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Applied nutritional investigation

A critical update on the role of mild and serious vitamin D deficiency prevalence and the COVID-19 epidemic in Europe

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A B S T R A C T

Objectives: Coronavirus disease 2019 (COVID-19) has emerged as a pandemic, affecting nearly 180 million people worldwide as of June 22, 2021. Previous studies have examined the association between the mean vitamin D (Vit D) concentration of each country and COVID-19 infection and mortality rate in European countries. The aim of the present study was to critically evaluate the relationship between prevalence of mild and severe Vit D deficiency in each country and COVID-19 infection, recovery, and mortality using updated data and a different methodological approach.

Methods: Information on Vit D concentration or deficiency for each country was retrieved through a literature search. COVID-19 infections and mortalities per million people and total recoveries, as of June 22, 2021, were obtained. The associations between Vit D deficiency and COVID-19 infection, recovery, and mortality were explored using correlation coefficients and scatterplots.

Results: Non-significant correlations were observed between both number of COVID-19 infections ($r = 0.363$, $P = 0.116$) and number of recoveries ($r = 0.388$, $P = 0.091$) and the prevalence of mild Vit D deficiency (<50 nmol/L). Similarly, non-significant correlations were observed between both infections ($r = 0.215$, $P = 0.392$) and recoveries ($r = 0.242$, $P = 0.332$) and the prevalence of severe Vit D deficiency (<30 nmol/L). Significant correlations were found between COVID-19 mortality and prevalence of both mild Vit D deficiency ($r = 0.634$, $P = 0.003$) and severe Vit D deficiency ($r = 0.538$, $P = 0.021$).

Conclusions: The prevalence of neither mild nor severe Vit D deficiency was associated with the number of COVID-19 infections in European countries. Thus, it is an important parameter to consider when implementing preventive measures to face COVID-19.

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Introduction

COVID-19 has become a global public health emergency, affecting more than 180 million people from 222 countries and territories [1] in less than a year from the first outbreak in Wuhan, China [2]. As of June 22, 2021, the lowest and highest number of confirmed cases were reported in Oceania (~70 000) and Europe (~47 500 000) [1]. This substantial variation in the number of infections, as well as the severity and mortality of the disease, can be accredited to several factors, both at the state level and the individual level. State-level parameters include diverse factors, such as a country's preparedness, actions of the governments, health infrastructure, timing of lockdowns, rapid border closures, implementation of social distancing, and socioeconomic status [3], whereas the individual level includes sociodemographic factors and other determinants of health status, such as sex, age, chronic diseases, obesity, and malnutrition [4,5].

It is well known that malnutrition constitutes a risk factor for increased mortality and morbidity in several diseases [6]. Protein and energy malnutrition and other specific micronutrient deficiencies have been shown to manifest adverse effects in immunity and thereby cause poor prognosis in viral infections [7]. Regarding micronutrients, the association between vitamin D (Vit D) deficiency and the prevalence and severity of various diseases, such as autoimmune disorders, diabetes, skeletal diseases, and acute respiratory tract infections, have been adequately established in the past years [8,9]. However, evidence with regard to Vit D concentration and preventive or curative mechanisms of SARS-CoV-2

infection is limited [10] or presents some controversies [11−13]. Recent studies have demonstrated the mechanisms for possible interactions between serum vitamin D concentration and rate of COVID-19 infections [14]. Particularly, Vit D modulates the expression of angiotensin-converting enzyme 2, angiotensin (1-7), and the MAS receptor axis and plays a crucial role in protection against lung infection [15−17]. It thereby acts as a renin-angiotensin system inhibitor in treating people with COVID-19 and underlying comorbidities [18,19] and can lead to a weakening of the cytokine storm and the risk of acute respiratory syndrome in people with COVID-19. But all this evidence lacks clinical validation [20,21].

In three recently published studies of the relationship between mean concentration of Vit D and number of cases and deaths of COVID-19 per million people in 20 European countries, negative correlations are reported [10,22,23]. In this study we aimed to critically evaluate the relationships between Vit D status and COVID-19 infections, recoveries, and mortalities in European countries, using more recent data and a different methodological approach. We also examined the relationships between severe Vit D deficiency (<30 nmol/L) and COVID-19 infections, recoveries, and mortalities.

Methods

Data sources and inclusion/exclusion criteria

Information on COVID-19 infections, recoveries, and mortalities was retrieved from the Worldometer website, which provides real-time statistics [1]. This source contains data derived directly from official government reports of individual countries and indirectly through reliable local media resources.

Data on the prevalence of Vit D deficiency in these countries were extracted by a comprehensive electronic search in the PubMed database (up to June 23, 2021). An advanced search was performed at the level of title/abstract by using keywords such as "Vitamin D" or "25-hydroxyvitamin D_3," combined with "deficiency," "prevalence," or "status" and the name of each European country. The final search string for each country and additional information about our search strategy are presented in Supplementary Table 1.

Inclusion criteria for our study were: population-based studies that reported data including the year 2010; studies reporting non-institutionalized adults (ages ≥ 18 y); studies defining mild Vit D deficiency as serum concentration < 20 ng/mL or < 50 nmol/L and/or severe deficiency as < 12 ng/mL or < 30 nmol/L; studies reporting the prevalence of Vit D deficiency in the sample population; European countries with population > 1 million; and European countries in which > 60 000 COVID-19 tests per million people were performed. Editorials, commentaries, book chapters, book reviews, and studies confined to a selective sample of community-dwelling people, such as pregnant women, menopausal women, and people with diagnosed illnesses, were excluded. As a last step, out of the articles screened for each country, the data on the prevalence of Vit D deficiency were retrieved from the most recently published study (with measurements completed not earlier than 2010), including the most representative sample for each country.

Data extraction

For each country, information on COVID-19 infections, recoveries, and mortalities per million people as of June 22, 2021, was extracted from the Worldometer website [1]. From the selected articles reporting Vit D deficiency in these countries, the name of the first author, year of publication, sample size, age range of the study population, mean Vit D concentration (nmol/L), and prevalence (%) of mild and severe Vit D deficiency were retrieved. All data were extracted by one reviewer (D. R. B.) using a standardized Excel form and were checked for accuracy by a second reviewer (M. C.).

Data analysis

The relationships between the prevalence of Vit D deficiency and variables such as the number of COVID-19 infections, recoveries, and mortalities per million people were explored with Pearson (*r*) correlation coefficients because the data were normally distributed. Scatterplots were used to visually represent the correlations. All countries were represented by a three-letter country code according to the ISO 3166 standard, as per the Terminology Bulletin for Country Names and the Country and Region Codes for Statistical Use maintained by the United Nations Statistics Divisions [24]. Pearson correlation (two-tailed) tests were performed using IBM SPSS version 25.0 software.

Results

A total of 20 European countries satisfying the inclusion and exclusion criteria were selected for the analysis [25−44] (Table 1). Countries and territories excluded because of their limited population or lower number of COVID-19 tests were Andorra, the Channel Islands, the Faeroe Islands, Gibraltar, Iceland, the Isle of Man, Liechtenstein, Luxembourg, Malta, Monaco, Montenegro, San Marino, and Vatican City. Moreover, Albania, Belarus, Hungary, Latvia, Lithuania, Moldova, the Netherlands, North Macedonia, Serbia, Slovakia, and Sweden were not part of our analysis because of absent or non-updated evidence regarding Vit D concentration, or a non-representative sample. The prevalence of Vit D deficiency (<50 nmol/L) ranged from 6.9% to 75.8%, with the lowest and highest rates reported in Finland [30] and Bulgaria [28], respectively. The prevalence of severe Vit D deficiency (<30 nmol/L) ranged from 0.9% in Finland [30] to 30.2% in Germany [32]. In nine of the countries, the majority (>50%) of the adult population studied had Vit D deficiency (i.e., <20 ng/mL or <50 nmol/L) [27,28,32,33,37,38,40,42,44]. The size of study population used to retrieve data for the prevalence of Vit D deficiency varied from 280 (Slovenia) [40] to 74 235 (Italy) [35].

As of June 22, 2021, with regard to the total number of COVID-19 infections per million people of total population, Finland reported the lowest, with 17 028/million people, and Slovenia had the highest, with 123 636/million people. Regarding COVID-19 mortalities per million people, the lowest number was documented in Norway (145), and the highest number was reported in Bosnia and Herzegovina (2959). Regarding recoveries per million people, the lowest number was reported in Finland (8289.6) and the highest number was observed in Slovenia (120 835.4).

Cases of COVID-19 infection per million people displayed a non-significant, positive correlation ($r = 0.363$, $P = 0.116$) with the prevalence of Vit D deficiency (<50 nmol/L; Fig. 1). A non-significant correlation ($r = 0.215$, $P = 0.392$) was also observed between COVID-19 infections and severe Vit D deficiency (<30 nmol/L; Fig. 2).

As illustrated in Figure 3, COVID-19 mortality per million people was correlated with the prevalence of Vit D deficiency (<50 nmol/L; $r = 0.634$, $P = 0.003$), and similarly, a positive correlation was found between the prevalence of severe Vit D deficiency (<30 nmol/L; $r = 0.538$, $P = 0.021$) and COVID-19 mortality rates, as can be seen in Figure 4.

As for recovered COVID-19 cases per million people, non-significant correlations with the prevalence of both Vit D deficiency and severe deficiency can be observed in Supplementary File 1 (respectively, $r = 0.388$, $P = 0.091$, and $r = 0.242$, $P = 0.332$).

Discussion

Our analysis concludes that available data on the prevalence of Vit D deficiency among the European population do not allow for concluding that it constitutes a strong risk factor in the COVID-19 epidemic. However, these findings are not in line with outcomes of similar research works published recently [10,22,23,45].

According to the outcomes of our study, in several of the European countries included in this analysis, more than 50% of the adult population was Vit D deficient, which constitutes a factor that should not be disregarded in the planning of public health preventive measures [27,28,32,33,37,38,40,42,44]. Factors that can influence Vit D concentration include the fluctuations in sunlight exposure across the seasons [46], especially the negligible amount of sunlight during winter and cloud cover during summer—which could potentially reduce the cutaneous synthesis of Vit D in some countries located less to the south [47,48]—as well as the extent of clothing coverage and sunscreen use [49,50]. Furthermore, dietary

Table 1
Prevalence of mild and severe vitamin D deficiency and COVID-19 data in 20 European countries

Country	Reference	Sample size (F/M)	Age range (y)	Mean ± SD vitamin D (nmol/L)	COVID-19 infections per million people[*]	COVID-19 deaths per million people[*]	COVID-19 recoveries per million people[*]	% Prevalence of vitamin D deficiency (<50 nmol/L)	% Prevalence of severe vitamin D deficiency (<30 nmol/L)
Austria	[25]	541 (334/237)	18−80	No info	71 742	1180	50 490.1	48.0	14.4[†]
Belgium	[26]	905 (464/441)	20−69	55.4 ± 22.7	92763	2160	87 344	44.8	6.4[†]
Bosnia and Herzegovina	[27]	1830 (no info)	>18	No info	62 831	2959	55 518.7	66.4	28.5[†]
Bulgaria	[28]	2016 (1068/948)	20−80	38.75 ± 17.18	61 073	2611	57 135.6	75.8	21.3[†]
Croatia	[29]	791 (660/131)	45.5[‡]	54.4	88 042	2007	85 922.3	46.1	21
Finland	[30]	798 (no info)	30−64	64.0 ± 28.8	17 028	176	8289.6	6.9	0.9
France	[31]	892 (429/463)	18−89	60.0 ± 20	89 748	1694	85 361.3	34.6	9.9
Germany	[32]	6995 (3635/3360)	18−79	45.6	44 396	1084	42 965.1	61.5	30.2
Greece	[33]	1084 (674/410)	≥18	41.8 ± 25.5	40 386	1212	38 689.8	64.8	28.8
Ireland	[34]	1118 (no info)	18−84	No info	53 992	998	50 912.7	43.7	11.4
Italy	[35]	74 235 (55 424/18 811)	18−104	68.5 ± 39	70 464	2109	67 224.7	33.3	14.5
Norway	[36]	4465 (2424/2041)	40−69	64 ± 19.2	23 756	145	16 284.2	24.7	1.9
Portugal	[37]	3092 (1995/1097)	≥18	42.2 ± 17.1	85 253	1679	80 909.7	66.6	21.2[†]
Romania	[38]	14 052 (12 347/1705)	>21	49.5 ± 25	56 525	1699	54 692.3	52.0	13.2[†]
Russia	[39]	1011 (824/187)	18−75	54.8 ± 22.3	36 772	897	33 577.1	47.9	No info
Slovenia	[40]	280 (152/128)	18−74	49 ± 26.8	123 636	2124	120 835.4	61.0	21.4
Spain	[44]	12 912 (no info)	30−105	30.25 ± 11.35	80 575	1726	76 319.8	64.6	No info
Switzerland	[41]	1291 (no info)	>60	No info	1248	1248	77 613.3	39.2	8[†]
United Kingdom	[42]	6004 (3291/2713)	>50	48.7	68 178	1876	63 114.2	55.3	23.7
Ukraine	[43]	1639 (no info)	18−82	56.7 ± 21.6	51 294	1197	49 538.4	41.9	4.8

[*]Data up to June 23, 2021.
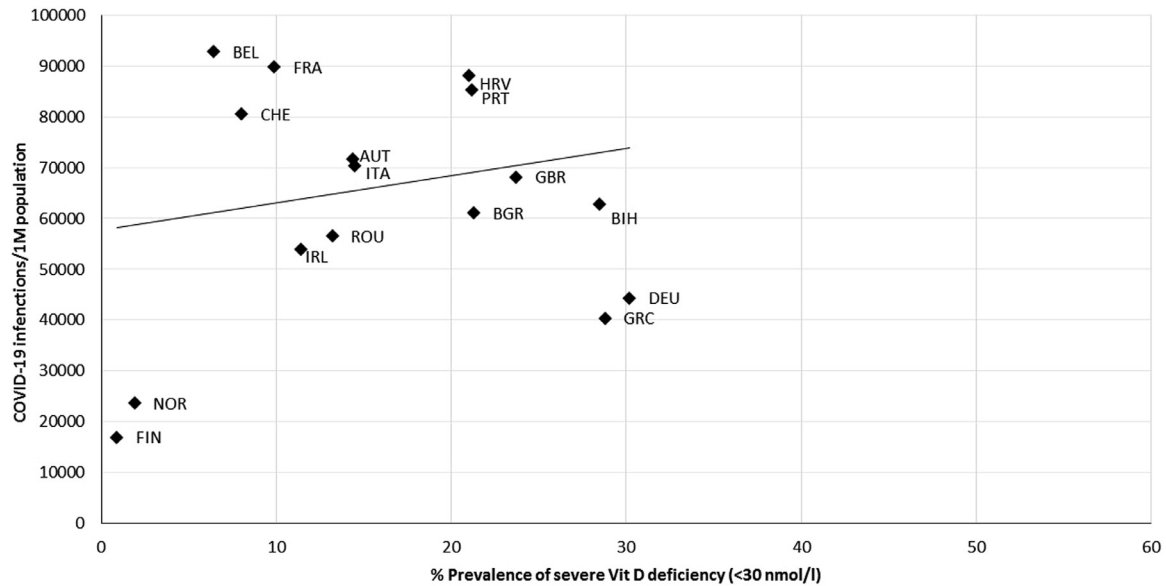[†]<25 nmol/L.
[‡]Mean age of participants.
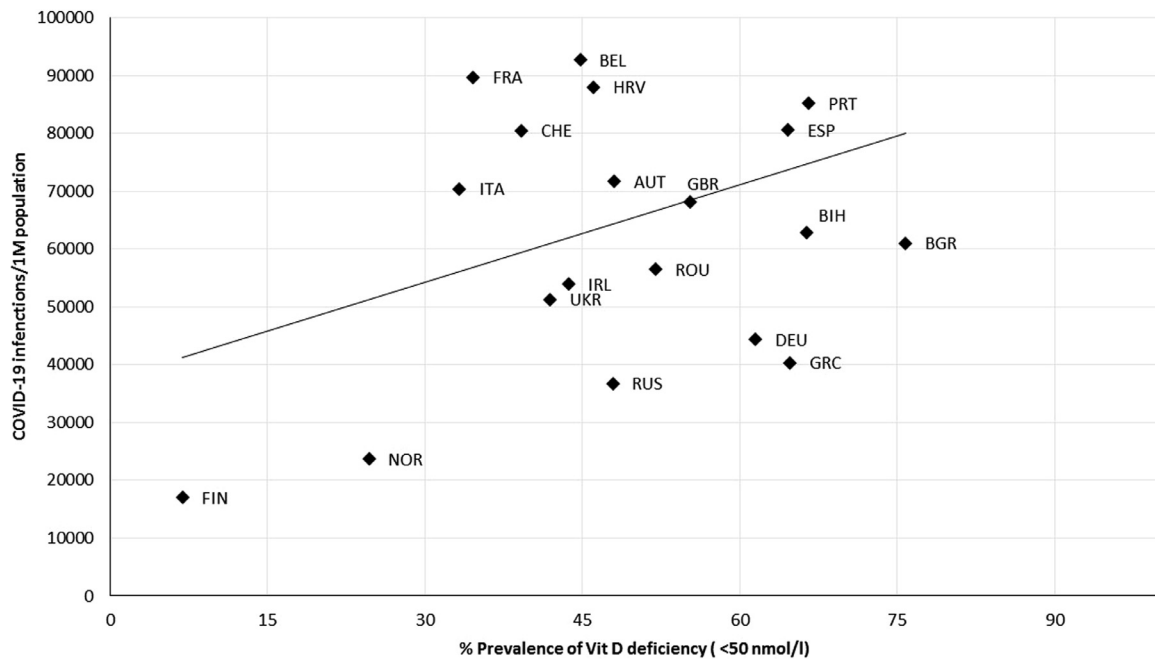
Fig. 1. Scatter diagram of the prevalence of vitamin D deficiency (<50 nmol/L) versus COVID-19 infections per million people, as of June 22, 2021 ($r = 0.363$, $P = 0.166$). AUT, Austria; BEL, Belgium; BGR, Bulgaria; BIH, Bosnia and Herzegovina; CHE, Switzerland; DEU, Germany; ESP, Spain; FIN, Finland; FRA, France; GBR, United Kingdom; GRC, Greece; HRV, Croatia; IRL, Ireland; ITA, Italy; NOR, Norway; PRT, Portugal; ROU, Romania; RUS, Russia; SVN, Slovenia; UKR, Ukraine.

sources of Vit D are limited and the obesity epidemic in the Europe, which is also related to poorer dietary choices, can worsen its deficiency [51]. Additionally, vegetarianism and veganism [52] and chronic diseases such as kidney disease [53,54], liver disease [55], malignancies [56], and genetic and epigenetic factors [57] can influence Vit D concentration.

The results of our analysis show that the prevalence of Vit D deficiency and severe deficiency are not associated with COVID-19 infections. The fact that these results differ from those of previous similar published studies [10,22,23] can be attributed to our alternative methodological approach, which we think is correct. In our study, only prevalence of Vit D deficiency for each European country was used, instead of mean Vit D concentration for each country (which was used in those other studies). A mean value cannot be representative of the Vit D concentration of a whole country, because it is influenced by outliers and skewed populations.

Fig. 2. Scatter diagram of the prevalence of severe vitamin D deficiency (<30 nmol/L) versus COVID-19 infections per million people, as of June 22, 2021 (r = 0.215, P = 0.392). AUT, Austria; BEL, Belgium; BGR, Bulgaria; BIH, Bosnia and Herzegovina; CHE, Switzerland; DEU, Germany; GBR, United Kingdom; GRC, Greece; HRV, Croatia; FIN, Finland; FRA, France; IRL, Ireland; ITA, Italy; NOR, Norway; PRT, Portugal; ROU, Romania; SVN, Slovenia; UKR, Ukraine.
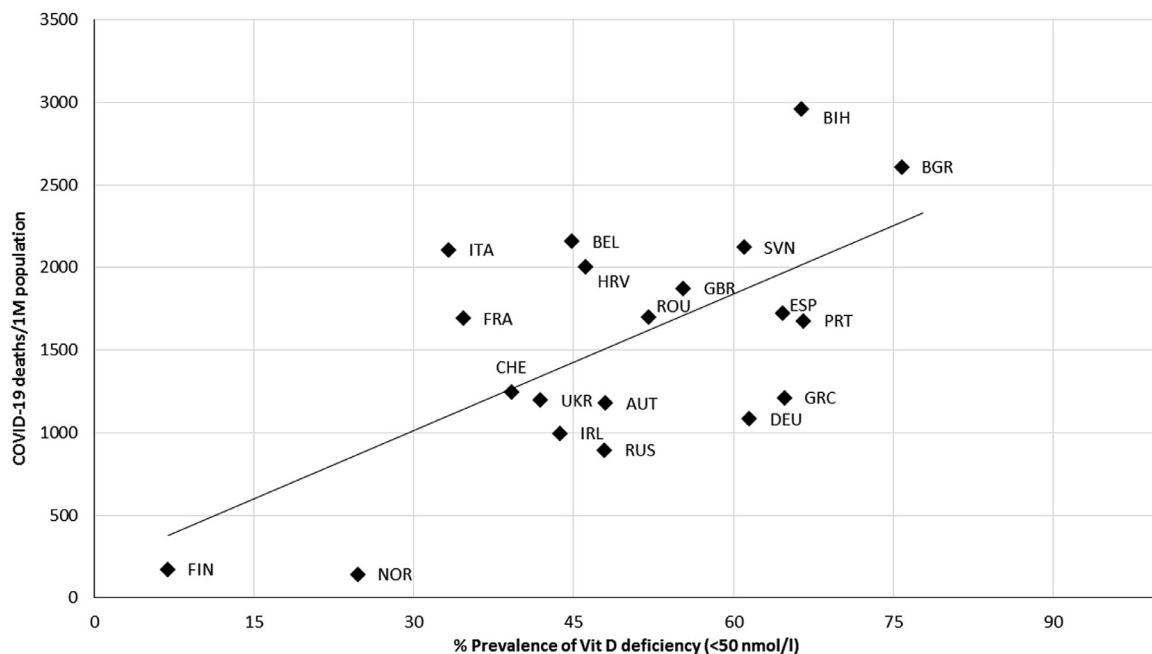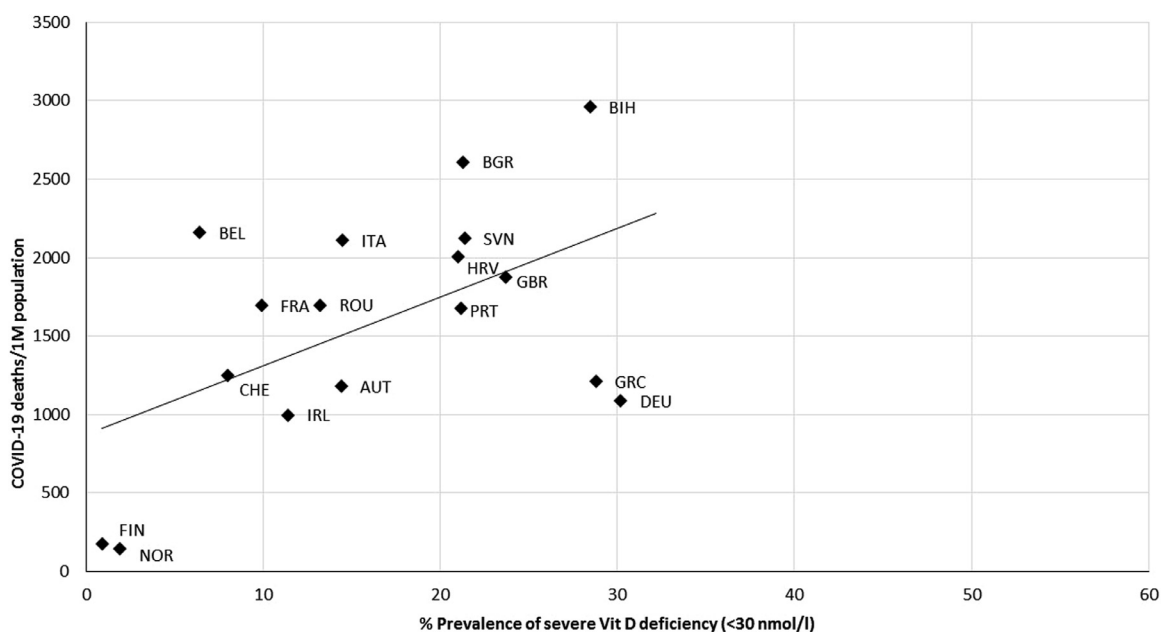

Fig. 3. Scatter diagram of the prevalence of vitamin D deficiency (<50 nmol/L) versus COVID-19 deaths per million people, as of June 22, 2021 (r = 0.634, P = 0.003). AUT, Austria; BEL, Belgium; BGR, Bulgaria; BIH, Bosnia and Herzegovina; CHE, Switzerland; DEU, Germany; ESP, Spain; FIN, Finland; FRA, France; GBR, United Kingdom; GRC, Greece; HRV, Croatia; IRL, Ireland; ITA, Italy; NOR, Norway; PRT, Portugal; ROU, Romania; RUS, Russia; SVN, Slovenia; UKR, Ukraine.

Therefore, we think that in the light of the most recent evidence of the COVID-19 pandemic, and using more updated information on the prevalence of Vit D deficiency for each country included (with measurements completed not earlier than 2010), we think that we have ended up with more accurate conclusions.

We need to underline the fact that COVID-19 mortalities seem to be correlated with the prevalence of Vit D deficiency (<50 nmol/L and <30 nmol/L). However, for a variety of reasons, this is not enough to allow for a conclusion that Vit D concentration can be associated with the COVID-19 epidemic. First of all, COVID-19 infection precedes

mortality, and the former was found to be correlated with the prevalence of neither mild nor severe deficiency. Moreover, underlying conditions, such as diabetes mellitus, cancer, cardiovascular diseases, autoimmune disorders, and infectious diseases, which are related with Vit D deficiency [58,59] can be co-factors of COVID-19−specific mortality [60,61]. Furthermore, recent analyses show that high ultraviolet A radiation exposure could be associated with lower COVID-19−specific mortality, which could be an effect independent of Vit D [62−64].

Undoubtedly, Vit D deficiency observed in several European countries is considered an important factor that should be treated−

Fig. 4. Scatter diagram of the prevalence of severe vitamin D deficiency (<30 nmol/L) versus COVID-19 deaths per million people, as of June 22, 2021 (r = 0.538, P = 0.021). AUT, Austria; BEL, Belgium; BGR, Bulgaria; BIH, Bosnia and Herzegovina; CHE, Switzerland; DEU, Germany; FIN, Finland; FRA, France; GBR, United Kingdom; GRC, Greece; HRV, Croatia; IRL, Ireland; ITA, Italy; NOR, Norway; PRT, Portugal; ROU, Romania; SVN, Slovenia; UKR, Ukraine.

frequently under medical supervision. Such a deficiency cannot be always tackled by advising enhanced dietary intake [65,66], nor should an often-unjustified (over)use of Vit D supplementation be used as a method to lower the risk for COVID-19 infection.

Numerous preprints regarding Vit D status and its association with COVID-19 infection, recovery, and mortality can be found in relevant databases (e.g., medRxiv), but these preprints have not been peer-reviewed and therefore should not be used as clinical practice guidance; additionally, such fast-track publications constitute a common risk for low-quality information and should not be considered of paramount importance during the COVID-19 pandemic. An editorial in *Lancet* is equally skeptical of findings regarding Vit D supplementation in people with COVID-19, until more solid data become available [67]. In addition, Szeto et al. examined the association between Vit D prehospitalized concentrations and COVID-19 clinical outcomes, and the data could not support any relationship [68]. Moreover, also outside the scope of COVID-19, evidence on associations of Vit D with any outcome seems not to be convincing, despite the great number of systematic reviews and meta-analyses that have been published [69].

According to our knowledge, this is the first review examining not only the prevalence of Vit D deficiency (<50 nmol/L) but also the prevalence of severe Vit D deficiency (<30 nmol/L). Although only 20 European countries satisfied our inclusion criteria, the analysis included a significant part of the European population [70]. Therefore, the results of our study could be generalized to most of the excluded European countries too. Moreover, along with the majority of high-income countries, upper-middle income countries such as Bosnia and Herzegovina were also included in the analysis [71], reflecting the effect of economic status in the outcomes.

Among the limitations of our study is that the data on the prevalence of Vit D deficiency in the countries included was not generated from national-level surveys. Therefore, very recently published studies with the most representative sample for each

country's population were carefully selected for our analysis. As described in our Methods, screened studies were limited to adults (ages ≥ 18 y), as the severity of COVID-19 infections in children has been rather mild [72]. More detailed data regarding either COVID-19 infection rates by age or age distribution for each country was not available, and therefore correlations for these subgroups could not be performed. The fact that data on the prevalence of Vit D deficiency were not reported over the same period of the COVID-19 pandemic could have an effect on the accuracy of our results. Moreover, seasonal values for Vit D concentrations were not available in the majority of the studies included, and therefore only annual averaged rates were used.

Governments should implement proper preventive measures to increase awareness among the population of the risk of Vit D deficiency rather than of its role during the COVID-19 pandemic. Vit D supplementation should be advised only for those in a high-risk group for deficiency, such as newborns, toddlers, people who are pregnant, older people, and non-Western immigrants [73], and always under medical supervision, not as a preventive factor against COVID-19 infection, because the long-term effects of such an approach are unknown. There might be several ongoing randomized controlled trials examining Vit D supplementation in people with COVID-19 [74], but until solid data are available from well-designed randomized controlled trials that will allow us to take relevant clinical decisions, the supplementation of Vit D as a way to prevent infection or improve recovery cannot be suggested based on evidence.

Conclusion

An absence of correlation was found between the total numbers of the COVID-19 epidemic and country-specific prevalence of Vit D deficiency and severe deficiency in 20 European countries. Our different methodological approach and the updated data regarding Vit D prevalence in each country included led to different results from those of previous published studies, and this should be considered for clinical practice.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.nut.2021.111441.

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