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Impact of the vitamin D deficiency on COVID-19 infection and mortality in Asian countries

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1 **Impact of the vitamin D deficiency on COVID-19 infection and morality in Asian countries**

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18

19 **ABSTRACT**

20 **Background and aims:** COVID-19 is a pandemic that has affected beyond 100 million and  
21 caused nearly 3 million deaths globally. Vitamin D is a known risk factor for COVID-19.  
22 Therefore, we aimed to investigate the association of prevalence of vitamin D deficiency and  
23 mean vitamin D level with COVID-19 infection and mortality in Asia, predicting with other  
24 confounding factors such as median age, obesity, and diabetes.

25 **Methods:** COVID-19 infections and mortalities among the Asian countries were retrieved  
26 from the Worldometer website. Information on prevalence of vitamin D deficiency and mean  
27 vitamin D values in each Asian country was retrieved through literature searching on  
28 PubMed<sup>®</sup> and Google scholar. The associations between COVID-19 infections and  
29 mortalities with prevalence of vitamin D deficiency and mean vitamin D level were explored  
30 with correlation coefficients. As a predictive analysis, multiple linear regression was carried  
31 out with all confounders.

32 **Results:** Positive correlations were observed for prevalence of vitamin D deficiency with  
33 COVID-19 infections ( $r=0.55$ ;  $p=0.01$ ;  $R^2=0.31$ ) and mortalities ( $r=0.50$ ;  $p=0.01$ ;  $R^2=0.25$ ).  
34 Moreover, the associations for the COVID-19 infections and mortalities improved to  $r=0.76$   
35 ( $p=0.002$ ;  $R^2=0.58$ ) and  $r=0.65$  ( $p=0.03$ ;  $R^2=0.42$ ) respectively after predicting with  
36 confounding factors. Similarly, mean vitamin D level had a significant negative correlation  
37 with COVID-19 infections ( $r=-0.77$ ;  $p=0.04$ ;  $R^2=0.59$ ) and mortalities ( $r=-0.80$ ;  $p=0.03$ ;  
38  $R^2=0.63$ ) when combining with confounders.

39 **Conclusion:** Prevalence of vitamin D deficiency is significantly positively associated  
40 whereas the mean vitamin D level is significantly negatively associated with both infection  
41 and mortality rate of COVID-19 among Asian countries upon predicting with all  
42 confounders.

43 **Keywords:** Vitamin D; COVID-19; infection; mortality; Asia.

44 **ABBREVIATIONS**

45 **1 M:** One million; **25(OH)D:** 25-hydroxyvitamin D<sub>3</sub>; **BMI:** Body mass index; **CIA:** Central  
46 Intelligence Agency; **COVID-19:** Coronavirus disease; **ISO:** International Organization for  
47 Standardization; **NCD:** Non-communicable disease; **NMH:** Non-communicable Diseases and  
48 Mental Health Cluster; **PCR:** Polymerase Chain Reaction; **VD:** Vitamin D; **VDD:** Vitamin D  
49 deficiency; **WHO:** World Health Organization.

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## 50 INTRODUCTION

51 The coronavirus disease (COVID-19) outbreak has rapidly extended globally reaching  
52 through to almost every country. The current COVID-19 infections and mortalities are at a  
53 staggering number of more than 100 million and nearly 3 million respectively across the  
54 world [1]. COVID-19 pandemic has emerged as a public health crisis globally testing the  
55 resilience of the health systems and it has been established that severity of the cases as well  
56 as the mortality is linked with underlying health conditions [2]. Determining the associated  
57 comorbidities with the virus is twofold; firstly, on an individual level which allows health  
58 workers to tailor the appropriate treatment and secondly in a national level allowing the  
59 country's government to improve public health recommendations [3]. Public health  
60 infrastructure, prevention of infection and control measures are an integral part of the  
61 COVID-19 management [4].

62 A systematic review conducted by Yang et al. on the prevalence of comorbidities in  
63 patients infected with the virus showed that both age and comorbidities are risk factors for  
64 critical patients [5]. Among other comorbid illnesses such as hypertension and cardiovascular  
65 diseases, diabetic individuals with dysregulated immune cell populations and activity may  
66 result in aggravating the severity of the disease [6]. Studying diabetes mellitus as a risk factor,  
67 an investigation showed that the biomarkers related to inflammation were significantly higher  
68 ( $p<0.01$ ) in diabetic patients comparatively to the non-diabetic [6]. Additionally, an  
69 underlying chronic condition obesity as a potential risk factor was studied and findings  
70 showed; total population affected ( $r=0.46$ ;  $p<0.001$ ) and mortalities per million population  
71 ( $r=0.34$ ;  $p<0.05$ ) by COVID-19 were both significantly positively correlated with obesity  
72 prevalence [7]. Asia being the largest continent includes an estimated equivalent to 60% of  
73 the world's population closing in on 4.7 billion currently [8] and expected to see an increased  
74 incidence of COVID-19 [9]. The first report and subsequent outbreak was traced in China [10]

75 and spreading to other neighbouring Asian countries [11]. The rate of COVID infections is  
76 uneven across countries and having contributed tremendously to the growth of the global  
77 economy the socio-economic evolution among the countries in Asia may cause to be a  
78 determinant besides the preparedness and management [9].

79 Differences in economic status with ethnicity and underlying health conditions may  
80 cumulatively provide to the unequal impact of COVID-19 [12]. Therefore, understanding the  
81 association between ethnicity and COVID-19 is necessary in order to reduce the  
82 disproportionate burden of disease in various ethnic groups; a meta-analysis showed  
83 individuals from Asian and Black ethnic groups are more likely to be infected by the virus  
84 than compared to those of White ethnicity [13]. The COVID-19 trend in Asia may have been  
85 contributed by multiple biological factors, environmental conditions, and the public health  
86 response [14]. Projections at the beginning had placed South Asia at a higher risk due to  
87 certain factors as its greater population density, increased burden of comorbidities and vast  
88 socioeconomic vulnerabilities [15]. These determinants are particularly salient in the Asian  
89 context, with its diversity among countries in terms of sociocultural heritage, healthcare setup  
90 and availability of resources [16]. Hence, in a situation as the COVID-19 pandemic, the study  
91 of the associated factors in the Asian countries plays an important role.

92 The key feature of COVID-19 is immune dysregulation, as a result restoring the  
93 immune balance and preventing the hyper-inflammatory cytokine storm could be a strategy to  
94 combat the virus [17]. Adequate amounts of certain micronutrients are essential to ensure  
95 proper function of the immune cells, among vitamins; A and D showed beneficial effect  
96 particularly in deficient populations [18]. Vitamin D (VD), is a steroid hormone endogenously  
97 produced via ultraviolet radiation effects on the skin or available exogenously from food  
98 sources or dietary supplements [19]. This vitamin is showed to play a critical role in acute  
99 respiratory tract infections [20]. One hypothesis for observed associations between ethnicity,

100 obesity, and worse COVID-19 out-comes is vitamin D deficiency (VDD) among COVID-19  
101 patients [21]. A review studying serum VD concentration with incidence/severity of COVID-  
102 19 showed that they are inversely correlated [22]. Therefore, VDD showed an increase in  
103 thrombotic episodes which were observed frequently in COVID-19 patients, mostly with  
104 obese and diabetic individuals [23].

105         The association between the severity and mortality of COVID-19 with VDD is  
106 distinct. On the whole, VD could act as an important risk factor for COVID-19 severity.  
107 Therefore, to further explore the association of VDD and COVID-19 in countries that belong  
108 to the Asia. This includes the multiple variants present across all countries; we aimed to  
109 investigate the country specific prevalence of VDD as well as mean VD with COVID-19  
110 infection and mortality rates in Asia, predicting with other confounders such as median age,  
111 prevalence of obesity and diabetes.

## 112 **METHODS**

### 113 *Data sources of COVID-19 statistics*

114 Real time numerical data on COVID-19 infections and mortalities among the Asian  
115 countries, as of December, 31<sup>st</sup> 2020, were retrieved from the Worldometer website [24],  
116 which includes records derived directly from official government reports of individual  
117 countries and/or indirectly through reliable local media resources. The countries which have  
118 not conducted minimum 10,000 PCR tests per one million (1M) of the country population as  
119 of December, 31<sup>st</sup> 2020, were excluded from the analysis.

120

### 121 *Data sources of VDD*

122 A comprehensive electronic search was performed in both PubMed<sup>®</sup> to retrieve the  
123 information on the prevalence of VDD among the selected countries. The articles were  
124 searched by using the key words, such as “Vitamin D” or “25-hydroxyvitamin D<sub>3</sub>”, combined  
125 with “deficiency”, “prevalence” or “status” and the name of each Asian country. Additional  
126 search was performed in the Google Scholar<sup>®</sup> for the missing countries using the similar key  
127 words. The search was limited to articles published in the last ten years and contained data  
128 for the adult population ( $\geq 18$  years). The resulted articles were screened based on the  
129 following inclusion criteria: a) Population-based studies; b) studies reporting non-institutional  
130 adults; c) studies defining VDD as the serum concentration of 25(OH)D  $< 20$  ng/ml or  $< 50$   
131 nmol/l; d) studies reporting VDD as the prevalence of the sample population. In addition,  
132 conference proceedings, editorials, commentaries, book chapters/book reviews and studies  
133 confined to selective sample, such as pregnant women, elderly people, and patients with  
134 diagnosed illnesses were excluded. Finally, out of the screened articles for each country, the  
135 most recently published study, with the most representative sample of each country was  
136 selected for extracting data on VDD and mean VD values in the respective populations.

137

138 *Data sources of other confounders*

139           The data on the prevalence of obesity and Diabetes Mellitus (DM) were extracted  
140 from Non-communicable disease (NCD) country profiles released recently by the Non-  
141 communicable Diseases and Mental Health Cluster (NMH) of World Health Organization,  
142 where BMI levels  $\geq 30 \text{ kgm}^{-2}$  and fasting plasma glucose concentrations  $\geq 7.0 \text{ mmol/l}$  had  
143 been considered as obesity and DM respectively [25]. In addition, the median age of each  
144 country population was retrieved from the world fact book of Central Intelligence Agency  
145 (CIA), which constitutes basic information on socio demographic factors of 266 world  
146 entities [26].

147

148 *Data extraction*

149           As of December, 31<sup>st</sup> 2020, the numbers of both COVID-19 infections and mortalities  
150 per 1M of the total country population, and as well as the number of PCR tests done per 1M  
151 population were retrieved from the Worldometer website for each Asian country [24]. From  
152 the selected studies reporting VDD among these Asian countries, name of the first author,  
153 published year, sample size, age range of the study population, prevalence of VDD and mean  
154 VD level were extracted. Moreover the prevalence of both obesity and DM of the adult  
155 population and as well as the published year of the individual reports were obtained from the  
156 NCD country profiles [25]. The median age of the total country population as estimated for  
157 the year 2020, was retrieved from CIA website [26]. All data were extracted by one reviewer  
158 (DTJ) using a standardized form and were checked for accuracy by a second reviewer (TVF).  
159 Discrepancies in the extracted data were resolved by consensus, with involvement of a third  
160 reviewer when necessary (RJ).

161

162 *Data analysis*

163           Statistical analysis was performed using SPSS (version 20.0; IBM, Inc.). Data  
164 normality was analyzed using the Kolmogorov-Smirnov test. The relationship between the  
165 independent variables - prevalence of VDD and mean VD level and dependent variables,  
166 such as total number of COVID-19 infections and mortalities per 1M population were  
167 explored with Pearson correlation coefficients. As a predictive analysis, multiple linear  
168 regression was carried out to determine the association between the rate of COVID-19  
169 infections and as well as mortalities with regards to prevalence of VDD and mean VD level,  
170 combined with other confounding factors - median age of the population, prevalence of  
171 obesity and prevalence of DM. All the outcomes were visually represented as scatter  
172 diagrams and evaluated by drawing a regression line in Microsoft Excel (version 2013;  
173 Microsoft Corp.). The countries in the scatter diagrams were denoted by a 3-letter country  
174 code based on the ISO (International Organization for Standardization) 3166, according to  
175 the Terminology Bulletin Country Names and the Country and Region Codes for Statistical  
176 Use maintained by the United Nations Statistics Divisions [27].

177

178 **RESULTS**

179 A total of 24 countries, satisfying the inclusion/exclusion criteria were selected for the  
180 analysis (**Table 1**) [28-51]. Study population size varied extensively, from 107 (Japan) to  
181 142,131 (Lebanon). All studies have both men and women participants from the age group of  
182 over 18 years with some limited to adult group (<65 years) but most studies included both  
183 adults and older adults. VDD was reported in all countries and mean VD level was only  
184 reported in 15 countries. Among three quarter of the countries, more than 50% of the adult  
185 population were VD deficient. The lowest VDD was reported in Vietnam with only 2.0% and  
186 the highest was reported in Oman at 87.5%. As expected, an inverse relationship was  
187 observed between the prevalence of VDD and mean VD levels and the countries, Oman and  
188 Vietnam had the lowest (32.5 nmol/l) and the highest (83.8 nmol/l) mean VD levels  
189 respectively.

190 As of December, 31<sup>st</sup> 2020, with regards to the number of COVID-19 infections per  
191 1M of the total population, Vietnam reported the lowest with 15/1M while Bahrain had the  
192 highest with 53,679/1M infections (**Table 2**). In the case of COVID-19 mortalities per 1M  
193 population, Vietnam documented the lowest number of 0.4 deaths/1M whereas the highest  
194 number of 655 deaths/1M occurred in Iran. Particularly, a distinctive pattern related to  
195 COVID-19 data was observed among the countries included in the analysis. All the Western  
196 Asian countries (e.g Qatar, Lebanon and Kuwait) reported higher values for both COVID-19  
197 infections and mortalities compared to South-Eastern Asian countries (e.g Vietnam,  
198 Singapore and Brunei). Median age of the population lies mostly in the thirties across more  
199 than half of the countries, with Japan as the outlier with a median age of 48.6 years. The  
200 prevalence of DM across the 24 countries were of close proximity, and a predominant of the  
201 countries reported a prevalence close to 10%. In contrast, obesity had a wider prevalence  
202 range with the highest value of 35% in Bahrain and the lowest of 2% in Vietnam.

203

204           The number of COVID-19 infections per 1 M population displayed a significant  
205 positive correlation ( $r=0.55$ ;  $p=0.01$ ) with prevalence of VDD and an insignificant negative  
206 correlation ( $r=-0.23$ ;  $p=0.42$ ) with mean VD levels (**Figure 1**). Moreover, our comparison  
207 suggested that the variation in the total infections can be attributed to the prevalence of VDD  
208 ( $R^2=0.31$ ) and the mean VD level ( $R^2=0.05$ ) of the total country population at the proportions  
209 of 33% and 5% respectively. With regards to prevalence of VDD, the regression line  
210 generated from the correlation analysis showed an upward trend, and as expected, most  
211 countries were scattered around the line, with a few countries as outliers (Lebanon, Qatar and  
212 Bahrain). Moreover, the correlation effect improved to  $r=0.66$ , after removing the outliers  
213 (Lebanon, Qatar and Bahrain) from the analysis ( $p=0.001$ ;  $R^2=0.44$ ). As expected, the  
214 regression line generated from the mean VD level analysis against COVID-19 infections,  
215 exhibited a downward trend, with only a few countries distributed across the line. However,  
216 the association increased to  $r=-0.44$ , upon the elimination of outliers such as Oman, Turkey  
217 and Lebanon from the analysis ( $p=0.17$ ;  $R^2=0.20$ ).

218           Similarly, COVID-19 mortalities per 1M population also showed a significant  
219 positive correlation ( $r=0.50$ ;  $p=0.01$ ) with the prevalence of VDD and an insignificant  
220 negative correlation ( $r=-0.38$ ;  $p=0.16$ ) with mean VD level, as depicted in **Figure 2**.  
221 Moreover, the regression lines resulted from the scatter diagrams revealed that prevalence of  
222 VDD and mean VD level were attributed to 25% ( $R^2=0.25$ ) and 15% ( $R^2=0.15$ ) variability  
223 among COVID-19 mortalities. With respect to the prevalence of VDD, almost all of the  
224 countries were found to be spread along the ascending regression line whereas Iran was the  
225 single outlier. Furthermore, the association reached the value of  $r=0.58$ , when Iran was  
226 removed from the analysis ( $p=0.004$ ;  $R^2=0.33$ ). In the case of mean VD levels, only some of  
227 the countries were seemed to lie across the descending regression line. Countries such as

228 Lebanon, Oman, Iraq and Turkey were positioned far away from the regression line and the  
229 correlation changed to  $r=-0.41$ , when they were omitted in the analysis ( $p=0.22$ ;  $R^2=0.17$ ).

230 As shown in **Table 3**, when the other confounders -median age of the population,  
231 prevalence of obesity and prevalence of DM were included along with the prevalence of  
232 VDD and mean VD levels in the multiple regression analysis, the respective associations  
233 improved gradually. With regards to COVID-19 infection rate, when the model was predicted  
234 with VDD prevalence and median age of the population, the correlation increased from  
235  $r=0.55$  ( $p=0.01$ ;  $R^2=0.31$ ) to  $r=0.58$  ( $p=0.01$ ;  $R^2=0.33$ ) and jumped to  $r=0.75$  ( $p=0.001$ ;  
236  $R^2=0.56$ ) with the addition of obesity prevalence. Finally the correlation reached to 0.76  
237 ( $p=0.002$ ;  $R^2=0.58$ ) upon the inclusion of DM prevalence to the predicted model (**Figure 3a**).  
238 On the other hand, when the model was projected with mean VD level and median age of the  
239 population, the association with COVID-19 infections per 1 M population increased from  $r=-$   
240  $0.23$  ( $p=0.42$ ;  $R^2=0.05$ ) to  $r=0.34$  ( $p=0.48$ ;  $R^2=0.12$ ) and then improved to  $r=0.76$  ( $p=0.02$ ;  
241  $R^2=0.58$ ) when obesity prevalence was added together. Lastly, when the model was  
242 constructed based on all confounders by including the prevalence of DM, a strong correlation  
243 of  $r=0.77$  ( $p=0.04$ ;  $R^2=0.59$ ) was observed (**Figure 3b**).

244 With respect to COVID-19 mortality rate, as depicted in **Table 3**, upon the addition  
245 of median age of the population to the predictive model, the correlation improved from  
246  $r=0.50$  ( $p=0.01$ ;  $R^2=0.25$ ) to  $r=0.52$  ( $p=0.04$ ;  $R^2=0.27$ ) for the VDD prevalence and from  $r=-$   
247  $0.38$  ( $p=0.16$ ;  $R^2=0.15$ ) to  $r=-0.56$  ( $p=0.10$ ;  $R^2=0.31$ ) for the mean VD level. Later, when the  
248 obesity prevalence was included in the above model, the association reached to  $r=0.64$   
249 ( $p=0.01$ ;  $R^2=0.40$ ) and  $r=-0.79$  ( $p=0.01$ ;  $R^2=0.62$ ) for VDD prevalence and mean VD level  
250 respectively. Finally, the correlation of VDD prevalence reached the level of  $r=0.65$  ( $p=0.03$ ;  
251  $R^2=0.42$ ) when the model was predicted with all the confounders including DM prevalence

252 **(Figure 4a)** and with respect to mean VD level and all the other cofounders, a correlation of  
253  $r=-0.80$  ( $p=0.03$ ;  $R^2=0.63$ ) was achieved **(Figure 4b)**.

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254 **DISCUSSION**

255 To the best of our knowledge this is the first analysis of VDD prevalence and mean  
256 VD level with COVID-19 infections and mortalities in Asian countries. The strength of this  
257 study is that other main confounders also have been included in a predictive analysis and as  
258 expected, it improved the correlation substantially.

259 Historically, discovery of vitamins as leading to major deficiency began in the 19<sup>th</sup>  
260 century with vitamin A as one of the earliest causing xerophthalmia [52]. Although VDD was  
261 recognized as rickets/osteomalacia in the early 1600s, it was only a century ago that VD as a  
262 nutritional factor was discovered [53]. Human body's best indicator of VD status is the  
263 concentration of serum 25(OH)D and is known to be obtained by sun exposure or dietary  
264 sources [54]. Many countries either have a low supply of foods rich in VD and or inadequate  
265 exposure to sunlight but supplement use, age, geographic latitude, cultural and lifestyle  
266 factors increase or reduce risk of being VD deficient [55].

267 Similar to previous studies, VDD is distinctively associated with COVID-19  
268 infections and mortalities. Gulf region countries receives endless supply of sunlight except,  
269 surprisingly continues with alarmingly high prevalence of VDD as the cultural and social  
270 habits limit exposure to sunlight [56]. Vietnam had a VDD prevalence of 2.0% which was  
271 comparatively lower, nevertheless showed slight variability between men and women as  
272 attitude differences towards clothing coverage of skin and exposure to sunlight explain the  
273 variations [51]. According to our correlation analysis of COVID-19 infections and mortalities  
274 with VDD prevalence, a significant positive correlation was seen. Individual Asian countries  
275 have reported association between VDD and COVID-19 infection and mortality, a study  
276 carried out in Chinese people revealed that 25(OH)D concentration on admission were  
277 significantly lower in COVID-19 patients than in controls ( $3.32 \pm 0.04$  vs.  $3.46 \pm 0.02$   
278 nmol/l) [57].

279           Once the confounding factors such as median age of the population, prevalence of  
280 obesity and prevalence of DM were included in the analysis, the total COVID-19 infections  
281 and mortalities increased gradually. Therefore, the addition of confounding factors as  
282 mentioned are additional risk factors with VDD for COVID-19 outcome. Obesity as a  
283 potential risk factor was investigated, obesity prevalence with the total number of COVID-19  
284 infections and mortalities among selected countries observed a significant positive correlation  
285 ( $r=0.46$ ;  $p<0.001$ ) [7]. A review on DM as a comorbidity reported a 14.3% prevalence with  
286 confirmed COVID-19 patients and showed a greater risk of severe illness and in hospital  
287 mortality among pre-existing diabetic patients [58]. As immunity often decreases with aging,  
288 the older adults would be considered as high risk patients for developing COVID-19.  
289 Disruption of the immune system, both innate and adaptive arms is a recognized feature of  
290 aging which makes them more susceptible to adverse outcomes of the virus infection [59].  
291 Therefore, median age of a country is a key decisive factor to predict both infection and  
292 mortality rate.

293           The occurrences of COVID-19 varied uneven across Asian countries as it may also be  
294 determined by predictors such as government action for COVID-19 containment and the  
295 degree of preparedness. A country level analysis showed government policy of lockdowns  
296 strongly associated with recovery rates and similarly the number of days to any border  
297 closure was associated with the number of cases per million [60]. Furthermore, COVID-19  
298 data on infections and mortalities were extracted only up to December, 31st 2020, as the  
299 vaccination gradually reduced the rate of infections and mortalities in vaccinated individuals  
300 [61].

301           Most of the studies included were not of national level surveys although a  
302 representative sample of each country population recently studying VD were carefully  
303 selected for the analysis for both VDD prevalence and mean VD level. Expectedly, an inverse

304 relationship was observed with VDD prevalence and mean VD levels across the Asian  
305 countries. A study outlining mean VD levels in different states of the Indian population,  
306 interestingly resulted in an inverse correlation between the mean VD and infection rate ( $r=-$   
307  $0.43$ ;  $p=0.02$ ) and mortality rate ( $r=-0.42$ ;  $p=0.02$ ) [62]. Additionally, another study analysed  
308 the correlation of mean VD and the number of infections and deaths per 1 M in the Asian  
309 Pacific region and showed an inverse correlation ( $r=-0.39$ ;  $p= 0.016$ ) [63].

310 Mean VD levels alone with COVID-19 infections and mortalities showed no  
311 significant correlation as this was due to the less number of studies that reported mean VD  
312 levels. When other confounders were added to mean VD levels, significant correlations were  
313 observed with the COVID-19 infections and mortalities. Growing body of evidence connects  
314 obesity with COVID-19 as mean VD levels alone are not important but with adiposity the  
315 circulatory mean VD levels may change as low mean VD is one of the metabolic  
316 disturbances that is associated with excess adiposity in particular the visceral adiposity [64].

317 Results of this study showcased that VDD and mean VD levels of the Asian countries  
318 have an association towards the incidence and mortality of the novel coronavirus disease.  
319 People who are deficient in VD may receive daily or weekly supplementation as it is studied  
320 to protect against acute respiratory tract infections [20]. Thus, the population at higher risk of  
321 VDD during this global pandemic should consider taking VD supplements to maintain the  
322 circulating 25(OH)D in optimal levels (75-125 nmol/l) [19]. On that account it shows that VD  
323 is a possible protective effect in reducing the infectivity and mortality of COVID-19.

#### 324 *Limitations*

325 VDD and mean VD values included from the studies reports one particular value  
326 which may affect the accuracy of the populations' VD status as most countries have seasonal  
327 changes that may differ the mean VD levels measured. Age group ranged from young adults

328 to older adults covering a wider pool but high risk of COVID-19 is seen in older adults.  
329 Consequently, studying only older adults would have been better. Obesity and DM  
330 prevalence data were extracted from WHO databases which is accurate but may be out-dated.  
331 Ideally prevalence data for each country would be more precise if searched for each country  
332 individually. Obesity cut off values may differ from this database ( $\text{BMI} < 30 \text{ kgm}^2$ ) when  
333 focused on Asia as the cut off value would be lower due to the different body composition  
334 [65].

335

336 **CONCLUSION**

337 Strong significant positive correlation was observed for prevalence of VDD with  
338 COVID-19 infections ( $r=0.55$ ;  $p=0.01$ ;  $R^2=0.31$ ) and mortalities ( $r=0.50$ ;  $p=0.01$ ;  $R^2=0.25$ ).  
339 Moreover, once confounding factors such as median age of population, prevalence of obesity  
340 and prevalence of DM were included in the multiple regression analysis with VDD  
341 prevalence, the associations for the number of COVID-19 infections and mortalities  
342 improved to  $r=0.76$  ( $p=0.002$ ;  $R^2=0.58$ ) and  $r=0.65$  ( $p=0.03$ ;  $R^2=0.42$ ) respectively. On the  
343 other hand, mean VD level alone with COVID-19 infections and mortalities did not result  
344 with significant correlation but once predicted with the other confounding factors, high  
345 correlations were achieved with the number of COVID-19 infections ( $r=-0.77$ ;  $p=0.04$ ;  
346  $R^2=0.59$ ) and mortalities ( $r=-0.80$ ;  $p=0.03$ ;  $R^2=0.63$ ).

347

348

349

350

351 **DECLARATIONS**

352

353 *Conflicts of interest*

354 The authors declare that there are no conflicts of interest regarding the publication of this  
355 paper.

356

357 *Authors' Contributions*

358 RJ conceived and designed the study. DTJ, TVF and RJ collected data. DTJ analysed the  
359 data. DTJ, TVF, and RJ drafted the manuscript. AM revised the paper. All authors read and  
360 approved the final manuscript.

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371 *Ethics approval and consent to participate*

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373

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550

**Table 1:** The prevalence of vitamin D deficiency and mean vitamin D levels among 24 Asian countries.

Country	Author, Year	Sample size (M/ F)	Age (years)	Prevalence of VDD (%)	Mean VD level (nmol/l) $\pm$ SD
Bahrain [6]	Almesri et al, 2020	314 (164/150)	>30	79.9	NR
Bangladesh [7]	Acherjya et al,2019	160 (69/91)	$\leq$ 70	63.7	46.5 $\pm$ 16.5
Brunei [8]	Leong et al, 2016	408 (77/331)	$\geq$ 18	60.5	50.4 $\pm$ 22.3
China [9]	Jiang et al, 2019	14302 (3002/11299)	18-65	50.3	55.8 $\pm$ 50.8
India [10]	Mechenro et al, 2018	424 (179/245)	$\geq$ 18	55.2	51.3 $\pm$ 23.3
Iran [11]	Esmacili et al, 2018	6089 (2837/3252)	19-65	70.3	NR
Iraq [12]	Al-Hilali, 2016	300 (120/180)	25-70	72.9	38.8 $\pm$ NR
Japan [13]	Asakura et al, 2020	107 (53/54)	20-69	28.2	44.8 $\pm$ NR
Jordan [14]	Khasawneh et al, 2018	3007 (710/2297)	15-83	67.9	NR
Kazakhstan [15]	Gromova et al, 2019	1347 (528/819)	$\geq$ 18	70.0	37.5 $\pm$ (NR)
Kuwait [16]	Zhang et al, 2016	960 (436/524)	$\geq$ 20	83.0	34.5 <sup>#</sup>
Lebanon [17]	Saad et al, 2020	142131 (46099/96032)	>18	35.5	69.0 $\pm$ 45.0
Malaysia [18]	Shafinaz and Moy, 2016	858 (77/781)	$\geq$ 18	67.4	45.0 $\pm$ 18.3
Mongolia [19]	Bromage et al, 2016	320 (160/160)	20 -58	35.5	37.8 $\pm$ 13.8
Nepal [20]	Sherchand et al, 2018	300 (109/191)	$\geq$ 18	51.3	47.5 <sup>#</sup>
Oman [21]	Abiaka et al, 2012	206 (101/105)	18-55	87.5	32.8 $\pm$ 15.4
Pakistan [22]	Kandhro et al, 2019	1244(519/725)	$\leq$ 84	51.5	NR
Qatar [23]	Zainel et al, 2019	102339 (34946/67393)	18-65	71.4	NR
Saudi Arabia [24]	Altowijri et al, 2018	350 (150/200)	$\geq$ 20	74.6	NR
Singapore [25]	Bi et al, 2016	114 (59/55)	$\geq$ 21	42.0	54.0 $\pm$ 17.3
Thailand [26]	Rajatanavin et al, 2018	120 (56/64)	25-60	19.2	66.3 $\pm$ 19.2
Turkey [27]	Gotkas et al, 2020	11734 (2592/9142)	$\geq$ 18	65.3	41.5 $\pm$ 28.8
United Arab Emirates [28]	Al Zarooni et al, 2019	12346 (4561/7785)	$\geq$ 18	72.0	NR
Vietnam [29]	Ho-Pham et al, 2011	637 (205/432)	18-87	2.0	83.8 $\pm$ 20.1

<sup>#</sup>Median values; F-Female; M-Male; NR: Not reported; VD: Vitamin D; VDD: Vitamin D deficiency; SD: Standard deviation.

**Table 2:** COVID-19 infection and mortality rates and other confounding variables among 24 Asian countries.

Country	COVID-19 infections/ 1 M population*	COVID-19 mortalities/ 1 M population*	Median age of population	Prevalence of DM (%)	Prevalence of obesity (%)
Bahrain	53679	203	32.9	9	29
Bangladesh	3108	46	27.9	8	3
Brunei	357	7	31.1	9	15
China	60	3	38.4	9	7
India	7429	108	28.7	8	4
Iran	14567	655	31.7	10	26
Iraq	14658	315	21.2	13	27
Japan	1856	27	48.6	10	4
Jordan	28843	376	23.5	13	33
Kazakhstan	8230	120	31.6	12	21
Kuwait	35066	218	29.7	15	37
Lebanon	27003	217	33.7	13	31
Malaysia	3533	15	29.2	10	15
Mongolia	369	0.3	29.8	10	20
Nepal	8878	63	25.3	9	4
Oman	24919	290	26.2	8	23
Pakistan	2162	46	22.0	10	8
Qatar	51301	87	33.7	13	34
Saudi Arabia	10342	178	30.8	14	35
Singapore	9982	5	35.6	9	7
Thailand	102	0.9	39.0	10	11
Turkey	26,190	249	32.2	13	32
UAE	21,072	67	38.4	8	30
Vietnam	15	0.4	31.9	5	2

\*As of December, 31<sup>st</sup> 2020; DM: Diabetes mellitus; M: Million.

**Table 3:** The summary of multiple regression analysis based on all independent variables.

Model summary	COVID-19 infection rate*			COVID-19 mortality rate*		
	Correlation (r)	P value	Variance (R <sup>2</sup> )	Correlation (r)	P value	Variance (R <sup>2</sup> )
VDD	0.55	0.01	0.31	0.50	0.01	0.25
VDD+MA	0.58	0.01	0.33	0.52	0.04	0.27
VDD+MA+OB	0.75	0.001	0.56	0.64	0.01	0.40
VDD+MA+OB+DM	0.76	0.002	0.58	0.65	0.03	0.42
MVD	-0.23	0.42	0.05	-0.38	0.16	0.15
MVD+MA	-0.34	0.48	0.12	-0.56	0.10	0.31
MVD+MA+OB	-0.76	0.02	0.58	-0.79	0.01	0.62
MVD+MA+OB+DM	-0.77	0.04	0.59	-0.80	0.03	0.63

\*As of December, 31<sup>st</sup> 2020; VDD: Vitamin D deficiency; MA: Median age of the population; MVD: Mean vitamin D level; OB: Prevalence of obesity; DM: Prevalence of diabetes mellitus

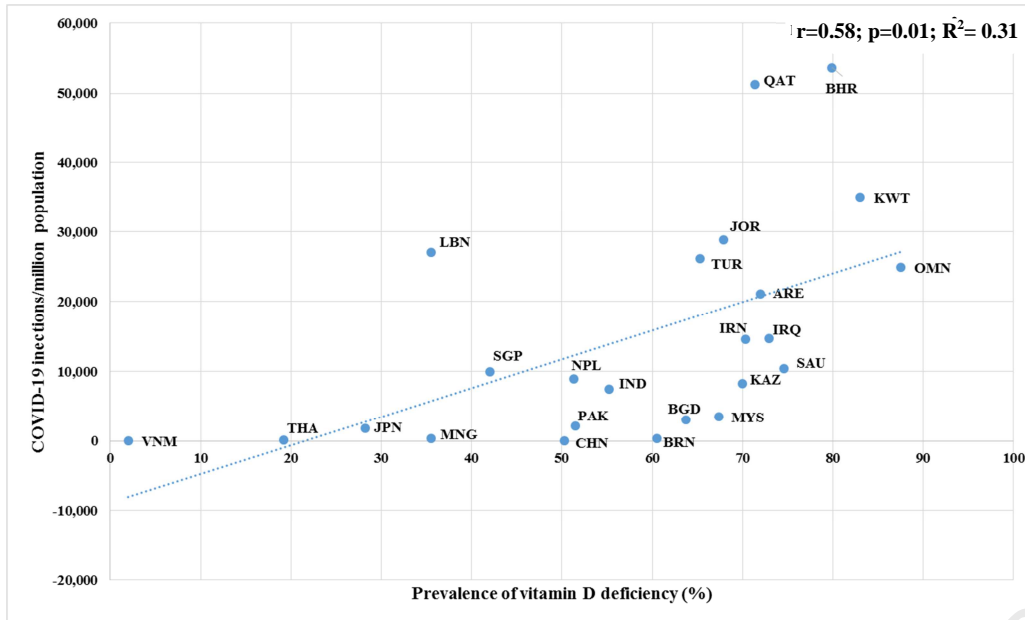


Figure 1a

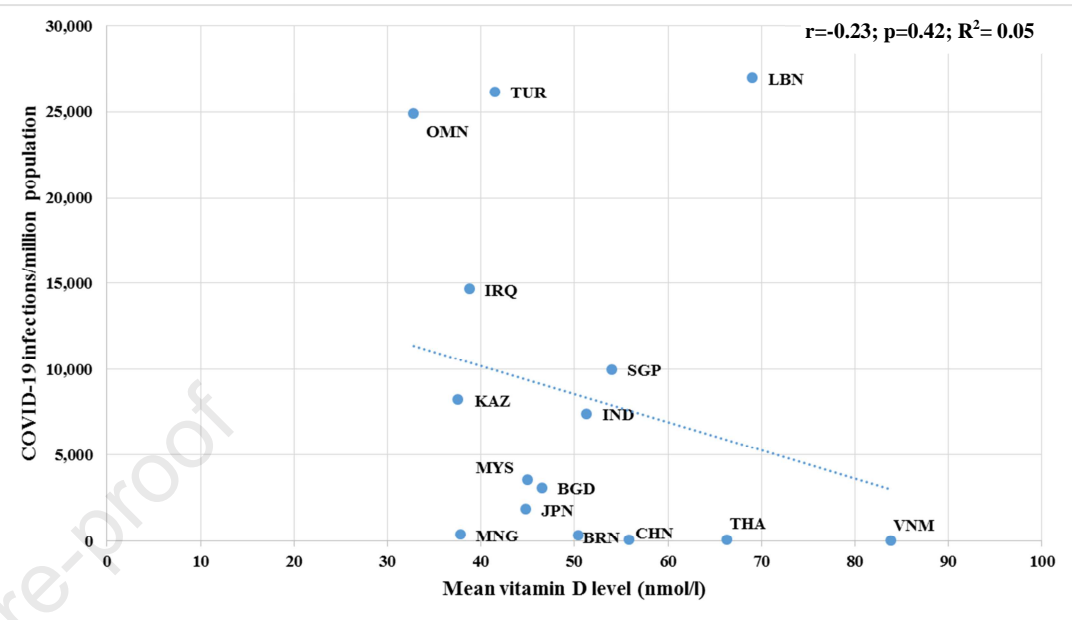


Figure 1b

**Figure 1:** Scatter diagrams of **a)** prevalence of vitamin D deficiency **b)** mean vitamin D levels, against COVID-19 infections as of December, 31<sup>st</sup> 2020.

ARE: United Arab Emirates; BGD: Bangladesh; BHR: Bahrain; BRN: Brunei; CHN: China; IND: India; IRN: Iran; IRQ: Iraq; JOR: Jordan; JPN: Japan; KAZ: Kazakazhtan; KWT: Kuwait; LBN: Lebanon; MNG: Mongolia; MYS: Malaysia; NPL: Nepal; OMN: Oman; QAT: Qatar; PAK: Pakistan; SAU: Saudi Arabia; SGP: Singapore; THA: Thailand; TUR: Turkey; VNM: Vietnam.

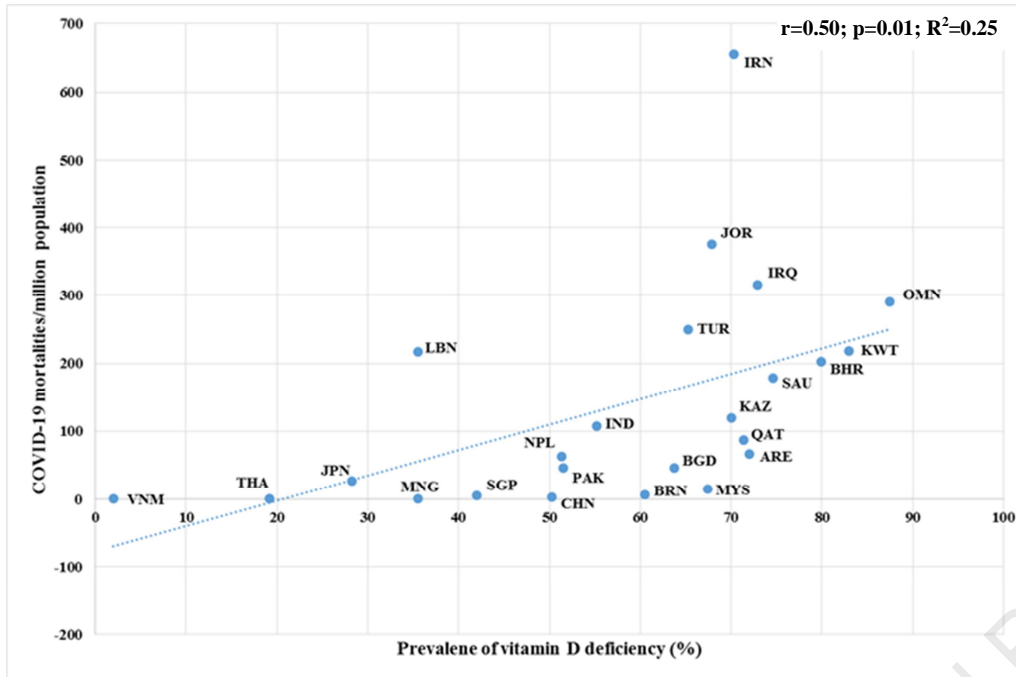


Figure 2a

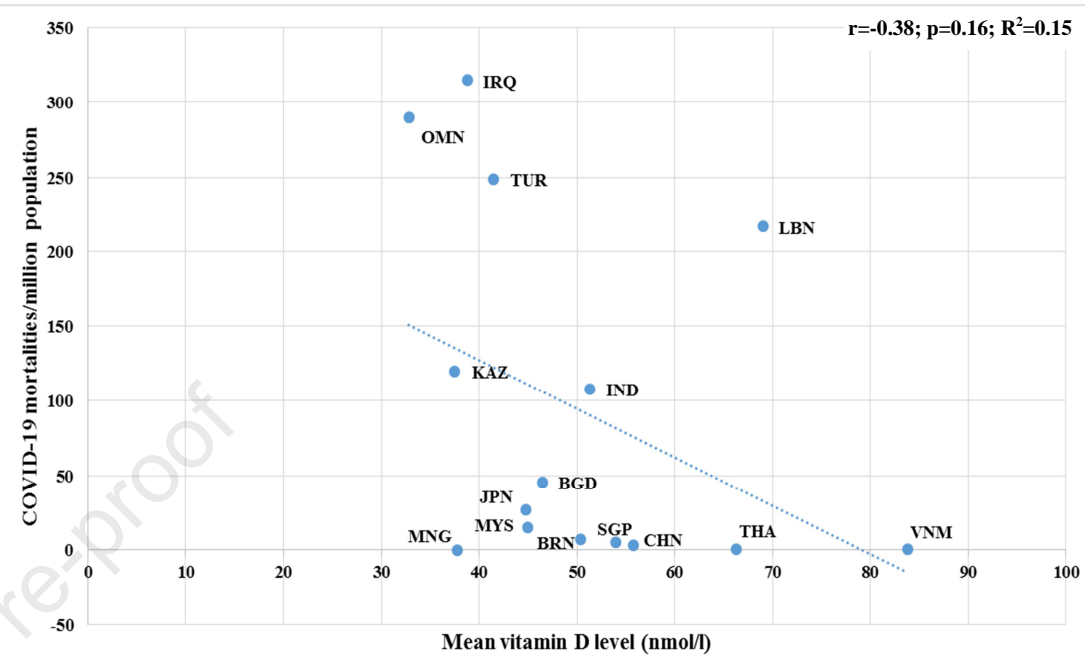


Figure 2b

**Figure 2:** Scatter diagrams of a) prevalence of vitamin D deficiency b) mean vitamin D levels, against COVID-19 mortalities as of December, 31<sup>st</sup> 2020.

ARE: United Arab Emirates; BGD: Bangladesh; BHR: Bahrain; BRN: Brunei; CHN: China; IND: India; IRN: Iran; IRQ: Iraq; JOR: Jordan; JPN: Japan; KAZ: Kazakazhtan; KWT: Kuwait; LBN: Lebanon; MNG: Mongolia; MYS: Malaysia; NPL: Nepal; OMN: Oman; QAT: Qatar; PAK: Pakistan; SAU: Saudi Arabia; SGP: Singapore; THA: Thailand; TUR: Turkey; VNM: Vietnam.

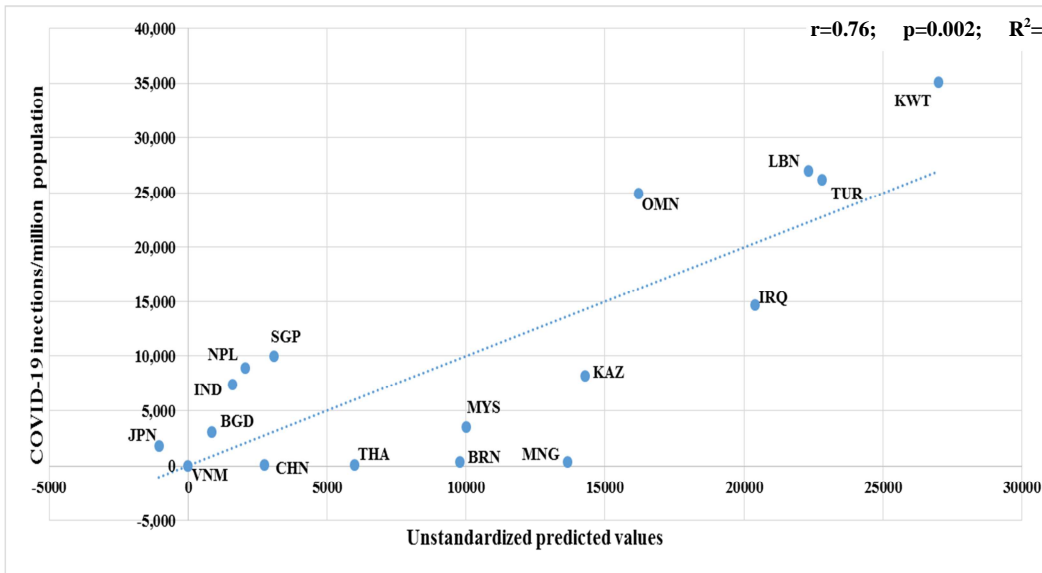


Figure 3a

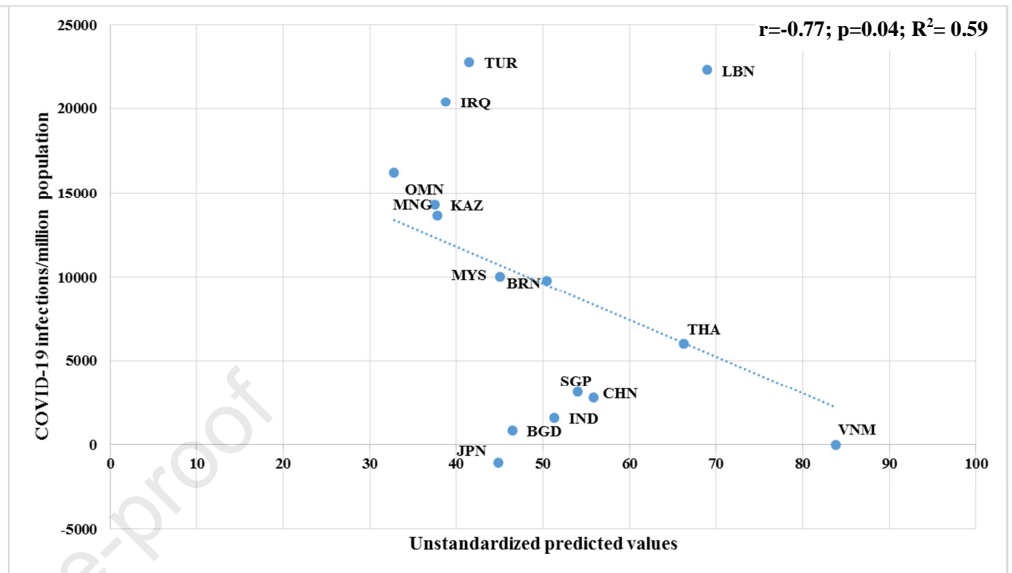


Figure 3b

**Figure 3:** Scatter diagrams based on all confounders with **a)** prevalence of vitamin D deficiency **b)** mean vitamin D levels, against COVID-19 infections as of December, 31<sup>st</sup> 2020.

ARE: United Arab Emirates; BGD: Bangladesh; BHR: Bahrain; BRN: Brunei; CHN: China; IND: India; IRN: Iran; IRQ: Iraq; JOR: Jordan; JPN: Japan; KAZ: Kazakazhtan; KWT: Kuwait; LBN: Lebanon; MNG: Mongolia; MYS: Malaysia; NPL: Nepal; OMN: Oman; QAT: Qatar; PAK: Pakistan; SAU: Saudi Arabia; SGP: Singapore; THA: Thailand; TUR: Turkey; VNM: Vietnam.

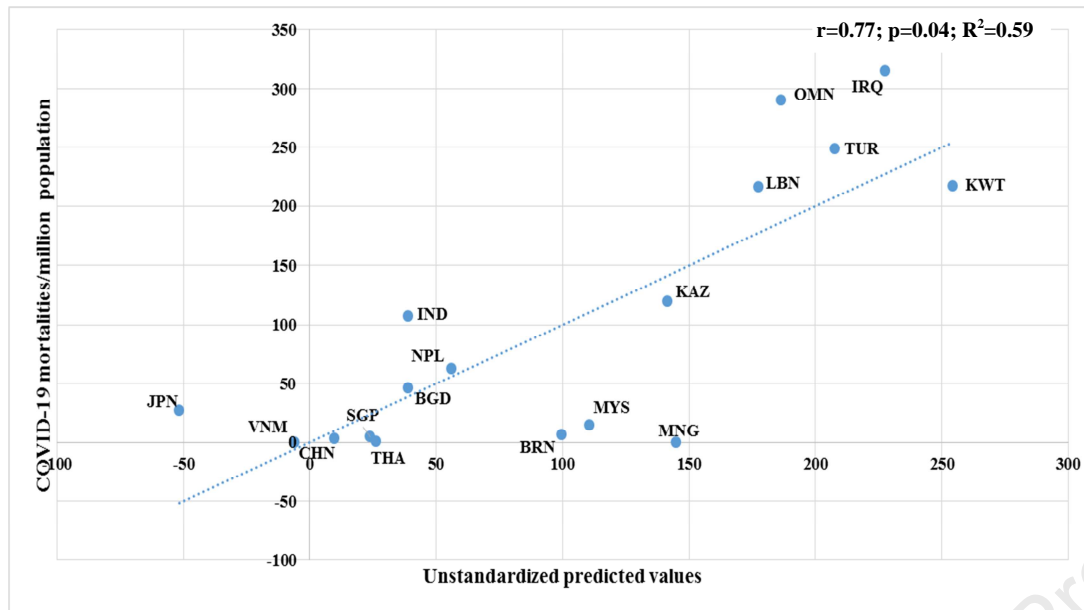


Figure 4a

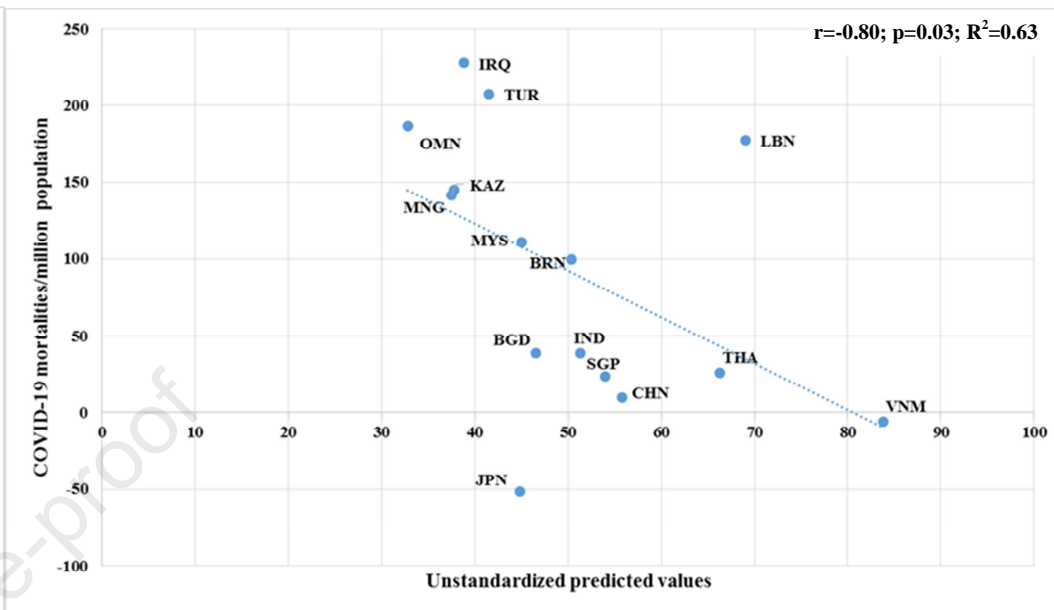


Figure 4b

**Figure 4:** Scatter diagrams based on all confounders with **a)** prevalence of vitamin D deficiency **b)** mean vitamin D levels, against COVID-19 mortalities as of December, 31<sup>st</sup> 2020.

ARE: United Arab Emirates; BGD: Bangladesh; BHR: Bahrain; BRN: Brunei; CHN: China; IND: India; IRN: Iran; IRQ: Iraq; JOR: Jordan; JPN: Japan; KAZ: Kazakazhtan; KWT: Kuwait; LBN: Lebanon; MNG: Mongolia; MYS: Malaysia; NPL: Nepal; OMN: Oman; QAT: Qatar; PAK: Pakistan; SAU: Saudi Arabia; SGP: Singapore; THA: Thailand; TUR: Turkey; VNM: Vietnam.

## HIGHLIGHTS

- Prevalence of vitamin D deficiency is positively correlated with COVID-19 infection and mortality in Asian countries.
- Correlation improved after including confounders such as median age, prevalence of obesity and diabetes.
- Mean vitamin D level is negatively correlated with COVID-19 infection and mortality when predicting with confounders.

## **Impact of the vitamin D deficiency on COVID-19 infection and mortality in Asian countries**

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## DECLARATIONS

### *Conflicts of interest*

The authors declare that there are no conflicts of interest regarding the publication of this paper.

### *Authors' Contributions*

RJ conceived and designed the study. DTJ, TVF and RJ collected data. DTJ analysed the data. DTJ, TVF, and RJ drafted the manuscript. AM revised the paper. All authors read and approved the final manuscript.

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### *Ethics approval and consent to participate*

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