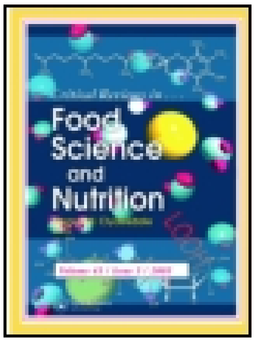

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Critical Reviews in Food Science and Nutrition

ISSN: 1040-8398 (Print) 1549-7852 (Online) Journal homepage: http://www.tandfonline.com/loi/bfsn20

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Epidemiology of vitamin D insufficiency and deficiency in a population in a sunny country: geospatial meta-analysis in Brazil

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Conflict of interest: none declared.

Running Head: Epidemiology of vitamin D deficiency and insufficiency a sunny country

Abstract

Studies conducted among populations of tropical countries have reported high prevalences of vitamin D deficiency and insufficiency. Information resulting from meta-analyses on the spatial distribution of vitamin D deficiency and insufficiency in tropical countries is still rare. The aim of this review was investigated the prevalence of vitamin D deficiency and insufficiency among the Brazilian population. Observational studies were searched in eight electronically databases. Additionally, theses and dissertations and abstracts were screened. Details on study design, methods, population, mean and data on serum concentrations of vitamin D in different age groups in Brazil were extracted. Data were pooled using a random-effects model and choropleth maps were created based on the geopolitical regions of the country. 72 published paper met the inclusion criteria. The mean vitamin D concentration among the Brazilian population between 2000 and 2017 of 67.65 nmol/L (95% CI: 65.91, 69.38 nmol/L).The prevalences of vitamin D deficiency and insufficiency were 28.16% (95% CI: 23.90, 32.40) and 45.26% (95% CI: 35.82, 54.71), respectively, for the Brazilian population. The highest prevalence of deficiency were observed in the southern and southeastern regions and the highest occurrence of vitamin D insufficiency was among the populations of the southeastern and northeastern regions. Finally, there are high prevalence of inadequate vitamin D concentrations among the population, regardless of age group in Brazil. The development of vitamin D food fortification policies in needs to be cautious and carefully planned.

Systematic Review Registration: PROSPERO number CRD42017076118.

Keywords: Vitamin D, Vitamin D deficiency, Systematic review, Meta-analysis, Sunny country.

Introduction

Vitamin D is an essential fat-soluble vitamin for calcium homeostasis and bone health (Palacios and Gonzalez, 2014). An estimated 80% to 90% of vitamin D in the human body originates from cutaneous synthesis by means of activation of 7-dehydrocholesterol through sunlight, while the remaining 20% to 10% are provided by either supplements or food (Holick, 2004).

Low-latitude regions, such as Brazil, allow photosynthesis of vitamin D at adequate concentrations during most seasons of the year because of the availability of ultraviolet rays (UVB) (Tsiaras and Weinstock, 2011) and the possibility that individuals can be exposed to sunlight. However, paradoxically, studies conducted among populations of tropical countries, such as Brazil, have reported high prevalences of vitamin D deficiency and insufficiency (Unger et al., 2010; Santos et al., 2012).

The nutritional state of vitamin D in the human body is measured from the plasma levels of 25-hydroxyvitamin D (25(OH)D). It was proposed from a review of the literature that 25(OH)D vitamin concentrations below 50 nmol/l in adults should be considered to represent vitamin deficiency, while those between 50 and 80 nmol/l 25(OH)D would indicate insufficiency (Holick, 2007). However, these cutoff points were defined based on data from Western countries with high proportions of elderly individuals in their populations (Hoteit et al., 2014).

Vitamin D deficiency and insufficiency are associated with several chronic endocrine-metabolic diseases (Holick and Chen, 2008). In this regard, meta-analysis of data has shown that vitamin D deficiency were associated with increased risk of cardiovascular diseases, diabetes, metabolic syndrome, obesity and cancer (Luo et al., 2017; Qi et al., 2017; Pereira-Santos et al., 2015; Zhang et al., 2017; Pludowski et al., 2013). The clinical manifestations of vitamin D deficiency include musculoskeletal disorders, such as rickets and osteoporosis, and increased occurrence of infections, while insufficiency predisposes individuals to the risk of developing chronic diseases with no clinical manifestations (Arabi et al., 2010).

The prevalence of vitamin D deficiency worldwide remains uncertain, since there is a lack of data from many countries (Palacios and Gonzalez, 2014). In 2007, an estimated one billion people worldwide presented either vitamin D insufficiency or deficiency (James, 2008). However, one decade later, the outcome from this estimate remains unknown. Moreover, the occurrence and distribution of vitamin D among South American populations is still poorly understood (van Schoor and Lips, 2011) and research on the nutritional state of vitamin D among the populations of sunny countries also remains scarce (Santos et al., 2012).

In Brazil, studies conducted over the past few years have revealed high prevalence of vitamin D deficiency and insufficiency among different age groups and in both sexes (Arabi, et al, 2010). In a healthy population in São Paulo, aged 18–90 years, vitamin D insufficiency (vitamin D serum 25 < 75 ml/L) was reported to affect 77.4%(Unger et al., 2010). Slightly lower prevalence of insufficiency (54.3%; 50-75 nmol/L) was identified among girls living in the municipality of Curitiba (Santos et al., 2012).

Regarding vitamin D deficiency (< 50 nmol/l), high occurrences have been observed among different groups in Brazil: 36.3% among girls living in the municipality of Curitiba(Santos et al., 2012) ; and 86% among elderly individuals in the southern region of the country (Scalco et al., 2008). Therefore, in Brazil, the results from studies on the nutritional state

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of vitamin D among different age groups, whether healthy or not, support the need to conduct a meta-analysis on vitamin D concentrations in Brazil, a tropical country with high incidence of ultraviolet rays. Thus, the objective of the present study was to estimate the prevalence and spatial distribution of vitamin D deficiency and insufficiency in the Brazilian population.

Methods

The present systematic review and meta-analysis followed the recommendations of the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines (]Stroup et al., 2000). In the supplementary file we have attached a MOOSE checklist. The protocol for this systematic review was registered in the PROSPERO registry prior to starting the literature search (CRD 42017076118).

Search strategy and eligibility criteria

The PubMed, Bireme, Scopus, Web of Science, Science Direct, SciELO and Lilacs databases were used to identify observational studies that estimated the serum concentrations of vitamin D among different age groups in Brazil. Published papers registered in these databases up to May 10, 2017 were identified using the descriptors "vitamin D", "ergocalciferols", "cholecalciferol", "Brazil" and "humans". Additionally, theses and dissertations were identified from the thesis database of Periódico Capes, and also abstracts from Brazilian conferences in the fields of endocrinology and nutrition. At the end of the search, we evaluated the reference lists of the articles on vitamin D, so as to identify any studies that were not indexed in the databases but might be pertinent for inclusion in this review (Table S1). The search strategy was designed and conducted by an epidemiologist with experience in development of systematic review and meta-analysis (MPereira-Santos).

The inclusion criteria were that the articles, theses, dissertations and conference papers should report on observational studies from research that measured the serum concentrations of vitamin D among non-hospitalized Brazilians, and should be original. These studies could be published in any language. Studies with an experimental design, opinionated reviews, editorials, review articles and case reports were excluded. The PICOS (population, intervention, comparison group, outcome, and study design) criteria was used to guide the determination of inclusion and exclusion criteria for this review (Table S2).

The published papers were managed using Mendeley and the inclusion and exclusion criteria were applied by independent reviewers (M Pereira-Santos and GQ Carvalho), who selected the eligible articles. Articles were screened and selected for full-text review if they met the selection criteria. At the end of the review, disagreements about article inclusion were resolved through reaching a consensus between the two reviewers, who discussed eligibility and came to an agreement. In the absence of a consensus, a third reviewer evaluated whether the study in question was eligible (AM Oliveira).

The serum level of 25(OH)D was used as an indicator for vitamin D status, because this metabolite reflects the combined effect of intake, skin synthesis, storage, blood transport protein and catabolism (Holick,2007). Moreover, hydroxylation of 25(OH)D to 1.25(OH)2D3 (active vitamin D) occurs in several tissues: the half-life of 25-OH-D is two to three weeks, while the half-life of 1.25(OH)2D3 is approximately six hours (Mosekilde, 2005).

Data extraction

The articles thus selected were read in their entirety and information regarding publication and design, sample, age of participants, period when the study was conducted, technique for assaying vitamin D, place of study and variables investigated was recorded using a form designed for gathering this information. The selected studies presented data from the outcomes of the study, and no contact with authors was necessary.

Means, standard deviations and prevalence data regarding vitamin D insufficiency and deficiency among the samples of the studies selected were gathered. All 25(OH)D values in nanograms per milliliter were converted to nanomoles per liter by multiplying by 2.496, as necessary.

The 25(OH)D serum concentrations were defined as the response variable in the present study. This measurement was considered in its continuous form (mean vitamin D level) and in categories, which were defined as either deficient (< 50 nmol/L) or insufficient (50 nmol/L to 80 nmol/L). Normal concentrations of vitamin D were not used in the present study.

Evaluation of the methodological quality of the studies

Two researchers (M Pereira-Santos, DB Santos) independently scored the quality of the observation studies included in the meta-analyses using an adapted version of the instrument proposed by Loney et al (1998) for critical evaluations on prevalence studies.

This instrument contains eight criteria for evaluating the methodological quality of studies. However, one criterion regarding impartial assessment made by trained evaluators was excluded because it was not considered pertinent to the nature of data collection, which in this case was blood sampling. Thus, the following criteria were used: 1) probabilistic or census sampling; 2) adequate source of sampling (official census or school census, among others); 3) previously calculated sample size; 4) adequate method for measuring vitamin D; 5) adequate response rate (> 70.0%) and description of refusals; 6) presentation of the confidence intervals and analysis of the subgroups of interest; and 7) well-described study subjects that are similar to those of the research question (Loney et al., 1998).

For each criterion met, one point was attributed to the study analyzed. High-quality studies were considered to be those that reached 6 to 7 points; moderate quality between 4 and 5 points; and low quality between 0 and 3 points (Loney et al., 1998).

The evaluation of methodological quality and risk of bias was performed in relation to dissertations, theses and articles. Conference abstracts were not assessed because the information regarding the methodological quality of this type of study was insufficient. Thus, abstracts were used to obtain vitamin D mean, prevalence and insufficiency data from studies that were not published in the form of articles or theses and dissertations. To do so, the Lattes curriculum of the authors of the abstracts was accessed to certify absence of publications regarding vitamin D.

Data analysis

The mean and prevalence of vitamin D deficiency and insufficiency were used as the meta-analysis summary measurements, according to the geopolitical regions of Brazil: north, northeast, center-west, southeast and south.

Mean vitamin D concentrations among the populations of each region in Brazil and their respective confidence intervals (95% CI) were obtained following either the fixed or the random effects model, depending on the heterogeneity among the studies. The heterogeneity and inconsistency of measurements was identified through Cochran's Q test. If heterogeneity was confirmed ($p < 0.05$; $I^2 > 50\%$), the random effects model was applied with inverse variance and weights according to the results of individual studies (Higgins and Thompson, 2002). Statistical analyses were performed using the Stata 12 software (Stata Corp, College Station, TX, USA).

Geospatial analysis

Geospatial analysis was used in the meta-analysis to obtain the mean values for the prevalences of vitamin D deficiency and insufficiency among the Brazilian population, which were calculated according to the fixed effects model. Choropleth maps were created based on the regions of the country (north, northeast, center-west, south and southeast), for the period of 2000 to 2017.

A quantification map was first created using the method of proportional symbols. To do so, occurrences of studies in each of the catalogued municipalities were quantitatively represented (Archela and Théry, 2008). This map also included the regional classification of Brazil (north, northeast, center-west, southeast and south) using the chorochromatic method, with colors as the visual variable for establishing zones. Thus, each region of the country received a specific color, which allowed them to be differentiated.

Maps of vitamin D deficiency, insufficiency and mean concentration were created using the mean vitamin D levels and prevalences of vitamin D deficiency and insufficiency from the meta-analysis. Thus, the data from each region were georeferenced such that higher prevalences of vitamin D deficiency and insufficiency were represented on a scale of increasing color intensity.

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The spatial representation of data was processed using the ArcGIS® 10.4 software, to produce thematic maps. The cartographic base used to produce the thematic maps of the present study was obtained from the Brazilian Institute for Geography and Statistics (IBGE, 2015).

Results

Studies included

Our initial search identified 3,853 published papers, of which 896 were duplicates. After screening (title and abstract), 112 studies were analyzed regarding eligibility and 36 were excluded because they did not meet the inclusion criteria. The reasons for excluding articles were that they did not meet the criteria for the type of design that had been previously defined; involved hospitalized participants; were not conducted within the study period defined; or reported on the development of quantification methods for vitamin D (Figure 1 and Table S2). In total, 72 studies were eligible for inclusion in the systematic review and meta-analysis (Figure 1, Table S3).

The studies thus analyzed (Table S4) involved a total of 340,476 Brazilians in different age groups. Most of them were cross-sectional studies (93.51%) and analyzed adults and elderly adults (Table 1 and 2). Most investigations diagnosed the vitamin D situation between 2006 and 2011 (26.7%) and between 2012 and 2017 (55%).

Quantification of serum 25(OH)D among the evaluated individuals was carried out using different techniques. Chemiluminescence was the most commonly used technique (38.15 %), followed by radioimmunoassay (21.4%). Regarding methodological quality, 52.3% of the studies were classified as presenting moderate and high levels of quality (33.5%) (Table 1).

Geospatial meta-analysis

Most of the studies were conducted in the southeastern region (58.67%) and northeastern region (20.00%), while lower proportions were conducted in the central-western and northern regions of Brazil (Figure 2. Graph A). The mean vitamin D concentration for the Brazilian population between the years 2000 and 2017, from the meta-analysis, was 67.65 nmol/L (95% CI: 65.91, 69.38 nmol/L; Figure 2. Graph B). The highest level was observed among the population in the northeastern region (74.9 nmol/L).

The prevalence of vitamin D deficiency was 28.16% (95% CI: 23.90,32.40) for the Brazilian population (Figure 4, Graph A). The highest levels of deficiency were observed in the southern and southeastern regions (Figure 3- Graph A). In turn, the rate of vitamin D insufficiency (Figure 3- Graph B) was 45.26% (95% CI: 35.82,54.71), and the highest occurrence was among the populations of the southeastern and northeastern regions (Figure 3- Graph B).

The situation of vitamin D deficiency and insufficiency did not change according to the year in which the research was conducted, nor was it influenced by the age group involved in the study (Table 2). However, the highest occurrence of vitamin D deficiency was reported among the elderly population (41.53%).

Discussion

The present study was the first meta-analysis to estimate the prevalence of vitamin D deficiency and insufficiency for the Brazilian population according to the country's geopolitical regions. The mean serum concentration of vitamin D for the population, which was obtained from observational studies, was characterized as insufficient and did not seem to differ significantly according to the age groups investigated. Thus, despite the high solar incidence in Brazil, the prevalence of vitamin D deficiency and insufficiency in this country was similar to that of nations with reduced solar availability, regardless of the age group investigated (Hilger et al., 2014).

The evidence available suggests that vitamin D deficiency can be considered to be a public health issue, since it affects all phases of life in populations on different continents. In European countries, for example, the prevalence of vitamin D deficiency among the population was reported to be 40.4% (Cashman et al., 2016). European data collected since 1913 (Mellaby, 1919) had already reported that vitamin D deficiency was more common among the population living in countries with higher solar incidence, such as Italy, Spain and Greece, than among the population of countries where solar exposure was considered inadequate (Mellaby,1919; Hilger et al., 2014). This paradox can be explained by the concern for adopting actions to prevent the risks of exposure to high levels of solar incidence, independent of the concentration of solar irradiation in these countries. This may lead to a decrease in individuals contact with solar irradiation, thus raising the prevalence of inadequate vitamin D levels in populations in tropical countries. This preventive action may also explain why there is a high prevalence of vitamin D deficiency in countries with low solar incidence.

High prevalence of vitamin D insufficiency and deficiency were identified in different age groups in the Brazilian population. A similar result was observed in a meta-analysis study that estimated occurrences of vitamin D deficiency and insufficiency in different populations around the world (Hilger et al., 2014).

Most of the studies included in the present meta-analysis evaluated sample populations of elderly individuals or menopausal women, which are populations that are vulnerable to vitamin deficiency and insufficiency due to their reduced capacity for cutaneous activation of 7-dehydrocholesterol, the precursor for vitamin D. This condition may have contributed towards increasing the prevalence of inadequate vitamin D concentrations, but does not decrease the epidemiological importance of the event. The studies selected also involved adults and adolescents. Children and pregnant women were the two least investigated groups.

Another possible cause of reduced synthesis of vitamin D is intensive use of sunscreen, which is greatly encouraged by dermatologists to prevent skin diseases. Use of sunscreen has been correlated with vitamin D insufficiency among the Brazilian population. The physiological mechanism that explains this process is the possible blocking of cutaneous activation of provitamin D due to the sun protection factor. Thus, sun protection factor (SPF) 8 can decrease vitamin D photoproduction capacity by 90%, while SPF 30 decreases it by 99% (Holick, 2007; Tsiaras and Weinstock, 2011). By analogy, this mechanism can also explain how use of sunscreen while performing daily activities, while at work, or when practicing physical activities in enclosed environments, with low solar exposure, can decrease exposure to UVB rays and thus how it may represent a risk factor for vitamin D deficiency and insufficiency.

Moreover, during winter, people use more layers of clothes and decrease their time spent outdoors. Air pollution and working in closed environments, which limit cutaneous synthesis of

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vitamin D, are other potential factor relating to vitamin D insufficiency and deficiency (Holick, 2007; Tsiaras and Weinstock, 2011).

The factors associated with vitamin D deficiency in the Brazilian studies are similar to those reported in other Western countries and include extremes of age, female sex, winter season, dark skin pigmentation, lack of sun exposure, a covered clothing style and obesity (Arabi et al., 2010). Conversely, younger age, practicing physical activities outdoors, the spring and summer seasons, living by the sea in sunny locations and lower latitudes are factors that seem to favor higher serum vitamin D concentrations among the Brazilian population (Maeda et al., 2014). However, Brazil is a continent-sized country, ranging in latitude from 5° N to 33° S. Thus, the intensity of UVB light also varies significantly across the different regions of Brazil, which can promote differences in occurrences of vitamin D insufficiency and deficiency in the populations of the various states of this country.

In lower-latitude regions, closer to the equator, cutaneous synthesis may be high due to higher temperatures and intensity of UVB rays (Palacios and Gonzalez., 2014). This explains the lower prevalence of vitamin D deficiency among the populations of the northern and northeastern regions of Brazil, where the availability of sunshine and intensity of ultraviolet rays are greater. Moreover, the habits and lifestyle of these populations also favor solar exposure, especially in coastal cities, which increases the possibility of vitamin D synthesis. Higher prevalences of deficiency were observed in the southern and southeastern regions, where the incidence of ultraviolet rays is lower. However, regarding vitamin D insufficiency, the highest occurrence was observed among the populations of states in the northeastern region. This indicates that availability of sunshine and the presence of tropical coastal cities did not seem to influence the occurrence of this problem, even if the population was protected from greater degrees of inadequacy.

The highest prevalences of vitamin D deficiency were reported from populations in the central-western, southeastern and southern regions. Environmental factors may influence the vitamin D levels in the populations of these regions. High levels of atmospheric pollution are among the environmental factors that have been reported to occur in the states of these regions (Vormittag et al., 2014). Air pollution due to particulate matter (PM_{10}), sulfur dioxide (SO_2), ozone (O_3), carbon monoxide (CO) and nitrogen oxides (NOx), among others, block ultraviolet rays and decrease the possibility that individuals will be able to photosynthesize vitamin D (Feizabad et al., 2017).

In Brazil, vitamin D intake through dietary sources is low. The small bioavailable quantities of this vitamin in food are insufficient for the physiological needs of the human body (Peters., et al. 2009). Conversely, the availability of vitamin D in foods in Brazil is mostly unknown. Not all food products include information regarding vitamin D in the tables of percentage composition. This hinders studies evaluating vitamin D intake and the repercussions of consuming dietary sources of vitamin D on the serum concentrations of this compound in any given population. Thus, quantification of vitamin D in Brazilian foods and compilation of food composition tables should be targeted in future studies.

In a prospective study on vitamin D levels in the adult population of a Finnish cohort, it was reported that food fortification, especially of fluid milk products, gave rise to adequate vitamin D status when vitamin D intake was based on nutritional recommendations [25(OH)D

≥50 nmol/L]. In such situations, supplementation would generally not be needed (Jääskeläinen et al., 2017).

Vitamin D and 25(OH)D concentrations were observed to increase after public policy actions aimed towards vitamin D fortification in foods that are frequently consumed by the population (Black et., 2012; Jääskeläinen et al., 2017). Current evidence does not support the recommendation of generalized supplementation of vitamin D through medications, for populations (Peters et al., 2009). However, the results from the present study and other studies support the recommendation that policies towards fortification of foods with vitamin D for the Brazilian population should be implemented, considering that the main source of vitamin D in Brazil consists of occasional exposure to sunlight.

The development of vitamin D food fortification policies in Brazil needs to be cautious and carefully planned. The interests of stakeholders within the pharmaceutical industry are predominantly focused towards implementation and commercialization of oral supplements and administration of mega-doses of vitamin D among individuals in different age groups, who may or may not be healthy, instead of promoting consumption of foods that have been enriched with vitamin D.

Regarding the methodological quality of the studies analyzed, most presented moderate quality and moderate risk of bias. The main problems of the studies related to absence of sample calculations and use of non-probabilistic sampling. Therefore, it is evident that epidemiological studies with representative samples should be conducted on the repercussions of vitamin D on the population's health, considering the scarcity of prevalence assessments on 25(OH)D_3 levels among specific population groups, such as pregnant women and children. The cutoff points available for evaluating vitamin D concentrations are another issue to be addressed, since these limits do not take into account climatic particularities and the physiological needs of each age group. The most common methods used to determine vitamin D concentrations were competitive assays based on specific antibodies and non-radioactive markers. However, high-performance liquid chromatography (HPLC), which requires methodological certification through DEQAS (International Vitamin D External Quality Assessment Scheme), was also used. Proficiency in determining vitamin D concentration was not observed in the methodologies of the published papers that were evaluated. Thus, there may be variations in the results regarding vitamin D concentrations in studies that do not adopt this parameter.

The present study provides contributions towards the field of public health through identifying the epidemiological situation of vitamin D deficiency and insufficiency among 340,476 Brazilians, including children, adolescents, pregnant women, adults and the elderly. Moreover, these results relating to vitamin D deficiency and insufficiency were spatially distributed across the country's geopolitical regions. However, most studies included in this meta-analysis were prevalence studies, which did not allow evaluation of causality relationships between vitamin D deficiency and insufficiency and associated factors. In addition, the northern and central-western regions were only represented by a few studies on the vitamin D situation among their populations, which hindered precise estimation of vitamin D occurrences and deficiencies.

The results from the present study indicate that there is a need for intervention actions towards controlling vitamin D deficiency. Public policies towards vitamin D fortification in foods consumed by the general public, except for specific groups, should be developed.

Supplementation can be reserved for clinical practice, to assist individuals in situations of vulnerability to vitamin D deficiency, such as elderly people, pregnant women or people for whom supplementation would have a significant impact, towards restoring and maintaining health. The standardization of cutoff points for 25(OH)D should also be further investigated, considering the physiological needs of each group. According to the evidence of this study, we recommend monitoring of vitamin D concentrations and complementation of daily needs through oral supplementation, when necessary, among groups that are vulnerable to vitamin D deficiency (Maeda et al., 2014). Vitamin D deficiency and insufficiency should be considered to be a worldwide public health issue, and Brazil forms part of this epidemiological scenario, with high prevalences of deficient and insufficient vitamin D levels among the country's population.

Funding. M. Pereira-Santos was supported by the Brazilian National Research Council (CNPq).

Declaration of interest. The authors have no interests to declare.

SUPPORTING INFORMATION

Table S1. Search strategy

Table S2. PICOS criteria for inclusion of studies

Table S3. Reasons for study exclusion

Table S4. Study inclusion

Table S5. Results of studies included in meta-analysis

MOOSE Checklist for Meta-analyses of Observational Studies

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Table 1. Main characteristics of selected studies on vitamin D concentration among the Brazilian population.

Variable	N	%
Year when study was published		
2005-2009	13	18.3
2010-2014	23	26.7
2015-2017	36	55.0
Study design		
Cross-sectional	67	92.8
Prospective cohort	5	7.1
Assay technique		
CLIA – chemiluminescence	27	38.5
HPLC – high-sensitivity liquid chromatography	14	20.0
RIA – radioimmunoassay	15	21.4
ECLIA – chemiluminescence immunoassay	4	5.7
ELISA – enzyme-linked immunosorbent assay	1	1.4
IRMA – immunoradiometric assay	3	4.5
Not reported	6	8.5

Methodological quality- 63 studies		
High quality - 6 to 7 points	21	33.5
Moderate quality - 4 to 5 points	33	52.3
Low quality - 0 to 3 points	9	14.2

Table 2. Serum vitamin D concentration and prevalence of deficiency and insufficiency of vitamin D, according to blood sampling and age group [95% confidence interval].

Variable	Number of studies	%	Mean of vitamina D	Vitamin D deficiency	Vitamin D insufficiency
Year of data colleted					
2000-2005	14	19.4	59.90 (49.47, 70.34)	39.25(20.41, 58.10)	38.24(27.03 ,49.44)
2006-2011	27	37.5	61.64(55.67, 67.617)	30.11 (18.18, 42.05)	55.54(45.48,65.60)
2012-2017	31	43.1	66.37(56.16, 76.59)	32.99 (24.28, 41.69)	46.65(40.06,53.25)
Group					

Pregnant women	5	6.6	65.0 (62.38, 67.70)	33.10 (8.84, 57.76)	48.91(8.81, 89.00)
Children	5	6.6	66.68 (35.51, 97.86)	22.95(10.00, 35.89)	44.04 (22.28,65.79)
Adolescents	11	15.7	72.44 (69.81, 75.08)	14.50 (1.80, 27.19)	57.93 (49.09, 66.76)
Adults	19	27.1	61.93 (51.18,72.68)	35.73(26.41, 45.04)	46.35 (35.78.56.92)
Elderly	20	28.5	52.859(45.01, 60.70)	41.53 (27.62, 55.44)	45.85 (36.21, 55.50)
Multiples groups	10	15.5	-	-	-

 ACCEPTED MANUSCRIPT

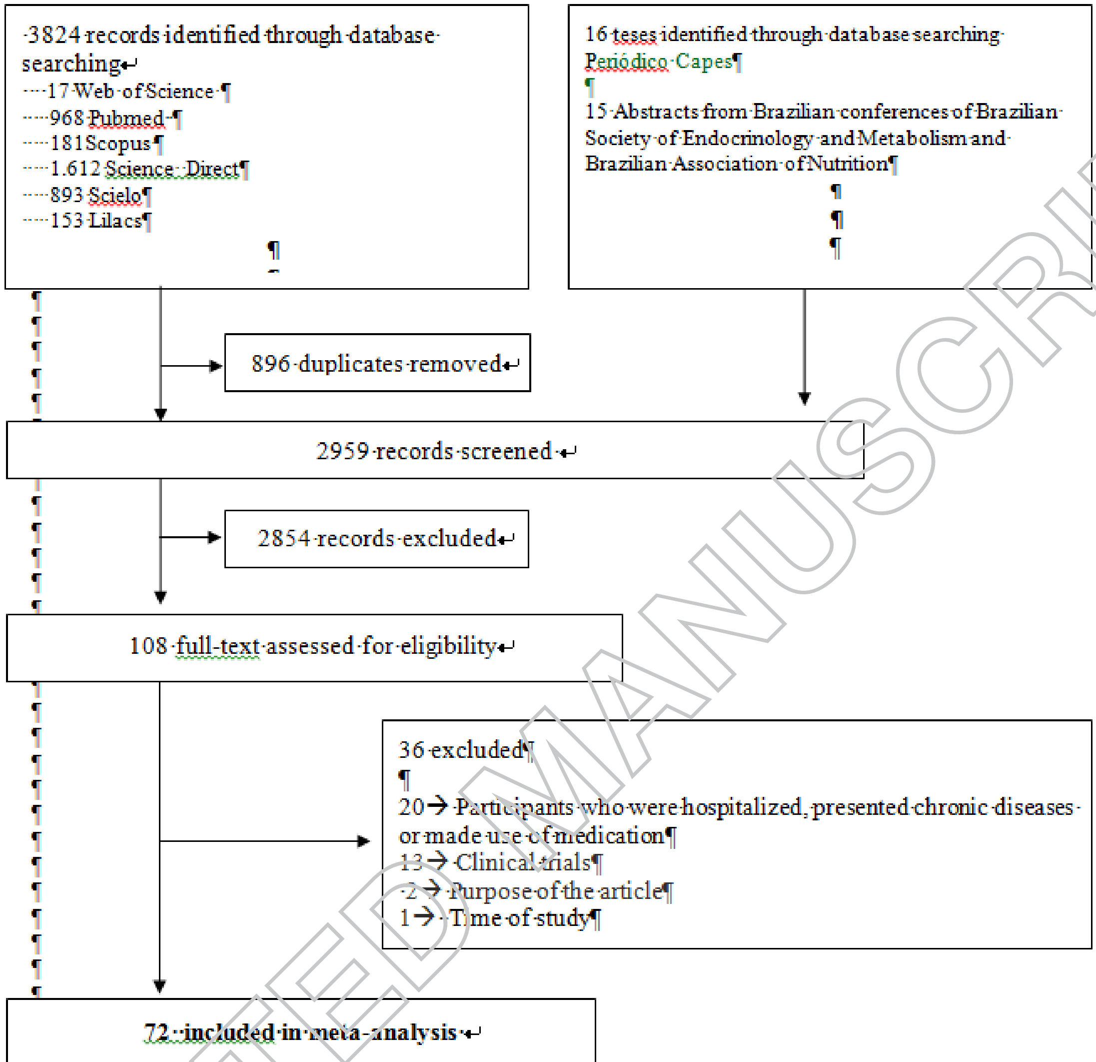
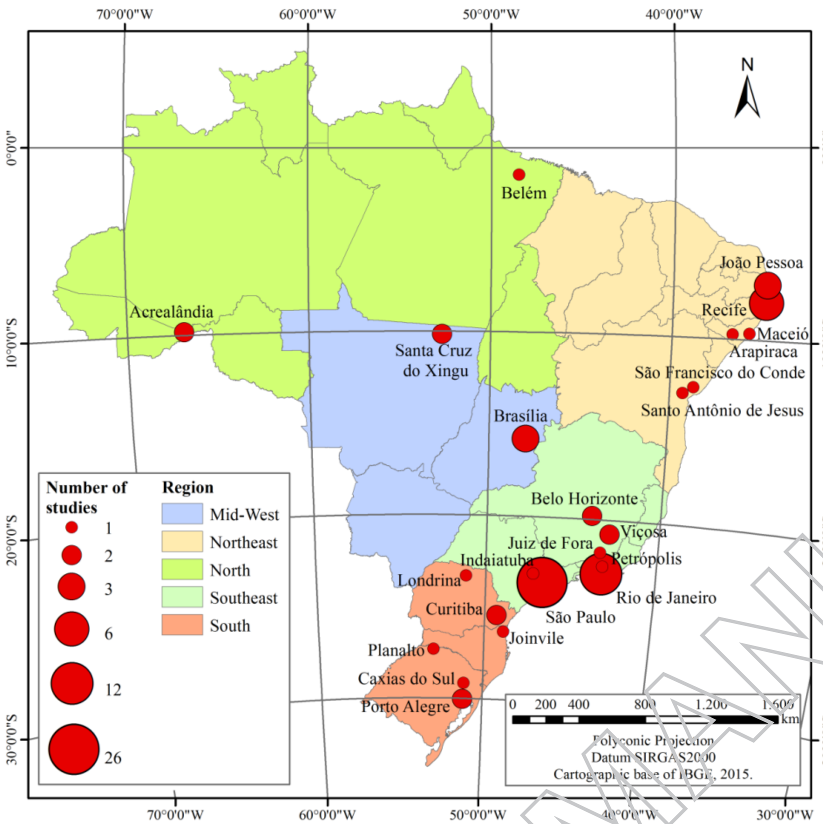


Figure 1. Study selection flowchart

A

B


70°0'0"W
60°0'0"W
50°0'0"W
40°0'0"W
30°0'0"W
0°0'0"
10°0'0"S
20°0'0"S
30°0'0"S
N
Belém
João Pessoa
Recife
Maceió
Arapiraca
São Francisco do Conde
Santo Antônio de Jesus
Acrealândia
Santa Cruz do Xingu
Brasília
Belo Horizonte
Viçosa
Juiz de Fora
Petrópolis
Indaiatuba
Londrina
Rio de Janeiro
São Paulo
Curitiba
Joinvile
Planalto
Caxias do Sul
Porto Alegre
Number of studies
1
2
3
6
12
26
Region
Mid-West
Northeast
North
Southeast
South
0 200 400 800 1.200 1.600 km
Polyconic Projection
Datum SIRGAS2000
Cartographic base of IBGE, 2015.

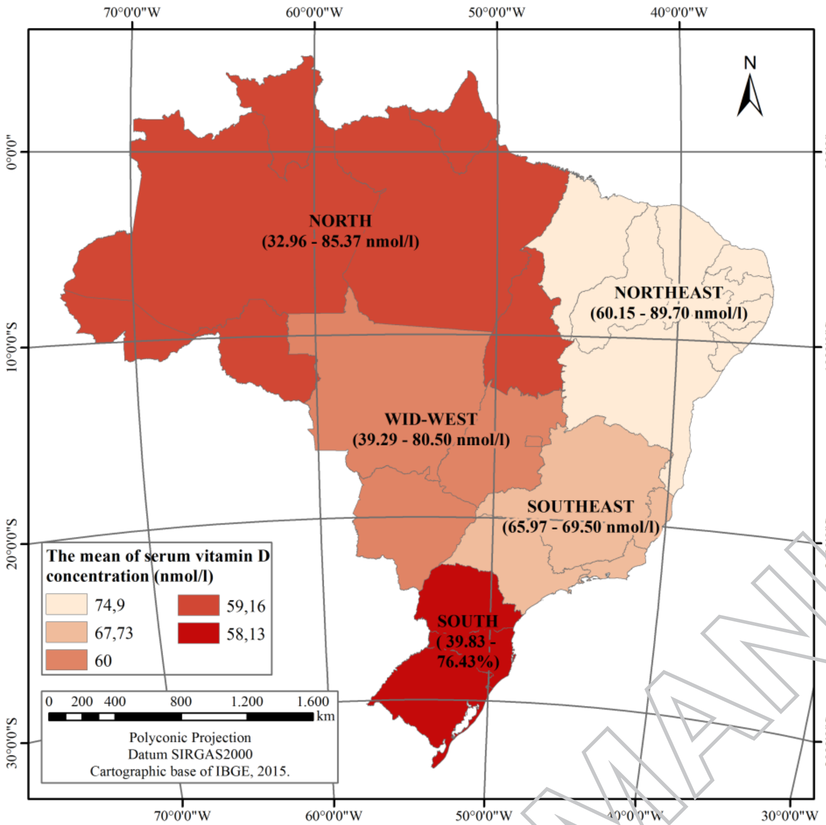


Figure 2. Occurrences of studies in each of the catalogued municipalities (A) and mean of vitamin D levels (B) among the Brazilian population.

A

B

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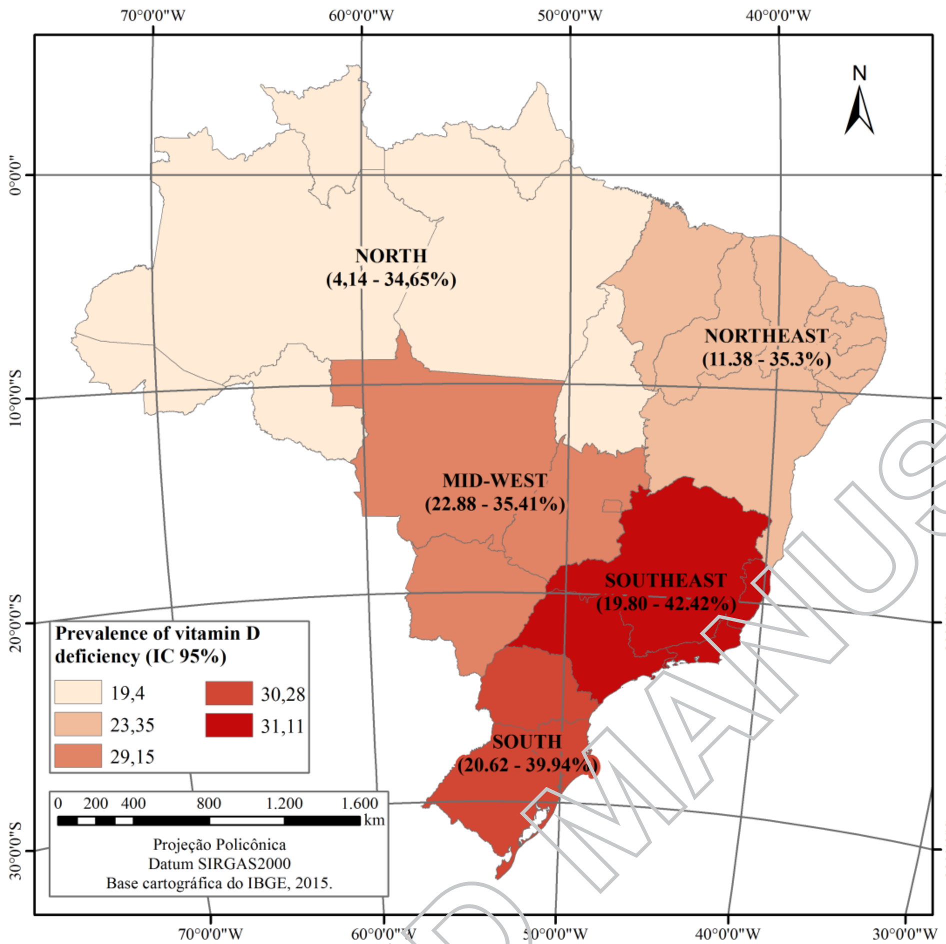

70°0'0"W
60°0'0"W
50°0'0"W
40°0'0"W
30°0'0"W
0°0'0"
10°0'0"S
20°0'0"S
30°0'0"S
N
NORTH
(4,14 - 34,65%)
NORTHEAST
(11.38 - 35.3%)
MID-WEST
(22.88 - 35.41%)
SOUTHEAST
(19.80 - 42.42%)
SOUTH
(20.62 - 39.94%)
Prevalence of vitamin D deficiency (IC 95%)
19,4
23,35
29,15
30,28
31,11
0 200 400 800 1.200 1.600
km
Projeção Policônica
Datum SIRGAS2000
Base cartográfica do IBGE, 2015.

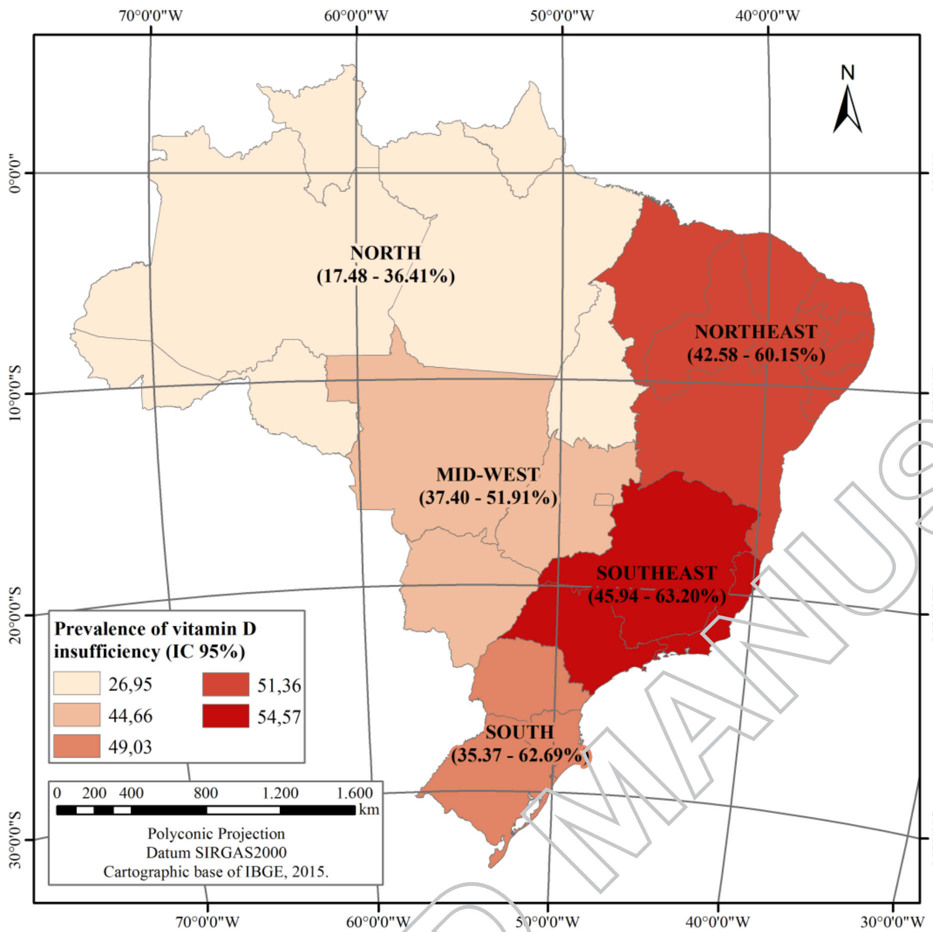
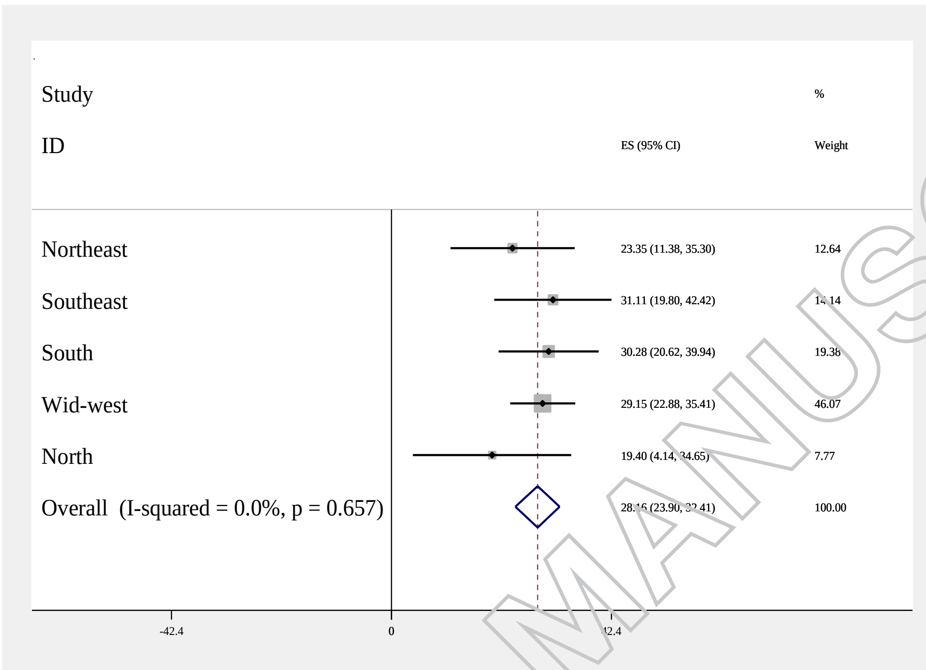


Figure 3. Spatial representation for the prevalences of vitamin D deficiency (A) and insufficiency (B) among the Brazilian population.

A

B


Study
ID
ES (95% CI)
%
Weight
Northeast
23.35 (11.38, 35.30)
12.64
Southeast
31.11 (19.80, 42.42)
South
30.28 (20.62, 39.94)
Wid-west
29.15 (22.88, 35.41)
46.07
North
7.77
Overall (I-squared = 0.0%, p = 0.657)
100.00
-42.4
0

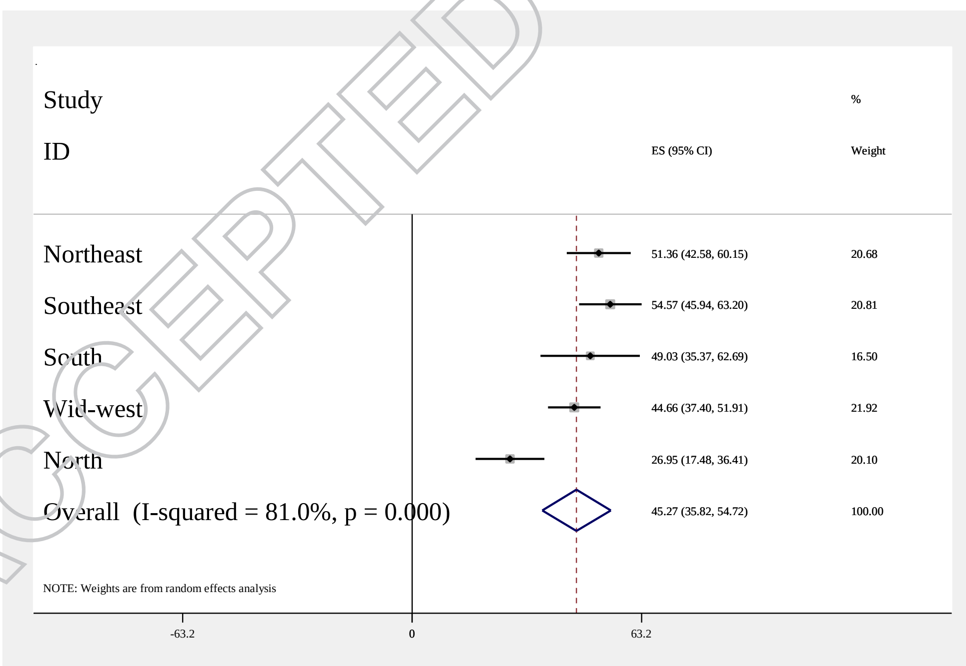

Study
ID
ES (95% CI)
%
Weight
Northeast
51.36 (42.58, 60.15)
20.68
Southeast
54.57 (45.94, 63.20)
20.81
South
49.03 (35.37, 62.69)
16.50
Wid-west
44.66 (37.40, 51.91)
21.92
North
26.95 (17.48, 36.41)
20.10
Overall (I-squared = 81.0%, p = 0.000)
45.27 (35.82, 54.72)
100.00
NOTE: Weights are from random effects analysis
-63.2
0
63.2

Figure 4. Meta-analysis of prevalence of vitamin D deficiency (A) and insufficiency (B) among the Brazilian population.

