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REVIEW

A systematic review of vitamin D status in southern European countries

Yannis Manios[1] · George Moschonis[2] · Christina-Paulina Lambrinou[1] · Konstantina Tsoutsoulopoulou[1] · Panagiota Binou[1] · Alexandra Karachaliou[1] · Christina Breidenassel[3] · Marcela Gonzalez-Gross[3] · Mairead Kiely[4,5] · Kevin D. Cashman[4,6]

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Abstract
Purpose Despite an acknowledged dearth of data on serum 25-hydroxyvitamin D (25(OH)D) concentrations from Southern European countries, inter-country comparison is hampered by inconsistent data reporting. The purpose of the current study was to conduct a systematic literature review of available data on serum 25(OH)D concentrations and estimate vitamin D status in Southern European and Eastern Mediterranean countries, both at a population level and within key population subgroups, stratified by age, sex, season and country.
Methods A systematic review of the literature was conducted to identify and retrieve scientific articles reporting data on serum 25(OH)D concentration and/or vitamin D status following standard procedures.
Results Data were extracted from 107 studies, stratified by sex and age group, representing 630,093 individuals. More than one-third of the studies reported mean 25(OH)D concentrations below 50 nmol/L and ~10% reported mean serum 25(OH)D concentrations below 25 nmol/L. Overall, females, neonates/ infants and adolescents had the higher prevalence of poor vitamin D status. As expected, there was considerable variability between studies. Specifically, mean 25(OH)D ranged from 6.0 (in Italian centenarians) to 158 nmol/L (in elderly Turkish men); the prevalence of serum 25(OH)D < 50 nmol/L ranged from 6.8 to 97.9% (in Italian neonates).
Conclusions Contrary to expectations, there was a high prevalence of low vitamin D status in the Southern Europe and the Eastern Mediterranean regions, despite abundant sunshine. These data further emphasize the need for strategies, such as fortification of foods with vitamin D and/or vitamin D supplementation, which will be tailored to the needs of specific population groups with higher risk of insufficiency or deficiency, to efficiently tackle the pandemic of hypovitaminosis D in Europe.

Keywords Vitamin D · South Europe · East Mediterranean · Prevalence

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✉ Yannis Manios
manios@hua.gr

1 Department of Nutrition and Dietetics, School of Health Science and Education, Harokopio University, 70 El Venizelou Avenue, Kallithea, 17671 Athens, Greece

2 Department of Rehabilitation, Nutrition and Sport, College of Science, Health and Engineering, La Trobe University, Bundoora, 3086 Melbourne, Australia

3 ImFINE Research Group, Department of Health and Human Performance, Universidad Politécnica de Madrid, Madrid, Spain

4 Cork Centre for Vitamin D and Nutrition Research, School of Food and Nutritional Sciences, University College Cork, Cork, Ireland

5 The Irish Centre for Fetal and Neonatal Translational Research (INFANT), University College Cork, Cork, Ireland

6 Department of Medicine, University College Cork, Cork, Ireland

Introduction

An enormous body of research over the last decade in relation to vitamin D and skeletal and non-skeletal health outcomes has contributed to the global interest in the vitamin. As a consequence of the potential multiple health effects of vitamin D, there have been several re-evaluations of vitamin

D recommendations around the globe over the last 6 years [1]. In Europe alone, a number of agencies [German Nutrition Society, Dutch Health Ministry, Nordic Council of Ministers (NORDEN), UK Scientific Advisory Committee on Nutrition (SACN), European Food Safety Authority (EFSA)] have recently revised their Dietary Reference Values (DRV) for vitamin D [2–6]. The DRV are crucial from public health perspective in providing a framework for the prevention of vitamin D deficiency and optimizing vitamin D status of individuals. The risk assessment framework, which has become the internationally adopted gold standard approach for the development of DRV, includes a comparative analysis of usual population intakes and status of vitamin D with proposed DRV as a critical step [6–8]. Knowledge of the distributions of serum 25-hydroxyvitamin D [25(OH)D; the biochemical indicator of vitamin D status] concentrations in representative populations, with appropriate consideration of sex, life stage, ethnicity and seasonality, is critical for the quantification of vitamin D deficiency as well as for devising effective preventive strategies [9].

It has been suggested that in contrast to the expected gradient in vitamin D status, improving from North to South, it is actually the inverse [10, 11], such that the prevalence of vitamin D deficiency in Southern Europe could be of concern. This is despite the much more abundant ultraviolet B (UVB) sunshine availability and potential for dermal synthesis of vitamin D in Southern compared to Northern regions of Europe [12]. Unfortunately, in our recent analysis of vitamin D status in Europe conducted as part of the EC-funded ODIN project, using standardized serum 25(OH)D data, there were very few nationally representative samples available for Southern European countries [12]. This limits the potential to fully assess the prevalence of vitamin D deficiency and inadequacy in the region. An alternative approach is to systematically and comprehensively gather published data on vitamin D status in Southern European countries, which could provide some insight. In their recent systematic review of vitamin D status in populations worldwide, Hilger et al. [13] identified 93 studies which provided European coverage, of which only 18 were from Southern European countries. Furthermore, these studies emerged when the outcome of the literature searches and study selection was stratified into geographic region. Countries of interest was not part of the a priori search strategy, as the primary focus of the review was identification of mean/median serum 25(OH)D concentrations for inclusion in World region-specific meta-analyses [13].

Therefore, the aim of the present work was to conduct a comprehensive systematic literature review of available data on mean/median serum 25(OH)D concentrations as well as estimates of the prevalence of low vitamin D status (as defined by a number of internationally used thresholds of serum 25(OH)D) in a priori defined Southern European countries (including Eastern Mediterranean ones), with appropriate consideration of sex, life stage, ethnicity, and seasonality.

Methods

Inclusion and exclusion criteria for study selection

Studies included in the present systematic review were those observational studies published in English after 1990 and which met the following requirements:

i. studies with well-defined/characterized samples of healthy subjects;
ii. conducted with randomly selected subjects from the general population or population subgroups stratified by age, sex and specific areas within one of our *a priori* defined Southern European countries i.e., France, Italy, Spain, Portugal, Greece, Malta, Cyprus, Turkey and Israel;
iii. reported mean values and standard deviation (or median and interquartile range [IQR]) of serum 25(OH)D concentrations and/or prevalence data on serum 25(OH)D below one or more of our specified thresholds (namely < 25, <30, < 37.5, < 50 and < 75 nmol/L);
iv. provided details on assay used for assessment of serum 25(OH)D concentrations; and,
v. reported season(s) in which blood sampling within the study occurred.

Studies were excluded if they were intervention studies or clinical studies in patient subgroups and/or in subgroups with specific characteristics (i.e. specific ethnic groups, specific professions and skin color), on the basis that they were not randomly selected and as such were not representative of the general population. As per Hilger et al. [13], studies published before 1990 were excluded on the basis of a general shift in lifestyle that may have affected population mean 25(OH)D concentrations.

Search strategy

Extensive literature searches were performed in PubMed/MEDLINE, Scopus, CENTRAL, Scielo, Cochrane databases for the period January 1st 1990 to July 29th 2016 (date of the final screen) by using a structured search strategy which accounted for the inclusion/exclusion criteria outlined above. A number of relevant keywords were identified from the Medical Subject Headings terms and the EMTREE thesaurus and were combined in the specific search strategy. The search strategy specifically adapted for PubMed/Medline is shown in Supplemental Table 1. The methods used in the present review follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [14].

Data collection and quality assessment of eligible studies

Titles and abstracts retrieved from electronic searches were initially screened by four independent reviewers, firstly for duplicates and secondly for eligible studies, based on stated inclusion and exclusion criteria. Eligible studies were further screened by two (out of the initial four) independent reviewers for assessment of the quality of their study design and reported data, following a thorough examination of the information available in the full text of the relevant articles.

Quality assessment was based on the scoring system proposed by Loney et al. [15] (and summarized in Supplemental Table 2), in which a "Yes" answer to each question received a score of "1 point", while a "No" answer received a score of "0 points". The minimum score a study could reach was 0 while the maximum score was 8. A minimum total score of 6 was used as the threshold for the final inclusion of a study into the systematic review [15].

In the present analysis, the identified studies from which data were extracted were presented in four age groups: i.e. neonates/ infants (0–1 years); children/adolescents (> 1–18 years); adults (> 18–65 years); and elderly (> 65 years). In the case of certain studies in which the age range of the populations under study intersected different age groups, these studies were categorized and presented as part of the age group with the greater overlap (e.g., if the age range of one study was 19–85 years, this study was categorized in the "adult" age group).

Data synthesis and extraction

A flowchart showing the number of studies assessed and included in the review is shown in Fig. 1. A standard form was used for recording the data extracted from each

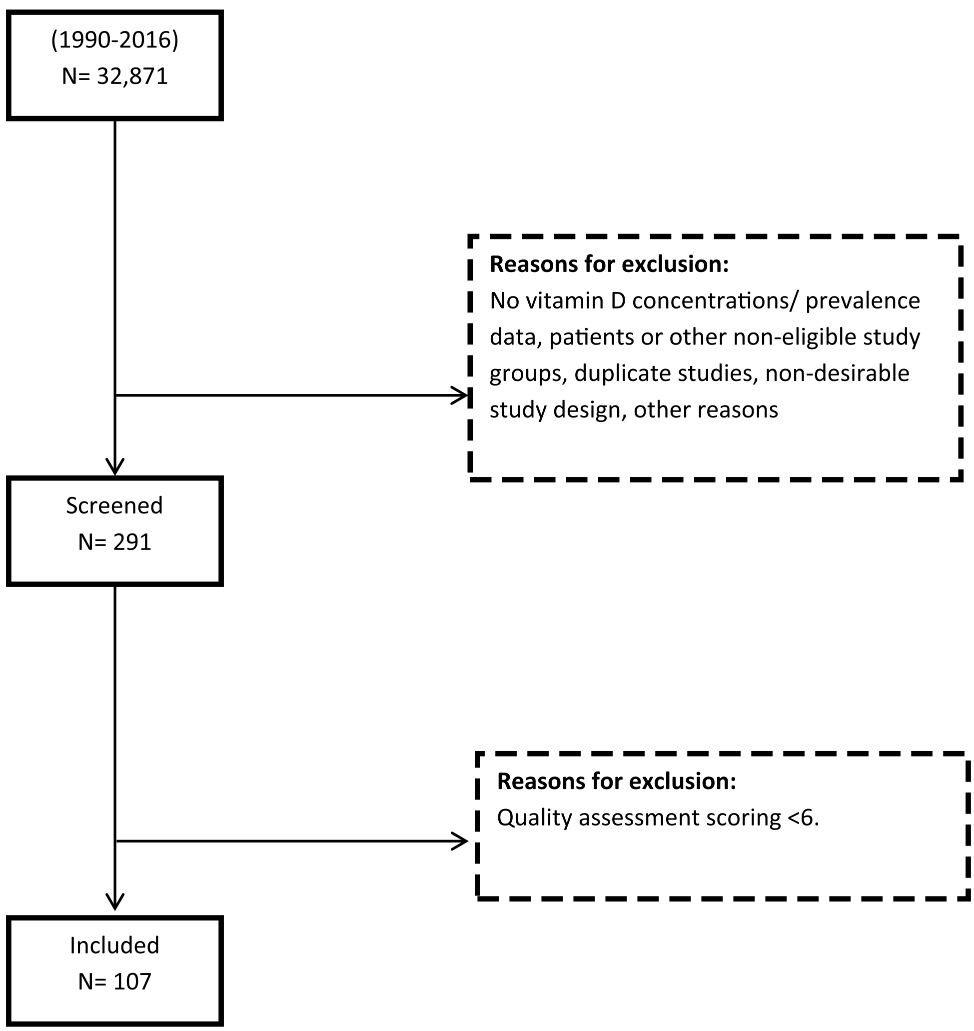

Fig. 1 Flow diagram of the screening procedure followed to identify eligible studies

of the eligible studies. The following main information was extracted from all eligible articles and used to fill in the respective data extraction forms: (a) first author's surname; (b) publication date; (c) country and latitude where the study was conducted; (d) the study design/characteristics; (e) the characteristics of the study population; (f) methods used for recruiting the study population; (g) sample size; (h) participants' age; (i) season or month when blood samples were collected; (j) type of biological sample used to measure 25(OH)D levels (i.e., primarily serum but also plasma); (k) mean ± standard deviation or median and IQR of serum/plasma 25(OH)D concentrations; (l) prevalence of circulating 25(OH)D less than 12.5, 25, 30, 37.5, 50 and/or 75 nmol/L, as used variably as cut-offs of low vitamin D status. In the vast majority of studies, the prevalence for vitamin D deficiency and insufficiency was presented as 25(OH)D concentrations < 25 and < 50 nmol/L, respectively; however, there were studies which used some of the above-mentioned alternative thresholds of 25(OH)D and these are included where appropriate; and (m) the biochemical method/assay used to measure serum 25(OH)D concentrations.

The vast majority of studies were represented by a single article and in only a small number of cases ($n = 13$), the required data were available in more than one article, e.g., studies presenting data stratified by age, sex or region in different articles.

Data presentation

Serum 25(OH)D concentrations were reported as mean ± SD or median (IQR). In all cases, serum/plasma 25(OH)D concentrations were expressed in nmol/L, following their conversion from ng/mL (i.e. ng/mL multiplied by 2.496), if required. Data on the prevalence of serum 25(OH)D < 12.5, 25, 30, 37.5, 50 and/or 75 nmol/L, are presented as available from the collection of 107 included studies. To gain some insight to the possible overall prevalence of vitamin D deficiency (serum 25(OH)D < 25 nmol/L) for the southern European population, estimates from those studies which reported prevalence of serum 25(OH)D < 25 nmol/L in all seasons, stratified by age group, were averaged and presented in the Tables. This was done separately for studies of neonates/ infants, adolescents/teenagers, adults and the elderly, but not for mothers of infants, young children or postmenopausal women, on the basis of the low number of studies providing these data or the fact that some age groups (e.g., mothers and postmenopausal women) were subsets of others, such as adults and elderly.

Results

In total, 32,281 titles and abstracts were screened (Fig. 1), and following a considerable reduction in number to 291 on the basis of assessment of eligibility criteria, these were then assessed in terms of quality criteria which yielded the final number of studies included at 107 [16–118]. Data were extracted for each of these 107 studies.

Description of studies, study participants and methods/assays used to measure circulating 25(OH)D concentrations

The 107 studies included in the current systematic review presented data on a total of 630,093 participants from seven southern European countries (including Turkey and Israel), with the sample sizes within individual studies ranging from 100 to 271,176 participants. Of the 107 eligible studies identified, 35 were conducted in Italy (32.7%), 20 in Spain (18.7%), 19 in Turkey (17.8%), 12 in France (11.2%), 11 in Israel (10.3%), 5 in Greece (4.7%), 2 in Cyprus (1.9%), 1 in Portugal (0.9%) and 2 studies in more than one southern European countries (1.9%). While the majority of the studies were presenting data on both males and females, 6 studies (5.6%) presented data only on males, while 13 studies (12.1%) presented data only on females.

The biochemical assays used to measure circulating 25(OH)D concentration in the included studies were radioimmunoassay (RIA) (in 42.1% of the studies), chemiluminescence assay (in 20.6% of the studies) and other assays, such as competitive protein-binding assays and high-performance liquid chromatography (HPLC), in the remaining of the studies.

Circulating 25(OH)D concentrations and vitamin D status per age group

There was a high degree of variability in the estimates of average (i.e., mean and/or median) serum/plasma 25(OH)D concentrations as well as in the prevalence of vitamin D deficiency and insufficiency (represented as serum 25(OH)D < 25 and < 50 nmol/L, respectively) across the collection of 107 included studies, as summarized on an age-group basis in Tables 1, 2, 3, 4 and 5.

Neonates/infants and mothers

The mean and/or median concentrations of 25(OH)D in serum of neonates/ infants from the nine included studies of neonate/infant–mother pairs from southern European countries are shown in Table 1, and ranged from 14.2 nmol/L (in large-for-gestational age born neonates from Turkey [18]), to 101 nmol/L, (in 0- to 12-month-old neonates/ infants

Table 1 Means and/or median circulating 25(OH)D concentrations and prevalence of circulating 25(OH)D concentrations below 12.5, 25, 50 and 75 nmol/L reported for studies of neonates/infants (I) and their mothers (M) from southern European (and east Mediterranean) countries, identified as part of the present systematic review

Reference	Country/region (latitude)	Sample size (*n*)	Age (years) (Mean ± SD and/or age range)[a]	Seasons	Serum 25(OH)D (nmol/L)[a] Mean ± SD or Median (IQR)	Prevalence below serum 25(OH)D threshold (%)				Method
						< 12.5 nmol/L	< 25 nmol/L	< 50 nmol/L	< 75 nmol/L	
Cadario et al., 2015 [34]	Italy/Novara, Piedmont (45° 32′ 54.65″ N)	533 mother–neonate pairs	0 years/3 days (I) 32.3 ± 5.6 (M)	All seasons	28.2 ± 19.2 (I) 39.9 ± 21 (M) Winter–spring 17.4 ± 11.9 (I-Migrant) 27.2 ± 14.9 (I-Italian) 31.2 ± 15.4 (M-Migrant) 37.6 ± 16.4 (M-Italian) Summer–autumn 23.2 ± 14.9 (I-Migrant) 43.9 ± 18.9 (I-Italian) 34.9 ± 17.2 (M-Migrant) 54.9 ± 21.4 (M-Italian)		52.1% (I) 27.7%(M) 76.2% (I–Migrant) 38% (I-Italian) 48.4% (M-Migrant) 89.9% (M-Italian)	85.4% (I) 70.6%(M) 97.9% (I–Migrant) 78.1% (I–Italian) 89.7% (M-Migrant) 61.6% (M-Italian)	97.9% (I) 92.5%(M) 99.5% (I–Migrant) 96.9% (I–Italian) 98.1% (M-Migrant) 89.9% (M-Italian)	LC-MS/MS (I) CIA (M)
Rodriguez et al. 2015 [89]	Spain/Valencia (39° 28′ 11.67"N)/ Sabadell (41° 32′ 46.59″ N)/ Gipuzkoa (43° 04′ 32.27″ N)/ Asturias (43° 21′ 41.02″ N)	2382 mother-neonate pairs	32.0 ± 4.2 (M)	All seasons	73.4 (54.4–92.9) (M)			19.7% (M)	31.8% (M)	HPLC
Alonso et al., 2014 [21]	Spain/Asturias Northern Spain (43° 21′ 41.02″ N)	102 neonates	0–1 m (I)	All seasons	101.3 ± 43.9 (I)		0.9% (I)	6.8% (I)		CIA

Table 1 (continued)

Reference	Country/region (latitude)	Sample size (*n*)	Age (years) (Mean ± SD and/or age range)[a]	Seasons	Serum 25(OH)D (nmol/L)[a] Mean ± SD or Median (IQR)	Prevalence below serum 25(OH)D threshold (%)				Method
						< 12.5 nmol/L	< 25 nmol/L	< 50 nmol/L	< 75 nmol/L	
Karras et al., 2013 [65]	Greece/ Thessaloniki (40° 38′ 24.23″ N)	60 mother-neonate pairs	32.8 ± 5.2 (M)	All seasons	44.7 ± 32.9 (M) 39.7 ± 33.9 (I)			66.7% (M) 70% (I)		LC-MS/MS
Nicolaidou et al., 2006 [83]	Greece /Athens (37° 59′ 0″ N)	123 mother-neonate pairs	28 (24–32) (M) 0 days (I)	All seasons	40.9 (27.5–52.7) (M) 50.9 (34.7–75.9) (I) Winter–spring 36.4 (25.2–46.2) (M) 47.7 (31.2–63.9) (CB) Summer–autumn 47.2 (32.2–58.2) (M) 60.0 (41.4–84.9) (CB)		19.5% (M) 8.1% (CB) Winter–spring 24% (M) Summer–autumn 15% (M)			CIA
Andıran et al., 2002 [23]	Turkey(38° 57′ 49.48″ N)	54 mother- neonate pairs	24.5 ± 4.7 (M) 19.5 ± 4.4 days (I)	Autumn	29.1 ± 10.5 (M) 18.6 ± 8.0 (I)		46.3% (M) 80% (I)			RIA
Parlak et al., 2014 [87]	Turkey/Kahramanmaras (37° 34′ 30.99″ N)	97 mother- neonate pairs	27.1 ± 4.5 (19–38) (M) 0 days (I)	Winter	12.4 ± 8.2 (M) 10.7 ± 6.1 (CB)	63.9% (M) 76.3% (CB)	88.7% (M) 94.8% (CB)	97.9% (M) 100% (CB)		ECIA
Akcacus et al., 2006 [18]	Turkey (38° 57′ 49.48″ N)	100 mother-neonate pairs	0 days (I)	All seasons	21.7 ± 7.5 (M of SGA I) 21.5 ± 7.5 (M of AGA I) 19.2 ± 7.0 (M of LGA I) 15.7 ± 6.2 (SGA I) 15.0 ± 5.5 (AGA I) 14.2 ± 4.5 (LGA I)		82% (M) 93% (I)			RIA

Table 1 (continued)

Reference	Country/region (latitude)	Sample size (n)	Age (years) (Mean ± SD and/or age range)[a]	Seasons	Serum 25(OH)D (nmol/L)[a] Mean ± SD or Median (IQR)	Prevalence below serum 25(OH)D threshold (%) < 12.5 nmol/L	< 25 nmol/L	< 50 nmol/L	< 75 nmol/L	Method
Halicioglu et al., 2011 [59]	Turkey/Izmir (38° 25′ 25.44″ N)	258 mother-neonate pairs	27.2 ± 4.9 (17–42) (M)	Spring	28.7 ± 13.5 (M) 28.7 ± 17.0 (I)		50.4% (M) 50.8% (I)	90.3% (M) 90.3% (I)		CIA

SGA small for gestational age, *AGA* appropriate for gestational age, *LGA* large for gestational age, *RIA* radioimmunoassay, *ECIA* electrochemiluminescence immunoassay, *LC-MS/MS* liquid chromatographic with tandem mass spectrometry, *CIA* chemiluminescence immunoassay, *M* mother, *I* infant, *CB* cord blood

[a]Unless otherwise specified

from a city of northern Spain [21]). The prevalence rates of circulating 25(OH)D concentration < 25 and < 50 nmol/L were highest in migrant Italian neonates, i.e., 76.2 and 97.9% respectively, and lowest in Spanish infants, i.e., 0.9 and 6.8% respectively (Table 1).

The lowest mean and/or median maternal circulating 25(OH)D concentration (i.e., 10.7 nmol/L) measured in umbilical cord blood samples (reflective of maternal circulating 25(OH)D) was observed in Turkish mothers [87]. These mothers were also found to have the highest prevalence rates of circulating 25(OH)D concentration < 25 and < 50 nmol/L, i.e., 94.8 and 100%, respectively [87]. It is also notable that one of the Turkish studies reported prevalence of serum 25(OH)D < 12.5 nmol/L at 76% for mothers based on 25(OH)D concentrations measured in umbilical cord blood, respectively [87]. In comparison to Greece, Spain and Italy, where the prevalence of low vitamin D status (i.e., < 50 nmol/L) ranged from ~ 7–78% for neonates/ infants and ~ 20 to 67% for mothers, the prevalence in Turkey was 90–100% among mothers and/or neonates/ infants (Table 1).

The highest mean and/or median serum 25(OH)D concentration (i.e., 73.4 nmol/L) was reported for mothers living in four cities in northern and eastern Spain, who also had the lowest prevalence of 25(OH)D < 50 nmol/L, i.e., 19.7% [89]. The lowest prevalence of 25(OH)D < 25 nmol/L was also observed for mothers living in the city of Athens, Greece during summer and autumn months at 15% [83]. Within Italy, the prevalence of vitamin D deficiency (< 25 nmol/L) was almost twice as high in migrant neonates/ infants and mothers compared to their native Italian equivalents [91].

The average prevalence of circulating 25(OH)D concentration below 25 and 50 nmol/L in studies of infants and their mothers from Southern European (and east Mediterranean) countries which reported these estimates are shown in Fig. 2. Of the studies that report prevalence estimates of serum 25(OH)D < 25 nmol/L in neonates/infants for all seasons (as an indication of vitamin D deficiency), the average prevalence was ~ 20%.

Children and adolescents

The mean and/or median serum 25(OH)D concentrations of children and adolescents in the 28 included studies from southern European countries are shown in Table 2. The lowest median concentration of circulating 25(OH)D was 21.7 nmol/L in 4- to16-year-old girls from Ankara, Turkey, assessed during winter/spring months [27]. Likewise, two additional studies of children and adolescents in Turkey reported relatively low Spring-time mean 25(OH)D concentrations, namely 22.3 nmol/L in 11- to 18-year-old girls from the north-eastern part of the country [64], and 24.6 nmol/L in adolescent boys and girls from Istanbul [45]. At the same time, the highest mean concentration of circulating 25(OH)

Table 2 Mean and/or median circulating 25(OH)D concentrations and prevalence of circulating 25(OH)D concentrations below 12.5, 25, 50 and 75 nmol/L reported for studies of children and adolescents from southern European (and east Mediterranean) countries, identified as part of the present systematic review

Reference	Country/region (Latitude)	Sample size (n)	Age (years) (Mean ± SD and/or age range)[1]	Seasons	Serum 25(OH)D (nmol/L)[a] Mean ± SD or median (IQR)	Prevalence below serum 25(OH)D threshold (%)				Method
						< 12.5 nmol/L	< 25 nmol/L	< 50 nmol/L	< 75 nmol/L	
Esterle et al., 2010 [46]	France/Caen (49° 10′ 58.31″ N)	211 (f)	11–16.9	All seasons	Summer–autumn 49.9 ± 15.2 Winter–spring 39.7 ± 18.5			Summer–autumn: 43% Winter–spring: 70%	94% (t)	HPLC
Gonzalez-Gross et al., 2011 [55]	Italy/Rome (41° 52′ 20.68″ N) Greece/Athens (37° 59′ 0″ N) & Heraklion Greece (35° 20′ 19.45″ N) /Spain/ Zaragoza (41° 38′ 55.76″ N) France/Lille (50° 37′ 45.3″ N)	1006	14.9 ± 1.2	Autumn/Summer	Rome (Italy) 70.0 ± 19.3 (t) 67.7 ± 17.5 (m) 71.8 ± 20.5 (f) Athens (Greece) 68.2 ± 20.8 (t) 70.4 ± 21.2 (m) 66.5 ± 20.5 (f) Zaragoza (Spain) 62.9 ± 19.2 (t) 62.9 ± 22.2 (m) 62.9 ± 16.4 (f) Lille (France) 54.9 ± 24.5 (t) 60.2 ± 27.1 (m) 51.1 ± 21.9 (f) Heraklion (Greece): 51.3 ± 13.4 (t) 51.9 ± 12.4 (m) 50.7 ± 14.4 (f) (Plasma samples)			Rome (Italy): 26.4% (t) Athens (Greece) 25.7% (t)		EIA
Di Nisio et al., 2015 [42]	Italy/Sapri (40° 04′ 23.69″ N)	108 (m)	12–13	Autumn	61.4 ± 1.25 (t) 59.6 ± 1.60 (OW/OB) 62.8 ± 1.57 (NW)				92% (OW/OB) 76% (NW)	CIA

Table 2 (continued)

Reference	Country/region (Latitude)	Sample size (n)	Age (years) (Mean ± SD and/or age range)[1]	Seasons	Serum 25(OH)D (nmol/L)[a] Mean ± SD or median (IQR)	Prevalence below serum 25(OH)D threshold (%)				Method
						< 12.5 nmol/L	< 25 nmol/L	< 50 nmol/L	< 75 nmol/L	
Bellone et al., 2014 [30]	Italy/North (41° 52′ 18.98″ N)	557	11.2 ± 0.1	All seasons	57.9 ± 1.2 (t) 68.1 ± 3 (NW) 54.4 ± 1.5 (OB)			31.8% (NW) 44.4% (OB) Winter 56.6% (OB) Summer 25.0% (OB)		CIA
Vierucci et al., 2014 [116]	Italy/Tuscany (43° 43′ 0″ N)	427	10–21	All seasons	50.0 (8.1–174.7) 48.3 (10.0–174.7) (m) 50.4 (8.1–174.3) (f)		49.9% (t)		82.2% (t)	RIA
Vierucci et al., 2013 [117]	Italy/Tuscany (43° 43′ 0″ N)	652	2–21	All seasons	51.8 (6.7–174.7) (t) 51.2 (6.8–174.7) (m) 52.3 (8.1–174.3) (f) 2–11 years: 55.6 (6.8–154.6) 12–21 years: 49.8 (8.1–174.7) Winter (Jan–Mar) 44.1 (6.8–147.1) Spring (Apr–Jun) 47.8 (12.1–122.3) Summer (Jul–Sep) 67.1 (10.8–174.3) Autumn (Oct–Dec): 56.6 (8.7–174.7)		9.5% (t)	45.9% (t)	79.5% (t)	RIA

Table 2 (continued)

Reference	Country/region (Latitude)	Sample size (n)	Age (years) (Mean ± SD and/or age range)[1]	Seasons	Serum 25(OH)D (nmol/L)[a] Mean ± SD or median (IQR)	Prevalence below serum 25(OH)D threshold (%)				Method
						< 12.5 nmol/L	< 25 nmol/L	< 50 nmol/L	< 75 nmol/L	
Stagi et al. 2014 [102]	Italy/Florence (43° 46′ 4.5″ N)	188 (control group)	15.3 (8.3–24.2)	All seasons	74.4 ± 28.0 (t) 51.7 ± 22.0 (m) 55.16 ± 18.22 (f) 8–11 years: 55.9 ± 19.7 12–18 years: 53.9 ± 18.7 19-24.2 years: 52.4 ± 19.2 Winter: 66.1 ± 21.2 Summer: 94.4 ± 33.7		5.1% (t)	41.3% (t)	38.2% (t)	CIA
Stagi et al. 2014 [102]	Italy/Mugello-Florence (43° 59′ 51.34″ N)	679	2.1–17.9	All seasons	47.6 ± 21.1 (t) 2.1–11 years: 50.6 ± 21.0 12-17.9 years: 29.3 ± 14.4 30.0 ± 14.2 (OB) 42.8 ± 19.6 (OW) 37.9 ± 18.3 (OW/OB) 64.1 ± 18.3 (NW) Spring: 37.4 ± 16.1 Summer: 64.2 ± 21.5 Autumn: 58.0 ± 16.4 Winter: 39.8 ± 21.6		20.5% (t)	38.2% (t)	30% (t)	CIA

Table 2 (continued)

Reference	Country/region (Latitude)	Sample size (n)	Age (years) (Mean ± SD and/or age range)[1]	Seasons	Serum 25(OH)D (nmol/L)[a] Mean ± SD or median (IQR)	Prevalence below serum 25(OH)D threshold (%)				Method
						< 12.5 nmol/L	< 25 nmol/L	< 50 nmol/L	< 75 nmol/L	
Franchi et al., 2014 [48]	Italy/Verona, (45° 26′ 30.66″ N)	1,374	0–17	All seasons	52.42 (34.94–73.88) (t)		44.2% (Caucasians) 65.2% (Africans) 69.2% (North Africans) 54% (Indians) 44.8% (others)		74.8% (Caucasians) 81.2% (Africans) 89.7% (North Africans) 76% (Indians) 75.9% (others)	CIA
Rodriguez-Rodriguez et al., 2010 [91]	Spain/Madrid (40° 23′ 0″ N)	149	10.8 ± 1.1 (8–13)	Winter	57.7 ± 20.5 (t)			37.6% (t)		CIA
Mouratidou et al., 2012 [82]	Spain/Zaragoza (41° 38′ 55.76″ N)	227	12.5–17.5	Autumn–summer	66.3 ± 20 72 ± 23 (m) 61 ± 16 (f)					IA
Valtueña et al., 2012 [114]	Spain/Zaragoza (41° 38′ 55.76″ N)	100	12.5–17.5	Summer–autumn	63.6 ± 18.9 (Plasma samples)				73% (t)	EIA
Dura-Trave et al., 2016 [43]	Spain/Pamplona (42° 48′ 45.09″ N)	413	3.1–15.4	All seasons	69.9 ± 19.0 (t) 70.6 ± 19.2 (m) 69.3 ± 19.2 (f) 3.1–11 years: 71.9 ± 18.9 12-15.4 years: 67.4 ± 19.3 Spring: 64.8 ± 16.6 Summer: 88.2 ± 18.8 Autumn: 67.3 ± 17.0 Winter: 68.6 ± 19.1			12.7% (t)	44.9% (t)	RIA

Table 2 (continued)

Reference	Country/region (Latitude)	Sample size (n)	Age (years) (Mean ± SD and/or age range)[1]	Seasons	Serum 25(OH)D (nmol/L)[a] Mean ± SD or median (IQR)	Prevalence below serum 25(OH)D threshold (%)				Method
						< 12.5 nmol/L	< 25 nmol/L	< 50 nmol/L	< 75 nmol/L	
Alonso et al., 2014 [21]	Spain/Asturias (43° 21′ 41.02″ N)	186	1 month–13 years	All seasons	2–5 years: 77.1 ± 29.9 ≥ 6 years: 65.9 ± 24.7 Spring–summer 95.3 ± 42.7 Autumn–winter 75.1 ± 31.2		2.1% (t) 2–5 years: 2.6% > 6 years: 2.7%	15.6% (t) 2–5 years: 16.1% > 6 years: 27%		CIA
Cabral et al., 2016 [33]	Portugal/Porto, 41º09′28.6″ N)	514	13	All seasons	41.23 ± 14.28 (t) 39.21 ± 12.63 (f) 44.33 ± 15.35 (m) March–July 43.03 ± 14.83 November–February 37.66 ± 12.38					DiaSorin LIAISON®
Kolokotroni et al., 2014 [68]	Cyprus/Nicosia (35° 11′ 8.04″ N) / Limassol (34° 42′ 25.67″ N)/ Larnaka (34° 54′ 0.91″ N)	671	16–18	All seasons	57.2 ± 16.0 (t) 59.6 ± 16.5 (m) 55.5 ± 15.5 (f)			35.7% (t)	90% (t)	IA
Kolokotroni et al., 2015 [69]	Cyprus/Nicosia (35° 11′ 8.04″ N) / Limassol (34o 42′ 25.67″ N)/ Larnaka (34° 54′ 0.91″ N)	671	16–18	Autumn–Spring	57.2 ± 16.0 (t) 59.6 ± 16.5 (m) 55.5 ± 15.5 (f) Autumn: 64.5 ± 16.8 Winter: 56.7 ± 16.2 Spring: 56.4 ± 15.2			35.7% (t) 30.2% (m) 39.4% (f) Autumn: 23.9% Winter: 36.1% Spring: 37.4%	90% (t)	EIA
Tekin et al., 2015 [106]	Turkey/Adiyaman (37° 54′ 28.18″ N)	64 (control group)	2 months–12 years	All seasons	68.9 ± 11.7 (t) 69.4 ± 12.5 (m) 68.4 ± 19.0 (f)					CIA

Table 2 (continued)

Reference	Country/region (Latitude)	Sample size (n)	Age (years) (Mean ± SD and/or age range)[1]	Seasons	Serum 25(OH)D (nmol/L)[a] Mean ± SD or median (IQR)	Prevalence below serum 25(OH)D threshold (%)				Method
						< 12.5 nmol/L	< 25 nmol/L	< 50 nmol/L	< 75 nmol/L	
Erdönmez et al., 2011 [44]	Turkey (38° 57′ 49.48″ N)	301	14.2 ± 1.8	Winter	45.4 ± 23.2 (t) 51.7 ± 23.7 (m) 40.9 ± 22.0 (f)		11.6% (t)	65.1% (t)		CPB
Turkeli et al., 2016 [112]	Turkey/Eskisehir (39° 46′ 0.14″ N)	102 (control group)	1–4	Winter	80.1 ± 36.8 (t)			24.5% (t)	23.5% (t)	ECIA
Akman et al., 2011 [19]	Turkey/Urban and rural Ankara (39° 56′ 0.11″ N)	849	1–16	Winter–spring (Feb–Mar)	Urban: 100.6 ± 38.0 Rural: 89.0 ± 34.5			Urban: 7.7% Rural: 8.3%	Urban:28.7% Rural: 38.3%	HPLC
Andıran et al., 2012 [22]	Turkey/Ankara (39° 56′ 0.11″ N)	440	0–16	All seasons	0–5 years: 85.4 ± 40.4 5–10 years: 51.2 ± 21.7 10–16 years: 46.7 ± 28.0			40% (t) 52.1% (m) 64.8% (f)		HPLC
Sonmez et al., 2015 [100]	Turkey/Ankara (39° 56′ 0.11″ N)	101	5–16	All seasons	58.4 ± 32.0 (t) Shorter daylight 44.0 ± 2.9 Longer daylight 76.9 ± 2.6			50.5% (t)		HPLC
Aypak et al., 2014 [27]	Turkey/Ankara (39° 56′ 0.11″ N)	168	4–16	Winter–spring (Feb–Mar)	25.2 (10.0–53.2) (t) 27.2 (13.5–53.2) (m) 21.7 (10.0–48.2) (f) 25.5 (13.0–48.2) (OB) 27.0 (10.0–47.7) (OW) 23.7 (10.0–53.2) (Lean)		50% (t)	98.2% (t)		CIA
Torun et al., 2013 [110]	Turkey/Marmara (40° 37′ 40.02″ N)	188	9–15	All seasons	35.9 ± 20.2 (OB) 46.4 ± 23.7 (non-OB)		34.5% (t)	27.4% (t)		ECIA

Table 2 (continued)

Reference	Country/region (Latitude)	Sample size (n)	Age (years) (Mean ± SD and/or age range)[1]	Seasons	Serum 25(OH)D (nmol/L)[a] Mean ± SD or median (IQR)	Prevalence below serum 25(OH)D threshold (%)				Method
						< 12.5 nmol/L	< 25 nmol/L	< 50 nmol/L	< 75 nmol/L	
Karaguzel et al., 2014 [64]	Turkey/Trabzon province (41° 00′ 9.71″ N)	746	11–18	Spring–autumn	34.3 ± 18.3 (t) 37.3 ± 20.8 (m) 31.3 ± 17.3 (f) Spring 27.8 ± 14.0 (t) 28.5 ± 17.0 (m) 22.3 ± 10.5 (f) Autumn 40.8 ± 19.8 45.0 ± 18.5 (m) 36.5 ± 20.3 (f) 25.8 ± 12.3 (covered f) 32.3 ± 17.8 (not covered f)		45% (t)	82% (t) 78% (m) 87% (f) Autumn: 71% Spring: 93%		HPLC
Erol et al., 2015 [45]	Turkey/Bagcilar – Instanbul (41° 02′ 44.33″ N)	280	3–17	All seasons	End of winter 28.5 ± 14.6 (t) 29.1 ± 13.0 (m) 28.01 ± 16.0 (f) < 12 years: 30.6 ± 15.3 > 12 years: 24.6 ± 12.3 End of summer 51.8 ± 22.5 (t) 55.7 ± 21.2 (m) 48.2 ± 23.1 (f) < 12 years: 53.6 ± 21.6 > 12 years: 48.3 ± 23.8			End of winter 92.4% (t) End of summer: 51.2% (t)		ECIA
Korchia et al., 2013 [70]	Israel/Jerusalem (31° 46′ 5.95″ N)	247	1.5–6	All seasons	64.1 ± 24.9 1.5–3 years: 71.4 ± 26.7 3–6 years: 59.9 ± 23.0 64.6 ± 25.4 (m) 63.4 ± 24.9 (f)			28% (t) Winter: 53% Spring: 16% Summer: 19% Autumn: 36%	70.3% (t)	CIA

Table 2 (continued)

t total sample of both males and females, *f* females, *m* males, *RIA* radioimmunoassay, *EIA* enzyme immunoassay, *CPB* competitive protein binding, *IA* immunoassay, *ECIA* electro chemiluminescence immunoassay, *HPLC* high-performance liquid chromatography method, *LC-MS/MS* liquid chromatographic with tandem mass spectrometry, *CIA* chemiluminescence immunoassay, *C* children, *A* adolescents, *NW* normal weight, *OB* obese, *OW* overweight

[a]Unless otherwise specified

D (at ~ 101 nmol/L) was reported in children and adolescents aged 1 to 16 years old, living in urban Ankara, Turkey during winter months [19]. Equally high circulating 25(OH)D concentrations, at a mean of 95.3 nmol/L, were observed for neonates/ infants and children between 1 month and 13 years during spring and summer months in the northern part of Spain [21]. A comparable mean 25(OH)D concentration of 94.4 nmol/L was observed for children, adolescents and young adults, between 8 and 24 years, in Florence, Italy, during summer [102]. In line with these data, the highest prevalence of circulating 25(OH)D < 50 nmol/L, at 98.2%, was reported for Turkish girls in Ankara [27], while the lowest prevalence was 7.7%, among children and adolescents, also living in Ankara [19].

Using a serum 25(OH)D < 25 nmol/L as a threshold of deficiency, the average percentage reported for studies of children/adolescents in Turkey (38%) [27, 44, 64, 110] was higher than that for five studies in Italy (26%) [48, 102, 116, 117]. Within a study in Northern Italy, children/adolescents of African, North African and Indian descent had a higher prevalence of vitamin D deficiency (54–69%) than their white counterparts (44%) [48]. Iin most studies reporting data in both girls and boys, mean/median circulating 25(OH) D concentrations were consistently lower in female than male participants [27, 45, 55, 64, 68, 82].

The average prevalence of circulating 25(OH)D concentration below 25 and 50 nmol/L in studies of children and adolescents/teenagers from Southern European (and east Mediterranean) countries which reported these estimates are shown in Fig. 3. As an indication of vitamin D deficiency among adolescents/teenagers (excluding children), across all seasons, the average prevalence of serum 25(OH) D < 25 nmol/L was ~ 27% in the studies that reported these data.

Adults

The mean and/or median serum 25(OH)D concentrations reported of adult men and women in the 40 included studies from southern European countries are shown in Table 3. The lowest mean serum concentration of 25(OH)D (i.e., 34.2 nmol/L) was observed for men and women (54–89 years old) living in the city of Oviedo in northern Spain during winter and spring months [51], whereas the highest median concentration of 25(OH)D was 107.2 nmol/L among men and women (30–70 years old) living in the Yozgat region of Turkey in winter [36]. None of the included studies reported serum 25(OH)D < 12.5 nmol/L and for those that used the < 25 nmol/L threshold, the range was between 4% and 27%, with no obvious latitudinal trend (Table 3). Of note, over half the Arab women in a study conducted in Israel had serum 25(OH)D < 25 nmol/L, whereas the prevalence was only 12% in the corresponding Jewish Israeli women [95]. There

Table 3 Mean and/or median circulating 25(OH)D concentrations and prevalence of circulating 25(OH)D concentrations below 12.5, 25, 50 and 75 nmol/L reported for studies of adult men and women from southern European (and east Mediterranean) countries, identified as part of the present systematic review

Reference	Country/region (latitude)	Sample size (*n*)	Age (years) (mean ± SD and/or age range)[a]	Seasons	Serum 25(OH)D (nmol/L)[a] Mean ± SD or median (IQR)	Prevalence below serum 25(OH)D threshold (%)				Method
						< 12.5 nmol/L	< 25 nmol/L	< 50 nmol/L	< 75 nmol/L	
Szulc et al., 2003 [104]	France/Lyon (45° 45′ 50.55″ N)	1,121 (m)	20–87	N/A	≤ 57 years: 59.4 ± 27.2 > 57 years: 54.7 ± 24.0					RIA
Touvier et al., 2015 [111]	France (46° 13′ 39.5″ N)	1,828	Middle-aged	All seasons	50.67 ± 25.71 (t)		14.8% (t)	57.8% (t)		ECIA
Assmann et al., 2015 [25]	France (46° 13′ 39.5″ N)	1,009	45–60	All seasons			14.6% (t)	42.3% (t)	27.3% (t)	ECIA
Souberbielle et al., 2015 [101]	France (46° 13′ 39.5″ N)	888	18–89	All seasons	59.4 ± 20.22					Liaison XL automated platform
Szulc et al., 2012 [105]	France/Montceau les Mines (46° 40′ 26.87″ N)	881 (m)	19–85	N/A	19–54 years: 74.9 ± 30 55–85 years: 67.4 ± 27.5					RIA
Chapuy et al., 1997 [38]	France/20 French cities Latitude varies from 43° to 51° N	1,579	50 ± 6 (35–65)	All seasons	61 ± 30 (t) 62 ± 30 (m) 60 ± 30 (f)		14% (t) *(< 30 nmol/L)*			RIA
Adami et al., 2009 [16]	Italy (41° 52′ 18.98″ N)	608 (f)	35.6 ± 8.3 (20–40)	Autumn–Winter (Sep–Dec)	North: 68.9 ± 27.7 (t) Centre: 72.1 ± 28.2 South: 61.9 ± 28.0			29.7% (t)	65.0% (t)	RIA
Cesareo et al., 2015 [37]	Italy (41° 52′ 18.98″ N)	15 (control group)	57 ± 4	All seasons	84.9 ± 17.5 (t)					DiaSorin immunoassay
Barchetta et al., 2014 [28]	Italy/Rome (41° 52′ 20.68″ N)	294	48.5 ± 12.4	All seasons	44.25 ± 22.2 (t) Autumn/Winter 40.5 ± 20.2 Spring/Summer 61.2 ± 25.5		17.7% (t)		80.6% (t)	CIA

Table 3 (continued)

Reference	Country/region (latitude)	Sample size (*n*)	Age (years) (mean ± SD and/or age range)[a]	Seasons	Serum 25(OH)D (nmol/L)[a] Mean ± SD or median (IQR)	Prevalence below serum 25(OH)D threshold (%)				Method
						< 12.5 nmol/L	< 25 nmol/L	< 50 nmol/L	< 75 nmol/L	
Barchetta et al., 2015 [29]	Italy/Rome (41° 52′ 20.68″ N)	294	18–65	All seasons	44.25 ± 22.2 (t) Autumn/Winter: 40.5 ± 20.2 Spring/Summer: 61.2 ± 25.5					DiaSorin immunoassay
Maggio et al., 2005 [74]	Italy Greve in Chianti (43° 34′ 59.03″ N) & Bagno a Ripoli (43° 45′ 8.18″ N)	1107	> 20	All seasons	53 ± 34.6 (t) 60.1 ± 34.9 (m) 47.1 ± 33.4 (f)					RIA
Gonnelli et al., 2014 [53]	Italy/Siena (43° 17′ 37.58″ N)	1019	65.3 ± 6.1 (m) 64.2 ± 6.4 (f)	All seasons	63.6 ± 42.2 (m) 58.7 ± 44.2 (f)					RIA
Gonnelli et al., 2013 [54]	Italy/Siena (43° 17′ 37.58″ N)	1034	65.1 ± 6.1 (m) 64.2 ± 6.5 (f)	All seasons	63.6 ± 42.2 (m) 58.7 ± 44.4 (f)					RIA
Lippi et al., 2015 [73]	Italy/Parma (44° 48′ 5.52″ N)	11,150	62 (49–73)		Winter birth: 59.2 (95% CI 35.5–82.9) Spring birth: 62.2 (95% CI 38.5–85.8) Summer birth: 60.7 (95% CI 38.5–82.9) Autumn birth: 60.7 (95% CI 38.5–82.9)			Winter birth: 37.3% Spring birth: 34.6% Summer birth: 35.6% Autumn birth: 36.4%		CIA
Pagliardini et al., 2015 [86]	Italy/Milan (45° 27′ 31.05″ N)	1072 (f)	36.3 ± 4.4	All seasons	60.9 ± 33.2 (t)		6.5% (t)	40.1% (t)	77.4% (t)	DiaSorin immunoassay
Gonzalez-Molero et al., 2013 [56]	Spain/Pizarra–Malaga (36° 45′ 52.81″ N)	1226	50.3 ± 14.4	All seasons	56.9 ± 15.5 (t)			34.7% (t)	88.9% (t)	ECIA

Table 3 (continued)

Reference	Country/region (latitude)	Sample size (*n*)	Age (years) (mean ± SD and/or age range)[a]	Seasons	Serum 25(OH)D (nmol/L)[a] Mean ± SD or median (IQR)	Prevalence below serum 25(OH)D threshold (%)				Method
						< 12.5 nmol/L	< 25 nmol/L	< 50 nmol/L	< 75 nmol/L	
González-Molero et al., 2012 [57]	Spain/Andalusia, southern Spain (37° 32′ 39.37″ N)	1226	50.3 ± 14.4	All seasons	55.9 (t) w/o diabetes: 58.2 ± 15.5					ECIA
Mata-Granados et al., 2008 [76]	Spain/Cordoba (37° 53′ 17.43″ N)	215	18–65	N/A	40.3 ± 34.6 (t)		14% (t)	64.8% (t)	82.4% (t)	HPLC
Rodriguez et al., 2016 [90]	Spain/Valencia (39° 28′ 11.67"N)/ Sabadell (41° 32′ 46.59"N)/ Gipuzkoa (43° 04′ 32.27″ N)	2036 pregnant	30.4 ± 4.3	All seasons	75.4 (56.7–93.9) (t)			18% (t)	31% (t)	HPLC
Gomez et al., 2004 [50]	Spain (40° 27′ 49.2″ N)	253	15–70	All seasons	Summer: 73.9 ± 16.6 Autumn: 53.9 ± 18.1 Winter: 39.6 ± 16.7 Spring: 46.7 ± 15.5		27.3% (t)			RIA
Guasch et al., 2012 [58]	Spain/Reus (41° 08′ 59.37″ N)	316	46.9	All seasons	56.28 (95% CI 51.58, 60.98) (t) 65.01 (95% CI 53.18, 76.83) (m) 53.55 (95% CI 48.60, 58.49) (f)					ECIA
Olmos et al., 2010 [85]	Spain/Camargo-Cantabria (43° 24′ 31.01″ N)	660	65 ± 9 (50–92)	N/A	59.9 ± 20.0 (t)				80.5% (t)	CIA

Table 3 (continued)

Reference	Country/region (latitude)	Sample size (*n*)	Age (years) (mean ± SD and/or age range)[a]	Seasons	Serum 25(OH)D (nmol/L)[a] Mean ± SD or median (IQR)	Prevalence below serum 25(OH)D threshold (%)				Method
						< 12.5 nmol/L	< 25 nmol/L	< 50 nmol/L	< 75 nmol/L	
Olmos et al., 2016 [84]	Spain/Camargo-Cantabria (43° 24′ 31.01″ N)	1811	44–93	All seasons	56.4 ± 19.7 (t) 58.7 ± 19.2 (m) 55.2 ± 19.7 (f) Summer/autumn 65.4 ± 20.7 Winter/Spring 75.9 ± 19.0		5% (t)	40% (t)	83% (t)	ECIA
Gomez-Alonso et al., 2003 [51]	Spain/Oviedo (43° 21′ 42.89″ N)	268	68 ± 9 (54–89)	All seasons	39.7 ± 20.0 (t) Summer/autumn 48.4 ± 25.7 (t) Winter/spring 34.2 ± 17.0		27% (t) < 65 years: 30% 65–74 years: 40% > 75 years: 27%			RIA
Hernandez et al., 2010 [61]	Spain/Camargo-Cantabria (43° 24′ 31.01″ N)	1063	64.8 ± 8.7 (m) 61.8 ± 9.6 (f)	All seasons	61.1 ± 18.5 (m) 60.9 ± 22.2 (f)					CIA
Singhellakis et al., 2011 [99]	Greece/Athens, Greece (37° 59′ 0″ N)	625	54.05 ± 14 (18–85)	N/A	55 (t)			57.7% (t) *(< 55 nmol/L)*		RIA
Kassi et al., 2014 [66]	Greece/Athens, Greece (37° 59′ 0″ N)	181 (m)	20–50	Autumn	49.5 ± 17.4 (t) 20–29 years: 46.7 30–39 years: 49.3 40–50 years: 52.9		4.4% (t)	50.3% (t) 20–29 years: 56.8% 40–50 years: 43.6%	40.9% (t)	LC-MS/MS
Hekimsoy et al., 2010 [60]	**Turkey**/Manisa -non-coastal Aegean region (38° 50′ 30.97″ N)	391	45.1 ± 17.3	Winter	42.2 ± 32.7 (t) 51.7 ± 38.7 (m) 38.1 ± 28.8 (f)			74.9% (t) 66.4% (m) 78.7% (f)	88.7%	HPLC

Table 3 (continued)

Reference	Country/region (latitude)	Sample size (*n*)	Age (years) (mean ± SD and/or age range)[a]	Seasons	Serum 25(OH)D (nmol/L)[a] Mean ± SD or median (IQR)	Prevalence below serum 25(OH)D threshold (%)				Method
						< 12.5 nmol/L	< 25 nmol/L	< 50 nmol/L	< 75 nmol/L	
Celikbilek et al., 2014 [36]	**Turkey**/ Yozgat (39° 43′ 37.91″ N)	49 (control group)	30–70	Winter	107.23 (67.42–157.57) (t)					EIA-5396, DRG
Usluogullari et al., 2015 [113]	Turkey/Istanbul (41° 00′ 29.66″ N)	112 (control group)	53.1 ± 12.5	Winter	53.4 ± 11.8 (t)					HPLC
Kavadar et al., 2015 [67]	Turkey/Istanbul (41° 00′ 29.66″ N)	147	41.4 ± 10.0	November – April	44.0 ± 26.1 (t)					RIA
Kristal-Boneh et al., 1999 [71]	Israel (31° 02′ 45.78″ N)	102 (m)	25–64	Summer–Winter	Summer: 85.1 ± 2.4 Winter: 63.4 ± 2.1					CPB
Saliba et al., 2012 [95]	Israel (31° 02′ 45.78″ N)	198,834	60 (Median)	All seasons	51.9 ± 24.5 (t) 54.8 ± 24.2 (m) 50.7 ± 24.6 (f) Jewish: 53.9 ± 24.1 Arabs: 35.7 ± 21.7 Winter–spring 46.8 ± 23.5 Summer–Autumn: 56.3 ± 24.5		14.4% (t) 10% (m) 16.2% (f) Jewish: 12.1% (f) Arab: 52% (f)	49.9% (t) 45% (m) 51.8% (f) Jewish: 46.5% Arabs: 76.7% Arab F: 84.8% Jewish F: 48.1% Winter–Spring: 41.7% Summer–Autumn: 59.3%	83.6% (t)	Competitive two-step CIA
Saliba et al., 2012 [93]	Israel (31° 02′ 45.78″ N)	271,176	> 20	All seasons	51.0 ± 23.2 (t)					CIA
Saliba et al., 2011 [92]	Israel (31° 02′ 45.78″ N)	19,172	62.0 ± 15.4	All seasons	62.3 ± 26.8 (t)					CIA

Table 3 (continued)

Reference	Country/region (latitude)	Sample size (*n*)	Age (years) (mean ± SD and/or age range)[a]	Seasons	Serum 25(OH)D (nmol/L)[a] Mean ± SD or median (IQR)	Prevalence below serum 25(OH)D threshold (%)				Method
						< 12.5 nmol/L	< 25 nmol/L	< 50 nmol/L	< 75 nmol/L	
Saliba et al., 2012 [93]	Israel (31° 02′ 45.78″ N)	8,881	> 10	All seasons	51.7 ± 24.0 (t) 55.0 ± 24.0 (m) 50.4 ± 23.5 (f) Summer/autumn 55.1 ± 24.1 Winter/spring 48.0 ± 23.3					CIA
Saliba et al., 2014 [94]	Israel (31° 02′ 45.78″ N)	1,757	60.6 ± 16.5	All seasons	50.9 ± 23.2 (t) 45.0 ± 21.5 (OB) 51.0 ± 22.2 (OW) 54.6 ± 24.4 (NW)					DiaSorin immunoassay
Moore et al., 2015 [79]	Israel/Jerusalem (31° 46′ 5.95″ N)	1,204	32	All seasons	54.2 ± 22.2 (t) 57.2 ± 20.97 (m) 51.17 ± 22.96 (f)			44% (t) 36% (m) 52% (f)		LC-MS/MS
Steinvil et al., 2011 [103]	Israel/Maccabi (32° 10′ 57.87″ N)	34,874	55 ± 17 (m) 55 ± 15 (f)	All seasons	57.9 ± 25.2 (m) 56.7 ± 24.7 (f)				79.2% (m) 77.5% (f)	RIA
Tepper et al., 2014 [107]	Israel/Haifa (32° 47′ 38.57″ N)	79 (m with 25(OH)D < 50 nmol/L)	25–65	All seasons	38.8 ± 9.1 (t) 37.34 ± 9.98 (OB) 39.16 ± 9.36 (OW) 39.04 ± 8.39 (NW)					DiaSorin immunoassay

t total sample of both males and females, *f* females, *m* males, *RIA* radioimmunoassay, *EIA* enzyme immunoassay, *CPB* competitive protein binding, *IA* immunoassay, *ECIA* electro chemiluminescence immunoassay, *HPLC* high-performance liquid chromatography method, *LC-MS/MS* liquid chromatographic with tandem mass spectrometry, *CIA* chemiluminescence immunoassay, *E* elderly, *NW* normal weight, *OB* obese, *OW* overweight

[a]Unless otherwise specified

Table 4 Mean and/or median circulating 25(OH)D concentrations and prevalence of circulating 25(OH)D concentrations below 12.5, 25, 50 and 75 nmol/L reported for postmenopausal women from southern European (and east Mediterranean) countries, identified as part of the present systematic review

Reference	Country/region (latitude)	Sample size (n)	Age (years) (Mean ± SD and/or age range)[a]	Seasons	Serum 25(OH)D (nmol/L)[a] Mean ± SD or median (IQR)	Prevalence below serum 25(OH)D threshold (%)				Method
						< 12.5 nmol/L	< 25 nmol/L	< 50 nmol/L	< 75 nmol/L	
Bruyere et al., 2007 [32]	France (46° 13′ 39.5″ N) / Italy (41° 52′ 18.98"N)/ Spain (40° 27′ 49.2″ N)/	8532	74.2	N/A	France: 47.7 (26.4) Italy: 51.1 (24.9) Spain: 81.7 (29.6)			France: 53.5% Italy: 47.5% Spain: 9.8%	France: 88.7% Italy: 85.1% Spain: 36.3%	RIA
Annweiler et al., 2009 [24]	France/Amiens (49° 53′ 38.64″ N)/ Lyon (45° 45′ 50.55″ N)/ Montpellier ((43° 36′ 38.77″ N)/ Paris (48° 51′ 23.81″ N)/ Toulouse (43° 36′ 16.75″ N)	440	≥ 75	All seasons)	43.4 ± 26.2				90.2%	RIA
Adami et al., 2008 [17]	Italy (41° 52′ 18.98″ N)	697	60–80	Winter-Spring (Feb-Mar)	37.9 ± 34.8 < 65: 38.1 ± 30.8 65–70: 41.5 ± 42.4 > 70: 33.7 ± 29.4					RIA
Isaia et al., 2003 [63]	Italy/Tuscany (43° 43′ 0″ N)	700	67.8 ± 5.7 (60–80)	Winter–spring (Feb-Mar)	67.9 ± 62.3 nmol/L		27%	78.4%		RIA
Malavolta et al., 2005 [75]	Italy/Bologna (44° 30′ 1.84″ N)	156	62.5 ± 7.9	All seasons	Summer/autumn: 55.5 ± 38.0 Winter/spring 43.7 ± 27.8		Summer/autumn: 44.2% Winter/spring: 51.3% (< 37.5 nmol/L)			competitive RIA

Table 4 (continued)

Reference	Country/region (latitude)	Sample size (n)	Age (years) (Mean ± SD and/or age range)[a]	Seasons	Serum 25(OH)D (nmol/L)[a] Mean ± SD or median (IQR)	Prevalence below serum 25(OH)D threshold (%)				Method
						< 12.5 nmol/L	< 25 nmol/L	< 50 nmol/L	< 75 nmol/L	
Bettica et al., 1999 [31]	Italy/Milan (45° 27′ 55.52″ N)	570	≥ 40	All seasons	45.7 ± 20.7		28% Dec–May: 38.5% > 70 years during Dec–May: 51% Jun-Nov: 12.5% > 70 years old during Jun–Nov: 17% (< 30 nmol/L)			RIA
Mezquita-Raya et al., 2001 [78]	Spain/Granada (37° 10′ 38.41″ N)	161	61 ± 7	All seasons	46.9 ± 21.0 Osteoporotic 39.2 ± 13.2 Non-osteoporotic 54.4 ± 24.2		39.1% (< 37.5 nmol/L)			RIA
Mezquita-Raya et al., 2004 [77]	Spain/Granada (37° 10′ 38.41″ N)	141	61 ± 7	N/A	46.4 ± 19.7 Osteoporotic 39.2 ± 12.7 Non-osteoporotic 53.4 ± 22.7			59.6% (< 46.4 nmol/L)		RIA
Moschonis et al., 2009 [80]	Greece/Athens, Greece Nea Smyrni (37° 56′ 39.44"N)/ Kallithea (37° 57′ 20.36"N)/ Neo Iraklio (38° 02′ 24.55″ N)	112	60.3 ± 5.0	Summer	66.1 ± 21.7	-				CIA

RIA radioimmunoassay, *CIA* chemiluminescence immunoassay

[a]Unless otherwise specified

Table 5 Mean and/or median circulating 25(OH)D concentrations and prevalence of circulating 25(OH)D concentrations below 12.5, 25, 50 and 75 nmol/L reported for elderly men and women from southern European (and east Mediterranean) countries, identified as part of the present systematic review

Reference	Country/region (latitude)	Sample size (*n*)	Age (years) (mean ± SD and/or age range)[a]	Seasons	Serum 25(OH)D (nmol/L)[a] Mean ± SD or Median (IQR)	Prevalence below serum 25(OH)D threshold (%)				Method
						< 12.5 nmol/L	< 25 nmol/L	< 50 nmol/L	< 75 nmol/L	
Cougnard-Gregoire et al., 2015 [39]	France/Bordeaux France (44° 50′ 16.04″ N)	697	72.7 ± 4.4	All seasons	35.9 ± 17.4 (t)		27.3% (t)	55.9% (t)		One-step Immunoassay (Architect)
Sarre et al., 2016 [96]	France/Angers (47° 28′ 42.31″ N)	90	83.0 ± 6.6	All seasons	34.9 ± 19.4 (t)			43% (t)		RIA
Goncalves et al., 2015 [52]	France/Angers (47° 28′ 42.31″ N)	150 Primary Open-Angle Glaucoma (POAG) patients 164 controls	POAG: 75.1 ± 8.5 Controls: 73 ± 7.9	All seasons	46.3 ± 27.9 (t) POAG: 42.9 ± 25.7 Controls: 49.4 ± 29.5				86.3% (t) POAG: 90.7% Controls: 82.3%	RIA
Cals et al., 1994 [35]	France/Paris (48° 51′ 23.81″ N)	193	≥ 70 (70–89)	All seasons	26 (9–64) (m) 21 (4–95) (f)		48.2% (t)			HPLC
Hicks et al., 2008 [62]	Italy/Tuscany (43° 43′ 0″ N)	958	65–102 73.9 ± 6.8 (m) 75.1 ± 7.3 (f)	All seasons	48.9 (35.4–73.6) (m) 33.9 (23.5–50.7) (f)	–				RIA
Shardell et al., 2009 [98]	Italy Greve in Chianti (43° 34′ 59.03″ N) & Bagno a Ripoli (43° 45′ 8.18″ N)	1,005	≥ 65 74.2 (7.0) (m) 75.6 (7.6) (f)	N/A	48.5 (34.1–73.1) (m) 33.4 (22.7–49.4) (f)	–				RIA
Lauretani et al., 2006 [72]	Italy Greve in Chianti (43° 34′ 59.03″ N) & Bagno a Ripoli (43° 45′ 8.18″ N)	807	≥ 65	N/A	55.2 (35.9–75.9) (m) 34.7 (24.5–21.0) (f)	–				RIA

Table 5 (continued)

Reference	Country/region (latitude)	Sample size (*n*)	Age (years) (mean ± SD and/or age range)[a]	Seasons	Serum 25(OH)D (nmol/L)[a] Mean ± SD or Median (IQR)	Prevalence below serum 25(OH)D threshold (%)				Method
						< 12.5 nmol/L	< 25 nmol/L	< 50 nmol/L	< 75 nmol/L	
Toffanello et al., 2014 [108]	Italy/Camposampi ero 45° 34′ 20.81″ N) /Rovigo (45° 01′ 27.05″ N)	1,675	> 65 years	N/A	101.0 ± 82.7 (m) 71.7 ± 42.3 (f)		5% (m) 13% (f)	11% (m) 34.2% (f)		RIA
De vita et al., 2014 [41]	Italy/Greve in Chianti (43° 34′ 59.03″ N) and Bagno a Ripoli (43° 45′ 8.18″ N)	867	75.1 ± 17.1	All seasons	40.4 (26.7–64.6) (t)	–				RIA
Toffanello et al., 2012 [109]	Italy/Camposampi ero 45° 34′ 20.81″ N) / Rovigo (45° 01′ 27.05″ N)	2694	≥ 65	All seasons	101.9 ± 62.4 (m) 65.0 ± 41.3 (f)		5.9% (m) 13.5% (f)	20% (m) 40% (f)		RIA
Toffanello et al., 2014 [151]	Italy/Camposampi ero (45° 34′ 20.81″ N) /) Rovigo (45° 01′ 27.05″ N)	1927	74.1 ± 7 (m) 74 ± 6.7 (f)	All seasons	84.1 ± 53.8 (t)		6.5% (t)	28% (t)		RIA
De rui et al., 2014 [40]	Italy/Camposampi ero 45° 34′ 20.81″ N) / Rovigo (45° 01′ 27.05″ N)	2349	69–81.5 (m) 69–80 (f)	All seasons	95.0 (61.6–133.5) (m) 59.0 (38–88) (f)		5% (m) 13% (f)	11% (m) 34.2% (f)		RIA
Passeri et al., 2003 [88]	Italy/Mantova (45° 10′ 0.38″ N)/ Parma (44° 48′ 5.52″ N)	104	≥ 98	All seasons	6.0 ± 7.0 (t)	–				RIA
Mosele et al., 2013 [81]	Italy/Padova (45° 21′ 58.27″ N)	134	72.9 ± 5.2	N/A	53.2 ± 28.1 (t)	–				RIA

Table 5 (continued)

Reference	Country/region (latitude)	Sample size (*n*)	Age (years) (mean ± SD and/or age range)[a]	Seasons	Serum 25(OH)D (nmol/L)[a] Mean ± SD or Median (IQR)	Prevalence below serum 25(OH)D threshold (%)				Method
						< 12.5 nmol/L	< 25 nmol/L	< 50 nmol/L	< 75 nmol/L	
Sergi et al., 2011 [97]	Italy/Padova (45° 21′ 58.27″ N)	100	70.5 ± 4.0	N/A	49.1 ± 30.9 (t)	–				RIA
Zamboni et al., 2002 [118]	Italy/Verona (45° 26′ 30.66″ N)	175	68–75	N/A	56.5 ± 37.5 (m) 39.4 ± 24.1 (f)			35.1% (m) 55.4% (f) (< 37.5 nmol/l)		RIA
Veronese et al., 2014 [115]	Italy/North (41° 52′ 18.98″ N)	2227	76.1 ± 7.8 (65–103)	All seasons	80.1 ± 54.7 (t)		11.4% (t)	32.6% (t)	55.2% (t)	RIA
Veronese et al., 2014 [115]	Italy/North (41° 52′ 18.98″ N)	2640	65–98	All seasons	80.2 ± 53.3 (t)		10.6% (t)	21.6% (t)	22.9% (t)	RIA
Almirall et al., 2009 [20]	Spain/Sabadell, Spain (41° 32′ 46.59″ N)	237	> 64	N/A	42.9 ± 18.7 (t)				86% (< 62.4 nmol/L)	RIA
Formiga et al., 2013 [47]	Spain/Baix Llobregat, Barcelona (41° 23′ 5.1″ N)	312	85	Winter–spring	69.9 ± 74.9 (t) 80.4 ± 109.8 (m) 62.9 ± 62.4 (f)		14.4% (t) (< 27.5 nmol/L)		52.5% (t) (< 62.4 nmol/L)	RIA
Atli et al., 2005 [26]	Turkey/Ankara (39° 56′ 0.11″ N)	420	> 65	N/A	old age home 93.8 ± 72.1 (m) 61.9 ± 74.1 (f) own home 157.7 ± 107.3 (m) 103.1 ± 97.3 (f)			33.4% (t) 15.3% (m) 40.7% (f) old age home: 40.1% (t) 18.4% (m) 54.1% (f) own home: 24.4% (t) 4.2% (m) 27.9% (f) (< 37.5 nmol/L)		RIA
Golan et al., 2011 [49]	Israel/Maccabi (32° 10′ 57.87″ N)	9167	≥ 60	All seasons	Age-related macular Degeneration (AMD): 60.2 ± 23.5 Control: 60.2 ± 23.7			AMD: 33.6% Control: 32.86% (< 39.9 nmol/L)		RIA

Table 5 (continued)

t total sample of both males and females, *m* males, *f* females, *RIA* radioimmunoassay, *HPLC* high-performance liquid chromatography method, *CIA* chemiluminescence immunoassay, *AMD* age-related macular degeneration group, *POAG* primary open angle glaucoma

[a]Unless otherwise specified

was also a large range in prevalence estimates < 50 nmol/L (18–75%) within the 40 included studies, again with no obvious latitudinal trend (Table 3). Furthermore, the preponderance of studies which presented data on both genders, seemed to suggest that women have a lower mean serum 25(OH)D concentrations than men [54, 58, 60, 74, 84, 93].

The average prevalence of circulating 25(OH)D concentration below 25 and 50 nmol/L in studies of adults from Southern European (and east Mediterranean) countries which reported these estimates are shown in Fig. 4. Of the studies that reported prevalence estimates of serum 25(OH)D < 25 nmol/L among adults for all seasons (as an indication of vitamin D deficiency), the average prevalence was ~ 16%.

Postmenopausal women

The mean and/or median serum 25(OH)D concentrations of postmenopausal women in the 9 included studies from southern European countries are shown in Table 4. The lowest mean concentration of serum 25(OH)D was 33.7 nmol/L in Italian women > 70 years old during winter and spring months [17], while the highest mean concentration was 81.7 nmol/L among 74-year-old women in Spain [32]. The Spanish group also had the lowest prevalence of 25(OH)D < 50 nmol/L (i.e. 9.8%) with the highest prevalence (78.4%) observed in 68-year-old women from central Italy during Winter–spring [63].

None of the included studies reported a prevalence of serum 25(OH)D < 12.5 nmol/L, and studies variably reported prevalence of serum 25(OH)D < 25/30 and < 37.5 nmol/L, with a range between 27–28% and 39–51%, respectively (Table 4). In the large study of 8,532 postmenopausal women, there were clear country-specific differences in the prevalence of serum 25(OH)D < 50 nmol/L at about 53%, 47% and 9% for those in France, Italy and Spain, respectively [32].

Elderly

The mean and/or median serum 25(OH)D concentrations of elderly individuals (i.e., >65 years old in the vast majority of studies) in the 21 included studies from southern European countries are shown in Table 5. The lowest average concentration of 25(OH)D was 6.0 nmol/L among Italian centenarians [88]. French men and women aged ≥ 70 years had very low vitamin D status, at 26 and 21 nmol/L, respectively [35]. On the other hand, a high mean circulating 25(OH)D concentration of ~ 158 nmol/L was reported in men > 65 years living in central Anatolia, Turkey [26] and of 102 nmol/L in men aged > 65 years in northern Italy [109]. As far as elderly women were concerned, those living in central Anatolia, Turkey, had the highest reported mean 25(OH)D concentration (i.e., ~103 nmol/L) [26],

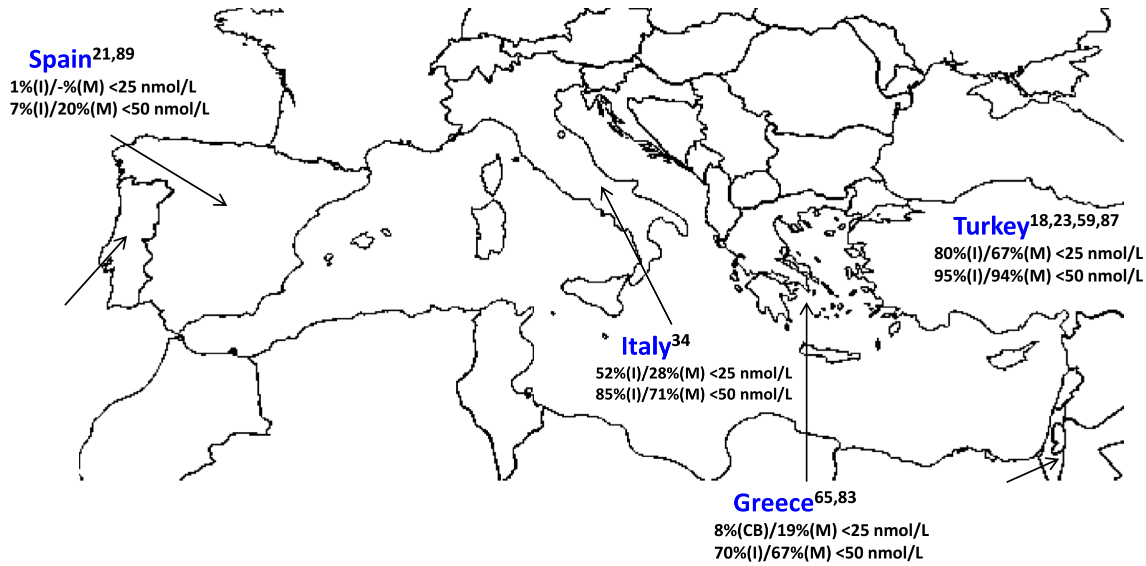

Fig. 2 The prevalence* of circulating 25(OH)D concentration below 25 and 50 nmol/L in studies of infants and their mothers from Southern European (and east Mediterranean) countries. *Estimates are averages of reported prevalences for those studies in which data available and reference numbers given in superscript. *M* maternal, *IF* infant, *CD* cord blood

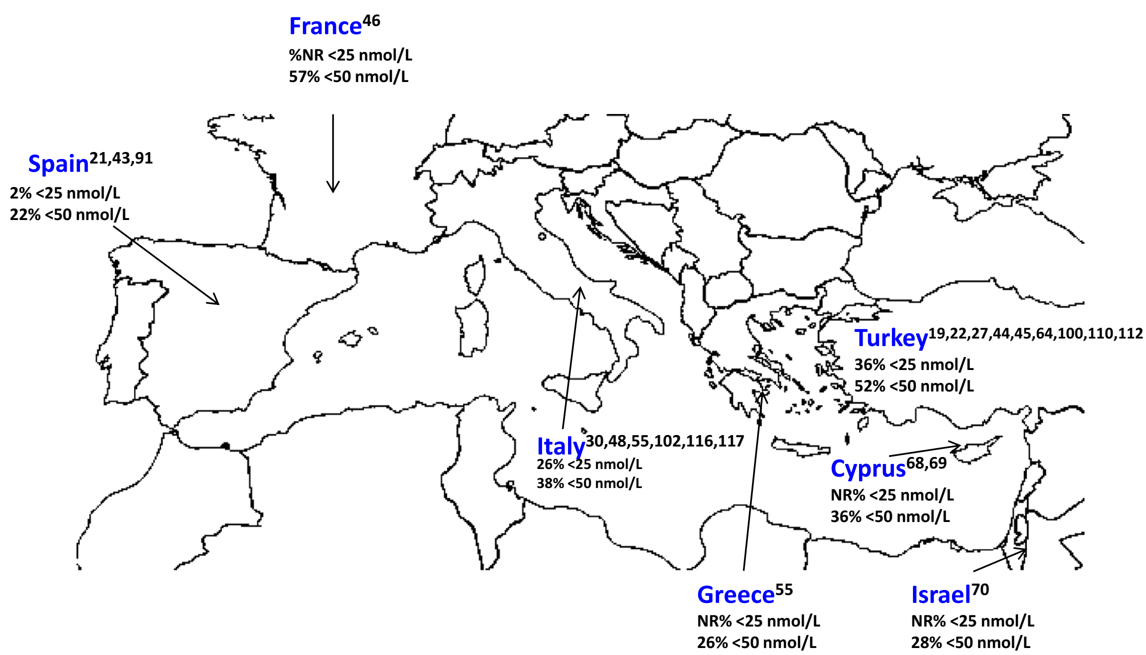

Fig. 3 The prevalence* of circulating 25(OH)D concentration below 25 and 50 nmol/L in studies of children and adolescents from Southern European (and east Mediterranean) countries. *Estimates are averages of reported prevalences for those studies in which data available and reference numbers given in superscript. *%NR* not reported

None of the included studies reported prevalence of serum 25(OH)D < 12.5 nmol/L. The reported prevalence of 25(OH)D concentrations < 25 nmol/L ranged from 5% in elderly men from northern Italy [40, 108] to 48.2% in those elderly men and women from France [35]. The lowest prevalence rates of 25(OH)D concentrations < 50 nmol/L was 4.2% among the elderly Turkish men from central Anatolia [26], while the highest, at 55.9%, was for elderly men and women from south-western France [39]. Similarly to the adult data, studies presenting data for both genders reported lower 25(OH)D among elderly women than men. Of note, in the study of adults aged > 65 years in Ankara, Turkey, those

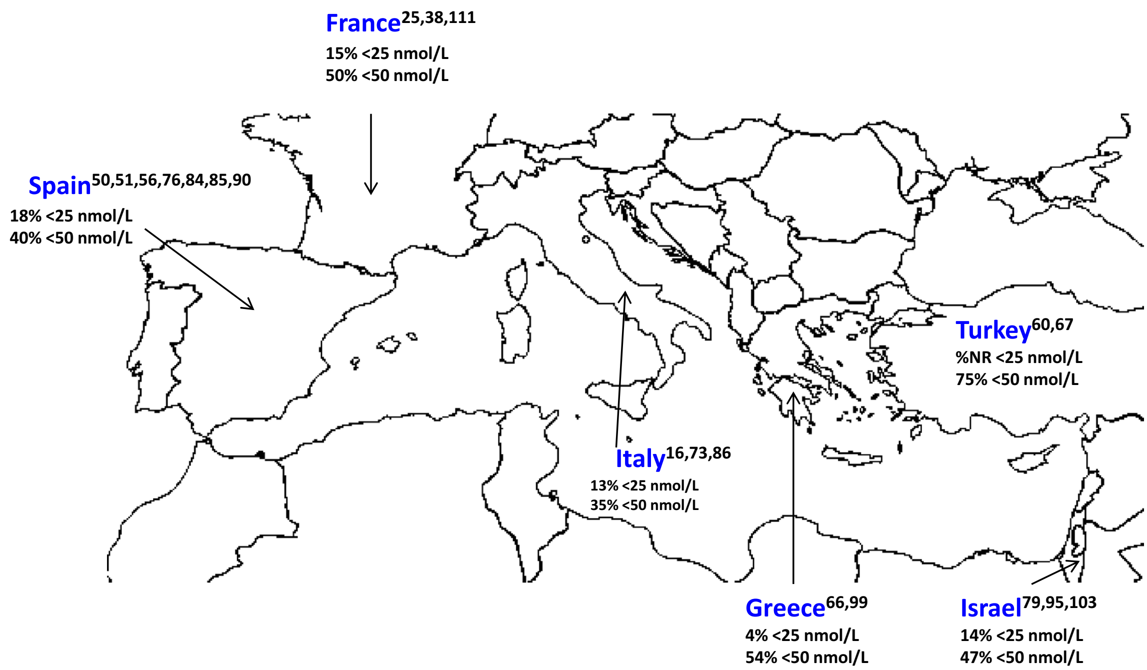

Fig. 4 The prevalence of circulating 25(OH)D concentration below 25 and 50 nmol/L in studies of adults from Southern European (and east Mediterranean) countries. *Estimates are averages of reported prevalences for those studies in which data available and reference numbers given in superscript. *%NR* not reported

in residential care had a much higher prevalence of 25(OH) D < 50 nmol/L, at 40%, than the 24% in those who lived in their own home.

The average prevalence of circulating 25(OH)D concentration below 25/27.5 and 50 nmol/L in studies of elderly (including postmenopausal women) from Southern European (and east Mediterranean) countries which reported these estimates are shown in Fig. 5. Of the studies that report prevalence estimates of serum 25(OH)D < 25 nmol/L in elderly for all seasons (as an indication of vitamin D deficiency), the average prevalence was ~ 16%.

Discussion

The present systematic review is characterized by a high degree of variability in circulating 25(OH)D concentrations and/or prevalence of vitamin D deficiency/insufficiency across studies and countries within the southern European region, including some eastern Mediterranean countries. This is entirely in line with findings in other systematic reviews and meta-analyses of the wider Europe region but also at a global level [13, 119, 120]. Such variability is not unexpected and is linked with the many differences in the populations under study and study characteristics per se, such as time of blood sampling and method of assessment of circulating 25(OH)D. In addition, differences in other factors known to influence vitamin D status (e.g., dietary intake, clothing style, time spent outdoors and use of sunscreen) across studies and populations are likely to have contributed to the variability of the results, but this level of information was not provided for all included studies. For this reason, we were of the view that applying meta-analyses to the data would hold little point as it would suffer from high levels of heterogeneity. Notwithstanding the variability in serum 25(OH)D data and cautious of the potential of over-interpretation, the results of the present systematic review clearly highlight that low vitamin D status is evident in southern European populations and that vitamin D deficiency (defined as serum 25(OH)D < 25 nmol/L) may be, on average, of the order of 16 to 27%, depending on the age group. These findings highlight the need to raise awareness of the contradictory nature of the evidence with regard to the generally held view that vitamin D status is expected to be good in the southern areas of Europe; this paper shows that despite relative abundance of UVB availability in the south compared to the northern parts of Europe, vitamin D deficiency is widespread. Furthermore, even allowing for differences arising from assay-related differences in serum 25(OH)D between studies [121–123], differences in the prevalence of vitamin D deficiency/insufficiency are evident in subsets of the populations included. Exploration of the contributory reasons behind such differences may be of value in identifying potential strategies for prevention of vitamin D deficiency among subgroups at risk within the southern European population.

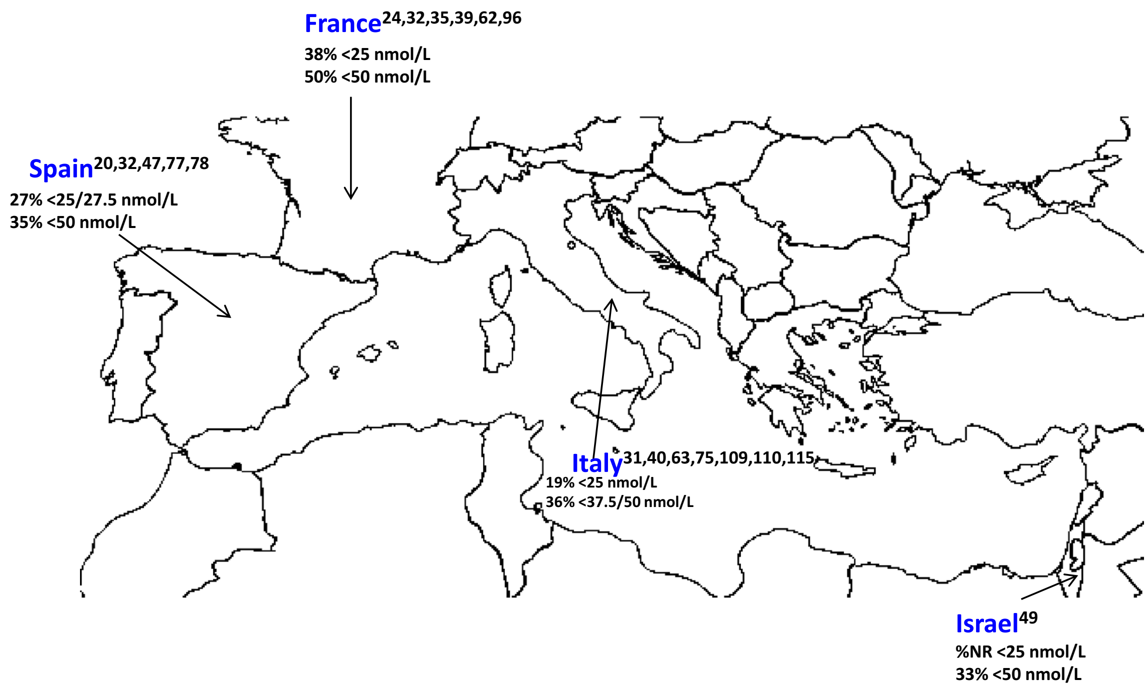

Fig. 5 The prevalence* of circulating 25(OH)D concentration below 25/27.5 and 50 nmol/L in studies of the elderly, including postmenopausal women, from Southern European (and east Mediterranean) countries. *Estimates are averages of reported prevalences for those studies in which data available and reference numbers given in superscript. *%NR* not reported

Although vitamin D deficiency and insufficiency can affect all age groups, as is evident in this systematic review, our analysis of 107 studies suggests that the degree of vitamin D deficiency and/or insufficiency was higher on average in neonates/ infants and adolescents (20 and 27%, respectively) than that in adults and elderly (both ~16% on average). In contrast to a number of previous reviews [119, 124, 125], Hilger et al. [13] in their systematic review of global vitamin D status undertook a meta-analysis and reported no significant age-related differences in serum 25(OH)D. It is important to note, however, that as the number of studies of neonates ($n=10$) and institutionalized elderly ($n=9$) was considered too low, this comparison was only of children/ adolescents and adults and elderly [13]. Infants, particularly neonates, are susceptible to vitamin D deficiency, as they are usually not exposed to sunlight, and as infant feeding practices and supplementation policies vary between countries, the risk is greater among those who are exclusively breastfeed without supplementation [126–129].

Adolescents have also been identified as a population subgroup at increased risk of low vitamin D status [130, 131]. Our previous analysis of the prevalence of vitamin D deficiency by age group (children/teens, adults and older adults), using standardized serum 25(OH)D data (thus minimizing method-related confounding), from 18 representative European populations (total n of 55,844 individuals), suggested that irrespective of latitude, teenagers may be at greater risk overall [12]. The range of deficiency rates in the various teenage study populations (age range 15–18 years) was 12–40%, whereas adults and older adults (>61 years) had rates in the order of 9–24 and 1–8%, respectively [12]. Such comparisons need to be interpreted cautiously, because differences in latitude of sample population, ethnic mix, and season of blood sampling differed for these populations.

Beyond age differences, there appeared to be a sex difference in serum 25(OH)D concentrations in these studies of southern European individuals. Lower mean concentrations of serum 25(OH)D among adolescent girls [27, 45, 55, 64, 68, 82], adult [54, 58, 60, 74, 84, 93] and elderly women [35, 40, 47, 62, 72, 98, 108, 109, 118] compared to their male counterparts were evident. This agrees with the reports from a number of other previous reviews [11, 124, 132]. However, this is not a universally reported finding; Hilger et al. showed no significant sex-related difference in 25(OH)D in their meta-analysis [13]. The observed sex differences in the studies we have analyzed may be a construct of lifestyle and personal characteristics of study samples in these southern European studies, which may be less evident in other parts of Europe or indeed beyond. For example, more wide-spread use of sun screen by women compared to men, as well as differences in clothing, particularly in eastern Mediterranean countries, may explain the sex differences observed in vitamin D status as both reduce cutaneous synthesis of vitamin D [133–135]. Regarding clothing practices, the use of veil by Arab women in Israel [95] and adolescent girls in Turkey [27] may partly explain the considerably high prevalence rates of poor vitamin D status observed in these population subgroups, since veil usually covers the greatest part of their body, except for the face and arms [136–138]. In addition, low serum concentrations of 25(OH)D may be further sustained in these population subgroups because sun-seeking behavior is rather avoided in southern countries both due to the avoidance of heat, or as a means of melanoma prevention, but also because fair skin is an indication of beauty in these cultures. Besides eastern Mediterranean countries, avoiding the heat has also been reported as determinant of poor vitamin D status among elderly populations in southern and subsequently warmer parts of Europe [139].

The degree of urbanization may impact on differences in serum 25(OH)D within and between countries. For example, the present review highlighted higher prevalence rates of vitamin D insufficiency among populations living in urban areas compared to rural communities. Urbanization has been described by previous studies as predictor of lower vitamin D status, since in urban areas both men and women are more likely to reside and work indoors [137, 140, 141]. In addition, air pollution in cities further acts as a barrier to UVB sunlight reaching the ground and as such people's skin, thus limiting endogenous vitamin D synthesis [142].

Latitude and season are two additional determinants of vitamin D status mainly affecting the levels of solar UVB radiation received and consequently the cutaneous synthesis of vitamin D [143]. In relation to latitude, countries located nearer to the earth's equator receive more UVB sunlight in comparison to those located nearer to the poles. Although the present review examined population groups from countries in southern Europe with latitudes ranging from 31°N (Jerusalem, Israel) to 50°N (Lille, France), the vast majority of the examined population groups were from regions within a relatively narrow latitude band of 35-45°N. According to Tavera-Mendoza and White [144], populations residing in this geographic zone receive more or less the same doses of solar UVB radiation. Thus, in the current systematic review, season was a stronger determinant of vitamin D status in southern Europe and eastern Mediterranean region compared to latitude, since the lowest serum 25(OH)D levels being consistently reported, in almost all age groups, during winter and spring months when there is depletion of 25(OH) D storages [17, 27, 51, 87].

Although the variability in dietary intake of vitamin D among different population groups could provide an additional interpretation of the variations in vitamin D status observed in the present systematic review, still the relatively low dietary intakes of vitamin D that are evident in Southern Europe and Eastern Mediterranean cannot support such an interpretation. For example, Roman Viñas et al. [145], on assessing recent estimates from 9 national nutrition surveys across Europe, indicate that for Spain, Italy and Portugal, the Southern European countries with survey data on vitamin D intake, 99.8–100% of adults (19–64 years) and older adults (> 64 years) have inadequate vitamin D intakes when compared to the Estimated Average Requirement (EAR). Strategies to bridge the gap between current and recommended intakes of vitamin D to minimize the prevalence of vitamin D deficiency and inadequacy are a priority, and the pros and cons of potential public health strategies to increase vitamin D intakes, such as vitamin D fortification of food and targeted vitamin D supplementation, have been outlined in detail elsewhere [146–148].

Considerations for interpreting the data presented in this systematic review are as follows. Methodological differences in serum 25(OH)D data are inherent. In particular, the most recent studies generally used either commercial radio-immunoassays (42.1%) or chemiluminescence assays (20.6%) to measure serum 25(OH)D concentration, while some, primarily older, studies mainly used competitive protein-binding assays for the same purpose. The Vitamin D External Quality Assurance Scheme serves as a quarterly monitor of performance of analysts and 25(OH)D analytical methods for approximately 700 laboratories worldwide. The Vitamin D External Quality Assurance Scheme in the UK suggests some method biases in terms of accuracy and precision as well as variability as high as 15–20% [149]. Our previous assessment of the prevalence of vitamin D deficiency from 18 representative childhood/teenage and adult/older adult European populations (total *n* of 55,844 European individuals) benefited from the fact that we were able to standardize the serum 25(OH)D data [12], and thus minimize the impact of method-related differences. This was not feasible in the present work as standardization entails selected reanalysis of carefully biobanked sera [150]. This potential limitation is inherent in all systematic reviews of vitamin D status to-date. As is also the case with most systematic reviews, the present review may suffer from publication bias (e.g., 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 [13]) and language bias, as only those articles written in English were included. By design we identified studies in healthy populations. Hilger et al. [13] in their systematic review of global vitamin D status, who took a similar approach, have suggested that this may raise the possibility of an overestimation of the prevalence of adequate vitamin D status.

Conclusion

Despite the abundance of solar UVB radiation in southern Europe and eastern Mediterranean region, more than one-third of the studies identified by the present systematic review reported mean 25(OH)D levels below 50 nmol/L and of those studies that reported the prevalence of serum 25(OH)D < 25 nmol/L in all seasons, between 16 and 27% of study participants, on average, were deficient on this basis, depending on the age group. Notwithstanding potential differences in serum 25(OH)D estimates across studies arising from the different analytical methods used, the vitamin D deficiency and insufficiency identified by the current systematic review for specific population groups in southern Europe could be attributed to the negative effect of certain demographic, cultural, seasonal and behavioral factors. The systematic review highlighted that vitamin D deficiency was evident across all population subgroups but were higher among neonates/ infants and adolescents, critical periods of bone and overall growth and development. Non-pharmacological strategies, such as fortification of foods with vitamin D and/or vitamin D supplementation, which will be tailored to the needs of specific population groups with higher risk of insufficiency or deficiency, could be an effective approach to tackle the pandemic of hypovitaminosis D even in the sunny regions of Southern Europe and Eastern Mediterranean.

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Compliance with ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethical standards The current review includes anonymized data from epidemiological and clinical studies on vitamin D status.

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