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Meta Analysis

Vitamin D deficiency status in Turkey: A meta-analysis

Medine Alpdemir, Mehmet Fatih Alpdemir

Department of Clinical Biochemistry, Balikesir State Hospital, Ministry of Health, Balikesir, Turkey

Abstract

Objectives: Vitamin D deficiency is a significant public health problem in both developed and developing countries, with a reported worldwide prevalence of 30% to 80% among children and adults. The purpose of this study was to examine vitamin D deficiency/insufficiency in Turkey based on a review of the existing research.

Methods: PubMed, DergiPark, The Scientific and Technological Research Council of Turkey (TUBITAK), Google Scholar, Google, and Scopus search engines were queried. The keywords of Turkey, vitamin D, serum 25-hydroxyvitamin D, 25(OH)D3, 25(OH) vitamin D, deficiency/insufficiency of vitamin D, and prevalence were used in the screening process. The review included prospective and retrospective research studies with healthy individuals of various communities. The Newcastle-Ottawa Quality Assessment Scale was used to assess the risk of bias of the included studies.

Results: A total of 40 studies with a sample size of 111.582 were included in the meta-analysis. The prevalence of vitamin D deficiency was estimated at 63% (95% confidence interval [CI]: 58.9-66.6) for the overall population. It was observed that vitamin D deficiency has been reported as 86.6% (95% CI: 70.2-94.6) for infants, 76% (95% CI: 65.2-84.3) for pregnant women, 39.8% (95% CI: 38-41.6) for children, and 63.5% (95% CI: 58.8-67.9) for adults. The prevalence of vitamin D deficiency among women and men was identified as 64.7% (95% CI: 57.5-71.2) and 39.5% (95% CI: 31.0-48.7), respectively.

Conclusion: The results obtained in this meta-analysis revealed a high rate of vitamin D deficiency in Turkey, which varies from 58.9% to 66.6% with 95% CI. In particular, neonates, pregnant women, and adult women have a higher risk of vitamin deficiency. The results of this meta-analysis demonstrate that the vitamin D level of the Turkish public should periodically be measured and supplemented as necessary.

Keywords: Age, covered clothing, pregnancy, season, sex, Turkish population, vitamin D status

Vitamin D is a steroid hormone that has a major role in bone mineralization through the regulation of calcium and phosphorus metabolism. The main sources of vitamin D are cutaneous synthesis and the ingestion of food, especially fish oil, eggs, and liver [1].

The most common forms of vitamin D absorption are vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol). Vitamin D3 is synthesized in the skin through sunlight exposure. This inactive form of vitamin D3 is then metabolized to the prohormone form, 25-hydroxyvitamin (OH)D3, in the liver. The biologically effective form, 1.25(OH)D3, is produced in the kidneys and has a half-life of approximately 2 to 3 weeks, while the circulating half-life of 1.25(OH)D is only 4 to 6 hours. Therefore, 25(OH)D3 is generally considered a measure of vitamin D status [1].

Vitamin D has a substantial function in the maintenance of bone health. A deficiency of vitamin D has been associated with the increased risk of a number of chronic conditions, including cardiovascular disease, diabetes, hypertension, some cancers, autoimmune diseases, neuropsychiatric disorders, metabolic disorders and infectious diseases associated with decreased immunity [2, 3].

The deficiency of vitamin D is a significant problem of public health in both the developed world and developing countries, with a reported prevalence of 30% to 80% of children and adults worldwide [4, 5]. There is not currently enough infor-

Address for correspondence: Medine Alpdemir, MD. Department of Clinical Biochemistry, Balikesir State Hospital, Ministry of Health, Balikesir, Turkey
Phone: +90 505 483 58 19 **E-mail:** bitigic@hotmail.com **ORCID:** 0000-0003-2625-0246

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mation available about the prevalence of vitamin D deficiency in Turkey. The aim of this meta-analysis was to investigate the vitamin D results of various studies of the healthy Turkish population and analyze the reported prevalence of a deficiency of vitamin D.

Materials and Methods

Search strategy

This meta-analysis comprised an evaluation and comparison of vitamin D status in the Turkish population of several provinces. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were observed, and the population/intervention/comparison/outcome/study type (PICOS) approach was used, with a focus on the P, O, and S elements, due to the descriptive nature of the study. The literature search was conducted in June and July 2017 using an electronic database search. The sources included international (PubMed, Google Scholar, Google, Scopus) and national (DergiPark, The Scientific and Technological Research Council of Turkey [TUBITAK], the Turkish Academic Network and Information Center [ULAKBIM]) databases, which were searched to identify studies published between 2000 and 2017. The search consisted of the following keywords: Turkey, vitamin D, serum 25-hydroxyvitamin D, 25(OH)D3, 25(OH)vitamin D, deficiency/insufficiency of vitamin D, and prevalence. "And" was used to connect all of the keywords. The retrieved studies were screened by reading the titles and abstracts. Publication year, province, study population, study design, sample size, measurement method of vitamin D, and outcomes were investigated by the authors. A total of 40 research studies were selected and examined.

Evaluated outcomes and inclusion criteria

Vitamin D deficiency was defined as <20 ng/mL, insufficiency was defined as 20-29.9 ng/mL, and sufficiency was described as >30 ng/mL. The review included studies of healthy participants reflecting all members of the community (neonatal, infant, child, adolescent, adult, elderly, and pregnant women), and studies using radioimmunoassay (RIA), high-performance liquid chromatography (HPLC), and liquid chromatography-tandem mass spectrometry (LC-MS/MS) to perform 25-hydroxyvitamin D measurement. The search was restricted to human studies published in English and Turkish.

Exclusion criteria

Studies related to vitamin D that included diseases of the thyroid gland, kidney, or liver; osteoporosis; stroke; lung emphysema; asthma; cancer; rheumatoid arthritis; multiple sclerosis; HIV; metabolic bone diseases; inflammatory diseases and other chronic diseases were excluded, as well as those that did not include usable data, or were a meta-analysis, review, or case report.

Risk of bias in included studies

The Newcastle-Ottawa Quality Assessment Scale (NOS) was used to assess the risk of bias in the included studies. The maximum NOS score is 10 points. Studies with a total score of 9-10, 7-8, 5-6 and <4 were considered very good, good, satisfactory, and unsatisfactory, respectively.

Summary measures

Prevalence with a 95% confidence interval was considered a summary measure of interest.

Data synthesis

Comprehensive meta-analysis software (Biostat Inc., Englewood, NJ, USA) was used to analyze the data of the selected studies. The prevalence rate was calculated as a summary measure. Heterogeneity was assessed using a chi-square test and the I^2 heterogeneity statistic. Forest plots were used to visually assess the effect size of the meta-analysis, the difference in means, and the 95% confidence interval (CI) in the selected studies. The groups were classified and analyzed according to the characteristics of neonates, pregnant women, children, adults, and gender.

Results

During the preliminary search, 767 articles were retrieved and a total of 40 research articles were evaluated. A flow diagram of the phases of the meta-analysis is presented in Figure 1. The total sample size was 111.582 patients. The age range of the study participants was 0 to >80 years. The result of a quality assessment according to NOS was between 6 and 9 points. The majority of the studies had a high score (>8), while 11 studies had a point score of <8. There was a high level of heterogeneity among the studies (I^2=98%; p<0.001). Thus, a random effects model meta-analysis was performed. In order to determine the frequency of vitamin D deficiency in the Turkish population, a total of 23 retrospective studies and 17 prospective cross-sectional studies were included: 17 studies of neonates, infants, children and adolescents; 12 studies of pregnant women; 9 studies of adults; 3 studies of the elderly; 7 studies examining clothing style; and 13 studies analyzing the effect of age, sex, and season. The basic characteristics of the included studies according to location are provided in Tables 1-3.

The prevalence rate of vitamin D deficiency was determined to be 63% (95% CI: 58.9-66.6) for the overall population. The prevalence of vitamin D deficiency for neonates, pregnant women, children, and adults was 86.6% (95% CI: 70.2-94.6), 76% (95% CI: 65.2-84.3), 39.8% (95% CI: 22.6- 57.5), and 63.5% (95% CI: 58.8-67.9), respectively. Female and male residents had a 64.7% (95% CI: 57.5-71.2) and 39.5% (95% CI: 31.0-48.7) prevalence of vitamin D deficiency, respectively. In neonates, the lowest rate reported was 53.3% (95% CI: 46.6-66.8) in a study performed in Istanbul by Ozdemir et al. [7], and the highest rate was 93% (95% CI: 89.2-95.5) in a study conducted in Izmir by Halicioglu et al. [8]. In children, the lowest rate was

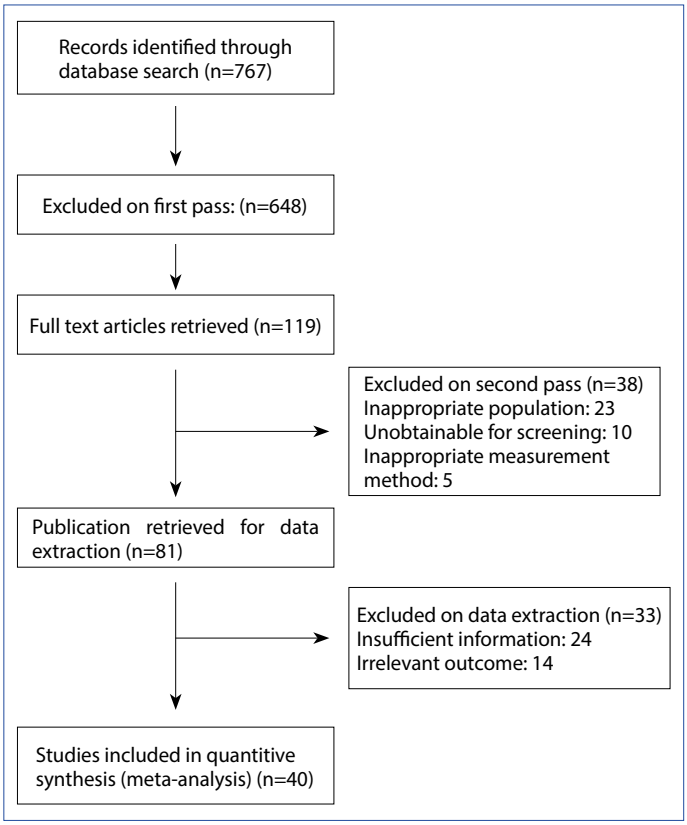

Figure 1. Flow diagram of the phases of the meta-analysis.

determined to be 8% (95% CI: 6-10) in a study in Ankara investigated by Akman et al. [19], and the highest rate was reported as 82% (95% CI: 79.1-84.6) in a study in Trabzon conducted by Karaguzel et al. [15] In adults, the lowest rate determined was 34%, observed in a study in İstanbul performed by Buyukuslu et al. [29], and the highest rate was 91%, reported by Bozkurt et al. in a study carried out in Ankara (Fig. 2-7).

Neonates and infants

Tables 1 and 2 illustrate the results of studies including neonates and infants. In the study performed by Arica et al. [6] in the Van region, 115 children of between 0 and 36 months of age were included between July and September. The mean length of breastfeeding was 9.4±6.6 months. There was no significant difference in the 25(OH)D3 level according to sex. The mean vitamin D deficiency (<20 ng/mL) of the participants was 49%. In all, 32% were taking a vitamin D supplement, and 80.2% of those receiving a supplement of 4 vitamin D drops or more had an 25(OH)D3 level >40 ng/mL. The mean length of daily sun exposure for infants with a 25 (OH) D3 level of >40 ng/mL was determined to be 56.48 minutes. Ozdemir et al. [7] included 90 neonates in their study. The mean 25(OH)D3 level was 13.16±7.16 ng/mL for all of the newborns. They found that 53.3% of 1-week-old infants in their study had vitamin D deficiency. In the study conducted by Halicioglu et al. [8], the mean concentration of 25(OH)D3 in infants was determined to be 11.5±6.8 ng/mL. In another study conducted in Ankara in 2010, 58.6% of infants were found to have vitamin D deficiency (≤20 ng/mL) [9]. In another study performed by Ergur et al. [10], 18.6% of the mothers and 2.9% of the neonates had normal vitamin D levels. Yildiz et al. [11] found a mean 25(OH) D3 level of 11.5±5.9 ng/mL and 10.9±5.9 ng/mL for mothers and infants, respectively, during winter months. Gülez et al. [12] found a prevalence of vitamin D deficiency of 31% in a study of 100 infants in Izmir aged 0-24 months. However, 63% of this patient group was receiving a vitamin D supplement and 52% of them were exposed to sunlight regularly.

In these studies, the rate of vitamin D deficiency prevalence among infants in Turkey ranged from 2.9% to 58.9%. Even though Turkey has high levels of sun exposure, vitamin D deficiency remains an important problem, particularly among pregnant women, infants, and adolescents [13].

Children and adolescents

The results of the studies investigating children are shown in Table 1. In a study performed on adolescent girls in Turkey, Hatun et al. [14] found a rate of deficiency of vitamin D of

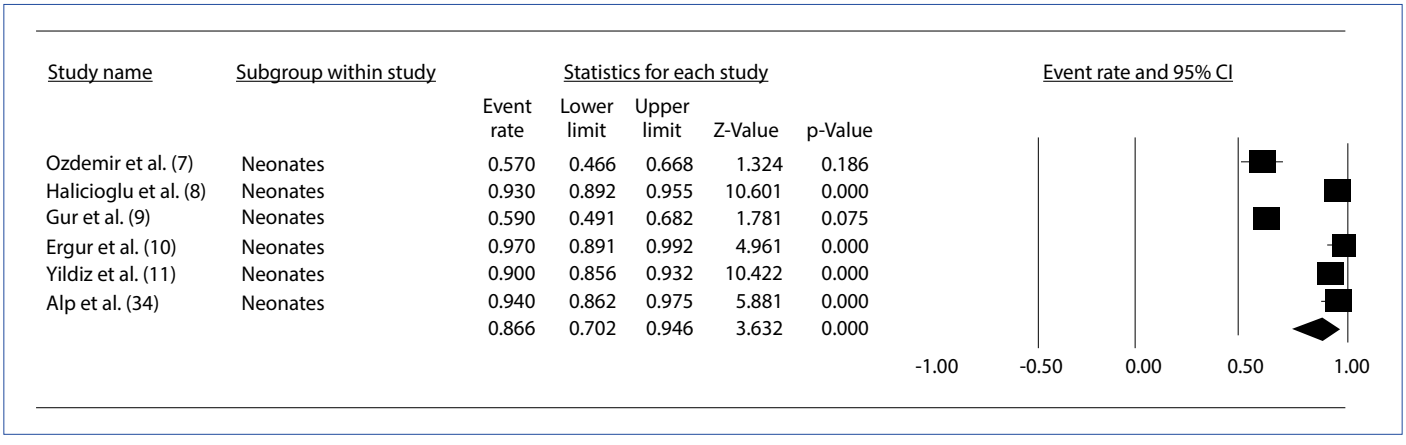

Figure 2. Forest plot of prevalence of vitamin D deficiency in neonates.

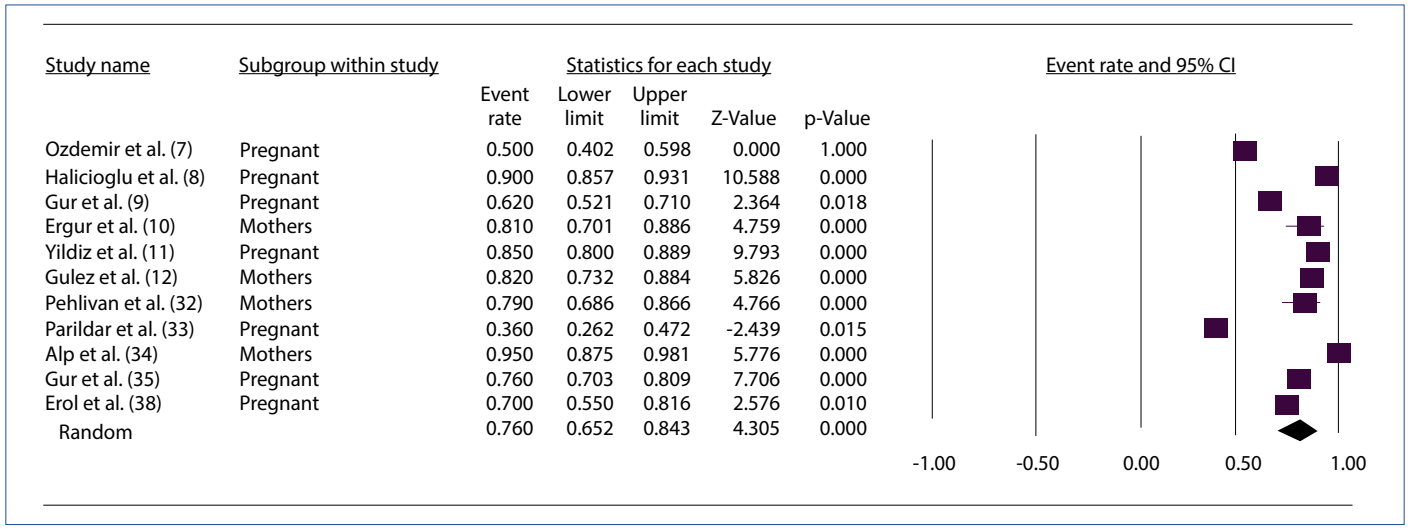

Figure 3. Forest plot of prevalence of vitamin D deficiency in pregnant/mother.

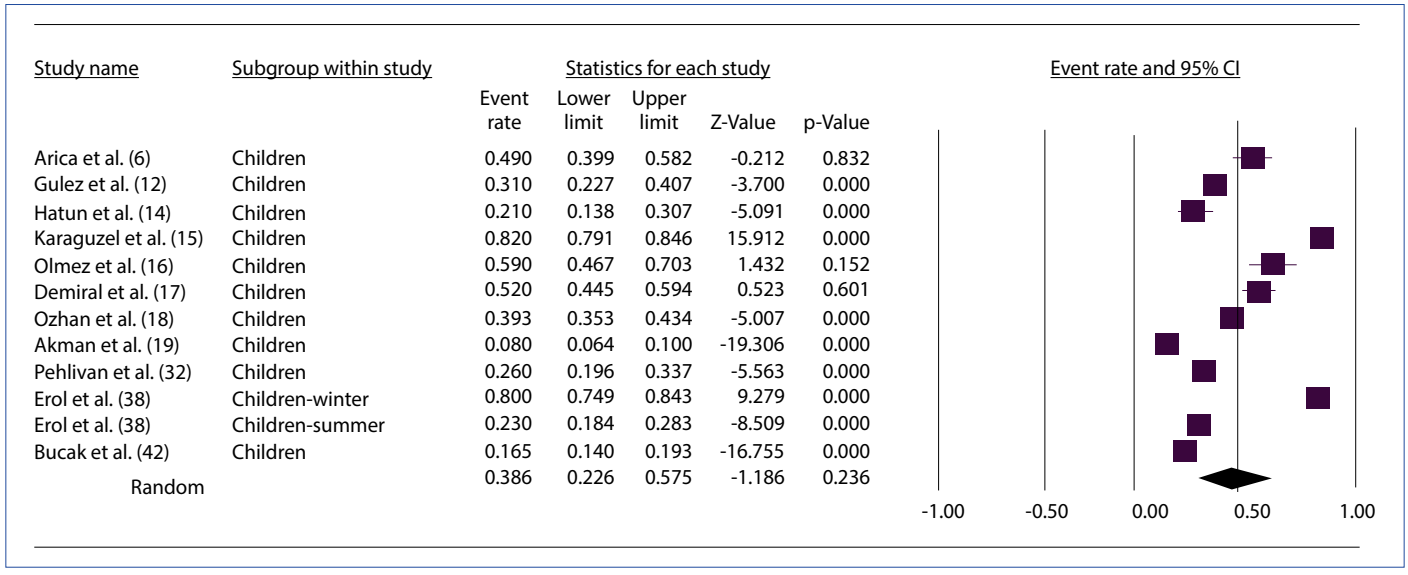

Figure 4. Forest plot of prevalence of vitamin D deficiency in children.

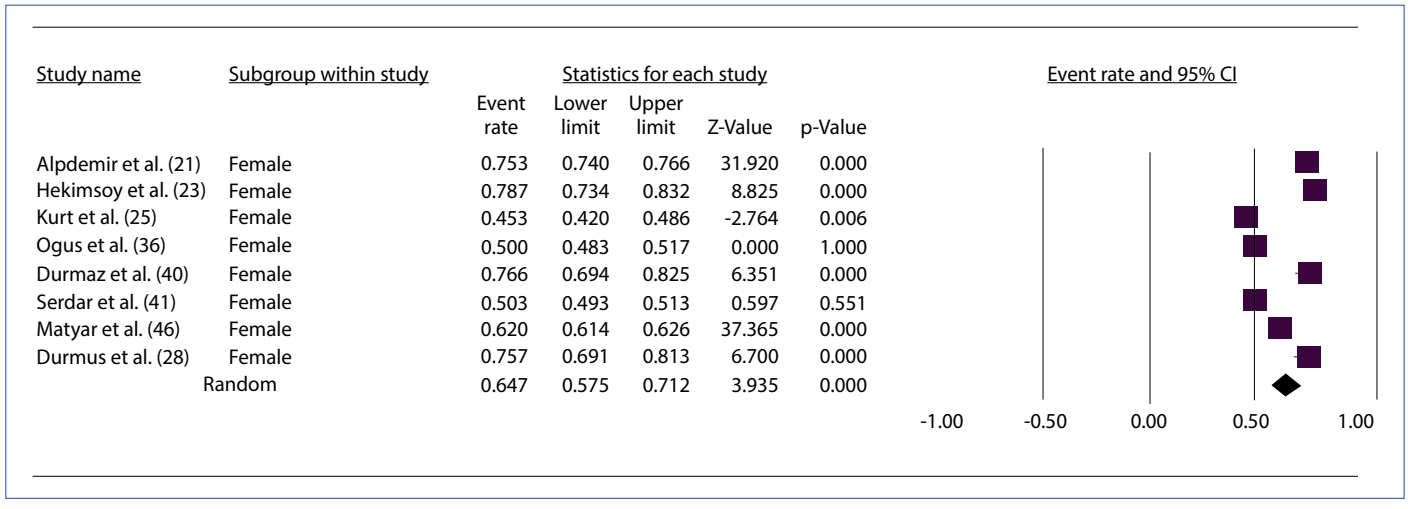

Figure 5. Forest plot of prevalence of vitamin D deficiency in female.

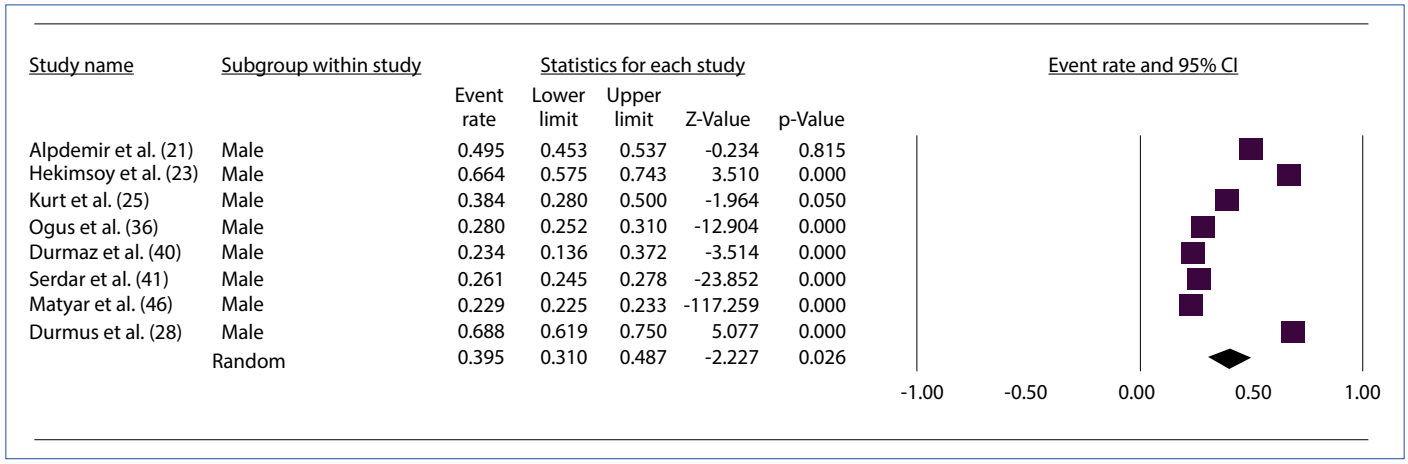

Figure 6. Forest plot of prevalence of vitamin D deficiency in male.

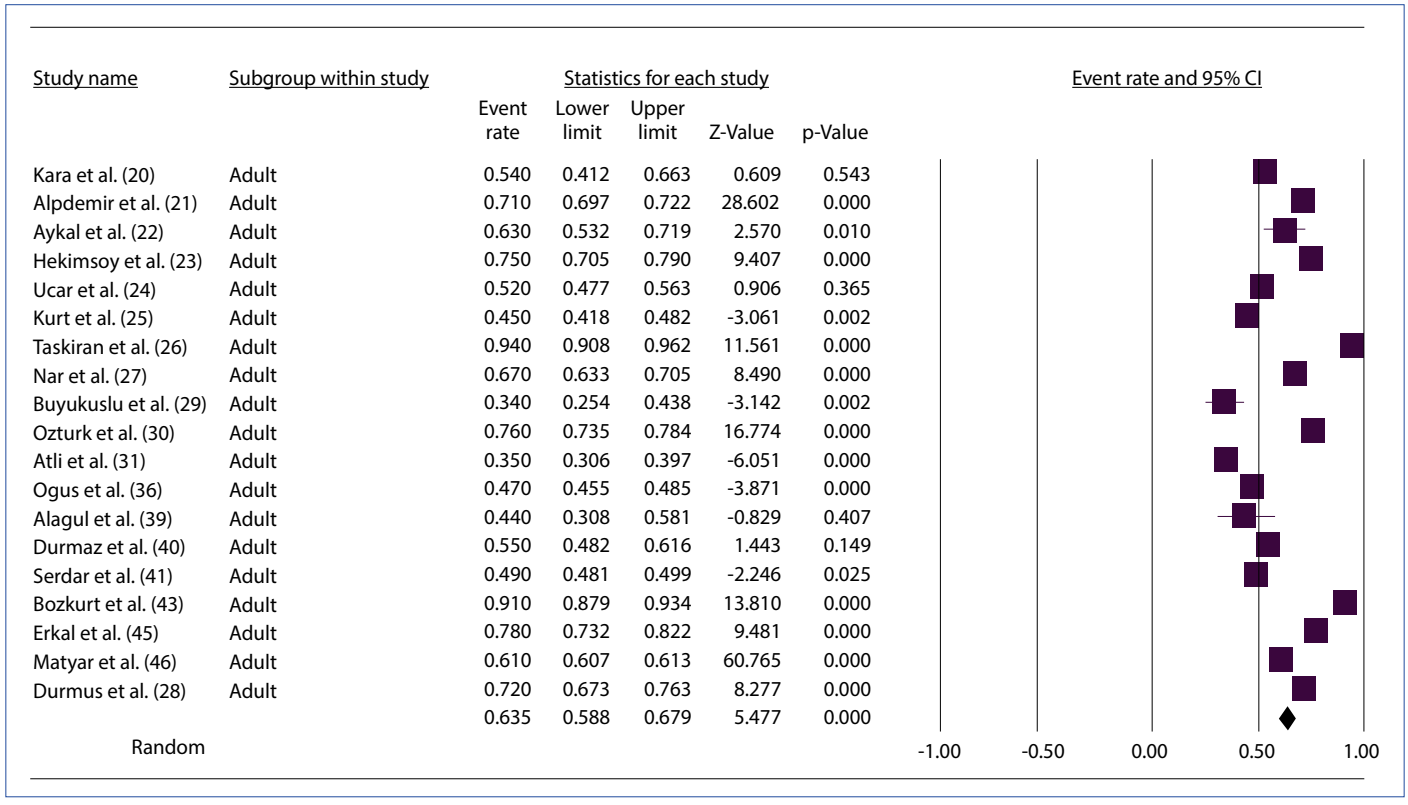

Figure 7. Forest plot of prevalence of vitamin D deficiency in adult.

21.3% and inadequacy of vitamin D of 43.8%. Karaguzel et al. [15] found a vitamin D deficiency level of 78% for males and 87% for females in the adolescents included in their study performed in Trabzon. This difference according to sex was statistically significant. Olmez et al. [16] determined a vitamin D deficiency of 59.4% in spring and 25% in autumn in a study of adolescents in Izmir aged 14-18 years. In the study conducted by Demiral et al. [17], the incidence of vitamin D deficiency was found to be 51.5% and inadequacy was recorded at a rate of 35.1% for children in the age group of 3-18 years in the Eskisehir region. Ozhan et al. [18] also found that among 556 children aged between 0-18 years there was a vitamin D deficiency of 39.3%. Vitamin D deficiency was observed in 13.8% of infants (0-1 years), 24.6% of toddlers-preschoolers (1-5 years), 54% in young school-age children (6-11 years), and 67.7% of teenagers (12-18 years) [18]. Akman et al. [19] found that there was vitamin D deficiency and inadequacy of 8% and 25.5%, respectively, in healthy children aged 1-16.

Adults

Table 3 displays the results obtained from studies of adults. Kara et al. [20] found a vitamin D deficiency of 53.7% in a study

Table 1. Vitamin D deficiency status of neonates, infants, children, and adolescents in Turkey

City	Latitude	Age range (mean±SD)	Sample size (n)	Female/male (n)	Year	Population	Timing/month/ season	Assay	25(OH)D, ng/mL (mean±SD)	Deficiency (%) <20 ng/mL	Insufficiency (%) 20-30 ng/mL	Ref.
Ankara	33°E/40°N	1-16	849	429/420	2007	Healthy, children	April-May/ spring	HPLC	All: 37.99±17.4 Urban: 34.26±15.2 Rural: 35.6±13.8	8%	25.5%	19
Ankara	33°E/40°N	0 days	99	90	2009-2010	Healthy, , mother neonates	November February /winter	RIA	15.0±10.3	58.6%	15.2%	9
Ankara	33°E/40°N	0-4 days	70	70	2003-2005	Healthy, mothers, nonpregnant, neonates	Two-years	HPLC		97.2%		10
Adiyaman	38°E/37°N	14.5±9	775	335/440	2017	Children	Annual	ECLIA	F: 32.9±13.9 M: 34.4±14.6	16.5%	25.3%	42
Denizli	29°E/38°N	0-16 6.26±6.18	556	303/253	2012	Healthy	Annual	HPLC	All: 27.21±15.90 F: 25.96 ± 5.52 M: 28.71±15.67	39.3 %	24.1%	18
Erzurum	41°E/40°N	0 days	81	81	2012-2013	Healthy, mothers, neonates	November-July/winter-April	ECLIA	7.0±6.2	93.9%	4.9%	34
Eskisehir	30°E/40°N	3-18 11.78±4	171	83/88	2015	Healthy, children		ECLIA	F: 11.8(4.3-44) M: 13.1(5-35)	All: 51.5% F: %64 M: %38.6	All: 35.1 F: 26.4 M: %42.4	17
Istanbul	29°E /42°N	3-17 10.4±2.6	280	146/134	2014	Healthy, children	Winter/ summer	ECLIA	Winter: 11.43±5.86 Summer: 20.76±9.01	M: 53.73% F: 68.49 % Winter: 80.36% Summer: 23.44%	Winter: 11.79% Summer: 27.75%	38
Izmir	27°E/38°N	0-2	100	44/56	2012	Healthy, mothers, children	July-September/ summer	ECLIA	28.1±14.7	31%		12
Izmir	27°E/38°N	0-3 days	258		2010	Healthy, infants, mothers	Spring	CLIA	:11.5±6.8	90.3%	7.4%	8
Izmir	27°E/38°N	0 days	250		2008	Healthy, pregnant, neonates	March-May/ spring	CLIA	10.9±5.9			11
Izmir	27°E/38°N	14-18	64	64	2003	Healthy, adolescent girls	End summer-end winter	RIA		59.4%	25%	16
Kocaeli	30°E/ 40°N	1-2 week	147	65	2000	Healthy, infants, mothers	Annual	RIA	32.5.3±20.3	24.6%		32

Table 1. Cont.

City	Latitude	Age range (mean±SD)	Sample size (n)	Female/male (n)	Year	Population	Timing/month/ season	Assay	25(OH)D, ng/mL (mean±SD)	Deficiency (%) <20 ng/mL	Insufficiency (%) 20-30 ng/mL	Ref.
Kocaeli	30°E/40°N	13-17 (14.8±0.6)	89	89	2002	Healthy, adolescent girls,	End winter	RIA	Suburban: 22.73±11.75 Urban: 20.0±10.09 Clothing 11.27±5.02	All group: 21.3% Suburban: 3.4% Urban: 3% Clothing: 50%	All group: 43.8% Suburban: 44.8% Urban: 43.3% Clothing: 43.3%	14
Istanbul	29°E/42°N	0-28 days	90	48/42	2016	Pregnant, neonates	Annual	ELFA	13.16±7.16	56.7%	32.2%	7
Trabzon	39°E/41°N	11-18	746	746	2009	Healthy, adolescents,	Annual	HPLC	F:31.3±17.3 M:37.3±17.3	Total: %82 F:87% M:78%		15
Van	43°E/38°N	0-3	112	52/60	2008	Healthy, children	June-September/ summer			48.7%	4.5%	6

CLIA: Chemiluminescence immunoassay; ECLIA: Electrochemiluminescence immunoassay; ELFA: Enzyme-linked fluorescent assay; F: Female; HPLC: High-performance liquid chromatography; M: Male; RIA: Radioimmunoassay.

of individuals aged 29-86 years. Alpdemir et al. [21] determined an incidence of vitamin D deficiency of 71% for individuals in the province of Balikesir aged 18-70 years. In a study conducted in Antalya by Aykal et al. [22], it was determined that there was vitamin D deficiency in 63% of the patients aged 20-40 years. Hekimsoy et al. [23] found that vitamin D deficiency in the Manisa region was 74.9%. Uçar et al. [24] reported an incidence of vitamin D deficiency of 51.8% in Ankara adults aged 18-70. There was no significant difference in the vitamin D concentration between age groups in this study. Kurt et al. [25] reported a vitamin D deficiency rate of 44.8% for individuals aged 23-89 years in Ankara. In another study conducted in Turkey's southeastern province of Diyarbakir, vitamin D deficiency was recorded at 94% [26]. Nar et al. [27] determined a vitamin D deficiency level of 66.3% in a study of adult patients in Kırşehir. In a summer study in Kayseri, Durmus et al. [28] determined that vitamin D deficiency was found in 72.1% of the adult patients studied. Buyukuslu et al. [29] reported that in samples obtained from women aged 18-29 years with a bachelor's degree measured in April and May, 34% displayed vitamin D deficiency.

Elderly

The findings of studies analyzing elderly individuals are provided in Table 2. There was no significant difference in the vitamin D level of individuals over 70 years of age compared with other age groups in the study performed by Uçar et al.[24]. Ozturk et al. [30] reported that vitamin D levels in geriatric patients were lower than those of adult patients, but without a statistically significant difference (p=0.437). In a study of individuals over 65 years of age conducted by Atli et al. [31], vitamin D deficiency was determined in 33.4% of all of the study subjects (n=420). The authors noted vitamin D deficiency in 40.1% of those living in a retirement home (54.1% of females and 18.4% of males) and in 24.4% of subjects living in their own home (27.9% of females and 4.2% of males).

Pregnant women

In Table 3 the outcomes of studies performed with pregnant women and infants in different regions of the country are shown. In 2003, Pehlivan et al. [32] reported that the vitamin D level of 94.8% of the mothers and 24.6% of the infants studied was <16 ng/mL. In 2008, Halicioglu et al. [8] reported that the vitamin D concentration in 90.3% of the pregnant women in a study in Izmir, which has a sunny climate, was ≤20 ng/mL. In a 2010 study in Ankara, the incidence of vitamin D deficiency (≤20 ng/mL) in pregnant women and their infants was found to be 62.6% and 58.6%, respectively [10]. In another study performed in Ankara, the rate of vitamin D deficiency in pregnant women was determined to be 35.9% [33]. In the

Table 2. Vitamin D deficiency status of pregnant women in Turkey

City	Latitude	Age range (mean±SD)	Pregnant Women (n)	Year	Population	Timing/ month/ season	Assay	25(OH)D, ng/mL (mean±SD)	Deficiency (%) <20 ng/mL	Insufficiency (%) 20-30 ng/mL	Ref.
Ankara	33°E/40°N	19-42	99	2009-2010	Healthy, Pregnant Infants	November-February/ Winter	RIA	Mother: 15.1±4.4 Infant: 15.0±10.3	Mother: 62.8% Infant: 58.6%	Mother: 18.2% Infant: 15.2%	9
Ankara	33°E/40°N	18-44 33.4±5.2	78	2009-2011	Healthy, Pregnant	Annual	CMIA	22.9±1	35.9%		33
Ankara	33°E/40°N	29.7±4.7	70	2003-2005	Healthy, Nonpregnant Mothers Neonates	Two years	HPLC		81.4%		10
Erzurum	41°E/40°N	29.1±5.1	245	2012	Pregnant	June-October/ Summer-Autumn	ELISA	16±5.8	75.5%	24.4%	35
Erzurum	41°E/40°N	16-50 29.9 ±3.4	81	2012-2013	Healthy, Mothers, Neonates	November-July/Winter -April	ECLIA	Mother: 7.1±5.5	94.6%	5.4%	34
Izmir	27°E/38°N	18-42	100	2012	Healthy, Mothers, Children	July-September/ Summer	ECLIA	28.1±14.7	81.8%		12
Kocaeli	30°E /40°N	18-42	78	2000	Healthy, Pregnant Infants	Annual	RIA	8.5±3.3	79.5%		32
Istanbul	29°E /42°N	20-40	97	2016	Healthy, Pregnant, Infants	Annual	ELFA	14.82±11.45	49.5%	36.1%	7
Istanbul	29°E/42°N	17-33 24.4±3.5	44	2005	Pregnant	Spring	RIA	11.1±3.86	%70.4		38
Izmir	27°E/38°N	27.2±4.9	250	2008	Healthy, Pregnant, Neonates	March-May/ Spring	CLIA	11.5±5.9			11
Izmir	27°E/38°N	17-42 27.2±4.9	258	2010	Healthy, Mothers, Neonates	Spring	CLIA	11.5±5.4	90.3%	9.3%	8
Izmir	27°E/38°N	28.4.1±4.5	387	2012	Pregnant	Summer-Autumn	ELISA	38±3.6	34.5%	35.3%	35

CLIA: Chemiluminescence immunoassay; CMIA: Carbonylmetalloimmunoassay; ECLIA: Electrochemiluminescence immunoassay; ELFA: Enzyme-linked fluorescent assay; ELISA: Enzyme-linked immunosorbent assay; F: Female; HPLC: High-performance liquid chromatography; M: Male; RIA: Radioimmunoassay.

Table 3. Vitamin D deficiency status of adult population in Turkey

City	Latitude	Age range (mean±SD)	Sample size (n)	Female/male (n)	Year	Population	Timing/ month/ season	Assay	25(OH)D, ng/mL (mean±SD)	Deficiency (%) <20 ng/mL	Insufficiency (%) 20-30 ng/mL	Ref.
Adana	35°E/37°N	18-44	77569	24726/52843	2003-2015	Healthy, Adult	Annual	HPLC	F: 48.42±0.54 M: 21.0 5±0.92	All: 60.6% F: 62.2% M: 22.9%	All: 23.75% F: 55.9% M: 27.35%	46
Amasya	36°E/41°N	18-80	209	160/49	2014	Healthy, Adult	Annual	ECLIA	F: 9.3(1.6-67.2) M: 17.4(3.0-74.7)	All: 55% F: 76.6% M: 23.4%		40
Antalya	36°E/36°N	20-40 38.6±5.5	100	67/23	2014	Healthy	December/Winter	CLIA.	14.7±8.5	63%		22
Ankara	33°E/40°N	10-90	4168	3242/926	2012	Healthy, Adult	Annual	LC-MS/MS	23.75±10.57	All: 47% F: 50% M:28%	28%	36
Ankara	33°E/40°N	18- >70	513	406 /107	2010-2011	Healthy, Adult	December-August	HPLC	F: 24.02±16 M: 22.76±8.5	51.8	20%	24
Ankara	33°E/40°N	21-52 34.1±7.4	118	65/53	2008 - 2009	Healthy, Premenopausal women, Men	August February/ Winter Summer	HPLC	Winter: 13.8±6.6 Summer: 28.4±10.3	Winter: 83.9% Summer:24.6%	Winter: 35.6% Summer: 24.6%	37
Ankara	33°E/40°N	20-87 48.7±14.2	435	398/37	2011- 2012	Healthy, Adult	June-April/ Summer-Winter	HPLC	16.3±11.0	90.8%		43
Ankara	33°E/40°N	69-81 75±7.0	420	309/111	2004	Healthy, Elderly		RIA		33.4%		31
Ankara	33°E/40°N	23-89 61.0±10.9	940	867/73	2003-2011	Healthy, Adult	Annual		26.13±18.62 F: 25.71±18.50 M: 31.5±19.36	All:44.8% F: 45.3% M: 38.4%	All: 23.7% F: 24.5% M: 15.1%	25
Balikesir	28°E/40°N	18-70	4956	4409/547	2010-2014	Healthy, Adult	Annual	ECLIA.	F: 15.17±7.02 M: 20.39±7.77	All:71.3% F: 75.32% M: 49.54%		21
Diyarbakir	40°E /37°N	41±14	313	264/49	2016	Healthy, Adult	January-March/Winter	ECLIA.	F: 9.2±4.1 M: 14.9±3.2	%94		26
Gaziantep	37°E/37°N	61±11	58	22/36	2016	Healthy, Adult		ECLIA	36.3±18.9	53.7%		20
Gaziantep	37°E/37°N	18-90 43.60	1161	363/798	2016-2017	Healthy, Adult	October 2016-March 2017		16.61±6.90 F: 15.24±7.40 M: 17.23±6.55	75.54%	19.38%	30
Kayseri		18-65	381	189/192	2016	Healthy, Adult	June/August	LC-MS/MS	15.11±9.07 F: 13.99±9.97 M: 16.21±7.97	All: 72.1% F: 75.7% M: 68.8%	All: 20.5%	28
Kirşehir	34°E/39°N	18-60	650		2015	Healthy, Adult	October-December	ECLIA	19.7±14.44	66.6%		27
Manisa	38°E /36°N	45.11±17.28	391	272 /119	2007	Healthy,	Winter	HPLC	16.91±91 F: 15.25±11.53 M: 20.70±15.50	All: 74.9% F: 78.7% M: 66.4%	13.8%	23

Table 3. Cont.

City	Latitude	Age range (mean±SD)	Sample size (n)	Female/male (n)	Year	Population	Timing/ month/ season	Assay	25(OH)D, ng/mL (mean±SD)	Deficiency (%) <20 ng/mL	Insufficiency (%) 20-30 ng/mL	Ref.
Istanbul	29°E/42°N	18-29 (20.9)	100	100	2013	Healthy, Women	Spring	ELISA	Total: 26.3±10 Covered: 21.1±6.7 Uncovered: 29.7±3.1	Total: 34% Covered: 55% Uncovered: 20%	Total: 36% Covered: 35% Uncovered: 36.7%	29
Istanbul	29°E/42°N	15-44 (26±8)	48	48	1998	Healthy, Women	August/ Summer	RIA	Control: 56±41.3 Semi-Covered: 31.9±24.4 All Covered: 9.9±5.7	Control: 44% Semi-covered: 60% All covered: 100%		39
Istanbul	29°E/42°N	1-97 (38.8±22.1)	12612	9890/2723	2009-2015	Healthy, Adult	Four years	LC-MS		All: 49.3% F: 50.3% M: 46.5%	F: 23.0% M: 26.1%	41
Istanbul, Mersin, Unye, Ankara	29°E/42°N 36°N 42°N 40°N	17-69	327	242/85	2006	Healthy, Adult	End of winter	ELISA		78%		45

CLIA: Chemiluminescence immunoassay; CMIA: Carbonylmetalloimmunoassay; ECLIA: Electrochemiluminescence immunoassay; ELISA: Enzyme-linked immunosorbent assay; F: Female; HPLC: High-performance liquid chromatography; LS-MS: Liquid chromatography–mass spectrometry; M: Male; RIA: Radioimmunoassay.

2016 study performed by Ozdemir et al. [7], the mean vitamin D concentration was 14.82±11.45 ng/mL in pregnant women and 13.16±7.16 ng/mL in their infants. Vitamin D deficiency was present in 49.5% of mothers and 56.7% of infants. Alp et al. [34] found that 94.6% of pregnant women in Erzurum province demonstrated vitamin D deficiency. In 2012, Gur el al. examined vitamin D deficiency in Izmir and Erzurum and reported results of 34.5% and 75.5%, respectively, in a total of 387 participants [35]. Gur et al. reported that a vitamin D deficiency prevalence among pregnant women in Izmir of 27.8% and 76.3% in Erzurum [35].

Effect of age, sex, and season

Ogus et al. [36] retrospectively determined a rate of vitamin D deficiency in men of 38% and 50% in women. In this study, the mean 25(OH)D3 was 22.49±13.88 ng/mL in women and 23.75±10.57 ng/mL in men. The patients were aged 10-90 years and it was noted that the 25(OH)D3 concentration measured in April was greater than that of October. In addition, the 25(OH) D3 concentration was higher in young people and lower in older adults (>70 years). Cinar et al. [37] also observed a significant difference in assessments according to season: The rate of vitamin D deficiency was 24.6% in summer and 83.9% in winter. Karaguzel et al. [15] reported that among adolescents in Trabzon, the vitamin D deficiency level recorded was 71% in the autumn and 92% in the spring. This difference was statistically significant. In a study in Istanbul, a city with a sunny climate, Erol et al. [38] found that the mean serum 25(OH)D3 levels at the end of winter were significantly lower compared with end of summer levels. Vitamin D deficiency was recorded among adolescents in this study in 53.3% of females and 68.49% of males. In 1998, Alagol et al. [39] found that vitamin D levels were low in 66.6% of women of reproductive age in Istanbul. Ozhan et al. [18] found that the rate of vitamin D deficiency was 45.1% for females and 32.4% for males in 556 children aged 0-18 years. The overall prevalence of vitamin D deficiency in this study was 33.3% in spring, 15.5% in summer, 55.5% in autumn, and 44.9% in winter. Durmaz et al. [40] observed a significant difference in vitamin D levels between women and men. They reported vitamin D deficiency in 76.6% of women and 17.4% of men. There was no significant difference observed between age groups in that study. Hekimsoy et al. [23] found a vitamin D deficiency rate of 75.5% among women and 66.4% among men in their study of Manisa residents. There was no significant difference in 25(OH)D3 level according to age group. In a study performed in the Balikesir region, Alpdemir and Alpdemir [21] measured a rate of vitamin D deficiency of 75.32% for women and 49.54% for men. The authors reported results of 84.84% in winter, 81.27% in spring, 63.63% in summer, and 59.06% in autumn. There was no statistically significant difference between groups

when examined by age group. In a study of seasonal changes in 25(OH)D3 values from 2009-2015 conducted by Serdar et al. [41], the findings indicated an increase starting in June, reaching a high concentration in September, and then decreasing by December. There was no statistical difference in 25(OH)D3 levels between men and women, while there were statistically significant differences between seasons. In their study, a variation in vitamin D according to age was observed. An increased level of vitamin D was seen in the first decade, which may have been due to vitamin D supplemention in this period. There was a significant reduction in vitamin D concentration between the ages 10–40 years. In other age groups (40-90 years), the mean value of vitamin D demonstrated an increase with age. Cinar et al. [37] did not observe any significant difference in the level of vitamin D between men and women. There was no significant difference in vitamin D measurements between seasons in a study of children performed by Buçak et al. [42]. There was no significant difference observed according to age groups or sex (aged 18-70 years) in research done by Uçar et al. [24] in Ankara. Bozkurt et al. [43] reported that a large percentage of the adult Turkish population had an insufficient level of vitamin D during the winter and summer. While they found that serum vitamin D concentrations were significantly lower in the winter compared with the summer season, the deficiency of vitamin D was 94% in the winter and 85% in the summer. There were no differences in vitamin D concentration with respect to age or sex [43].

The available data on vitamin D status vary regarding sex and age. In general, the prevalence of vitamin D deficiency is higher in women. In addition, vitamin D levels did not change in the adult age group in the majority of studies. However, there was a different prevalence of vitamin D deficiency when analyzed according to the season.

Clothing style

The effect of clothing on vitamin D levels is demonstrated in Tables 1, 2 and 3. In Istanbul, Alagol et al. [39] studied 3 groups classified by the style of dress. The first group (Group I), the control group, consisted of 18 women who dressed in a style that exposed the usual areas of the skin to sunlight. In the second group (Group II), 15 women covered their whole body, excluding the hands and face, and 15 women in the third group (Group III) covered their whole body, including the hands and face with a veil and gloves due to religious belief. The mean serum vitamin D concentration in the summer season was 56±41.3 ng/mL in Group I, 31.9±24.4 ng/mL in Group II, and 9.9±5.7 ng/mL in Group III. In another study conducted among pregnant women in Izmir, the mean vitamin D concentration was 24.5 ng/mL in covered women and 31.6 ng/mL in uncovered women. The mean vitamin D concentration was 15 ng/mL in covered pregnant women and 17.9 ng/mL in uncovered pregnant women in Erzurum [35]. In another study of pregnant women, Halicioglu et al. [8] found a significant difference between covered and uncovered styles of dress among women. Erol et al. [38] observed a deficiency of vitamin D in 70% of 44 pregnant women who observed a covered dressing style. Hatun et al. [14] identified vitamin D deficiency in 3% of girls who did not wear a headscarf and 50% in those who did. Similarly, Pelivan et al. [32] reported that pregnant women who wore an abaya had lower levels of vitamins D. In another study conducted in Adana, there was a significant difference in the concentration of vitamin D between women who observed covered and uncovered styles of dress (mean: 33.1±16 ng/mL and 53.9±27.3 ng/mL, respectively) [44]. Buyukuslu et al. [29] observed vitamin D deficiency in 55.0% of covered students and 20.0% of uncovered students. The vitamin D status was statistically significant and there was a negative correlation with the age at which young women adopt an Islamic style of dress ($p<0.05$; $r=-0.334$).

Regional difference

Vitamin D levels according to region are displayed in Tables 1, 2 and 3. Gur et al. [35], compared the 25(OH)D3 concentrations of pregnant women living in 2 provinces located in the eastern and western regions of Turkey. Izmir and Erzurum are very distinct provinces with respect to both geographical and climatic conditions and social life: Izmir (latitude 27°) has an elevation of 2 m above sea level, while Erzurum (latitude 41.1°) has an elevation of 1893 m. The mean 25(OH)D3 concentration was 38±3.5 ng/mL in Izmir and 16±5.8 ng/mL in Erzurum. The prevalence of vitamin D deficiency reported was 27.8% in Izmir and 76.3% in Erzurum in the study performed by Gur et al. [35]. Karaguzel et al. [15] determined that the deficiency of vitamin D in Trabzon (latitude 41°) was 93% at the end of winter and 7% at the end of summer [15]. In their study conducted in the Izmir region, Olmez et al. [16] recorded a deficiency of vitamin D of 59.4% at the end of winter and 25% at the end of summer. Erkal et al. [45] found that the median 25(OH)D3 concentration in Turks from Mersin (37°N, a southern Turkish city) was statistically significantly higher than values assessed in cities further north, such as Istanbul, Ankara and the town of Unye (40–41°N) (females: $p=0.0018$; males: $p=0.0015$). Matyar et al. [46] observed that vitamin D deficiency and insufficiency was 60.6% and 23.78 %, respectively, among residents of the Cukurova area (a southern region) aged 18-44 years.

Discussion

In this study, we reviewed the literature and identified 40 original studies related to vitamin D concentration in Turkey. We conducted a screening study considering age, gender, pregnancy, clothing style, region, and season in terms of vitamin

D concentrations. The prevalence of vitamin D deficiency observed varied from 24% to 99% in various studies and regions. The pooled prevalence rate of vitamin D deficiency was 63% for the overall population in our meta-analysis review. Therefore, vitamin D deficiency continues to be a severe problem throughout Turkey. Vitamin D serum concentrations may be affected by gender, age, pregnancy, season, and cultural differences.

Vitamin D deficiency is a widespread condition that is said to affect about 1 billion people worldwide [4]. A previous review of vitamin D deficiency in Turkey revealed a wide rate of severe deficiency of 8% to 84% [47]. Over the past 2 decades, several national population-based epidemiological studies in the United States, Canada, the United Kingdom, and New Zealand have reported a deficiency rate of 18% to 36%. It was reported that the vitamin D deficiency rate among the Australian population was 39% for women and 22% for men [48].

The prevalence rate of vitamin D deficiency was determined to be 86.6% for neonates and 76% for mothers in this meta-analysis. As seen in our study, vitamin D deficiency is still a serious health problem, especially in pregnant women, neonates, and infants among those of low socio-economic status in the Turkish population. A vitamin D supplement program was initiated to provide vitamin D supplementation of 400 IU D per day for all infants from birth to 1 year of age, and for all pregnant women at dose of 1200 IU/day starting from 12 weeks of pregnancy [9]. Nonetheless, all of these data confirm that vitamin D deficiency continues to be a problem in pregnant women in Turkey and their infants. It has been reported that the level of vitamin D in pregnant women can be affected by factors such as geographical region, sunbathing habits, style of dress, body mass index, the educational level of the mother, socioeconomic status, dairy product consumption, and external vitamin D supplementation [6-12]. It was observed in this meta-analyses study that rate of vitamin D deficiency varied from 57% to 93% for infants and from 62% to 95% for pregnant women. In studies conducted in other countries, the prevalence of vitamin D deficiency was 3% to 86% for pregnant women and 4% to 60% for infants [42, 49].

In this meta-analysis, the prevalence rate of vitamin D deficiency ranged between 8% and 80%. The growth period of childhood and adolescence are the most critical time intervals for skeletal development and are closely related to the levels of calcium and vitamin D absorbed. Vitamin D deficiency is common in this period. As was evident in this review, it is also important to consider the season and province [14-20].

The results of this meta-analysis suggest that the serum 25(OH) D3 concentration level may be associated with gender and season. Biological differences, behavioral differences, and style of dress (e.g., wearing a veil) are often mentioned as reasons for a higher prevalence of vitamin D deficiency among women than men. As seen in studies performed in Turkey and other countries, vitamin D deficiency is significantly common in women [18, 21, 23, 38-41]. A lower serum 25(OH)D3 concentration among older participants may partly be the result of the lower capacity of the skin to produce vitamin D after exposure to sunlight, reduced activity and immobility among the elderly, and insufficient sunshine exposure [31, 50]. There is an apparent change in the level of vitamin D according to the season. According to many studies, the incidence of vitamin D deficiency increases in autumn and winter, and decreases in summer and spring [15, 18, 21, 41, 35-37, 38, 43]. A negative correlation between age and vitamin D concentrations has been reported in many studies, though in some research, vitamin D concentration did not change with age in adults [21, 23, 39, 41-43].

Studies conducted to compare regional differences in vitamin D levels have revealed that the prevalence of vitamin D deficiency was lower in cities at a lower latitude. Populations living at southern latitudes are exposed to more sunlight, which contributes to the serum vitamin D level [7,15, 45].

Traditional and regional clothing styles and Islamic beliefs that promote a more covered style of dress for women are common in Turkey. Clothing is a factor that affects the level of vitamin D absorption because it prevents exposure to direct sunlight. Our analysis showed that vitamin D status was affected by a covered style of dress and had a negative correlation with the duration of the observation of a covered style of dress [8, 16, 27, 31, 37, 38].

There are some limitations that should be considered. The prevalence of vitamin D deficiency was not mentioned directly in all of the studies used in this analysis; the prevalence rate for some studies was calculated by the authors based on the data available from the study. Different methods (RIA, enzyme-linked immunosorbent assay, electrochemical luminescence immunoassay, electron ionization, HPLC, and LC-MS/MS) were used to measure vitamin D concentrations. Therefore, the results should be evaluated carefully.

Conclusion

In light of the results obtained in this meta-analysis, there is a clear vitamin D deficiency in Turkey, which varies from 58.9% to 66.6% in studies with a 95% CI. Gender, age, season, location, exposure to sunlight, clothing, socioeconomic status, and religious beliefs affect the vitamin D level in the body.

To our knowledge, this study is the first meta-analysis to describe the current national status of vitamin D levels in Turkey. Vitamin D deficiency or insufficiency continues to be a significant public health issue in Turkey. Neonates, pregnant women, women, and the elderly in particular have a higher risk of vitamin deficiency. Our results support a recommendation that the level of vitamin D in the Turkish population should be periodically measured and if necessary, appropriate supplements should be taken to prevent a secondary chronic disease due to deficiency of vitamin D.

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