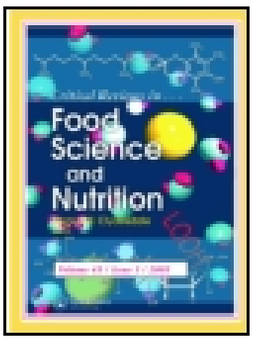

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REVIEW

Vitamin D deficiency aggravates COVID-19: systematic review and meta-analysis

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ABSTRACT

There is still limited evidence regarding the influence of vitamin D in people with COVID-19. In this systematic review and meta-analysis, we analyze the association between vitamin D deficiency and COVID-19 severity, via an analysis of the prevalence of vitamin D deficiency and insufficiency in people with the disease. Five online databases—Embase, PubMed, Scopus, Web of Science, ScienceDirect and pre-print Medrevix were searched. The inclusion criteria were observational studies measuring serum vitamin D in adult and elderly subjects with COVID-19. The main outcome was the prevalence of vitamin D deficiency in severe cases of COVID-19. We carried out a meta-analysis with random effect measures. We identified 1542 articles and selected 27. Vitamin D deficiency was not associated with a higher chance of infection by COVID-19 (OR = 1.35; 95% CI = 0.80–1.88), but we identified that severe cases of COVID-19 present 64% (OR = 1.64; 95% CI = 1.30–2.09) more vitamin D deficiency compared with mild cases. A vitamin D concentration insufficiency increased hospitalization (OR = 1.81, 95% CI = 1.41–2.21) and mortality from COVID-19 (OR = 1.82, 95% CI = 1.06–2.58). We observed a positive association between vitamin D deficiency and the severity of the disease.

KEYWORDS

Coronavirus; COVID-19; meta-analysis; pandemic; vitamin D

Introduction

The COVID-19 pandemic has raised discussions regarding the benefits of vitamin D in preventing and treating the disease. This is because sufficient blood vitamin D levels play an effective role in immune system functioning, which can help in a satisfactory cellular response and in protecting against the severity of infections caused by microorganisms (Ali 2020). Vitamin D deficiency (25(OH)D below 50 nmol/l) has been associated with severe COVID-19 (Speeckaert and Delanghe 2020), raising discussions about the benefits of supplementation of this vitamin when treating the illness caused by SARS-CoV-2.

Exposure to sunlight contributes to vitamin D production in the human body, which supports the hypothesis that populations with more regular exposure to UV radiation from the sun may have less vitamin D deficiency than those with less exposure and, consequently, lower COVID-19 mortality rates (Whittemore 2020). From this perspective, ecological studies have been conducted associating latitude, mean vitamin D levels in the population, and COVID-19 mortality rates (Whittemore 2020).

In Europe, an association has been identified between vitamin D deficiency in the population and higher COVID-19 mortality rates (Ali 2020). It has been suggested that countries closer to the equator present lower COVID-19 mortality rates than those further from the equator. This is probability because UV radiation from sunlight increases with proximity to the equator, which can contribute to the prevention of vitamin D deficiency in populations (Whittemore 2020). This draws attention since exactly these outcomes have been indicated in countries with a high prevalence of vitamin D deficiency in the population, such as Italy, France, and Spain (Ali 2020). It also warrants mentioning that most of the ecological studies available are subject to various biases, including confounding bias, involving the incidence of disease and demography of countries at different stages of the pandemic. These studies are also insufficient in demonstrating any causality relationship.

It should be noted that other factors are also related to the severity of the COVID-19 disease, such as respiratory disorders, heart conditions, obesity, and hypertension (Alberca et al. 2020). Some of these factors are also intimately linked with vitamin D deficiency (de Oliveira et al. 2020; Alberca et al. 2020). Thus, the association between COVID-19 and vitamin D may be confounded with chronic diseases.

Despite the growing number of studies on vitamin D and COVID-19, no meta-analyses were found, including in the international epidemiological literature, on the relationship

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between vitamin D deficiency and COVID-19 severity in different populations. It is thus important to aggregate the evidence and systematize information on this topic. Therefore, the aim of this study is to evaluate the association between vitamin D deficiency and COVID-19 severity, via an analysis of the prevalence of vitamin D deficiency and insufficiency in people with the disease.

Methodology

This study is a systematic review involving a meta-analysis developed according to the norms of Meta-Analysis of Observational Studies in Epidemiology (MOOSE) (Stroup et al. 2000), with the following investigative questions: What is the prevalence of vitamin D deficiency in people with COVID-19? Is vitamin D deficiency associated with COVID-19 severity?

Sources of information and search strategies

Three independent reviewers conducted the search for studies in the Embase, PubMed, Scopus, Web of Science, and ScienceDirect databases and pre-print Medrevix published up to October 9, 2020. To identify the publications, the descriptors "Vitamin D" and "COVID-19" (supporting information Table S1) were adopted. In addition, the lists of bibliographical references of the relevant studies were examined in order to identify potentially eligible ones.

The publications were managed in the Mendeley Desktop application (version 1.18; © 2008–2018 Mendeley Ltd.) to remove the duplicates and apply the inclusion criteria.

Eligibility criteria

Using the PECO strategy (patient, exposure, comparison, outcome—a strategy that helps in the construction of the research question and search for evidence), we adopted as inclusion criteria the studies that:

- only involved individuals in the adult and elderly age group;
- involved individuals with COVID-19;
- compared the prevalence of vitamin D deficiency according to COVID-19 severity;
- classified the serum VitD concentration outcome in the study's participants: mean VitD (nmol/l; ng/ml), insufficiency, and deficiency; and
- are case series, cross-sectional, cohort, and case-control studies.

We applied no language or publication status limits. We excluded ecological studies, as they did not measure the vitamin D levels in the population, as well as literature or editorial reviews.

Study selection and data extraction

According to the eligibility criteria, the authors A.D.D. and L.M.G.A. chose the studies independently in two stages, evaluating the title and abstract and, subsequently, by reading the full text. Disagreements were resolved by consensus. In the absence of a consensus, a third reviewer was consulted (M.P.).

To extract the data, we elaborated an electronic spreadsheet in which information about the following was recorded: the authors, year of publication, city, region of the country, age group, sample size, prevalence of vitamin D deficiency and insufficiency, mean age, standard deviation of age, vitamin D dosage technique, and COVID-19 diagnostic method.

Evaluation of the methodological quality of the studies included

Methodological quality was assessed according to the Research Triangle Institute Item Bank (RTI–Item Bank) scale, which assesses the risk of bias (Viswanathan and Berkman 2012). The RTI-Item Bank contains 29 items for evaluating studies, of which seven were applied to observational studies included in this review (supporting information Table S2). This tool considers the following issues: (1) clear inclusion and exclusion criteria; (2) uniformly distributed inclusion and exclusion criteria; (3) appropriate sample size; (4) whether the inclusion and exclusion criteria were applied using valid and reliable measures; (5) whether the results were analyzed using valid and reliable measures, including all participants; and (6) whether important confounding and effect variables were taken into account in the study and/or analysis.

One point (yes) or zero (no) was scored for each item. The total score in all items can generate an overall quality index that ranges from 0 to 6. According to the scores, the risk of bias is classified as low risk (=6 points) or high risk (<6 points) (Viswanathan and Berkman 2012).

Study outcomes

The main outcome was vitamin D deficiency and COVID-19 severity. We therefore compared the proportion of patients with vitamin D deficiency in those with mild versus severe COVID-19. Second, we analyzed the occurrence of vitamin D deficiency and insufficiency and the association for vitamin D deficiency and the occurrence of infection, hospitalization, and mortality from COVID-19.

Data analysis

We used the odds ratio (OR) to estimate the association between vitamin D and severe COVID-19. An OR with 95% confidence intervals (CIs) was obtained following the random effects model, depending on the heterogeneity between the studies (Higgins and Thompson 2002). We used the weighted mean difference (WMD) and its 95% CI to compare the means according to subgroup analyses. The DerSimonian and Laird method was used to estimate the

Table 1. Main characteristics of included articles evaluate the association between vitamin D deficiency and COVID-19.

Authors	Location	Who region	Type of study	Age, mean (SD)	Sample	Female, N (%)	Risk of bias score	Included in the meta-analysis
Alipio (2020)	Southern Asian countries	South Asia	Restrospective multicenter		212	—	1	Yes
Baktash et al. (2020)	UK	European	Cohort	81	70 COVID-19 patients and 35 COVID-19 negative	48 (45.7)	1	Yes
Carpagnano et al. (2020)	Saarland, Germany	European	Retrospective	65(13)	42	12(39)	4	Yes
Cuñat, Ojeda, and Calvo (2020)	Barcelona, Spain	European	Retrospective cross-sectional	64.94 (10.69)	17	7 (41.2)	1	No
D'Avolio et al. (2020)	Switzerland	European	Cohort	74	27	8 (29.6)	4	No
Darling et al. (2020)	England	European	Retrospective cross-sectional	57.5 (8.7)	COVID-19 positive (n = 580), negative controls (n = 723)	244 (42.0)	2	Yes
Lau et al. (2020)	Louisiana, USA	Americas	Retrospective	65.2 (16.2)	20	11 (55.0)	2	Yes
Faniyi et al. (2020)	London, England	European	Cohort	Median (IQR) = 41 (30–50)	168	100 (26)	6	Yes
Faul et al. (2020)	Abbotstown, Dublin	European	Cohort	60(15)	33	0.0	3	Yes
Hastie, Mackay, et al. (2020) and Hastie, Pell, et al. (2020)	United Kingdom	European	Cohort	49	COVID-19 (n = 449) No COVID-19 (n = 348.598)	184 (40.9)	4	Yes
Im et al. (2020)	South Korea	Western Pacific	Cross-sectional	52.2 (20.7)	50 hospitalized patients with COVID-19 and 150 COVID-19 negative	29 (58)	4	Yes
Karonova, Andreeva, and Vashukova (2020)	Saint-Petersburg, Russia	European	Cross-sectional	53.2(15.7)	80	37 (46.2)	4	Yes
Macaya et al. (2020)	Madrid, Spain	European	Retrospective	63	80 patients	45 (56,2)	4	Yes
Maghbooli et al. (2020)	Tehran, Iran	Eastern Mediterranean	Cross-sectional	58.7 (15.2)	235 patients	91 (38,7)	6	Yes
Mardani et al. (2020)	Tehran, Iran	Eastern Mediterranean	Cross-sectional	42	63 COVID-19 patients and 60 COVID-19 negative	58	4	Yes
Meltzer et al. (2020)	Chicago, USA	Americas	Retrospective cohort	45.7	758	2970 (65)	3	Yes
Mendy et al. (2020)	Ohio, Kentucky, and Indiana—USA	Americas	Cohort	49.5 (1.3)	689	324 (47)	4	Yes
Merzon et al. (2020b)	Israel	European	Population-based	35.58	782	397 (50.7)	6	Yes
Panagiotou et al. (2020)	United Kingdom	European	Retrospective	68.7	134 COVID-19 Non- ITU wards (n = 92) Intensive Therapy Unit (n = 42)	61 (45.5)	5	Yes
Pinzon, Angela, and Pradana (2020)	Yogyakarta, Indonesia	South-East Asia	Case series	49.6	10 cases	5 (50.0)	1	Yes
Pizzini et al. (2020)	Innsbruck, Austria	Western Pacific	Cohort	58 (14)	109 patients	44 (40)	3	Yes
Radujkovic et al. (2020)	Heidelberg, Germany	European	Cohort		185	90 (49)	5	Yes

(*continued*)

Table 1. Continued.

Authors	Location	Who region	Type of study	Age, mean (SD)	Sample	Female, N (%)	Risk of bias score	Included in the meta-analysis
				Median age [years] (IQR) 60 (49–70)				
Raharusun et al. (2020)	Sukamara, Indonesia	South-East Asia	Retrospective cohort study	54.5	780 Expired (n = 380) Active (n = 400)	400 (51,3)	3	Yes
Raisi et al. (2020)	United Kingdom	European	Prospective cohort	68.11 (9.23)	4510 (positive, n = 1326; negative, n = 3184)	630 (47.5)	6	Yes
Smet et al. (2020)	West Flanders, Belgium	European	Retrospective	69.5	186	77 (41.4)	4	Yes
Sun et al. 2020	China	Western Pacific	Clinical retrospective	65	241 and 26 were tested to determine vitamin D levels	129 (53,5)	3	Yes
Glicio (2020)	South Asia	South Asia	Retrospective	72.80	176	53	0	Yes

parameter of variability between the studies, and we evaluated the heterogeneity using Cochran's Q test, deriving its magnitude from the I square (I^2) (DerSimonian and Laird 1986). We considered a minimum number of eight studies for the elaboration of the funnel graph (Lau et al. 2006).

We also calculated the prevalence of vitamin D deficiency and insufficiency, with a 95% CIs in people with COVID-19. The data included in the meta-analysis were transformed using the logit function to satisfy the assumption of normality of the meta-analytical random-effects model. The CIs for the results of individual studies were calculated using the Copper–Pearson method. Publication bias was not evaluated since it was not appropriate in the case of prevalence assessment in meta-analyses (Hunter et al. 2014).

In all the analyses, we considered a p value <0.05 as statistically significant. We conducted the statistical analyses using the STATA 14 program (Stata Corp, College Station, TX).

Results

Characteristics and qualitative synthesis

The search strategies are presented in Figure 1. We identified 1542 studies in the databases consulted. After removing the duplicate records, 714 remained for the titles and abstracts analysis, of which we chose 27 for qualitative synthesis and included 25 in the meta-analysis. The reasons for exclusion of the articles were the objective of the studies (n = 5), review study (n = 5) and ecological study designs (n = 3).

The main characteristics and results of the selected studies are presented in Table 1 and supporting information Table S3. The studies published in 2020 and presented 372332 participants. Regarding the regions where the studies were conducted, we observed a greater concentration in Europe (n = 15; 55.5%; Table 1). In terms of design, we noted the predominance of a cohort design (n = 11; 40.7%).

There was a predominance of articles with a methodological quality classified as high risk of bias (n = 23, 74%). Four articles had a low risk of bias (Merzon et al. 2020a; Raisi et al. 2020; Maghbooli et al. 2020; Faniyi et al. 2020). Adequate evaluation of the outcome, appropriate sample selection and uniformity of the inclusion criteria were the main problems that contributed to the high risk of bias (Figure 2).

Results of the meta-analysis

The meta-analysis included 8176 COVID-19 patients participating in 26 studies and the mean age was 58 years old (95% CI = 54–62). The results of the meta-analysis can be found in Figures 3–5.

Three studies (four article) recorded the absence of a statistically significant association between vitamin D concentrations <50nmol/l and infection by COVID-19 (OR = 1.35; 95% CI = 0.80–1.88; I^2 = 83.0%; Figure 3). However, the values of serum vitamin D in patients with COVID-19 in relation to healthy ones was low concentration (WMD = −17.02, 95% CI = −29.61 to −4.43; I^2 = 99.5%; supporting information Figure S1).

In 17 studies, we observed the prevalence of vitamin D deficiency in 39% (95% CI = 30–48; I^2 = 97.90%; supporting information Figure S2A) of the individuals with COVID-19; the insufficiency of this vitamin, obtained in 13 studies, was 38 (95% CI = 20–56; I^2 = 99.42%; supporting information Figure S2B) in this group.

Regarding the severity of the disease, it was recorded that individuals with severe COVID-19 present 65% (OR = 1.65; 95% CI = 1.30–2.09; I^2 = 35.7%; Figure 4) more vitamin D deficiency compared with mild cases of the disease. Furthermore, the funnel plot, produced from the data of the studies included in the meta-analysis, shows a satisfactory distribution within the funnel plot, evidencing that there was no publication bias (Figure 4). In a meta-

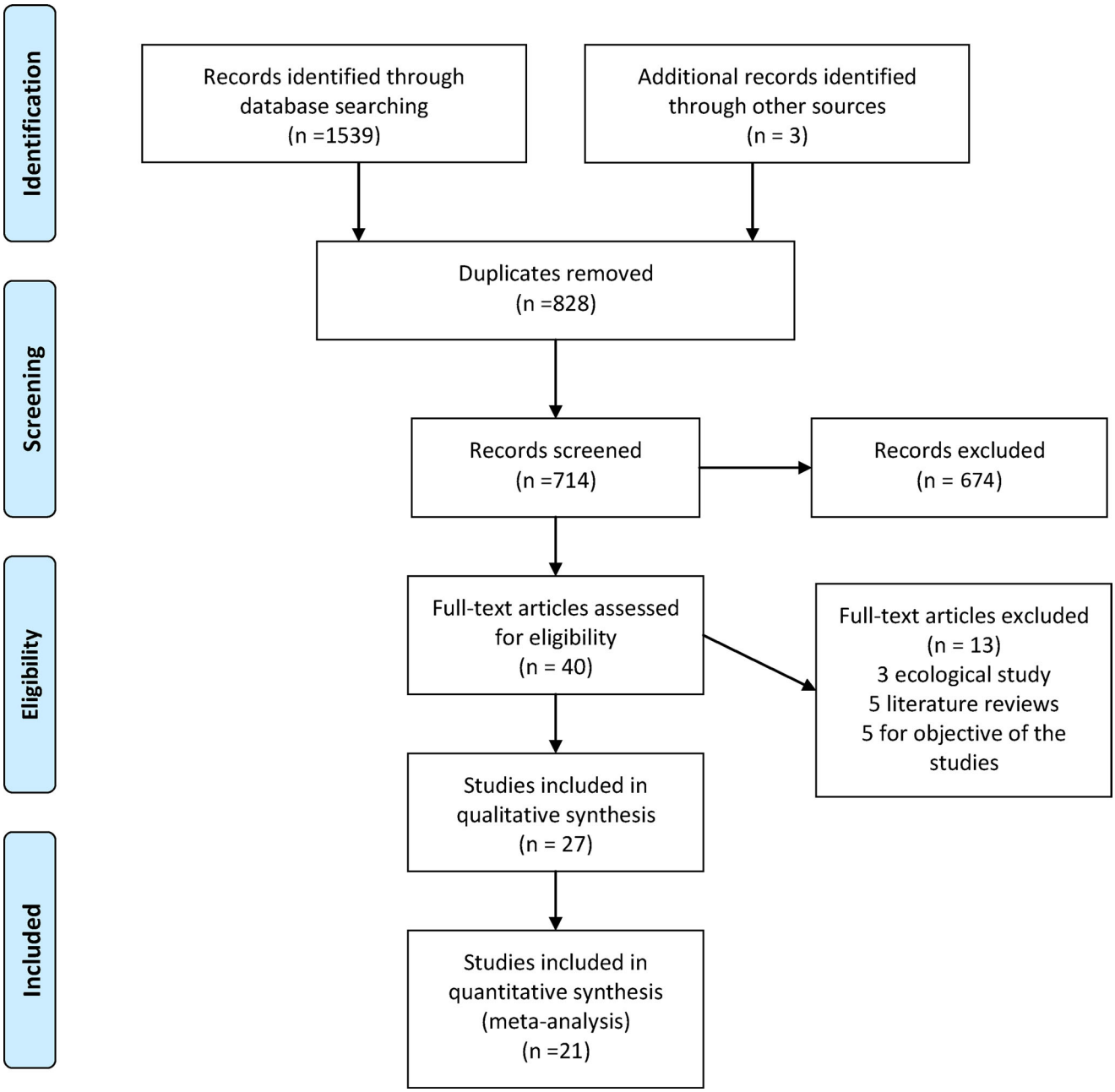

Figure 1. Study selection flowchart.

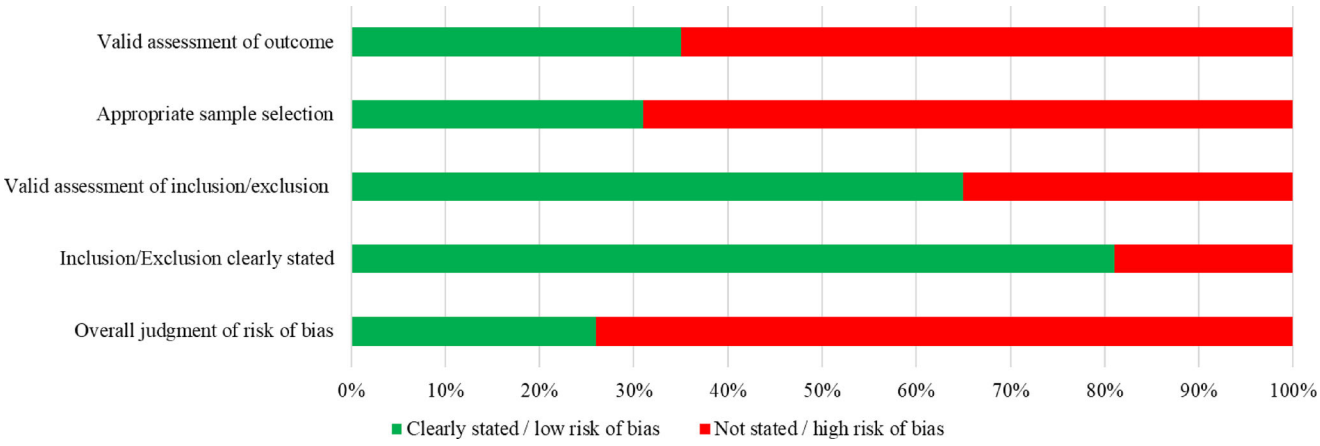

Figure 2. Risk of bias: summary of all studies.

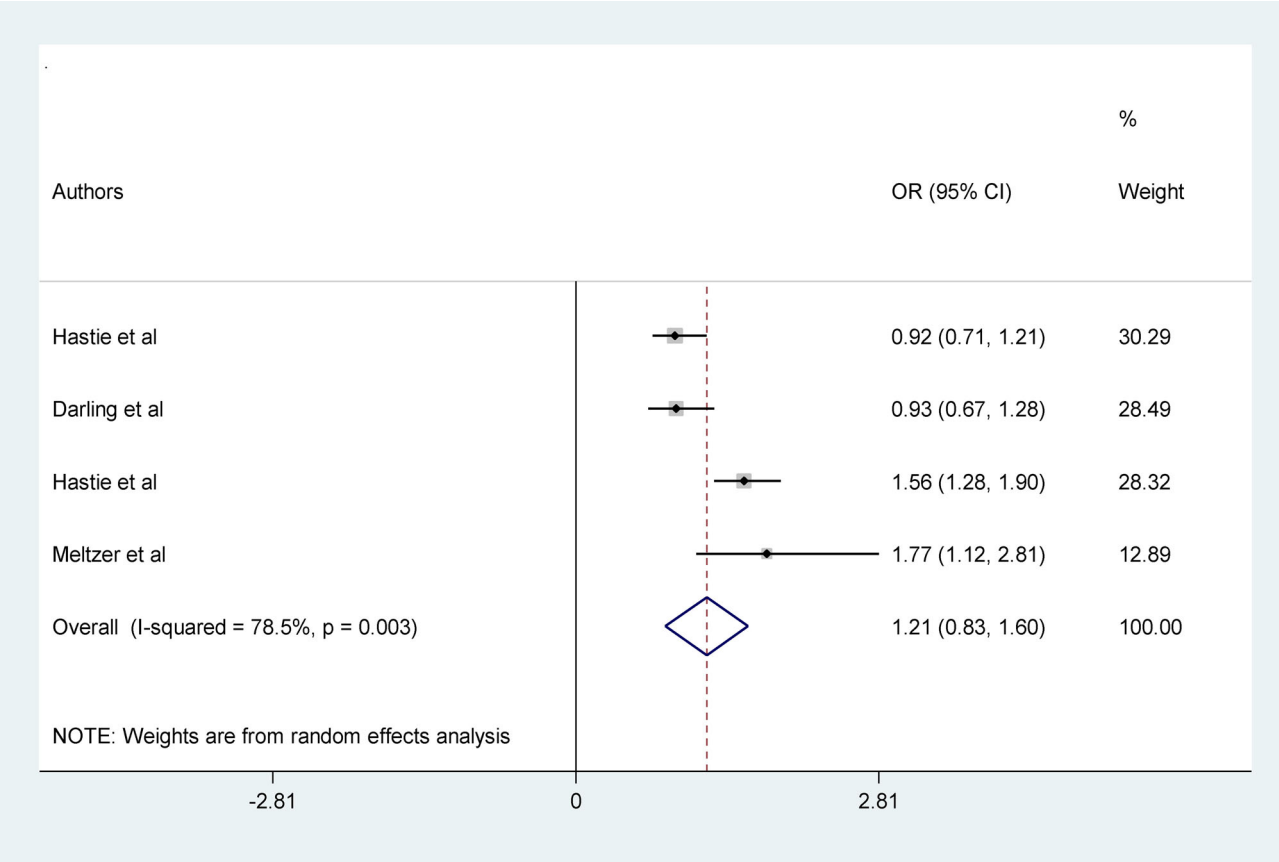

Figure 3. Vitamin D deficiency (<50 nmol/L) and chance of infection for COVID-19.

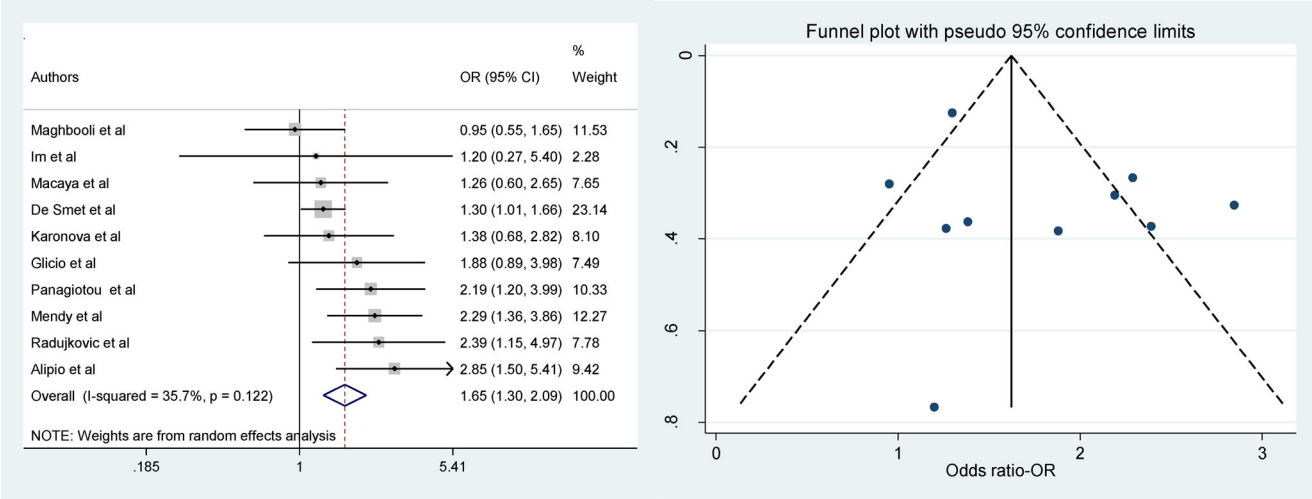

Figure 4. Forest plot and funnel plot of the association between vitamin D deficiency and occurrence of several COVID-19.

analysis with eight studies, it was recorded that patients with severe COVID-19 have −15.63 nmol/L of the vitamin (95% CI = −27.73 to −3.53; I^2 = 92.3%; supporting information Figure S3). In tree studies, a vitamin D concentration of less than 75 nom/L increased hospitalization for COVID-19 (OR = 1.81, 95% CI = 1.41–2.21; I^2 = 0.0%; Figure 4), and this deficiency was associated with COVID-19 mortality (OR = 1.82, 95% CI = 1.06–2.58; I^2 = 59.0%; Figure 5).

Discussion

The results of this study reveal that vitamin D deficiency can present an association with COVID-19 severity, especially in the elderly. This is explained by both lower exposure to sunlight and lower 7-dehydrocholesterol values in the skin, which compromises the cutaneous synthesis of 25(OH)D in the elderly (Adami et al. 2009). Moreover, ageing is accompanied by a greater occurrence of chronic diseases (Pimenta et al. 2015), considered a risk factor for

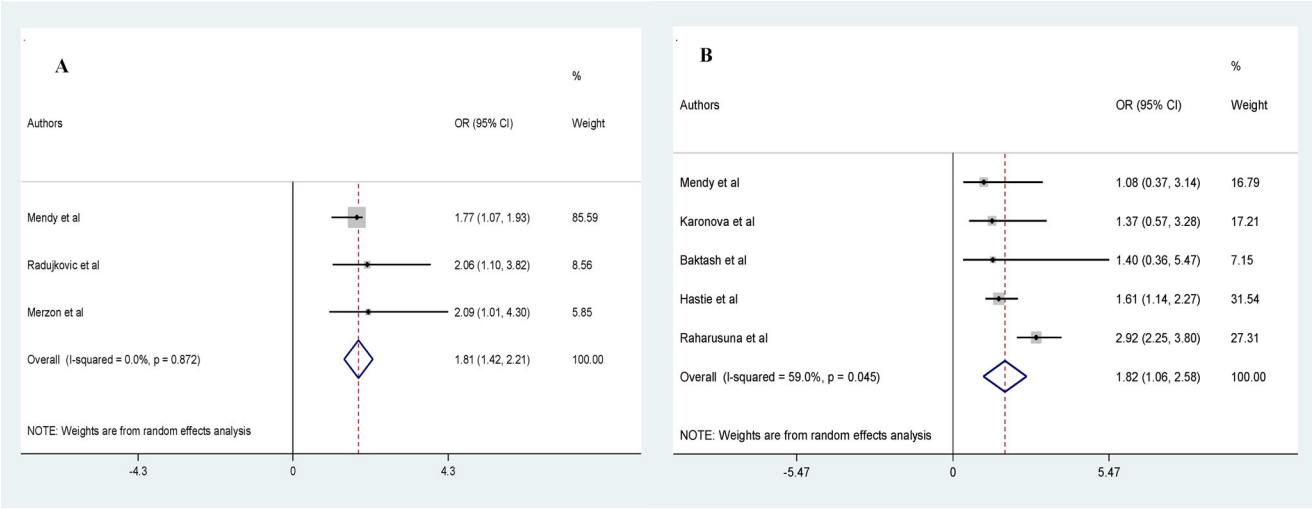

Figure 5. Vitamin D deficiency and chance of hospitalization (A) and death (B) in patients with COVID-19 infection.

COVID-19 severity (Jin et al. 2020), and which are commonly treated with anti-inflammatory, anti-hypertensive, and endocrine agents and with drugs that can also interfere in blood vitamin D levels (Grant et al. 2020).

Within this context, studies conducted in the United Kingdom, Italy and in China (Zhou et al. 2020; Hewitt et al. 2020) reveal high COVID-19 mortality rates in those older than 65, a group that is more susceptible to inadequate levels of vitamin D. In this sense, it is observed that patients with severe cases of COVID-19, characterized by respiratory difficulty, oxygen saturation at rest $\leq$93%, a partial pressure of arterial oxygen to fraction of inspired oxygen ratio $\leq$300 mmHg, or complications of the disease, such as the need for mechanical ventilation, septic shock, or insufficiency of non-respiratory organs (Liu et al. 2020), are also those who tend to present inadequate blood vitamin D levels. One possible explanation is that 25(OH)D concentration is inversely associated with pro-inflammatory cytokines, such as IL-6, an increase in C-reactive protein (CRP), an increased risk of SDRA, and cardiac insufficiency (Alipio 2020), conditions that relate to the severity of the case and to its unfavorable outcomes. One retrospective study conducted in the south of Asia reinforces this hypothesis, as it shows significantly lower vitamin D levels according to the severity of the disease, with a confirmed association for critical cases of COVID-19 and low blood 25(OH)D levels (Alipio 2020).

Despite higher levels of this being associated with defenses and with a favorable prognoses in other viral infections (Chirumbolo et al. 2017), it cannot be affirmed that there is an association between 25(OH)D deficiency and greater vulnerability to infection by COVID-19, given that, until now, no causal relationship has been tested and blood vitamin D levels have not been evaluated in patients infected by SARS-CoV-2.

Apparently, vitamin D is related with controlling the progression of COVID-19 and with the evolution of mortality due to the infection; however, other factors should be observed, such as the previous existence of comorbidities in these patients and, especially, their age, since reduced blood 25(OH)D levels are more prevalent in the elderly portion of the population (Marazuela, Giustina, and Puig-Domingo 2020; Naja and Hamadeh 2020). Besides the severity of the disease, the vitamin D levels can reduce levels of the C-reactive protein (CRP)—an increased inflammatory marker in infection—as well as the negative immunomodulation of the inflammatory cytokine storm caused by COVID-19.

We observed that vitamin D deficiency does not increase the risk of COVID-19. However, we should recognize that maintaining adequate nutrition is essential for health in the pandemic context, given that there are other important nutrients for maintaining health and immune system modulation, such as proteins, polyunsaturated fatty acids, vitamins (B6, B12, C, D, E, and folate) and minerals (zinc, copper, and selenium), among others (Marazuela, Giustina, and Puig-Domingo 2020; Naja and Hamadeh 2020). Therefore, correcting nutritional deficiencies is important for improving individuals' health, independently of the presence of comorbidities.

Limitations and recommendations of the study

This is the first systematic review we know of that reports the relationship between vitamin D levels and COVID-19 severity. This review also has its limitations. We perceived that the results of the studies included in this review were not stratified according to the sex of the participants. This limitation may be detrimental to the validity of some findings, as body composition and percentage of body fat differ between men and women and may affect vitamin D levels and COVID-19 severity. Moreover, the studies showed various methodological divergences that prevent exploring the heterogeneity of the meta-analysis and conducting subgroup analyses due to confounding variables. Furthermore, most of the studies chosen presented a high risk of bias. This is because the studies were conducted using hospital-based samples and the data in these studies are taken from secondary recordings in patient records. In addition, some studies did not clearly report the vitamin D dosage strategies or COVID-19 detection method. It should also be

considered that confounding factors, such as age, sex, and the presence of comorbidities, were not used in most of the studies. Such variables are determinants of COVID-19 severity. Thus, it is necessary to consider these aspects in future studies on the topic.

Our review has some strong points. The information generated based on our study has biological plausibility and importance for the field of public health and finds robustness and coherence in the literature on the topic. In this review, we carried out a search for studies in pre-print databases, and although the use of published studies such as pre-prints may be criticized, pre-prints enabled us to obtain a greater number of studies to include in the meta-analysis. We carried out the eligibility process and data collection using independent authors and analyzed the risk of bias. These procedures reduce the possibility of bias in the results of this review.

We recommend developing prospective studies, especially clinical trials, with different age groups and climatic conditions, designed to evaluate causality with vitamin D and COVID-19 outcomes. The same COVID-19 diagnostic criteria and vitamin D determination for all participants in the study should also be adopted.

In conclusion, the results of the meta-analysis confirm the high prevalence of vitamin D deficiency in people with COVID-19, especially the elderly. We should add that vitamin D deficiency was not associated with COVID-19 infection. However, we observed a positive association between vitamin D deficiency and the severity of the disease. From this perspective, evaluating blood vitamin D levels could be considered in the clinical practice of health professionals. Moreover, vitamin D supplementation could be considered in patients with vitamin D deficiency and insufficiency, if they have COVID-19. However, there is no support for supplementation among groups with normal blood vitamin D values with the aim of prevention, prophylaxis or reducing the severity of the disease.

Authors' contributions

A.D.D. and L.M.G.A. coleted the data and drafted the manuscript. J.M.S. and T.A.O. revised the manuscript. M.P. contributed to the conception of the work, drafted, revised the manuscript and supervised the study process. The authors approved the final version of the manuscript for publication.

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