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Vitamin D and bone health in adults: a systematic review and meta-analysis

Vitamina D e saúde óssea em adultos: uma revisão sistemática e metanálise

Kátia Josiany Segheto (https://orcid.org/0000-0003-4605-0823) [1]
Marcos Pereira (https://orcid.org/0000-0003-3766-2502) [2]
Danielle Cristina Guimarães da Silva (https://orcid.org/0000-0001-5456-0853) [3]
Cristiane Junqueira de Carvalho (https://orcid.org/0000-0001-8574-6669) [4]
Felipe Ribeiro Massardi (https://orcid.org/0000-0003-4630-6948) [4]
Adriana Maria Kakehasi (https://orcid.org/0000-0001-9411-7493) [5]
Leidjaira Lopes Juvanhol (https://orcid.org/0000-0001-8012-6006) [1]
Giana Zarbato Longo (https://orcid.org/0000-0001-7666-5007) [6]

Abstract *Low bone health is associated with vitamin D deficiency in older individuals; however, this association is not well established in adults. The aim of the study was to analyze the association between serum concentrations of 25-hydroxyvitamin D and bone health in adults by systematic review and meta-analysis. The search was carried out in the LILACS, PubMed, Scopus, Web of Science, ScienceDirect databases from March 2017 to October 2018 with adult individuals (20-59 years). Bone health was evaluation performed through dual X-ray absorptiometry and serum concentrations of 25(OH)D. The random effect model was used to analyze data from bone mineral content and bone mineral. Random effects models were used and the sources of heterogeneity were explored by means of meta-regression. Thirty-five articles were selected. There was positive correlation between vitamin D and bone health in most of the evaluated sites. Correlation was observed in the analysis of subgroups for lumbar spine among men. When stratified, the studies presented high heterogeneity, which was explained by the sample size, mean serum vitamin D levels and risk of bias. Vitamin D is positively correlated to bone health in adult individuals.*

Key words *Mineral density, Vitamin D, Adults*

Resumo *A baixa saúde óssea está associada à deficiência de vitamina D em indivíduos mais velhos; no entanto, isso não está bem estabelecido em adultos. O estudo objetivou-se analisar a associação entre concentrações séricas de 25-hidroxivitamina D e baixa saúde óssea em adultos por revisão sistemática e metanálise. A pesquisa foi realizada nas bases LILACS, PubMed, Scopus, Web of Science, ScienceDirect de março de 2017 a outubro de 2018 com indivíduos adultos (20-59 anos). A avaliação da saúde óssea foi realizada através da absorciometria dupla de raios X e concentrações séricas de 25(OH)D. O modelo de efeito aleatório foi utilizado para analisar dados do conteúdo mineral ósseo e densidade mineral óssea. Modelos de efeitos aleatórios foram utilizados e a heterogeneidade foi explorada por meio de meta -regressão. Trinta e cinco artigos foram selecionados. Houve correlação positiva entre a vitamina D e a saúde óssea na maioria dos locais avaliados. Observou-se correlação na análise de subgrupos da coluna lombar entre homens. Quando estratificados, os estudos apresentaram alta heterogeneidade, explicada pelo tamanho da amostra, pelos níveis séricos médios da vitamina e pelo risco de viés. A vitamina D está positivamente correlacionada com a saúde óssea em indivíduos adultos.*

Palavras-chave *Densidade mineral, Vitamina D, Adultos*

[1] Departamento de Nutrição e Saúde, Universidade Federal de Viçosa (UFV). Ed. Centro de Ciências Biológicas II s/n, Campus Universitário. 36570-900 Viçosa MG Brasil. kaseghetto@gmail.com
[2] Instituto de Saúde Coletiva, Universidade Federal da Bahia. Salvador BA Brasil.
[3] Centro das Ciências Biológicas e da Saúde, Universidade Federal do Oeste da Bahia. Barreiras BA Brasil.
[4] Departamento de Medicina e Enfermagem, UFV. Viçosa MG Brasil.
[5] Faculdade de Medicina, Universidade Federal de Minas Gerais. Belo Horizonte MG Brasil.
[6] Departamento de Nutrição, Universidade Federal de Santa Catarina. Florianópolis SC Brasil.

Introduction

Over the last four decades there have been epidemiological and sociodemographic changes, with significant repercussions on living conditions and on the burden of chronic non-communicable diseases which constitute a global health problem[1]. Among the most common, the World Health Organization (WHO) has highlighted those related to complications arising from low bone mass, such as osteoporosis[2].

Osteoporosis is defined as a progressive, skeletal disease characterized by alterations in microarchitecture and consequent bone fragility[2]. This is an asymptomatic disease, usually identified when the individual presents a fracture, not only bringing damage in relation to the biological aspects, but also to the quality of life, as well as contributing to the increase in mortality and overloading the public health system due to the need for continued care[2-4].

The evolution of osteoporosis and associated fractures are conditioned by some risk factors[5-10], which lead to an osteometabolic imbalance caused by the deficiency of essential nutrients to maintain active bone metabolism, with the main nutrients being calcium and vitamin D[7,11,12].

Vitamin D plays a determining role in the initial stages of skeletal development[12,13], constituting a factor for preventing rickets and osteomalacia[14]. However, in adulthood there are still controversies regarding the relationship between this vitamin and low bone mineral density (BMD) and bone mineral content (BMC), which are biophysical parameters used to assess bone health[15,16]. Some studies report a positive association[17,18], while others suggest that these are not correlated[19,20].

Considering the controversial results of studies on the influence of serum vitamin D levels on bone metabolism in adults and that vitamin D deficiency has been presented as a global public health problem, it is necessary to summarize the available evidence on the subject. In addition, there are few systematic review studies with a meta-analysis employing this approach in adults[21,22]. Thus, the objective of this systematic review was to analyze the association between serum concentrations of 25-hydroxyvitamin D (25(OH)D) and BMC and BMD in adults.

Methods

This is a systematic review study with meta-analysis supported by the PRISMA rules (Preferred Reporting Items for Systematic reviews and Meta-Analyses)[23] on the relationship between vitamin D and BMD/BMC in adults. In this perspective, we sought to answer the following question: are serum concentrations of 25(OH)D associated with BMC and BMD in adults?

Search strategy

Two independent reviewers (KJ Segheto and M Pereira) conducted study searches in the LILACS, PubMed, Scopus, Web of Science and ScienceDirect electronic databases from March 2017 to October 2018, with the following descriptors/Mesh terms: "vitamin D", "bone density", "BMD", "BMC", "adult" and "observational study" and their respective corresponding terms in Portuguese and Spanish. The search strategy included truncating the terms to exclude texts which did not fit the objectives of this review, such that they were adjusted according to the search form of each database (Chart 1).

The search results were managed in the Mendeley® program to remove duplicates and apply the inclusion criteria. The manuscript titles were initially read and then the abstracts of those publications which fulfilled the inclusion criteria. Once the articles were selected, the reading was completed in full. The last selection stage was an analysis of the references of the original articles and the identified revisions, thus guaranteeing refinement in searching for relevant works for this review.

The whole selection and evaluation process of the articles was done in pairs. At the end of the review, disagreements on eligibility were resolved by consensus with a third reviewer (CJ Carvalho).

Eligibility criteria

The articles selected for this review had to meet the following eligibility criteria: original studies whose objective was to analyze the association between 25(OH)D and BMC and/or BMD, performed with adult individuals aged 20 to 59 years of age, having no association to diseases, with bone health evaluation performed through dual X-ray absorptiometry (DXA) and serum concentrations of 25(OH)D.

Chart 1. Database search strategies and results.

Database	Search Strategy	Items Found
PubMed http://www.ncbi.nlm.nih.gov/pubmed	"vitamin D "[MeSH Terms] AND "Bone Density"[MeSH Terms] AND "Adult"[MeSH Terms] AND (("2000/01/01"[PDAT]: "3000/12/31"[PDAT]) AND "humans"[MeSH Terms])	1980
Web of science http://apps-webofknowledge.ez	#1 (TI= (bone density AND vitamin D AND adult)) AND TIPOS DE DOCUMENTO: (Article) Índices=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Tempo estipulado=2000-2018 = 12#2 TI= (TI = (vitamin D AND bmd OR bmc AND adult)) AND TIPOS DE DOCUMENTO: (Article)Índices=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Tempo estipulado=2000-2018 =15 #2 OR #1=26	26
Scopus http://www.scopus.com/	TITLE-ABS-KEY ("vitamin D " AND "bone density" OR bmd OR bmc AND adult AND " Observational Study") AND (LIMIT-TO (PUBYEAR , 2018) OR LIMIT-TO (PUBYEAR , 2017) OR LIMIT-TO (PUBYEAR , 2016) OR LIMIT-TO (PUBYEAR , 2015) OR LIMIT-TO (PUBYEAR , 2014) OR LIMIT-TO (PUBYEAR , 2013) OR LIMIT-TO (PUBYEAR , 2012) OR LIMIT-TO (PUBYEAR , 2011) OR LIMIT-TO (PUBYEAR , 2010) OR LIMIT-TO (PUBYEAR , 2009) OR LIMIT-TO (PUBYEAR , 2008) OR LIMIT-TO (PUBYEAR , 2007) OR LIMIT-TO (PUBYEAR , 2006) OR LIMIT-TO (PUBYEAR , 2005) OR LIMIT-TO (PUBYEAR , 2004) OR LIMIT-TO (PUBYEAR , 2003) OR LIMIT-TO (PUBYEAR , 2002) OR LIMIT-TO (PUBYEAR , 2001) OR LIMIT-TO (PUBYEAR , 2000))	214
Science Direct http://www.sciencedirect.com/	"vitamin D " AND "Bone Density" AND "Adult" AND "Observational Study"	222
LILACS http://lilacs.bvsalud.org/	(tw:(Vitamin D)) OR (tw:(Vitamina D)) AND (tw:(Bone Density)) OR (tw:(Densidad Ósea)) OR (tw:(Densidad Ósea)) AND (tw:(Adult)) OR (tw:(Adult))	120

Source: Elaborated by the authors.

In this study, it was decided to evaluate the serum concentrations of 25(OH)D because they are the best indicator of this vitamin[24]. Thus, studies that included individuals with vitamin D supplementation were excluded. In addition, serum concentrations of 25(OH)D were converted when necessary using the following criteria: 1ng/ml=2.496 nmol/l (24). In this way, it was possible to guarantee standardization and comparison of the presented results.

Data extraction

Eligible articles were read in full and information on the year of study publication, sample size, type of study, vitamin D results, correlation coefficient and/or linear regression and fit variables used in the modeling were registered in specific form.

Risk of bias

The risk of bias of the studies was individually assessed through the Research Triangle Institute Item Bank (RTI-Item Bank) scale[25]. This scale is composed of 29 questions, among which 7 items were selected to assess the risk of bias of the articles due to the methodological diversity of the designs of observational studies. After the analysis, the risk of bias was classified as: high risk of bias – a study with one or more negative answers to the items; moderate risk of bias – when one or more items were considered "partially" or "cannot be determined"; and low risk of bias - all items on the scale had a positive response[25] (Chart 2).

Chart 2. Assessment of bias risk using RTI Item Bank for the studies included in the meta-analysis.

Authors/Year	Question Numbers							Overall Judgment on Risk of Bias
	Q1	Q2	Q3	Q4	Q5	Q6	Q7	
Sherman et al., 1992	+	+	+	+	+	+	-	High
Brot et al., 1999	+	+	+	+	+	+	-	High
Güller et al., 2007	-	-	+	-	+	+	-	High
Lamberg-Allardt et al., 2001	+	+	+	+	+	+	-	High
Guzel et al., 2001	+	+	+	+	+	+	-	High
Tandon et al 2003	-	-	+	-	+	+	+	High
Bischoff- Ferrari et al., 2004	-	-	+	+	+	+	+	High
Saadi et al., 2006	+	+	+	-	+	+	-	High
Islam et al., 2008	+	+	+	-	+	+	-	High
Marwaha et al., 2009	+	+	+	-	+	+	+	High
Allali et al., 2009	+	+	+	-	+	+	+	High
Adami et al., 2009	+	+	+	+	+	+	+	Low
Multani et al., 2010	+	+	+	-	+	+	+	High
Gutiérrez et al., 2011	+	+	+	+	+	+	+	Low
Sadat-Ali et al., 2011	+	+	+	-	+	+	-	High
Harinarayan et al., 2011	+	+	+	-	+	+	-	High
Powe et al., 2011	-	-	+	+	+	+	+	High
Nakamura et al., 2001	-	-	+	-	+	+	+	High
Shivane et al., 2012	+	+	+	+	+	+	+	Low
Lim et al., 2012	+	+	+	+	+	+	+	Low
Kassi et al., 2015	+	+	+	-	+	+	+	High
Khashayar et al., 2016	+	+	+	+	+	+	-	High
Sayed-Hassan et al., 2014	+	+	+	-	+	+	+	High
Hannan et al., 2008	+	+	+	+	+	+	+	High
Arya et al., 2004	+	?	+	+	+	+	+	Moderate
Högström et al., 2006	+	+	+	+	-	+	+	High
Frost et al., 2010	+	+	+	+	+	+	+	Low
Boot et al., 2011	+	+	+	+	-	+	+	High
Kull et al., 2012	+	+	+	+	+	+	+	Low
Joo et al., 2013	+	+	+	+	+	+	+	Low
George et al., 2014	-	+	+	+	+	+	+	High
Wei et al., 2015	+	+	+	+	+	+	+	Low
Zhang et al., 2016	-	+	+	+	+	+	+	High
Callegari et al., 2017	-	+	+	+	+	+	+	High
Ardawi et al., 2012	+	+	+	+	+	+	+	Low

+ = low risk of bias; - = high risk of bias; ? = clear risk of bias. Q1 - Does the article clearly state its own inclusion/exclusion criteria (i.e. it does not require the reader to deduce)? Q2 - Did the study apply inclusion/exclusion criteria uniformly to all study comparison groups? Q3 - Was the strategy to recruit study participants the same across study groups? Q4 - Is the sample appropriate? Q5 - Are the inclusion/exclusion criteria measured using valid and reliable measures? Q6 - Are results evaluated using valid and reliable measures, consistently implemented in all study participants? Q7 - Were confounding and effect modifying variables taken into account in the design and/or analysis (e.g., by correspondence, stratification, interaction terms, multivariate analysis or other statistical adjustment)?

Source: Elaborated by the authors.

Statistical analysis

Correlation coefficients and sample size were used to calculate the standard error to evaluate the correlation between 25(OH)D and bone health. The Z-test was used to analyze the data for the following bone sites: BMC, lumbar spine BMD (LS-BMD), hip (H-BMD), femoral neck (FN-BMD) and trochanter (T-BMD). The Cochran Q statistical test and the inconsistency test (I^2)[25] were used to evaluate the heterogeneity and consistency of the studies. When heterogene-

ity (I^2>25%) was identified, the random effects model was used[26].

The publication bias was evaluated through the funnel plot symmetry[26]. The statistical evaluation of the effect of small studies was performed by the Egger test[27]. The criterion for the application of these tests was the minimum number of eight studies. Gender-based subgroup analysis was also performed to identify possible sources of heterogeneity. The overall effect was derived from the DerSimonian and Laird method[26], using the random effects model, which takes into account the variation between the studies.

In addition to gender, meta-regressions were performed considering the following variables: age, group evaluated (1-men, 2-women, 3-men and women), sample size, mean concentration serum levels of vitamin D, latitude and longitude of the study site, and risk of bias score of each study. The results obtained from the correlation between vitamin D and bone health in adults are presented using a Forest Plot chart. A p-value less than 0.05 was considered significant in all analyzes. The STATA 14 program (Stata Corp, College Station) was used for data analysis.

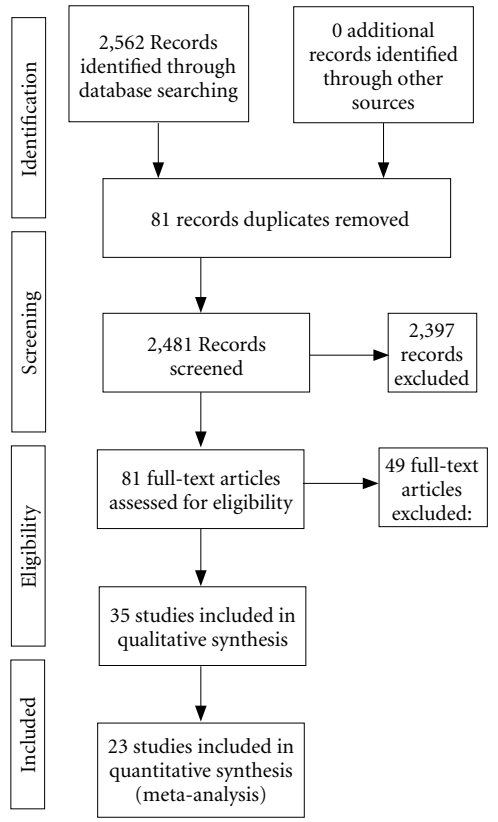

Figure 1. Identification and selection flowchart for articles. BMC: Bone mineral content; BMD: bone mineral density; DXA: Double X-ray Absorptiometry; 25(OH)D: 25-Hydrovitamin D.

Source: Elaborated by the authors.

Results

Characterization of the selected studies

A total of 2,562 articles were identified and 2,397 were excluded by reading the title and abstract, and thus 84 articles were selected for reading in full (Figure 1). In the end, 35 articles were included in the qualitative synthesis[17,18,20,28-59], and those that presented a linear correlation coefficient as a measure of association were included in the meta-analysis, totaling 23 articles[18,20,28,29,33,35-43,47,49,51-53,55-58] (Figure 1). The main reasons for exclusion of the complete articles were the age group not corresponding to the studied age group (n=26), no evaluation of the influence of vitamin D concentration on BMC/BMD (n=9), participants in the study with associated diseases (n=6), review study (n=4), pregnancy (n=1), letter to the Editor (n=1), did not use the DXA to evaluate bone health (n=1), and did not evaluate 25(OH)D (n=1) (Figure 1, Chart 3).

All the studies included in this review have a cross-sectional design. We included studies with year of publication from 1992 to 2017, most of which were published between 2011-2015 (37.1%)[43-55]. Most of the studies were carried out in Asian countries (48.6%)[17,18,20,32,33,40,42,45,47,48,50-52,55-58] and with a sample consisting of up to 500 individuals (42.8%)[17,20,28,31,40,42,43,45,47,49,53-55,57,59]. There was a predominance of studies with individuals of both genders (51.4%)[28,31-34,42-44,46,47,49-53,55-57]. Articles that evaluated only women corresponded to 28.6% of the studies[17,18,20,29,30,36,38,39,45,59] and only men at 20%[35,37,40,41,48,54,58]. In addition to BMC (2 5.7%)[17,18,29,35,43,44,49,53,59], there was a predominance of studies which evaluated the following bone sites: LS-BMD (85.7%)[17,20,28-30,32,33,35-43,46-52,54-59], FN-BMD (80%)[17,28-30,32,33,36-43,45,47-59], H-BMD (65,7%)[20,29,32,34-42,45,47,49,50-53,56-59] and T-BMD (42.8%)[17,29,32,33,36,37,39,40,42,45,47,49-51,56]. Among the adjustment variables identified in articles using multiple linear regression, the most frequent were age (40%)[29,34,35,37-41,44,46,49,52,55,58], gender (25 .7%)[28,31,32,34,43,44,46,51,57], height (20%)[29,35,37,40,52,57,59] and total body mass (20%)[18,29,35,34,40,52,57] (Table 1).

Chart 3. Reasons for study exclusion.

Age range
1. Saliba W, Barnett-Griness O, Rennert G. Obesity and Association of Serum 25(OH)D Levels with All-Cause Mortality. *Calcif Tissue Int* 2014; 95(3):222-228.
2. Viljakainen HT, Saarnio E, Hytinantti T, Miettinen M, Surcel H, Mäkitie O, Andersson S, Laitinen K, Lamberg-Allardt C. Maternal Vitamin D Status Determines Bone Variables in the Newborn. *J Clin Endocrinol Metab* 2010; 95(4):1749-1757.
3. McConda DB, Boukhemis KW, Matthews LJ. Watkins CM. Bone mineral density and vitamin D level compared to lifestyle in resident physicians. *W V Med J* 2016; 112(4):32-37.
4. Hamson C, Goh L, Sheldon P, Samanta A. Comparative study of bone mineral density, calcium, and vitamin D status in the Gujarati and white populations of Leicester. *Postgrad Med J* 2003; 79(931):279-283.
5. Diamond TH, Levy S, Smith A, Day P. High bone turnover in Muslim women with vitamin D deficiency. *Med J Aust* 2002; 177(3):139-141.
6. Ahuja M. Normal variation in the density of selected human bones in north India: a necropsy study. *J Bone Joint Surg Br* 1969; 51(4):719-735.
7. Kim BK, Choi YJ, Chung YS. Other than daytime working is associated with lower bone mineral density: the Korea National Health and Nutrition Examination Survey 2009. *Calcif Tissue Int* 2013; 93(6):495-501.
8. Goswami R, Gupta N, Goswami D, Marwaha RK, Tandon N, Kochupillai N. Prevalence and significance of low 25-hydroxyvitamin D concentrations in healthy subjects in Delhi. *Am J Clin Nutr* 2000; 72(2):472-475.
9. Yeum K-J, Song BC, Joo N-S. Impact of Geographic Location on Vitamin D Status and Bone Mineral Density. *Int J Environ Res Public Health* 2016; 13(2):184.
Associated diseases
10. Kantorovich V, Gacad MA, Seeger LL, Adams JS. Bone mineral density increases with vitamin D repletion in patients with coexistent vitamin D insufficiency and primary hyperparathyroidism. *J Clin Endocrinol Metab* 2000; 85(10):3541-3543.
11. Dietrich T, Joshipura KJ, Dawson-Hughes B, Bischoff-Ferrari HA. Association between serum concentrations of 25-hydroxyvitamin D3 and periodontal disease in the US population. *Am J Clin Nutr* 2004; 80(1):108-113.
12. Silva BCC, Camargos BM, Fujii JB, Dias EP, Soares MMS. Prevalence of vitamin D deficiency and its correlation with PTH, biochemical bone turnover markers and bone mineral density, among patients from ambulatories. *Arq Bras Endocrinol Metabol* 2008; 52(3):482-488.
13. Wöfl C, Englert S, Moghaddam AA, Zimmermann G, Schmidt-Gayk G, Höner B, Hogan A, Lehnhardt M, Grützner PA, Kolios L. Time course of 25(OH)D3 vitamin D3 as well as PTH (parathyroid hormone) during fracture healing of patients with normal and low bone mineral density (BMD). *BMC Musculoskelet Disord* 2013; 14:6.
14. Perry HM 3rd, Horowitz M, Morley JE, Fleming S, Jensen J, Caccione P, Miller DK, Kaiser FE, Sundarum M. Aging and bone metabolism in African American and Caucasian women. *J Clin Endocrinol Metab* 1996; 81(3):1108-1117.
15. Hwang S, Choi HS, Kim KM, Rhee Y, Lim SK. Associations between serum 25-hydroxyvitamin D and bone mineral density and proximal femur geometry in Koreans: the Korean National Health and Nutrition Examination Survey (KNHANES) 2008-2009. *Osteoporos Int* 2015; 26(1):163-171.

it continues

Results of individual studies

Regarding the statistical test, it was observed that most of the articles evaluated the associations by linear correlation (n=27)[20,28-30,32,33,36,37,39-43,45-47,49-59]. The majority of studies identified a positive correlation between 25(OH)D and bone health for both men (n=5)[37,41,48,52,58] and for women (n=8)[17,18,29,36,38,39,47,56]. The bone site most frequently evaluated in men was LS-BMD (n=17)[20,40,37,51,52,54,58], while among women it was FN-BMD (n=12)[28-30,32,36,39,42,45,55-57,59].

Risk of Bias Results

We performed the risk assessment of individual bias of each study included in the review (Chart 2). We observed that 71.4% articles presented a high risk of bias[17,18,28-32,34-37,40,42,43,45-47,53,54,57-59]. Only 25.7% were identified as having moderate risk of bias[,41,44,48-52,55] and 2.8% with low risk of bias[33].

The main aspects that contributed to the high risk of bias were: uniform inclusion and exclusion criteria; valid outcome evaluation, appropri-

Chart 3. Reasons for study exclusion.

Age range
16. Zhang M, Li Y, Ma Q, Mao W, Gao Y, Liu Y, Liang B. Relevance of parathyroid hormone (PTH), vitamin 25(OH)D3, calcitonin (CT), bone metabolic markers, and bone mass density (BMD) in 860 female cases. *Clin Exp Obstet Gynecol* 2015; 42(2):129-132.
17. Fradinger EE, Zanchetta JR. Vitamin D and bone mineral density in ambulatory women living in Buenos Aires, Argentina. *Osteoporos Int* 2001; 12(1):24-27.
18. del Puente A, Esposito A, Savastano S, Carpinelli A, Postiglione L, Oriente P. Dietary calcium intake and serum vitamin D are major determinants of bone mass variations in women. A longitudinal study. *Aging Clin Exp Res* 2002; 14(5):382-388.
19. Chandran M, Hoeck HC, Wong HC, Zhang RF, Dimai HP. Vitamin D status and Its Relationship with Bone Mineral Density and Parathyroid Hormone in Southeast Asian Adults with Low Bone Density. *Endocr Pract* 2011; 17(2):226-234.
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21. Joo N-S, Dawson-Hughes B, Kim Y-S, Oh K, Yeum K-J. Impact of calcium and vitamin D insufficiencies on serum parathyroid hormone and bone mineral density: Analysis of the fourth and fifth Korea National Health and Nutrition Examination Survey (KNHANES IV-3, 2009 and KNHANES V-1, 2010). *J Bone Miner Res* 2013; 28(4):764-770.
22. Kota S, Jammula S, Kota S, Meher L, Modi K. Correlation of vitamin D, bone mineral density and parathyroid hormone levels in adults with low bone density. *Indian J Orthop* 2013; 47(4):402-407.
23. Rocha AKS, Bos AJG, Carnenaz G, Machado DC. Bone mineral density, metabolic syndrome, and vitamin D in indigenous from south of Brazil. *Arch Osteoporos* 2013; 8:134.
24. Mosele M, Coin A, Manzato E, Sarti S, Berton L, Bolzetta F, et al. Association between serum 25-hydroxyvitamin d levels, bone geometry, and bone mineral density in healthy older adults. *J Gerontol Biol Sci Med Sci* 2013; 68(8):992-998.
25. Sohl E, Jongh RT, Swart KMA, Enneman AW, van Wijngaarden JP, van Dijk SC, Ham AC, van der Zwaluw NL, Brouwer-Brolsma EM, van der Velde N, Groot CPGM, te Velde SJ, Lips P, van Schoor NM. The association between vitamin D status and parameters for bone density and quality is modified by body mass index. *Calcif Tissue Int* 2015; 96(2):113-122.
26. Choi S-W, Kweon S-S, Choi J-S, Rhee J-A, Lee Y-H, Nam H-S, Jeong S-K, Park K-S, Ryu S-Y, Song H-R, Shin M-H. The association between vitamin D and parathyroid hormone and bone mineral density: The Dong-gu Study. *J Bone Miner Metab* 2016; 34(5):555-563.
27. Olmos JM, Hernandez JL, Garcia-Velasco P, Martinez J, Llorca J, Gonzalez-Macias J. Serum 25-hydroxyvitamin D, parathyroid hormone, calcium intake, and bone mineral density in Spanish adults. *Osteoporos Int* 2016; 27(1):105-113.
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31. Budak N, Çiçek, B, Sahin, H, Tutus, A. Bone mineral density and serum 25-hydroxyvitamin D level: is there any difference according to the dressing style of the female university students. *Int J Food Scie Nutr* 2004; 55(7):569-575.
32. Ghannam NN, Hammami MM, Bakheet SM, Khan BA. Bone mineral density of the spine and femur in healthy Saudi females: relation to vitamin D status, pregnancy, and lactation. *Calcif Tissue Int* 1999; 65(1):23-28.
33. Kota S, Jammula S, Kota S, Meher L, Modi K. Correlation of vitamin D, bone mineral density and parathyroid hormone levels in adults with low bone density. *Indian J Orthop* 2013; 47(4):402-407.
34. Overgaard K, Nilas L, Johansen JS, Christiansen C. Lack of seasonal variation in bone mass and biochemical estimates of bone turnover. *Bone* 1988; 9(5):285-258.

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Chart 3. Reasons for study exclusion.

Age range
35. Kadam N, Chiplonkar S, Khadilkar A, Divate U, Khadilkar V. Low bone mass in urban Indian women above 40 years of age: prevalence and risk factors. *Gynecol Endocrinol* 2010; 26(12):909-917. 36. Scharla SH, Scheidt-Nave C, Leidig G, Woitge H, Wüster C, Seibel MJ, Ziegler R. Lower serum 25-hydroxyvitamin D is associated with increased bone resorption markers and lower bone density at the proximal femur in normal females: a population-based study. *Exp Clin Endocrinol Diabetes* 1996; 104(3):289-292. 37. Wei QS, Chen ZQ, Tan X, Su HR, Chen XX, He W, Deng WM. Relation of Age, Sex and Bone Mineral Density to Serum 25-Hydroxyvitamin D Levels in Chinese Women and Men. Orthop Surg 2015; 7(4):343-349. 38. Araujo AB, Travison TG, Esche GR, Holick MF, Chen TC, McKinlay JB. Serum 25-hydroxyvitamin D and bone mineral density among Hispanic men. *Osteoporos Int* 2009; 20(2):245-255. 39. Garg MK, Tandon N, Marwaha RK, Menon AS, Mahalle N. The relationship between serum 25-hydroxy vitamin D, parathormone and bone mineral density in Indian population. *Clin Endocrinol* 2014; 80(1):41-46. 40. Nguyen HT, Von Schoultz B, Nguyen TV, Dzung DN, Duc PT, Thuy VT, Hirschberg AL. Vitamin D deficiency in northern Vietnam: prevalence, risk factors and associations with bone mineral density. *Bone* 2012; 51(6):1029-1034. 41. van Ballegooijen AJ, Robinson-Cohen C, Katz R, Criqui M, Budoff M, Li, D, de Boer IH. Vitamin D metabolites and bone mineral density: The multi-ethnic study of atherosclerosis. *Bone* 2015; 78:186-193.
Pregnancy
42. Shao H, Tao M, Fan Y, Jing J, Lu J. Vitamin D levels and other factors related to bone mineral density during pregnancy. *Aust N Z J Obstet Gynaecol* 2012; 52(6):571-575.
Revision
43. Bell NH. Bone and mineral metabolism in African Americans. *Trends Endocrinol Metab* 1997; 8(6):240-245. 44. Pérez-López FR, Cano A, Calaf J, Vázquez F, Barriendos JF. Factores reguladores del recambio óseo: estrógenos y vitamina D. *Progresos de obstetricia y ginecología* 2009; 52(2)99-108. 45. Holick MF. High prevalence of vitamin D inadequacy and implications for health. *Mayo Clin Proc* 2006; 81(3):353-373. 46. Pérez-López FR. Vitamin D and its implications for musculoskeletal health in women: an update. *Maturitas* 2007; 58(2):117-137.
Bone evaluation by methods other than DXA
47. Garton M, Martin J, New S, Lee S, Loveridge N, Milne J, Reid D, Reid I, Robins S. Bone mass and metabolism in women aged 45-55. *Clin Endocrinol* 1996; 44(5):563-570.
Letter to the Editor
48. Boucher BJ, Mannan N, Cunningham J. Vitamin D status and bone mass in UK South Asian women. *Bone* 2007; 40(4):1182.
Did not evaluate 25(OH)D
49. Högström M, Nordström A, Nordström P. Relationship between vitamin D metabolites and bone mineral density in young males: a cross-sectional and longitudinal study. *Calcif Tissue Int* 2006; 79(2):95-101.

25(OH)D: 25-hydroxyvitamin D; BMC: Bone Mineral Content; BMD: Bone mineral density; DXA: Double X-ray Absorptiometry.

Source: Elaborated by the authors.

ate sample selection and general judgment of risk of bias, respectively (Figure 2).

Meta-analysis results

In the meta-analysis, only articles using Pearson's linear correlation were included for the following bone sites: BMC - 7/9[18,29,35,43,47,49,53]; LS-BMD - 11/30[20,28,35,38,39,41,43,51,55-57]; H-BMD - 14/23[29,35-37,38,41,42,49,51-53,56-58]; FN-BMD - 20/28[28,29,33,36-43,49,51-58]; and T-BMD - 10/15[29,33,36,37,39,40,42,49,51,56].

Significant correlation of 25(OH)D was identified with: BMC (Fisher Z=0.31; 95%CI=0.18-0.44), H-BMD (Fisher Z=0.07; 95%CI=0.02-0.12), FN-BMD (Fisher Z=0.08; 95%CI=0.03-0.13) and T-BMD (Fisher Z=0.08; 95%CI=0.1-0.15). There was no statistically significant association between 25(OH)D and LS-BMD (Fisher Z=0.03; 95%CI=-0.01-0.08). In the subgroup analysis, a positive correlation was found between 25(OH)D and LS-BMD concentrations in men (Table 2). The evaluated studies

Table 1. Characteristics of the studies included in the systematic review.

	n	%	Reference
Year of publication			
1992-2005	8	22.86	[18,28-34]
2006-2010	10	28.57	[17,20,35-42]
2011-2015	13	37.14	[43-55]
2016-2017	4	11.43	[56-59]
Location			
United States	5	14.28	[28,34,37,44,46]
Europe (Denmark, Finland, Turkey, Italy, Greece, Estonia, Germany, Sweden)	8	22.86	[29,30,31,35,38,41,49,54]
Asia (India, Bangladesh, United Arab Emirates, Japan, Korea, Syria, China, Iran, Saudia Arabia)	17	48.57	[17,18,20,32,33,40,42,45,47,48,50-52,55-58]
Africa (Morocco, South Africa)	2	5.72	[39,53]
Oceania (Australia)	1	2.85	[59]
No location	2	5.72	[36,43]
Sample size			
<100	7	20	[18,30,32,33,35,36,46]
100-500	15	42.86	[17,20,28,31,40,42,43,45,47,49,53-55,57,59]
>500	13	37.17	[29,34,37-39,41,44,48,50-52,56,58]
Gender			
Both	18	51.43	[28,31-34,42-44,46,47,49,50-55,57]
Women	10	28.57	[17,18,20,29,30,36,38,39,45,59]
Men	7	20	[35,37,40,41,48,54,58]
Evaluated bone sites			
BMC	9	25.71	[17,18,29,35,43,44,49,53,59]
LS-BMD	30	85.71	[17,20,28-30,32,33,35-43,46-52,54-59]
H-BMD	23	65.71	[20,29,32,34-42,45,47,49-53,56-59]
FN-BMD	28	80	[17,28-30,32,36-43,45,47-59]
T-BMD	15	42.86	[17,29,32,33,36,37,39,40,42,45,47,49-51,56]
IT-BMD	6	17.14	[32,33,42,45,47,51]
WT-BMD	5	14.29	[17,32,33,36,45]
R-BMD	8	22.86	[18,28,31-33,37,40,45]

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presented high heterogeneity for all bone sites, with significant Q-test ($p<0.05$) and I^2 values above 70% (Figures 3 and 4).

It was possible to observe that there is no evidence of publication bias through the funnel graph (Figure 5). Considering the Egger's test, the effect of small studies was only observed for the femoral neck (LS-BMD: p=0.083; H-BMD: p=0.088; FN-BMD: p=0.024; and T-BMD: p=0.074).

Meta-regressions were performed to investigate possible sources of heterogeneity identified in the meta-analysis. We observed statistically significant sources of heterogeneity for: sample size for FN-BMD ($p<0.01$) and H-BMD ($p=0.01$); mean serum 25(OH)D concentrations of participants for H-BMD (p=0.03); and risk of bias for BMC (p=0.03). On the other hand, the mean age of the participants, the analyzed group (1-men, 2-women, 3-men and women), as well as the latitude and longitude did not significantly contribute to the occurrence of heterogeneity in the meta-analyzes (Table 3).

Discussion

We observed a significant positive correlation between serum 25(OH)D concentrations and bone health in adults in the evaluated bone sites. The

Table 1. Characteristics of the studies included in the systematic review.

	n	%	Reference
Adjustment Variables			
Age	14	40	[29, 34, 35, 37-41,44,46,49,52,55,58]
Gender	9	25.71	[28,31,32,34,43,44,46,51,57]
Height	7	20	[28,35,37,40,52,57,59]
Total Body Mass	7	20	[18,29,35,37,40,52,57]
Body Mass Index	6	17.14	[34,38,40,41,46,49]
Physical Activity	6	17.14	[34,35,41,49,57,59]
Smoking	4	11.42	[34,41,49,58]
Season of the Year	4	11.42	[34,37,49,52]
Race/skin color	3	8.57	[34,37,46]
Drinking Alcohol	2	5.72	[41,49]
Latitude/Longitude	2	5.72	[38,59]
Lean mass	1	2.85	[59]
Fat %	1	2.85	[49]
Fat Free Mass	1	2.85	[49]
Socioeconomic level	1	2.85	[34]
Solar Exposure	1	2.85	[38]
Use of Hormones (estrogen, birth control)	1	2.85	[34]
Others (age of menarche, total caloric intake, calcium intake, supplements, milk and coffee consumption, creatine level, chronic diseases, number of children and breastfeeding)	7	20	[34,40,41,43,49,52,58]

BMC: Bone Mineral Content; LS-BMD: Lumbar Spine Bone Mineral Density; H-BMD: Hip Bone Mineral Density; FN-BMD: Femoral Neck Bone Mineral Density; T-BMD: Trochanter Bone Mineral Density; IT-BMD: Intertrochanter Bone Mineral Density; WT-BMD: Ward's Triangle Bone Mineral Density; R-BMD: Radio Bone Mineral Density.

Source: Elaborated by the authors.

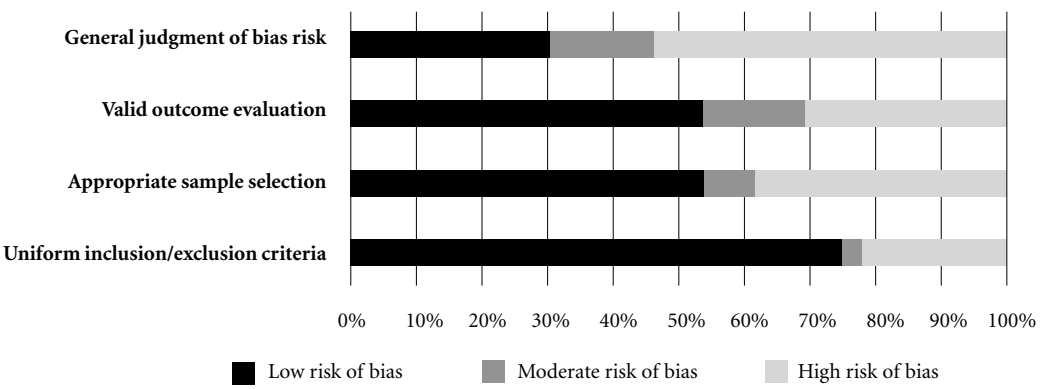


Figure 2. Main issues related to risk of bias in selected studies.

Source: Elaborated by the authors.

Table 2. Results of the individual studies on the association between vitamin D and bone health according to gender, bone site, statistical test and type of association.

Type of Association	Linear Correlation (n=27)					Linear Regression (n=15)				
	Women (n=21)									
	BMC (n=2)	LS-BMD (n=12)	H-BMD (n=11)	FN-BMD (n=12)	T-BMD (n=8)	BMC (n=2)	LS-BMD (n=7)	H-BMD (n=4)	FN-BMD (n=5)	T-BMD (n=5)
Positive	---	3 [39*; 47; 56]	3 [39*; 47; 56]	3 [39*; 47; 56]	3 [39*; 47; 56]	2 [18; 29]	5 [17; 29; 36; 38; 39*]	3 [36; 38; 39*]	4 [17; 36; 38; 39*]	5 [17; 29; 36; 38; 39*]
Negative	---	1 [36]	1 [36]	1 [36]	1 [36]	---	1 [36]	1 [36]	1 [36]	---
Null	2 [29; 59]	9 [28*; 29; 30; 32; 36; 39; 42; 55; 59]	8 [29; 32; 36; 39; 42; 45; 57; 59]	11 [28*; 29; 30; 32; 36; 39; 42; 45; 55; 57; 59]	6 [29; 32; 36; 39; 42; 45]	---	2 [20; 28*]	1 [20]	1 [28*]	---
	Men (n=10)									
	BMC (n=0)	LS-BMD (n=7)	H-BMD (n=5)	FN-BMD (n=6)	T-BMD (n=1)	BMC (n=2)	LS-BMD (n=1)	H-BMD (n=0)	FN-BMD (n=1)	T-BMD (n=0)
Positive	---	4 [37; 41; 52; 58]	4 [37; 41; 52; 58]	4 [37; 41; 52; 58]	1 [37]	---	1 [48]	---	1 [48]	---
Negative	---	2 [20; 40]	1 [20]	---	---	2 [18; 35]	---	---	---	---
Null	---	2 [40; 54]	---	2 [40; 54]	---	---	---	---	---	---
	Both genders (n=8)									
	BMC (n=4)	LS-BMD (n=11)	H-BMD (n=7)	FN-BMD (n=10)	T-BMD (n=6)	BMC (n=2)	LS-BMD (n=3)	H-BMD (n=3)	FN-BMD (n=1)	T-BMD (n=1)
Positive	4 [43; 49*; 50; 53]	7 [33; 43; 46*; 49*; 51*; 53; 55]	4 [49*; 50; 51*; 53]	7 [33; 43; 49*; 50; 51*; 53; 55]	4 [33; 49*; 50; 51*]	2 [44; 49*]	3 [46*; 49*; 51*]	3 [34; 49*; 51*]	2 [49*; 51*]	2 [49*; 51*]
Negative	---	3 [42; 56; 57]	3 [42; 56; 57]	3 [42; 56; 57]	2 [42; 56]	---	---	---	---	---
Null	---	---	---	---	---	---	---	---	---	---

*Article which used Pearson's Linear Correlation and Linear Regression. BMC: Bone Mineral Content; LS-BMD: Lumbar Spine Bone Mineral Density; H-BMD: Hip Bone Mineral Density; FN-BMD: Femoral Neck Bone Mineral Density; T-BMD: Trochanter Bone Mineral Density.

Source: Elaborated by the authors.

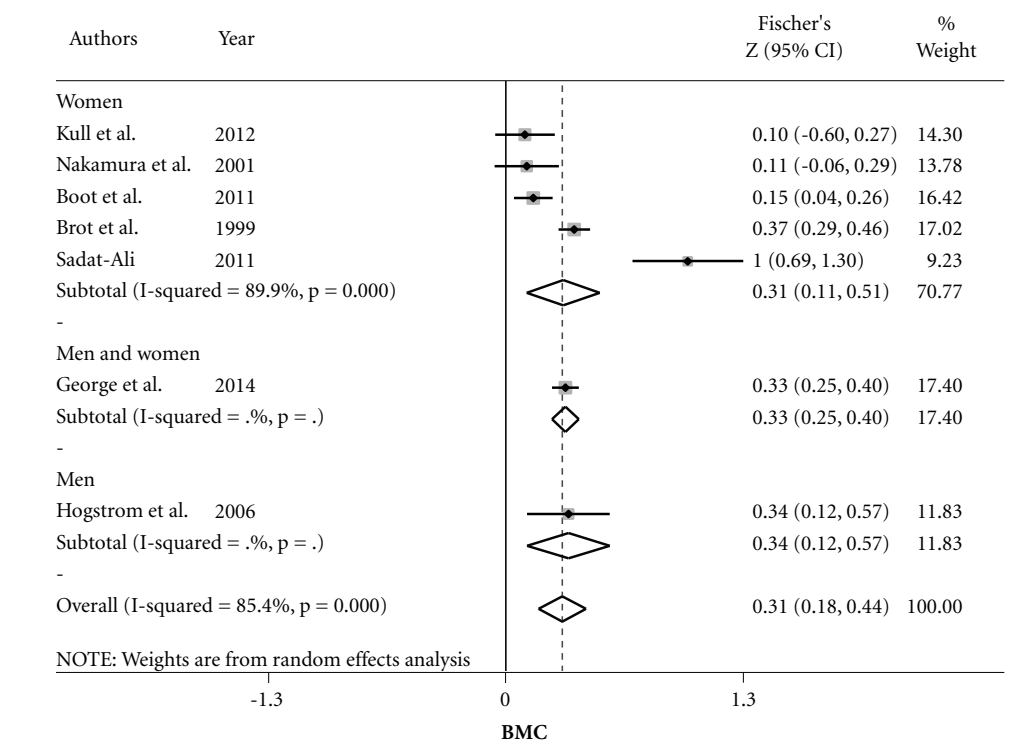


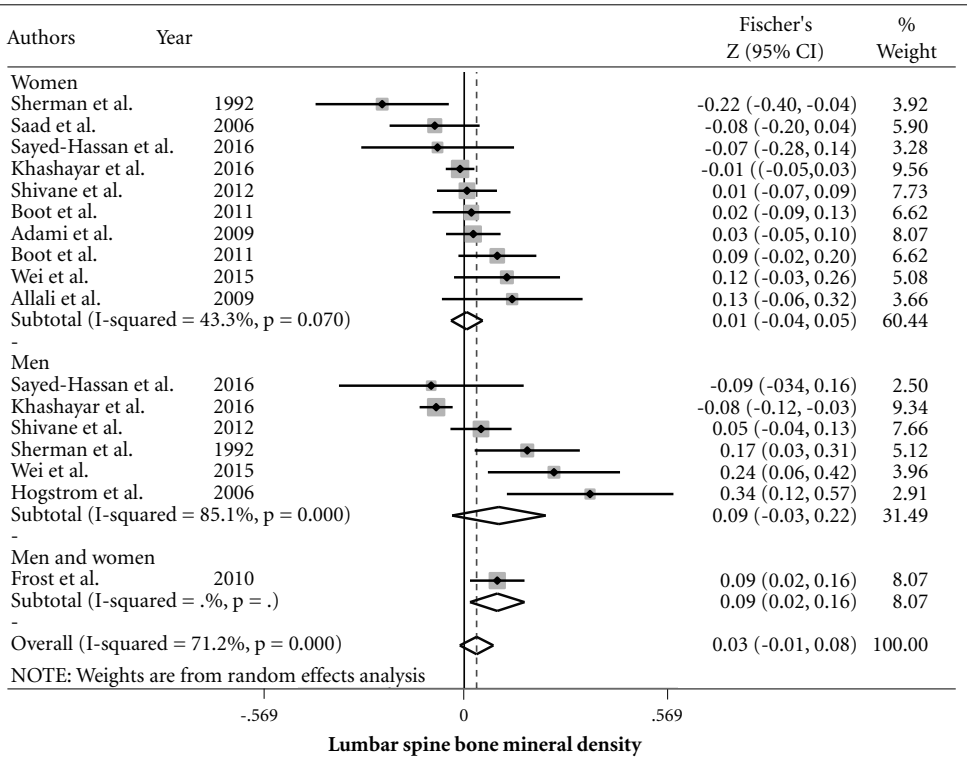
Figure 3. Correlation between serum vitamin D concentrations and bone mineral content.

Source: Elaborated by the authors.

studies selected for this review presented high heterogeneity and high coverage in relation to gender, ethnicity, study population, and countries, among other aspects. An effect of small studies were not observed except for the FN-BMD site (Chart 4).

The relationship between 25(OH)D and bone health in adults is biologically plausible, since deficiency of this vitamin has been considered an important determinant of several diseases, especially those related to bone health[60-63]. Vitamin D is important throughout development, as it allows a greater absorption of calcium in the intestine, which also positively contributes to bone health[13,24]. Deficiency of vitamin D in the early stages of development may lead to developing weak, narrow and soft bones, providing a greater probability of fractures[13,24]. In a systematic review, it was identified that low 25(OH)D in childhood increases the risk of fractures in this age group, requiring supplementation in these cases[64]. Although all the factors associated with the occurrence of osteoporosis have not yet been well established, it is known that peak bone mass during childhood and adolescence (the period for accumulating 50% of total bone mass) and the rate of bone loss during aging are determinants[65]. Thus, adequate concentrations of vitamin D during these development stages contribute to optimizing mineral gain, and consequently to better bone health in adulthood[65]. This may ease the process of loss at more advanced ages.

A meta-analysis conducted with randomized clinical trials aimed at assessing the relationship between calcium and vitamin D supplementation and fracture prevention in middle-aged and older adult individuals found that those who underwent vitamin D supplementation had a reduction in the risk of general fractures by 15% and of hip fractures by 30%[63]. Another meta-analysis identified similar results, noting an association between vitamin D insufficiency and hip fracture risk, with a 40% increase in risk of occurrence[62]. Another study with predominantly white adults evaluating 2,294 individuals submitted to vitamin D supplementation found a positive association in six of the ten studies evaluated, four with beneficial effect on only one bone site and two on the hip, de-



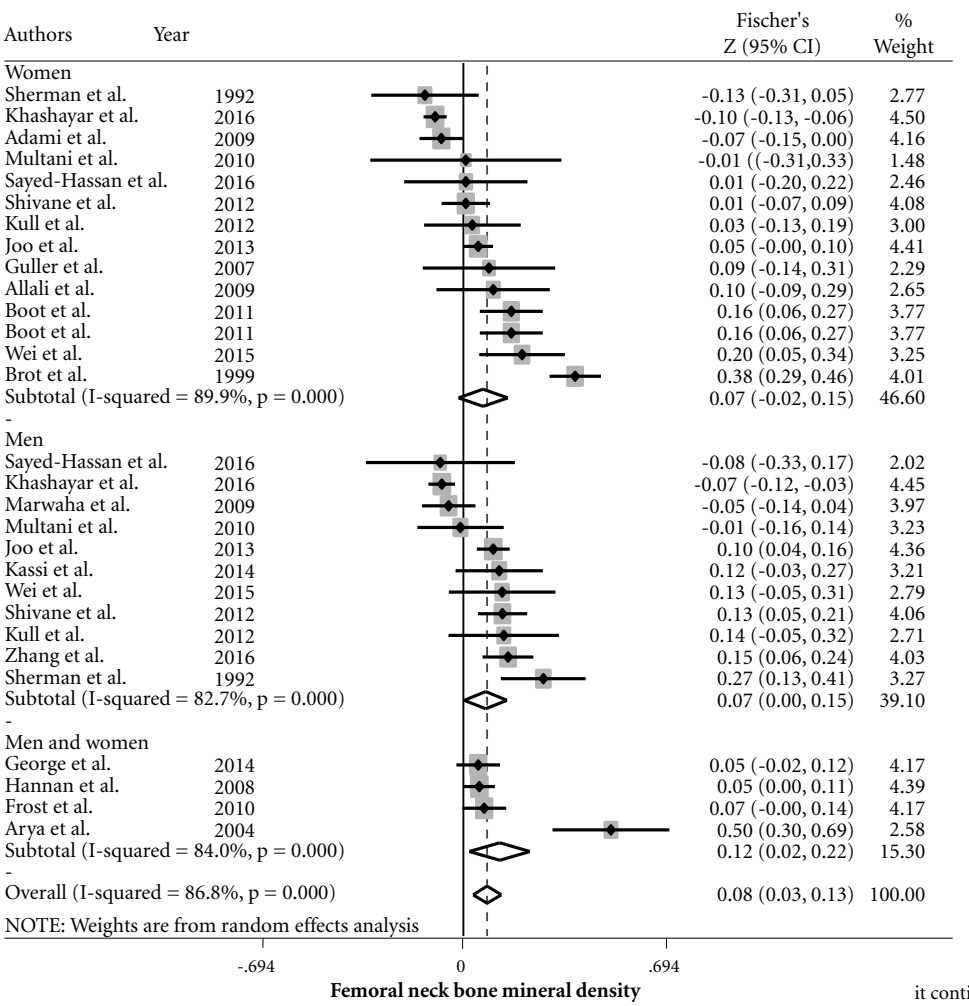


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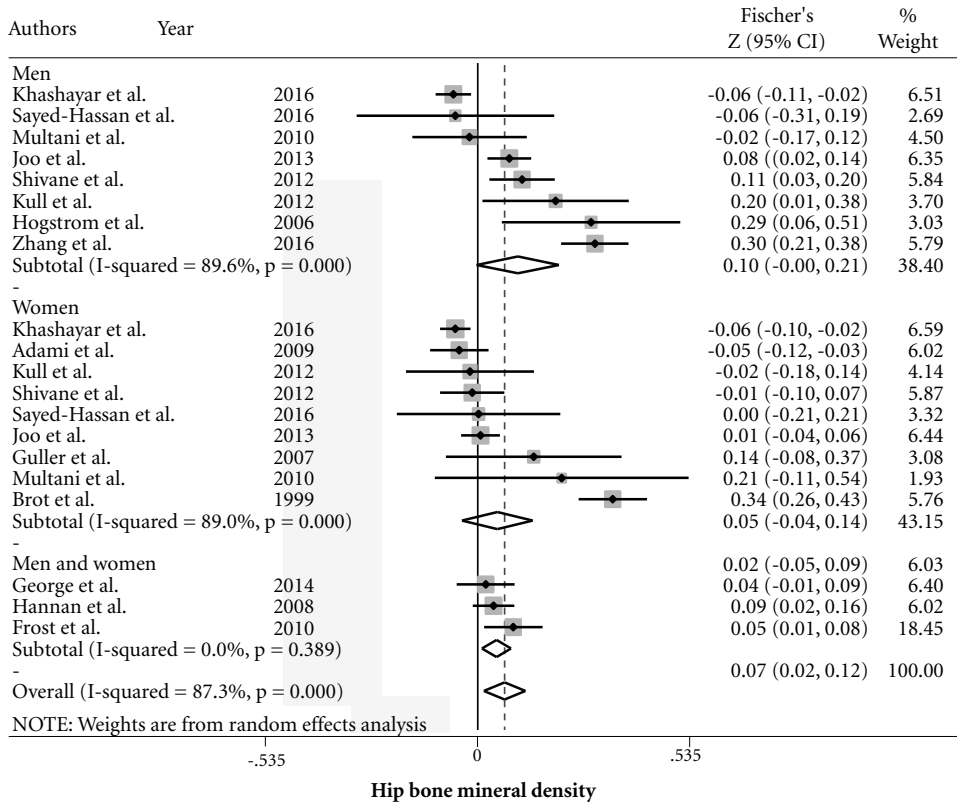
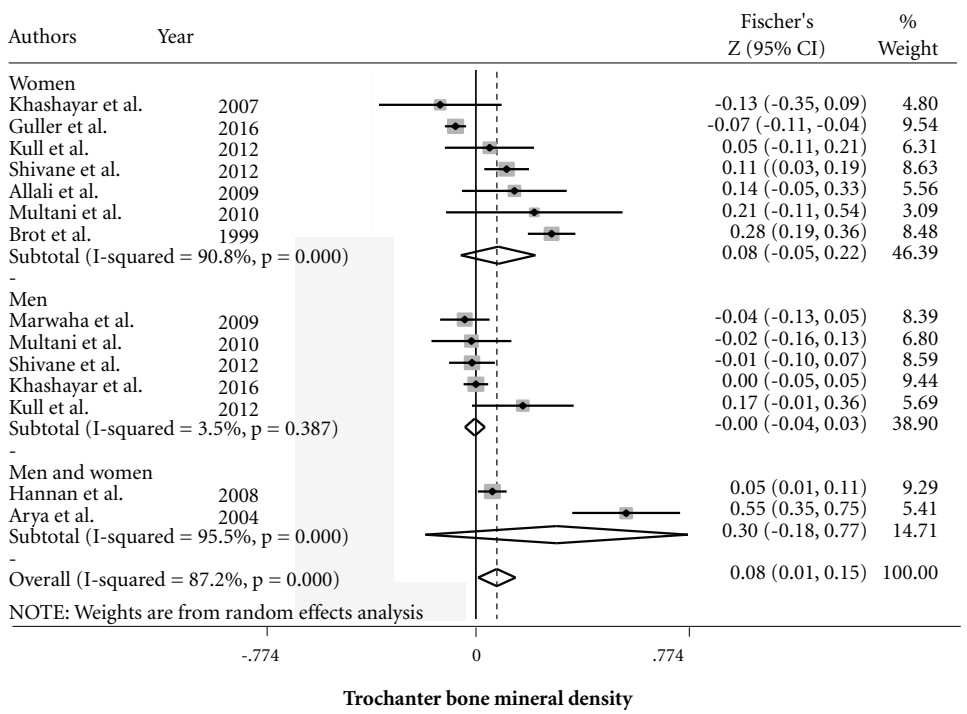
Figure 4. Correlation between serum vitamin D concentrations and bone health in adults. Lumbar spine bone mineral density; Hip bone mineral density; Femoral neck bone mineral density; Trochanter bone mineral density.



Hip bone mineral density



Trochanter bone mineral density

Figure 4. Correlation between serum vitamin D concentrations and bone health in adults. Lumbar spine bone mineral density; Hip bone mineral density; Femoral neck bone mineral density; Trochanter bone mineral density.

Source: Elaborated by the authors.

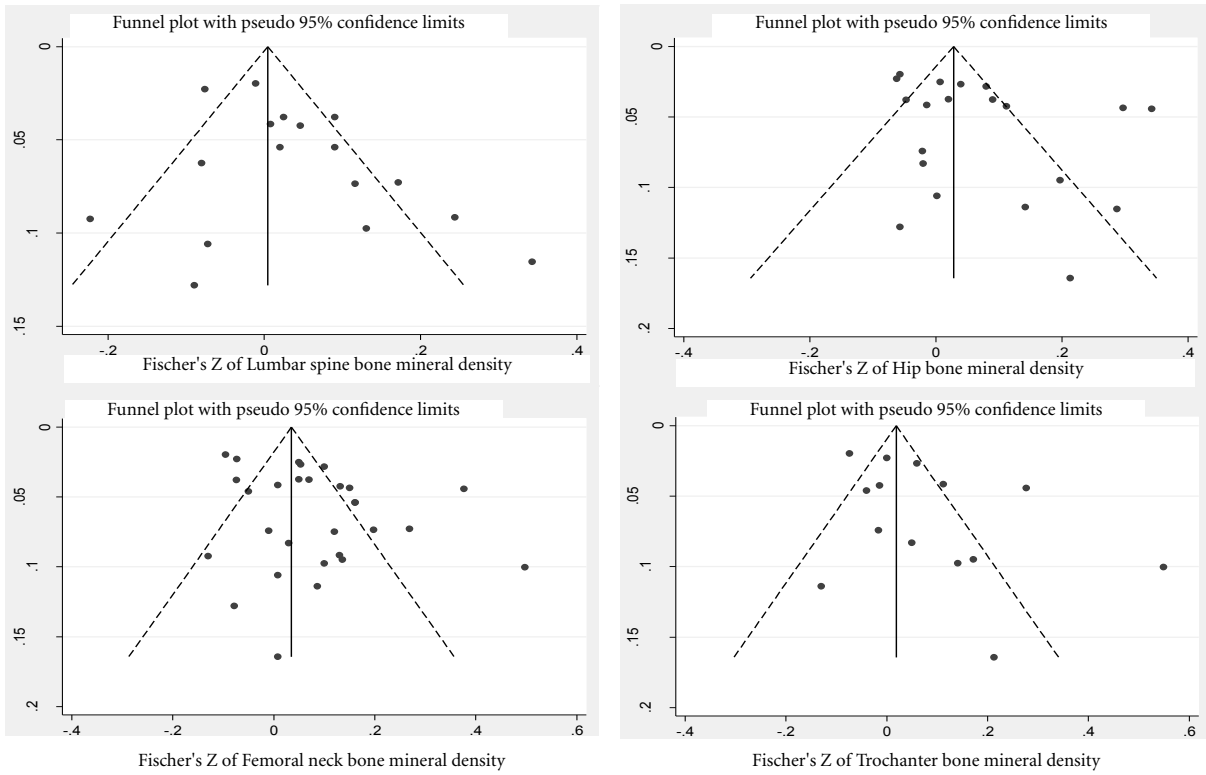


Figure 5. Funnel graph for studies on the association between serum vitamin D concentrations and bone health. Lumbar spine bone mineral density; Hip bone mineral density; Femoral neck bone mineral density; Trochanter bone mineral density.

Source: Elaborated by the authors.

Table 3. Meta-regression for studies on the association between serum vitamin D concentrations and bone health.

Bone sites	n	I^2 (%)	Meta-regression p-values						
			Mean age	Sample size	Gp	Mean 25(OH)D	Lat	Long	Risk of bias
Z BMC	7	85.4	0.64	0.81	0.95	0.68	0.43	0.80	0.03*
Z LS-BMD	11	97.8	0.64	0.20	0.75	0.27	0.85	0.98	0.29
Z H-BMD	14	87.3	0.50	0.01*	0.80	0.03*	0.14	0.66	0.71
Z FN-BMD	19	84.0	0.30	<0.01*	0.32	0.07	0.15	0.49	0.36
Z T-BMD	8	87.2	0.13	0.16	0.60	0.78	0.16	0.32	0.29

n: number of studies; I^2: inconsistency test; Gp: Group; 25(OH)D: 25 hydroxyvitamin D; Lat: Latitude; Long: Longitude; BMC: Bone Mineral Content; FN-BMD: Femoral Neck Bone Mineral Density; H-BMD: Hip Bone Mineral Density; LS-BMD: Lumbar Spine Bone Mineral Density; T-BMD: Trochanter Bone Mineral Density.

Source: Elaborated by the authors.

spite the heterogeneity between the trials[66]. These authors emphasized that, although maintaining adequate serum levels of vitamin D is important, supplementation should be performed only in individuals identified with inadequate levels[66].

In our review, the most evaluated bone sites were LS-BMD, H-BMD and FN-BMD. These results are consistent with the recommendations for clinical practice, since they are anatomical regions where the initial process of bone loss (osteopenia)

Chart 4. Sample characterization and mean age values, 25-hydroxyvitamin d and bone mass of the studies included in the review.

Author/ Year	Country/City	Sample (n)	Age (Years) Mean (±SD)	25(OH)D (ng/ml) Mean (±SD)	BMC (g)/BMD (g/cm²) Mean (±SD)
Sherman et al., 1992*	United States - Baltimore	Men and Women, White (n=312)	---	---	---
Brot et al., 1999	Denmark - Copenhagen	Women Perimenopausa (n=510)	50.6±2.8	----	BMC: 2,294±363; LS-BMD: 1.021±0.142; H-BMD: 0.906±0.115; FN-BMD: 0.792±0.114; T-BMD: 0.682±0.094.
Güller et al., 2007		Group 1: typical garments (n=40); Group 2: only the skin of the hands and face is not covered (n=40)	Group 1: 36.1±3.2; Group 2: 34.8±3.3 (p>0.05)	Group 1: 25.43±11; Group 2: 13.7 ±9.83 (p<0.05)	Group 01: LS-BMD: 1.02±0.12; T-BMD: 0.68±0.12; TW-BMD 0.80±0.18; FN-BMD: 0.87±0.17; H-BMD: 0.90±0.11. Group 02: LS-BMD: 0.99±0.11; T-BMD: 0.68±0.10; TW-BMD: 0.76±0.13; FN-BMD: 0.88±0.14; H-BMD: 0.91±0.13. (p>0.05)
Lamberg-Allardt et al., 2001+	Finland	Men: (n=126); Women (n=202)	Men: 37.0±4; Women:38.0±.3 (p>0.05)	Men: 18.02±14.02; Women: 17.62±13.62 (p>0.05)	---
Guzel et al., 2001	Turkey	Women (n=60) Group 1: Veiled (n=30) Group 2: Unveiled (n=30)	Group 1: 24.6±5.1; Group 2: 24.9±6.2. (p>0.05)	Group 1: 33.1±16; Group 2: 53.9±27.3 (p≤0.001)	Group 1: LS-BMD: 0.960±0.140; FN-BMD: 0.810±0.130. Group 2: LS-BMD: 1.010±0.090; FN-BMD: 0.850±0.090. (p>0.05)
Tandon et al., 2003	India	Men (n=40) Women (n=50).	Men: 22.7±2.8; Women: 23.4±3.1 (p>0.05)	Men: 18.4±5.3; Women: 25.3±7.4 (p <0.001)	Men: LS-BMD: 0.947±0.086; FN-BMD: 0.911±0.129; H-BMD: 1.016±0.133; T-BMD: 0.740±0.117; TW-BMD: 0.798±0.146; FIT-BMD: 1.167±0.159; DR-BMD: 0.619±0.072. Women: LS-BMD: 0.981±0.092; FN-BMD:0.850±0.101; H-BMD: 0.957±0.103; T-BMD: 0.707±0.121; TW-BMD: 0.769±0.121; FIT-BMD: 1.137±0.122; DR-BMD: 0.541±0.034.
Bischoff-Ferrari et al., 2004*+	United States	White (n=2,482) Mexican-American: (n=2,516) Black (n=2,517).	White: 34.8±8.1; Mexican-American: 32.6±8.4; Black: 33.5±8.0	White: 33.17±12.25; Mexican-American: 24.63±9.17; Black: 18.45±7.97	White: H-BMD: 0.97±0.14. Mexican-American: H-BMD: 1.00±0.14. Black: H-BMD: 1.07±0.17.
Saadi et al., 2006*+	United Arab Emirates	Women (n=259): Pre-Menopause (n=175)	Pre-Menopause: 37.5±9.5	Pre-Menopause 9.73±4.16	Pre-Menopause LS-BMD: 1.1±0.13; H-DMB: 0.970±0.13.
Islam et al., 2008*+	Bangladesh	Women (n=200)	22.6±3.7	14.7±4.48	FN-BMD: 0·788±0·106; T-BMD: 0.624±0.0893; TW-BMD: 0.645±0.118; LS-BMD: 0.894±0·116.
Marwaha et al., 2009*+	Indian-Deli	Men (n=473)	---	13.66±6.33	TR-BMD: 0.605±0.061; DR-BMD: 0.451±0.080; H-BMD: 1.129±0.130; FN-BMD: 1.115±0.134; T-BMD: 0.926±0.126; LS-BMD: 1.170±0.137
Allali et al., 2009*	Morocco-Rabat	Women (n=415) Pre-Menopause (n=108)	Women: 50±9.3; Pre-Menopause 42.8±6.2	Women: 18.1±7.9 Pre-Menopause; 18.6±7.7	Women: LS-BMD: 1.1±0.13; FN-BMD: 0.97±0.6; T-BMD: 0.79±0.11; H-BMD: 1.02±0.16.

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Chart 4. Sample characterization and mean age values, 25-hydroxyvitamin d and bone mass of the studies included in the review.

Author/ Year	Country/City	Sample (n)	Age (Years) Mean (±SD)	25(OH)D (ng/ml) Mean (±SD)	BMC (g)/BMD (g/cm²) Mean (±SD)
Adami et al., 2009	Italy (North, Center and South)	Women, white, pre-menopause (n=608) North (n=364) Center (n=111) South (n=133)	North: 35.9±8.3 Center: 36.5±8.2 South: 35.7±8.3 (p>0.05)	North: 27.6±11.1 Center: 28.9±11.3 South: 24.8±11.2 (p>0.05)	25(OH)D Suf (≥20ng/ml): LS-BMD: 1.028±0.121*; FN-BMD: 0.907±0.128**; H-BMD; 0.791±0.116***. 25(OH)D Insuf (<20ng/ml).: LS-BMD: 1.061±0.122*; FN-BMD: 0.923±0.115**; H-BMD: 0.810±0.128***. (*p=0.002; **p=0.089; ***p= 0.063)
Multani et al., 2010	Indian-Mumbai	Resident Physicians (n=214) Men (n=174); Women (n=40)	Men: 26.87±1.6; Women: 26.33±1.58.	Men: 12.80±7.94 Women: 10.94±4.54	Men: LS-BMD: 0.907±0.112; FN-BMD: 0.800±0.116; T-BMD: 0.662±0.099; FIT-BMD: 1.087±0.167; H-BMD 0.094±0.120. Women: LS-BMD: 0.899±0.101; FN-BMD: 0.740±0.106; T-BMD: 0.610±0.091; FIT-BMD: 0.971±0.203; H-BMD: 0.830±0.115.
Gutiérrez et al., 2011	United States	White (n=2,239); Mexican-American (n=989); Black (n=978); both sexes	White:45.3±0.5; Mexican-American: 37.0±0.7; Black 41.3±0.6	White: 25.6±0.4. Mexican-American: 19.5±0.5. Black: 14.8±0.4	White: 25(OH)D Suf. (≥30 ng/ml): BMC: 1.03±0.01; 25(OH)D Insuf. (<30 ng/ml e >10ng/ml): BMC:1.03±0.01; 25(OH)D Def. (≤10ng/ml): BMC:1.02±0.01; (p=0.79) Mexican-American: 25(OH)D Suf. (≥30 ng/ml): BMC:1.03±0.01; 25(OH)D Insuf. (<30 ng/ml e >10ng/ml): BMC: 1.03±0.01; 25(OH)D Def. (≤10ng/ml): BMC: 1.01±0.01; (p<0.01) Black: 25(OH)D Suf. (≥30 ng/ml): BMC:1.08±0.02; 25(OH)D Insuf. (<30 ng/ml e >10ng/ml): BMC: 1.09±0.01; 25(OH)D Def. (≤10ng/ml): BMC:1.09±0.01; (p=0.21)
Sadat-Ali et al., 2011*	Saudi Arabia -Al Khobar	Men and women (n=400): 100 men e 100 women for each (age group 25 and 35 years and ≥50 years)	25(OH)D Suf. (>30 pg/ml): Men: 27.96±3.5; Women: 29.81±3.8; 25(OH)D Insuf. (21-29 pg/m): Men: 28.89±4.28; Women: 28.05±3.13; 25(OH)D Def. (<20 pg/ml): Men: 28.5±4.5.; Women: 23.9±1.87.	---	LS-BMD Men: 25(OH)D Suf. (>30 pg/ml): 1.100±0.09; 25(OH)D Insuf. (21-29 pg/mLl): 0.903±0.13; 25(OH)D Def. (<20 pg/ml): 0.612±0.25. LS-BMD Women: 25(OH)D Suf. (>30 pg/ml): 0.844±0.14; 25(OH)D Insuf. (21-29 pg/ml): 0.747±0.09; 25(OH)D Def. (<20 pg/ml): 0.618±0.13 (p <0.001)
Harinarayan et al., 2011*	Indian	Hospital staff and patients (n=191) Pre-menopause (n=55); Post- menopause (n=136)	Pre-Menopause: 37.42±0.72 Post-menopause: 53.29±0.72 (p<0.001)	Pre-menopause (20-30 years): 24.08±1.12.	Pre-menopause (20-30anos): FR-BMD: 0.645±0.021; PR-BMD: 0.533±0.018; R-BMD: 0.403±0.012; TR-BMD: 0.527±0.016; T-BMD: 0.641±0.019; FIT-BMD: 1.058±0.021; FN-BMD: 0.757±0.015; TW-BMD 0.639±0.025; H-BMD: 0.886±0.017.
Powe et al., 2011*+	United States -Boston	Men (n=27); Women (n=22)	23.5±3.4	Men: 21.14±7.73. Women: 31.36±12.13 (p<.001)	Men: LS-BMD: 1.040±0.14; Women: LS-BMD 1.070±0.13. (p=0.371)

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Chart 4. Sample characterization and mean age values, 25-hydroxyvitamin d and bone mass of the studies included in the review.

Author/ Year	Country/City	Sample (n)	Age (Years) Mean (±SD)	25(OH)D (ng/ml) Mean (±SD)	BMC (g)/BMD (g/cm²) Mean (±SD)
Nakamura et al., 2001*+	Japan	Women (n=77)	32.9±11.3	16.86±6.04	---
Shivane et al., 2012	Indian	Men (n=558); Women (n=579)	Men: 30.11±3.53; Women: 30.52±3.57	Men: 18.93±8.93; Women: 15.85±9.07	Men: FN-BMD: 0.827±0.125; T-BMD: 0.642±0.103; FIT-BMD: 0.986±0.140; H-BMD: 0.887±0.122; LS-BMD: 0.912±0.123 Women: FN-BMD: 0.755±0.108; T-BMD 0.595±0.109; FIT-BMD: 0.904±0.130; H-BMD: 0.814±0.111; LS-BMD: 0.899±0.120
Lim et al., 2012***	Korea	Men (n=1,926); Women (n=2,350)	Men: 28.61±8.34; Women: 29.24±7.98	Men: 18.85±6.67; Women: 16.74±5.74	Men: LS-BMD: 0.97±0.14; T-BMD: 0.70±0.09; FN-BMD: 0.87±0.13; H-BMD: 1.00±0.13. Women: LS-BMD: 0.97±0.13; T-BMD: 0.65±0.08; FN-BMD: 0.77±0.11; H-BMD: 0.90±0.11
Kassi et al., 2015	Greece - Athens	Men (n=181)	34.69±7.38	19.81±6.96	LS-BMD: 1.220 ±0.13; H-BMD: 1.020± 011
Khashayar et al., 2016	Iran – Tehran; Tabriz; Mashhad; Shiraz; Bandar; Busher	Men (n=1,900); Women (n=2,2250)	42.6±13.9	Osteoporosis: 42.03±34.59 Osteoponics: 35.97±26.49 Normal: 33.04±23.78 (p<0.001)	---
Sayed-Hassan et al., 2014	Syria - Damascus	Men (n=156); Women (n=64)	Men: 32.2±9.2; Women: 36.9±10 (p=0.006)	Men: 13.5±7.4 Women: 8±5.1 (p<0.001)	Men: LS-BMD: 0.938±0.12*; FN-BMD: 0.861±0.13**; H-BMD: 0.989±0.12***. Women: LS-BMD: 0.954±0.12*; FN-BMD: 0.766±0.11**; H-BMD: 0.872±0.12***. (p=0.39*2; p<0.001**; p<0.001***).
Hannan et al., 2008	United States - Massachusetts	Men: Black (n=331), Hispacnic (n=362); White (n=421).	Black: 48.0±12.5; Hispacnic: 44.4±10.9 White: 48.3±13.1 (p<0.001)	Black: 25.0 ±14.7; Hispacnic: 32.9±13.9; White: 37.4±14.0 (p<0.001)	Black: FN-BMD: 0.94±0.15; T-BMD: 0.81±0.14; H-BMD: 1.09±0.15; LS-BMD: 1.10±0.15; TR-BMD: 0.80±0.07; DR-BMD: 0.56±0.08. Hispacnic: FN-BMD: 0.88±0.14; T-BMD: 0.76±0.12; H-BMD: 1.02±0.15; LS-BMD: 1.00±0.13; TR-BMD: 0.75±0.06; DR-BMD: 0.52±0.07. White: FN-BMD: 0.84±0.12; T-BMD: 0.75±0.12; H-BMD: 1.00±0.14; LS-BMD: 1.03±0.15; TR-BMD: 0.76±0.06; DR-BMD: 0.52±0.07. (p<0.001, comparing the same bone site between groups)
Arya et al., 2004	Indian - Lucknow	Hospital worker: Men (n=35); Women (n=67)	34.2± 6.7	12.3±10.9	---
Högström et al., 2006+	Sweden - Umea	Men, White (n=73)	22.6±0.7	39.26±13.82	BMC: 1.31±0.08; H-BMD: 1.26±0.15; LS-BMD: 1.27±0.12.

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Chart 4. Sample characterization and mean age values, 25-hydroxyvitamin d and bone mass of the studies included in the review.

Author/ Year	Country/City	Sample (n)	Age (Years) Mean (±SD)	25(OH)D (ng/ml) Mean (±SD)	BMC (g)/BMD (g/cm²) Mean (±SD)
Frost et al., 2010*+	Denmark - Odense	Men (n=700)	25(OH)D Suf.: 25.6±2.9 25(OH)D Insuf.: 25.6±2.8 25(OH)D Def.: 25.3±2.8 (p>0.05))	Spring: 23.75±10.85 Summer: 24.27±11.17 Autum: 30.04±7.85 Winter: 28.20±11.81g (p<0.001)	25(OH)D Suf. LS-BMD: 1.08±0.12*; FN-BMD: 0.95±0.13; H-BMD: 1.09±0.14. 25(OH)D Insuf. LS-BMD: 1.09±0.13*; FN-BMD: 0.97±0.14**; H-BMD: 1.10±0.14***. 25(OH)D Def. LS-BMD:1.06±0.12*; FN-BMD: 0.93±0.13**; H-BMD: 1.05±0.14***. (p=0.024*; p=0.004**; p=0.032***)
Boot et al., 2011+	---	Men (n=117); Women (n=347)	Men: 24.8±3.0; Women: 24.1±2.8	Men: 28.44±10.81; Women: 35.65±12.62	Men: BMC: 1.276±0.09; LS-BMD: 1.272±0.15; FN-BMD: 1.139±0.16. Women: BMC: 1.182±0.07; LS-BMD: 1.248±0.13; FN-BMD:1.063±0.13.
Kull et al., 2012+	Estônia - Lääne-Viru County	Men (n=122); Women (n=151).	Men: 48.3±11.8; Women: 49.2±12.9. (p=0.41)	Measured in winter: Men: 17.1±5.0; Women: 17.58±6.08 Measured in summer: Men: 24.63±7.57; Women: 23.35±7.13 (p=0.19)	Men: LS-BMD: 1.202±0.175; FN-BMD: 1.017±0.127; T-BMD: 0.965±0.155; H-BMD: 1.102±0.134; BMC: 1.264±0.086. Women: LS-BMD: 1.127±0.191; FN-BMD: 0.969±0.150; T-BMD: 0.848±0.136; H-BMD: 763.5±142.6; BMC: 1.032±0.149. (p=0.08; p=0.003; p<0.0001; p<0.0001; p<0.0001, comparing the same bone site between groups)
Joo et al., 2013*+	Korea	22-29 years Men (n=574); Women (n=775)	Men: 25.5±0.1; Women: 25.6±0.1	Men: 17.78±0.04; Women: 15.5±0.2	Men: FN-BMD: 5.06±0.04; H-BMD: 42.76±0.32; LS-BMD: 68.82±0.49. Women: FN-BMD: 3.47±0.02; H-BMD: 28.70±0.18; LS-BMD: 57.26±0.36. (Results presented in grams)
George et al., 2014*+	South African - Johannesburg	Women: Black African (n=187); Indian Asian (n=187) Men: Black African (n=181); Indian Asian (n=160)	Women: Black African: 41.7±13.1; Asian Indian: 43.8±12.7 (p=0.08) Men: Black African: 41.7±13.2; Asian Indian 43.0±13.2 (p=0.36)	Women: Black African: 23.35 (17.18-34.29) Asian Indian: 14.30 (9.21-21-83) (p<0.0001) Men: Black African: 29.12 (20.47-37-70) Asian Indian: 18.18 (13.46-25.12) (p<0.0001)	Men: Black African: ST-BMD 0.695(0.683-0.707*); H-BMD: 1.068(0.934-1.162)**; FN-BMD: 0.938(0.826-1.026)***. Asian Indian: ST-BMD 0.671(0.659-0.683)*; H-BMD: 0.946(0.882-1.051)**; FN-BMD: 0.793(0.723-0.873). (p=0.02*; p<0.0001**; p<0.0001***) Women: Black African: ST-BMD 0.702(0.691-0.713)*; H-BMD: 0.998(0.909-1.088)**; FN-BMD: 0.919(0.830-0.995)***. Asian Indian: ST-BMD 0.648(0.636-0.659)*; H-BMD: 0.887(0.803-0.978)**; FN-BMD: 0.777(0.692-0.859)***. (p<0.0001*; p<0.0001**; p<0.0001***)
Wei et al., 2015*	China - Guangzhou	Men (122); Women (n=188).	Men: 43.89±21.29 Women: 49.67±17.61 (p<0.05)	Men: 27.25±7.94 Women: 25.35±6.59 (p<0.05)	Men: LS-BMD: 1.17±0.18; FN-BMD: 0.97±0.18. Women: LS-BMD: 1.04±0.17; FN-BMD: 0.84±0.15. (p<0.001, for all bone sites)

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Chart 4. Sample characterization and mean age values, 25-hydroxyvitamin d and bone mass of the studies included in the review.

Author/ Year	Country/City	Sample (n)	Age (Years) Mean (±SD)	25(OH)D (ng/ml) Mean (±SD)	BMC (g)/BMD (g/cm²) Mean (±SD)
Zhang et al., 2016*+	China - Guiyang	Men: Young (n=346); Middle-age (n=182)	Young: 30±6.4 (p<0.05) Middle-age: 49.2±5.8 (p<0.01)	Young: 17.46±9.49 (p<0.01) Middle-age: 23.59±8.04 (>0.05)	Young: FN-BMD: 0.95±0.12; (p<0.001); H-BMD: 1.000±0.12 (p<0.001); LS-BMD: 1.10±0.12. Middle-age: FN-BMD: 0.88±0.12; (p<0.01); H-BMD: 0.95±0.14 (p<0.01); LS-BMD: 1.10±0.14.
Callegari et al., 2017+	Canada - Victoria	Women (n=400)	22±3	27.64±11.21	BMC: 1.527±236; LS-BMD: 1.04±0.13; H-BMD: 0.93±0.12; FN-BMD: 0.87±0.13.
Ardawi et al., 2012*+	Saudi Arabia - Jeddah,	Men (<50 years) (n=550)	35.7±10.6	12.52±7.02	LS-BMD: 1.116±0.143; FN-BMD: 1.029±0.168.

*Studies that presented stratification by age group, considering only the one of interest in this review. +Studies whose data of 25 (OH) D were converted; 1ng/ml = 2.496 nmol /l. SD: Standard Deviation; BMC: Bone Mineral Content; BMD: Bone Mineral Density; 25(OH)D Suf: 25-hydroxy vitamin D Sufficient; 25-hydroxy vitamin D 25(OH)D Insuf: 25-hydroxy vitamin D Insufficient; 25(OH)D Def: 25-hydroxy vitamin D Deficient; BMD-LS: Bone Mineral Density - Lumbar Spine; FN-BMD: Bone Mineral Density-Femoral Neck; H-BMD: Bone Mineral Density - Hip; DR-BMD: Bone Mineral Density - Distal Radio; TR-BMD: Bone Mineral Density-Total Radio; T-BMD: Bone Mineral Density-Trocânter; FIT-BMD: Bone Mineral Density-Intertrochanteric Femur; TW-BMD: Bone Mineral Density-Triangulo Ward; FR-BMD: Bone Mineral Density - Frontal Radio; PR-BMD-Bone Mineral Density - Previous Radio; R-BMD: Bone Mineral Density - Radio; TR-BMD: Bone Mineral Density - Total Radio; ST-BMD: Subtotal Bone Mineral Density; ns: Not Significant.

Source: Elaborated by the authors.

occurs[15]. However, recent studies have shown that evaluation of total bone health from BMC is also important[17,18,29,35,43,44,49,53,59], with the identification of mean bone mass values for the overall evaluation of the individual being necessary.

The relationship between vitamin D status and gender is still unclear. In this perspective, we identified a correlation between vitamin D and bone mineral density, regardless of gender. Thus, this variable does not appear to be an effect modifier on the relationship between vitamin D concentrations and total amount of bone mass of the individual. It should be considered that some evidence points to better bone health in men because higher concentrations of 25(OH)D have been identified[67,68]. Another question concerns the relationship between 25(OH)D and different parathyroid hormones between genders, with a more pronounced influence in men than in women[69]. Although the studies are not entirely conclusive, some authors claim that adequate vitamin D concentrations are also related to excess fat and hormones, especially estrogen[70,71], and this may contribute to women having a higher prevalence of vitamin D deficiency, negatively influencing their bone health.

The risk of bias in the studies included in this review was mostly high, which may influence the results identified herein. There is considerable variation in the inclusion and exclusion criteria of the studies analyzed in this review, and consequently in the samples from the selected studies. In addition, according to the meta-regression results, sample size, mean serum vitamin D concentrations and risk of bias contributed significantly to the heterogeneity observed between the analyzed studies, suggesting that these variables should be considered in planning studies about this subject.

Most of the studies, as observed, used the correlation coefficient to evaluate the association between serum vitamin D concentrations and bone health, which is why the meta-analysis of this review was conducted using this measure of association as a reference. A very small number of studies used linear regression and presented results adjusted by confounding factors. The main variables used for adjustment in these models were age, gender, ethnicity, height and total body mass[18,28,29,31,32,34,35,37-41,43,44,46,49,51,52,55,57,58]. These are important factors which have an influence on bone health, but others are also relevant and should be considered in studies on the association between vitamin D and bone health. Genetics, behavior, sun exposure, dietary intake of calcium and foods reinforced with vitamin D, in addition to the vitamin supplementation itself, may have an impact on the status of 25(OH)D and consequently on bone health[34,39,40,41,43,49,52,58,59]. It is therefore recommended that these issues be

considered in future work, particularly through forward-looking approaches.

The present study has some limitations. The first one refers to the fact that all the selected studies have a cross-sectional design, and therefore by character these studies do not enable an establishment of a temporal relation between the studied variables. Another issue is the non-standardization of the evaluated bone sites, which makes it difficult to summarize the results. Finally, the comparison of vitamin D status may be hampered by a high variation of serum 25(OH)D measurement between different analytical methods.

As a positive, we highlight that this review includes an evaluation of the association between serum vitamin D concentrations in different bone sites in adults and the analysis of data exploring subgroups and heterogeneity sources. Moreover, the performance of all the review stages by independent authors is also worth mentioning, reducing the chance of selection bias of the studies.

In conclusion, we showed a positive association between serum concentrations of 25(OH) D and bone health from the results of this systematic review and meta-analysis. It should be noted that clinically healthy individuals without osteometabolic diseases were evaluated in this study. This is an important issue because given the positive association identified, there is need to maintain adequate vitamin D levels even in adults due to its biological importance.

It is therefore recommended that bone health evaluation be incorporated into clinical practice aimed at adults with vitamin D insufficiency or deficiency. It is known that osteoporosis is a silent disease and therefore requires preventive measures and early diagnosis in order to avoid critical illness or possible fractures.

Collaborations

KJ Segheto: responsible for writing the article, collecting data, analyzing and interpreting the results. M Pereira: responsible for writing the article, analyzing and interpreting the results. DCG Silva: responsible for writing the article and critical review. CJ Carvalho: responsible for writing the article, responsible for data collection and analysis and interpretation of results. FR Massardi: responsible for data collection and analysis and interpretation of results. AM Kakehasi: responsible for writing the article and critical review. LL Juvanhol: responsible for writing the article and critical review. GZ Longo: responsible for writing the article and critical review.

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