

# 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.**

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## 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].

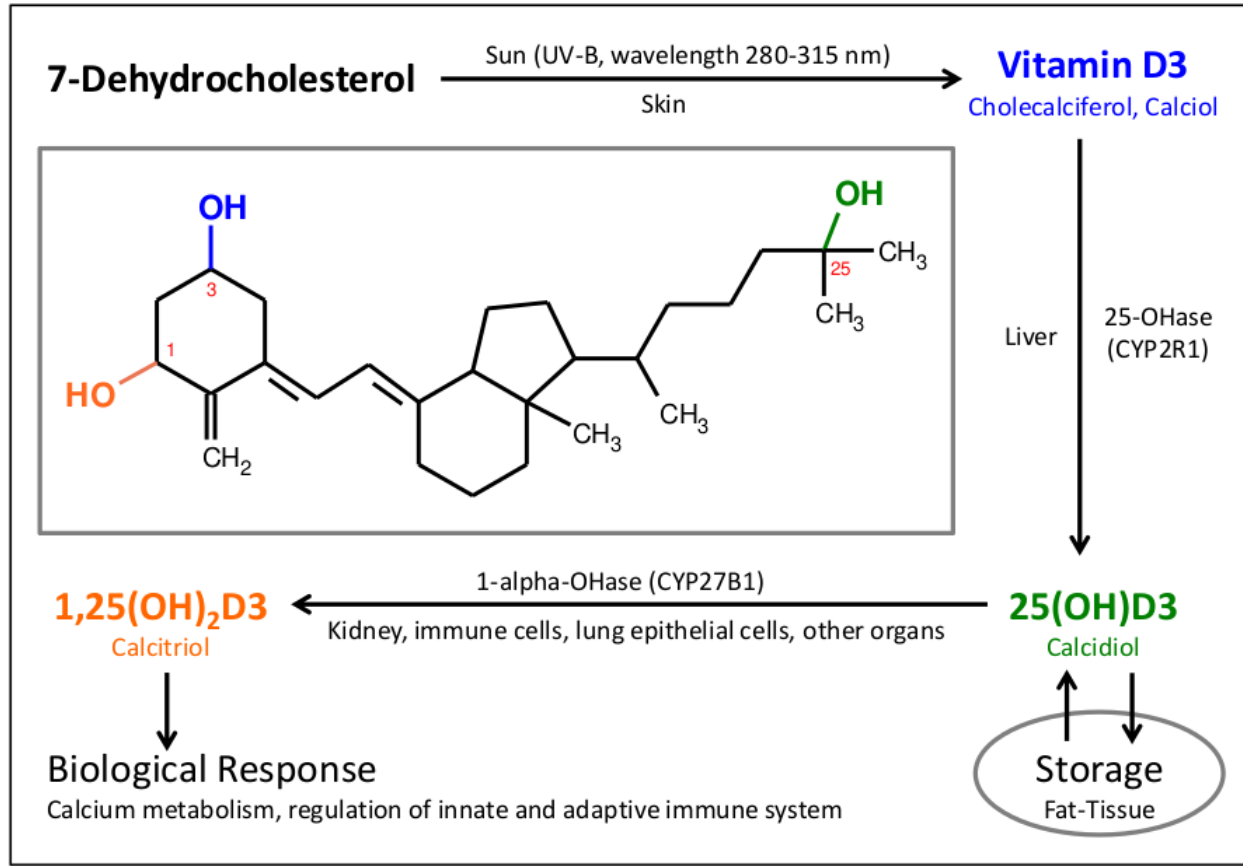
63 In this publication, we will demonstrate that vitamin D3 deficiency, which is a well-documented  
64 worldwide problem [13–19,179], is one of the main reasons for severe courses of SARS-CoV-2  
65 infections. The fatality rates correlate well with the findings that elderly people, black people and 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)2D3 (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.

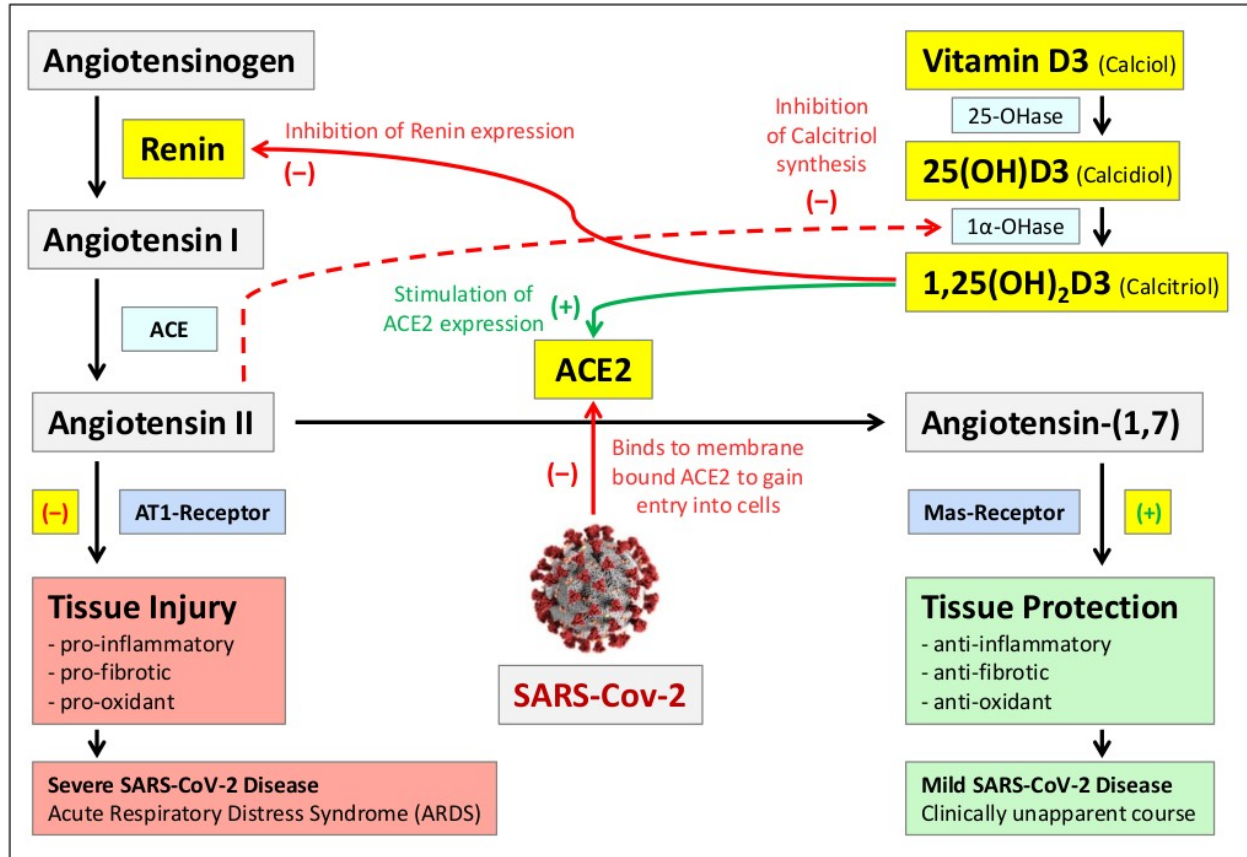
116 Long before the SARS-CoV-2 pandemic, an increasing number of scientific publications showed the  
117 effectiveness of a sufficient vitamin D<sub>3</sub> blood level in curing many of the human diseases caused by a  
118 weak or unregulated immune system [37,57–59]. This includes all types of virus 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 D<sub>3</sub>, 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.

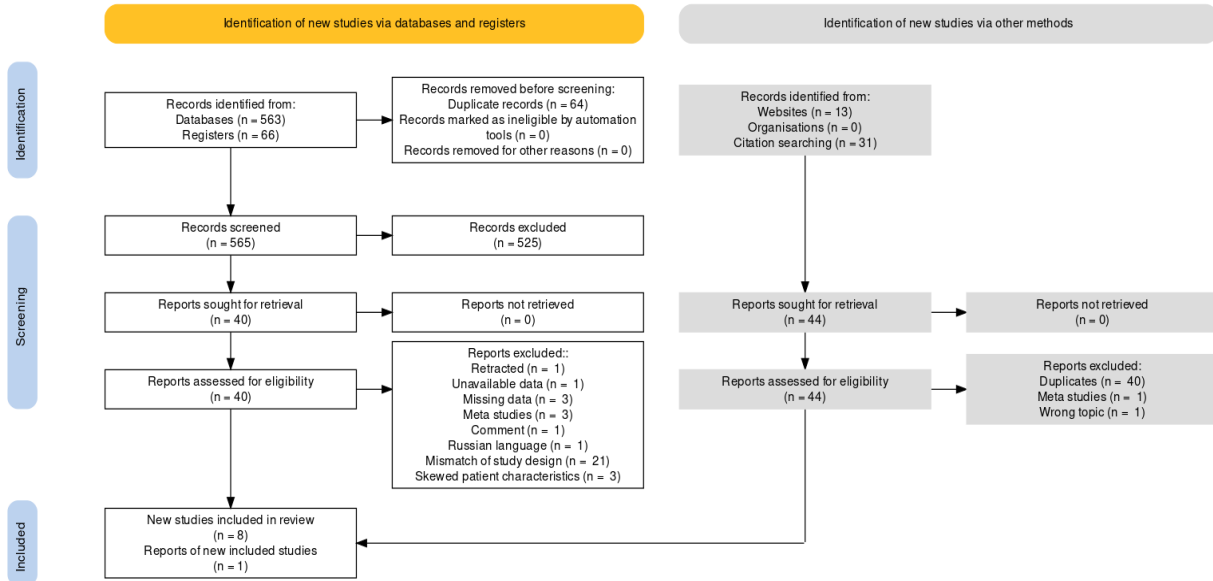
231 The two datasets were combined, and the mortality rates of the hospital studies were scaled according to  
232 the mortality range of the population studies, resulting in a uniform list of patient cohorts, their vitamin D  
233 status and dimensionless mortality coefficients. Linear regressions (OLS) 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**

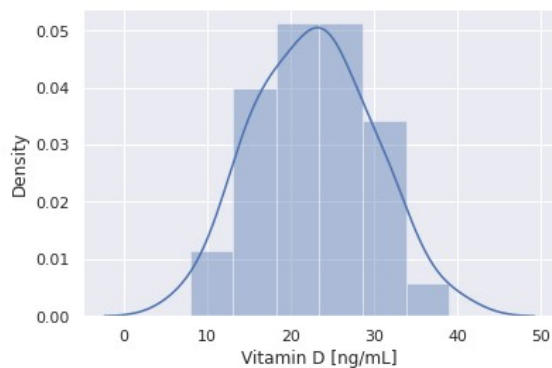
Author	Reference	Cohort	No. of patients	Laboratory results recorded pre-/post-infection	Mortality	Vitamin D level [ng/ml]
Ahmad et al., 2021	[143]	19 European countries	448,785,546	Up to 10 months in advance	Refer to source study	
Angelidi et al., 2021	[153]	< 30 ng/ml	79	Within 1 day after admission	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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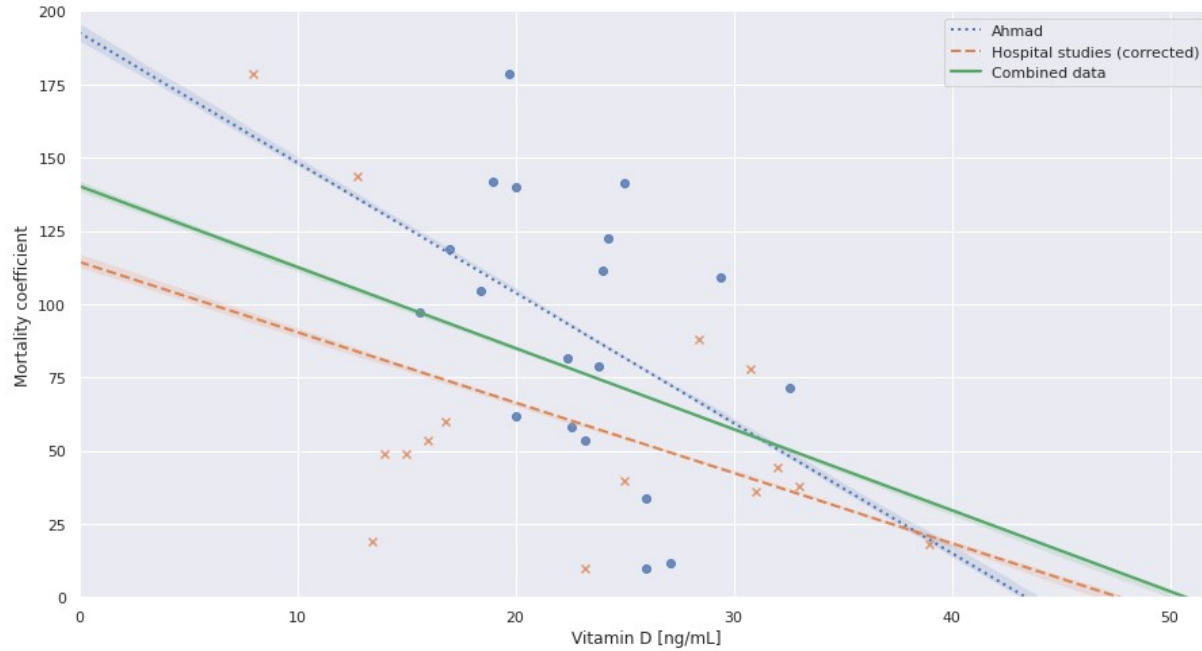
256 One population study by Ahmad et al. [143] was identified. Therein, the CMRs are compiled for 19  
257 European countries based on COVID-19 pandemic data from Johns Hopkins University [156] in the time  
258 frame from March 21, 2020, to January 22, 2021, as well as D3 blood levels for the respective 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.

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