

Prevalence of hypovitaminosis D in postmenopausal women: a systematic review

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SUMMARY

BACKGROUND: Hypovitaminosis D is considered a global public health issue. Knowledge of its true dimensions will allow us to design interventions and plan preventive measures that can have a significant impact on human health.

OBJECTIVES: The aim of this study was to evaluate the prevalence of hypovitaminosis D, defined as a serum 25-hydroxyvitamin D concentration < 30 ng/ml, in postmenopausal women around the world, as well as to identify the potential associated factors.

METHODS: A systematic review was performed in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analyses recommendations. Specific search terms were consulted in Medline, Excerpta Medica, and Latin-American and Caribbean Health Sciences Literature databases, with no restriction for the year or language of publication.

RESULTS: Of 451 studies initially identified, 32 were selected for analysis. Collectively, those 32 studies evaluated 21,236 postmenopausal women, of whom 16,440 (77.4%) had serum 25-hydroxyvitamin D concentrations < 30 ng/ml. The reported prevalence of hypovitaminosis D ranged from 29% (in the United States) to 99.4% (in China). In six of the studies, the prevalence was above 90%.

CONCLUSIONS: If the criterion is the 30 ng/ml cut-off point, the majority of postmenopausal women in the world could be classified as having hypovitaminosis D. Among the studies evaluated, the lowest prevalence reported was nearly 30%. Neither latitude, region of the world, nor laboratory methodology were found to be associated with the prevalence of hypovitaminosis D.

KEYWORDS: Vitamin D deficiency, Vitamin D, Postmenopause, Climacteric, Prevalence

INTRODUCTION

Vitamin D deficiency represents a major public health problem, not only because its prevalence is high (so high that it is considered a true epidemic) but also because of the considerable clinical repercussions¹⁻³. Its importance concerned to calcium homeostasis and bone metabolism are well known, but, following the identification of vitamin D recep-

tors in various cells and organs of the body, including the pancreas, macrophages, endothelium, stomach, epidermis, colon, and placenta⁴, vitamin D has been shown to have major extra-skeletal (autocrine and paracrine) effects⁵. Vitamin D treatment has also been associated with reduced rate of falls⁶, mobility, worsening of muscle function, an increased risk

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of falls, and cognitive decline, as well as with an increased risk of Alzheimer's disease and depression¹.

Vitamin D is naturally produced by the skin, and exposure to ultraviolet radiation is a key step in its synthesis^{7,8}. Factors influencing that exposure, such as geographic location, cultural norms, skin color, use of sunscreen, and the modern lifestyle (more time spent indoors), can affect serum concentrations of 25-hydroxyvitamin D (25[OH]D).

Because human life expectancy has increased, many women live longer after menopause, when hypovitaminosis D can become more severe, not only because of the reduction in intestinal absorption due to the aging process but also because of the inherent hypoestrogenism in the postmenopausal period. In combination, these factors increase the risk of loss of bone mass⁹. From the above, it can be deduced that hypovitaminosis D can affect a large part of the population, and knowledge of its true population frequency can contribute to the formulation of public policies involving preventive measures and interventions¹⁰. Therefore, the objective of this systematic review was to evaluate the prevalence of hypovitaminosis D in postmenopausal women around the world.

METHODS

We conducted a search for cross-sectional studies that estimated the prevalence of hypovitaminosis D in postmenopausal women. We followed the recommendations established in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines¹¹, selecting studies in which the serum concentrations of 25(OH)D had been determined in postmenopausal women and, although measurements over the 20 ng/mL limit are considered normal by important entities^{12,13}, the 30 ng/ml (75 nmol/L) cut-off point had been used to distinguish between normality and insufficiency or deficiency because this is limit associated with the optimization of intestinal calcium absorption in postmenopausal women¹⁴. We excluded studies jointly evaluating women of reproductive age and postmenopausal women, studies that did not collect information regarding the menopausal status of the women, cohort studies of women with diseases, and case-control studies. When there was a control group comprising healthy postmenopausal women, data related to those women were included in the review, because the biochem-

ical data from the controls were representative of the general population.

To identify eligible studies, we consulted the Medline, Latin-American and Caribbean Health Sciences Literature, and *Excerpta Medica* databases for entries up to September 2016, using the strategy outlined in Chart 1, without restricting the year of publication or language. The articles were selected through the process described in Figure 1. We also reviewed the publications listed in the bibliographies of the articles selected. The selection, evaluation of the titles, and evaluation of the abstracts of the studies identified in the databases consulted were conducted by two investigators with experience in conducting systematic reviews. The investigators worked independently, strictly adhering to the inclusion and exclusion criteria. To extract data of interest for this review, the investigators then evaluated the remaining articles for information regarding the measurement of serum 25(OH)D concentrations; study locale; participant ages and menopausal status; sample size and selection criteria; and the methods used in the clinical and biochemical analyses. When there was disagreement between the investigators regarding the selection of studies, a third investigator was consulted. The data were compiled into a Microsoft Office Excel spreadsheet. The primary endpoint of interest was the prevalence of hypovitaminosis D, the reference range for serum 25(OH)D concentrations being ≥ 30 ng/ml.

RESULTS

Of a total of 448 articles initially identified, 32 were selected for inclusion in the final analysis (Figure 1). One study was excluded because it presented conflicting results between the prevalence of hypovitaminosis D and the maximum serum concentration of 25(OH)D reported. Most of the studies selected were cross-sectional cohort studies that employed the baseline measures required for inclusion in this review, although a few were case-control studies in

CHART 1 SEARCH STRATEGIES, PER DATABASE

Database	Strategy
Medline/PubMed	"postmenopause"[All Fields] AND "vitamin d deficiency"[All Fields]
Latin-American and Caribbean Health Sciences Literature	postmenopause [words] AND vitamin d deficiency [words]
Excerpta Medica	"vitamin d deficiency" AND "postmenopause" AND "prevalence"

TABLE 1. STUDIES SELECTED

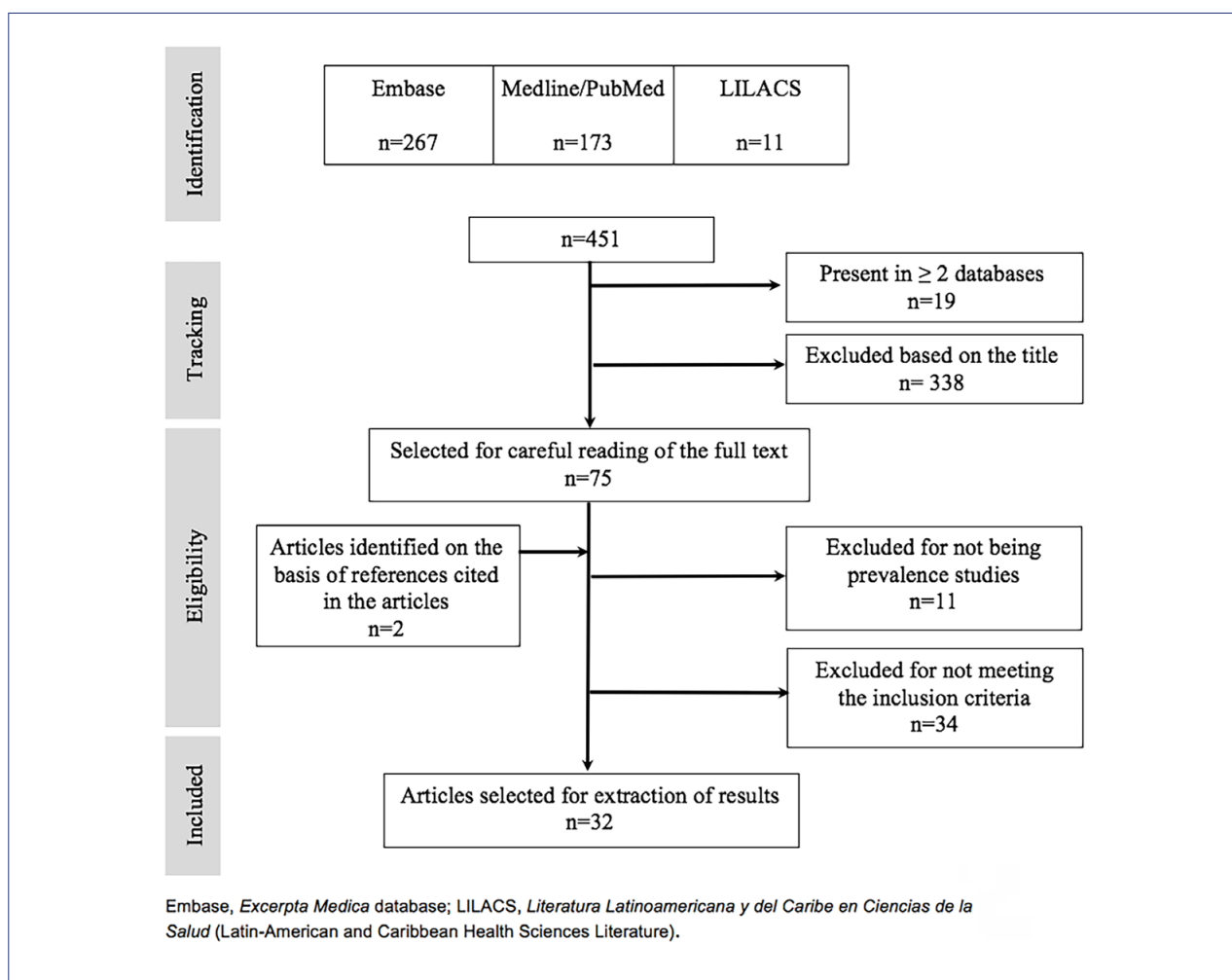
Author and year of publication	Mean age, years	Women	Women with HD	25(OH)D, ng/ml	Latitude	VDS (%)	Locale
	Mean (SD)	N	n (%)	Mean*			
El Maataoui et al., 2016 ³²	59 (8.2)	186	144 (77.4)	20.1	32°N	no	Morocco
Andreozzi et al., 2015 ³⁷	64.4 (8.4)	62	48 (77.4)	ND	41.87°N	no	Italy
Alipour et al., 2014 ³³	ND	140	113 (80.7)	ND	35.7°N	no	Iran
Godala et al., 2014 ²⁶	55.4 (3.5)	36	30 (83.3)	23.52 (13.39–45.87)	51.76°N	no	Poland
Cheng et al., 2014 ¹⁷	ND	3345	2727 (81.5)	ND	25–40°N	47.8	USA (40 clinical facilities)
Aloia et al., 2014 ¹⁸	58.8 (4.9)	76	59 (78.0)	25.2	40.44°N	no	USA (Mineola, NY)
Gómez-de-Tejada Romero et al., 2014 ³⁴	54.8 (11.8)	1221	892 (73.0)	24.3	28.12°N	ND	Spain (Canary Islands)
Hoon et al., 2014 ^{19**}	ND	605	509 (84.2)	ND	37.56°N	no	Korea
Kliscic et al., 2014 ^{35**}	ND	188	151 (80.3)	ND	42.44°N	ND	Montenegro
Stolarczyk et al., 2014 ²⁷	70.8 (7.6)	107	95 (88.8)	19.55	52.26°N	no	Poland
Mata-Granados et al., 2013 ³⁸	5.4 (6.4)	232	217 (93.7)	17.5	37.5°N	no	Spain (Junta de Andalucía)
Asadi et al., 2013 ²⁸	52.7 (5.0)	110	77 (70.0)	19.28	35.7°N	no	Iran
Casado-Díaz et al., 2013 ⁴²	57.4 (12.8)	229	190 (83.0)	21.76	37.8°N	no	Spain (Cordoba)
Hacker-Thompson et al., 2012 ¹⁵	63.9 (7.8)	122	36 (29.5)	ND	41°N	82.0	USA (San Francisco, CA)
Hussein et al., 2012 ^{43**}	ND	223	212 (95.0)	ND	21.29°N	ND	Saudi Arabia
El Maghraoui et al., 2012 ³⁶	58.8 (8.2)	178	152 (85.3)	15.8 (3.0–49.1)	34°N	no	Morocco
Rudenska et al., 2012 ^{29**}	63 (7.8)	205	189 (92.0)	ND	53.9°N	62.1	Belarus
Baro; 2011 ^{44**}	ND	150	119 (79.3)	ND	41.38°N	ND	Spain (Barcelona)
Harinarayan et al., 2011 ²⁰	53 (0.2)	136	124 (89.7)	ND	13.40° N	no	India
Sternberg et al., 2011 ^{21**}	61.4	112	65 (57.9)	ND	35°S	ND	Argentina
Zhao et al., 2011 ¹⁶	64.1 (9.2)	1724	1714 (99.4)	13.2 (4.0–35.6)	39.54°N	no	China
Laktasic-Zerjavic et al., 2010 ³⁹	61.2 (8.8)	120	111 (92.5)	46.94 (10–110.9)	42–46°	no	Croatia
Allali et al., 2009 ³⁰	55.9 (6.8)	307	282 (92.0)	17.7	33.97°N	no	Morocco
Bobinac et al., 2009 ^{45**}	ND	720	455 (63.3)	27.33	45.32°N	ND	Croatia
Maddah et al., 2009 ⁴⁰	63.4 (8.7)	646	536 (83.0)	19.99	37.12°N	ND	Iran
Poiana et al., 2009 ^{46**}	58.4	174	144 (82.8)	ND	44.43°N	ND	Romania
Stewart et al., 2009 ²²	54.3 (3.3)	242	153 (63.3)	ND	41.8°N and 38.6°N	53.7	USA (Ames, IA and Davis, CA)
Lee et al., 2009 ²³	58 (8)	254	112 (44.0)	33.3	37.56°N	35.8	Korea
Al-Turki et al., 2008 ²⁴	56.1 (4.9)	200	110 (55.0)	ND	26.22°N	no	Saudi Arabia
Manicourt et al., 2008 ³¹	65 (8)	85	53 (62.0)	25.6	50.85°N	no	Belgium
Bruyère et al., 2007 ²⁵	74.2 (7.1)	8532	6186 (72.7)	24.04	40.46–55.17°N	24	Belgium, France, Spain, Germany, Hungary, Italy, Poland, and the United Kingdom
Garnero et al., 2007 ⁴¹	62.2 (8.8)	669	490 (73.2)	ND	45.76°N	ND	France

HD, hypovitaminosis D; VDS, Vitamin D supplementation; ND, no data. *Plus minimum and maximum values, where provided. **Published in poster form.

which the control group was representative of the population of interest. We also included eight poster publications that presented the necessary minimum information (Table 1).

Table 1 shows the information obtained from the selected studies¹⁵⁻⁴⁶: the names of the authors and year of publication; the mean ages of the participants; the number of women evaluated; the number

FIGURE 1



of subjects with serum 25(OH)D concentrations < 30 ng/ml; the prevalence of hypovitaminosis D; the mean 25(OH)D concentrations, with minimum and maximum values when available; and the latitude and locale of the study. Collectively, the selected studies evaluated 21,236 women, 16,440 (77.4%) of whom had serum 25(OH)D concentrations < 30 ng/ml. Sample sizes ranged from 36 to 8,532, the prevalence of hypovitaminosis D ranging from 29.5% (in San Francisco, CA) [15] to 99.4% (in Beijing, China)¹². The laboratory techniques used were radioimmunoassay, in nine studies¹⁷⁻²⁵; chemiluminescent immunoassay, in six²⁶⁻³¹; electrochemiluminescence, in six^{16,32-36}; high-performance liquid chromatography (HPLC), in three^{15,37,38}, ELISA, in two^{39,40}, and competitive protein-binding techniques, in one⁴¹. In five studies, the laboratory technique employed was not reported⁴²⁻⁴⁶.

In six of the 32 studies, the prevalence of hypovitaminosis D was above 90%^{16,29,30,38,39,43}. In the study conducted in Beijing¹⁶, only 10 of the 1,724 women

evaluated had serum concentrations of 25(OH)D above 30 ng/ml. The prevalence of hypovitaminosis D was above 90% in seven other cities around the world: 95.0% in Jeddah, Saudi Arabia⁴³; 93.7% in Junta de Andalucía, Spain³⁸; 92.5% in Zagreb, Croatia³⁹; 92.0% in Minsk, Belarus²⁹; and 92.0% in Rabat, Morocco³². Even at the sites where the prevalence of hypovitaminosis D was lowest, it was relatively high: approximately 30% in San Francisco, CA¹⁵; 44.0% in (one of the studies conducted in) South Korea²³, and 55.0% in Saudi Arabia²⁴.

Stratifying the results by continent, we found that the prevalence of hypovitaminosis D in North America, Europe, Africa, the Middle East, and Asia was 78.6%, 73.6%, 86.1%, 81.5%, and 90.4%, respectively. The fact that the prevalence was highest in Asia was due to the study conducted in Beijing, which involved 1,724 women, almost all of whom had hypovitaminosis D¹⁶. With the search strategy adopted, only one study from South America was selected, a study conducted in Argentina and involving 112 women, in

which the estimated prevalence of hypovitaminosis D was 57.9%²¹.

Multiple studies carried out in a single country presented very different results. In a study conducted in South Korea in 2009 and involving 254 women²³, the prevalence of hypovitaminosis D was 44.0%, compared with 84.2% in another, more recent study involving 605 women evaluated in that same country¹⁹. In the studies conducted in the United States, the reported prevalence ranged from 29.5%¹⁵ to 81.5%¹⁷. In two studies conducted in Saudi Arabia, one in the city of Al Khobar in 2008²⁴ and the other in the city of Jeddah in 2012⁴³, the reported prevalence was 55.0% and 95.0%, respectively.

Although comparisons were made among latitudes and continents, we identified no factors that could explain the differences observed. The reported prevalence of hypovitaminosis D was high even in populations in which the rate of vitamin D supplementation was near 50%¹⁹, or even above 60%²⁹, although it was lower in the studies in which women receiving vitamin D supplementation were excluded²⁴. We identified no association between the prevalence of hypovitaminosis D and the laboratory techniques employed.

DISCUSSION

One of the most important aspects of this review is the fact that, to our knowledge, this is the first study to show the worldwide distribution of the prevalence of hypovitaminosis D according to the laboratory technique employed, specific geographic location, and latitude. Another important aspect was the selection of studies involving healthy postmenopausal women, with the objective of avoiding biases caused by treatments or diseases concerning the serum concentrations of 25(OH)D. We chose to include studies in which a portion of the population was using vitamin D supplementation, as long as the samples were representative of the local population of healthy postmenopausal women.

In this review, we did not find the prevalence of hypovitaminosis D to be associated with geographic location, latitude, use of vitamin D supplementation, or the laboratory technique employed. We identified considerable variation among studies conducted in the same country, in terms of the prevalence of hypovitaminosis D. Between the two studies conducted in South Korea, the one conducted in 2009²³, in which

the prevalence of hypovitaminosis D was 44.0%, included women under treatment for osteoporosis or menopause, which could account for the difference in relation to the 2014 study¹⁹, which involved only women not receiving such treatment and in which the prevalence was 84.2%. It is of note that both of those studies were conducted in the city of Seoul. For the 2009 study²³, if only the women not receiving vitamin D supplementation (n = 91) were evaluated, the prevalence would be 56%. In addition, the women evaluated by those authors were under treatment at a referral center for hormone replacement therapy or osteoporosis. Those treatments could have generated behavioral changes that had a positive influence on serum concentrations of 25(OH)D (engaging in outdoor activities, increased exposure to the sun, and consumption of foods rich in vitamin D). Similarly, in the United States, the prevalence of hypovitaminosis D ranged from as high as 81.5%, in a multicenter study¹⁷, to as low as 29.5%, in the study conducted in San Francisco¹⁵. Those two studies, however, were quite different. The first was an assessment of baseline serum 25(OH)D concentrations measured at the start of the follow-up of the Women's Health Initiative Observational Study, involving a total of 3,345 postmenopausal women followed at 40 clinical institutions throughout the United States, where approximately 50% of the participants were receiving vitamin D supplementation. The second study, conducted by Hacker-Thompson et al.¹⁵, involved a much smaller sample, comprising 122 participants, 82% of whom were receiving vitamin D supplementation. In addition, the laboratory technique used in both studies was HPLC, a technique described as being highly sensitive¹⁴. In Saudi Arabia, blood samples were collected between January and May 2008 in the study conducted in the city of Al Khobar²⁴, whereas they were collected throughout 2011 in the study conducted in the city of Jeddah⁴³. However, the latter study provided no information on the laboratory technique used.

The countries of Europe were represented in 15 studies, the largest of which involved more than 8,500 postmenopausal women in nine countries²⁵. In that study, serum 25(OH)D concentrations were determined by radioimmunoassay, although all of the laboratory techniques described in this review were used in at least one of the studies conducted in Europe. The prevalence of hypovitaminosis D was the lowest (62.0%) in Belgium and the highest (92.5%) in

Spain. The high prevalence in the study conducted in Spain was not explained by geographic location or laboratory technique, and the most sensitive technique, HPLC, was used in that study. Morocco, the only African country represented in this review, accounted for three of the studies evaluated^{30,32,36}, among which the prevalence ranged from 77.4%, in a study using electrochemiluminescence and collecting samples between November 2008 and October 2009³², to 92.0%, in a study using chemiluminescent immunoassay and collecting samples between June and August of an unspecified year³⁰. These data did little to explain the difference found, given that the prevalence was higher in the study conducted only during the months of maximum solar radiation in that country³⁰. Five of the studies selected had been conducted in the Middle East, three in Iran^{28,33,40} and two in Saudi Arabia^{24,43}. The lowest and highest values for the prevalence of hypovitaminosis D in the Middle East (55.0% and 95.0%, respectively) were both reported in studies conducted in Saudi Arabia^{24,43}. Researchers working in countries where Islam is the predominant religion often cite cultural and clothing issues as major factors inhibiting the endogenous production of vitamin D. In this review, we found that the mean prevalence of hypovitaminosis D in the Middle East was 78.6%, lower than that found in North America (81.4%), where the culture is very different from that of Muslim countries and the clothing designed for women does not necessarily cover their entire bodies. Therefore, we can't assume that the low serum concentrations of 25(OH)D reported for Muslim countries correlate with the type of clothing used.

Studies about hypovitaminosis D in postmenopausal women brings knowledge about a factor

strongly associated with osteoporosis, which is particularly prevalent in this group. The knowledge about other population groups, such as premenopausal women, however, is desirable to allow comparisons that improve the understanding of hypovitaminosis D and its possible triggers.

This review has some limitations. The lack of standardization of the laboratory technique employed in the measurement of serum 25(OH)D concentrations and the different times of year during which the blood samples were collected made it difficult to compare the results across studies. Also, some studies with large sample sizes had to be excluded, some because they evaluated women with diseases such as osteopenia or osteoporosis and others because they did not present serum 25(OH)D concentrations with a cut-off point of 30 ng/ml. Furthermore, in some countries, a large part of the postmenopausal population use vitamin D supplementation, which creates a situation in which the potential vitamin D status of those populations could be masked. Nevertheless, we believe that this review has achieved its primary goals, showing the available information on the prevalence of hypovitaminosis D in postmenopausal women around the world and providing a global perspective on the problem.

CONCLUSION

The analysis of the selected studies revealed that the prevalence of hypovitaminosis D is high among postmenopausal women, affecting a large part of the population, even in the regions where that prevalence is lowest. Given the importance of vitamin D in women's health, further studies are needed in order to determine the actual impact of this finding.

RESUMO

INTRODUÇÃO: A hipovitaminose D é considerada um problema de saúde pública global. O conhecimento de suas verdadeiras dimensões nos permitirá projetar intervenções e planejar medidas preventivas que possam ter um impacto significativo na saúde humana.

OBJETIVO: O objetivo deste estudo foi avaliar a prevalência de hipovitaminose D, definida como concentração sérica de 25-hidroxivitamina D <30 ng/ml, em mulheres na pós-menopausa em todo o mundo, bem como identificar os potenciais fatores associados.

MÉTODOS: Uma revisão sistemática foi realizada de acordo com as recomendações de Itens de Relatórios Preferenciais para Revisão Sistemática e Meta-Análises. Os termos de pesquisa específicos foram consultados nas bases de dados Medline, Excerpta Medica e Literatura Latino-Americana e do Caribe em Ciências da Saúde, sem restrição para o ano ou idioma de publicação.

RESULTADOS: Dos 451 estudos inicialmente identificados, 32 foram selecionados para análise. Coletivamente, esses 32 estudos avaliaram 21.236 mulheres na pós-menopausa, das quais 16.440 (77,4%) apresentavam concentrações séricas de 25-hidroxivitamina D <30 ng/ml. A prevalência relatada de hipovitaminose D variou de 29% (nos Estados Unidos) a 99,4% (na China). Em seis dos estudos, a prevalência foi superior a 90%.

CONCLUSÕES: Se o critério é o ponto de corte de 30 ng/ml, a maioria das mulheres na pós-menopausa no mundo poderia ser classificada como tendo hipovitaminose D. Entre os estudos avaliados, a menor prevalência relatada foi de quase 30%. Nem latitude, região do mundo, nem metodologia laboratorial foram encontrados para ser associados com a prevalência de hipovitaminose D.

PALAVRAS-CHAVE: Deficiência de vitamina D; Vitamina D; Pós-menopausa; Clima; Prevalência.

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