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## Original article

## Impact of vitamin D deficiency on COVID-19

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## SUMMARY

**Background & aims:** COVID-19 has emerged as a global pandemic affecting millions of people. Vitamin D deficiency is one of the risk factors for increased susceptibility to COVID-19. This study aimed to examine the correlation between the prevalence of vitamin D deficiency and COVID-19 infection and mortality rates among the adult population in European and Asian continents.

**Methods:** Prevalence of vitamin D deficiency in each country was retrieved through literature searching on PubMed® database for the last ten years. As of December, 31<sup>st</sup> 2020, COVID-19 infections and mortalities per million population were extracted from the 'real time' statistics of the *Worldometer* website. The association between both vitamin D deficiency and COVID-19 infections and mortalities were explored.

**Results:** Forty seven countries were included in the analysis. The prevalence of vitamin D deficiency ranged from 6.9 to 81.8% in European countries and 2.0–87.5% in Asian countries. Significantly positive correlations were observed for both COVID-19 infection ( $r = 0.76$ ;  $p < 0.001$ ) and mortality rates ( $r = 0.75$ ;  $p < 0.001$ ) in the Asian continent. The correlation values for the infections and mortality rates in the European continent were ( $r = 0.37$ ;  $p = 0.08$ ) and ( $r = 0.43$ ;  $p = 0.04$ ) respectively. When both the continents were combined, the correlation results for both infection ( $r = 0.42$ ;  $p = 0.003$ ) and mortality ( $r = 0.35$ ;  $p = 0.016$ ) rates with vitamin D deficiency values remained significant.

**Conclusion:** Prevalence of vitamin D deficiency was significantly associated with the mortality rate of COVID-19 in Europe and Asia. The association between the infection rate and prevalence of vitamin D deficiency was significant for Asia only. Both the associations were significant when the two continents were combined in the analysis. Therefore we suggest that vitamin D supplementation could play a key role in the prevention and/or treatment of the COVID-19 patients.

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## 1. Introduction

The novel coronavirus infection (COVID-19) which was originated in Wuhan, China [1], in late 2019 is continuing its spread across the world affecting more than 100 million people and claiming nearly 2.4 million lives in 221 countries and territories [2]. The control and prevention of the pandemic has become challenging due to the rapid transmission and relatively high mortality rates specially among vulnerable populations [3]. The disease has

now spread rapidly to almost every region of the world causing significant loss of life, disrupting livelihoods, and threatening the recent advances in health.

A significant variation in the number of infections and as well as the severity and mortality of the disease have been observed due to several state level and individual level predisposing factors [4]. The individual factors include age, sex, ethnicity, social conditions, malnutrition, pre-existing conditions and immunity status [5], while state level factors include, but not limited to, a country's level of preparedness, policies and interventions of governments, health infrastructure, timing of lockdown, rapid border closures, implementation of social distancing and socioeconomic status [4].

Vitamin D deficiency is a major public health problem worldwide in all age groups [6]. A number of factors are known to influence

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vitamin D levels and contribute to risk of impaired vitamin D status. These factors include variation in the sun exposure due to latitude, season, time of day, atmospheric components, clothing, sunscreen use, skin pigmentation, as well as age, obesity [7], nutrition and supplements [8]. Epidemiological studies have exhibited a strong relationship between seasonal differences in nutrient D levels and the occurrence of varied infectious diseases, such as sepsis [9], respiratory infection [10], and seasonal influenza [11]. In addition to classic actions related to mineral homeostasis, vitamin D has pleiotropic physiological actions including immune system regulation [12]. Vitamin D can modulate the innate and adaptive immune responses [13]. Deficiency in vitamin D is associated with decreased autoimmunity and an increased susceptibility to infections.

Several mechanisms have been reported in reducing the risk of viral infection and mortality by vitamin D [14]. To reduce the risk of common cold, vitamin D uses three pathways: physical barrier, cellular natural immunity, and adaptive immunity [15]. It improves the body's physical immunity barrier by regulating the production of proteins for tight junctions, adherens junctions, and gap junctions, which can be disturbed by infection by microorganisms, including viruses [16]. In addition vitamin D enhances cellular immunity by decreasing the cytokine storm which causes immunogenic damage to the endothelium and alveolar membrane [17]. It also regulates adaptive immunity through inhibiting T helper cell type 1(Th1) responses and stimulating Th2 responses [18]. It is evident that vitamin D deficiency might increase the risk of respiratory tract infections including COVID-19.

Therefore this study aimed to investigate the association between the prevalence of vitamin D deficiency and the infection and mortality rates of COVID-19 in two major continents specifically Asia and Europe, where the infection first spread prior to other parts of the world. Besides, these two continents were specially selected due to their rich ethnic and cultural diversity among populations with Caucasian and Asian backgrounds.

## 2. Methods

### 2.1. Data sources and inclusion/exclusion criteria

The number of reported COVID-19 cases and deaths per one million population as of December 31<sup>st</sup>, 2020, by country were obtained from the *Worldometer* website [2]. This is a reference webpage providing real-time world statistics of COVID-19 directly from official Government's communication channels of individual countries or through local media sources when deemed reliable.

The prevalence of vitamin D deficiency data among the countries were extracted by conducting a comprehensive electronic search in the PubMed® database. An advanced search was performed at the level of title/abstract by using the keywords such as "Vitamin D" OR "25-hydroxyvitamin D<sub>3</sub>", combined with "Deficiency", "Prevalence" OR "Status" and the names of each European and Asian countries. In addition, some of the published work was taken from references and other relevant websites. The search was limited to the articles published in the last ten years (As of January 31<sup>st</sup>, 2021). Among the suggestions resulted from each search, the following inclusion criteria were applied to screen the articles: a) Population-based studies; b) studies reporting non-institutional adults; c) studies defining the vitamin D deficiency as the serum levels <20 ng/ml or <50 nmol/L; d) studies reporting the vitamin D deficiency as the prevalence of the sample population. In addition, conference proceedings, editorials, commentaries, book chapters/book reviews and studies confined to selective sample of community-dwelling people such as pregnant women, elderly people aged ≥60 years and patients with diagnosed illnesses were excluded. Finally, out of the screened articles, the prevalence of vitamin D deficiency data were

retrieved from the most recently published article with the most representative study sample for each country.

### 2.2. Data extraction

Information on both COVID-19 infections and mortalities per one million (1M) population as of December, 31<sup>st</sup> 2020, were extracted from the *Worldometer* website and rounded off to the nearest whole number. From the selected articles reporting vitamin D deficiency among these countries, name of the first author, published year, sample size, age range of the study population and prevalence of vitamin D deficiency were retrieved. All data were extracted by two reviewers (PS and DTJ) using a standardized form and were checked for accuracy by a third reviewer (RJ). Any discrepancies in the data extracted in this manner were re-checked and resolved by discussion.

### 2.3. Data analysis

The relationship between the prevalence of vitamin D deficiency and other dependent variables such as total number of COVID-19 infections and mortalities per 1million (M) population were explored with correlation coefficients. The number of COVID-19 infections and mortalities per 1M population of each country were converted to log<sub>10</sub> prior to statistical analysis because the variances in the data were not normally distributed [19]. Scatter plots and regression lines were used to visually demonstrate the correlations and to evaluate the outcome for each continent and for both combined.

## 3. Results

A total of 23 countries in the European continent (Table 1) and 24 countries of the Asian continent (Table 2), fulfilling the inclusion/exclusion criteria were included in the analysis. Among European countries the highest and the lowest vitamin D deficiency rates were observed in Ukraine and Finland respectively with vitamin D deficiency values ranging from 6.9 to 81.8%. In most of the European countries (n = 13) more than the half of the adult population was vitamin D deficient. The size of the population used for testing vitamin D deficiency among the countries varied from 125 (Slovenia) to 74,235 (Italy). Study participants were adults except in one which included subjects from 5 to 18 years. The highest and the lowest number of COVID-19 infections per 1M of the total population were from Slovenia (58,779 cases/M) and Finland (6517 deaths/M) accordingly. With respect to the COVID-19 mortalities per 1M population, the highest number, was documented in Belgium (1677 deaths/1M), whereas the lowest number was reported in Norway (80 deaths/1M). The results of the correlation analysis in the European continent for vitamin D deficiency with COVID-19 cases per 1M of population demonstrated a weak positive correlation which is close to being statistically significant (r = 0.37; p = 0.08) (Fig. 1a). Similarly, COVID-19 mortality per 1M population was also significant and positively correlated with the prevalence of vitamin D deficiency (r = 0.43; p = 0.04) (Fig. 1b).

Among the countries from Asian continent, the vitamin D deficiency values varied from 2.0 to 87.5% with the lowest and highest values recorded in Vietnam and Oman respectively. Similar to Europe, half of the Asian countries (n = 17) also had vitamin D deficiency rates exceeding 50% among adults. The population sizes included in studies ranged from 107 to 142,131 consisting of all adults and elderly participants.

As of December, 31<sup>st</sup> 2020, among the countries in the Asian region, Bahrain (954,464) and Vietnam [15] reported the highest and lowest COVID-19 infections per 1M of the total population,

**Table 1**  
The prevalence of vitamin D deficiency among European countries.

Country	Author, Year	Sample size (M/F)	Age (years)	Prevalence of vit D deficiency* (%)	COVID-19 cases/M	COVID-19 mortalities/M
Belgium [20]	Hoge et al., 2015	697 (378/319)	20–69	51.1	55587.8	1677.4
Bosnia and Herzegovina [21]	Sokolovic et al., 2016	2483 (603/1880)	>18	58.7	33828.4	1234.4
Bulgaria [22]	Borissova et al., 2013	2016 (948/1068)	20–80	75.8	29109.5	1090.3
Croatia [23]	Barić et al., 2016	791 (660/131)	45.5	46.1	51357.7	954.9
Denmark [24]	Hansen et al., 2018	2565 (1048/1517)	18–69	51.5	28224.0	224.1
Finland [25]	Adebayo et al., 2020	798 (352/446)	30–64	6.9	6516.7	101.3
France [26]	Deplanque et al., 2017	297 (127/170)	18–65	75.1	40145.3	992.4
Germany [27]	Rabenberg et al., 2018	6995 (3360/3635)	18–79	61.5	20833.6	408.1
Greece [28]	Dimakopoulos et al., 2019	1084 (410/674)	≥18	32.4	13321.4	464.2
Ireland [29]	Griffin et al., 2020	17,590	≥18	51.5	18587.1	453.0
Italy [30]	Giuliani et al., 2019	74,235 (18,811/55,424)	>18	33.3	34851.2	1226.5
Norway [31]	Petrenya et al., 2020	4465 (2041/2424)	40–69	24.7	9143.1	80.4
Poland [32]	Pludowski et al., 2016	5775 (1311/4464)	16–90	65.8	34210.9	754.5
Portugal [33]	Duarte et al., 2020	3092 (1907/1995)	≥18	66.6	40569.8	677.3
Romania [34]	Niculescu et al., 2017	812	>21	56.5	32865.8	819.6
Russia [35]	Karonova et al., 2016	1544 (205/1294)	18–75	45.7	21648.7	390.7
Slovakia [36]	Sebekova et al., 2016	578 (254/324)	5–81	15.0	32885.5	391.6
Slovenia [37]	Hribar et al., 2020	125	18–64	58.2	58779.0	1297.3
Spain [38]	González-Molero et al., 2011	1262	20–83	33.9	43246.9	1087.3
Sweden [39]	Nälsén et al., 2020	268 (124/144)	18–80	22.4	45029.5	971.8
Switzerland [40]	Guessous et al., 2012	367 (167/200)	25–70	38.2	52260.6	883.3
Ukraine [41]	Povoroznyuk et al., 2012	1575	20–95	81.8	24124.3	423.8
United Kingdom [42]	Jolliffe et al., 2016	222 (89/133)	48–94	64.9	36661.2	1082.9

F-Female; M-Male.

\*Prevalence of Vitamin D deficiency; Serum 25-hydroxyvitamin D<sub>3</sub> level <20 ng/ml or <50 nmol/L; cases/M-cases per million population; mortalities/M-mortalities per million population.

**Table 2**  
The prevalence of vitamin D deficiency among Asian countries.

Country	Author, Year	Sample size (M/F)	Age (years)	Prevalence of vit D deficiency* (%)	COVID-19 cases/M	COVID-19 mortalities/M
Bahrain [43]	Almesri et al., 2020	314 (164/150)	>30	79.9	54464.2	206.9
Bangladesh [44]	Acherjya et al., 2019	160 (69/91)	≤70	63.7	3118.1	45.9
Brunei [45]	Leong et al., 2016	446 (77/331)	>18	52.0	358.9	6.9
China [46]	Jiang et al., 2020	14,302 (3002/11,299)	18–65	50.3	60.5	3.2
India [47]	Mechenro et al., 2018	424 (179/245)	>18	55.2	7453.8	108.0
Iran [48]	Esmaili et al., 2019	7504 (3552/3952)	18–65	65.3	14586.3	657.5
Iraq [49]	K.A Al-Hilali et al., 2016	300 (120/180)	25–70	75.3	14800.0	318.6
Japan [50]	Asakura et al., 2020	107 (53/54)	20–69	28.2	1820.9	27.0
Jordan [51]	Khasawneh et al., 2018	3007 (710/2297)	<83	67.9	28863.1	375.8
Kazakhstan [52]	Gromova et al., 2019	1347 (528/819)	>18	70.0	8240.0	121.7
Kuwait [53]	Zhang et al., 2016	960 (436/524)	≥20	83.0	35260.9	218.7
Lebanon [54]	Saad et al., 2020	(46,099/96,032)	>19	35.5	26592.1	237.1
Malaysia [55]	Shafinaz and Moy et al., 2016	858 (77/781)	≥18	67.4	3491.6	14.6
Mongolia [56]	Bromage et al., 2016	320 (160/160)	20–58	35.5	370.6	0.3
Nepal [57]	Sherchand et al., 2018	300 (109/191)	≥18	51.3	8943.8	63.7
Oman [58]	Abiaka et al., 2013	206 (101/105)	18–55	87.5	25235.3	293.5
Pakistan [59]	Kandhro et al., 2019	1255 (519/725)	≤84	36.0	2171.7	45.7
Qatar [60]	Zainel et al., 2019	102,342 (34,946/67,393)	18–65	71.4	49924.1	85.0
Saudi Arabia [61]	Altowijri et al., 2018	350 (150/200)	20–40	74.6	10419.4	178.8
Singapore [62]	Bi et al., 2016	114 (59/55)	21–100	42.1	10016.3	5.0
Thailand [63]	Rajatanavin et al., 2019	120 (56/64)	25–60	19.1	98.6	0.9
Turkey [64]	Gotkas et al., 2020	11,734 (2592/9142)	≥18	70.6	26187.8	247.6
UAE [65]	Al Zarooni et al., 2019	12,346 (4561/7785)	≥18	72.0	21012.5	67.6
Vietnam [66]	Ho-Pham et al., 2011	637 (205/432)	18–87	2.0	15.1	0.4

F-Female; M-Male.

\*Prevalence of Vitamin D deficiency; Serum 25-hydroxyvitamin D<sub>3</sub> level <20 ng/ml or <50 nmol/L; cases/M-cases per million population; mortalities/M-mortalities per million population.

while Iran (658) and Mongolia (0.3) had the highest and lowest mortalities per 1M population. The correlation analysis in the Asian region displayed a significant, strong positive correlation ( $r = 0.76$ ;  $p < 0.001$ ) with the prevalence of vitamin D deficiency and cases of COVID-19 infections per 1M population. In addition 58% of the variation ( $R^2 = 0.58$ ) in total infections was attributed to the high prevalence of vitamin D deficiency (Fig. 1c). As illustrated by the (Fig. 1d) COVID-19 mortality per 1M population also had a strong

positively significant correlation with the prevalence rates of vitamin D deficiency ( $r = 0.75$ ;  $p > 0.001$ ). Majority of the countries were scattered around the regression line, indicating 56% variability ( $R^2 = 0.56$ ) among the mortalities due to the high prevalence of vitamin D deficiency. China was positioned as an outlier in both Fig. 1c and Fig. 1d graphs and the correlation was increased markedly when it was removed from the analysis. After removing China from the analysis the correlation values were increased for both

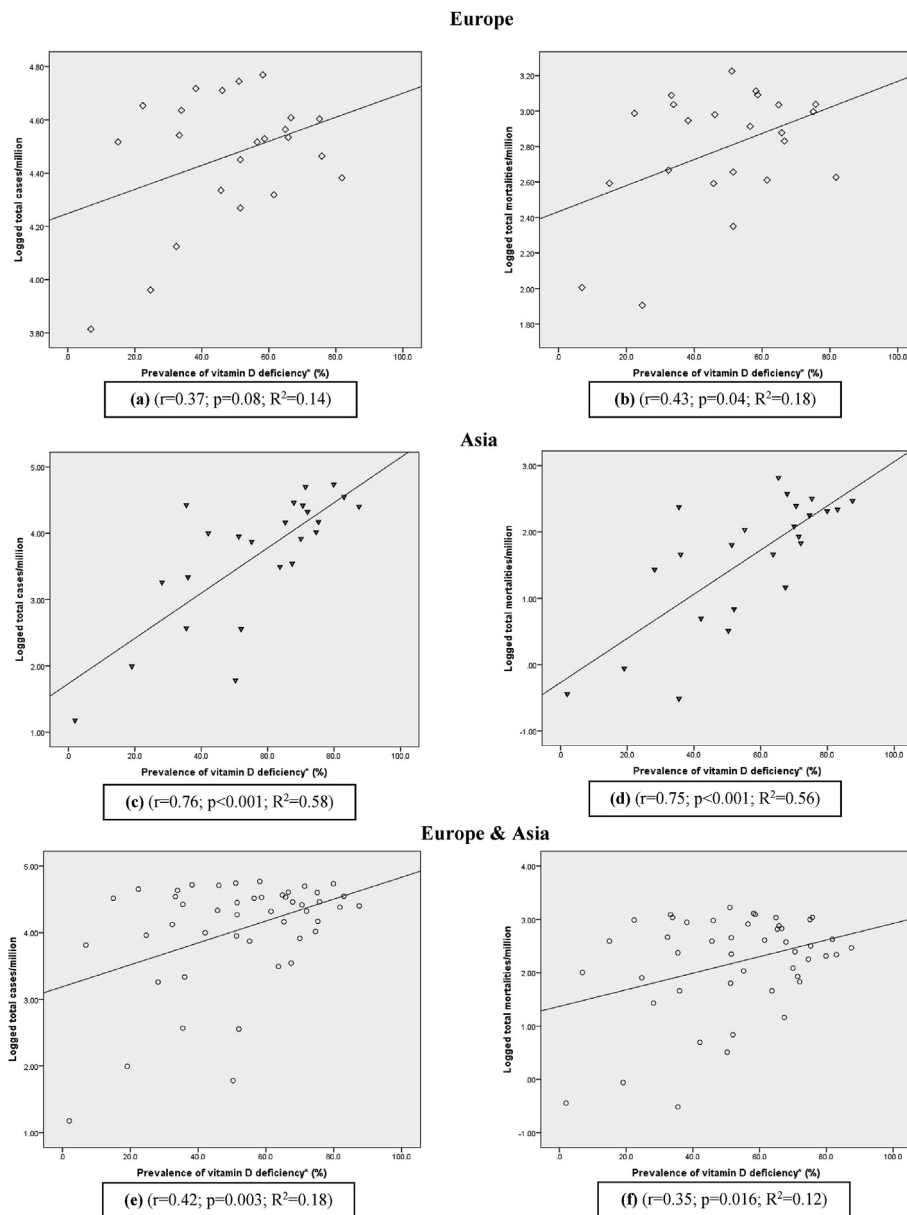


Fig. 1. Scatter diagrams of the prevalence of vitamin D deficiency against COVID-19 infections and mortality rates.

infection and  $(r = 0.81; p < 0.001; R^2 = 0.65)$  and mortality  $(r = 0.76; p < 0.001; R^2 = 0.57)$  rates.

When both the continents were combined, the correlation analysis between vitamin D deficiency and cases of COVID-19 infections per 1M population, yielded a significant, moderately positive correlation  $(r = 0.42; p = 0.003; R^2 = 0.18)$  (Fig. 1e). Similarly, in the analysis between the mortalities per 1M population and vitamin D deficiency, a positive, significant correlation could be observed  $(r = 0.35; p = 0.016; R^2 = 0.12)$  (Fig. 1f).

#### 4. Discussion

To the best of our knowledge, this is the first study reporting the correlation of vitamin D and COVID-19 in two major continents. We have identified a positive association between the vitamin D deficiency levels and COVID-19 infections and mortality rates among populations in European and Asian continents. Prior research work also has reported similar results [67–69]. A study by Pugach et al.,

investigated the association between vitamin D deficiency and COVID-19 severity, revealed that severe cases of COVID-19 present 65% more vitamin D deficiency compared with mild cases of the disease  $(OR = 1.64; 95\% CI = 1.30–2.09)$  [70].

Vitamin D deficiency is a common public health problem affecting individuals of all ages worldwide. 75% of countries had more than 50% of the adult population suffering from vitamin D deficiency. Vitamin D status can be highly varied between different countries of these regions due to several reasons such as different exposure to sunshine, dietary intake of vitamin D and the use of supplements [71].

According to our analysis, the Asian countries demonstrated a strong positive correlation with both the number of COVID 19 infections as well as mortalities than the countries in the European region. Although some countries in Asia are at similar latitude to countries in Europe, and receive sunlight throughout the year unlike European countries, the vitamin D deficiency is much more prevalent [72]. This could be due to the lower dietary intake of



vitamin D in Asian countries in comparison to European countries where vitamin D fortified food and supplements are readily available in the market [73]. Indeed, the use of vitamin D supplements and cod liver oil is common in Northern European countries and has a strong positive influence on vitamin D status [73]. In addition, skin pigmentation and cultural behaviors such as clothing and avoidance of outdoor activities in Mediterranean countries can contribute to vitamin D insufficiency [74].

Although the correlation analysis between the prevalence of vitamin D deficiency and COVID-19 infections and mortality rates resulted higher values for European and Asian continents separately, the association became modest after combining the both continents. The regression line depicting the association between vitamin D deficiency and number of infections for all the countries indicated 18% variability ( $R^2 = 0.18$ ) which infers approximately 18% of death rate from COVID-19 can be explained by prevalence of vitamin D deficiency. Therefore, the causes of high prevalence of vitamin D deficiency and increased deaths from COVID-19 are multifactorial. The identification of vitamin D deficiency as a contributor provides a useful target for treatment and prevention.

Since sufficient information on vitamin D deficiency could not be found for African and Latin American countries, we limited our study only to the continents of Europe and Asia. However, the majority of the data on prevalence of vitamin D deficiency among these countries were not from national level surveys. Due to the lack of national survey information in some countries, the sample sizes of studies were heterogeneous and were not representing the whole nation. This is a main limitation of this study as it could affect the power of the analysis. Therefore, to resolve this issue the most recently published studies with the most representative sample of each country population were carefully selected for the analysis. In addition, the overall prevalence of vitamin D deficiency was considered in the adult population, although there were substantial differences in the prevalence between different age groups. However, the younger population was hardly affected by the COVID-19 pandemic. Furthermore, serum vitamin D level fluctuates seasonally, due to climate, and possibly diet, especially in European countries [75]. Therefore, when different prevalence values were identified across different seasons, the mean prevalence of vitamin D deficiency throughout the year was considered. Furthermore, COVID-19 cases and mortality numbers only up to 31<sup>st</sup> of December were considered. Because the vaccination seemed to be reducing infections and death rates in vaccinated individuals thereafter [76]. This study included almost half the number of both European and Asian countries. Therefore, we believe that the results of this study can be generalized to the whole Asian and the European continents.

From the result of this study it is now evident that there is an association between vitamin D deficiency and incidence or mortality of the COVID-19 pandemic. Therefore, supplementation with vitamin D might be recommended to vitamin D deficient and insufficient patients suffering from COVID-19 [77]. In addition introducing mandatory fortification of products to the public such as dairy with vitamin D [67] and also promoting supplementation to individuals belonging to high risk groups of deficiency [78] could be effective strategies to reduce the prevalence of vitamin D deficiency. Moreover, vitamin D status 'by country' should be screened as part of standard health practices, as these results could provide valuable insights into how public health initiatives can better protect the population's health during public health emergencies, such as infectious disease pandemics [79].

## 5. Conclusion

We observed strong, positively significant correlations for both COVID-19 infection ( $r = 0.76$ ;  $p < 0.001$ ) and mortality rates

( $r = 0.75$ ;  $p < 0.001$ ) with vitamin D deficiency prevalence values in the Asian continent. Comparatively lower, near marginal and significant correlation values were observed for both COVID-19 infection ( $r = 0.371$ ;  $p = 0.08$ ) and mortality rates ( $r = 0.43$ ;  $p = 0.04$ ) for the European continent respectively. The correlation values for both COVID-19 cases ( $r = 0.42$ ;  $p = 0.003$ ) and mortalities ( $r = 0.35$ ;  $p = 0.016$ ) still remained positive and significant, when the two continents were combined in the analysis.

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None.

## Authors' contributions

RJ devised the conceptual idea. PS and DTJ searched databases. PS and DTJ were involved in retrieving data and analysis. PS and RJ drafted the manuscript. NK revised the manuscript. All authors provided critical feedback on the manuscript. All authors read and approved the final manuscript.

## Ethics declarations

Not applicable.

## Declaration of competing interest

The authors declare no conflict of interest.

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