Systematic Review

Obesity Facts

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A Systematic Review and Meta-Analysis of Vitamin D Status of Patients with Severe Obesity in Various Regions Worldwide

Neda Haghighat[a] Zahra Sohrabi[b] Reza Bagheri[c] Marzieh Akbarzadeh[b] Zahra Esmaeilnezhad[b] Damoon Ashtary-Larky[a] Reza Barati-Boldaji[b] Morteza Zare[b] Masoud Amini[a] Seyed Vahid Hosseini[d] Alexei Wong[e] Hamidreza Foroutan[a]

[a]Laparoscopy Research Center, Shiraz University of Medical Sciences, Shiraz, Iran; [b]Department of Community Nutrition, Shiraz University of Medical Sciences, Shiraz, Iran; [c]Department of Exercise Physiology, University of Isfahan, Isfahan, Iran; [d]Colorectal Research Center, Shiraz University of Medical Sciences, Shiraz, Iran; [e]Department of Health and Human Performance, Marymount University, Arlington, VA, USA

Keywords
Obesity · Vitamin D · Vitamin D deficiency · Meta-analysis

Abstract

Introduction: Managing nutritional deficiencies is an essential component in the treatment of severe obesity. Vitamin D deficiency is often reported in investigations in severely obese cohorts. However, no prior study has summarized findings on this topic. Consequently, the aim of this systematic review and meta-analysis was to investigate the 25-hydroxyvitamin D [25(OH)D] status in individuals with severe obesity in different regions worldwide. We also evaluated levels of calcium, parathyroid hormone (PTH), and magnesium as secondary outcome measures. ***Methods:*** We searched Medline, PubMed, Scopus, the Cochrane Library, and EMBASE for relevant observational studies published in English from 2009 to October 2021. The heterogeneity index among the studies was determined using the Cochran (Q) and I^2 tests. Based on the heterogeneity results, the random-effect model was applied to estimate the prevalence of vitamin D deficiency. ***Results:*** We identified 109 eligible observational studies. Overall, 59.44% of patients had vitamin D deficiency [25(OH)D <20 ng/mL], whereas 26.95% had vitamin D insufficiency [25(OH)D 20–30 ng/mL]. Moreover, the mean 25(OH)D level was 18.65 ng/mL in 96 studies. The pooled mean estimate of the serum calcium, PTH, and magnesium was 9.26 mg/dL (95% confidence interval [CI]: 9.19–9.32, I^2 = 99.7%, p < 0.001), 59.24 pg/mL (95% CI: 54.98, 63.51, I^2 = 99.7%, p < 0.001), and 0.91 mg/dL (95% CI: 0.84, 0.98, I^2 = 100.0%, p < 0.001), respectively. The results of the subgroup analysis indicated that the mean estimates of 25(OH)D were highest in North America (21.71 ng/mL [19.69, 23.74], [I^2 = 97.2%, p < 0.001]) and lowest in Southeast Asia (14.93 ng/mL [14.54, 15.33], [I^2 = 0.0%, p = 0.778]). ***Conclusion:*** The results obtained showed a significant prevalence of vitamin D deficiency among severely obese individuals in various geographical regions, whereas the highest and lowest mean estimates were reported for North America and Southeast Asia, respectively.

Introduction

Morbid obesity, characterized by body mass index (BMI) higher than 40 kg/m, showed an increased prevalence in the last 30 years [1]. It is associated with

karger@karger.com
www.karger.com/ofa

Correspondence to:
Hamidreza Foroutan, forotanh@sums.ac.ir

significant severity and mortality including enhanced morbidity from cardiovascular, cerebrovascular, hepatobiliary, and colonic diseases [2–4]. It is well established that despite high-calorie intakes, micronutrient deficiencies are prevalent in severe obesity [5, 6]. Indeed, a high BMI is correlated with nutrient deficiency [7–11]. Therefore, the management of nutrient deficiencies in severe obesity is an important component for the treatment of this condition, especially since these deficiencies could worsen after the surgeries [12].

Vitamin D deficiency is often reported in severely obese cohorts [13], and its prevalence is further increased in those who are candidates for bariatric surgery [14–19]. The causes for vitamin D deficiency in this population include a lower sun exposure due to lower outdoor physical activity [6, 20], a reduced dietary intake of vitamin D as well as an impaired liver function which decreases the synthesis of this vitamin [12]. Moreover, vitamin D uptake [21, 22] and vitamin D sequestration by the adipose tissue can be considered another important trigger of vitamin D deficiency in the severely obese cohort [23–25]. Lower vitamin D levels [12] in severe obesity are frequently concurrent to higher parathyroid hormone (PTH) concentrations which can impair calcium metabolism and lead to declines in bone health and the development of chronic diseases, including diabetes, cardiovascular disease, and hypertension [26–37].

Various degrees of vitamin D deficiency and high PTH levels in severe obese cohorts are reported in the available literature, which results from various fortification policies, seasonal and geographical differences, assay methods, and ethnicity differences [12]. For instance, some studies reported a vitamin D deficiency prevalence of 50–60% [38, 39], while others showed more than 70% in bariatric surgery candidates [12, 18, 40, 41]. It should be noted that previous studies reported that PTH levels were linked to calcium and magnesium levels [42, 43].

Vitamin D deficiency is the most common cause of secondary hyperparathyroidism that will result in bone resorption and fracture. Moreover, vitamin D deficiency can decelerate chronic disease including metabolic syndrome, type 2 diabetes, hypertension, and hyperlipidemia in patients with severe obesity [44]. Consequently, there is a lack of consensus regarding serum levels of vitamin D, PTH, calcium, and magnesium in this population. It is important to better elucidate vitamin D status in various geographical zones for better management of this deficiency before the surgeries in this high-risk group. Thus, we sought to conduct a systematic review and meta-analysis to assess vitamin D deficiency prevalence as well as serum levels of vitamin D, magnesium, calcium, and PTH in severely obese individuals in different regions worldwide.

Materials and Methods

This study was performed based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) for reporting systematic reviews and meta-analyses [45]. The protocol was previously published in the PROSPERO database (http://www.crd.york.ac.uk/PROSPERO), under registration no. CRD42019139937.

Search Strategy

We searched PubMed, Scopus, EMBASE, ISI Web of Science, and Cochrane databases through October 2021 in the English language to find studies investigating the prevalence of vitamin D status in patients with severe obesity who were candidates for bariatric surgeries. The systematic literature search was based on the following strategy: controlled vocabulary (i.e., MeSH and EMTREE terms) and specific text words. For each database search, adapted combinations of terms and words were applied. For example, in the search on the PubMed database, the following search terms were used: ("vitamin D," "25-hydroxy vitamin D," "vitamin D deficiency," 25(OH) D, "Vitamin D deficiency" OR "Deficiency, Vitamin D" OR "Deficiencies, Vitamin D" OR "Vitamin D Deficiencies") AND ("morbid obesity" OR "severe obesity" OR "Morbid Obesities" OR "Obesities, Morbid" OR "Obesity, Severe" OR "Obesities, Severe" OR "Severe Obesities" OR "Severe Obesities"). Moreover, bibliographies of all prior reviews and primary studies identified by search strategy were scanned for additional relevant publications. The authors decided which trials to include (authors 1, 2, and 3) in a blinded manner, with discrepancies resolved via discussion.

Inclusion and Exclusion Criteria

Three reviewers independently screened all abstracts and selected articles for the meta-analysis if they met all of the following criteria: prospective or retrospective studies or randomized controlled trials that reported the level of serum vitamin D, calcium, PTH, and magnesium status or prevalence of vitamin D deficiency or insufficiency in individuals with severe obesity (BMI >40 or BMI >35 with at least one comorbidity) preoperatively [46], (2) written in the English language, and (3) reported at least serum vitamin D or calcium or PTH or magnesium or vitamin D deficiency or insufficiency. Only data associated with severe obesity were considered for inclusion in studies that analyzed multiple interventions. The exclusion criteria were (1) the absence of information on serum vitamin D or calcium or PTH or magnesium or prevalence of vitamin D deficiency or insufficiency and (2) studies with case-control design, reviews, comments, case reports, abstracts, and animal studies.

Study Selection

Three authors (N.H., Z.S., and M.A.) independently conducted the study selection process in two phases. The first phase consisted of screening the articles through their titles and abstracts and eliminating studies that did not meet the eligibility criteria. The remaining articles were read in full, and those eligible were selected for review. In the absence of consensus on including a study by the three authors, a fourth author (M.A.) contributed to the final decision-making. The level of disagreement was calculated using a percentage of agreement and reliability, Cohen's Kappa [47]. Three authors (N.H., Z.S., and M.A.) analyzed the lists of references in the included articles.

Data Collection

Three authors (S.E., R.B., and M.A.) extracted the data, and an additional author (N.H.) performed the cross-checking of all information. The following details were collected from all selected studies: authors, publication year, aim of the study, sample size, age, sex, country of origin, serum vitamin D level, serum calcium level, serum PTH level, serum magnesium level, and their deficiencies.

Statistical Analysis

The statistical analyses were performed using Stata, version 14 (Stata Corp., College Station, TX). We calculated the mean difference with 95% confidence interval (CI) for continuous data for each study. Cochrane Q test and I^2 were used to evaluate heterogeneity among the included studies. I^2 values greater than 50% represented moderate to high heterogeneity, and $p < 0.01$ was considered statistically significant. Because of the significant heterogeneity, the pooled weighted mean difference and 95% CI were calculated using the random-effects model (DerSimonian and Laird) [12]. The subgroup analysis was performed to explore possible sources of observed heterogeneity among the included studies. Subgroup analysis was conducted according to the following variables: climate zone (Middle East, North America, South America, Asia, Europe). p values for pooled effect sizes were considered statistically significant at the level of $p < 0.05$, a priori.

Results

Literature Search

In the initial search, 10,491 articles were found in the selected databases. After exclusion of the duplicates, 1,778 documents underwent assessment via screening of titles and abstracts. Of these, 1,086 articles were determined to be non-relevant, while the remaining 692 articles underwent full-text revision. Following these procedures, 119 documents were determined to be eligible, and another 18 studies were added for consideration after assessment of the article's references. The evaluation of inclusion/exclusion criteria resulted in the omission of 25 records. Consequently, 109 articles were included in the meta-analysis (Fig. 1).

Study Characteristics

The study design of the included studies was cross-sectional, case-control, cohorts, and interventional, which reported serum 25(OH)D, PTH, calcium, and magnesium levels in patients with severe obesity and bariatric surgery candidates. Included studies were published from 2009 to 2021, consisting of 109 articles on bariatric surgery candidates reporting their pre-operation information. The total number of individuals who underwent meta-analysis from 109 articles was 21,565, which varied from 10 to 2,008. The mean age of the individuals was 41.5 years, varying from 30 to 51 years. Both male and female participants were included in 109 articles, while 13 articles were reported on data related to only females (Table 1).

Meta-Analysis

Vitamin D Status

Vitamin D deficiency and insufficiency were reported in 51 and 28 studies conducted on 12,479 and 3,390 individuals, respectively. The overall pooled prevalence estimates of vitamin D status were as follows: vitamin D deficiency (25(OH)D <20 ng/mL): 59.44% (95% CI: 54.16, 64.73, $I^2 = 100.0\%$, $p < 0.001$), vitamin D insufficiency (25[OH]D 20–30 ng/mL): 26.95% (95% CI: 22.12, 31.78, $I^2 = 100.0\%$, $p < 0.001$), and vitamin D deficiency + insufficiency (25[OH]D <30 ng/mL): 76.24% (95% CI: 66.96, 85.52, $I^2 = 100.0\%$, $p < 0.001$) (Fig. 2a–c, respectively).

A mean serum level of 25(OH)D was reported in 96 studies on 18,998 individuals. The pooled mean estimate of the serum 25(OH)D level was 18.65 ng/mL (95% CI: 17.85, 19.45, $I^2 = 99.4\%$, $p < 0.001$). The lowest and highest serum 25(OH)D levels were reported in Lancha's (2014) and Damms-Machado's (2012) reports, respectively (Fig. 3a).

The mean serum levels of 25(OH)D were also analyzed in different geographical zones. Based on the results of subgroup analysis, the pooled mean estimate of serum 25(OH)D levels in different geographical zones was as follows: Europe – 18.94 ng/mL (17.86, 20.02) (I2 = 99.5%, $p < 0.001$); Middle East – 15.29 ng/mL (13.93, 16.65) (I2 = 98.3%, $p < 0.001$); Southeast Asia – 14.93 ng/mL (14.54, 15.33) (I2 = 0.0%, $p = 0.778$); South America – 21.12 ng/mL (16.07, 26.16) (I2 = 99.1%, $p < 0.001$); North America – 21.71 ng/mL (19.69, 23.74) (I2 = 97.2%, $p < 0.001$); Australia – 17.77 ng/mL (14.90, 20.63) (I2 = 79.1%, $p = 0.001$). The highest and lowest mean estimates were reported for North America and Southeast Asia, respectively (Table 2).

Parathyroid Hormone

Fifty-nine studies reported the serum PTH levels of the 11,545 individuals. The pooled mean estimate of serum PTH level was 59.24 pg/mL (95% CI: 54.98, 63.51) ($I^2 = 99.7\%$, $p < 0.001$) (Fig. 3b). In a subgroup analysis based on the geographical location, the highest and lowest pooled mean estimates were seen in South America and Southeast Asia, respectively (Table 2).

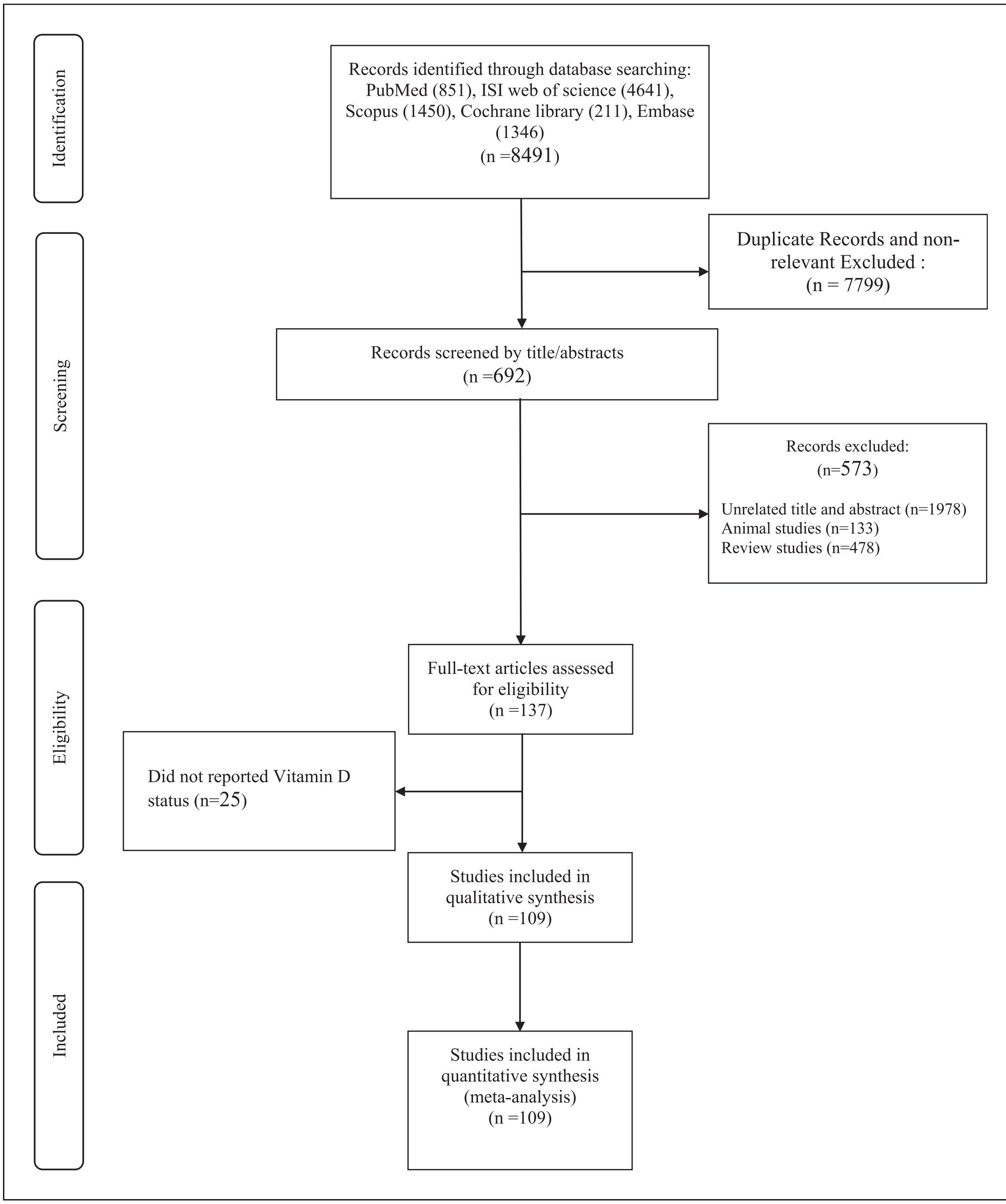


Fig. 1. Flowchart of study selection for inclusion trials in the systematic review.

Calcium

Data on the serum calcium levels of 13,355 individuals were reported in 56 studies. According to the meta-analysis, the pooled mean estimate of the serum calcium level was 9.26 mg/dL (95% CI: 9.19–9.32, I^2 = 99.7%, $p < 0.001$) (Fig. 3c). Subgroup analysis by geographical location established that Australia (pooled mean estimate of 9.36 mg/dL [9.25, 9.47, I^2 = 98.2%, $p < 0.001$]) and South America (pooled mean estimate of 9.00 mg/dL [8.53, 9.48, I^2 = 99.2%, $p < 0.001$]) had the highest and lowest estimates, respectively (Table 2).

Magnesium

Data on serum magnesium levels were reported in 15 studies, including 2,527 individuals. The pooled mean estimate of the serum magnesium level was 0.91 (0.84, 0.98,

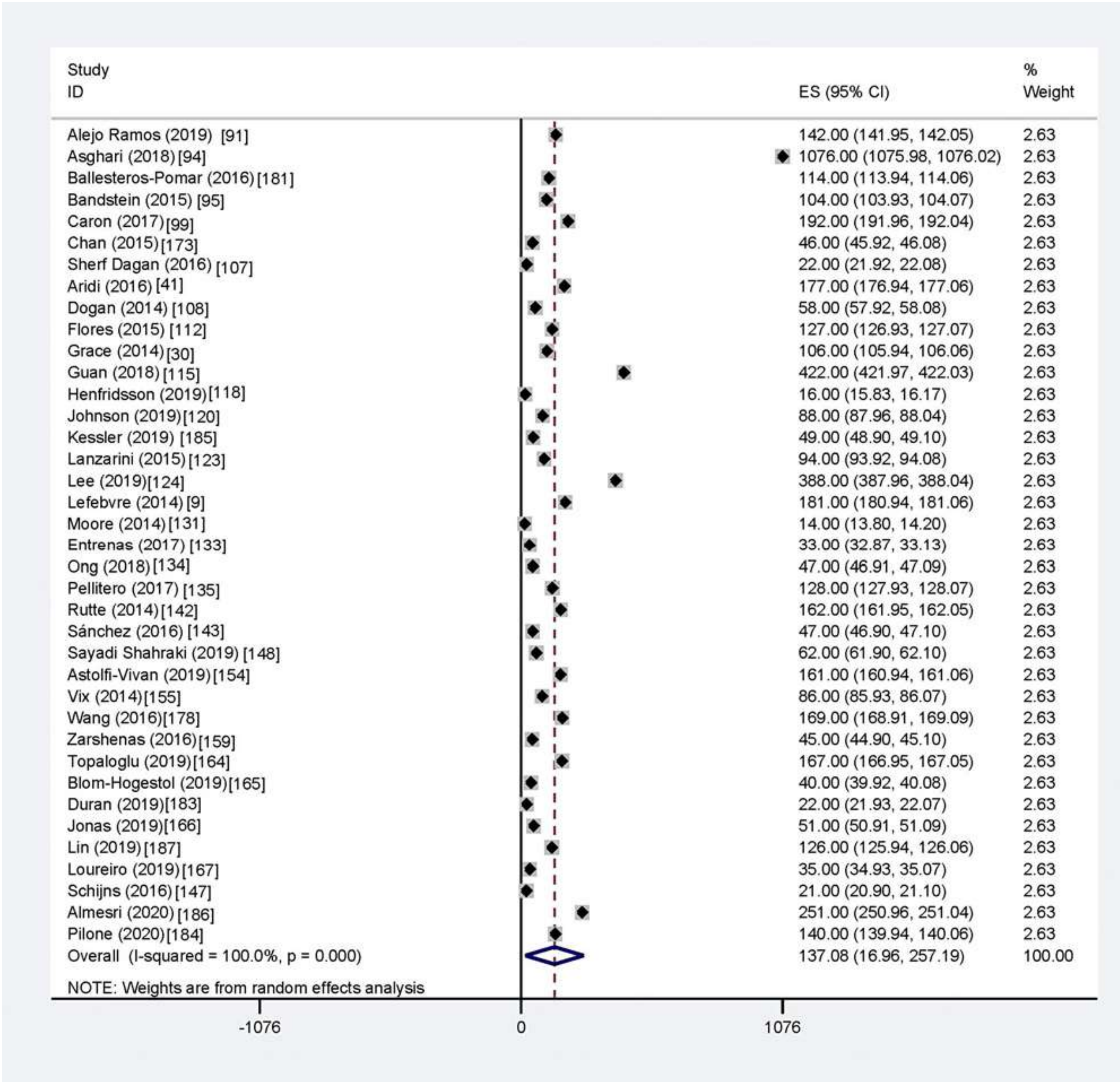
Table 1. Characteristics of the included studied evaluating vitamin D status of morbidly obese patients or bariatric surgery candidates

Author	Year	Country	Sex	Age, years	BMI	Sample size	Outcome
Alejo Ramos et al. [48]	2019	Spain	M/F	43.07	49.82	321	Vit D, PTH
Al-Mutawa et al. [49]	2018	Kuwait	M/F	35	46.1	1,793	Vit D
Arias et al. [50]	2019	Argentina	M/F	40.25	43.74	169	Vit D
Asghari et al. [51]	2018	Iran	M/F	37.8	37.8	2,008	Ca
Bandstein et al. [52]	2015	Switzerland	M/F	42.8	45.2	210	Vit D
Beckman et al. [53]	2013	USA	F	48	48	29	Vit D
Ben-Porat al. [54]	2017	Israel	M/F	39.8	45.2	27	Vit D, PTH
Bredella et al. [55]	2017	United States	M/F	49	43.9	21	Ca, Vit D, PTH
Caron et al. [56]	2017	Canada	M/F	48	48.1	537	Ca, Vit D, PTH
Carrasco et al. [57]	2014	Chile	F	33.5	40	43	Vit D, PTH
Carrasco et al. [58]	2018	USA	F	35	39.1	58	Ca, Mg, Vit D, PTH
Casella et al. [59]	2018	Italy	M/F	37	44.34	226	Ca, Vit D, PTH
Chereau et al. [60]	2017	France	M/F	46	44.9	48	Vit D
Cloutier et al. [61]	2018	Canada	M/F	40.4	45.9	20	Ca, Vit D, PTH
Coupaye et al. [62]	2014	France	M/F	45	48.5	86	Ca, Mg, Vit D, PTH
Cuesta et al. [63]	2014	Spain	M/F	42.28	44.1	178	Vit D
Sherf Dagan et al. [64]	2016	Israel	M/F	41.9	42.3	100	Vit D
Aridi et al. [41]	2016	Lebanon	M/F	39.7	43.1	257	Vit D
Dogan et al. [65]	2014	Netherlands	F	74	44.8	148	Ca, Mg, Vit D, PTH
Ducloux et al. [66]	2014	France	M/F	55.9	32.5	547	Vit D
Elhag et al. [67]	2018	Qatar	M/F	16	46.04	79	Ca, Mg, Vit D, PTH
Elias et al. [68]	2014	Finland	M/F	NS	42.65	63	Vit D, PTH
Flores et al. [69]	2015	Spain	M/F	44	46	176	Ca, Vit D, PTH
Ghiassi et al. [70]	2018	USA	M/F	50.8	48.4	96	Ca, Vit D, PTH
Gillon et al. [71]	2017	Norway	M/F	41	45.3	336	Ca, Vit D, PTH
Guan et al. [72]	2018	China	M/F	32	40.11	120	Ca, Mg, Vit D, PTH
Guglielmi et al. [73]	2018	Italy	M/F	40	48.5	42	Ca, Vit D, PTH
Smelt et al. [74]	2019	Netherlands	M/F	45	42.6	100	Ca, Vit D, PTH
Henfridsson et al. [75]	2019	Sweden	M/F	16.5	45.5	85	Ca, Vit D
Hultin et al. [76]	2018	Sweden	M/F	40	54.5	20	Ca, Vit D, PTH
Johnson et al. [77]	2019	Minnesota	M/F	43	45.75	468	Ca, Vit D, PTH
Karefylakis et al. [78]	2014	Sweden	M/F	49	43.4	293	Ca, Vit D, PTH
Kim et al. [79]	2014	Korea	M/F	45.8	32.9	33	Ca, Vit D
Lanzarini et al. [80]	2015	Spain	M/F	45.7	43	164	Vit D, PTH
Lee et al. [11]	2019	Singapore	M/F	40.6	42.4	577	Ca, Vit D, PTH
Luger et al. [81]	2015	Austria	M/F	46	45.4	50	Ca, Vit D, PTH
Luger et al. [82]	2017	Austria	M/F	42.2	43.8	50	Ca, Vit D, PTH
Luger et al. [83]	2018	Austria	M/F	42.2	43.8	50	Ca, Vit D, PTH
Malek et al. [84]	2019	Iran	M/F	37.4	45.7	170	Vit D
Menegati et al. [85]	2016	Brazil	F	38.9	52.2	25	Ca, Vit D, PTH
Mihmanli et al. [86]	2017	Turkey	M/F	37	49	119	Ca, Vit D, PTH
Moore et al. [87]	2014	USA	F	40.5	46.2	11	Vit D, PTH
Kosisochi et al. [88]	2014	USA	F	44.6	46.7	34	Ca, Mg, VitD, PTH
Entrenas et al. [89]	2017	Spain	M/F	41	45.5	46	Vit D
Ong et al. [90]	2018	Singapore	M/F	40.4	40.1	111	Ca, Vit D, PTH
Pellitero et al. [16]	2017	Spain	M/F	49.3	46.7	176	Ca, Vit D, PTH
Perin et al. [91]	2018	USA	M/F	43.1	46.2	47	Vit D
Marengo et al. [92]	2017	Spain	F	46.3	42.9	38	Ca, Vit D, PTH
Ben-Porat et al. [15]	2016	Israel	M/F	36.5	42.9	192	Vit D, PTH
Quraishi et al. [93]	2014	USA	M/F	47.2	47.2	385	Ca, Vit D, PTH
Raoof et al. [94]	2016	Sweden	F	41.6	44.5	32	Ca, Vit D, PTH
Rodríguez et al. [95]	2014	Spain	M/F	44.18	46.8	110	Vit D, PTH
Ruiz-Tovar et al. [96]	2013	SPAIN	M/F	43.6	51.2	42	Ca, Vit D, PTH

Table 1 (continued)

Author	Year	Country	Sex	Age, years	BMI	Sample size	Outcome
Rutte et al. [97]	2014	Netherlands	M/F	42.7	46.2	200	Ca, Mg, Vit D, PTH
Sánchez et al. [98]	2016	Chile	F	36	43.1	103	Ca, Vit D, PTH
Schaaf et al. [99]	2017	France	M/F	41.7	40.9	258	Vit D
Schafer et al. [100]	2016	USA	M/F	45.4	44.7	33	Vit D, PTH
Schijns et al. [101]	2018	Netherlands	M/F	46	44.2	569	Vit D
Schijns wt al. [102]	2016	Netherlands	M/F	47.1	44.7	75	Ca, Mg, Vit D, PTH
Shahraki et al. [103]		Iran	M/F	35.6	43.8	33	Vit D
Sundbom et al. [104]	2016	Sweden	M/F	39.7	42.7	26	Ca, Vit D, PTH
Svanevik et al. [105]	2019	Norway	M/F	40	53.4	56	Ca, Mg, Vit D, PTH
Santos et al. [106]	2018	Brazil	F	45	31.7	49	Vit D
Vilarrasa et al. [107]	2013	Spain	F	47.7	47.9	33	Ca, Vit D, PTH
Vinolas et al. [108]	2019	France	M/F	44	45.4	58	Mg, Vit D, PTH
Vivan et al. [39]	2019	Brazil	M/F	44.9	49.3	291	Ca, Vit D, PTH
Vix et al. [109]	2014	France	M/F	35.1	46	50	Vit D, PTH
Wei et al. [110]	2018	Taiwan	M/F	34.2	39.4	1,470	Ca, Vit D, PTH
Worm et al. [111]	2015	Denmark	M/F	43.3	47.2	417	Ca, Mg, Vit D, PTH
Yu et al. [112]	2015	USA	M/F	47	45	30	Ca, Vit D, PTH
Zarshenas et al. [113]	2016	Australia	M/F	51.9	42.8	91	Ca, Mg, Vit D, PTH
Zubiaga Toro et al. [114]	2014	Spain	F	47.7	50.4	50	Vit D
Lancha et al. [115]	2014	Spain	M/F	44	42	40	Ca, Vit D, PTH
Wolf et al. [116]	2015	Germany	M/F	46	45	38	Ca, Mg, Vit D, PTH
Peterson et al. [10]	2016	USA	M/F	42.6	46.3	58	Vit D
Topaloglu et al. [117]	2019	Turkey	M/F	38	44.3	199	Vit D
Blom-Hogestol et al. [118]	2019	Norway	M/F	50.3	35.6	122	Vit D
Jonas et al. [119]	2019	Poland	M/F	41.49	46.85	55	Vit D
Loureiro et al. [120]	2019	Brazil	M/F	38.86	42.9	223	Vit D
Ben-Porat et al. [17]	2019	Israel	M/F	36.5	42.4	722	Vit D
Ministrini et al. [121]	2020	Italy	M/F	43.5	45.5	152	Vit D
Damms-Machado et al. [14]	2012	Germany	M/F	44	51	54	Vit D
Belfiore et al. [122]	2015	Italy	M/F	34.9	45.9	47	Vit D
Capoccia et al. [123]	2012	Italy	M/F	43.9	44.4	138	Vit D
Toh et al. [124]	2009	Australia	M/F	46	51	188	Vit D
Chan et al. [125]	2015	USA	M/F	48	54.1	134	Vit.D
Grace et al. [30]	2014	UK	M/F	44	52.6	118	Vit.D, Ca
Salazar et al. [126]	2020	Portugal	M/F	41	43.6	290	Vit.D
Fox et al. [127]	2020	UK	M/F	48	50	460	Vit.D, Ca, PTH
Silveira et al. [128]	2021	Brazil	M/F	40	41	150	Vit.D
Pinto et al. [129]	2020	Brazil	M/F	38.7	42.3	50	Vit.D
Wang et al. [130]	2020	China	M/F	46	31.37	230	Vit.D, Ca, PTH
Altaw et al. [131]	2021	Saudi Arabia	M/F	31.3	44.95	143	Vit.D, Ca
Pellergini et al. [132]	2021	Italy	M/F	43.2	42.8	200	Vit.D, Ca, Mg
Ballesteros-Pomar et al. [133]	2016	Spain	M/F	43.2	50.1	299	Vit.D
Van der Beek et al. [134]	2015	Netherland	M/F	47.3	45.3	427	Vit.D
Duran et al. [135]	2019	Turkey	M/F	41.5	47.9	73	Vit.D
Pilone et al. [136]	2020	Italy	M/F	34.9	44.3	206	Vit.D
Kessler et al. [137]	2020	Israel	M/F	46.1	42.0	86	Vit.D
Almesri et al. [138]	2020	Bahrain	M/F	33.1	46	314	Vit.D
Lefebvre et al. [9]	2014	France	M/F	40.5	43.2	267	Vit.D
Lin et al. [139]	2011	USA	F	33.8	47.5	20	Vit.D
Moizé et al. [140]	2013	Spain	M/F	45.8	49.5	355	Vit.D
Nath et al. [141]	2019	USA	M/F	46.7	49.3	271	Vit.D
Wang et al. [142]	2016	China	M/F	33.3	39.3	211	Vit.D
Peterson et al. [143]	2018	USA	M/F	43	46.3	265	Vit D

LRYGB, laparoscopic Roux-en-Y gastric bypass; LSG, laparoscopic sleeve gastrectomy; AGB, adjustable gastric banding; BPD, biliopancreatic diversion.



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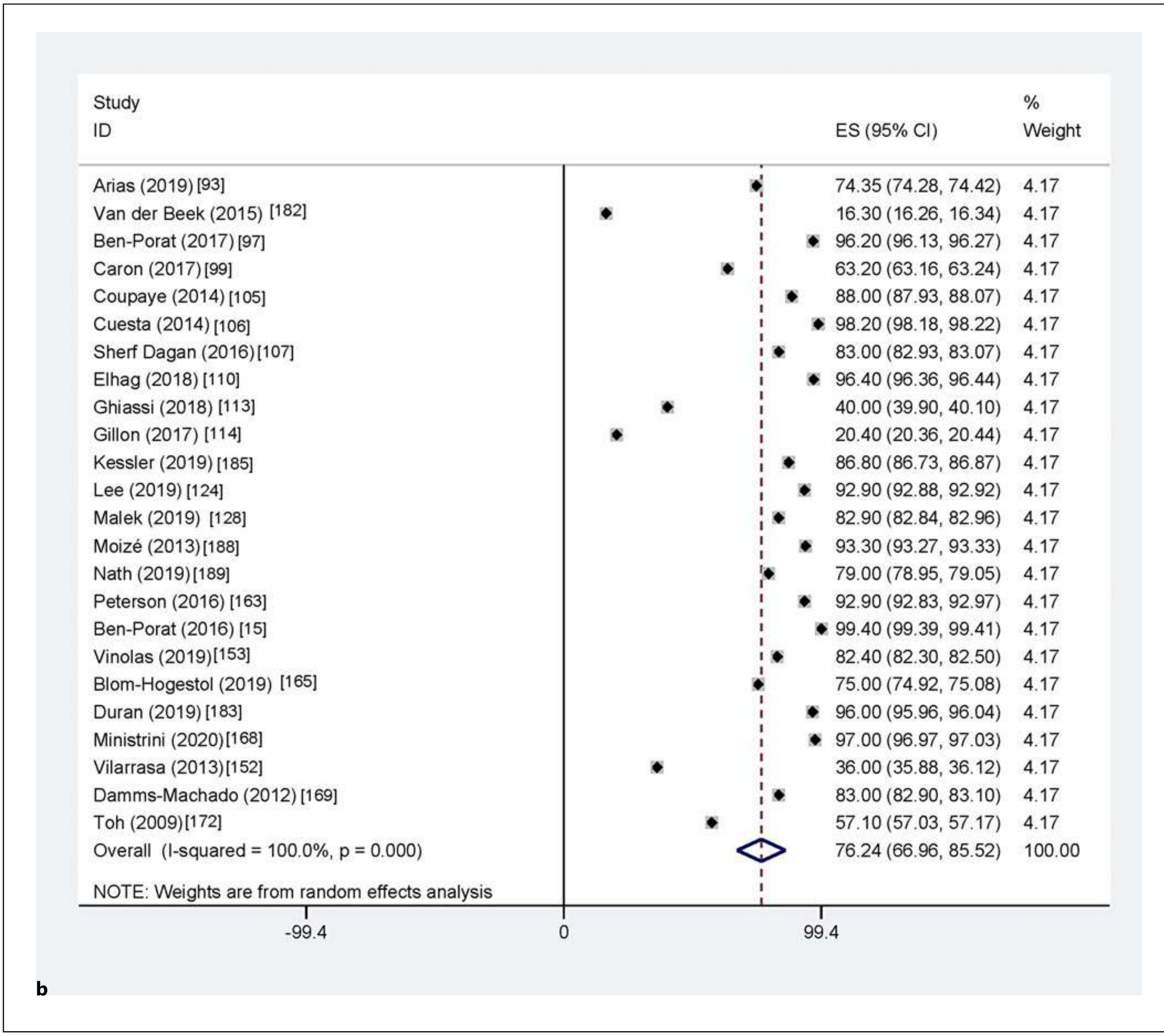
$I^2 = 100.0\%$, $p < 0.001$) (Fig. 3d). Subgroup analysis based on the geographical location determined that North America had the highest serum magnesium level estimate (1.44 mg/dL (0.77, 2.11) ($I^2 = 99.7\%$, $p = 0.000$ [Table 2]).

Sensitivity Analysis

According to the sensitivity analysis, omitting each individual study did not affect the result of the meta-analysis significantly.



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Discussion

This is the first systematic review and meta-analysis to evaluate vitamin D status and serum calcium, magnesium, and PTH in bariatric surgery candidates (severely obese people). Vitamin D status is essential for bone mineralization and muscle function, especially in patients with severe obesity who are at higher risk of deficiency before and after bariatric surgeries [41]. Vitamin D deficiency has been associated with increased risk of inflammatory diseases and also bone disease including rickets, osteomalacia, and osteoporosis [144]. According to the pooled estimates in the current meta-analysis, 59.44% of patients had vitamin D deficiency, and 26.95% had insufficiency. Considering the studies reporting deficiency + insufficiency, 76.24% had this condition. The pooled mean serum vitamin D was 18.65 ng/mL. Moreover, our subgroup analysis based on the geographical zones showed that the highest estimated vitamin D

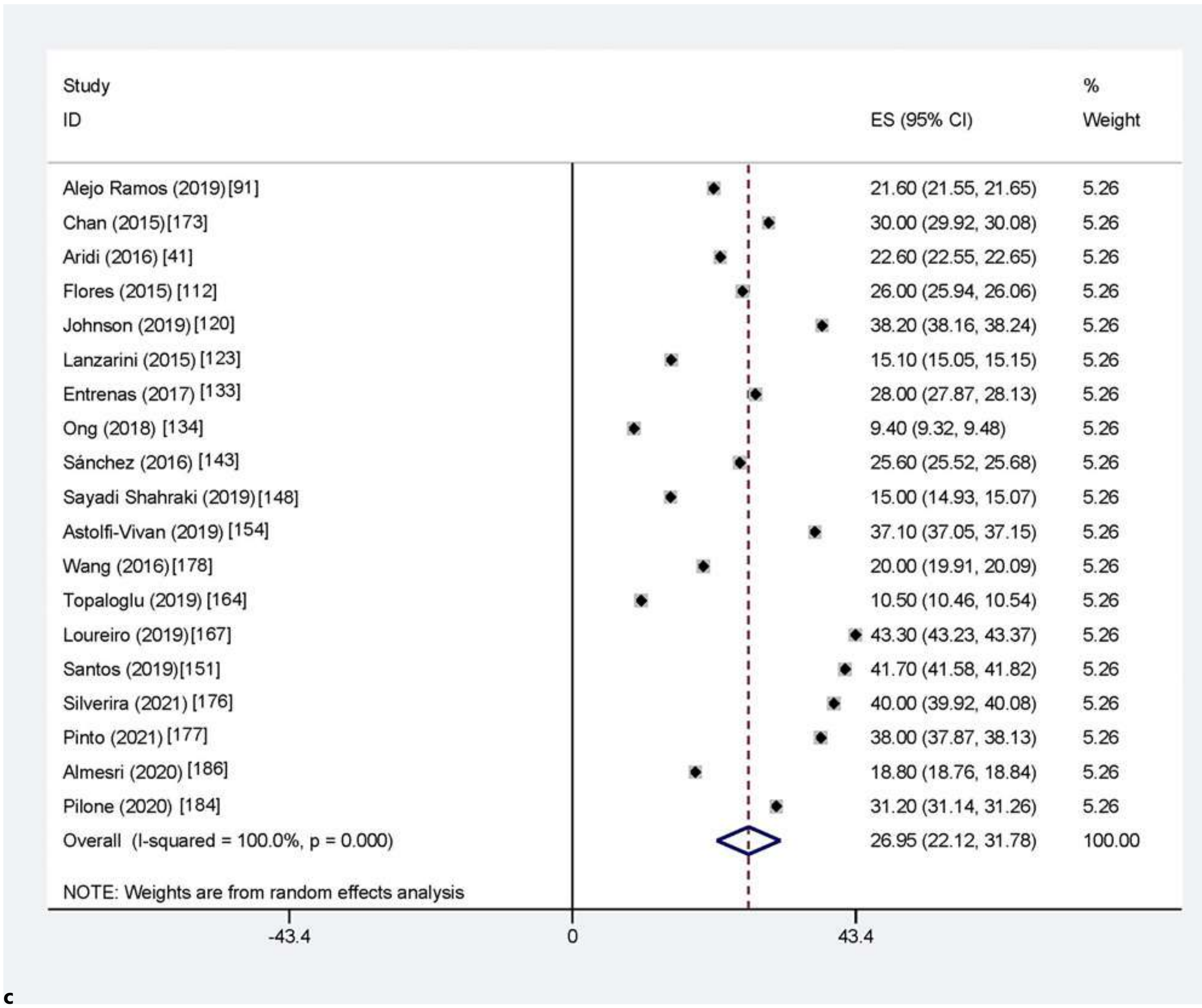
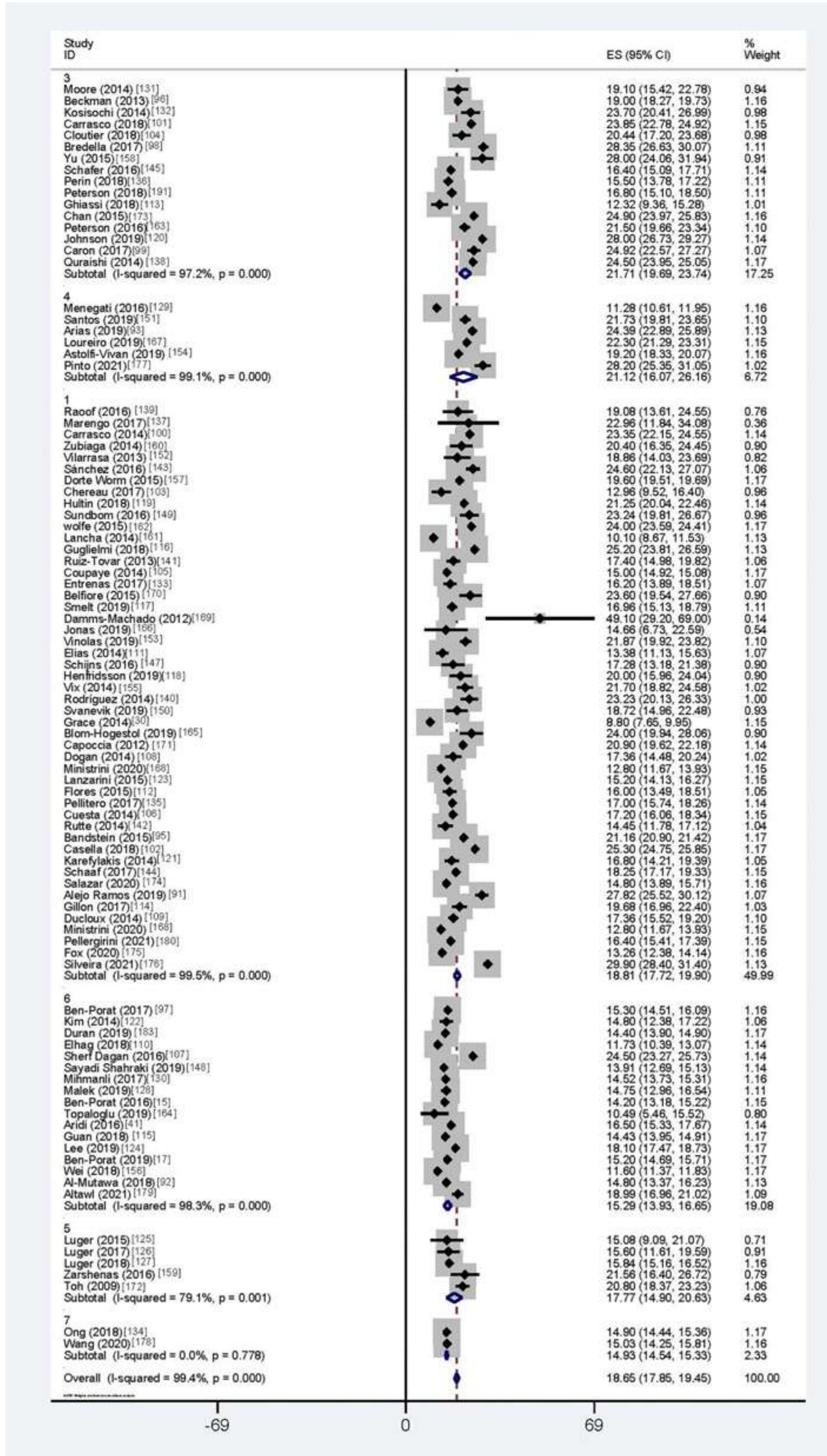


Fig. 2. Forest plots of the pooled prevalence estimate of vitamin D status in morbidly obese patients or bariatric surgery candidates, 25(OH)D <30 ng/mL (**a**), 25(OH)D <20 ng/mL (**b**), 25(OH)D 20–30 ng/mL (**c**).

levels were reported in North and South America, and the lowest levels were seen in Southeast Asia and the Middle East.

In accordance with our findings, a prior study reported a 57.4% deficiency of vitamin D (<20 ng/mL) in severely obese bariatric surgery candidates [38]. However, there was a higher prevalence of vitamin D deficiency in the black (78.4%) compared to white cohort (36.5%), which seems logical due to the higher skin pigmentation of the black individuals [38]. Skin pigmentation, such as melanin, absorbs the ultraviolet radiation that initiates vitamin D synthesis and hence decreases the amount of vitamin D that is made for a given exposure compared to less pigmented skin [145]. Our results are also in line with the previous investigations reporting more than 50% of vitamin D deficiency in patients with severe obesity [12, 18, 39, 40]. In regards to serum levels of vitamin D, some studies reported higher [39], while some reported lower levels [12, 18]. Variations between studies about the exact estimates of vitamin D deficiency prevalence or vitamin D concentrations can possibly be due to the differences among studies regarding population, geographical locations, seasonal variations, race, gender,



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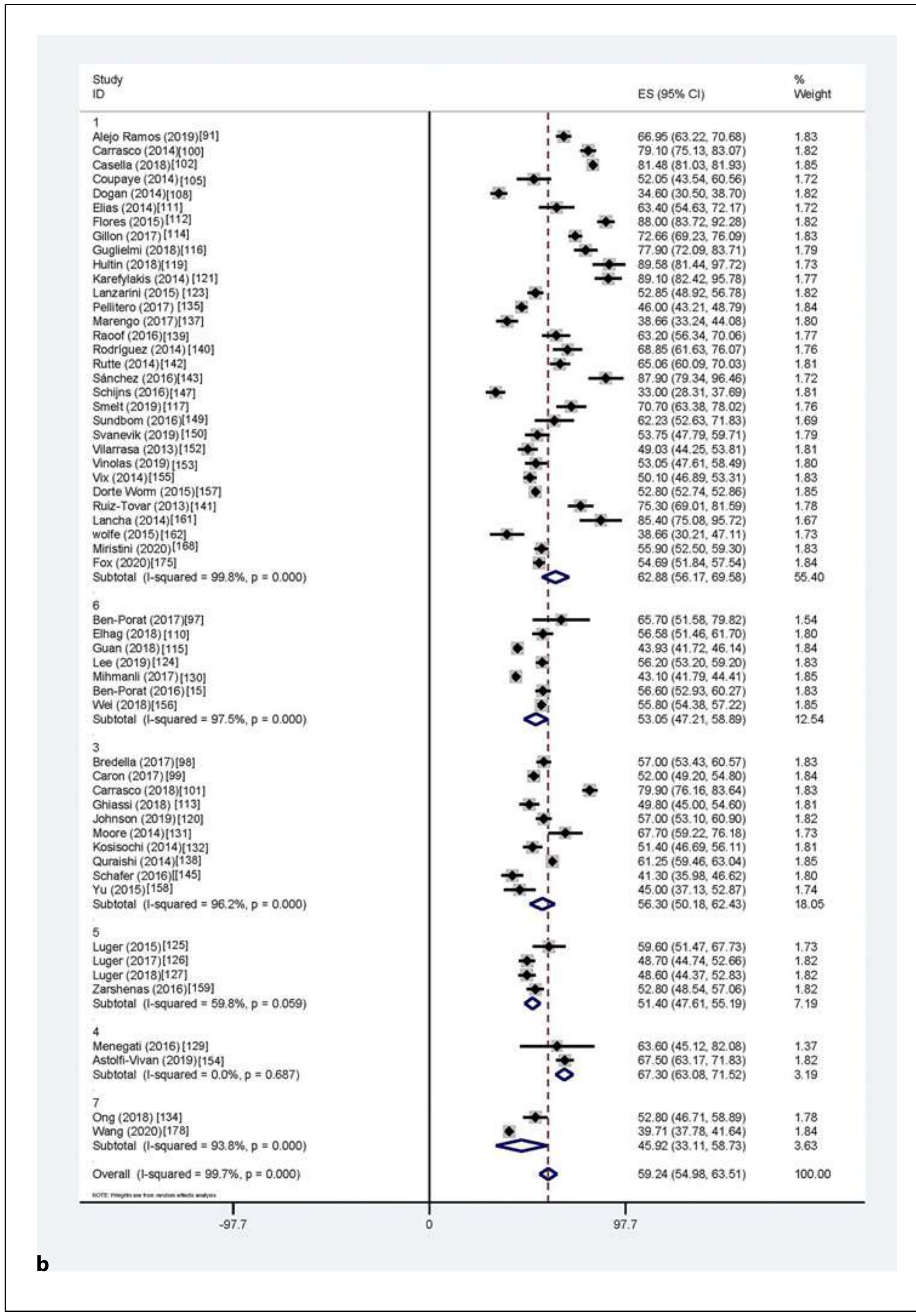

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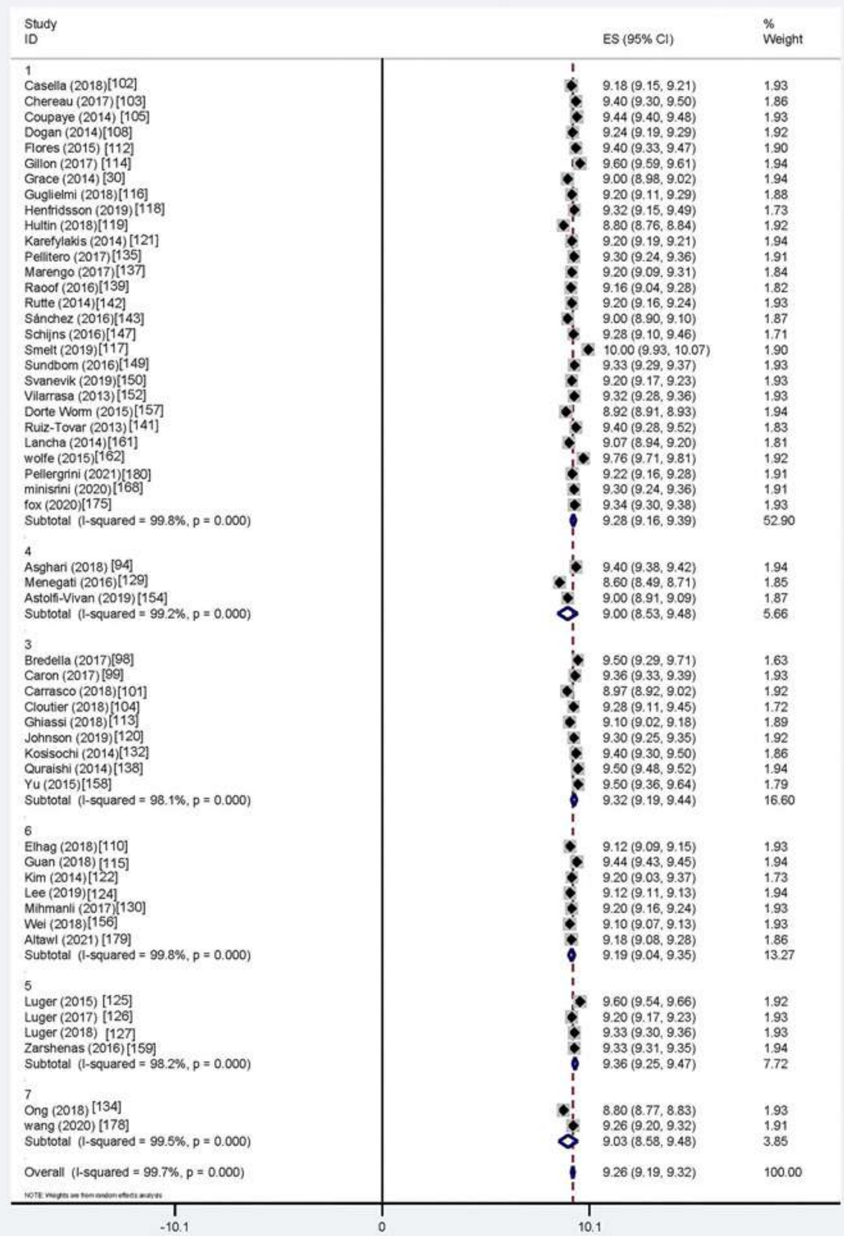
culture, religion, among others. On the other hand, the policy of different countries regarding food fortification can affect vitamin D intake and status in various regions [12]. For example, a large improvement in vitamin D status in different counties has been reported due to fortification of dairy products with vitamin D [146–148]. Moreover, fortification of fruit juice, flour, cooking oil, and rice showed positive results in improving vitamin D status [149–151]. Furthermore, different studies used various methods or laboratories for evaluating vitamin D status, and the results should be interpreted with caution [152].



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There are many potential causes for vitamin D deficiency in severely obese individuals. One of the most important ones is related to the less sun exposure of this group due to decreased outdoor activities [6, 20]. Another reason may be lower intakes of dietary sources of vitamin D, including fortified foods, in this population. On the other hand, vitamin D deficiency can emanate from vitamin D sequestration in the adipose tissue or uptake by this tissue in obese people [23–25, 153]. Further, it is hypothesized that fatty liver in severely obese people can impair liver vitamin D synthesis [12]. Nevertheless, due to its effects on bone mineralization and muscle function

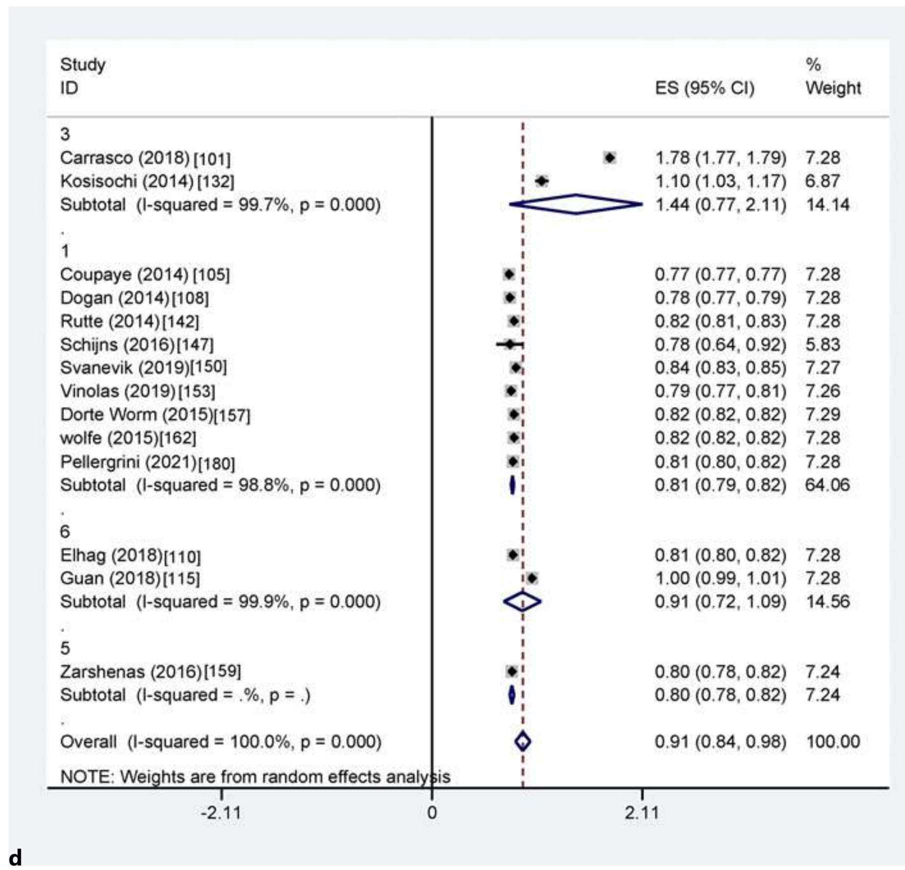

Fig. 3. Forest plots of the pooled mean estimates of serum 25(OH) D (**a**), PTH (**b**), calcium (**c**), and magnesium (**d**) in morbidly obese patients or bariatric surgery candidates (in subgroup analysis: 1: Europe, 2: Africa, 3: North America, 4: South America, 5: Australia, 6: Middle East, 7: Southeast Asia).

and its correlation with various diseases [26–37, 66], optimizing vitamin D status in patients with severe obesity is an essential component for the treatment of this condition, especially since these vitamin D deficiencies could worsen after bariatric surgery [12].

Our subgroup analysis revealed that lowest vitamin D levels were reported in Southeast Asia and the Middle East. Contrary to our findings, it was reported that vitamin D deficiency prevalence gradually increased in Southeast Asia due to the excellent sun exposure of the residents in these areas in the past. However, even in Southeast Asian countries with good sun exposure, many people have limited sun exposure due to lifestyle changes. These changes include fewer outdoor activities and better access to transportation. In addition, some traditional protections (masks, gloves, etc.), especially at the hotter times of the day (e.g., noon), may cause lower sun exposure [154]. On the other hand, vitamin D-rich foods are few, and they are not consumed frequently by Southeast Asian inhabitants [155]. Indeed, strong recommendations exist to improve vitamin D status in Southeast Asia through different strategies, including food fortification [154].

Regarding lower vitamin D concentration in the Middle East, it is reported that vitamin D deficiency and insufficiency can be seen frequently in the Middle East, despite year-round sunny days. The main reason for such observation is pertinent to the traditional attire of the population of this geographical area [156]. The clothing style in the Middle East can deteriorate vitamin D status as their clothes are different from the western style due to hijab and nigab [157–159]. Moreover, in many Middle East countries, outdoor physical activity is limited due to the hot and humid climate (such as Arab countries), and this can decrease sun exposure and adversely affect vitamin D status [41, 160]. Dietary factors and cultural beliefs can also affect vitamin D status and deficiency [156]. Lower calcium intake in the Middle East can also affect vitamin D status [156], which can cause rickets or secondary

Table 2. Subgroup analysis of the mean estimates of serum 25(OH)D, PTH, calcium and magnesium in morbidly obese patients or bariatric surgery candidates based on geographical zones

Subgroup	Included studies	Sample size	Pooled mean estimate	95% confidence interval	Heterogeneity I^2, %
Serum 25(OH)D, ng/mL, total	96	18,998	18.65	17.85, 19.45	99.4
Europe	50		18.94	17.86, 20.02	99.5
North America	16		21.71	19.69, 23.74	97.2
South America	6		21.12	16.07, 26.16	99.1
Australia	5		17.77	14.90, 20.63	79.1
Middle East	17		15.29	13.93, 16.65	98.3
Southeast Asia	2		14.93	14.54–15.33	0.0
Serum PTH, pg/mL, total	56	11,545	59.24	54.98, 63.51	99.7
Europe	31		62.88	56.17–69.58	99.8
North America	10		56.3	50.18–62.43	96.2
South America	2		67.3	63.08–71.52	0.0
Australia	4		51.4	47.61–55.19	59.8
Middle East	7		53.05	47.21–58.89	97.5
Southeast Asia	2		45.92	33.11–55.73	93.8
Serum calcium, mg/dL, total	53	13,355	9.26	9.19–9.32	99.7
Europe	28		9.28	9.16, 9.39	99.8
North America	9		9.32	9.19, 9.44	98.1
South America	3		9.00	8.53, 9.48	99.2
Australia	4		9.36	9.25, 9.47	98.2
Middle East	7		9.19	9.04, 9.35	99.8
Southeast Asia	2		9.03	8.58, 9.48	99.5
Serum magnesium, mg/dL, total	13	2,527	0.91	0.84, 0.98	100.0
Europe	9		0.81	0.79, 0.82	98.8
North America	2		1.44	0.77, 2.11	99.7
South America	–	–	–	–	–
Australia	–	–	–	–	–
Middle East	2		0.91	0.72, 1.09	99.9
Southeast Asia	–	–	–	–	–

hyperparathyroidism and eventually low bone mass density. Other factors affecting lower vitamin D levels in the Middle East include urban living and pollution [161]. Additionally, lower vitamin D supplementation and lower intakes of vitamin D-rich foods such as cod liver oil and oily fish are dietary factors associated with vitamin D deficiency in the Middle Easterners. Further, some genetic factors and polymorphisms related to vitamin D metabolism and degradation could adversely affect vitamin D status [152].

According to the current meta-analysis, another region with low vitamin D levels is Australia. According to Nowson et al. [162], the deficiency was more pronounced in dark-skinned people and veiled women. However, due to the lack of sun exposure in the winter, Australia's deficiency is more observed. Another problem that needs to be resolved in the region is making a balance between sun exposure and sunshine avoidance for skin cancer protection. In a nationally representative sample of Australian adults aged ≥25 years, one in five Australian resident (19% men; 21% women) were classified as vitamin D deficient, and 43% were classified as insufficient (45% men; 42% women) [163]. According to this study, independent predictors of vitamin D deficiency in Australia are being born in a country other than Australia or the main English-speaking countries, residing in southern (higher latitude) states of Australia, being assessed during winter or spring, being obese, smoking (women only), having low physical activity levels and not taking vitamin D or Ca supplements. According to the serum levels of vitamin D in the present study, average levels were somehow higher in Europe. In European countries, vitamin D status is better despite the deficiencies seen in some areas [152]. Large observational data have reported that almost 40% of Europeans are vitamin D deficient, and 13% are severely deficient [164]. This may vary by age, with lower levels in childhood and the elderly [165] as vitamin D deficiency is prevalent among older adults [166], and also ethnicity in different regions, for example, European Caucasians show lower rates of vitamin D deficiency compared with nonwhite individuals [164, 165]. Nordic countries in northern Europe encounter the lowest efficiencies of vitamin D due to the higher consumption of cod liver oil, supplements [167], and vitamin D-fortified foods [146]. However, poor vitamin D status was observed in the non-western immigrants in Europe [168–173].

The highest vitamin D levels were observed in severe obese cohorts in the South and North American regions. This observation is in agreement with the results of a previous systematic review about vitamin D deficiency in various age groups and genders [174]. According to their findings, the highest mean vitamin D status was generally observed in North America. Extensive food fortifications can justify higher vitamin D levels in North America than vitamin D in the USA (such as cereals, milk, and juice) [175]. Higher intake of vitamin D-fortified foods by obese individuals may be the main cause of higher vitamin D levels in severe obese cohorts.

In the current study, evaluating the pooled estimated serum levels of PTH in the included studies showed higher levels of PTH in the severely obese patients. However, the lowest average level was seen in the Southeast Asians. The highest average level was reported in those from South America which was higher than the normal range. Lower dietary intakes of calcium with decreased serum calcium levels can justify the higher levels of PTH in South American cohorts [176, 177], which can be detrimental for bone health.

It was previously reported that PTH levels are increased in severely obese people and are highly correlated with BMI [178]. Vitamin D deficiency is the major cause of higher PTH levels in this population [179]. Other than an increase in PTH before bariatric surgeries, an elevation could possibly happen in PTH levels following the surgeries. It may be related to the correlations between high PTH and metabolic syndrome, non-alcoholic steatohepatitis, and lower bone mineral density [180]. Consequently, optimizing serum levels of PTH by correcting serum calcium and vitamin D is crucial in severely obese bariatric surgery candidates.

Our outcomes showed that the pooled estimate of calcium levels was in the normal range. However, the lowest and highest levels were reported in South America and Australia. Literature in various populations reported lower dietary calcium intake and higher hip fractures in South America [181, 182]. In contrast, higher calcium intake has been described in Australia [181], which is in line with the serum levels of calcium reported for these regions in the present meta-analysis. The higher levels of serum calcium concentrations together with normal PTH levels in Australian severely obese individuals should be accompanied with optimal vitamin D levels to ensure bone health. However, our outcomes showed Australia is an area with low serum levels of vitamin D. Since there are a high number of bariatric surgeries in Australia [183], optimizing serum levels of vitamin D in severely obese bariatric surgery candidates seems essential.

Regarding serum magnesium levels, we established that pooled estimated magnesium level was in the normal range in severely obese bariatric surgery candidates. The higher levels were reported in North America, possibly due to adequate dietary intake, and are important for bone health. According to previous findings, obesity is not related to hypomagnesemia, and only dietary magnesium intake is related to serum magnesium levels in obese populations [184]. Most of obese individuals have high intakes of this essential nutrient in their diets [184].

The present meta-analytic work has some limitations that need to be acknowledged. For instance, the studies were only categorized according to the geographical zones for subgroup analysis as other variables were not completely accounted for (such as season of data collection). Moreover, the measurement methods of vitamin D and other values, cut-off points, limit values according to countries and regions were not the same. Furthermore, the effects of some health conditions on blood values were not considered in this study. Additionally, only few studies reported serum levels of PTH, calcium, and magnesium. Consequently, our results for these parameters should be interpreted with caution. Furthermore, we evaluated bariatric surgery candidates, and our results should not generalize to those not qualifying for surgery. On the other hand, numerous studies were included in the evaluation of vitamin D, which can be considered the main strength of this meta-analysis.

Conclusion

To sum up, this systematic review and meta-analysis pooled the results of vitamin D status and serum levels of PTH, calcium, and magnesium in severely obese bariatric surgery candidates. Vitamin D deficiency was observed in more than 50 percent of this population. More than 70 percent had deficiency+ insufficiency. The highest serum levels of vitamin D were reported in South and North America, possibly due to the effect of vast fortification, and the lowest were seen in Southeast Asia and the Middle East, which may be related to cultural and dietary factors. Pooled estimated serum levels of calcium and magnesium were in the normal range, and the lowest calcium levels were observed in South America. On the contrary, higher pooled estimated levels of PTH were also reported in severely obese people, and South Americans had the greatest concentrations. Due to the high prevalence of vitamin D deficiency and the risk of hyperparathyroidism before and after bariatric surgeries, optimizing vitamin D levels through better fortification and supplementation policies, especially in high-risk populations (such as Southeast Asia and the Middle East), is recommended for ensuring bone health and preventing some chronic diseases. Strategies for better sun exposure are recommended for all countries. On the other hand, appropriate dietary calcium and magnesium intake and early assessment of PTH levels are recommended for this population.

Statement of Ethics

An ethics statement is not applicable because this study is based exclusively on published literature. The protocol was previously published in the PROSPERO database (http://www.crd.york.ac.uk/PROSPERO), under registration no. CRD42019139937.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Neda Haghighat and Hamidreza Foroutan contributed to conceptualization, investigation, supervision, validation, visualization, medical oversight, and preparation of the original draft and final manuscript. Zahra Sohrabi, Reza Barati-Boldaji, Zahra Esmaeilnezhad, and Marzieh Akbarzadeh contributed to conceptualization, data extraction, visualization, and writing of the final manuscript. Morteza Zare contributed to formal analysis, methodology, software, and validation. Neda Haghighat, Reza Bagheri, and Damoon Ashtary-Larky contributed to investigation, conceptualization, visualization, and preparation of the original draft. Seyed Vahid Hosseini, Alexei Wong, and Masoud Amini contributed to conceptualization, supervision, validation, project administration, and critical revision of the draft and final manuscript. All the authors approved the final manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this manuscript. Further inquiries can be directed to the corresponding author.

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