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Systematic Review

A systematic review of vitamin D status in populations worldwide

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Abstract

Vitamin D deficiency is associated with osteoporosis and is thought to increase the risk of cancer and CVD. Despite these numerous potential health effects, data on vitamin D status at the population level and within key subgroups are limited. The aims of the present study were to examine patterns of 25-hydroxyvitamin D (25(OH)D) levels worldwide and to assess differences by age, sex and region. In a systematic literature review using the Medline and EMBASE databases, we identified 195 studies conducted in forty-four countries involving more than 168 000 participants. Mean population-level 25(OH)D values varied considerably across the studies (range 4·9–136·2 nmol/l), with 37·3 % of the studies reporting mean values below 50 nmol/l. The highest 25(OH)D values were observed in North America. Although age-related differences were observed in the Asia/Pacific and Middle East/Africa regions, they were not observed elsewhere and sex-related differences were not observed in any region. Substantial heterogeneity between the studies precluded drawing conclusions on overall vitamin D status at the population level. Exploratory analyses, however, suggested that newborns and institutionalised elderly from several regions worldwide appeared to be at a generally higher risk of exhibiting lower 25(OH)D values. Substantial details on worldwide patterns of vitamin D status at the population level and within key subgroups are needed to inform public health policy development to reduce risk for potential health consequences of an inadequate vitamin D status.

Key words: Vitamin D: Populations: Public health

Vitamin D plays an important role in bone mineralisation and other metabolic processes in the human body such as Ca and phosphate homeostasis and skeletal growth[1,2]. Vitamin D deficiency, for example, causes rickets in children, leading to skeletal abnormalities, short stature, delayed development or failure to thrive[3]. In adults, low values of vitamin D are associated with osteomalacia, osteopenia, osteoporosis and subsequent risk of fractures[1]. In addition to beneficial effects on musculoskeletal health, observational studies have suggested that low 25-hydroxyvitamin D (25(OH)D) values are associated with an increased risk for several extra-skeletal diseases including cancer, infections, autoimmune diseases and CVD[4]. In light of the global ageing population[5], an almost fourfold increase in osteoporotic hip fractures since 1990[6] and the possible risk of other chronic diseases, patterns of low 25(OH)D levels are of substantial public health interest.

Vitamin D status is traditionally measured through assays of 25(OH)D, the major circulating form of vitamin D[7]. Although 25(OH)D levels below 25 nmol/l have been associated with disorders of bone metabolism[8] and are used to indicate severe vitamin D deficiency, the threshold for defining adequate stores of vitamin D in humans has not been established clearly[9]. The Institute of Medicine has suggested, for example, that approximately 97·5 % of the population across all age groups meet their requirements for vitamin D, having serum 25(OH)D values higher than 50 nmol/l[10]. However, others consider 25(OH)D values of 75 nmol/l or higher to be adequate[11,12].

Abbreviation: 25(OH)D, 25-hydroxyvitamin D.

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Given the absence of uniformly accepted definitions, previous reviews have reported substantial variations in the prevalence of vitamin D deficiency across countries throughout the world, with estimates ranging from 2 to 90 % depending on the cut-off value and study population selected[8,13–16]. Insights from these earlier studies are limited, however, due to a focus on specific geographical regions, age or risk groups. Moreover, use of a binary approach to define the presence of vitamin D deficiency in some studies might have also obscured important relationships with chronic disease that might exist across a broader spectrum of values.

To provide a basis for future efforts to limit the health consequences of vitamin D deficiency and insufficiency worldwide, we conducted a systematic literature review of studies performed worldwide using continuous values for 25(OH)D to enable comparisons across studies and between different subgroups within the population. The specific objective of the present study, therefore, was to assess vitamin D status across a range of values at the population level and within key population subgroups defined by age, sex and region.

Methods

Literature search

We searched the Medline and EMBASE databases for original articles on vitamin D status in the general population. Keywords were chosen from the Medical Subject Headings terms and the EMTREE thesaurus, respectively, using the following search strategy: (vitamin D/D3 OR 25-hydroxyvitamin D/D3 OR 25(OH)D/D3 OR calcidiol) AND (epidemiologic studies OR population-based OR population OR survey OR representative OR cross-sectional OR observational) NOT (dihydroxycholecalciferols OR case reports OR case–control studies OR clinical trials OR reviews) AND humans. Search terms for vitamin D included the controlled term ‘vitamin D’ (including calcifediol and 25-hydroxycholecalciferol) and several free-text terms taking different notations of 25(OH)D into account.

Articles published in English between 1 January 1990 and 28 February 2011 (date of the final screen) were considered. We excluded articles published before 1990 because of a general shift in lifestyle, particularly in industrialised nations (e.g. spending less time outdoors), that might have affected mean population-level 25(OH)D values[17]. The final screen produced 2566 hits from both databases after excluding 449 exact duplicates identified using EndNote X6 (Thomson Reuters). Wherever possible, the methods used in the present review follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[18].

Study selection

Studies were included in the present review if they met the following criteria defined *a priori*: (1) outcomes – report of mean or median plasma level for 25(OH)D; (2) study participants – randomly selected samples from the general population as well as subgroups defined by age, sex and specific areas within a country; (3) study designs – cross-sectional studies or baseline data from population-based cohorts. Studies were excluded if vitamin D status was estimated (e.g. through self-reported nutritional intake) or if data were available only on vitamin D_2. We also did not consider studies using a binary indicator for vitamin D deficiency or insufficiency as the sole outcome measure, given differing thresholds used in the literature to define either state[5]. Furthermore, clinical samples or studies restricted to subgroups with specific characteristics (e.g. ethnicity, job and skin colour) were excluded, as they were not randomly selected from the general population.

All studies were independently screened and evaluated for selection by two of the authors (R. H. and A. F.). Inter-rater agreement was good to moderate, and disagreements were discussed and resolved by consensus in each case (abstract selection: $\kappa = 0{\cdot}719$; full-text selection: $\kappa = 0{\cdot}544$). Following the application of exclusion criteria to information contained in the study abstract, we reduced the 2566 screened records to 601 (Fig. 1); application of these criteria following review of each full-text article reduced the pool of potentially eligible articles to 272. Given the presence of multiple reports based on the same data, our final analytical sample comprised 195 unique studies. In several instances, multiple articles from single studies were retained for analysis as they provided separate 25(OH)D values for subgroups with the characteristics of interest (age, sex and region).

Data extraction, data elements and quality assessment

Each study was evaluated using a standardised data extraction form. In each case, we assessed a wide range of variables including vitamin D values, assays used and study characteristics as well as characteristics of the study population and method of recruitment. Data from most studies were represented in the dataset by a single entry for the total study population. Multiple subentries for a single study were included if data were presented by age, sex or region. All 25(OH)D values were expressed in nmol/l, following conversion from ng/ml (multiplied by a factor of 2·496) as necessary.

Based on the WHO recommendations, we classified geographical regions as follows: Latin America; North America; Europe; Asia/Pacific; Middle East/Africa[19]. To determine age-related differences, we defined four age groups: newborns/infants (0–1 years); children/adolescents (>1–17 years); adults (>17–65 years); elderly (>65 years). In instances where details about age were not provided, we created a separate category (‘other’). Where possible, we also distinguished elderly living in nursing homes (institutionalised elderly) from those living in the community.

We assessed study quality using data reported in each study on representativeness, validity and reliability. A study was considered representative if (1) this feature of the study was explicitly addressed in the corresponding full-text article or (2) any statement made by the authors suggested that the actual sample reflected the target population. A study was classified as non-representative if the corresponding full-text article contained information about an existing selection bias, which might also occur in a randomly selected sample (e.g. overestimation of females). Measurement validity was

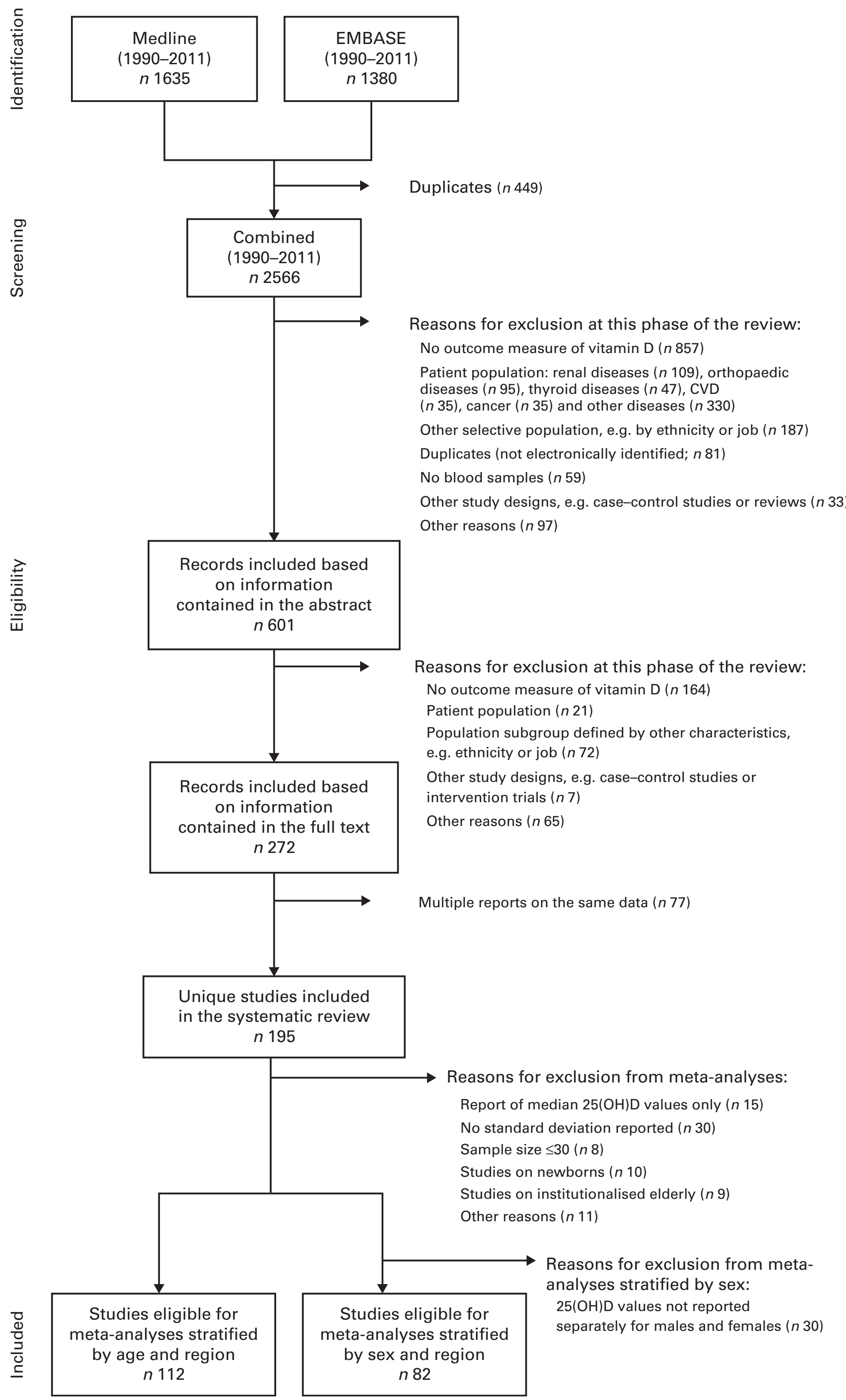

Fig. 1. Flow chart of the study selection (1990–2011). 25(OH)D, 25-Hydroxyvitamin D.

evaluated using information about the 25(OH)D measure (e.g. participation of the laboratory in the International Vitamin D Quality Assessment Scheme)[20]. Finally, a study was classified as reliable if the intra- and inter-assay coefficients of variation were below 10 and 15 %, respectively. In instances where details about representativeness, validity or reliability were not provided, we created a separate category ('unknown') for each quality criterion.

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Table 1. Characteristics and main results from single studies on 25-hydroxyvitamin D (25(OH)D)*

Region and country	City/region within the country	Reference	*n*	Male (%)	Age group	Season	25(OH)D (nmol/l)	Reliability	Representativeness
Europe									
Austria									
	Whole country	Koenig & Elmadfa[33]	1452	NA	O	NA	27·5	Unknown	Unknown
	Whole country	Kudlacek *et al.*[34]	1048	38·2	A	Winter	52·2	Unknown	No
Belgium									
	Brabant	Boonen *et al.*[35]	245	0·0	E	NA	56·4	Unknown	No
	Brussels	MacFarlane *et al.*[36]	126	31·0	A	Winter	48·4	Unknown	No
	Brussels	Moreno-Reyes *et al.*[37]	401	50·1	A	NA	35·0	Yes	No
	Northern Belgium	Richart *et al.*[38]	542	49·8	NA	NA	71·4†; 73·4‡	Unknown	Unknown
Czech Republic									
	Prague	Zofkova & Hill[39]	47	0·0	A	NA	58·2	Unknown	No
Denmark									
	Copenhagen	Andersen *et al.*[40]	112	NA	C; E	Winter	24·4§; 47·8§	Yes	No
	Copenhagen	Brot *et al.*[41]	510	0·0	A	NA	24·0§	Yes	No
	Faroe Islands	Dalgard *et al.*[42]	669	51·1	E	Mixed	47·6	Unknown	Unknown
	Odense	Frost *et al.*[43]	700	100·0	A	Whole year	64·9	Unknown	No
	Aarhus	Rejnmark *et al.*[44]	315	0·0	A	NA	57·0§	Unknown	No
	Aarhus	Rejnmark *et al.*[45]	2316	0·0	A	Mixed	62·0§	Unknown	Yes
	Copenhagen	Rudnicki *et al.*[46]	125	42·4	A	Whole year	25·5	Yes	Yes
Estonia									
	Vaike-Maarja	Kull *et al.*[47]	367	45·5	A	Winter	43·7	Yes	Yes
Finland									
	Porvoo (region)	Andersen *et al.*[40]	120	NA	A; E	Winter	29·2§; 45·2§	Yes	No
	Whole country	Kauppi *et al.*[48]	6035	45·3	A	NA	45·1†; 45·2‡	Yes	No
	Whole country	Lamberg-Allardt *et al.*[49]	328	38·4	A	Mixed	45·0†; 47·0‡	Yes	Unknown
	Whole country	Matilla *et al.*[50]	4097	47·0	A	Whole year	43·6	Yes	Unknown
	Whole country	Partti *et al.*[51]	6241	45·0	A	Mixed	45·1	Unknown	No
	North Savo	Parviainen *et al.*[52]	776	53·9	A	Mixed	34·0†; 35·0‡	Unknown	Unknown
	Turku	Piirainen *et al*[53]	82	NA	C	Mixed	54·7	Unknown	Unknown
	Helsinki	Viljakainen *et al.*[54]	64	0·0	C	Summer; winter	59·5; 37·3	Yes	Unknown
	Helsinki	Viljakainen *et al.*[55]	125	52·8	I	Winter	50·7	Yes	Unknown
France									
	Montpellier	Blain *et al.*[56]	248	0·0	A	NA	64·1§	Yes	No
	Caen	Bougle *et al.*[57]	82	NA	I	NA	74·9	Unknown	No
	France	Chapuy *et al.*[58]	1569	48·8	A	Winter	61·0	Yes	Unknown
	Burgundy	De Carvalho *et al.*[59]	164	42·7	A	Whole year	74·4†; 52·8‡	Unknown	No
	Poitiers	Deplas *et al.*[60]	64	31·3	E	Spring	21·4	Unknown	No
	Whole country	Malvy *et al.*[61]	1191	42·7	A	Winter	79·5	Unknown	Unknown
Germany									
	Bonn	Braemswig *et al.*[62]	21	100·0	A	Mixed	51·3	Unknown	Unknown
	Whole country	Hintzpeter *et al.*[63]	4030	43·7	O	NA	45·2§†; 44·7§‡	Yes	Yes
	Southern Germany	Scharla *et al.*[64]	415	50·4	A	Summer; winter	67·4; 42·4	Yes	Unknown
	Southern Germany	Woitge *et al.*[65]	41	36·6	O	Mixed	65·6	Unknown	No
	Bonn	Zittermann *et al.*[66]	76	0·0	A	Summer; winter	69·8; 30·3	Unknown	No
Greece									
	Athens	Nicolaidou *et al.*[67]	123	57·7	I	Whole year	50·9§	Yes	Yes
	Athens	Papapetrou *et al.*[68]	279	17·2	E	Mixed	42·9	Unknown	No

Table 1. *Continued*

Region and country	City/region within the country	Reference	*n*	Male (%)	Age group	Season	25(OH)D (nmol/l)	Reliability	Representativeness
Iceland									
	Reykjavik	Kristinsson *et al.*[69]	259	0·0	C	Winter	43·9	Yes	No
	Reykjavik	Sigurdsson *et al.*[70]	308	0·0	E	Mixed	53·1	Yes	NA
	Reykjavik	Steingrimsdottir *et al.*[71]	944	52·0	A	Whole year	45·7	Yes	No
Ireland									
	Cork (region)	Andersen *et al.*[40]	62	NA	C; E	Winter	41·3§; 43·7§	Yes	No
	Cork (city)	Hill *et al.*[72]	44	0·0	A	Winter	54·5	Yes	Unknown
	Dublin	Keane *et al*[73]	116	NA	E	NA	37·1	Unknown	Unknown
Israel									
	Whole country	Oren *et al.*[74]	195	48·7	O	Whole year	57·2	Unknown	Yes
Italy									
	Whole country	Adami *et al.*[75]	697	0·0	E	Winter	37·9	Unknown	No
	Southern Italy	Carnevale *et al.*[76]	90	35·6	A	Winter	42·7	Yes	No
	Rome	Romagnoli *et al.*[77]	135	NA	A	Summer; winter	90·1; 45·9	Yes	No
	Greve, Bagno a Ripoli	Vezzoli *et al.*[78]	595	50·8	O	NA	61·2†; 48·2‡	Yes	Unknown
Netherlands									
	Bilthoven, Utrecht	Al-Delaimy *et al.*[79]	65	46·2	A	NA	91·2†; 77·2‡	Unknown	Unknown
	Zutphen	Baynes *et al.*[80]	142	100·0	E	Spring	42·0	Yes	No
	Rotterdam	Fang *et al.*[81]	1317	NA	E	Whole year	65·5	Yes	No
	Whole country	Kuchuk *et al.*[82]	1319	48·7	E	Whole year	53·2	Yes	Yes
	Whole country	Löwik *et al.*[83]	529	50·7	E	NA	40·0†; 38·0‡	Unknown	No
	Hoorn	Pilz *et al.*[84]	614	NA	E	Whole year	56·5†; 50·8‡	Yes	No
	Amsterdam	Van Summeren *et al.*[85]	307	50·8	C	NA	69·6	Unknown	No
Norway									
	Skjervoy	Brustad *et al.*[86]	32	65·6	A	NA	67·2	Unknown	No
	Northern Norway	Brustad *et al.*[87]	300	0·0	A	Mixed	56·9	Yes	Unknown
	Tromso	Grimnes *et al.*[88]	6932	39·0	A	NA	58·9	Yes	No
	Oslo	Meyer *et al.*[89]	869	42·8	A	Mixed	74·8	No	No
Poland									
	Sadyba (Warsaw)	Andersen *et al.*[40]	126	NA	C; E	Winter	30·6§; 32·5§	Yes	No
	Warsaw	Napiorkowska *et al.*[90]	274	0·0	E	Winter	33·7	Yes	Yes
Russia									
	NA	Sapir-Koren *et al.*[91]	122	0·0	E	NA	29·1	Unknown	No
Spain									
	Sabadell	Almirall *et al.*[92]	237	46·8	E	Winter	42·9	Unknown	No
	L'Hospitalet de Llobregat	Gomez *et al.*[93]	253	49·8	A	Whole year	52·7†; 49·9‡	Unknown	Yes
	Betanzos	Moreiras *et al.*[94]	55	45·5	E	Spring	25·3	Unknown	Unknown
	Lleida	Muray *et al.*[95]	391	58·1	A	Autumn	23·4†; 21·3‡	Unknown	No
	Murica	Perez-Llamas *et al.*[96]	86	33·7	E	Mixed	50·1	Yes	Unknown
Sweden									
	Central Sweden	Burgaz *et al.*[97]	116	0·0	E	Winter	69·0	Yes	Unknown
	Uppsala, Västmanland	Burgaz *et al.*[98]	100	0·0	E	Winter	72·0	Unknown	No
	Malmo	Gerdhem *et al.*[28]	986	0·0	E	Whole year	95·0	Yes	No
	Uppsala	Hagström *et al.*[99]	958	100·0	E	NA	69·0	Unknown	Unknown
	Uppsala	Lind *et al.*[100]	34	100·0	A	NA	90·0	Unknown	No
	Stockholm	Melin *et al.*[101]	104	22·1	E	Spring	69·9†; 64·9‡	Yes	No
	Stockholm	Salminen *et al.*[102]	350	0·0	E	Whole year	91·0§	Yes	No

Table 1. *Continued*

Region and country	City/region within the country	Reference	*n*	Male (%)	Age group	Season	25(OH)D (nmol/l)	Reliability	Representativeness
Switzerland									
	Vaud, Fribourg, Ticino	Burnand *et al.*[103]	3276	51·7	O	Mixed	50·0	Unknown	Yes
	Lausanne	Krieg *et al.*[104]	349	29·5	E	NA	26·5†; 23·2‡	Unknown	Unknown
	Basel	Theiler *et al.*[29]	505	57·4	E	Mixed	17·5†‖; 18·2‡‖; 91·6†; 67·4‡	Yes	No
UK									
	Central, South, West England, Wales	Bates *et al.*[105]	924	NA	E	Mixed	51·9	Unknown	No
	East Kent	Carter *et al.*[106]	188	25·5	E	Mixed	31·2§	Unknown	No
	Northern Ireland	Cashman *et al.*[107]	1015	49·8	C	Mixed	61·1†§; 59·0‡§	Yes	Yes
	Great Britain	Davies *et al.*[108]	756	NA	C	Mixed	51·8	Unknown	Yes
	South England	Elia *et al.*[109]	1026	NA	E	NA	52·5	Unknown	No
	Isle of Ely	Forouhi *et al.*[110]	524	40·8	A	NA	60·2	Yes	Unknown
	Cambridge	Hegarty *et al.*[111]	96	49·0	E	Winter	23·1	Yes	Unknown
	Northern Ireland	Hill *et al.*[112]	1015	49·8	C	Whole year	64·3	Yes	Yes
	England	Hirani & Primatesta[113]	1297	40·3	E	Whole year	40·0†‖; 37·4‡‖ 58·3†; 49·4‡	Unknown	Yes
	Great Britain	Hypponen & Power[114]	7437	50·1	A	Summer; winter	60·3; 41·1	Yes	No
	Grampian	Macdonald *et al.*[115]	2905	0·0	A	Mixed	53·9	Yes	No
	Aberdeen	Mavroeidi *et al.*[116]	325	0·0	E	Mixed	53·3	No	No
	Isle of Ely	Wareham *et al.*[117]	1057	43·3	NA	Whole year	54·4†; 46·2‡	Yes	No
North America									
Canada									
	Quebec	Barake *et al.*[118]	404	51·2	E	Mixed	74·0	Yes	No
	Nunavut	El Hayek *et al.*[119]	282	46·8	C	Mixed	48·3§	No	Yes
	Whole country	Langlois *et al.*[120]	5306	48·4	O	Whole year	67·7	Yes	Yes
	St Theresa Point, Garden Hill	Lebrun *et al.*[121]	76	NA	I	Summer	26·2	Unknown	Unknown
	Toronto	Liu *et al.*[122]	155	49·7	E	Autumn	44·9	Unknown	Unknown
	Quebec	Mark *et al.*[123]	1753	50·3	C	Mixed	46·0	Yes	No
	Avalon Peninsula	Newhook *et al.*[124]	51	NA	I	Summer; winter	63·6; 48·6	Unknown	No
	Edmonton	Overton & Basu[125]	36	100·0	E	Summer	122·0	Unknown	No
	Calgary	Rucker *et al.*[126]	188	31·9	E	Winter	57·3	No	No
	Quebec	Sinotte *et al.*[127]	741	0·0	A	Winter	64·9	Yes	No
USA									
	NA	Alvarez *et al.*[128]	50	0·0	A	Mixed	55·7	Unknown	No
	New York	Arunabh *et al.*[129]	410	0·0	A	Whole year	54·2	Yes	No
	Connecticut	Avery *et al.*[130]	114	NA	E	NA	113·1; 81·8‖	Yes	No
	Honolulu	Chai *et al.*[131]	182	0·0	A	NA	72·3	Unknown	Unknown
	Framingham	Cheng *et al.*[132]	3890	46·0	A	Whole year	92·9	No	No
	Boston	Dawson-Hughes *et al.*[133]	391	46·5	E	Whole year	82·4†; 68·9‡	Yes	Unknown
	Oakland	Dror *et al.*[134]	199	NA	I	Mixed	43·7	Unknown	Unknown
	Whole country	Looker *et al.*[135]	18462	47·2	O	Summer, winter	77·3; 67·2	No	Yes
	Framingham	Hannan *et al.*[136]	341	NA	E	NA	71·9	Yes	No
	Boston, Houston, West Lafayette	Hill *et al.*[137]	735	30·5	C	NA	66·2	Unknown	Unknown
	Whole country	Iannuzzi-Sucich *et al.*[138]	337	42·1	E	NA	67·4†; 57·7‡	Yes	No
	Connecticut	Ilich *et al.*[139]	136	0·0	E	Whole year	52·8	Unknown	No
	Framingham	Jaques *et al.*[140]	759	38·2	E	NA	82·0†; 71·0‡	Yes	Unknown
	Northern Georgia	Johnson *et al.*[141]	317	20·2	E	Whole year	66·7	Yes	Unknown
	Rochester	Khosla *et al.*[142]	138	0·0	A	NA	77·6	Unknown	Unknown
	Whole country	Kim *et al.*[143]	8351	0·0	O	NA	61·0	Unknown	No

Table 1. *Continued*

Region and country	City/region within the country	Reference	*n*	Male (%)	Age group	Season	25(OH)D (nmol/l)	Reliability	Representativeness
	California	Kremer *et al.*(144)	90	0·0	A	Summer	75·1	Unknown	No
	Eastern Nebraska	Lappe *et al.*(145)	1179	0·0	E	Whole year	71·8	Yes	No
	Whole country	Mansbach *et al.*(146)	4558	49·6	C	Whole year	68·0	Unknown	Yes
	Farmington	Mirza *et al.*(147)	40	0·0	A; E	NA	74·9; 84·9	Yes	No
	Rancho Bernardo	Reis *et al.*(148)	654	36·4	E	NA	103·6	Yes	No
	Marion County	Rock *et al.*(149)	1042	39·4	O	Mixed	31·9†; 29·3‡	Yes	Yes
	Greenwich	Sabetta *et al.*(150)	198	42·9	O	Autumn	70·9	Unknown	Unknown
	Framingham	Shea *et al.*(151)	1381	48·4	A	NA	49·4	Unknown	No
	Athens	Stein *et al.*(152)	168	0·0	C	Whole year	93·8	Yes	No
	Bangor	Sullivan *et al.*(153)	22	0·0	C	Summer	74·4	Yes	Unknown
	Philadelphia	Weng *et al.*(154)	382	47·6	C	Whole year	69·9§	Yes	Yes
Asia/Pacific									
Australia									
	Sydney	Bowyer *et al.*(155)	901	NA	I	Winter	60·0§	Unknown	No
	Sydney	Brock *et al.*(156)	186	NA	E	NA	36·0; 33·0‖	Yes	No
	Dubbo	Center *et al.*(157)	437	100·0	E	NA	70·7	Yes	No
	Tasmania	Ding *et al.*(158)	1002	NA	A	Mixed	52·8	Yes	Unknown
	North-Western Adelaide	Ngo *et al.*(159)	253	43·5	E	NA	72·2	Yes	No
	Barwon	Pasco *et al.*(160)	861	0·0	A	Whole year	70·0	Yes	No
	Melbourne	Stein *et al.*(161)	99	26·3	E	Winter	26·0§	Yes	No
	Sydney	Zochling *et al.*(162)	584	21·2	E	Mixed	21·4†; 16·9‡	Unknown	No
China									
	Linxian	Abnet *et al.*(163)	720	42·2	A	Spring	33·1	Yes	Unknown
	Hong Kong	Chan *et al.*(164)	53	0·0	E	NA	57·7	Unknown	No
	Linxian	Chen *et al.*(165)	2018	54·0	A	Spring	31·7	Unknown	Unknown
	Beijing	Du *et al.*(166)	649	0·0	C	Winter	33·5	Yes	Yes
	Shanxi	Strand *et al.*(167)	250	52·4	C	Spring	42·3†; 25·5‡	Unknown	Unknown
	Taipei	Tsai *et al.*(168)	262	0·0	A	Mixed	76·6	Yes	No
Fiji Islands									
	Whole country	Heere *et al.*(169)	511	0·0	A	Winter	76·0	Unknown	Unknown
India									
	Agota	Goswami *et al.*(170)	57	56·1	A	Winter	36·4	Unknown	Unknown
	Tirupati	Harinarayan *et al.*(171)	1146	21·2	A	NA	46·3†; 38·7‡	Unknown	No
	Lucknow	Sachan *et al.*(172)	117	NA	I	Mixed	21·0	Yes	No
Indonesia									
	Jakarta, Bekasi	Rinaldi *et al.*(173)	62	0·0	E	Summer	68·2	Unknown	Unknown
	Jakarta, Bekasi	Setiati *et al.*(174)	74	0·0	E	NA	38·7	No	Yes
Japan									
	NA	Kuwabra *et al.*(175)	50	30·0	E	NA	27·7§	Unknown	Unknown
	Tokyo	Kwon *et al.*(176)	1094	41·7	E	Winter	71·7†; 65·8‡	Unknown	No
	Toyosaka	Nakamura *et al.*(177)	160	0·0	E	Summer	78·3	Yes	No
	Toyosaka	Nakamura *et al.*(178)	117	0·0	E	Summer	59·1	Yes	Yes
	Tokyo	Suzuki *et al.*(179)	2957	32·1	E	Autumn	71·1†; 60·4‡	Unknown	No
Malaysia									
	Kuala Lumpur	Rahman *et al.*(180)	101	0·0	A	NA	44·4	Yes	No
Mongolia									
	Ulaanbaatar	Lander *et al.*(181)	98	72·4	C	Autumn	24·1	Yes	No

Table 1. *Continued*

Region and country	City/region within the country	Reference	*n*	Male (%)	Age group	Season	25(OH)D (nmol/l)	Reliability	Representativeness
New Zealand									
	Auckland	Bolland *et al.*[182]	1984	19·1	A; E	NA	84·0†; 51·0‡	Yes	No
	Auckland	Bolland *et al.*[183]	116	0·0	A	NA	54·0	Unknown	Unknown
	Auckland	Bolland *et al.*[184]	100	50·0	A; E	NA	91·0†; 51·0‡	Yes	No
	Wellington; Christchurch	Camargo *et al.*[185]	922	50·7	I	Whole year	44·0§	Yes	Unknown
	Auckland	Grant *et al.*[186]	353	47·6	I	Whole year	55·0	Yes	Unknown
	Dunedin	Houghton *et al.*[187]	193	57·5	C	Mixed	52·0	Yes	Unknown
	Auckland	Ley *et al.*[188]	39	0·0	E	Winter	26·1	Unknown	No
	Auckland	Lucas *et al.*[189]	1606	0·0	E	Whole year	51·2	Unknown	No
	Whole country	Rockell *et al.*[190]	1585	50·5	C	Mixed	50·0	Yes	No
	Dunedin; Invercargill	Rockell *et al.*[191]	342	34·8	A	Summer	85·0	Unknown	Unknown
	Auckland	Scragg *et al.*[192]	295	100·0	A	Whole year	39·8	No	Yes
South Korea									
	Chungju	Kim *et al.*[193]	1330	38·0	E	Whole year	46·1	Unknown	No
	Seoul	Namgung *et al.*[194]	71	50·7	I	Summer; winter	74·9; 26·7	Yes	Unknown
Thailand									
	NA	Chailurkit *et al.*[195]	158	48·7	O	NA	168·2†; 105·8‡	Unknown	Unknown
	Khon Kaen	Chailurkit *et al.*[196]	251	50·2	O	NA	128·3†; 93·6‡	No	Yes
	Bangkok	Chailurkit *et al.*[197]	229	47·2	O	NA	135·0†; 72·6‡	No	Unknown
	Bangkok	Chailurkit *et al.*[26]	446	0·0	E	NA	67·6	Yes	Unknown
	Khon Kaen	Soontrapa *et al.*[198]	65	0·0	E	Summer	83·2	No	Unknown
Vietnam									
	Ho Chi Minh (city)	Ho-Pham *et al.*[199]	637	32·2	A	Mixed	91·9†; 75·1‡	Yes	Yes
Middle East/ Africa									
Cameroon									
	Ntam	Njemini *et al.*[200]	152	60·5	E	NA	52·7	Unknown	No
Iran									
	Tehran	Bassir *et al.*[201]	44	NA	I	Mixed	4·9	Unknown	Unknown
	Tehran	Dahifar *et al.*[202]	414	0·0	C	Mixed	74·9	Unknown	Unknown
	Tehran	Hashemipour *et al.*[203]	1210	59·1	O	NA	20·7§	Yes	No
	Tehran	Hossein-Nezhad *et al.*[204]	646	24·8	A	NA	31·3	Yes	Unknown
	Tehran	Hosseinpanah *et al.*[205]	245	0·0	A	NA	73·0	Yes	Yes
	Zanjan	Kazemi *et al.*[206]	61	NA	I	Mixed	16·7	Unknown	Unknown
	Shiraz	Masoompour *et al.*[207]	520	100·0	A	Winter	35·0	Yes	Yes
	Tehran	Mirsaeid Ghazi *et al.*[208]	1171	41·8	O	Mixed	87·4†; 52·4‡	Yes	No
	Isfahan	Moussavi *et al.*[209]	318	48·1	C	Winter	93·1†; 41·8‡	Yes	No
	Tabriz	Niafar *et al.*[210]	300	0·0	A	Mixed	35·4§	Yes	Unknown
	Tehran	Rabbani *et al.*[211]	963	44·0	C	Winter	116·1†; 60·3‡	Yes	No
	Isfahan	Salek *et al.*[212]	88	NA	I	Summer	68·4	Yes	Unknown
Jordan									
	Northern Jordan	Gharaibeh & Stoecker[22]	186	27·4	A	Summer	25·6	Unknown	Unknown
Lebanon									
	NA	Arabi *et al.*[213]	443	64·6	E	Spring	28·5	Unknown	Unknown
	Beirut, Bekaa	Gannage-Yared *et al.*[214]	316	31·3	A	Winter	24·2	Yes	No

Table 1. *Continued*

Region and country	City/region within the country	Reference	*n*	Male (%)	Age group	Season	25(OH)D (nmol/l)	Reliability	Representativeness
Nigeria									
	Jos	Pfitzner *et al.*[215]	218	45·0	C	Mixed	66·8	Unknown	Unknown
South Africa									
	Cape Town	Charlton *et al.*[216]	173	48·0	E		36·9	Unknown	No
Gambia									
	Whole country	Aspray *et al.*[217]	113	0·0	O	NA	97·7	No	No
Latin America									
Argentina									
	Ushuaia	Oliveri *et al.*[218]	42	57·1	C	Winter	24·5	Unknown	No
Brazil									
	Sao Paulo	Canto-Costa *et al.*[219]	11	36·4	E	NA	61·2	Yes	No
	Sao Paulo	Saraiva *et al.*[220]	250	30·8	E	Whole year	52·4	No	Yes

NA, not available; O, others; A, adults; C, children and adolescents; I, newborns/infants.
* Data from three studies not indicating geographical region have been excluded[221–223]; data from a single study[40] providing country-specific data on four nations in Europe are represented separately. In some cases, 25(OH)D mean values were available by age, sex or region only. For some studies, multiple reports have been published, which are not listed in this table[23,27,30,224–297].
† 25(OH)D mean values for men.
‡ 25(OH)D mean values for women.
§ 25(OH)D median values.
|| 25(OH)D mean values for institutionalised elderly.

Statistical analyses

Descriptive statistics were calculated for baseline characteristics of all the included studies. If mean 25(OH)D values were not reported in an article, we used median values (9·2 % of the studies) in our descriptive analyses.

Meta-analyses were performed for subgroups stratified by age, sex and geographical region using random-effects models. Studies reporting median 25(OH)D values (*n* 15) or mean values without a corresponding standard deviation (*n* 30) were not included in this phase of the analyses (Fig. 1). In addition, our focus in the meta-analyses was limited to studies/subgroups with sample sizes greater than 30, given concerns about the precision of estimates. Studies on newborns (*n* 10) and institutionalised elderly (*n* 9) were also not included in the meta-analyses. For analyses stratified by sex, we also excluded studies that did not report separate 25(OH)D values for males and females (*n* 30).

Heterogeneity between the studies was assessed by visual inspection of forest plots and calculation of I^2 statistics. Because we found substantial heterogeneity across the studies, we decided to further explore potential explanatory factors. Therefore, we conducted heterogeneity analyses within each subgroup by accounting for a range of characteristics other than age and sex, which included season, assay type, distance from the equator[5] and components of study quality. Studies were grouped by study characteristics (e.g. season and assay type) to assess whether heterogeneity was reduced as indicated by the I^2 statistics and the inspection of forest plots.

Supplementary analyses explored patterns of vitamin D status within specific subgroups (e.g. institutionalised elderly) and for selected associations reported in previous work. The purpose of these exploratory analyses was to support further research in this area by generating hypotheses that might be tested more thoroughly in future studies. All statistical analyses were conducted using STATA version 12.1 (StataCorp).

Results

Description of studies

Studies included in the present review (Table 1) contained data on a total of 168 389 participants from forty-four countries. The sample size of individual studies ranged from 11 to 18 462 participants with a median of 316 (interquartile range 117–861). While the majority of studies contained data on males and females, nine studies (4·7 %) restricted their focus to males, while fifty-four studies (28·0 %) contained data on only females. The overall proportions of males and females were 33·3 and 66·7 %, respectively, and the mean age of the participants was 51·7 (SD 24·3) years. Most studies were conducted in Europe (45·1 %), followed by the Asia/Pacific region (23·8 %) and North America (19·7 %). In terms of the country in which studies were conducted, most were carried out in the USA (*n* 28), followed by Iran (*n* 12), New Zealand (*n* 11) and Canada (*n* 10).

The assays reported to measure 25(OH)D values included RIA (55·9 %), competitive protein-binding assays (14·0 %) and other methods such as chemiluminescence immunoassay and HPLC.

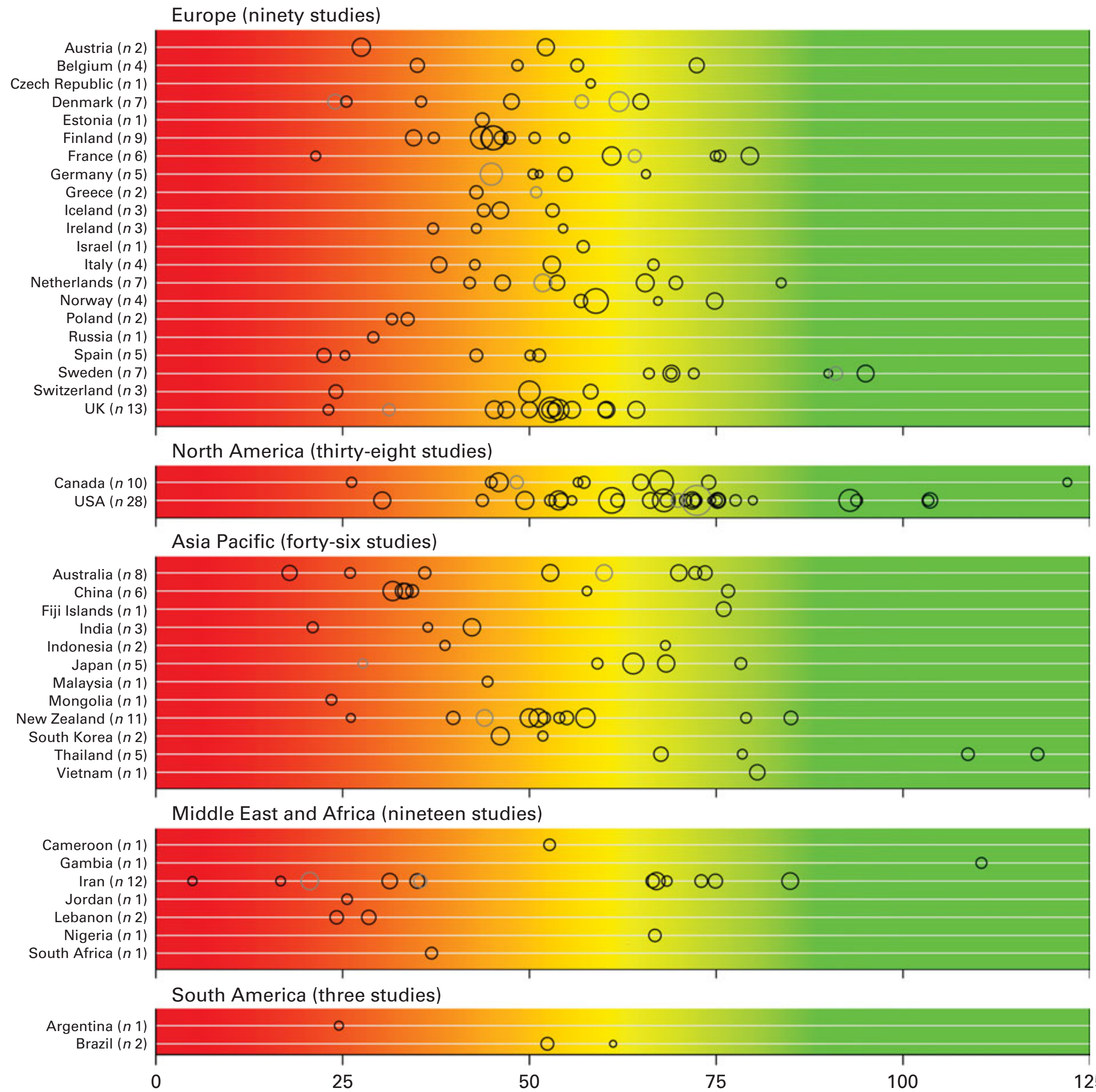

Fig. 2. Mean/median 25-hydroxyvitamin D (25(OH)D) values, by geographical region and country. Note: medians (○) are shown where mean values (○) are not reported; Study size is indicated by circle size. The background colour scheme is intended to reflect the current uncertainty around the definition of thresholds for deficient, insufficient and adequate 25(OH)D levels. Mean/median values falling within the intensely red zone are most consistent with severe vitamin D deficiency; those in the green zone reflect adequate vitamin D levels. Values within the yellow zone are those thought to be indicative of insufficiency. Data from three studies not indicating geographical region have been excluded[221–223]; data from a single study[40] providing country-specific data on four nations in Europe are represented separately. One study[195] reported a mean 25(OH)D value of 136·2 nmol/l and therefore is not presented in the figure due to graphical reasons.

In terms of study quality, more than half of the studies (50·2 %) were classified as non-representative of the target population and 14·9 % qualified as representative according to the criteria defined previously. Evidence of representativeness could not be established in 34·9 % of the studies due to missing information. Information on assay reliability was provided in 61·0 % of the studies with 52·8 % classified as providing reliable 25(OH)D measurements. Assay validity was reported in a minority of studies (9·7 %).

Global vitamin D status

There was a significant variability in the estimates of 25(OH)D values across the studies with mean and median values ranging from 4·9 to 136·2 nmol/l and 20·7 to 91·0 nmol/l, respectively. We found that 88·1 % of the samples presented in the present review had mean 25(OH)D values below 75 nmol/l, 37·3 % had mean values below 50 nmol/l and 6·7 % had mean values below 25 nmol/l. Fig. 2 provides an overview

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References	Country	Distance from the equator (°)	Season	Age group	Number of participants	ES (95 % CI)	Weight (%)
Female							
Brustad *et al.* (2004)[87]	Norway	68	Mixed	Adults	300	56·90 (54·77, 59·03)	1·91
Kauppi *et al.* (2009)[48]	Finland	65		Adults	3299	45·20 (44·30, 46·10)	1·92
Sigurdsson *et al.* (2000)[70]	Iceland	64	Mixed	Elderly	308	53·10 (50·87, 55·33)	1·91
Kristinsson *et al.* (1998)[69]	Iceland	64	Winter	Children/adolescents	118	45·80 (42·14, 49·46)	1·88
Parviainen *et al.* (1992)[52]	Finland	63	Mixed	Adults	358	35·00 (33·24, 36·76)	1·91
Viljakainen *et al.* (2006)[54]	Finland	60	Winter	Children/adolescents	35	41·90 (36·47, 477·33)	1·84
Kull *et al.* (2009)[47]	Estonia	60	Winter	Adults	200	44·60 (42·41, 46·79)	1·91
Lamberg-Allardt *et al.* (2001)[49]	Finland	60	Mixed	Adults	202	47·00 (42·31, 51·69)	1·86
Burgaz *et al.* (2009)[98]	Sweden	60	Winter	Elderly	100	72·00 (67·49, 76·51)	1·86
Burgaz *et al.* (2007)[97]	Sweden	60	Winter	Elderly	116	69·00 (64·81, 73·19)	1·87
Melin *et al.* (1999)[101]	Sweden	59	Spring	Elderly	81	64·90 (58·37, 71·42)	1·80
Mavroeidi *et al.* (2010)[116]	UK	57	Mixed	Elderly	325	53·30 (51·20, 55·40)	1·91
Macdonald *et al.* (2006)[115]	Scotland	57		Adults	2905	53·91 (53·12, 54·70)	1·92
Gerdhem *et al.* (2005)[28]	Sweden	56	Whole year	Elderly	986	95·00 (93·13, 96·87)	1·91
Hill *et al.* (2008)[112]	Ireland	54·5	Whole year	Children/adolescents	510	62·80 (60·46, 65·14)	1·90
Hirani & Primatesta (2005)[113]	England	54	Whole year	Elderly	320	48·40 (45·85, 50·95)	1·90
Forouhi *et al.* (2008)[110]	England	52		Adults	310	57·10 (54·50, 59·70)	1·90
Al-Delaimy *et al.* (2006)[79]	Netherlands	52		Adults	35	77·20 (75·25, 79·15)	1·91
Kuchuk *et al.* (2009)[82]	Netherlands	52	Whole year	Elderly	676	48·80 (47·08, 50·52)	1·91
Löwik *et al.* (1990)[83]	Netherlands	52		Elderly	261	38·00 (36·06, 39·94)	1·91
Hill *et al.* (2005)[72]	Ireland	51	Winter	Adults	44	54·50 (46·29, 62·71)	1·74
Macfarlane *et al.* (2004)[36]	Belgium	51	Winter	Adults	87	60·40 (56·63, 64·18)	1·88
Zittermann *et al.* (1998)[66]	Germany	51	Winter	Adults	38	30·30 (24·23, 36·37)	1·82
Boonen *et al.* (1996a)[35]	Belgium	51		Elderly	245	56·40 (52·57, 60·23)	1·88
Zofkova & Hill (2008)[39]	Czech Republic	50		Adults	47	58·23 (32·93, 83·54)	0·98
Theiler *et al.* (1999a)[29]	Switzerland	47	Summer	Elderly	109	67·39 (59·66, 75·12)	1·76
Chapuy *et al.* (1997)[58]	France	47	Winter	Adults	804	60·00 (57·93, 62·07)	1·91
de Carvalho *et al.* (1996)[59]	France	47	Whole year	Adults	39	81·10 (67·00, 98·20)	1·34
Adami *et al.* (2008)[75]	Italy	46	Winter	Elderly	697	37·90 (35·32, 40·48)	1·90
Vezzoli *et al.* (2005)[78]	Italy	43		Elderly	293	48·20 (44·46, 51·94)	1·88
Gomez *et al.* (2004)[93]	Spain	41	Whole year	Adults	127	49·90 (46·16, 53·64)	1·88
Carnevale *et al.* (2001)[76]	Italy	40	Winter	Adults	58	38·00 (34·35, 41·65)	1·88
Papapetrou *et al.* (2007)[68]	Greece	38	Winter	Elderly	231	41·60 (39·09, 44·11)	1·90
Sapir-Koren *et al.* (2003)[91]	Russia			Elderly	122	29·13 (26·09, 32·17)	1·89
Subtotal (I^2 = 99·3 %, P = 0·000)						53·30 (48·66, 57·94)	62·47
Male							
Kauppi *et al.* (2009)[48]	Finland	65		Adults	2736	45·10 (44·06, 46·14)	1·92
Parviainen *et al.* (1992)[52]	Finland	63	Mixed	Adults	418	34·00 (32·56, 35·44)	1·91
Lamberg-Allardt *et al.* (2001)[49]	Finland	60	Mixed	Adults	126	45·00 (38·89, 51·11)	1·82
Kull *et al.* (2009)[47]	Estonia	60	Winter	Adults	167	42·70 (40·58, 44·82)	1·91
Lind *et al.* (1995)[100]	Sweden	59·8		Adults	34	90·00 (83·61, 96·39)	1·81
Hagstrom *et al.* (2009)[99]	Sweden	59		Elderly	958	69·00 (67·80, 70·20)	1·92
Frost *et al.* (2010)[43]	Denmark	55	Whole year	Adults	700	64·90 (62·85, 66·95)	1·91
Hill *et al.* (2008)[72]	Ireland	54·5	Whole year	Children/adolescents	505	65·80 (63·40, 68·20)	1·90
Hirani & Primatesta (2005)[113]	England	54	Whole year	Elderly	322	56·20 (53·26, 59·14)	1·89
Baynes *et al.* (1997)[80]	Netherlands	53	Spring	Elderly	142	42·00 (37·21, 46·79)	1·86
Löwik *et al.* (1990)[83]	Netherlands	52		Elderly	268	40·00 (37·73, 42·27)	1·90
Forouhi *et al.* (2008)[110]	England	52		Adults	214	64·70 (61·04, 68·36)	1·88
Kuchuk *et al.* (2009)[82]	Netherlands	52	Whole year	Elderly	643	57·90 (56·01, 59·79)	1·91
MacFarlane *et al.* (2004)[36]	Belgium	51	Winter	Adults	39	34·44 (32·02, 36·87)	1·90
Theiler *et al.* (1999a)[29]	Switzerland	47	Summer	Elderly	203	91·60 (83·67, 99·53)	1·75
Chapuy *et al.* (1997)[58]	France	47	Winter	Adults	765	62·00 (59·87, 64·13)	1·91
Vezzoli *et al.* (2005)[78]	Italy	43		Elderly	302	61·20 (57·61, 64·79)	1·88
Gomez *et al.* (2004)[93]	Spain	41	Whole year	Adults	126	52·70 (49·05, 56·35)	1·88
Carnevale *et al.* (2001)[76]	Italy	40	Winter	Adults	32	51·20 (46·52, 55·88)	1·86
Papapetrou *et al.* (2007)[68]	Greece	38	Winter	Elderly	48	49·20 (42·82, 55·58)	1·81
Subtotal (I^2 = 99·3 %, P = 0·000)						55·82 (49·75, 61·89)	37·53
Overall (I^2 = 99·3 %, P = 0·000)						54·24 (50·65, 57·82)	100·00

Note: weights are from random-effects analysis

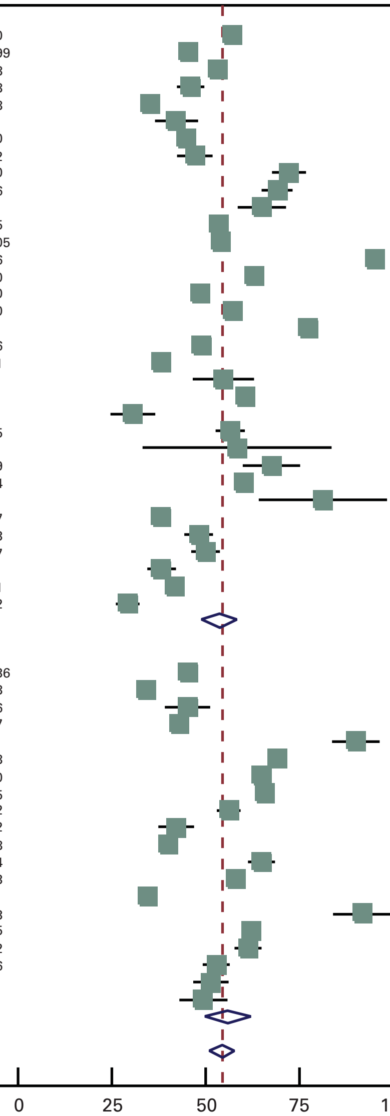

Fig. 3. Forest plot for Europe stratified by sex. ES, effect estimator. (A colour version of this figure can be found online at http://www.journals.cambridge.org/bjn)

of the distribution of country- and study-specific mean 25(OH)D values, stratified by region. In addition, a visualisation of the available data on a global map can be found elsewhere[21].

Vitamin D status by age, sex and region

Due to a limited number of studies being identified from Latin America, it was not possible to perform meta-analyses for this region. Depending on the stratifying variable, I^2 values ranged from 84·5 to 99·7 %, indicating substantial heterogeneity between the studies.

No significant age- or sex-related differences in 25(OH)D values were observed in the sample of eligible studies worldwide (data not shown). However, we observed differences by region with values being significantly higher in North America than in Europe or the Middle East/Africa region (Figs. 3–6). In an analysis stratified by age and region, we did not find age-related differences for Europe and North America (Table 2). However, in the Asia/Pacific region, children/adolescents were found to have significantly lower 25(OH)D values than adults and elderly. In contrast, children/adolescents from the Middle East/Africa region had significantly higher values than the other two age groups. No significant sex-related differences were observed in any of the regions (Figs. 3–6). However, reports of 25(OH)D values in women tended to be lower, especially in the Asia/Pacific and Middle East/Africa regions.

Heterogeneity analyses

The substantial heterogeneity that we observed within the different geographical regions could not be explained by the characteristics of the study population or features of study quality. Grouping studies by age category and sex, assay type,

References	Country	Distance from the equator (°)	Season	Age group	Number of participants	ES (95 % CI)	Weight (%)
Female							
Sinotte *et al.* 2009[127]	Canada	54	Winter	Adults	741	64·90 (63·49, 66·31)	4·76
Khosla *et al.* 1997[142]	USA	43		Adults	138	77·60 (71·74, 83·46)	4·48
Dawson-Hughes *et al.* 1997[133]	USA	42	Whole year	Elderly	209	68·90 (64·55, 73·25)	4·61
Shea *et al.* 2009[290]	USA	42		Elderly	919	49·20 (47·95, 50·45)	4·76
Jaques *et al.* 1997[140]	USA	42		Elderly	469	71·00 (68·38, 73·62)	4·71
Ilich *et al.* 2003[139]	USA	41	Whole year	Adults	136	52·80 (50·65, 54·95)	4·73
Lappe *et al.* 2006[145]	USA	41	Whole year	Elderly	1179	71·80 (70·64, 72·96)	4·76
Iannuzzi-Sucich *et al.* 2002[138]	USA	40		Elderly	195	57·66 (54·82, 60·50)	4·70
Arunabh *et al.* 2003[129]	USA	40	Whole year	Adults	410	54·20 (50·84, 57·56)	4·67
Kremer *et al.* 2009[144]	USA	37	Summer	Children/adolescents	90	75·13 (68·43, 81·83)	4·40
Hill *et al.* (2010)[137]	USA	36		Children/adolescents	511	66·20 (63·85, 68·55)	4·72
Stein *et al.* (2006)[152]	USA	34	Whole year	Children/adolescents	168	93·80 (89·55, 98·05)	4·62
Johnson *et al.* (2008)[141]	USA	32·5	Whole year	Elderly	200	67·90 (63·04, 72·76)	4·57
Chai *et al.*. (2010)[131]	Hawaii	21		Adults	182	72·30 (68·45, 76·15)	4·64
Alvarez *et al.* (2010)[128]	USA		Mixed	Adults	50	55·66 (46·18, 65·14)	4·08
Subtotal (I^2 = 98·8 %, *P* = 0·000)						66·57 (60·94, 72·20)	69·23
Male							
Overton & Basu (1999)[125]	Canada	53	Summer	Elderly	36	122·00 (106·32, 137·68)	3·26
Jaques *et al.* (1997)[140]	USA	42		Elderly	290	82·00 (78·66, 85·34)	4·68
Shea *et al.* (2009)[290]	USA	42		Elderly	843	49·00 (47·81, 50·19)	4·78
Dawson-Hughes *et al.* (1997)[133]	USA	42	Whole year	Elderly	182	82·40 (77·20, 87·60)	4·54
Iannuzzi-Sucich *et al.* (2002)[138]	USA	40		Elderly	142	67·39 (64·03, 70·76)	4·67
Hill *et al.* (2010)[137]	USA	36		Children/adolescents	224	65·70 (62·83, 68·57)	4·70
Johnson *et al.* (2008)[141]	USA	32·5	Whole year	Elderly	37	60·50 (51·70, 69·30)	4·16
Subtotal (I^2 = 99·0 %, *P* = 0·000)						74·44 (61·65, 87·24)	30·77
Overall (I^2 = 98·9 %, *P* = 0·000)						68·73 (63·71, 73·75)	100·00

Note: weights are from random-effects analysis

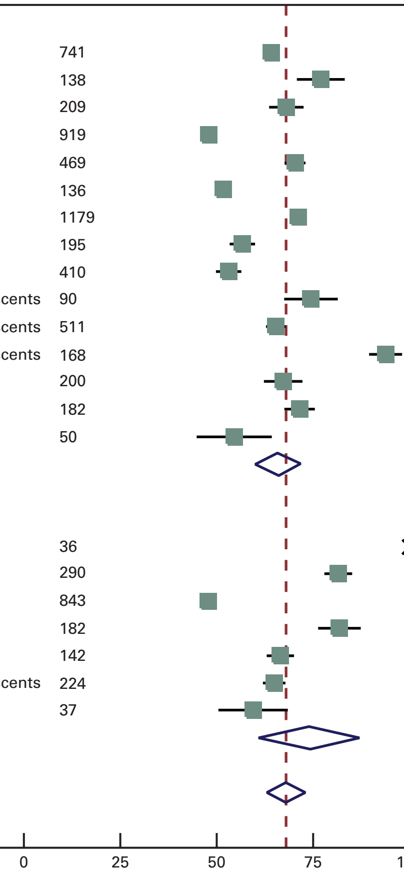

Fig. 4. Forest plot for North America stratified by sex. ES, effect estimator. (A colour version of this figure can be found online at http://www.journals.cambridge.org/bjn)

season, distance from the equator or representativeness, for example, did not significantly reduce heterogeneity across the studies in our sample, as measured by the I^2 statistics.

Exploratory analyses

We found that mean 25(OH)D values for institutionalised elderly were lower than those for non-institutionalised elderly, especially in Europe and the Asia/Pacific region. Moreover, in specific subgroups in single countries within Europe, we observed differences, with Swedish elderly having higher 25(OH)D mean values than the elderly in other European countries. In addition, we found that newborns had lower 25(OH)D values than the other three age groups in several countries worldwide.

Discussion

Summary of the main findings

The published evidence on vitamin D status at the population level, as assessed by mean or median 25(OH)D values, is characterised by a high degree of variability across studies, countries and regions. Although no age- or sex-related significant differences in 25(OH)D values were observed across the sample of studies that we reviewed, we did observe differences by region with values being significantly higher in North America than in Europe or the Middle East/Africa region. In stratified analyses, significant age-related differences were observed in the Asia/Pacific and Middle East/Africa regions, but not elsewhere. However, exploratory analyses suggested that newborns and institutionalised elderly were more likely to have lower reported 25(OH)D values in several regions worldwide. We found substantial heterogeneity between the studies in our sample from each geographical region that could not be explained in a detailed analysis.

Interpretation and comparison with previous studies

In contrast to previous reviews[5,13,14], we could not find differences in 25(OH)D values for children/adolescents, adults and elderly. However, in analyses stratified by geographical region, significant age-related differences could be observed for the Asia/Pacific region, with children/adolescents having lower 25(OH)D values than older groups. This might be primarily due to the low 25(OH)D values found for Chinese children/adolescents as reported in previous work[13], who were observed to have low dietary Ca intake and limited sunlight exposure as possible reasons. In contrast, in the Middle East/Africa region, children/adolescents were found to have significantly higher 25(OH)D values than adults and elderly, a finding consistent with at least one previous study[8]. One

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References	Country	Distance from the equator (°)	Season	Age group	Number of participants	ES (95 % CI)	Weight (%)
Female							
Bolland *et al.* (2006b)[183]	New Zealand	40		Adults	116	54·00 (50·00, 58·00)	4·21
Du *et al.* (2001)[166]	China	40	Winter	Children/adolescents	649	33·45 (32·01, 34·89)	4·31
Nakamuta *et al.* (2001)[178]	Japan	38	Winter	Elderly	117	59·10 (56·18, 65·02)	4·26
Nakamuta *et al.* (1999)[177]	Japan	38	Summer	Adults	160	78·30 (75·54, 81·06)	4·27
Lucas *et al.* (2005)[189]	New Zealand	37	Whole year	Adults	1606	51·20 (50·25, 52·15)	4·32
Bolland *et al.* (2007a)[184]	New Zealand	37		Adults	50	67·00 (60·62, 73·38)	4·04
Bolland *et al.* (2006a)[182]	New Zealand	37		Adults	1606	51·00 (50·07, 51·93)	4·32
Strand *et al.* (2009)[167]	China	37	Spring	Children/adolescents	119	25·48 (19·69, 31·27)	4·09
Suzuki *et al.* (2008)[179]	Japan	36	Autumn	Elderly	2007	60·40 (59·87, 60·94)	4·32
Kwon *et al.* (2007)[176]	Japan	35	Winter	Elderly	638	65·80 (64·83, 66·77)	4·32
Tsai *et al.* (1997)[168]	China	25	Mixed	Adults	262	76·63 (74·15, 79·11)	4·28
Soontrapa *et al.* (2005)[291]	Thailand	16	Summer	Elderly	48	80·10 (75·44, 84·79)	4·17
Chailurkit *et al.* (2011)[26]	Thailand	13		Elderly	446	67·60 (66·14, 69·06)	4·31
Harinarayan *et al.* (2007)[171]	India	13			807	38·69 (37·22, 40·15)	4·31
Ho-Pham *et al.* (2011)[199]	Vietnam	11	Mixed	Adults	432	75·13 (73·74, 76·52)	4·31
Rahman *et al.* (2004)[180]	Malaysia	3		Adults	101	44·40 (42·33, 46·47)	4·29
Subtotal (I^2 = 99 %, P = 0·000)						58·03 (52·27, 63·79)	68·10
Male							
Strand *et al.* (2009)[167]	China	37	Spring	Children/adolescents	131	42·33 (27·59, 57·07)	3·14
Bolland *et al.* (2006a)[182]	New Zealand	37		Adults	378	84·00 (80·87, 87·13)	4·25
Bolland *et al.* (2007a)[184]	New Zealand	37		Adults	50	91·00 (80·19, 101·81)	3·59
Suzuki *et al.* (2008)[179]	Japan	36	Autumn	Elderly	950	71·14 (70·34, 71·93)	4·32
Kwon *et al.* (2007)[176]	Japan	35	Winter	Elderly	456	71·70 (70·49, 72·91)	4·31
Goswami *et al.* (2008)[170]	India	29	Winter	Adults	32	44·20 (35·75, 52·65)	3·85
Harinarayan *et al.* (2007)[171]	India	13			134	46·28 (42·35, 50·21)	4·21
Ho-Pham *et al.* (2011)[199]	Vietnam	11	Mixed	Adults	205	91·85 (88·37, 95·34)	4·23
Subtotal (I^2 = 98·6 %, P = 0·000)						60·00 (62·43, 75·57)	31·90
Overall (I^2 = 99·6 %, P = 0·000)						61·39 (56·40, 66·37)	100·00
Note: weights are from random-effects analysis							

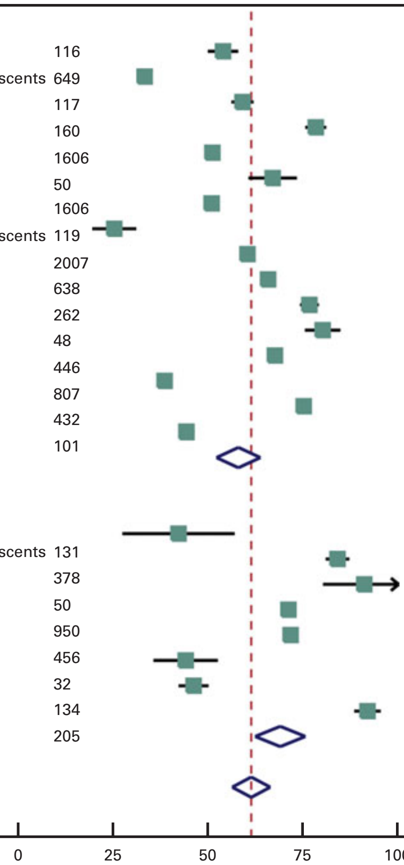

Fig. 5. Forest plot for the Asia/Pacific region stratified by sex. ES, effect estimator. (A colour version of this figure can be found online at http://www.journals.cambridge.org/bjn)

potential explanation for this pattern in the Middle East/Africa region could be that children/adolescents from this region generally spend more time outdoors compared with the other age groups (e.g. indoor working by the adult population)[22]. However, others have also found age-related differences in other regions[5,13,14], which could not be confirmed in the present meta-analyses. A reduction in differences and thus greater similarities across age groups might be attributable to lifestyle changes over the course of time in which younger individuals from industrialised countries spend more time indoors watching television, using computers and playing video games compared with older adults[23].

In contrast to previous reviews, we were also unable to find significant sex-related differences[8,13,16]. On examining our data by region, however, we observed that females tended to have lower 25(OH)D values, especially in the Middle East/Africa and Asia/Pacific regions. Some have suggested that this finding may be related to cultural factors such as differences in clothing styles that may impede vitamin D conversion in the skin[24].

The highest mean 25(OH)D values were generally observed in North America, a finding that might be explained by the routine fortification of several foods (e.g. milk, juice and cereals) in the USA[25]. The absence of significant differences between studies conducted in North America and those carried out in the Asia/Pacific region, however, may have been influenced by relatively high values found in Thailand, a country located near the equator with significant year-round sunlight exposure and higher daytime temperatures, resulting in the use of lighter-weight clothes, which afford less UV protection[26]. Studies conducted in Japan and other Asian countries may have further contributed to somewhat higher regional values, resulting from diets rich in vitamin D foods such as oily fish[27].

Previous reviews[5,8,15] have reported an apparent north–south gradient for 25(OH)D in Europe, with Scandinavian countries showing generally higher values than the Southern European countries. This finding is thought to result, in part, from population-based differences in skin pigmentation, diets rich in oily fish, the common use of cod-liver oil and a higher degree of vitamin D supplementation in Scandinavian countries[14,15]. Although we did not find such a gradient in the present review, we observed generally higher 25(OH)D values in Swedish elderly than in those from other European countries. Some have suggested that this finding can be

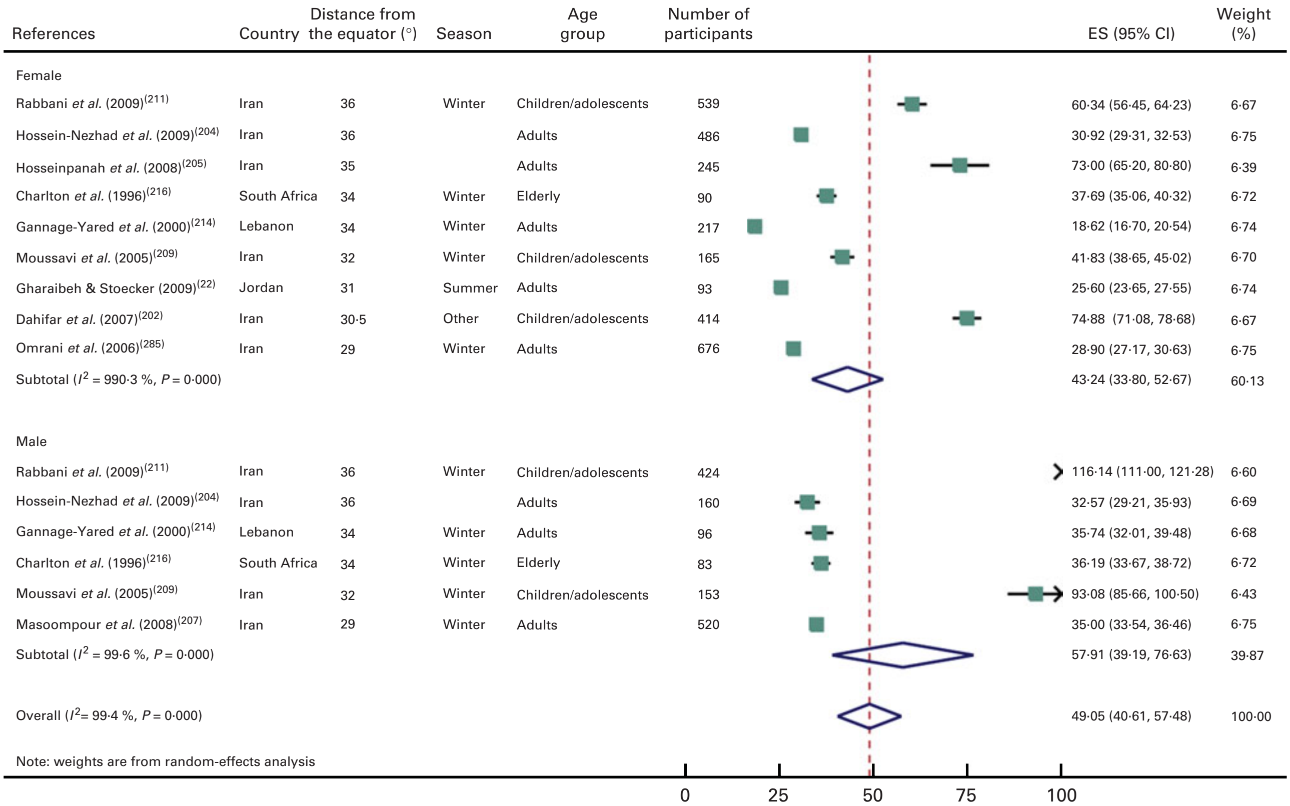

Fig. 6. Forest plot for the Middle East/Africa region stratified by sex. ES, effect estimator. (A colour version of this figure can be found online at http://www.journals.cambridge.org/bjn)

explained by the routine fortification of oil and low-fat milk products with vitamin D in Sweden[28].

In accordance with other reviews[5,8,15], our exploratory analyses also suggested that institutionalised elderly in Europe and the Asia/Pacific region had lower mean 25(OH)D values than the elderly living in the community. It is possible that such a finding may result from less time spent outdoors due to poorer health status[29], although similar findings in other groups of institutionalised individuals could be expected elsewhere. Further investigations of the patterns of vitamin D deficiency and insufficiency are needed in this vulnerable subgroup. Another interesting finding from our exploratory analyses was that newborns/infants were reported to have lower 25(OH)D values than the members of other age groups in several countries worldwide. Because newborn vitamin D status is mainly determined by maternal vitamin D status[30], this finding may be

Table 2. Effect estimators (ES) from the meta-analyses stratified by age and region*
(ES and 95 % confidence intervals)

Regions	I^2 (%)	*n* (studies)	*n* (participants)	ES	95 % CI
Europe					
Children/adolescents (>1–17 years)	99·5	6	1816	50·56	34·35, 66·77
Adults (>17–65 years)	99·4	35	28 844	52·98	45·01, 56·58
Elderly (>65 years)	99·4	30	10 894	51·74	45·81, 57·66
North America					
Children/adolescents (>1–17 years)	98·5	3	993	78·35	59·44, 97·25
Adults (>17–65 years)	99·7	8	6201	71·83	57·71, 86·00
Elderly (>65 years)	99·3	15	5307	71·70	64·84, 78·57
Asia/Pacific					
Children/adolescents (>1–17 years)	85·4	3	899	31·89†	24·94, 38·84
Adults (>17–65 years)	99·5	13	3709	67·99	59·73, 76·25
Elderly (>65 years)	98·8	9	4965	66·16	62·16, 70·22
Middle East/Africa					
Children/adolescents (>1–17 years)	99·2	6	1913	75·41†	56·43, 94·38
Adults (>17–65 years)	98·5	6	2079	34·66	29·32, 40·01
Elderly (>65 years)	99·2	4	874	38·20	29·15, 47·25

* Meta-analyses were not conducted for studies carried out in Latin America due to the limited number of eligible studies.
† Values were significantly different from those of the other age groups.

explained by generally inadequate vitamin D levels in pregnant women as suggested in previous work[31]. Future research in these groups is needed to confirm these findings and test interventions aimed at interrupting this putative mechanism.

Strengths and limitations

To our knowledge, the present systematic review, conducted in accordance with the PRISMA statement[18], is among the first to focus on patterns of vitamin D status worldwide and in key population subgroups. We purposefully sought to identify studies with randomly selected samples from the general population to reduce sources of bias, which may otherwise obscure the public health importance of vitamin D status across the world. Use of continuous 25(OH)D values in our analyses is another important strength of the present study, given the inconsistent application of thresholds to indicate 25(OH)D deficiency, insufficiency and adequacy. A systematic search strategy based on two of the largest biomedical literature databases also reduced the probability of missing relevant articles. Besides the detailed data on 25(OH)D values among important subgroups by age, sex and region, the present review adds to the current understanding of vitamin D status in both developed and developing countries worldwide. We used the random-effects model to account for the substantial heterogeneity that we observed across the studies. Between-study heterogeneity is common in systematic reviews, especially in observational epidemiology where unobserved characteristics at both the study and individual levels affect the outcomes of interest. The random-effects model adjusts for this heterogeneity by incorporating a between-study component of variance in the weights used for calculating the summary estimate[32].

It is important to consider the findings of the present review in the context of several potential limitations. First, we cannot fully exclude publication bias as studies reporting vitamin D deficiency might have been more likely to be published than those reporting mean or median levels within the normal range. Second, language bias may have affected the results, as we limited the present review to articles written in English. This may have accounted, for example, for the relative under-representation of studies conducted in Latin America in our sample. Efforts to identify and review studies published in languages other than English are needed in the future to gain a clear understanding of the full scope of vitamin D deficiency worldwide. Third, our strict inclusion criteria (e.g. inclusion of studies with randomly selected samples) might also explain the limited number of studies identified from some regions. However, previous reviews using more liberal inclusion criteria have also identified a limited number of studies conducted in these regions[8,16]. Fourth, recruitment strategies in the studies that we sampled may have focused to an extent on healthier populations, resulting in an overestimation of the prevalence of adequate vitamin D levels and a consequent minimisation of observable differences between the sexes or age-related subgroups. Fifth, we observed substantial heterogeneity between the studies in our sample that could not be explained by variables such as age, sex, season, distance from the equator, assay type or representativeness. Other unmeasured factors influencing vitamin D status (e.g. dietary intake, clothing style, time spent outdoors and use of sunscreen) may have contributed to the heterogeneity of results. Differences across the studies in study quality, adjustment for potential confounders and the definition of some characteristics or factors such as season may have contributed substantially to the heterogeneity that we observed. Finally, the precision of the estimates of vitamin D status in the subgroups of interest in the present review was probably affected by their relative under-representation in studies conducted in many regions of the world. High-quality population-based studies that assess and report all relevant data on 25(OH)D levels and central covariates including lifestyle factors to enable comparison of 25(OH)D values in the future, at least for population subgroups within the same country, have to be conducted.

Conclusion

Although we found a high degree of variability in reports of vitamin D status at the population level, more than one-third of the studies in the present systematic review reported mean 25(OH)D values below 50 nmol/l. Given the substantial heterogeneity of published evidence to date, further research on worldwide patterns of vitamin D deficiency at the population level and within key subgroups is needed to inform public health policy development to reduce risk for potential health consequences of an inadequate vitamin D status. The present review further suggests the importance of developing and implementing research designs that minimise potential sources of bias and consequently strengthen our understanding on vitamin D status in key subgroups worldwide.

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All authors declare that they have no conflicts of interest.

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