on the adjusted model. These estimates contain large variation, much of which was attributable to less than 10% of the population (i.e., moving from the 90th–97.5th percentile) and hence this needs to be considered with caution. These estimates will be impacted to some extent by the relatively high total vitamin D intakes (between 50 and 124 μg/day) in some Black individuals, particularly adults, which can influence the slope of intake-status relationship at the lower serum 25(OH)D thresholds, which has generally been considered to be a more linear fit [42]. Using data from the South Asian participants only, which had total vitamin D intakes in the range ~ 1–34 μg/day, showed that the vitamin D intakes required to maintain 97.5% of individuals with serum 25(OH)D concentrations ≥ 25 and ≥ 30 nmol/L were 24–26 μg/day and 27–29 μg/day, respectively, depending on the model. The variation in estimates for both serum 25(OH)D thresholds on moving from the 90th to 97.5th percentiles in the South Asian participants was considerably less than that observed in the Black participants. Furthermore, when the analysis was restricted to only those Black participants who had total vitamin D intakes < 50 μg/day, so as to compare with our initial IPD of White individuals [32], the vitamin D intakes required to maintain 97.5% of serum 25(OH)D concentrations ≥ 25 and ≥ 30 nmol/L were 21 μg/day and 27 μg/day, respectively, using the adjusted model. These various estimates were about two-times higher than the equivalent for White participants from our previous IPD [32]. In addition, the estimates at the 25 nmol/L threshold, are higher, and strikingly so, than the recommended 10 μg/day by SACN,

which based their analyses on data from White participants [3]. All of the various estimates at the two lower serum 25(OH)D thresholds in the present work were well below the age-specific ULs for vitamin D intake and the upper 97.5th percentile serum 25(OH)D concentration of either 150 or 200 nmol/L.

The present IPD analysis had some limitations. The collection of RCTs was such that the baseline vitamin D status, total vitamin D intake and achieved 25(OH)D concentrations in the South Asian versus Black participants were quite heterogeneous which likely increased the variability in estimates at the lower serum 25(OH)D thresholds. This increased variability would explain the higher estimates for vitamin D intake requirement compared to those reported in some of the individual constituent studies [24, 25]. It may be that IPD analyses in each ethnic subgroup separately would yield more reflective estimates of vitamin D intake requirements, although the ethnic group-specific datasets can be limited. There were also likely other potential sources of variability within the analyses. For example, there can be substantial variability associated with laboratory measurement of serum 25(OH)D [57]. The use of standardized serum 25(OH)D data has many merits in overcoming some of this method-related differences in estimates [58], but this is not always feasible, particularly for RCTs. However, sensitivity analyses within the present work only showed a marginal effect of assay on the estimates. The estimates of total vitamin D intake used in the analyses are also subject to measurement errors arising from the variety of different dietary assessment techniques used by the various RCTs, as discussed by us previously [33]. Furthermore, differences in the coverage of vitamin D in foods, especially ethnic foods, within different food compositional databases [17, 59] used to estimate vitamin D intake, as well as the vitamin D compounds included, may also have introduced variability into our analysis. Sensitivity analyses showed a moderate effect of dietary assessment technique on the requirement estimates.

There are also a number of considerations in relation to the requirement estimates generated in the present work. DRI are intended for a general healthy population [2]. While reflective of the situation within the general population in many countries, it should be noted that a significant portion of the present sample were either overweight or obese, particularly within the adult subset. However, RCTs used by various agencies in establishing the DRI for vitamin D [2–5] would likewise have included participants who were overweight or obese. The present work provided vitamin D requirement estimates which adjusted for BMI and also presented estimates stratified by BMI $<$ and ≥ 30 kg/m^2. It should also be emphasised again that the estimates from the present IPD of dark-skinned individuals were compared with equivalent IPD estimates from White individuals

generated in separate analyses, and thus, no direct comparisons between dark-skinned and White individuals have been made in the present work. Furthermore, the analyses did not have the ability to explore reasons for racial differences in requirements, as beyond baseline 25(OH)D and BMI (which were adjusted for), it did not have data on other parameters. For example, it is possible that beyond differences in baseline 25(OH)D, vitamin D stores within the body differed between White and dark-skinned participants, which could impact requirement estimates. Exploration of this and other possible reasons warrants further investigation. The estimates of vitamin D requirement were linked to serum 25(OH)D thresholds identified by a number of expert agencies internationally [2–5]. These thresholds relate to bone health outcomes and are based predominantly on an assumption that physiological vitamin D requirements between racial groups do not differ. This is not from neglect or a lack of consideration of the issues, but largely due to an absence of data. For example, the IOM acknowledged that available, emerging evidence would suggest that there is perhaps a lower requirement for vitamin D among African Americans in relation to ensuring bone health, at least compared with Whites, however, the notable lack of high quality and convincing evidence limited their ability to act on this possibility [2]. Thus, while the 50 nmol/L threshold to ensure adequacy from a bone health perspective may possibly be higher than needed for dark-skinned individuals, the 25 and 30 nmol/L serum 25(OH)D thresholds are protective against rickets and osteomalacia in all ethnic groups [6]. Finally, the use of serum 25(OH)D targets to establish vitamin D intake recommendations in DRI exercises stems from the fact that available data have not sufficiently explored the relationship between total intake of vitamin D per se and health outcomes and dose–response relationship between vitamin D intake and bone health (or other health outcomes) is lacking [2]. In addition, the use of serum 25(OH)D concentrations to simulate a dose–response relationship for bone health, was under conditions of minimal sun exposure, thereby reducing the confounding introduced by the effect of sun exposure on serum 25(OH)D concentrations. In the present work, while only studies conducted during, or at least incorporating, an extended winter (October through April [4]) were included to try and achieve minimal impact of UVB on the vitamin D intake-25(OH)D dose–response relationship, some production of pre-vitamin D$_3$ in the skin of participants, particularly those at lower latitudes, could not be discounted. However, if this were the case, it would likely lower the dietary requirement estimates.

The strengths of the present work include the application of the IPD approach to the data from ten vitamin D-supplement-/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 nine of ten of trials published in the last 8 years. The majority of studies had a low risk of bias across the seven categories.

In conclusion, this IPD analyses of vitamin D RCTs, several of which had been published since the various DRV review exercises during 2011–2016, has provided new dark-skinned population-specific vitamin D intake estimates required to maintain serum 25(OH)D above commonly used thresholds. These vitamin D intake estimates are radically different from the equivalent estimates for White individuals, and highlight the urgent need to re-configure the approach for setting RDAs for vitamin D. The present IPD-derived RDA estimate of 67 µg/day in dark-skinned individuals, capturing between-participant variability, at the 50 nmol/L 25(OH)D threshold is much higher than the recommendations from NNR, IOM and EFSA (10–15 µg/day), which used standard meta-regression based on aggregate data from vitamin D supplement RCTs, and of predominantly White individuals [2, 4, 5]. Likewise, the higher estimated vitamin D intakes needed to maintain 97.5% of individuals with serum 25(OH)D concentrations above 25 nmol/L (as recommended by SACN) and 30 nmol/L is of particular note as these thresholds are of critical importance for musculoskeletal health in all ethnic groups.

Declarations

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