

# 1 **COVID-19 mortality risk correlates inversely with vitamin D3** 2 **status, and a mortality rate close to zero could theoretically be** 3 **achieved at 50 ng/ml 25(OH)D3: Results of a systematic review and** 4 **meta-analysis.**

5 Lorenz Borsche, Bernd Glauner, Julian von Mendel\*

6 \*Correspondence: borsche@gmx.de

## 7 **Abstract**

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### 8 **Background**

9 Much research shows that blood calcidiol (25(OH)D3) levels correlate strongly with SARS-CoV-2  
10 infection severity. There is open discussion regarding whether low D3 is caused by the infection or if  
11 deficiency negatively affects immune defense. The aim of this study was to collect further evidence on  
12 this topic.

### 13 **Methods**

14 Systematic literature search was performed to identify retrospective cohort as well as clinical studies on  
15 COVID-19 mortality rates versus D3 blood levels. Mortality rates from clinical studies were corrected for  
16 age, sex and diabetes. Data were analyzed using correlation and linear regression.

### 17 **Results**

18 One population study and seven clinical studies were identified, which reported D3 blood levels pre-  
19 infection or on the day of hospital admission. They independently showed a negative Pearson correlation  
20 of D3 levels and mortality risk ( $r(17)=-.4154$ ,  $p=.0770$ / $r(13)=-.4886$ ,  $p=.0646$ ). For the combined data,  
21 median (IQR) D3 levels were 23.2 ng/ml (17.4 – 26.8), and a significant Pearson correlation was  
22 observed ( $r(32)=-.3989$ ,  $p=.0194$ ). Regression suggested a theoretical point of zero mortality at  
23 approximately 50 ng/ml D3.

## 24 Conclusions

25 The two datasets provide strong evidence that low D3 is a predictor rather than a side effect of the  
26 infection. Despite ongoing vaccinations, we recommend raising serum 25(OH)D levels to above 50 ng/ml  
27 to prevent or mitigate new outbreaks due to escape mutations or decreasing antibody activity.

## 28 Trial registration

29 Not applicable.

## 30 Keywords

31 mortality; vitamin D; calcidiol; calcitriol; D3; COVID-19; inflammation; SARS-CoV-2; ARDS; immune  
32 status; immunodeficiency; renin; angiotensin; ACE2; virus infection; cytokine release syndrome; CRS

## 33 **Background**

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34 The SARS-CoV-2 pandemic causing acute respiratory distress syndrome (ARDS) has lasted for more  
35 than 18 months. It has created a major global health crisis due to the high number of patients requiring  
36 intensive care, and the high death rate has substantially affected everyday life through contact restrictions  
37 and lockdowns. According to many scientists and medical professionals, we are far from the end of this  
38 disaster and hence must learn to coexist with the virus for several more years, perhaps decades [1,2].

39 It is realistic to assume that there will be new mutations, which are possibly more infectious or more  
40 deadly. In the known history of virus infections, we have never faced a similar global spread. Due to the  
41 great number of viral genome replications that occur in infected individuals and the error-prone nature of  
42 RNA-dependent RNA polymerase, progressive accrual mutations do and will continue to occur [3–5].  
43 Thus, similar to other virus infections such as influenza, we have to expect that the effectiveness of  
44 vaccination is limited in time, especially with the current vaccines designed to trigger an immunological  
45 response against a single viral protein [6–8].

46 We have already learned that even fully vaccinated people can be infected [9]. Currently, most of these  
47 infections do not result in hospitalization, especially for young individuals without comorbidities.  
48 However, these infections are the basis for the ongoing dissemination of the virus in a situation where  
49 worldwide herd immunity against SARS-CoV-2 is rather unlikely. Instead, humanity could be trapped in  
50 an insuperable race between new mutations and new vaccines, with an increasing risk of newly arising  
51 mutations becoming resistant to the current vaccines [3,10,11]. Thus, a return to normal life in the near  
52 future seems unlikely. Mask requirements as well as limitations of public life will likely accompany us  
53 for a long time if we are not able to establish additional methods that reduce virus dissemination.

54 Vaccination is an important part in the fight against SARS-CoV-2 but, with respect to the situation  
55 described above, should not be the only focus. One strong pillar in the protection against any type of virus  
56 infection is the strength of our immune system [12]. Unfortunately, thus far, this unquestioned basic  
57 principle of nature has been more or less neglected by the responsible authorities. It is well known that  
58 our modern lifestyle is far from optimal with respect to nutrition, physical fitness and recreation. In  
59 particular, many people are not spending enough time outside in the sun, even in summer. The  
60 consequence is widespread vitamin D deficiency, which limits the performance of their immune systems,  
61 resulting in the increased spread of some preventable diseases of civilization, reduced protection against  
62 infections and reduced effectiveness of vaccination [13].

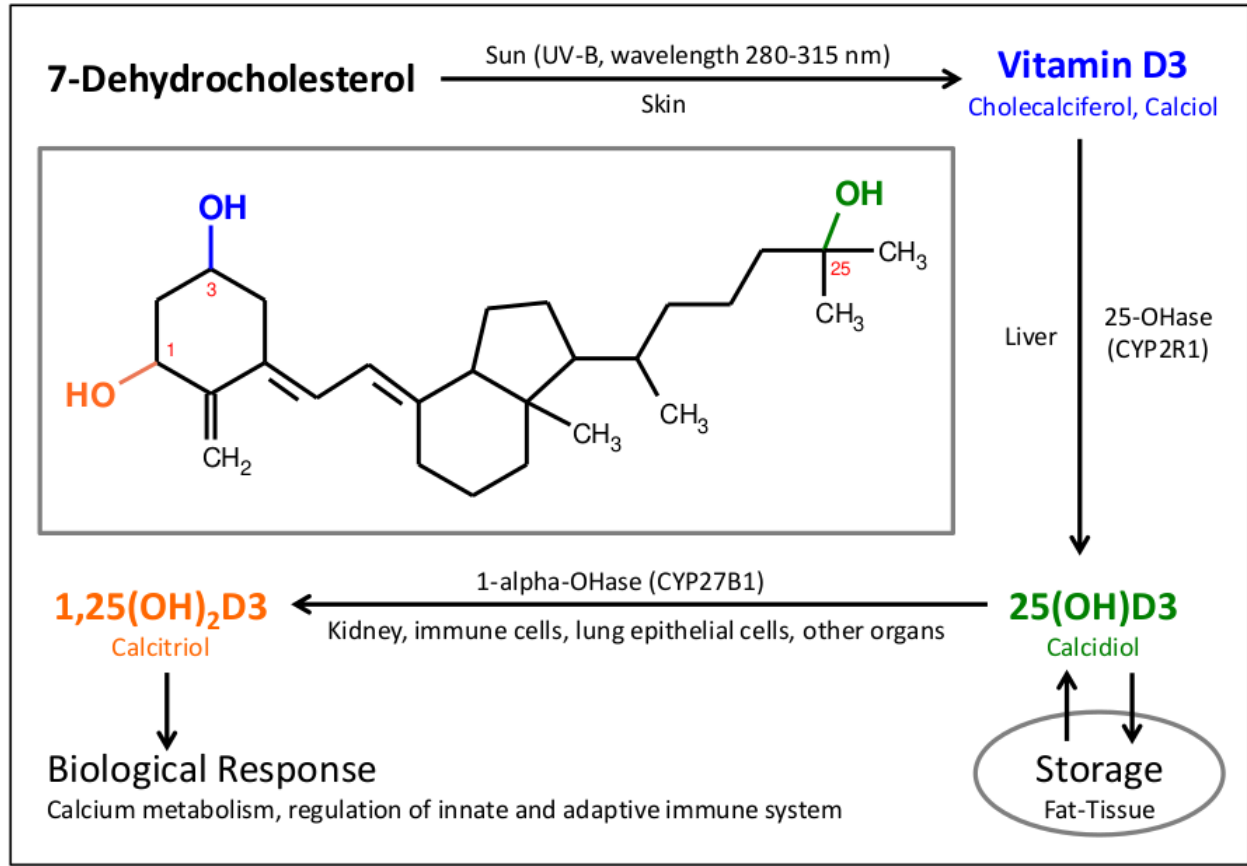
63 In this publication, we will demonstrate that vitamin D3 deficiency, which is a well-documented  
64 worldwide problem [13–19,179], is one of the main reasons for severe courses of SARS-CoV-2  
65 infections. The fatality rates correlate well with the findings that elderly people, black people and people  
66 with comorbidities show very low vitamin D3 levels [16,20–22]. Additionally, with only a few  
67 exceptions, we are facing the highest infection rates in the winter months and in northern countries, which  
68 are known to suffer from low vitamin D3 levels due to low endogenous sun-triggered vitamin D3  
69 synthesis [23–26].

70 Vitamin D3 was first discovered at the beginning of the 19<sup>th</sup> century as an essential factor needed to

71 guarantee skeletal health. This discovery came after a long period of dealing with the dire consequences  
72 of rickets, which causes osteomalacia (softening of bones). This disease especially affected children in  
73 northern countries, who were deprived of sunlight and often worked in dark production halls during the  
74 industrial revolution [27]. At the beginning of the 20<sup>th</sup> century, it became clear that sunlight can cure  
75 rickets by triggering vitamin D3 synthesis in the skin. Cod liver oil is recognized as a natural source of  
76 vitamin D3 [28]. At the time, a blood level of 20 ng/ml was sufficient to stop osteomalacia. This target is  
77 still the recommended blood level today, as stated in many official documents [29]. In accordance with  
78 many other publications, we will show that this level is considerably too low to guarantee optimal  
79 functioning of the human body.

80 In the late 1920s, Adolf Windaus elucidated the structure of vitamin D3. The metabolic pathway of  
81 vitamin D3 (biochemical name cholecalciferol) is shown in Figure 1 [30]. The precursor, 7-  
82 dehydrocholesterol, is transformed into cholecalciferol in our skin by photoisomerization caused by UV-  
83 B exposure (wavelength 280–315 nm). After transportation to the liver, cholecalciferol is hydroxylated,  
84 resulting in 25-hydroxycholecalciferol (25(OH)D3, also called calcidiol), which can be stored in fat tissue  
85 for several months and is released back into blood circulation when needed. The biologically active form  
86 is generated by a further hydroxylation step, resulting in 1,25-dihydroxycholecalciferol (1,25(OH)<sub>2</sub>D3,  
87 also called calcitriol). Early investigations assumed that this transformation takes place mainly in the  
88 kidney.

89 **Fig. 1 Metabolic Pathway of Vitamin D3**



90 Fig. 1 legend: The vitamin D pathway is characterized by two subsequent hydroxylation steps. In the liver, 25-  
91 Hydroxylase produces 25(OH)D3 (calcidiol), which can be stored in fat tissue. 1-Alpha-hydroxylase generates the  
92 active steroid hormone 1,25(OH)<sub>2</sub>D3 (calcitriol), which regulates calcium metabolism as well as the innate and  
93 adaptive immune system.

94 Over the last decades, knowledge regarding the mechanisms through which vitamin D3 affects human  
95 health has improved dramatically. It was discovered that the vitamin D3 receptor (VDR) and the vitamin  
96 D3 activating enzyme 1- $\alpha$ -hydroxylase (CYP27B1) are expressed in many cell types that are not involved  
97 in bone and mineral metabolism, such as the intestine, pancreas, and prostate as well as cells of the  
98 immune system [31–35]. This finding demonstrates the important, much wider impact of vitamin D3 on  
99 human health than previously understood [36,37]. Vitamin D turned out to be a powerful epigenetic  
100 regulator, influencing more than 2500 genes [38] and impacting dozens of our most serious health  
101 challenges [39], including cancer [40,41], diabetes mellitus [42], acute respiratory tract infections [43],  
102 chronic inflammatory diseases [44] and autoimmune diseases such as multiple sclerosis [45].

103 In the field of human immunology, the extrarenal synthesis of the active metabolite calcitriol-  
104 1,25(OH)<sub>2</sub>D<sub>3</sub>-by immune cells and lung epithelial cells has been shown to have immunomodulatory  
105 properties [46–51]. Today, a compelling body of experimental evidence indicates that activated vitamin  
106 D<sub>3</sub> plays a fundamental role in regulating both innate and adaptive immune systems [52–55]. Intracellular  
107 vitamin D<sub>3</sub> receptors (VDRs) are present in nearly all cell types involved in the human immune response,  
108 such as monocytes/macrophages, T cells, B cells, natural killer (NK) cells, and dendritic cells (DCs).  
109 Receptor binding engages the formation of the “vitamin D<sub>3</sub> response element” (VDRE), regulating a  
110 large number of target genes involved in the immune response [56]. As a consequence of this knowledge,  
111 the scientific community now agrees that calcitriol is much more than a vitamin but rather a highly  
112 effective hormone with the same level of importance to human metabolism as other steroid hormones.  
113 The blood level ensuring the reliable effectiveness of vitamin D<sub>3</sub> with respect to all its important  
114 functions came under discussion again, and it turned out that 40–60 ng/ml is preferable [37], which is  
115 considerably above the level required to prevent rickets.

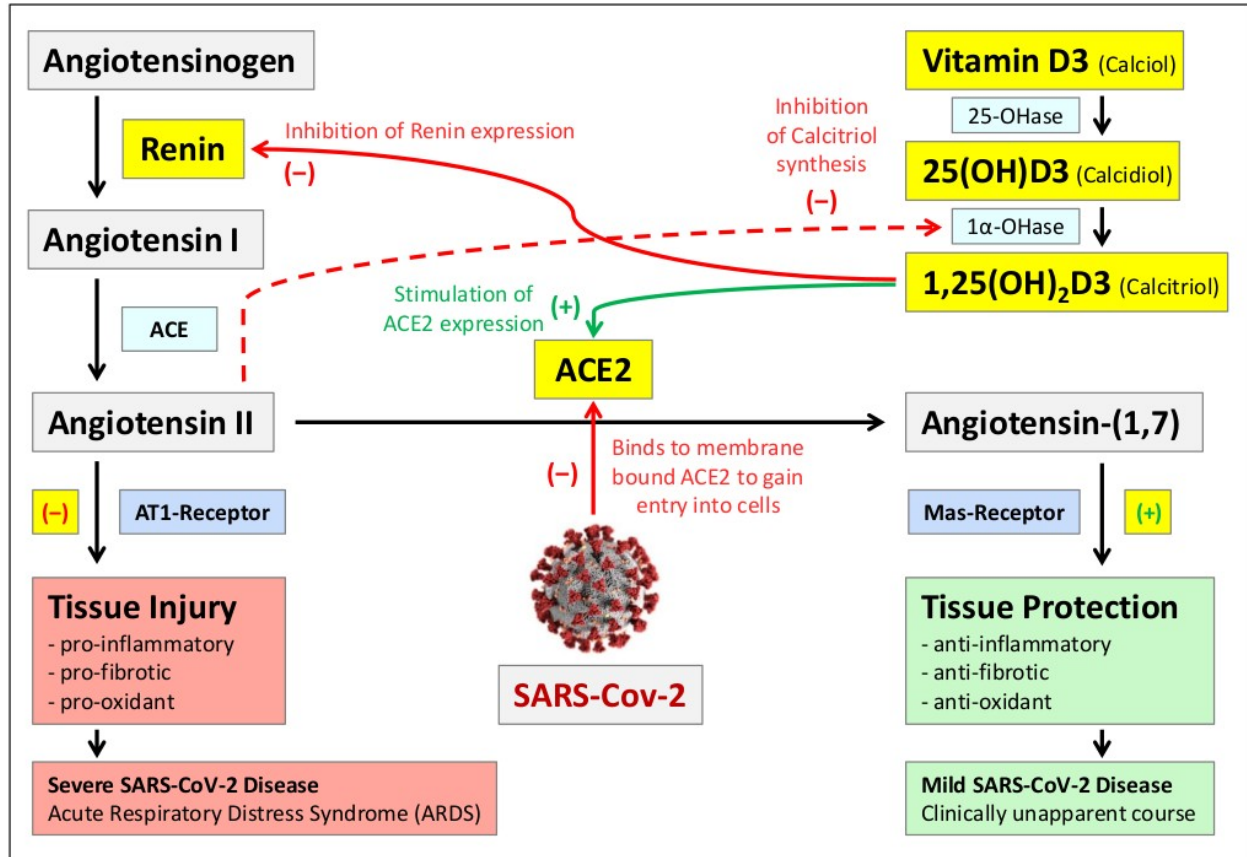
116 Long before the SARS-CoV-2 pandemic, an increasing number of scientific publications showed the  
117 effectiveness of a sufficient vitamin D<sub>3</sub> blood level in curing many of the human diseases caused by a  
118 weak or unregulated immune system [37,57–59]. This includes all types of virus infections [43,60–  
119 68,180], with a main emphasis on lung infections that cause ARDS [69–71], as well as autoimmune  
120 diseases [45,62,72,73]. However, routine vitamin D<sub>3</sub> testing and supplementation are still not established  
121 today. Unfortunately, it seems that the new findings about vitamin D<sub>3</sub> have not been well accepted in the  
122 medical community. Many official recommendations to define vitamin D<sub>3</sub> deficiency still stick to the 20  
123 ng/ml established 100 years ago to cure rickets [74].

124 Additionally, many recommendations for vitamin D<sub>3</sub> supplementation are in the range of 5 to 20 µg per  
125 day (200 to 800 international units), which is much too low to guarantee the optimal blood level of 40–60  
126 ng/ml [37,75]. One reason for these incorrect recommendations turned out to be calculation error [76,77].  
127 Another reason for the error is because vitamin D<sub>3</sub> treatment to cure osteomalacia was commonly

128 combined with high doses of calcium to support bone calcification. When examining for the side effects  
129 of overdoses of such combination products, it turned out that there is a high risk of calcium deposits in  
130 blood vessels, especially in the kidney. Today, it is clear that such combination preparations are  
131 nonsensical because vitamin D3 stimulates calcium uptake in the intestine itself. Without calcium  
132 supplementation, even very high vitamin D3 supplementation does not cause vascular calcification,  
133 especially if another important finding is included. Even when calcium blood levels are high, the culprit  
134 for undesirable vascular calcification is not vitamin D but insufficient blood levels of vitamin K2. Thus,  
135 daily vitamin D3 supplementation in the range of 4000 to 10,000 units (100 to 250 µg) needed to generate  
136 an optimal vitamin D3 blood level in the range of 40–60 ng/ml has been shown to be completely safe  
137 when combined with approximately 200 µg/ml vitamin K2 [78–80]. However, this knowledge is still not  
138 widespread in the medical community, and obsolete warnings about the risks of vitamin D3 overdoses  
139 unfortunately are still commonly circulating.

140 Based on these circumstances, the SARS-CoV-2 pandemic is becoming the second breakthrough in the  
141 history of vitamin D3 association with disease (after rickets), and we have to ensure that full advantage is  
142 being taken of its medical properties to keep people healthy. The most life-threatening events in the  
143 course of a SARS-CoV-2 infection are ARDS and cytokine release syndrome (CRS). It is well established  
144 that vitamin D3 is able to inhibit the underlying metabolic pathways [81,82] because a very specific  
145 interaction exists between the mechanism of SARS-CoV-2 infection and vitamin D3:

146 **Fig. 2 Interaction of Vitamin D3 with the Renin-Angiotensin System (RAS)**



148 Fig. 2 legend: The renin-angiotensin system (RAS) is an important regulator of blood volume and systemic vascular  
 149 resistance for the adjustment of blood pressure. The balance between angiotensin II and angiotensin-(1,7) is a  
 150 critical factor for the proper functioning of the system (175). Angiotensin-converting enzyme 2 (ACE2) is  
 151 responsible for converting angiotensin II to angiotensin-(1,7). Angiotensin II primarily triggers vasoconstriction but  
 152 can also cause inflammation, fibrosis and oxidative stress in the absence of its counterpart, angiotensin-(1,7). ACE2  
 153 is the primary receptor of SARS-CoV-2, which decreases its activity, leading to an increase in angiotensin II levels  
 154 and a decrease in angiotensin-(1,7) levels. This effect ultimately triggers SARS-CoV-2-induced "acute respiratory  
 155 distress syndrome" (ARDS) [83,84]. Calcitriol, the active metabolite of vitamin D3, minimizes this effect by  
 156 inhibiting renin expression and thus angiotensin II synthesis and by stimulating ACE2 expression [172,173],  
 157 enhancing the conversion of angiotensin II to angiotensin-(1,7). Thus, insufficient vitamin D blood levels lead to the  
 158 development of severe courses of SARS-CoV-2 disease. In addition, it has been shown that high angiotensin II levels  
 159 lead to downregulation of the enzyme 1-alpha-hydroxylase [174], which is required for the formation of calcitriol,  
 160 thereby exacerbating the negative consequences of vitamin D deficiency.



161 Angiotensin-converting enzyme 2 (ACE2), a part of the renin-angiotensin system (RAS), serves as the  
162 major entry point for SARS-CoV-2 into cells (Fig. 2). When SARS-CoV-2 is attached to ACE2 its  
163 expression is reduced, thus causing lung injury and pneumonia [83,84,175]. Vitamin D3 is a negative  
164 RAS modulator by inhibition of renin expression and stimulation of ACE2 expression. It therefore has a  
165 protective role against ARDS caused by SARS-CoV-2. Sufficient vitamin D3 levels prevent the  
166 development of ARDS by reducing the levels of angiotensin II and increasing the level of angiotensin-  
167 (1,7) [18,85,86,172,173,176].

168 There are several additional important functions of vitamin D3 supporting immune defense [18,75,87,88]:

- 169 • Vitamin D decreases the production of Th1 cells. Thus, it can suppress the progression of  
170 inflammation by reducing the generation of inflammatory cytokines [72,89,90].
- 171 • Vitamin D3 reduces the severity of cytokine release syndrome (CRS). This “cytokine storm”  
172 causes multiple organ damage and is therefore the main cause of death in the late stage of SARS-  
173 CoV-2 infection. The systemic inflammatory response due to viral infection is attenuated by  
174 promoting the differentiation of regulatory T cells [91–94].
- 175 • Vitamin D3 induces the production of the endogenous antimicrobial peptide cathelicidin (LL-37)  
176 in macrophages and lung epithelial cells, which acts against invading respiratory viruses by  
177 disrupting viral envelopes and altering the viability of host target cells [51,95–100].
- 178 • Experimental studies have shown that vitamin D and its metabolites modulate endothelial  
179 function and vascular permeability via multiple genomic and extragenomic pathways [101,102].
- 180 • Vitamin D reduces coagulation abnormalities in critically ill COVID-19 patients [103–105].

181 A rapidly increasing number of publications are investigating the vitamin D3 status of SARS-CoV-2  
182 patients and have confirmed both low vitamin D levels in cases of severe courses of infection [106–121]  
183 and positive results of vitamin D3 treatments [122–128]. Therefore, many scientists recommend vitamin  
184 D3 as an indispensable part of a medical treatment plan to avoid severe courses of SARS-CoV-2 infection

185 [14,18,75,82,129,130], which has additionally resulted in proposals for the consequent supplementation  
186 of the whole population [131]. A comprehensive overview and discussion of the current literature is given  
187 in a review by Linda Benskin [132]. Unfortunately, all these studies are based on relatively low numbers  
188 of patients. Well-accepted, placebo-controlled, double-blinded studies are still missing.

189 The finding that most SARS-CoV-2 patients admitted to hospitals have vitamin D3 blood levels that are  
190 too low is unquestioned even by opponents of vitamin D supplementation. However, there is an ongoing  
191 discussion as to whether we are facing a causal relationship or just a decline in the vitamin D levels  
192 caused by the infection itself [82,133,134,181].

193 There are reliable data on the average vitamin D3 levels in the population [15,19,135] in several  
194 countries, in parallel to the data about death rates caused by SARS-CoV-2 in these countries [136,137].  
195 Obviously, these vitamin D3 data are not affected by SARS-CoV-2 infections. While meta-studies using  
196 such data [25,130,134,138] are already available, our goal was to analyze these data in the same manner  
197 as selected clinical data. In this article, we identify a vitamin D threshold that virtually eliminates excess  
198 mortality caused by SARS-CoV-2. In contrast to published D3/SARS-CoV-2 correlations [139–141,182-  
199 185], our data include studies assessing preinfection vitamin D values as well as studies with vitamin D  
200 values measured post-infection latest on the day after hospitalization. Thus, we can expect that the  
201 measured vitamin D status is still close to the preinfection level. In contrast to other meta-studies which  
202 also included large retrospective cohort studies [184-185], our aim was to perform regressions on the  
203 combined data after-correcting for patient characteristics.

204 These results from independent datasets, which include data from before and after the onset of the  
205 disease, also further strengthen the assumption of a causal relationship between vitamin D3 blood levels  
206 and SARS-CoV-2 death rates. Our results therefore also confirm the importance of establishing vitamin  
207 D3 supplementation as a general method to prevent severe courses of SARS-CoV-2 infections.

## 208 **Methods**

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### 209 **Search Strategy and Selection Criteria**

210 Initially, a systematic literature review was performed to identify relevant COVID-19 studies. Included  
211 studies were observational cohort studies that grouped two or more cohorts by their vitamin D3 values  
212 and listed mortality rates for the respective cohorts. PubMed and the <https://c19vitamind.com> registry  
213 were searched according to Table 1. Subsequently, titles and abstracts were screened, and full-text articles  
214 were further analyzed for eligibility.

### 215 **Table 1 Search Strategy**

Source	Search Strategy	Time frame
PubMed	COVID-19 Search String from [142] AND (“vitamin d” or “d3” or “25(OH)D” or “25-hydroxyvitamin D”)	November 1, 2019 - March 27, 2021
<a href="https://c19vitamind.com">https:// c19vitamind.com</a>	Restriction to category “Levels”	November 1, 2019 - March 27, 2021

### 216 **Data Analysis**

217 Collected studies were divided into a population study [143] and seven hospital studies. Notably, these  
218 data sources are fundamentally different, as one assesses vitamin D values long-term, whereas the other  
219 measures vitamin D values postinfection, thereby masking a possible causal relationship between the  
220 preinfection vitamin D level and mortality.

221 Several corrections for the crude mortality rates (CMRs) recorded by Ahmad were attempted to  
222 understand the underlying causes within the population study data and the outliers. In the end, none were  
223 used in the final data evaluation to avoid the risk of introducing hidden variables that also correlate with  
224 D3.

225 Mortality rates and D3 blood levels from studies on hospitalized COVID-19 patients were assembled in a  
226 separate dataset. When no median D3 blood levels were provided for the individual study cohorts, the  
227 IQR, mean±SD or estimated values within the grouping criteria were used in that order. Patient  
228 characteristics, including age IQR, sex and diabetes status, were used to compute expected mortality rates  
229 with a machine learning model [144]. Based on the expected mortality rate, the observed mortality rates  
230 were corrected for the specific cohorts.

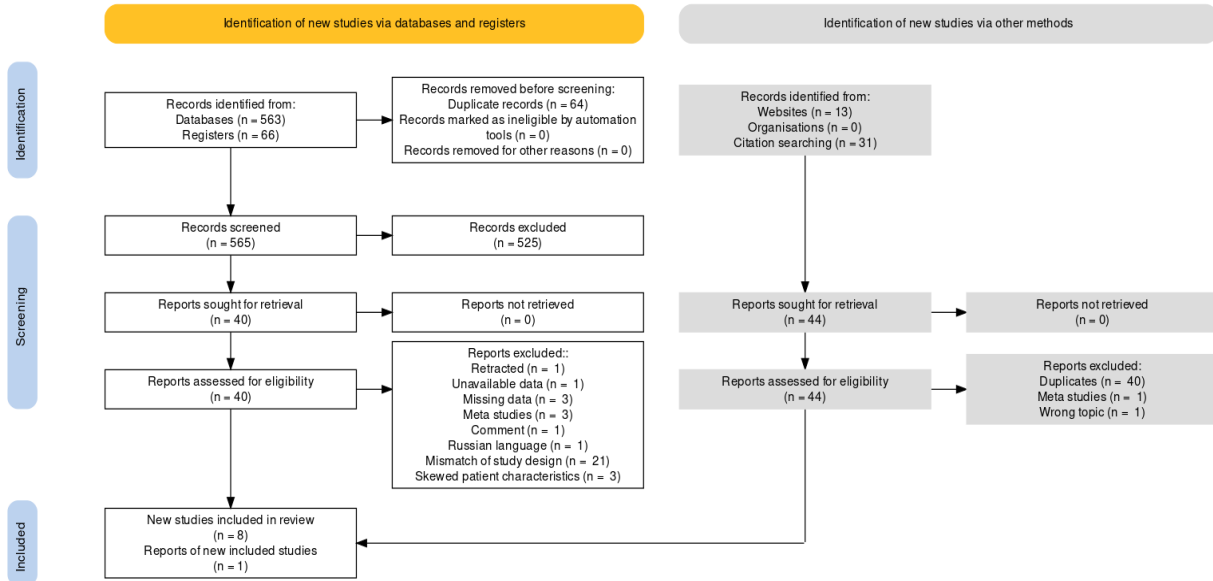
231 The two datasets were combined, and the mortality rates of the hospital studies were scaled according to  
232 the mortality range of the population studies, resulting in a uniform list of patient cohorts, their vitamin D  
233 status and dimensionless mortality coefficients. Linear regressions (OLS) and Pearson and Spearman  
234 correlations of vitamin D and the mortality values for the separate and combined datasets were generated  
235 with a Python 3.7 kernel using the scipy.stats 1.7.0 and statsmodels 0.12.2 libraries in a  
236 <https://deepnote.com> Jupyter notebook.

## 237 **Results**

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238 Database and registry searches resulted in 563 and 66 records, respectively. Nonsystematic web searches  
239 accounted for 13 studies, from which an additional 31 references were assessed. After removal of 104  
240 duplicates and initial screening, 44 studies remained. Four meta-studies, one comment, one retracted  
241 study, one report with unavailable data, one wrong topic report and one Russian language record were  
242 excluded. The remaining 35 studies were assessed in full text, 20 of which did not meet the eligibility  
243 criteria due to their study design or lack of quantitative mortality data. Four further studies were excluded  
244 due to missing data for individual patient cohorts. Finally, three studies were excluded due to skewed or  
245 nonrepresentative patient characteristics, as reviewed by LB and JVM [145–147]. Eight eligible studies  
246 for quantitative analysis remained, as listed in Table 2. A PRISMA flowchart [148] is presented in Figure  
247 3.

248 **Fig. 3 Flowchart of the search strategy and selection process [149]**



249

250 **Table 2 Eligible studies**

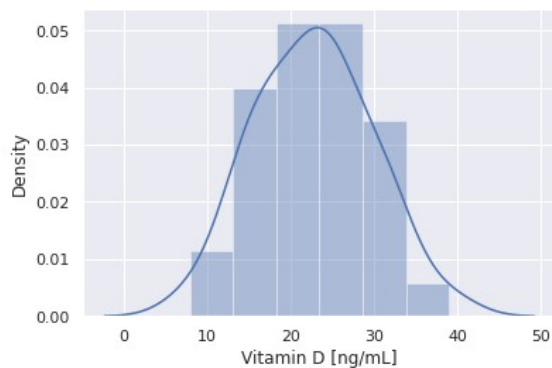
Author	Reference	Cohort	No. of patients	Laboratory results recorded pre-/post-infection	Mortality	Vitamin D level [ng/ml]
Ahmad et al., 2021	[143]	19 European countries	448,785,546	Up to 10 months in advance	Refer to source study	
Angelidi et al., 2021	[153]	< 30 ng/ml	79	Within 1 day after admission	25.30%	NR <sup>a</sup> Median (IQR): 28 ng/ml (16.80 – 39.00 ng/ml)
		≥ 30 ng/ml	65		9.20%	
Charoenngam et al., 2021	[154]	< 20 ng/ml	96	Up to 1 year in advance	14.58%	NR <sup>a</sup>
		20–30 ng/ml	91		16.48%	
		≥ 30 ng/ml	100		12.00%	
Gavioli et al.,	[155]	Deficient	177	Up to 3	29.00%	14.00

2021				months in advance		31.00
		Sufficient	260		31.00%	
Susianti et al., 2021	[150]	< 49.92 nmol/L	42	Within 1 day after admission	45.00%	8.00
		≥ 49.92 nmol/L	8		42.00%	28.40
Szeto et al., 2021	[151]	< 20 ng/ml	35	Up to 12 months in advance	23.00%	16.00
		≥ 20 ng/ml	58		24.00%	32.00
Vanegas-Cedillo et al., 2021	[152]	≤ 20 ng/ml	251	Within 1 day after admission	23.50%	NR <sup>a</sup>
		> 20 ng/ml	300		19.00%	Mean±SD 21.78±9.01 ng/ml
Vassiliou, 2020	[113]	≤ 19.9 ng/ml	32	Within 1 day after admission	25.00%	NR <sup>a</sup>
		20–29.9 ng/ml	7		14.30%	

251 <sup>a</sup>Not reported

252 The observed median (IQR) vitamin D value over all collected study cohorts was 23.2 ng/ml (17.4 –  
253 26.8). A frequency distribution of vitamin D levels is shown in Figure 4.

254 **Fig. 4 Frequency distribution of vitamin D levels of all evaluated study cohorts**



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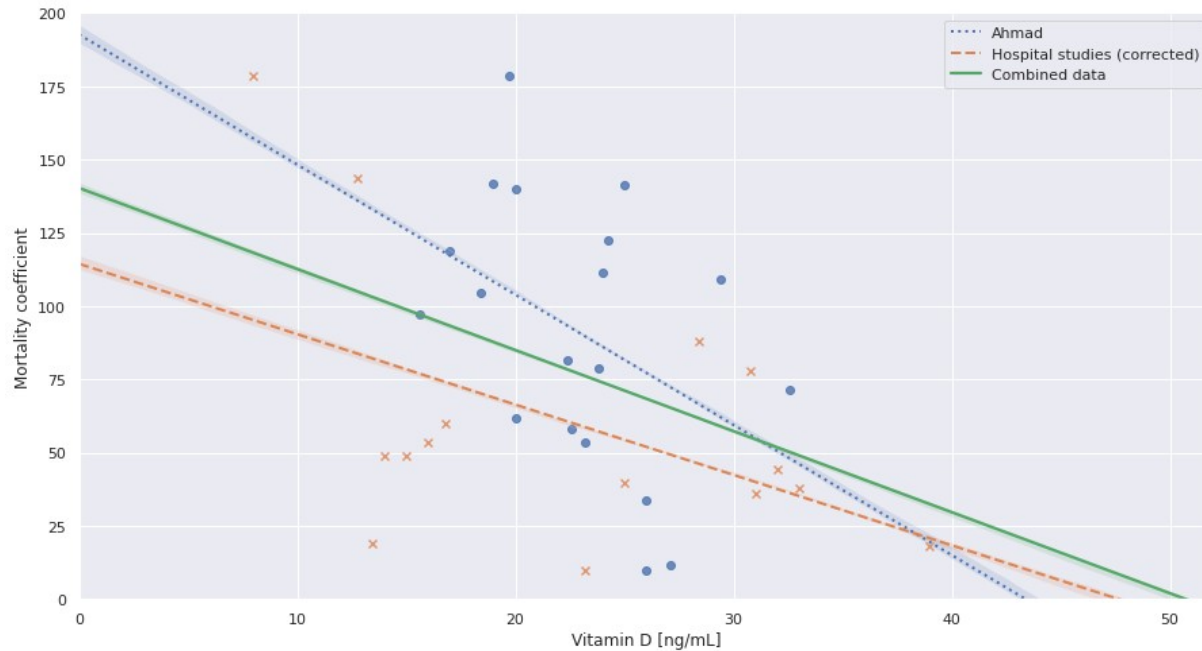
256 One population study by Ahmad et al. [143] was identified. Therein, the CMRs are compiled for 19  
257 European countries based on COVID-19 pandemic data from Johns Hopkins University [156] in the time  
258 frame from March 21, 2020, to January 22, 2021, as well as D3 blood levels for the respective countries  
259 collected by literature review. Furthermore, the proportions of the 70+ age population were collected. The  
260 median vitamin D3 level across countries was 23.2 ng/ml (19.9 – 25.5 ng/ml). A moderately negative  
261 Spearman’s correlation with the corresponding mean vitamin D3 levels in the respective populations was  
262 observed at  $r_s = -.430$  (95% CI:  $-.805 - -.081$ ). No further adjustments of these CMR values were  
263 performed by Ahmad. The correlations shown in Table 3 suggest the sex/age distribution, diabetes and  
264 the rigidity of public health measures as some of the causes for outliers within the Ahmad dataset.  
265 However, this has little effect on the further results discussed below.

266 **Table 3 Attempted corrections of the CMR values in the population study by Ahmad**

Method	Reference	Resulting Pearson correlation CMR ~ D3
None	–	$r(17) = -.4154$ , $p = .0770$
Two most extreme outliers removed	–	$r(15) = -.3471$ , $p = .1722$
Rigidity of public health measures	[157]	$r(17) = -.4662$ , $p = .0442$
Sex/age distribution, diabetes	[158,159]	$r(17) = -.5113$ , $p = .0253$
Expected SARS-COV-2 positive rate for given D3 level	[115]	$r(17) = -.5997$ , $p = .0066$

267 The extracted data from seven hospital studies showed a median vitamin D3 level of 23.2 ng/ml (14.5 –  
268 30.9 ng/ml). These data are plotted after correction of patient characteristics and scaling in combination  
269 with the data points from Ahmad in Figure 5.

270 **Fig. 5 Scatter plot and OLS regressions of the individual and combined datasets**



271

272 The correlation results are shown in Table 4 in which the combined data show a significant negative  
 273 Pearson correlation at  $r(32)=-.3989$ ,  $p=.0194$ . The linear regression results can be found in Table 5. The  
 274 regression for the combined data intersects the D3 axis at 50.7 ng/ml, suggesting a theoretical point of  
 275 zero mortality.

276 **Table 4 Correlation of mortality and vitamin D blood levels for the respective datasets**

	Ahmad	Hospital studies (corrected)	Combined
<b>Pearson correlation (Mortality~Vit D)</b>	$r(17)=-.4154$ , $p=.0770$	$r(13)=-.4886$ , $p=.0646$	$r(32)=-.3989$ , $p=.0194$
<b>Spearman correlation (Mortality~Vit D)</b>	$r_s=-.4300$ , $p=.0661$ , $N=19$	$r_s=-.469$ , $p=.0786$ , $N=15$	$r_s=-.3698$ , $p=.03136$ , $N=34$

277 **Table 5 OLS regressions for the respective datasets**

	Ahmad	Hospital studies (corrected)	Combined
<b>Intercept</b>	192.6788	114.4156	140.2880
<b>Coefficient</b>	-4.4408	-2.4015	-2.7654



<b>R<sup>2</sup></b>	.173	.239	.159
<b>Adj. R<sup>2</sup></b>	.124	.180	.133
<b>Prob (F-Statistic)</b>	.0770	.0646	.0194
<b>AIC</b>	198.7	156.5	356.8
<b>BIC</b>	200.6	158.0	359.8
<b>Prob (Omnibus)</b>	.342	.568	.436
<b>Durbin-Watson</b>	1.238	1.514	1.217
<b>Prob (Jarque-Bera)</b>	.591	.662	.572

## 278 **Discussion**

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279 This study illustrates that, at a time when vaccination was not yet available, patients with sufficiently high  
280 D3 serum levels preceding the infection were highly unlikely to suffer a fatal outcome. The partial risk at  
281 this D3 level seems to vanish under the normal statistical mortality risk for a given age and in light of  
282 given comorbidities. This correlation should have been good news when vaccination was not available  
283 but instead was widely ignored. Nonetheless, this result may offer hope for combating future variants of  
284 the rapidly changing virus as well as the dreaded breakthrough infections, in which severe outcomes have  
285 been seen in 10.5% of the vaccinated versus 26.5% of the unvaccinated group [177], with breakthrough  
286 even being fatal in 2% of cases [178].

287 Could a virus that is spreading so easily and is much deadlier than H1N1 influenza be kept under control  
288 if the human immune system could work at its fullest capacity? Zero mortality, a phrase used in the  
289 abstract, is of course an impossibility, as there is always a given intrinsic mortality rate for any age.

290 Statistical variations in genetics as well as in lifestyle often prevent us from identifying the exact medical  
291 cause of death, especially when risk factors (i.e., comorbidities) and an acute infection are in competition  
292 with one another. Risk factors also tend to reinforce each other. In COVID-19, it is common knowledge  
293 that type II diabetes, obesity, and high blood pressure easily double the risk of death [160], depending on  
294 age. The discussion of whether a patient has died “because of” or “with” COVID-19 or “from” or only  
295 “with” his or her comorbidities thus seems obsolete. SARS-CoV-2 infection is statistically just adding to  
296 the overall mortality risk, but obviously to a much higher degree than most other infectious diseases or  
297 general risk factors.

298 The background section has shown that the vitamin D system plays a crucial role not only in the  
299 healthiness and strength of the skeletal system (rickets/osteoporosis) but also in the outcome of many  
300 infectious and/or autoimmune diseases [161,162]. Preexisting D3 deficiency is highly correlated in all of  
301 these previously mentioned cases.

302 Many argue that, because a *correlation does not imply causality*, a low D3 level may be merely a  
303 biomarker for an existing disease rather than its cause. However, the range of diseases for which existing  
304 empirical evidence shows an inverse relationship between disease severity and long-term D3 levels  
305 suggests that this assumption should be reversed [163].

306 This study investigated the correlation between vitamin D levels as a marker of a patient’s immune  
307 defense and resilience against COVID-19 and presumably other respiratory infections. It compared and  
308 merged data from two completely different datasets. The strength of the chosen approach lies in its  
309 diversity, as data from opposite and independent parts of the data universe yielded similar results. This  
310 result strengthens the hypothesis that a fatal outcome from COVID-19 infection, apart from other risk  
311 factors, is strongly dependent on the vitamin D status of the patient. The mathematical regressions  
312 suggested that the lower threshold for healthy vitamin D levels should lie at approximately 125 nmol/L or  
313 50 ng/ml 25(OH)D3, which would save most lives, reducing the impact even for patients with various  
314 comorbidities.

315 This is – to our knowledge – the first study that aimed to determine an optimum D3 level to minimize  
316 COVID-19 mortality, as other studies typically limit themselves to identifying odds ratios for 2–3 patient  
317 cohorts split at 30 ng/ml or lower.

318 Another study confirmed that the number of infections clearly correlated with the respective D3 levels,  
319 with a cohort size close to 200,000 [115]. A minimum number of infections was observed at 55 ng/ml.

320 Does that mean that vitamin D protects people from getting infected? Physically, an infection occurs  
321 when viruses or bacteria intercept and enter body cells. Medically, infections are defined as having  
322 symptomatic aftereffects. However, a positive PCR test presumes the individual to be infectious even  
323 when there are no clinical symptoms and can be followed by quarantine. There is ample evidence that  
324 many people with a confirmed SARS-CoV-2 infection have not shown any symptoms [166].

325 A “physical infection”, which a PCR test can later detect, can only be avoided by physical measures such  
326 as disinfection, masks and/or virucidal sprays, which will prevent the virus from either entering the body  
327 or otherwise attaching to body cells to infect them. However, if we define “infection” as having to be  
328 clinically symptomatic, then we have to refer to it as “silent” to describe what happens when the immune  
329 system fights down the virus without showing any symptoms apart from producing specific T-cells or  
330 antibodies. Nevertheless, the PCR test will show such people as being “infected/infectious”, which  
331 justifies that they are counted as “cases” even without confirmation by clinical symptoms, e.g., in  
332 Worldometer Statistics [164].

333 Just as the D3 status correlates not only with the severity of symptoms but also with the length of the  
334 ongoing disease [165], it is fair to assume that the same reasoning also applies for silent infections. Thus,  
335 the duration in which a silent infection itself is active, i.e., infectious and will therefore produce a positive  
336 PCR result, may be reduced. We suggest that this may have a clear effect on the reproduction rate.

337 Thus, it seems clear that a good immune defense, be it naturally present because of good preconditioning  
338 or from an acquired cross immunity from earlier human coronavirus infections, cannot “protect” against  
339 the infection like physical measures but can protect against clinical symptoms. Finding only half as many

340 “infected” patients (confirmed by PCR tests) with a vitamin D level >30 ng/ml [115] does not prove  
341 protection against physical infection but rather against its consequences – a reduction in the number of  
342 days of people being infectious must statistically lead to the demonstrated result of only half as many  
343 positive PCR tests recorded in the group >30 ng/ml vs. the group <30 ng/ml. This “protection” was most  
344 effective at ~55 ng/ml, which agrees well with our results.

345 This result was also confirmed in a 2012 study, which showed that one of the fatal and most feared  
346 symptoms of COVID-19, the out-of-control inflammation leading to respiratory failure, is directly  
347 correlated with vitamin D levels. Cells incubated in 30 ng/ml vitamin D and above displayed a  
348 significantly reduced response to lipopolysaccharides (LPS), with the highest inflammatory inhibition  
349 observed at 50 ng/ml [167].

350 This result matches scientific data on the natural vitamin D3 levels seen among traditional hunter/gatherer  
351 lifestyles in a highly infectious environment, which were 110–125 nmol/L (45–50 ng/ml) [168].

352 There is a major discrepancy with the 30 ng/ml D3 value considered by the WHO as the threshold for  
353 sufficiency and the 20 ng/ml limit assumed by D-A-CH countries.

354 Three directors of Iranian Hospital Dubai also state from their practical experience that among 21  
355 COVID-19 patients with D3 levels above 40 ng/ml (supplemented with D3 for up to nine years for  
356 ophthalmologic reasons), none remained hospitalized for over 4 days, with no cytokine storm,  
357 hypercoagulation or complement deregulation occurring [169].

358 Thus, we hypothesize that long-standing supplementation with D3 preceding acute infection will reduce  
359 the risk of a fatal outcome to practically nil and generally mitigate the course of the disease.

360 However, we have to point out that there are exceptions to that as a rule of nature: as in any multifactorial  
361 setting, we find a bell curve distribution in the activation of a huge number of genes that are under the  
362 control of vitamin D. There may be genetic reasons for this finding, but there are also additional  
363 influencing parameters necessary for the production of enzymes and cells of the immune system, such as

364 magnesium, zinc, and selenium. Carlberg et al. found this bell curve distribution when verifying the  
365 activation of 500 - 700 genes contributing to the production of immune system-relevant cells and proteins  
366 after D3 supplementation [170]. Participants at the low end showed only 33% activation, while others at  
367 the high end showed well over 80% “of the 36 vitamin D3-triggered parameters”. Carlberg used the term  
368 (vitamin D3) low and high responders to describe what he saw.

369 This finding may explain why a “D3 deficient” high responder may show only mild or even no  
370 symptoms, while a low responder may experience a fatal outcome. It also explains why, on the one hand,  
371 many so-called “autoimmune” inflammation-based diseases do highly correlate with the D3 level based  
372 on, e.g., higher latitudes or higher age, when D3 production decreases, but why only parts of the  
373 population are affected: it is presumably the low responders who are mostly affected. Thus, for 68%-95%  
374 (1 or 2 sigma SDs), the suggested D3 level may be sufficient to fight everyday infections, and for the  
375 2.5%-16% of high responders, it is more than sufficient and is completely harmless. However, for the  
376 2.5%-16% of low responders, this level should be raised further to 75 ng/ml or even >100 ng/ml to  
377 achieve the same immune status as mid-level responders. A vitamin D3 test before the start of any  
378 supplementation in combination with the patient’s personal history of diseases might provide a good  
379 indication as to which group the patient belongs to and thus whether 50 ng/ml would be sufficient, or, if  
380 “normal” levels of D3 are found (between 20 and 30 ng/ml) along with any of the known D3-dependent  
381 autoimmune diseases, a higher level should be targeted as a precaution, especially as levels up to 120  
382 ng/ml are declared to have no adverse effects by the WHO.

383 As future mutations of the SARS-CoV-2 virus may not be susceptible to the acquired immunity from  
384 vaccination or from a preceding infection, the entire population should raise their serum vitamin D level  
385 to a safe level as soon as possible. As long as enough vitamin K2 is provided, the suggested D3 levels are  
386 entirely safe to achieve by supplementation. However, the body is neither monothematic nor monocausal  
387 but a complicated system of dependencies and interactions of many different metabolites, hormones,  
388 vitamins, micronutrients, enzymes, etc. Selenium, magnesium, zinc and vitamins A and E should also be

389 controlled for and supplemented where necessary to optimize the conditions for a well-functioning  
390 immune system.

391 A simple observational study could prove or disprove all of the above. If one were to test PCR-positive  
392 contacts of an infected person for D3 levels immediately, i.e., before the onset of any symptoms, and then  
393 follow them for 4 weeks and relate the course of their symptomatology to the D3 level, the same result as  
394 shown above must be obtained: a regression should cross the zero baseline at 45-55 ng/ml. Therefore, we  
395 strongly recommend the performance of such a study, which could be carried out with very little human  
396 and economic effort.

397 Even diseases caused by low vitamin D3 levels cannot be entirely resolved by ensuring a certain (fixed)  
398 D3 level for the population, as immune system activation varies. However, to fulfill Scribonius Largus'  
399 still valid quote "primum non nocere, secundum cavere, tertium sanare" from 50 A.D., it should be the  
400 duty of the medical profession to closely look into a medication or supplementation that might help  
401 (tertium sanare) as long as it has no known risks (primum non nocere) within the limits of dosages that  
402 are needed for the blood level mentioned (secundum cavere).

403 Unfortunately, this does not imply that in the case of an acute SARS-CoV-2 infection, newly started  
404 supplementation with 25(OH)D3 will be a helpful remedy when calcidiol deficiency is evident, especially  
405 if this deficiency has been long lasting and caused or exacerbated typical comorbidities that can now  
406 aggravate the outcome of the infection. This was not a question we aimed to answer in this study.

407 **Limitations:** This study does not question the vital role that vaccination will play in coping with the  
408 COVID-19 pandemic. Nor does it claim that in the case of an acute SARS-CoV-2 infection, a high boost  
409 of 25(OH)D3 is or could be a helpful remedy when vitamin D deficiency is evident, as this is another  
410 question. Furthermore, empirical data on COVID-19 mortality for vitamin D3 blood levels above 35  
411 ng/ml are sparse.

412 **Conclusions**

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413 Although there are a vast number of publications supporting a correlation between the severity and death  
414 rate of SARS-CoV-2 infections and the blood level of vitamin D3, there is still an open debate about  
415 whether this relation is causal. This is because in most studies, the vitamin D level was determined  
416 several days after the onset of infection; therefore, a low vitamin D level may be the result and not the  
417 trigger of the course of infection.

418 In this publication, we used a meta-analysis of two independent sets of data. One analysis is based on the  
419 long-term average vitamin D3 levels documented for 19 countries. The second analysis is based on 1601  
420 hospitalized patients, 784 who had their vitamin D levels measured within a day after admission, and 817  
421 whose vitamin D levels were known pre-infection. Both datasets show a strong correlation between the  
422 death rate caused by SARS-CoV-2 and the vitamin D blood level. At a threshold level of 30 ng/ml,  
423 mortality decreases considerably. In addition, our analysis shows that the correlation for the combined  
424 datasets intersects the axis at approximately 50 ng/ml, which suggests that this vitamin D3 blood level  
425 may prevent any excess mortality. These findings are supported not only by a large infection study,  
426 showing the same optimum, but also by the natural levels observed in traditional people living in the  
427 region where humanity originated from that were able to fight down most (not all) infections in most (not  
428 all) individuals.

429 Vaccination is and will be an important keystone in our fight against SARS-CoV-2. However, current  
430 data clearly show that vaccination alone cannot prevent all SARS-CoV-2 infections and dissemination of  
431 the virus. This scenario possibly will become much worse in the case of new virus mutations that are not  
432 very susceptible to the current vaccines or even not sensitive to any vaccine.

433 Therefore, based on our data, the authors strongly recommend combining vaccination with routine  
434 strengthening of the immune system of the whole population by vitamin D3 supplementation to  
435 consistently guarantee blood levels above 50 ng/ml (125 nmol/l). From a medical point of view, this will  
436 not only save many lives but also increase the success of vaccination. From a social and political point of  
437 view, it will lower the need for further contact restrictions and lockdowns. From an economical point of

438 view, it will save billions of dollars worldwide, as vitamin D3 is inexpensive and – together with vaccines  
439 – provides a good opportunity to get the spread of SARS-CoV-2 under control.

440 Although there exists very broad data-based support for the protective effect of vitamin D against severe  
441 SARS-CoV-2 infections, we strongly recommend initiating well-designed observational studies as  
442 mentioned and/or double-blind randomized controlled trials (RCTs) to convince the medical community  
443 and the health authorities that vitamin D testing and supplementation are needed to avoid fatal  
444 breakthrough infections and to be prepared for new dangerous mutations.

#### 445 **Declarations**

#### 446 **Ethics approval and consent to participate**

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447 Not applicable.

#### 448 **Consent for publication**

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449 Not applicable.

#### 450 **Availability of data and materials**

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451 The datasets generated and/or analyzed during the current study have been made available online [171].

#### 452 **Competing interests**

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453 The authors declare that they have no competing interests.

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#### 456 **Authors' Information**

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##### 457 **Affiliations**

458 None.



## 459 **Contributions**

460 Conceptualization: L.B.

461 Data curation: L.B. and J.V.M.

462 Writing – Background: B.G.

463 Writing – Methods and Results: J.V.M.

464 Writing – Discussion: L.B.

465 Writing – Abstract/Conclusion/review & editing: L.B., B.G., and J.V.M.

466 **Corresponding author:** L.B. (Email: borsche@gmx.de)

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## 469 **References**

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470 1. Xue KS. Coexisting with the Coronavirus. New Yorker [Internet]. 2021; Available from:

471 <https://www.newyorker.com/science/annals-of-medicine/coexisting-with-the-coronavirus>

472 2. Can we predict the limits of SARS-CoV-2 variants and their phenotypic consequences? [Internet]. Sci.

473 Advis. Gr. Emergencies [SAGE]. 2021 [cited 2021 Aug 27]. Available from:

474 [https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment\\_data/file/](https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1007566/S1335_Long_term_evolution_of_SARS-CoV-2.pdf)

475 [1007566/S1335\\_Long\\_term\\_evolution\\_of\\_SARS-CoV-2.pdf](https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1007566/S1335_Long_term_evolution_of_SARS-CoV-2.pdf)

476 3. Denison MR, Graham RL, Donaldson EF, Eckerle LD, Baric RS. Coronaviruses. RNA Biol [Internet].

477 Informa UK Limited; 2011;8:270–9. Available from: <https://doi.org/10.4161/rna.8.2.15013>

478 4. Dawood AA. Mutated COVID-19 may foretell a great risk for mankind in the future. New Microbes

479 New Infect [Internet]. Elsevier BV; 2020;35:100673. Available from:

480 <https://doi.org/10.1016/j.nmni.2020.100673>

481 5. Harvey WT, Carabelli AM, Jackson B, Gupta RK, Thomson EC, Harrison EM, et al. SARS-CoV-2

482 variants, spike mutations and immune escape. Nat Rev Microbiol [Internet]. Springer Science and

483 Business Media LLC; 2021;19:409–24. Available from: <https://doi.org/10.1038/s41579-021-00573-0>

484 6. Williams TC, Burgers WA. SARS-CoV-2 evolution and vaccines: cause for concern? Lancet Respir

485 Med [Internet]. Elsevier BV; 2021;9:333–5. Available from: [https://doi.org/10.1016/s2213-](https://doi.org/10.1016/s2213-2600(20)2821(29)00075-8)

486 [2600\(20\)2821\(29\)00075-8](https://doi.org/10.1016/s2213-2600(20)2821(29)00075-8)

- 487 7. Karim SSA. Vaccines and SARS-CoV-2 variants: the urgent need for a correlate of protection. *Lancet*  
488 [Internet]. Elsevier BV; 2021;397:1263–4. Available from: <https://doi.org/10.1016/s0140->  
489 [6736%2821%2900468-2](https://doi.org/10.1016/s0140-6736%2821%2900468-2)
- 490 8. Starr TN, Greaney AJ, Addetia A, Hannon WW, Choudhary MC, Dingens AS, et al. Prospective  
491 mapping of viral mutations that escape antibodies used to treat COVID-19. *Science (80- )* [Internet].  
492 American Association for the Advancement of Science (AAAS); 2021;371:850–4. Available from:  
493 <https://doi.org/10.1126/science.abf9302>
- 494 9. Brown CM, Vostok J, Johnson H, Burns M, Gharpure R, Sami S, et al. Outbreak of SARS-CoV-2  
495 Infections, Including COVID-19 Vaccine Breakthrough Infections, Associated with Large Public  
496 Gatherings -- Barnstable County, Massachusetts, July 2021. *MMWR Morb Mortal Wkly Rep* [Internet].  
497 Centers for Disease Control MMWR Office; 2021;70:1059–62. Available from:  
498 <https://doi.org/10.15585/mmwr.mm7031e2>
- 499 10. Rella SA, Kulikova YA, Dermitzakis ET, Kondrashov FA. Rates of SARS-CoV-2 transmission and  
500 vaccination impact the fate of vaccine-resistant strains. *Sci Rep* [Internet]. Springer Science and Business  
501 Media LLC; 2021;11. Available from: <https://doi.org/10.1038/s41598-021-95025-3>
- 502 11. Rella SA, Kulikova YA, Dermitzakis ET, Kondrashov FA. SARS-CoV-2 transmission, vaccination  
503 rate and the fate of resistant strains. Cold Spring Harbor Laboratory; 2021; Available from:  
504 <https://doi.org/10.1101/2021.02.08.21251383>
- 505 12. Iddir M, Brito A, Dingo G, Campo SSF Del, Samouda H, Frano MR La, et al. Strengthening the  
506 Immune System and Reducing Inflammation and Oxidative Stress through Diet and Nutrition:  
507 Considerations during the COVID-19 Crisis. *Nutrients* [Internet]. MDPI AG; 2020;12:1562. Available  
508 from: <https://doi.org/10.3390/nu12061562>
- 509 13. Holick MF, Chen TC. Vitamin D deficiency: a worldwide problem with health consequences. *Am J*  
510 *Clin Nutr* [Internet]. Oxford University Press (OUP); 2008;87:1080S--1086S. Available from:  
511 <https://doi.org/10.1093/ajcn/87.4.1080s>
- 512 14. Manson JE, Bassuk SS. Commentary. Eliminating vitamin D deficiency during the COVID-19  
513 pandemic: A call to action. *Metabolism* [Internet]. Elsevier BV; 2020;112:154322. Available from:  
514 <https://doi.org/10.1016/j.metabol.2020.154322>
- 515 15. Palacios C, Gonzalez L. Is vitamin D deficiency a major global public health problem? *J Steroid*  
516 *Biochem Mol Biol* [Internet]. Elsevier BV; 2014;144:138–45. Available from:  
517 <https://doi.org/10.1016/j.jsbmb.2013.11.003>

- 518 16. Forrest KYZ, Stuhldreher WL. Prevalence and correlates of vitamin D deficiency in US adults. *Nutr*  
519 *Res* [Internet]. Elsevier BV; 2011;31:48–54. Available from: <https://doi.org/10.1016/j.nutres.2010.12.001>
- 520 17. Tangpricha V, Pearce EN, Chen TC, Holick MF. Vitamin D insufficiency among free-living healthy  
521 young adults. *Am J Med* [Internet]. Elsevier BV; 2002;112:659–62. Available from:  
522 <https://doi.org/10.1016/s0002-9343%2802%2901091-4>
- 523 18. Honardoost M, Ghavideldarestani M, Khamseh ME. Role of vitamin D in pathogenesis and severity  
524 of COVID-19 infection. *Arch Physiol Biochem* [Internet]. Informa UK Limited; 2020;1–7. Available  
525 from: <https://doi.org/10.1080/13813455.2020.1792505>
- 526 19. Lips P, Cashman KD, Lamberg-Allardt C, Bischoff-Ferrari HA, Obermayer-Pietsch B, Bianchi ML,  
527 et al. Current vitamin D status in European and Middle East countries and strategies to prevent vitamin D  
528 deficiency: a position statement of the European Calcified Tissue Society. *Eur J Endocrinol* [Internet].  
529 *Bioscientifica*; 2019;180:P23--P54. Available from: <https://doi.org/10.1530/eje-18-0736>
- 530 20. Biesalski HK. Vitamin D deficiency and co-morbidities in COVID-19 patients -- A fatal relationship?  
531 *Nfs J*. Elsevier; 2020;20:10.
- 532 21. Gloth FM. Vitamin D Deficiency in Homebound Elderly Persons. *JAMA J Am Med Assoc* [Internet].  
533 American Medical Association (AMA); 1995;274:1683. Available from:  
534 <https://doi.org/10.1001/jama.1995.03530210037027>
- 535 22. Giménez VMM, Inserra F, Ferder L, García J, Manucha W. Vitamin D deficiency in African  
536 Americans is associated with a high risk of severe disease and mortality by SARS-CoV-2. *J Hum*  
537 *Hypertens* [Internet]. Springer Science and Business Media LLC; 2020;35:378–80. Available from:  
538 <https://doi.org/10.1038/s41371-020-00398-z>
- 539 23. Berry DJ, Hesketh K, Power C, Hyppönen E. Vitamin D status has a linear association with seasonal  
540 infections and lung function in British adults. *Br J Nutr*. Cambridge University Press; 2011;106:1433–40.
- 541 24. Kohlmeier M. Avoidance of vitamin D deficiency to slow the COVID-19 pandemic. *BMJ Nutr Prev*  
542 *Heal* [Internet]. BMJ; 2020;3:67–73. Available from: <https://doi.org/10.1136/bmjnph-2020-000096>
- 543 25. Rhodes JM, Subramanian S, Laird E, Kenny RA. Editorial: Low population mortality from COVID-  
544 19 in countries south of latitude 35 degrees North supports vitamin D as a factor determining severity.  
545 *Aliment Pharmacol & Ther*. Wiley-Blackwell; 2020;51:1434.
- 546 26. Abhimanyu A, Coussens AK. The role of UV radiation and vitamin D in the seasonality and  
547 outcomes of infectious disease. *Photochem Photobiol Sci* [Internet]. Springer Science and Business  
548 Media LLC; 2017;16:314–38. Available from: <https://doi.org/10.1039/c6pp00355a>

- 549 27. Zhang M, Shen F, Petryk A, Tang J, Chen X, Sergi C. English Disease: Historical Notes on Rickets,  
550 the Bone Lung Link and Child Neglect Issues. *Nutrients* [Internet]. MDPI AG; 2016;8:722. Available  
551 from: <https://doi.org/10.3390/nu8110722>
- 552 28. Rajakumar K. Vitamin D, cod-liver oil, sunlight, and rickets: a historical perspective. *Pediatrics. Am*  
553 *Acad Pediatrics*; 2003;112:e132--e135.
- 554 29. Ross AC, Manson JE, Abrams SA, Aloia JF, Brannon PM, Clinton SK, et al. The 2011 Report on  
555 Dietary Reference Intakes for Calcium and Vitamin D from the Institute of Medicine: What Clinicians  
556 Need to Know. *J Clin Endocrinol Metab* [Internet]. The Endocrine Society; 2011;96:53–8. Available  
557 from: <https://doi.org/10.1210/jc.2010-2704>
- 558 30. DeLuca HF. History of the discovery of vitamin D and its active metabolites. *Bonekey Rep. Nature*  
559 *Publishing Group*; 2014;3.
- 560 31. Prietl B, Treiber G, Pieber TR, Amrein K. Vitamin D and immune function. *Nutrients.*  
561 *Multidisciplinary Digital Publishing Institute*; 2013;5:2502–21.
- 562 32. Kongsbak M, Levring TB, Geisler C, von Essen MR. The Vitamin D Receptor and T Cell Function.  
563 *Front Immunol* [Internet]. Frontiers Media SA; 2013;4. Available from:  
564 <https://doi.org/10.3389/fimmu.2013.00148>
- 565 33. Hewison M. An update on vitamin D and human immunity. *Clin Endocrinol (Oxf)* [Internet]. Wiley;  
566 2012;76:315–25. Available from: <https://doi.org/10.1111/j.1365-2265.2011.04261.x>
- 567 34. Holick MF. Vitamin D deficiency. *N Engl J Med. Mass Medical Soc*; 2007;357:266–81.
- 568 35. Battault S, Whiting SJ, Peltier SL, Sadrin S, Gerber G, Maixent JM. Vitamin D metabolism, functions  
569 and needs: from science to health claims. *Eur J Nutr. Springer*; 2013;52:429–41.
- 570 36. Christakos S, Hewison M, Gardner DG, Wagner CL, Sergeev IN, Rutten E, et al. Vitamin D: beyond  
571 bone. *Ann N Y Acad Sci* [Internet]. Wiley; 2013;1287:45–58. Available from:  
572 <https://doi.org/10.1111/nyas.12129>
- 573 37. Charoenngam N, Holick MF. Immunologic Effects of Vitamin D on Human Health and Disease.  
574 *Nutrients* [Internet]. MDPI AG; 2020;12:2097. Available from: <https://doi.org/10.3390/nu12072097>
- 575 38. Carlberg C. Vitamin D Signaling in the Context of Innate Immunity: Focus on Human Monocytes.  
576 *Front Immunol* [Internet]. Frontiers Media SA; 2019;10. Available from:  
577 <https://doi.org/10.3389/fimmu.2019.02211>
- 578 39. Grant WB, Anouti F Al, Moukayed M. Targeted 25-hydroxyvitamin D concentration measurements

- 579 and vitamin D3 supplementation can have important patient and public health benefits. *Eur J Clin Nutr*  
580 [Internet]. Springer Science and Business Media LLC; 2020;74:366–76. Available from:  
581 <https://doi.org/10.1038/s41430-020-0564-0>
- 582 40. Feldman D, Krishnan A V, Swami S, Giovannucci E, Feldman BJ. The role of vitamin D in reducing  
583 cancer risk and progression. *Nat Rev Cancer* [Internet]. Springer Science and Business Media LLC;  
584 2014;14:342–57. Available from: <https://doi.org/10.1038/nrc3691>
- 585 41. Jeon S-M, Shin E-A. Exploring vitamin D metabolism and function in cancer. *Exp Mol Med*  
586 [Internet]. Springer Science and Business Media LLC; 2018;50:1–14. Available from:  
587 <https://doi.org/10.1038/s12276-018-0038-9>
- 588 42. Berridge MJ. Vitamin D deficiency and diabetes. *Biochem J* [Internet]. Portland Press Ltd.;  
589 2017;474:1321–32. Available from: <https://doi.org/10.1042/bcj20170042>
- 590 43. Martineau AR, Jolliffe DA, Greenberg L, Aloia JF, Bergman P, Dubnov-Raz G, et al. Vitamin D  
591 supplementation to prevent acute respiratory infections: individual participant data meta-analysis. *Health*  
592 *Technol Assess (Rockv)* [Internet]. National Institute for Health Research; 2019;23:1–44. Available from:  
593 <https://doi.org/10.3310/hta23020>
- 594 44. Agrawal D, Yin K. Vitamin D and inflammatory diseases. *J Inflamm Res* [Internet]. Informa UK  
595 Limited; 2014;69. Available from: <https://doi.org/10.2147/jir.s63898>
- 596 45. Hayes CE, Ntambi JM. Multiple Sclerosis: Lipids, Lymphocytes, and Vitamin D. *Immunometabolism*  
597 [Internet]. Hapres; 2020; Available from: <https://doi.org/10.20900/immunometab20200019>
- 598 46. Hewison M, Gacad MA, Lemire J, Adams JS. Vitamin D as a cytokine and hematopoietic factor. *Rev*  
599 *Endocr Metab Disord*. Springer; 2001;2:217–27.
- 600 47. Adams JS, Hewison M. Update in vitamin D. *J Clin Endocrinol & Metab*. Oxford University Press;  
601 2010;95:471–8.
- 602 48. Sassi F, Tamone C, D’Amelio P. Vitamin D: Nutrient, Hormone, and Immunomodulator. *Nutrients*  
603 [Internet]. MDPI AG; 2018;10:1656. Available from: <https://doi.org/10.3390/nu10111656>
- 604 49. Baeke F, Takiishi T, Korf H, Gysemans C, Mathieu C. Vitamin D: modulator of the immune system.  
605 *Curr Opin Pharmacol* [Internet]. Elsevier BV; 2010;10:482–96. Available from:  
606 <https://doi.org/10.1016/j.coph.2010.04.001>

- 607 50. Chun RF, Liu PT, Modlin RL, Adams JS, Hewison M. Impact of vitamin D on immune function:  
608 lessons learned from genome-wide analysis. *Front Physiol* [Internet]. Frontiers Media SA; 2014;5.  
609 Available from: <https://doi.org/10.3389/fphys.2014.00151>
- 610 51. Hansdottir S, Monick MM, Hinde SL, Lovan N, Look DC, Hunninghake GW. Respiratory Epithelial  
611 Cells Convert Inactive Vitamin D to Its Active Form: Potential Effects on Host Defense. *J Immunol*  
612 [Internet]. The American Association of Immunologists; 2008;181:7090–9. Available from:  
613 <https://doi.org/10.4049/jimmunol.181.10.7090>
- 614 52. Adams JS, Hewison M. Unexpected actions of vitamin D: new perspectives on the regulation of  
615 innate and adaptive immunity. *Nat Clin Pract Endocrinol Metab* [Internet]. Springer Science and Business  
616 Media LLC; 2008;4:80–90. Available from: <https://doi.org/10.1038/ncpendmet0716>
- 617 53. Chambers ES, Hawrylowicz CM. The Impact of Vitamin D on Regulatory T Cells. *Curr Allergy*  
618 *Asthma Rep* [Internet]. Springer Science and Business Media LLC; 2010;11:29–36. Available from:  
619 <https://doi.org/10.1007/s11882-010-0161-8>
- 620 54. Bishop EL, Ismailova A, Dimeloe S, Hewison M, White JH. Vitamin D and Immune Regulation:  
621 Antibacterial, Antiviral, Anti-Inflammatory. *JBMR Plus* [Internet]. Wiley; 2020;5. Available from:  
622 <https://doi.org/10.1002/jbm4.10405>
- 623 55. Gruber Bzura BM. Vitamin D and Influenza -- Prevention or Therapy? *Int J Mol Sci* [Internet]. MDPI  
624 AG; 2018;19:2419. Available from: <https://doi.org/10.3390/ijms19082419>
- 625 56. Lowe KE, Maiyar AC, Norman AW. Vitamin D-mediated gene expression. 1992;2:65–109. Available  
626 from: <https://pubmed.ncbi.nlm.nih.gov/1543898/>
- 627 57. de Haan K, Groeneveld ABJ, de Geus HRH, Egal M, Struijs A. Vitamin D deficiency as a risk factor  
628 for infection, sepsis and mortality in the critically ill: systematic review and meta-analysis. *Crit Care*  
629 [Internet]. Springer Science and Business Media LLC; 2014;18. Available from:  
630 <https://doi.org/10.1186/s13054-014-0660-4>
- 631 58. Braun A, Chang D, Mahadevappa K, Gibbons FK, Liu Y, Giovannucci E, et al. Association of low  
632 serum 25-hydroxyvitamin D levels and mortality in the critically ill. *Crit Care Med* [Internet]. Ovid  
633 Technologies (Wolters Kluwer Health); 2011;39:671–7. Available from:  
634 <https://doi.org/10.1097/ccm.0b013e318206ccdf>
- 635 59. Autier P, Boniol M, Pizot C, Mullie P. Vitamin D status and ill health: a systematic review. *Lancet*  
636 *Diabetes Endocrinol* [Internet]. Elsevier BV; 2014;2:76–89. Available from:  
637 <https://doi.org/10.1016/s2213-8587%2813%2970165-7>



- 638 60. Zhou Y-F, Luo B-A, Qin L-L. The association between vitamin D deficiency and community-  
639 acquired pneumonia. *Medicine (Baltimore)* [Internet]. Ovid Technologies (Wolters Kluwer Health);  
640 2019;98:e17252. Available from: <https://doi.org/10.1097/md.00000000000017252>
- 641 61. Goodall EC, Granados AC, Luinstra K, Pullenayegum E, Coleman BL, Loeb M, et al. Vitamin D3  
642 and gargling for the prevention of upper respiratory tract infections: a randomized controlled trial. *BMC*  
643 *Infect Dis* [Internet]. Springer Science and Business Media LLC; 2014;14. Available from:  
644 <https://doi.org/10.1186/1471-2334-14-273>
- 645 62. Vanherwegen A-S, Gysemans C, Mathieu C. Regulation of Immune Function by Vitamin D and Its  
646 Use in Diseases of Immunity. *Endocrinol Metab Clin North Am* [Internet]. Elsevier BV; 2017;46:1061–  
647 94. Available from: <https://doi.org/10.1016/j.ecl.2017.07.010>
- 648 63. Greiller C, Martineau A. Modulation of the Immune Response to Respiratory Viruses by Vitamin D.  
649 *Nutrients* [Internet]. MDPI AG; 2015;7:4240–70. Available from: <https://doi.org/10.3390/nu7064240>
- 650 64. Zdrengeha MT, Makrinioti H, Bagacean C, Bush A, Johnston SL, Stanciu LA. Vitamin D modulation  
651 of innate immune responses to respiratory viral infections. *Rev Med Virol* [Internet]. Wiley;  
652 2016;27:e1909. Available from: <https://doi.org/10.1002/rmv.1909>
- 653 65. Sabetta JR, DePetrillo P, Cipriani RJ, Smardin J, Burns LA, Landry ML. Serum 25-hydroxyvitamin d  
654 and the incidence of acute viral respiratory tract infections in healthy adults. *PLoS One*. Public Library of  
655 Science San Francisco, USA; 2010;5:e11088.
- 656 66. Ingham TR, Jones B, Camargo CA, Kirman J, Dowell AC, Crane J, et al. Association of vitamin D  
657 deficiency with severity of acute respiratory infection: A case-control study in New Zealand children. *Eur*  
658 *Respir J*. Eur Respiratory Soc; 2014;44.
- 659 67. F Gunville C, M Mourani P, A Ginde A. The role of vitamin D in prevention and treatment of  
660 infection. *Inflamm Allergy-Drug Targets (Formerly Curr Drug Targets-Inflammation Allergy)*. Bentham  
661 Science Publishers; 2013;12:239–45.
- 662 68. Khoo AL, Chai L, Koenen H, Joosten I, Netea M, van der Ven A. Translating the role of vitamin D3 in  
663 infectious diseases. *Crit Rev Microbiol* [Internet]. Informa UK Limited; 2012;38:122–35. Available from:  
664 <https://doi.org/10.3109/1040841x.2011.622716>
- 665 69. Martineau AR, Jolliffe DA, Hooper RL, Greenberg L, Aloia JF, Bergman P, et al. Vitamin D  
666 supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of  
667 individual participant data. *BMJ* [Internet]. BMJ; 2017;i6583. Available from:  
668 <https://doi.org/10.1136/bmj.i6583>

- 669 70. Dancer RCA, Parekh D, Lax S, D'Souza V, Zheng S, Bassford CR, et al. Vitamin D deficiency  
670 contributes directly to the acute respiratory distress syndrome (ARDS). *Thorax* [Internet]. *BMJ*;  
671 2015;70:617–24. Available from: <https://doi.org/10.1136/thoraxjnl-2014-206680>
- 672 71. Thickett DR, Moromizato T, Litonjua AA, Amrein K, Quraishi SA, Lee-Sarwar KA, et al.  
673 Association between prehospital vitamin D status and incident acute respiratory failure in critically ill  
674 patients: a retrospective cohort study. *BMJ Open Respir Res* [Internet]. *BMJ*; 2015;2:e000074. Available  
675 from: <https://doi.org/10.1136/bmjresp-2014-000074>
- 676 72. Cantorna MT, Mahon BD. D-hormone and the immune system. *J Rheumatol Suppl. The Journal of*  
677 *Rheumatology*; 2005;76:11–20.
- 678 73. Antico A, Tampoia M, Tozzoli R, Bizzaro N. Can supplementation with vitamin D reduce the risk or  
679 modify the course of autoimmune diseases? A systematic review of the literature. *Autoimmun Rev*  
680 [Internet]. Elsevier BV; 2012;12:127–36. Available from: <https://doi.org/10.1016/j.autrev.2012.07.007>
- 681 74. Michigami T. Rickets/Osteomalacia. Consensus on Vitamin D Deficiency and Insufficiency in  
682 Children. *Clin Calcium*. 2018;28:1307–11.
- 683 75. Grant W, Lahore H, McDonnell S, Baggerly C, French C, Aliano J, et al. Evidence that Vitamin D  
684 Supplementation Could Reduce Risk of Influenza and COVID-19 Infections and Deaths. *Nutrients*  
685 [Internet]. MDPI AG; 2020;12:988. Available from: <https://doi.org/10.3390/nu12040988>
- 686 76. Veugelers P, Ekwaru J. A Statistical Error in the Estimation of the Recommended Dietary Allowance  
687 for Vitamin D. *Nutrients* [Internet]. MDPI AG; 2014;6:4472–5. Available from:  
688 <https://doi.org/10.3390/nu6104472>
- 689 77. Papadimitriou DT. The Big Vitamin D Mistake. *J Prev Med Public Heal* [Internet]. Korean Society  
690 for Preventive Medicine; 2017;50:278–81. Available from: <https://doi.org/10.3961/jpmp.16.111>
- 691 78. van Ballegooijen AJ, Pilz S, Tomaschitz A, Gröbler MR, Verheyen N. The Synergistic Interplay  
692 between Vitamins D and K for Bone and Cardiovascular Health: A Narrative Review. *Int J Endocrinol*  
693 [Internet]. Hindawi Limited; 2017;2017:1–12. Available from: <https://doi.org/10.1155/2017/7454376>
- 694 79. Maresz K. Proper calcium use: vitamin K2 as a promoter of bone and cardiovascular health. *Integr*  
695 *Med A Clin J. InnoVision Media*; 2015;14:34.
- 696 80. Mandatori D, Pelusi L, Schiavone V, Pipino C, Pietro N Di, Pandolfi A. The Dual Role of Vitamin  
697 K2 in “Bone-Vascular Crosstalk”: Opposite Effects on Bone Loss and Vascular Calcification. *Nutrients*  
698 [Internet]. MDPI AG; 2021;13:1222. Available from: <https://doi.org/10.3390/nu13041222>



- 699 81. Quesada-Gomez JM, Entrenas-Castillo M, Bouillon R. Vitamin D receptor stimulation to reduce acute  
700 respiratory distress syndrome (ARDS) in patients with coronavirus SARS-CoV-2 infections. *J Steroid*  
701 *Biochem Mol Biol* [Internet]. Elsevier BV; 2020;202:105719. Available from:  
702 <https://doi.org/10.1016/j.jsbmb.2020.105719>
- 703 82. Mercola J, Grant WB, Wagner CL. Evidence Regarding Vitamin D and Risk of COVID-19 and Its  
704 Severity. *Nutrients* [Internet]. MDPI AG; 2020;12:3361. Available from:  
705 <https://doi.org/10.3390/nu12113361>
- 706 83. Giménez VMM, Inserra F, Tajer CD, Mariani J, Ferder L, Reiter RJ, et al. Lungs as target of COVID-  
707 19 infection: Protective common molecular mechanisms of vitamin D and melatonin as a new potential  
708 synergistic treatment. *Life Sci*. Elsevier; 2020;254:117808.
- 709 84. Imai Y, Kuba K, Penninger JM. Angiotensin-converting enzyme 2 in acute respiratory distress  
710 syndrome. *Cell Mol Life Sci* [Internet]. Springer Science and Business Media LLC; 2007;64:2006–12.  
711 Available from: <https://doi.org/10.1007/s00018-007-6228-6>
- 712 85. Li YC, Qiao G, Uskokovic M, Xiang W, Zheng W, Kong J. Vitamin D: a negative endocrine  
713 regulator of the renin-angiotensin system and blood pressure. *J Steroid Biochem Mol Biol* [Internet].  
714 Elsevier BV; 2004;89–90:387–92. Available from: <https://doi.org/10.1016/j.jsbmb.2004.03.004>
- 715 86. Mahdavi AM. A brief review of interplay between vitamin D and angiotensin-converting enzyme 2:  
716 Implications for a potential treatment for COVID -19. *Rev Med Virol* [Internet]. Wiley; 2020;30.  
717 Available from: <https://doi.org/10.1002/rmv.2119>
- 718 87. Aygun H. Vitamin D can prevent COVID-19 infection-induced multiple organ damage. *Naunyn*  
719 *Schmiedebergs Arch Pharmacol*. Springer; 2020;393:1157–60.
- 720 88. Malaguarnera L. Vitamin D3 as Potential Treatment Adjuncts for COVID-19. *Nutrients* [Internet].  
721 MDPI AG; 2020;12:3512. Available from: <https://doi.org/10.3390/nu12113512>
- 722 89. Schleithoff SS, Zittermann A, Tenderich G, Berthold HK, Stehle P, Koerfer R. Vitamin D  
723 supplementation improves cytokine profiles in patients with congestive heart failure: a double-blind,  
724 randomized, placebo-controlled trial. *Am J Clin Nutr* [Internet]. Oxford University Press (OUP);  
725 2006;83:754–9. Available from: <https://doi.org/10.1093/ajcn/83.4.754>
- 726 90. Palmer MT, Lee YK, Maynard CL, Oliver JR, Bikle DD, Jetten AM, et al. Lineage-specific effects of  
727 1, 25-dihydroxyvitamin D3 on the development of effector CD4 T cells. *J Biol Chem*. ASBMB;  
728 2011;286:997–1004.
- 729 91. Lemire JM, Archer DC, Beck L, Spiegelberg HL. Immunosuppressive actions of 1, 25-

- 730 dihydroxyvitamin D3: preferential inhibition of Th1 functions. *J Nutr.* Oxford University Press;  
731 1995;125:1704S--1708S.
- 732 92. Boonstra A, Barrat FJ, Crain C, Heath VL, Savelkoul HFJ, O'Garra A. 1,25-Dihydroxyvitamin  
733 D3 has a direct effect on naive CD4+ T cells to enhance the development of Th2 cells. *J Immunol. Am*  
734 *Assoc Immunol*; 2001;167:4974–80.
- 735 93. Jeffery LE, Burke F, Mura M, Zheng Y, Qureshi OS, Hewison M, et al. 1,25-Dihydroxyvitamin D3  
736 and IL-2 Combine to Inhibit T Cell Production of Inflammatory Cytokines and Promote Development of  
737 Regulatory T Cells Expressing CTLA-4 and FoxP3. *J Immunol [Internet]. The American Association of*  
738 *Immunologists*; 2009;183:5458–67. Available from: <https://doi.org/10.4049/jimmunol.0803217>
- 739 94. Daneshkhan A, Agrawal V, Eshein A, Subramanian H, Roy HK, Backman V. Evidence for possible  
740 association of vitamin D status with cytokine storm and unregulated inflammation in COVID-19 patients.  
741 *Aging Clin Exp Res. Springer*; 2020;32:2141–58.
- 742 95. Herr C, Shaykhiev R, Bals R. The role of cathelicidin and defensins in pulmonary inflammatory  
743 diseases. *Expert Opin Biol Ther [Internet]. Informa Healthcare*; 2007;7:1449–61. Available from:  
744 <https://doi.org/10.1517/14712598.7.9.1449>
- 745 96. Shahmiri M, Enciso M, Adda CG, Smith BJ, Perugini MA, Mechler A. Membrane core-specific  
746 antimicrobial action of cathelicidin LL-37 peptide switches between pore and nanofibre formation. *Sci*  
747 *Rep. Nature Publishing Group*; 2016;6:1–11.
- 748 97. Liu PT, Stenger S, Li H, Wenzel L, Tan BH, Krutzik SR, et al. Toll-like receptor triggering of a  
749 vitamin D-mediated human antimicrobial response. *Science (80- )*. American Association for the  
750 *Advancement of Science*; 2006;311:1770–3.
- 751 98. Gombart AF, Borregaard N, Koeffler HP. Human cathelicidin antimicrobial peptide (CAMP) gene is  
752 a direct target of the vitamin D receptor and is strongly up-regulated in myeloid cells by 1,25-  
753 dihydroxyvitamin D 3. *FASEB J [Internet]. Wiley*; 2005;19:1067–77. Available from:  
754 <https://doi.org/10.1096/fj.04-3284com>
- 755 99. Beard JA, Bearden A, Striker R. Vitamin D and the anti-viral state. *J Clin Virol [Internet]. Elsevier*  
756 *BV*; 2011;50:194–200. Available from: <https://doi.org/10.1016/j.jcv.2010.12.006>
- 757 100. Barlow PG, Findlay EG, Currie SM, Davidson DJ. Antiviral potential of cathelicidins. *Future*  
758 *Microbiol [Internet]. Future Medicine Ltd*; 2014;9:55–73. Available from:  
759 <https://doi.org/10.2217/fmb.13.135>
- 760 101. Zhang J, McCullough PA, Tecson KM. Vitamin D deficiency in association with endothelial

- 761 dysfunction: Implications for patients with COVID-19. *Rev Cardiovasc Med* [Internet]. IMR Press;  
762 2020;21:339. Available from: <https://doi.org/10.31083/j.rcm.2020.03.131>
- 763 102. Kim D-H, Meza CA, Clarke H, Kim J-S, Hickner RC. Vitamin D and Endothelial Function.  
764 *Nutrients* [Internet]. MDPI AG; 2020;12:575. Available from: <https://doi.org/10.3390/nu12020575>
- 765 103. Sengupta T, Majumder R, Majumder S. Role of vitamin D in treating COVID-19-associated  
766 coagulopathy: problems and perspectives. *Mol Cell Biochem*. Springer; 2021;476:2421–7.
- 767 104. Mohammad S, Mishra A, Ashraf MZ. Emerging role of vitamin D and its associated molecules in  
768 pathways related to pathogenesis of thrombosis. *Biomolecules*. Multidisciplinary Digital Publishing  
769 Institute; 2019;9:649.
- 770 105. Levi M, Thachil J, Iba T, Levy JH. Coagulation abnormalities and thrombosis in patients with  
771 COVID-19. *Lancet Haematol*. Elsevier; 2020;7:e438--e440.
- 772 106. Abrishami A, Dalili N, Torbati PM, Asgari R, Arab-Ahmadi M, Behnam B, et al. Possible  
773 association of vitamin D status with lung involvement and outcome in patients with COVID-19: a  
774 retrospective study. *Eur J Nutr*. Springer; 2021;60:2249–57.
- 775 107. Smet D De, Smet K De, Herroelen P, Gryspeerdt S, Martens GA. Serum 25(OH)D Level on Hospital  
776 Admission Associated With COVID-19 Stage and Mortality. *Am J Clin Pathol* [Internet]. Oxford  
777 University Press (OUP); 2020;155:381–8. Available from: <https://doi.org/10.1093/ajcp/aqaa252>
- 778 108. Vanegas-Cedillo PE, Bello-Chavolla OY, Ramírez-Pedraza N, Encinas BR, Carrión CIP, Ávila  
779 MIJ, et al. Serum Vitamin D levels are associated with increased COVID-19 severity and mortality  
780 independent of visceral adiposity. Cold Spring Harbor Laboratory; 2021; Available from:  
781 <https://doi.org/10.1101/2021.03.12.21253490>
- 782 109. Carpagnano GE, Lecce V Di, Quaranta VN, Zito A, Buonamico E, Capozza E, et al. Vitamin D  
783 deficiency as a predictor of poor prognosis in patients with acute respiratory failure due to COVID-19. *J*  
784 *Endocrinol Invest* [Internet]. Springer Science and Business Media LLC; 2020;44:765–71. Available  
785 from: <https://doi.org/10.1007/s40618-020-01370-x>
- 786 110. Pizzini A, Aichner M, Sahanic S, Böhm A, Egger A, Hoermann G, et al. Impact of Vitamin D  
787 Deficiency on COVID-19 -- A Prospective Analysis from the CovILD Registry. *Nutrients* [Internet].  
788 MDPI AG; 2020;12:2775. Available from: <https://doi.org/10.3390/nu12092775>
- 789 111. Lau FH, Majumder R, Torabi R, Saeg F, Hoffman R, Cirillo JD, et al. Vitamin D insufficiency is  
790 prevalent in severe COVID-19. Cold Spring Harbor Laboratory; 2020; Available from:  
791 <https://doi.org/10.1101/2020.04.24.20075838>

- 792 112. Luo X, Liao Q, Shen Y, Li H, Cheng L. Vitamin D Deficiency Is Associated with COVID-19  
793 Incidence and Disease Severity in Chinese People. *J Nutr* [Internet]. Oxford University Press (OUP);  
794 2020;151:98–103. Available from: <https://doi.org/10.1093/jn/nxaa332>
- 795 113. Vassiliou. Vitamin D deficiency correlates with a reduced number of natural killer cells in intensive  
796 care unit (ICU) and non-ICU patients with COVID-19 pneumonia. 2020;
- 797 114. Meltzer DO, Best TJ, Zhang H, Vokes T, Arora V, Solway J. Association of Vitamin D Status and  
798 Other Clinical Characteristics With COVID-19 Test Results. *JAMA Netw Open* [Internet]. American  
799 Medical Association (AMA); 2020;3:e2019722. Available from:  
800 <https://doi.org/10.1001/jamanetworkopen.2020.19722>
- 801 115. Kaufman HW, Niles JK, Kroll MH, Bi C, Holick MF. SARS-CoV-2 positivity rates associated with  
802 circulating 25-hydroxyvitamin D levels. *PLoS One* [Internet]. 2020;15:1–10. Available from:  
803 <http://dx.doi.org/10.1371/journal.pone.0239252>
- 804 116. Merzon E, Tworowski D, Gorohovski A, Vinker S, Cohen AG, Green I, et al. Low plasma 25(OH)  
805 vitamin D level is associated with increased risk of COVID-19 infection: an Israeli population-based  
806 study. *FEBS J* [Internet]. Wiley; 2020;287:3693–702. Available from: <https://doi.org/10.1111/febs.15495>
- 807 117. Maghbooli Z, Sahraian MA, Ebrahimi M, Pazoki M, Kafan S, Tabriz HM, et al. Vitamin D  
808 sufficiency, a serum 25-hydroxyvitamin D at least 30 ng/mL reduced risk for adverse clinical outcomes in  
809 patients with COVID-19 infection. Adrish M, editor. *PLoS One* [Internet]. Public Library of Science  
810 (PLoS); 2020;15:e0239799. Available from: <https://doi.org/10.1371/journal.pone.0239799>
- 811 118. D’Avolio A, Avataneo V, Manca A, Cusato J, Nicolò A De, Lucchini R, et al. 25-Hydroxyvitamin D  
812 Concentrations Are Lower in Patients with Positive PCR for SARS-CoV-2. *Nutrients* [Internet]. MDPI  
813 AG; 2020;12:1359. Available from: <https://doi.org/10.3390/nu12051359>
- 814 119. Radujkovic A, Hippchen T, Tiwari-Heckler S, Dreher S, Boxberger M, Merle U. Vitamin D  
815 Deficiency and Outcome of COVID-19 Patients. *Nutrients* [Internet]. MDPI AG; 2020;12:2757.  
816 Available from: <https://doi.org/10.3390/nu12092757>
- 817 120. Gavioli EM, Miyashita H, Hassaneen O, Siau E. An Evaluation of Serum 25-Hydroxy Vitamin D  
818 Levels in Patients with COVID-19 in New York City. *J Am Coll Nutr* [Internet]. Informa UK Limited;  
819 2021;1–6. Available from: <https://doi.org/10.1080/07315724.2020.1869626>
- 820 121. Szeto B, Zucker JE, LaSota ED, Rubin MR, Walker MD, Yin MT, et al. Vitamin D Status and  
821 COVID-19 Clinical Outcomes in Hospitalized Patients. *Endocr Res* [Internet]. Informa UK Limited;  
822 2020;46:66–73. Available from: <https://doi.org/10.1080/07435800.2020.1867162>

- 823 122. Ohaegbulam KC, Swalih M, Patel P, Smith MA, Perrin R. Vitamin D supplementation in COVID-19  
824 patients: a clinical case series. *Am J Ther*. Wolters Kluwer Health; 2020;e485.
- 825 123. Rastogi A, Bhansali A, Khare N, Suri V, Yaddanapudi N, Sachdeva N, et al. Short term, high-dose  
826 vitamin D supplementation for COVID-19 disease: a randomised, placebo-controlled, study (SHADE  
827 study). *Postgrad Med J [Internet]*. *BMJ*; 2020;postgradmedj--2020--139065. Available from:  
828 <https://doi.org/10.1136/postgradmedj-2020-139065>
- 829 124. Annweiler G, Corvaisier M, Gautier J, Dubée V, Legrand E, Sacco G, et al. Vitamin D  
830 Supplementation Associated to Better Survival in Hospitalized Frail Elderly COVID-19 Patients: The  
831 GERIA-COVID Quasi-Experimental Study. *Nutrients [Internet]*. MDPI AG; 2020;12:3377. Available  
832 from: <https://doi.org/10.3390/nu12113377>
- 833 125. Han JE, Jones JL, Tangpricha V, Brown MA, Hao L, Hebbar G, et al. High dose vitamin D  
834 administration in ventilated intensive care unit patients: A pilot double blind randomized controlled trial.  
835 *J Clin Transl Endocrinol [Internet]*. Elsevier BV; 2016;4:59–65. Available from:  
836 <https://doi.org/10.1016/j.jcte.2016.04.004>
- 837 126. Panagiotou G, Tee SA, Ihsan Y, Athar W, Marchitelli G, Kelly D, et al. Low serum 25-  
838 hydroxyvitamin D (25[OH]D) levels in patients hospitalized with COVID-19 are associated with greater  
839 disease severity. *Clin Endocrinol (Oxf) [Internet]*. Wiley; 2020;93:508–11. Available from:  
840 <https://doi.org/10.1111/cen.14276>
- 841 127. Castillo ME, Costa LME, Barrios JMV, Díaz JFA, Miranda JL, Bouillon R, et al. Effect of  
842 calcifediol treatment and best available therapy versus best available therapy on intensive care unit  
843 admission and mortality among patients hospitalized for COVID-19: A pilot randomized clinical study {\  
844 textquotedblright}. *J Steroid Biochem Mol Biol [Internet]*. Elsevier BV; 2020;203:105751. Available  
845 from: <https://doi.org/10.1016/j.jsbmb.2020.105751>
- 846 128. Annweiler C, Hanotte B, de l’Eprevier CG, Sabatier J-M, Lafaie L, Célarier T. Vitamin D and  
847 survival in COVID-19 patients: A quasi-experimental study. *J Steroid Biochem Mol Biol [Internet]*.  
848 Elsevier BV; 2020;204:105771. Available from: <https://doi.org/10.1016/j.jsbmb.2020.105771>
- 849 129. Zemb P, Bergman P, Camargo CA, Cavalier E, Cormier C, Courbebaisse M, et al. Vitamin D  
850 deficiency and the COVID-19 pandemic. *J Glob Antimicrob Resist [Internet]*. Elsevier BV; 2020;22:133–  
851 4. Available from: <https://doi.org/10.1016/j.jgar.2020.05.006>
- 852 130. Laird E, Rhodes J, Kenny RA, others. Vitamin D and inflammation: potential implications for  
853 severity of Covid-19. *Ir Med J*. 2020;113:81.

- 854 131. McCartney DM, O'Shea PM, Faul JL, Healy MJ, Byrne G, Griffin TP, et al. Vitamin D and SARS-  
855 CoV-2 infection -- evolution of evidence supporting clinical practice and policy development. *Irish J Med*  
856 *Sci* (1971 -) [Internet]. Springer Science and Business Media LLC; 2020;190:1253–65. Available from:  
857 <https://doi.org/10.1007/s11845-020-02427-9>
- 858 132. Benskin LL. A Basic Review of the Preliminary Evidence That COVID-19 Risk and Severity Is  
859 Increased in Vitamin D Deficiency. *Front Public Heal* [Internet]. Frontiers Media SA; 2020;8. Available  
860 from: <https://doi.org/10.3389/fpubh.2020.00513>
- 861 133. Silva MC, Furlanetto TW. Does serum 25-hydroxyvitamin D decrease during acute-phase response?  
862 A systematic review. *Nutr Res* [Internet]. Elsevier BV; 2015;35:91–6. Available from:  
863 <https://doi.org/10.1016/j.nutres.2014.12.008>
- 864 134. Annweiler C, Cao Z, Sabatier J-M. Point of view: Should COVID-19 patients be supplemented with  
865 vitamin D? *Maturitas* [Internet]. Elsevier BV; 2020;140:24–6. Available from:  
866 <https://doi.org/10.1016/j.maturitas.2020.06.003>
- 867 135. Ahmad A, Heumann C, Ali R, Oliver T. Mean Vitamin D levels in 19 European Countries &  
868 COVID-19 Mortality over 10 months. Cold Spring Harbor Laboratory; 2021; Available from:  
869 <https://doi.org/10.1101/2021.03.11.21253361>
- 870 136. Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time.  
871 *Lancet Infect Dis*. Elsevier; 2020;20:533–4.
- 872 137. Porcher S. Response2covid19, a dataset of governments' responses to COVID-19 all around the  
873 world. *Sci Data* [Internet]. Springer Science and Business Media LLC; 2020;7. Available from:  
874 <https://doi.org/10.1038/s41597-020-00757-y>
- 875 138. Ilie PC, Stefanescu S, Smith L. The role of vitamin D in the prevention of coronavirus disease 2019  
876 infection and mortality. *Aging Clin Exp Res* [Internet]. Springer Science and Business Media LLC;  
877 2020;32:1195–8. Available from: <https://doi.org/10.1007/s40520-020-01570-8>
- 878 139. Pal R, Banerjee M, Bhadada SK, Shetty AJ, Singh B, Vyas A. Vitamin D supplementation and  
879 clinical outcomes in COVID-19: a systematic review and meta-analysis. *J Endocrinol Invest* [Internet].  
880 Springer Science and Business Media LLC; 2021; Available from: [https://doi.org/10.1007/s40618-021-](https://doi.org/10.1007/s40618-021-01614-4)  
881 01614-4



- 882 140. Nikniaz L, Akbarzadeh MA, Hosseinfard H, Hosseini M-S. The impact of vitamin D  
883 supplementation on mortality rate and clinical outcomes of COVID-19 patients: A systematic review and  
884 meta-analysis. Cold Spring Harbor Laboratory; 2021; Available from:  
885 <https://doi.org/10.1101/2021.01.04.21249219>
- 886 141. Hariyanto TI, Intan D, Hananto JE, Harapan H, Kurniawan A. Vitamin D supplementation and  
887 Covid-19 outcomes: A systematic review, meta-analysis and meta-regression. *Rev Med Virol* [Internet].  
888 Wiley; 2021; Available from: <https://doi.org/10.1002/rmv.2269>
- 889 142. CADTH. CADTH COVID-19 Search Strings [Internet]. 2020 [cited 2020 Apr 13]. Available from:  
890 <https://covid.cadth.ca/literature-searching-tools/cadth-covid-19-search-strings/>
- 891 143. Ahmad A, Heumann C, Ali R, Oliver T, Dhahi A, Statistics D, et al. Mean Vitamin D levels in 19  
892 European Countries & COVID-19 Mortality over 10 months. 2021;
- 893 144. Covid-19 Risk Estimator [Internet]. 2021. Available from: [https://github.com/TheEconomist/covid-](https://github.com/TheEconomist/covid-19-risk-estimator)  
894 [19-risk-estimator](https://github.com/TheEconomist/covid-19-risk-estimator)
- 895 145. Ricci A, Pagliuca A, D'Ascanio M, Innammorato M, De Vitis C, Mancini R, et al. Circulating  
896 Vitamin D levels status and clinical prognostic indices in COVID-19 patients. *Respir Res* [Internet].  
897 BioMed Central; 2021;22:1–8. Available from: <https://doi.org/10.1186/s12931-021-01666-3>
- 898 146. De Smet D, De Smet K, Herroelen P, Gryspeerdt S, Martens GA. Serum 25(OH)D Level on Hospital  
899 Admission Associated With COVID-19 Stage and Mortality. *Am J Clin Pathol*. 2021;155:381–8.
- 900 147. Bennouar S, Cherif AB, Kessira A, Bennouar DE, Abdi S. Vitamin D Deficiency and Low Serum  
901 Calcium as Predictors of Poor Prognosis in Patients with Severe COVID-19. *J Am Coll Nutr* [Internet].  
902 Taylor & Francis; 2020;40:104–10. Available from: <https://doi.org/10.1080/07315724.2020.1856013>
- 903 148. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA  
904 2020 statement: An updated guideline for reporting systematic reviews. *BMJ*. 2021;372.
- 905 149. Haddaway NR, McGuinness LA. PRISMA2020: R package and ShinyApp for producing PRISMA  
906 2020 compliant flow diagrams (Version 0.0.1) [Internet]. Zenodo; 2020. Available from:  
907 <http://doi.org/10.5281/zenodo.4287835>
- 908 150. Susianti H, Wahono CS, Rahman PA, Pratama MZ, Wulanda IA, Hartanti KD, et al. Low Levels of  
909 Vitamin D were Associated with Coagulopathy Among Hospitalized Coronavirus Disease-19 (COVID-  
910 19) Patients: A Single-Centered Study in Indonesia. *J Med Biochem*. 2021;1–10.
- 911 151. Szeto B, Zucker JE, LaSota ED, Rubin MR, Walker MD, Yin MT, et al. Vitamin D Status and

- 912 COVID-19 Clinical Outcomes in Hospitalized Patients. *Endocr Res* [Internet]. Taylor & Francis;  
913 2021;46:66–73. Available from: <https://doi.org/10.1080/07435800.2020.1867162>
- 914 152. Vanegas-Cedillo PE, Bello-Chavolla OY, Ramírez-Pedraza N, Rodríguez Encinas B, Pérez Carrión  
915 CI, Jasso Ávila MI, et al. Serum Vitamin D levels are associated with increased COVID-19 severity and  
916 mortality independent of visceral adiposity. *medRxiv* [Internet]. 2021;52:2021.03.12.21253490.  
917 Available from: <http://medrxiv.org/content/early/2021/03/14/2021.03.12.21253490.abstract>
- 918 153. Angelidi AM, Belanger MJ, Lorinsky MK, Karamanis D, Chamorro-Pareja N, Ognibene J, et al.  
919 Vitamin D Status is Associated With In-hospital Mortality and Mechanical Ventilation: A Cohort of  
920 COVID-19 Hospitalized Patients. *Mayo Clin Proc* [Internet]. Mayo Foundation for Medical Education  
921 and Research; 2021;1–12. Available from: <https://doi.org/10.1016/j.mayocp.2021.01.001>
- 922 154. Charoenngam N, Shirvani A, Reddy N, Vodopivec DM, Apovian CM, Holick MF. Association of  
923 Vitamin D Status With Hospital Morbidity and Mortality in Adult Hospitalized COVID-19 Patients With  
924 COVID-19. *Endocr Pract* [Internet]. Elsevier Inc; 2021;25. Available from:  
925 <http://www.ncbi.nlm.nih.gov/pubmed/33705975>
- 926 155. Gavioli EM, Miyashita H, Hassaneen O, Siau E. An Evaluation of Serum 25-Hydroxy Vitamin D  
927 Levels in Patients with COVID-19 in New York City. *J Am Coll Nutr* [Internet]. Taylor & Francis;  
928 2021;0:1–6. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/33605826>
- 929 156. Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time.  
930 *Lancet Infect Dis* [Internet]. Elsevier Ltd; 2020;20:533–4. Available from:  
931 [http://dx.doi.org/10.1016/S1473-3099\(20\)30120-1](http://dx.doi.org/10.1016/S1473-3099(20)30120-1)
- 932 157. Porcher S. Response2covid19, a dataset of governments' responses to COVID-19 all around the  
933 world. *Sci Data* [Internet]. Springer US; 2020;7:1–9. Available from: [http://dx.doi.org/10.1038/s41597-](http://dx.doi.org/10.1038/s41597-020-00757-y)  
934 [020-00757-y](http://dx.doi.org/10.1038/s41597-020-00757-y)
- 935 158. IDF. IDF Diabetes Atlas, 9th edition 2019 [Internet]. 2019 [cited 2021 Aug 3]. Available from:  
936 <https://www.diabetesatlas.org/en/>
- 937 159. UN. Population interpolated by single age and single year [Internet]. 2019 [cited 2021 Apr 10].  
938 Available from: <https://population.un.org/wpp/Download/Standard/CSV/>
- 939 160. Zheng Z, Peng F, Xu B, Zhao J, Liu H, Peng J, et al. Risk factors of critical & mortal COVID-19  
940 cases: A systematic literature review and meta-analysis. *J Infect* [Internet]. Elsevier BV; 2020;81:e16--  
941 e25. Available from: <https://doi.org/10.1016/j.jinf.2020.04.021>
- 942 161. Murdaca G, Tonacci A, Negrini S, Greco M, Borro M, Puppo F, et al. Emerging role of vitamin D in



- 943 autoimmune diseases: An update on evidence and therapeutic implications. *Autoimmun Rev* [Internet].  
944 Elsevier BV; 2019;18:102350. Available from: <https://doi.org/10.1016/j.autrev.2019.102350>
- 945 162. Yang C-Y, Leung PSC, Adamopoulos IE, Gershwin ME. The Implication of Vitamin D and  
946 Autoimmunity: a Comprehensive Review. *Clin Rev Allergy & Immunol* [Internet]. Springer Science  
947 and Business Media LLC; 2013;45:217–26. Available from: <https://doi.org/10.1007/s12016-013-8361-3>
- 948 163. Stanhope KL. Sugar consumption, metabolic disease and obesity: The state of the controversy. *Crit*  
949 *Rev Clin Lab Sci* [Internet]. Informa UK Limited; 2015;53:52–67. Available from:  
950 <https://doi.org/10.3109/10408363.2015.1084990>
- 951 164. Worldometer FAQ [Internet]. Worldometer. 2021 [cited 2021 Aug 23]. Available from:  
952 <https://www.worldometers.info/faq/>
- 953 165. Reis BZ, Fernandes AL, Sales LP, Santos MD, Dos-Santos CC, Pinto AJ, et al. Influence of vitamin  
954 D status on hospital length of stay and prognosis in hospitalized patients with moderate to severe COVID-  
955 19: a multicenter prospective cohort study. *Am J Clin Nutr* [Internet]. Oxford University Press (OUP);  
956 2021;114:598–604. Available from: <https://doi.org/10.1093/ajcn/nqab151>
- 957 166. Sekine T, Perez-Potti A, Rivera-Ballesteros O, Strålin K, Gorin J-B, Olsson A, et al. Robust T Cell  
958 Immunity in Convalescent Individuals with Asymptomatic or Mild COVID-19. *Cell* [Internet]. Elsevier  
959 BV; 2020;183:158--168.e14. Available from: <https://doi.org/10.1016/j.cell.2020.08.017>
- 960 167. Zhang Y, Leung DYM, Richers BN, Liu Y, Remigio LK, Riches DW, et al. Vitamin D inhibits  
961 monocyte/macrophage proinflammatory cytokine production by targeting MAPK phosphatase-1. *J*  
962 *Immunol. Am Assoc Immunol*; 2012;188:2127–35.
- 963 168. Luxwolda MF, Kuipers RS, Kema IP, Dijck-Brouwer DAJ, Muskiet FAJ. Traditionally living  
964 populations in East Africa have a mean serum 25-hydroxyvitamin D concentration of 115 nmol/l. *Br J*  
965 *Nutr. Cambridge University Press*; 2012;108:1557–61.
- 966 169. Afshar P, Ghaffaripour M, Sajjadi H. Suggested role of Vitamin D supplementation in COVID-19  
967 severity. *J Contemp Med Sci* [Internet]. 2020;6. Available from:  
968 <http://www.jocms.org/index.php/jcms/article/view/822>
- 969 170. Vukić M, Neme A, Seuter S, Saksa N, De Mello VDF, Nurmi T, et al. Relevance of vitamin D  
970 receptor target genes for monitoring the vitamin D responsiveness of primary human cells. *PLoS One*.  
971 2015;10:1–15.
- 972 171. von Mendel J, Borsche L. COVID-19 mortality risk correlates inversely with vitamin D3 status,  
973 mortality close to zero could theoretically be achieved at 50 ng/ml 25(OH)D3: Results of a systematic

- 974 review and meta-analysis [Internet]. Harvard Dataverse; 2021. Available from:  
975 <https://doi.org/10.7910/DVN/7FSWNL>
- 976 172. Zwart SR, Smith SM. Vitamin D and COVID-19: Lessons from Spaceflight Analogs. *J Nutr*  
977 [Internet]. Oxford University Press (OUP); 2020;150:2624–7. Available from:  
978 <https://doi.org/10.1093/jn/nxaa233>
- 980 173. Pouya FD, Rasmi Y, Nemati M, Asl ER. Vitamin D Double-edged Sword Against COVID-19. *Int J*  
981 *Infect* [Internet]. Kowsar Medical Institute; 2021;8. Available from: <https://doi.org/10.5812/iji.109043>
- 983 174. de Borst MH, Vervloet MG, ter Wee PM, Navis G. Cross Talk Between the Renin-Angiotensin-  
984 Aldosterone System and Vitamin D-FGF-23-klotho in Chronic Kidney Disease: Figure 1. *J Am Soc*  
985 *Nephrol* [Internet]. American Society of Nephrology (ASN); 2011;22:1603–9. Available from:  
986 <https://doi.org/10.1681/asn.2010121251>
- 988 175. Simko F, Hrenak J, Adamcova M, Paulis L. Renin-Angiotensin-Aldosterone System: Friend or Foe--  
989 The Matter of Balance. Insight on History, Therapeutic Implications and {COVID}-19 Interactions. *Int J*  
990 *Mol Sci* [Internet]. MDPI AG; 2021;22:3217. Available from: <https://doi.org/10.3390/ijms22063217>
- 992 176. Getachew B, Tizabi Y. Vitamin D and COVID-19: Role of ACE2, age, gender, and ethnicity. *J Med*  
993 *Virol* [Internet]. Wiley; 2021;93:5285–94. Available from: <https://doi.org/10.1002/jmv.27075>  
994
- 995 177. Butt AA, Nafady-Hego H, Chemaitelly H, Abou-Samra A-B, Khal A Al, Coyle P V, et al. Outcomes  
996 Among Patients with Breakthrough SARS-CoV-2 Infection After Vaccination. *Int J Infect Dis* [Internet].  
997 Elsevier BV; 2021;110:353–8. Available from: <https://doi.org/10.1016/j.ijid.2021.08.008>
- 999 178. Birhane M, Bressler S, Chang G, Clark T, Dorough L, Fischer M, et al. COVID-19 Vaccine  
1000 Breakthrough Infections Reported to CDC - United States, January 1-April 30, 2021. *MMWR Morb*  
1001 *Mortal Wkly Rep* [Internet]. Centers for Disease Control MMWR Office; 2021;70:792–3. Available  
1002 from: <https://doi.org/10.15585/mmwr.mm7021e3>
- 1004 179. Amrein K, Scherkl M, Hoffmann M, Neuwersch-Sommeregger S, Köstenberger M, Berisha AT, et  
1005 al. Vitamin D deficiency 2.0: an update on the current status worldwide. *Eur J Clin Nutr*.  
1006 2020;74(11):1498–513.

- 1008 180. Taha R, Abureesh S, Alghamdi S, Hassan RY, Cheikh MM, Bagabir RA, et al. The Relationship  
1009 Between Vitamin D and Infections Including COVID-19: Any Hopes? *Int J Gen Med*. 2021;14:3849.
- 1011 181. Antonelli M, Kushner I. Low Serum Levels of 25-hydroxyvitamin D Accompany Severe COVID-19  
1012 Because it is a Negative Acute Phase Reactant. *Am J Med Sci*. 2021;  
1013
- 1014 182. Kazemi A, Mohammadi V, Aghababae SK, Golzarand M, Clark CCT, Babajafari S. Association of  
1015 Vitamin D Status with SARS-CoV-2 Infection or COVID-19 Severity: A Systematic Review and Meta-  
1016 analysis. *Adv Nutr* [Internet]. 2021; Available from: <https://doi.org/10.1093/advances/nmab012>  
1017
- 1018 183. Munshi R, Hussein MH, Toraih EA, Elshazli RM, Jardak C, Sultana N, et al. Vitamin D  
1019 insufficiency as a potential culprit in critical COVID-19 patients. *J Med Virol* [Internet]. 2020;93(2):733–  
1020 40. Available from: <https://doi.org/10.1002/jmv.26360>  
1021
- 1022 184. Crafa A, Cannarella R, Condorelli RA, Mongioi LM, Barbagallo F, Aversa A, et al. Influence of 25-  
1023 hydroxy-cholecalciferol levels on SARS-CoV-2 infection~and COVID-19 severity: A systematic review  
1024 and meta-analysis. *EClinicalMedicine* [Internet]. 2021 Jul;37:100967. Available from:  
1025 <https://doi.org/10.1016/j.eclinm.2021.100967>  
1026
- 1027 185. Teshome A, Adane A, Girma B, Mekonnen ZA. The Impact of Vitamin D Level on {COVID}-19  
1028 Infection: Systematic Review and Meta-Analysis. *Front Public Heal* [Internet]. 2021;9. Available from:  
1029 <https://doi.org/10.3389/fpubh.2021.624559>