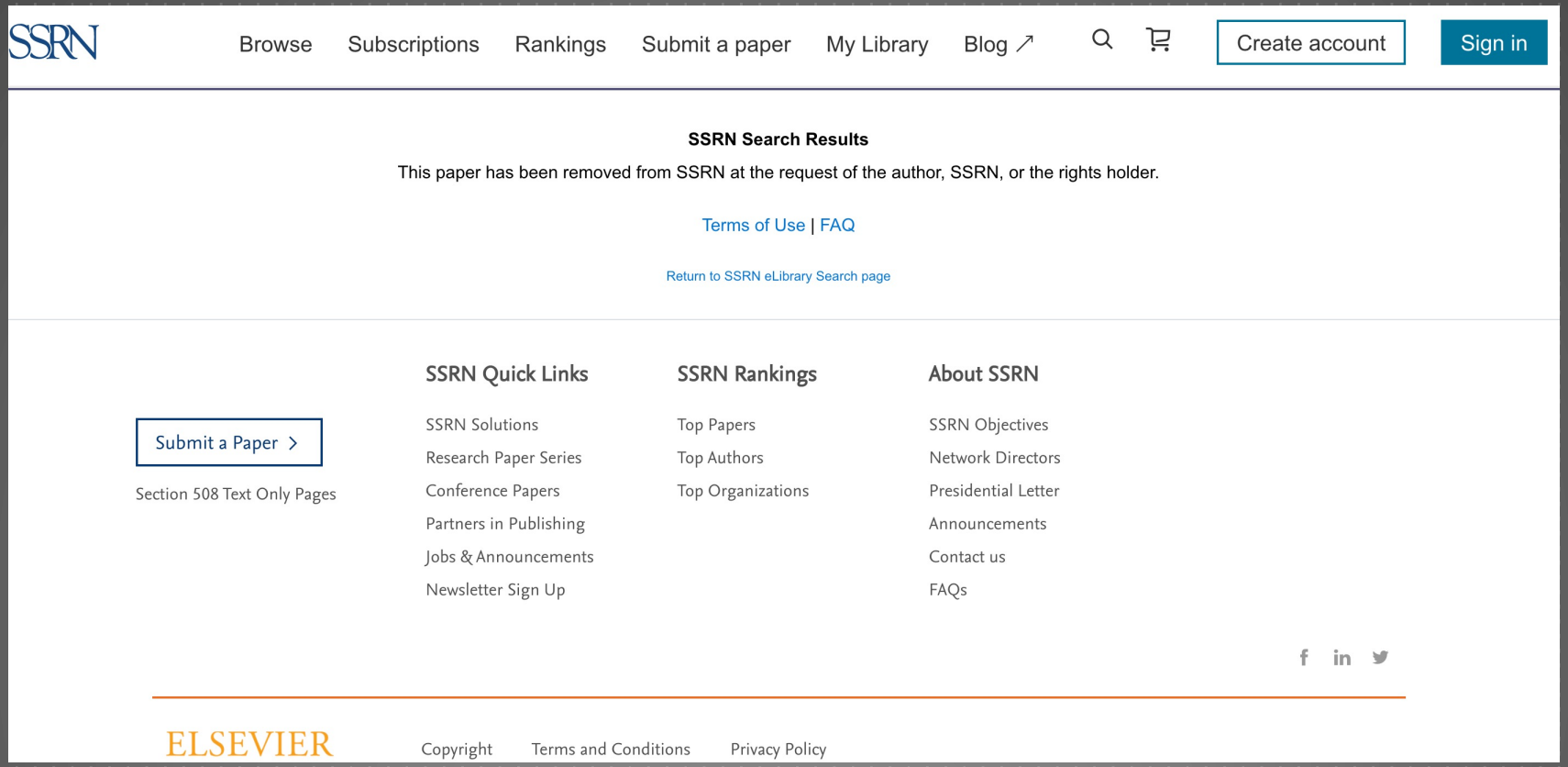
Vitamin D and COVID-19

Chris Masterjohn, PhD

AHS 2021

The first vitamin D and COVID-19 study



SSRN Browse Subscriptions Rankings Submit a paper My Library Blog ↗ Create account Sign in

SSRN Search Results

This paper has been removed from SSRN at the request of the author, SSRN, or the rights holder.

Terms of Use | FAQ

Return to SSRN eLibrary Search page

Submit a Paper >

Section 508 Text Only Pages

SSRN Quick Links

SSRN Solutions
Research Paper Series
Conference Papers
Partners in Publishing
Jobs & Announcements
Newsletter Sign Up

SSRN Rankings

Top Papers
Top Authors
Top Organizations

About SSRN

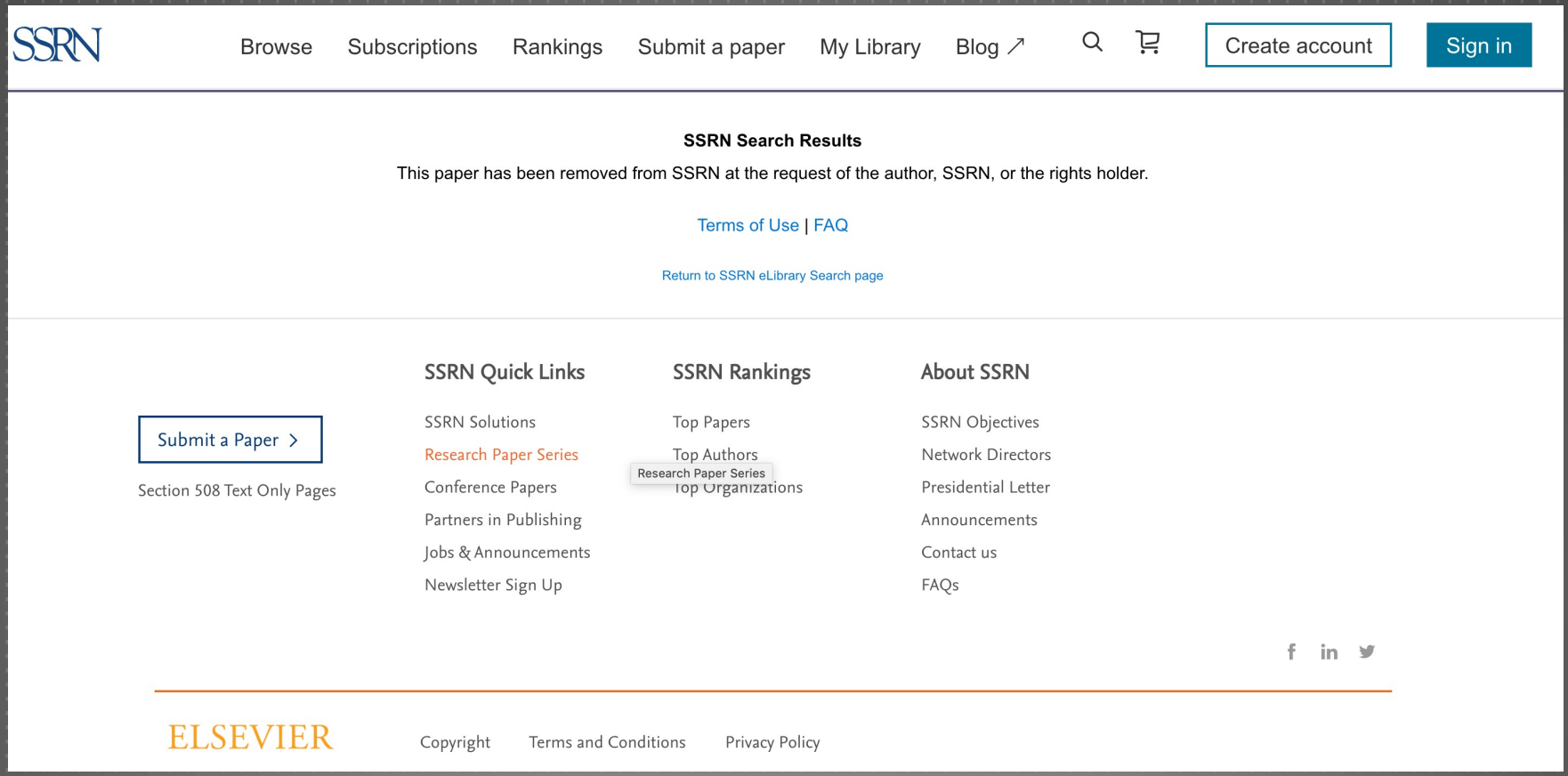
SSRN Objectives
Network Directors
Presidential Letter
Announcements
Contact us
FAQs

ELSEVIER Copyright Terms and Conditions Privacy Policy

Alipio, 2020. Vitamin D supplementation could possibly improve clinical outcomes of patients infected with Coronavirus-2019 (COVID-2019)

chrismasterjohnphd.com/vitamind

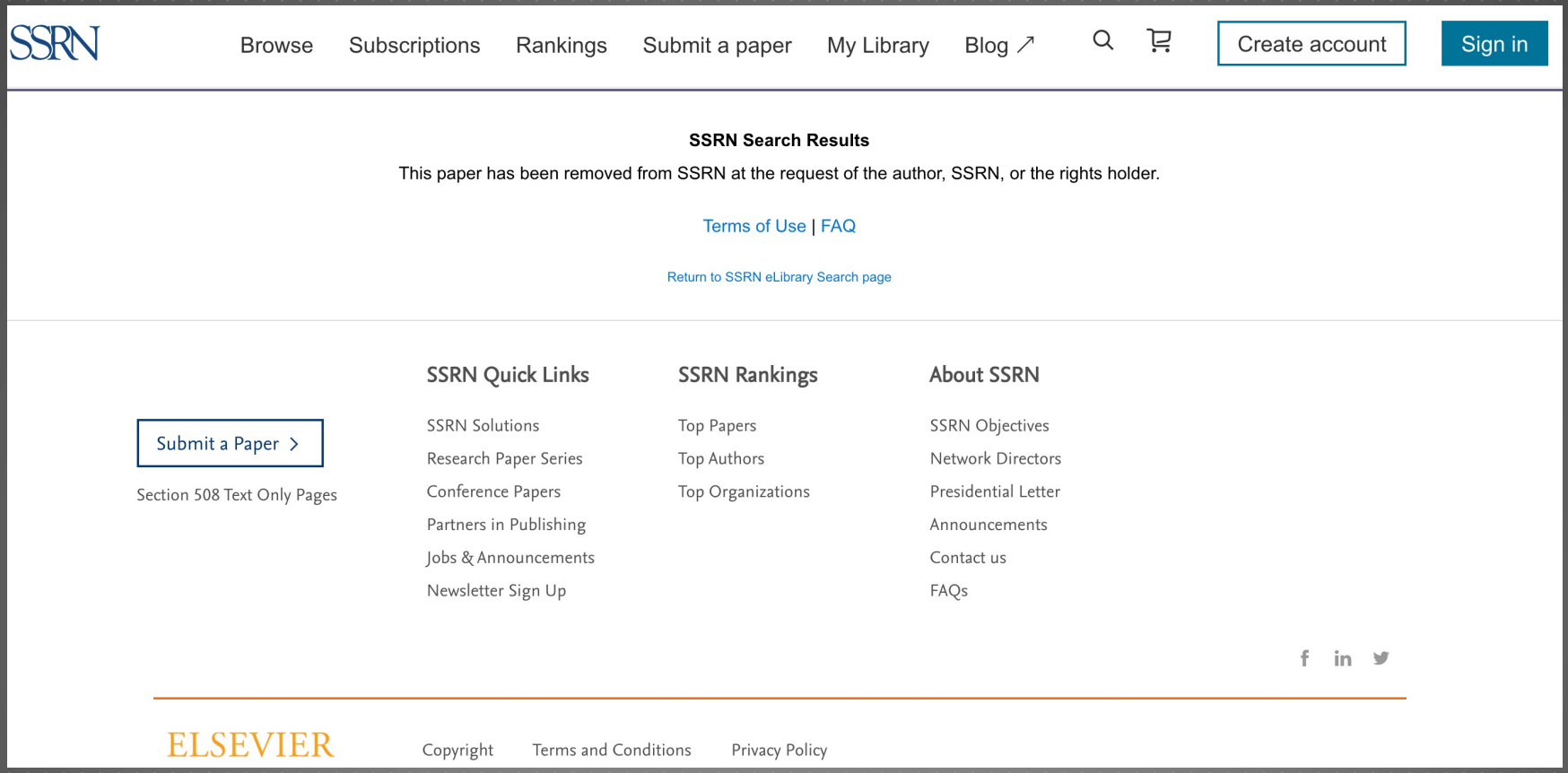
The second Vitamin D and COVID-19 Study



Raharusuna, et al. Patterns of COVID-19 Mortality and Vitamin D: An Indonesian Study

chrismasterjohnphd.com/vitamind

The third study on vitamin D and COVID-19



Vitamin D Level of Mild and Severe Elderly Cases of COVID-19: A Preliminary Report by El James Glicio

chrismasterjohnphd.com/vitamind

The Raharusuna paper was accused of fraudulently fueling an "infodemic" of misinformation about vitamin D by a group of authors that don't exist.

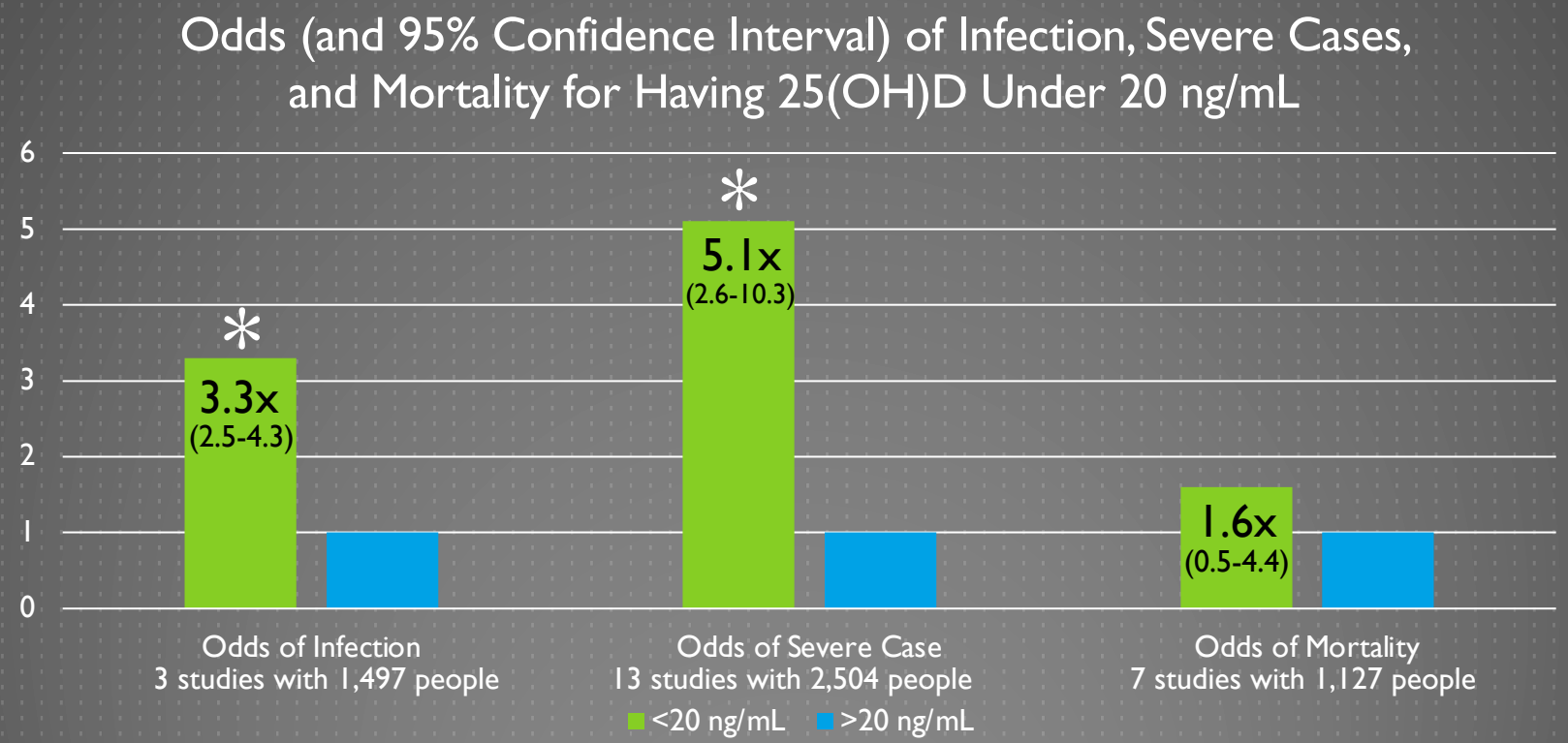
Br J Nutr. 2020 Jul 27 : 1–2.
Published online 2020 Jul 27. doi: 10.1017/S0007114520002950
PMCID: PMC7443564
PMID: 32713358

COVID-19 and misinformation: how an infodemic fuelled the prominence of vitamin D

Joshua Henrina,[1] Michael Anthonius Lim,[2] and Raymond Pranata[3]

We are now swimming in legitimate vitamin D and COVID-19 research!

Vitamin D deficiency (<20 ng/mL) is associated with 3.3x odds of infection and 5.1x odds of a severe case.

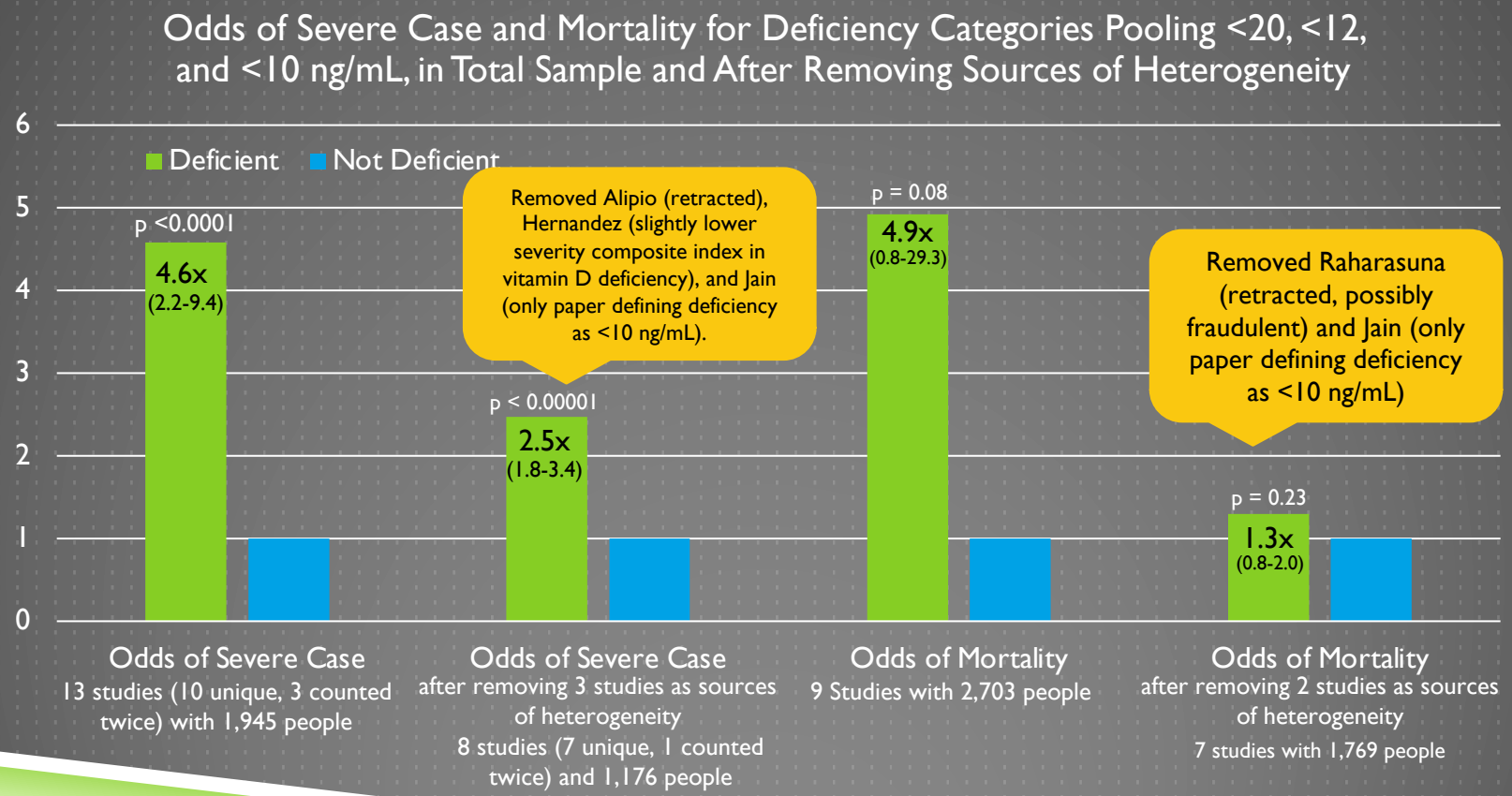


*, P<0.05

Ghasemian, et al. The role of vitamin D in the age of COVID-19: A systematic review and meta-analysis. Int J Clin Pract. 2021 Jul 29

chrismasterjohnphd.com/vitamind

Vitamin D deficiency (<10, 12, or <20 ng/mL) is associated with 4.6x odds of a severe case and 4.9 odds of mortality, but with important caveats.

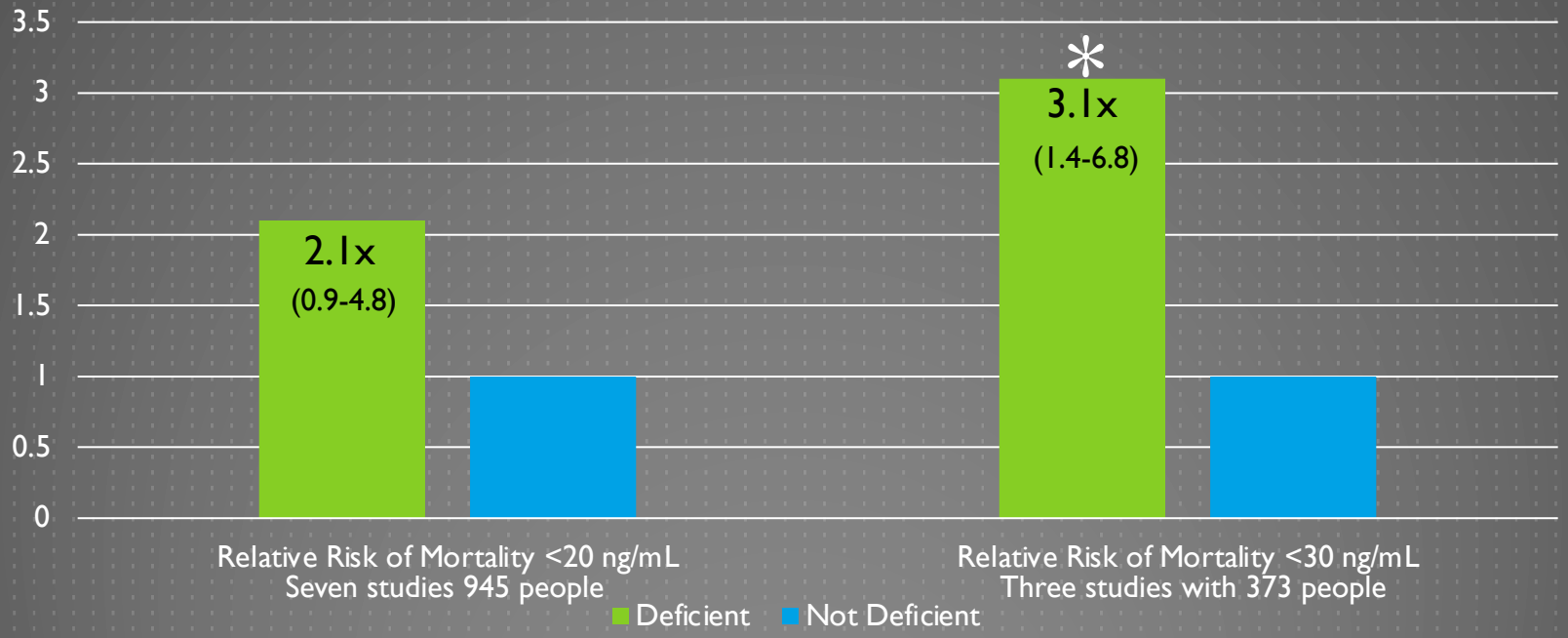


Crafa et al. Influence of 25-hydroxy-cholecalciferol levels on SARS-CoV-2 infection and COVID-19 severity: A systematic review and meta-analysis. EClinicalMedicine. 2021 Jul; 37: 100967.

chrismasterjohnphd.com/vitamind

Vitamin D deficiency (<20 or <30 ng/mL) is associated with a 2-3-fold increased mortality risk.

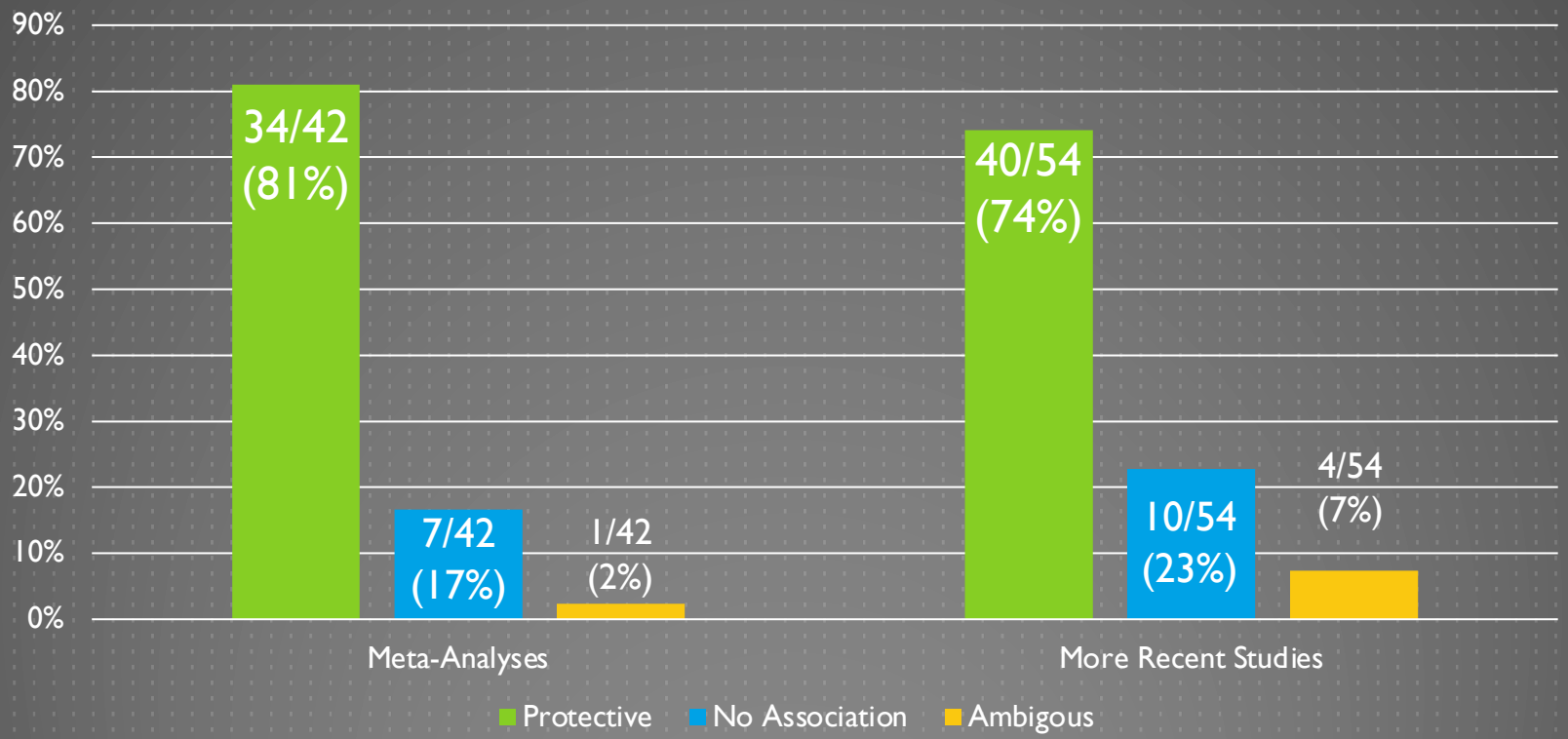
Relative risk of mortality with vitamin D deficiency defined as <20 ng/mL (left) or <30 ng/mL (right).



*, P<0.05

Bassante, et al. The link between COVID-19 and Vitamin D (VIVID): A systematic review and meta-analysis. Metabolism. 2021 Jun; 119: 154753.

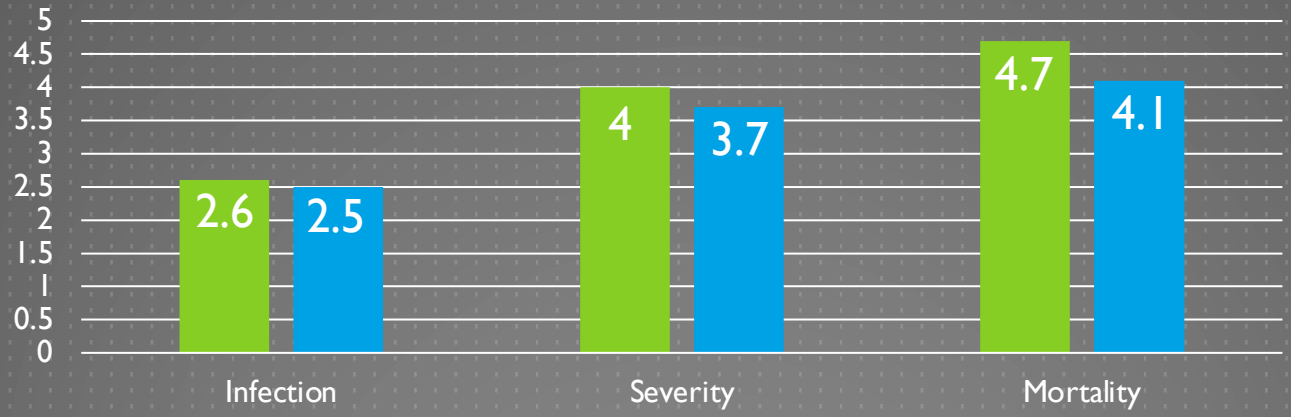
Studies published since the most recent meta-analyses are similar, except for an increase in the small number of ambiguous results.



If percentages remained the same, more recent studies would be 44 protective, 9 no association 1 ambiguous. P=0.5 in chi square analysis.

The effect sizes of the 40 positive studies published since the most recent meta-analyses are similar to those of the 34 earlier studies.

Mean Effect Size Score of Studies Published Earlier (Green) and Later (Blue) Than the Most Recent Meta-Analyses



Effect sizes were assigned points as follows:
1 — an HR, OR, RR, or prevalence ratio between 1.0-1.5, or a mean difference in 25(OH)D of 1-5 ng/mL
2 — an HR, OR, RR, or prevalence ratio beween1.5-2.0
3 — an HR, OR, RR, or prevalence ratio between 2.0-3.0, or a mean difference in 25(OH)D of 5-10 ng/mL
4 — an HR, OR, RR, or prevalence ratio between 3.0-4.0,
5 — an HR, OR, RR, or prevalence ratio between 4.0-5.0, or a mean difference in 25(OH)D of 10-15 ng/mL
6 — an HR, OR, RR, or prevalence ratio >5.0

Vitamin D appears to be associated with between 2-fold and 5-fold increases in COVID-19 infection, severity, and mortality.

- Data from these meta-analyses converge toward between 2-fold and 5-fold increases in the odds or risk of COVID-19 infection, severity, and mortality.
- 95% confidence intervals may reach towards 10 for severity and toward 30 for mortality, and may include a slightly decreased risk of mortality. However, I suspect that future meta-analyses incorporating the studies that have been published more recently will start to narrow the confidence intervals and will achieve consistent statistical significance for mortality.
- The majority of these studies are rated as poor in quality or at high risk of bias, and these studies do not clarify cause-and-effect relationships.

Vitamin D status is a predictor of severity and mortality, with the cutoff for the severe danger zone likely lying somewhere between 9-25 ng/mL.

Author, Year	Endpoint	Cutoff	Sensitivity	Specificity
Teama, 2021	Severity	<18 ng/mL	76%	61%
Abrishami, 2021	Mortality	<25 ng/mL	75%	72%
Bychinin, 2021	Mortality	<10 ng/mL	82%	56%
Infante, 2021	Mortality	<9 ng/mL	59%	70%
Bennouar, 2021	Mortality	<15 ng/mL	76%	69%

Ecological studies suggest population-level vitamin D status explains up to 58% of COVID-19 infection rates and up to 63% of COVID-19 mortality rates.

chrismasterjohnphd.com/vitamind

Author	Date	Populations	Predictor	% of Variation Explained by Vitamin D		
				Infection	**Severity**	**Mortality**
Ali	October, 2020	20 European Countries	Mean 25(OH)D	22.8%		12.7% (P=0.123)
Yadav	Feb, 2021	37 Asian Pacific Countries	Mean 25(OH)D	15.5%		7.8% (P=0.093)
Ahmad	March, 2021 (preprint)	19 European Countries	Mean 25(OH)D			26.7%
Bakaloudi	March, 2021 (preprint)	24 European Countries	<12 and <20 ng/mL POOLED (!)	3.6% (P=0.374)		1.7% (P=0.549)
Pugach	April, 2021	10 European Countries	<10 ng/mL			62%
Papadimitriou	May, 2021	26 European Countries	<20, 20-25, 25-30, >30 ng/mL		22%	63%, controlling for life expectancy
Jayawardena	June, 2021	24 Asian Countries, adjusting for age and obesity	<20 ng/mL	30% → 56%		25%-→ 41%
Mariani	June, 2021	46 Countries	<20 ng/mL	15%		16%
Sooriyaarachchi	August, 2021	47 Countries	<20 ng/mL	Asia 58% Europe 14%		Asia 56% Europe 18.5%

Higher vitamin D status up to 55 ng/mL is associated with the lowest risk of infection.

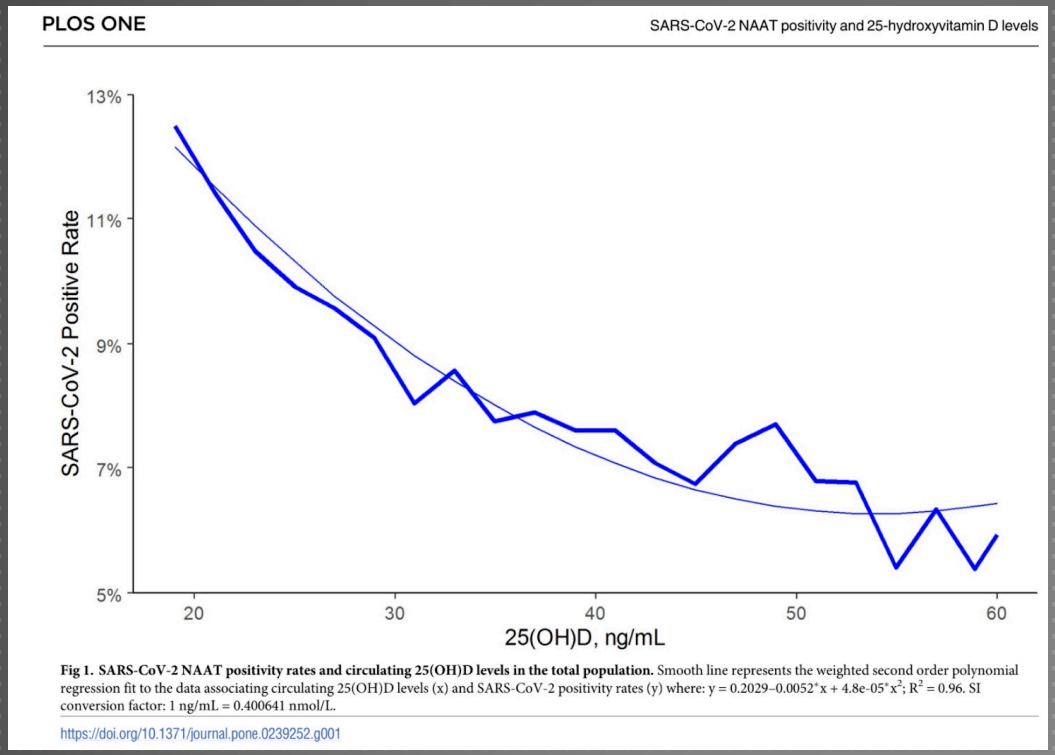


Fig 1. SARS-CoV-2 NAAT positivity rates and circulating 25(OH)D levels in the total population. Smooth line represents the weighted second order polynomial regression fit to the data associating circulating 25(OH)D levels (x) and SARS-CoV-2 positivity rates (y) where: $y = 0.2029 - 0.0052^{*}x + 4.8e\text{-}05^{*}x^2$; $R^2 = 0.96$. SI conversion factor: 1 ng/mL = 0.400641 nmol/L.

https://doi.org/10.1371/journal.pone.0239252.g001

All Quest Diagnostics patients in the United States who had SARS-CoV-2 testing between March 9 and June 19, 2020 and a 25(OH)D from the preceding 12 months were included. This totaled 191,779 subjects.

This included 4,016 people with 55-59 ng/mL and 8,305 with levels 60 ng/mL or higher.

For repeat SARS-CoV-2 testing, someone was considered positive if any one of the tests were positive.

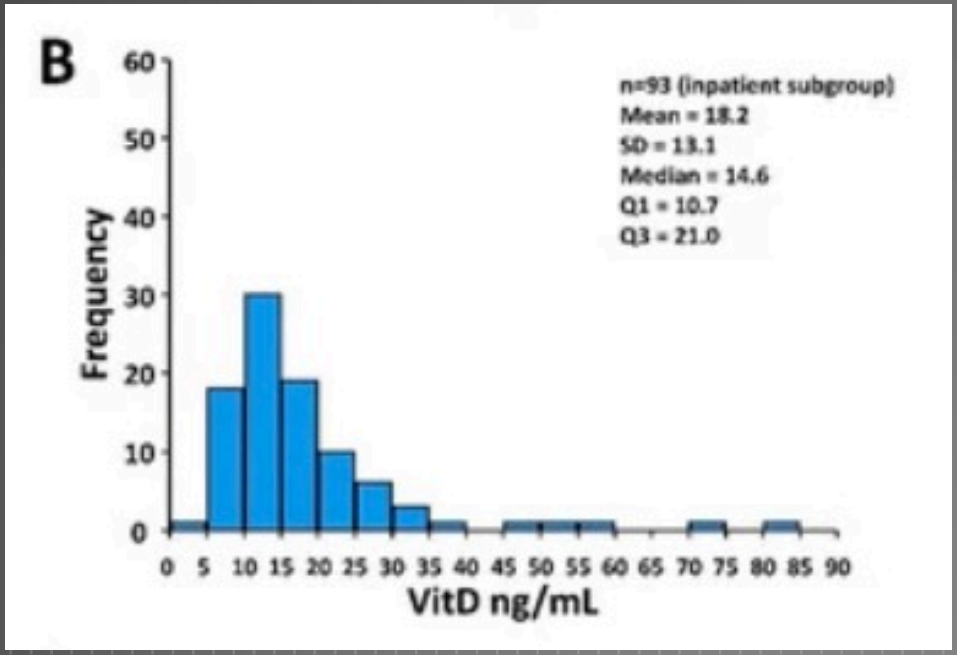
When subjects were stratified by age, sex, latitude, seasonality, and race, 25(OH)D explained 96% of the variation in infection rate.

Odds of getting infected went down 2% for every 1 ng/mL increase in 25(OH)D, bottoming out around 55 ng/mL at 6% risk of infection.

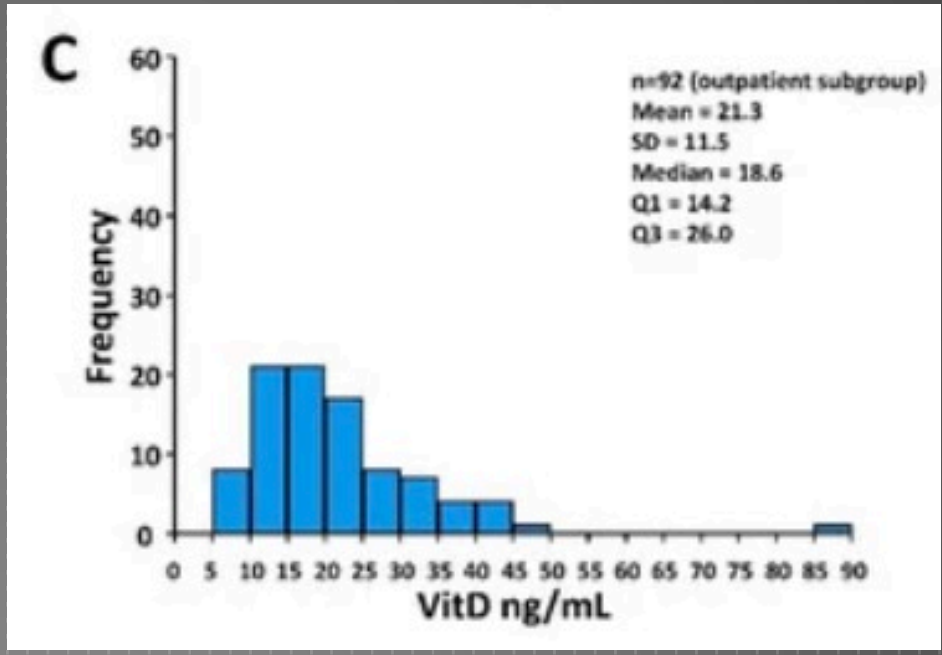
Kaufman, et al. SARS-CoV-2 positivity rates associated with circulating 25-hydroxyvitamin D levels. PLoS One. 2020 Sep 17;15(9):e0239252.

chrismasterjohnphd.com/vitamind

Radujkovic, 2020 had 7 subjects with 25(OH)D 45 ng/mL or higher, 5 of whom were hospitalized.



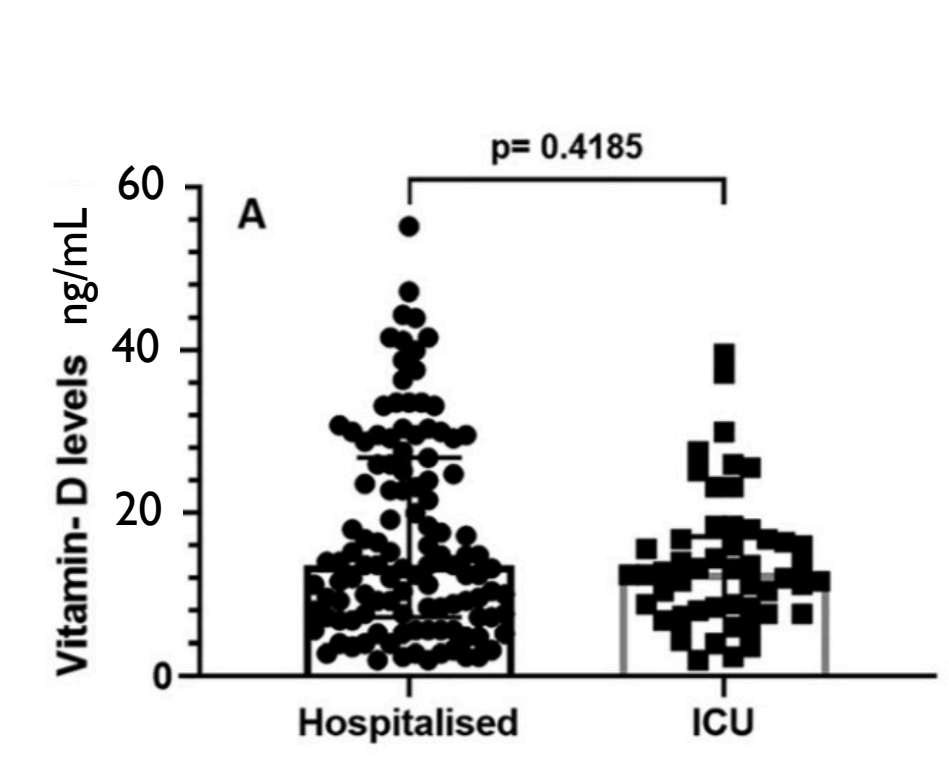
Hospitalized



Non-hospitalized

Radujkovic, et al. Vitamin D Deficiency and Outcome of COVID-19 Patients. Nutrients 2020, 12(9), 2757.

Vague low-confidence suggestion that 40-60 ng/mL won't guarantee you stay out of the hospital but may keep you out of the ICU.



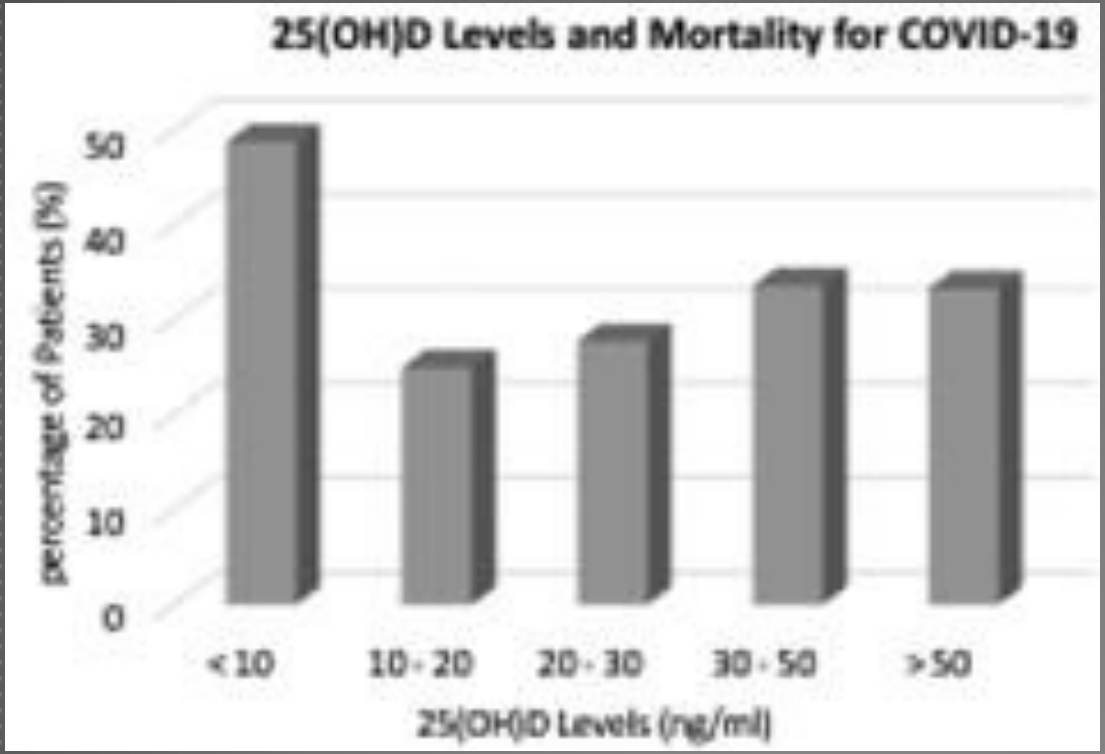
From patients hospitalized in the UK. This study did find a significant difference in the prevalence of deficiency between groups, but results here show mean and distribution of vitamin D levels between groups and are not significant.

About seven people 40-60 ng/mL are hospitalized but none are in ICU.

Orchard, et al. Vitamin-D levels and intensive care unit outcomes of a cohort of critically ill COVID-19 patients. Clin Chem Lab Med. 2021 Jan 19;59(6):1155-1163.

chrismasterjohnphd.com/vitamind

Having 25(OH)D >50 ng/mL upon hospital admission is not a guarantee against COVID-19 mortality.



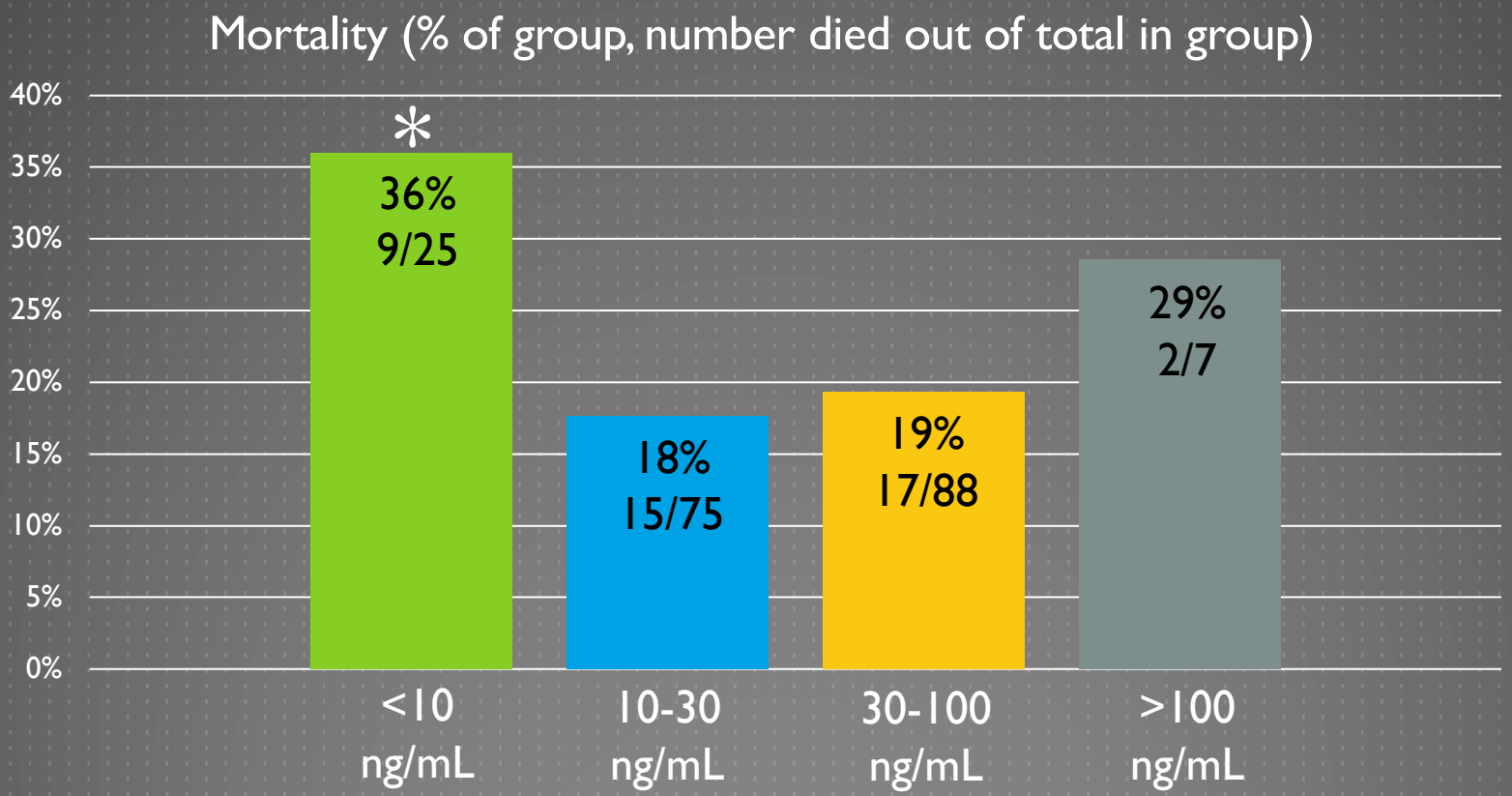
COVID-19 patients admitted to the hospital within the Mount Sinai Health System during the early peak of the pandemic in New York City between March 1 and May 8, 2020.

Roughly 25% of patients (n=65) had 25(OH)D over 40 ng/mL, but the distribution is not further described.

Differences in >10 groups are not statistically significant and are confounded by older subjects having better vitamin D status.

Gavioli, et al. An Evaluation of Serum 25-Hydroxy Vitamin D Levels in Patients with COVID-19 in New York City. J Am Coll Nutr. 2020:1–6.

Vague hints of a U-shaped curve with increased mortality above 100 ng/mL: very low confidence.



Results from hospitalized patients in Iran. Only the <10 group is significantly different from the others. Results confounded by higher vitamin D status being associated with older age.

Tehrani, et al. Evaluation of vitamin D levels in COVID-19 patients referred to Labafinejad hospital in Tehran and its relationship with disease severity and mortality. Clin Nutr ESPEN. 2021 Apr; 42: 313–317.

Conclusions about levels above 30 ng/mL

- The lowest risk of infection appears to occur at 55 ng/mL.
- If you do get infected, there is no evidence that being in the >40 ng/mL range is associated with a lower risk of severity than being in the 30-40 ng/mL range.
- Being in the 30-60 ng/mL range does not provide a guarantee against hospitalization or death, though being above 30 ng/mL in general is associated with the least risk of severity and death.
- Little is known about higher levels, but there are some suggestions there could be a U-shaped curve above 100 ng/mL.

- We are still only talking about the *association* with baseline levels leading up to infection or at time of hospital admission and we are not yet addressing the *causal effect* of supplementing with vitamin D.

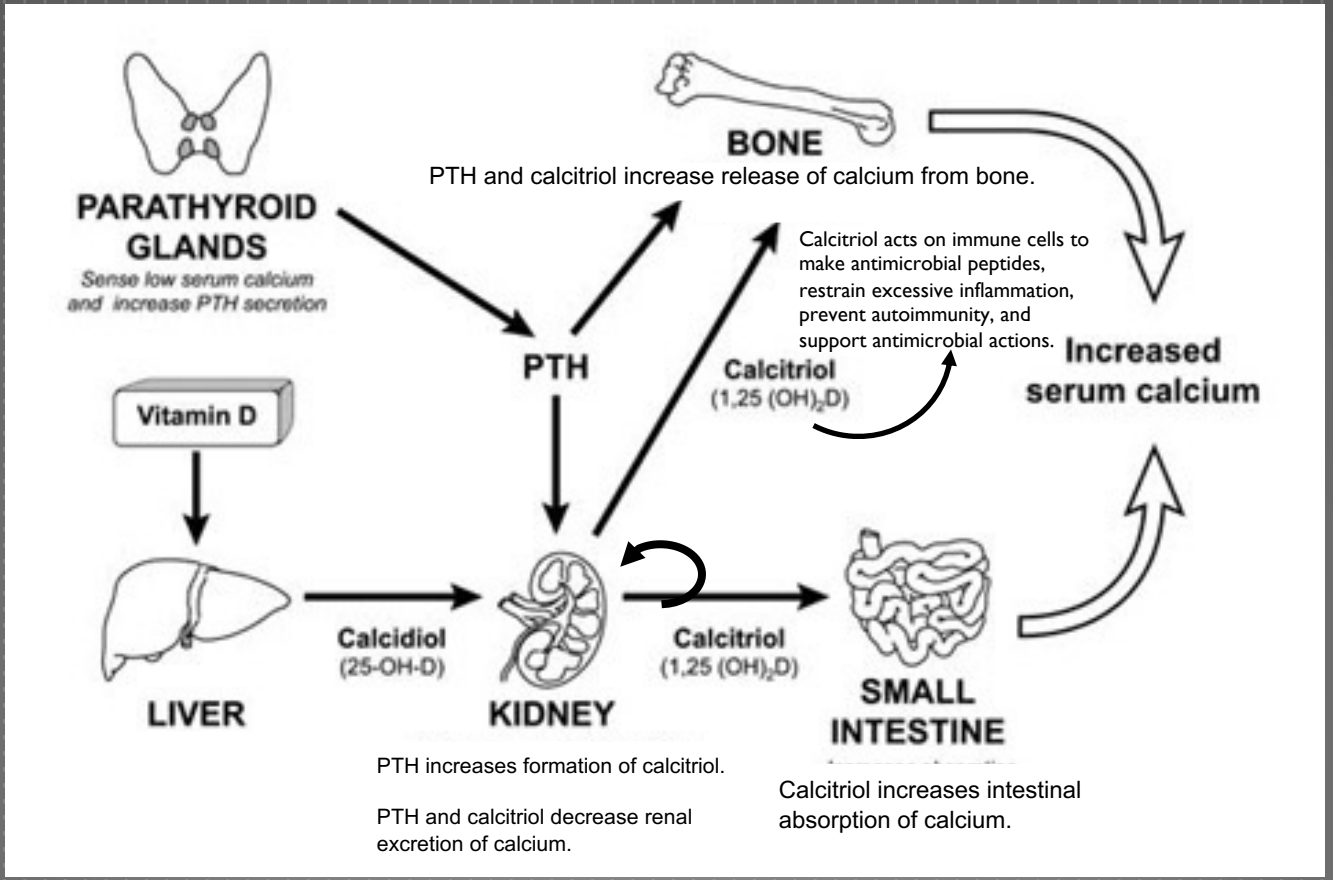
COVID-19 depletes vitamin D levels.

- Herrera-Quinta, 2021 showed that proportion with 25(OH)D >20 dropped five-fold from 16.7% to 3.2% after just three days of being in the ICU.

- Mazzioti, 2021 reported, "Pre-COVID-19 serum 25(OH)D values were available in 28 patients. In these patients, the hospitalization for COVID-19 was accompanied by a significant [42%] decrease in serum 25(OH)D (from 20.8 ng/mL, range 8.0–52.0 to 12.0 ng/mL, range 4.0–36.0; $P < 0.001$)."

That 25(OH)D is a negative acute phase reactant is *NOT* an argument against protective causality!!!

Calcitriol increases in response to the supply of vitamin D or the demand from PTH to increase serum calcium, and also supports immunity.



Key Markers of Vitamin D Activity

- PTH acts as a signal that the vitamin D/calcium economy is deficient.
- 25(OH)D acts as a marker of the supply of vitamin D.
- 1,25(OH)2D reflects the biological activity of vitamin D.
- Biological activity *may* better be reflected in an index of calculated from 25(OH)D and 1,25(OH)D together, but this is not studied.

In a study of 26 patients in a German ICU, 1,25(OH)2D levels were more associated with clinical outcomes than 25(OH)D levels.

Patients with 1,25-dihydroxyvitamin D below 20 pg/ml tended towards worse PaO_2/FiO_2 ratios, requiring significantly longer mechanical ventilation with higher acute physiology and chronic health evaluation (APACHE) II scores (Table 3). There was a correlation between 1,25-dihydroxyvitamin D levels after 10–15 days and the minimal recorded PaO_2/FiO_2 ratios ($r_s = 0.599$, $p = 0.007$) of the patients. Also 1,25-dihydroxyvitamin D levels and the duration of mechanical ventilation ($r_s = -0.641$, $p = 0.003$) as well as duration of ICU treatment ($r_s = -0.509$, $p = 0.026$) correlated inversely. There was no association between both forms of vitamin D, age, body mass index and parameters of inflammation.

Levels of immune cells and pro- and anti-inflammatory cytokines did not differ as a function of vitamin D levels with the only exception being circulating plasmablasts (Fig. 4). Circulating plasmablasts were significantly higher in patients with 25-hydroxyvitamin D levels ≥30 ng/ml ($p = 0.029$).

Notz, 2021. Vitamin D deficiency in critically ill COVID-19 ARDS patients. Clin Nutr. 2021 Mar 7.

In 348 patients hospitalized in Italy, high PTH was a more important predictor of hypoxemic respiratory failure than low 25(OH)D, but the worst outcomes were in patients with both.

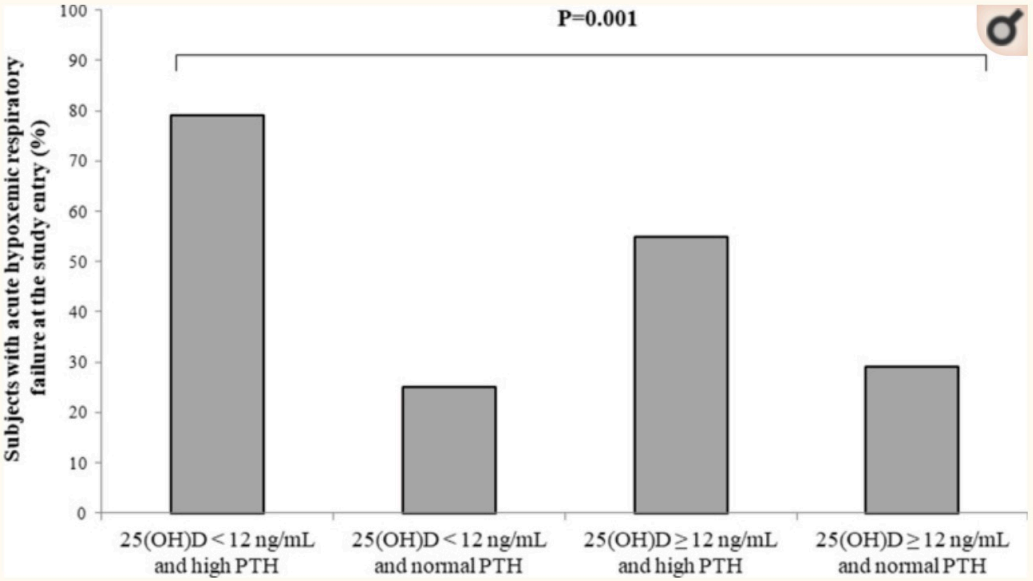


Fig. 1

Prevalence of acute hypoxemic respiratory failure at study entry in 97 patients with COVID-19 stratified for serum 25hydroxy-vitamin D [25(OH)D] and parathyroid hormone (PTH) values

Mazziotti, et al. Vitamin D deficiency, secondary hyperparathyroidism and respiratory insufficiency in hospitalized patients with COVID-19. J Endocrinol Invest. 2021 Mar 5 : 1–9.

chrismasterjohnphd.com/vitamind

Cochrane Library

Cochrane Database of Systematic Reviews

Vitamin D supplementation for the treatment of COVID-19: a living systematic review (Review)

Stroehlein JK, Wallqvist J, Iannizzi C, Mikolajewska A, Metzendorf MI, Benstoem C, Meybohm P, Becker M, Skoetz N, Stegemann M, Piechotta V

Three RCTs were included in the most recent edition of the Cochrane review.

- Entrenas-Castillo (Spain) studied the effect of oral 25(OH)D on ICU admissions and 28-day mortality.
- Murai (Brazil) studied the effect of oral vitamin D on length of hospital stay, ICU admissions, and mortality.
- Rastogi (North India) studied the effect of oral vitamin D on the proportion of asymptomatic or mild cases who tested PCR negative within three weeks.

- Since the Cochrane review was focused on mortality, hospital admissions, severity of disease, and quality of life, Rastogi was largely ignored and the bulk of the review was focused on the opposing results of Entrenas-Castillo and Murai.

The Entrenas-Castillo/Murai Showdown

Entrenas-Castillo (Spain)

- 76 patients treated with hydroxychloroquine, azithromycin, and if needed a broad-spectrum antibiotic, randomized to oral 25(OH)D or control.
- Blinded committee made ICU decisions. Patients and their physicians not blinded but also not told what group they were in.
- Dose was the equivalent of 106,400 IU vitamin D on day 1, 53,200 IU on days 3 and 7, and 53,200 IU weekly thereafter.
- 50% of control and 2% of treatment groups required ICU. Odds of ICU reduced 98%.
- 2 deaths in control group and 0 in treatment group.

Murai (Brazil)

- 240 patients with respiratory distress or comorbidity predictors of severity were randomized to a single dose of 200,000 IU vitamin D or placebo.
- Double-blind.
- No effect on length of hospital stay, ICU admission, or mortality.

The Entrenas-Castillo/Murai Showdown

Entrenas-Castillo (Spain)

- Rated as "of some concerns" for risk of bias.
- Protocol stated that mortality would be measured over 28 days, but publication did not say anything about how long patients were followed up for until death.
- Randomization list was available to "nonmasked specialists" whose roles are not defined in the paper.

Murai (Brazil)

- Rated as "low risk of bias" for all main outcomes.

Differences between the two trials that are not discussed in the Cochrane review.

Entrenas-Castillo (Spain)

- Treatment started on average 7 days from symptom onset and on the day of hospital admission.
- Patients were included on the basis of hospitalization, and none are said to have required oxygen support at baseline.
- Oral 25(OH)D takes 5 hours to maximize blood levels of 25(OH)D.

Murai (Brazil)

- Treatment started on average 10 days from symptom onset and 1.4 days after hospital admission.
- Respiratory distress was a major inclusion criterion, and 90% of subjects were already on supplemental oxygen before they received vitamin D treatment.
- Large doses of vitamin D take ~5 days to maximize blood levels of 25(OH)D (possibly longer in the presence of excessive inflammation).

References on the pharmacokinetics of the two types of supplements:

Jetter et al. Pharmacokinetics of oral vitamin D3 and calcifediol. Bone. 2014 Feb;59:14-9.

Ilahi et al. Pharmacokinetics of a single, large dose of cholecalciferol. Am J Clin Nutr. 2008 Mar;87(3):688-91.

Comments (1)

Mathematical analysis of Córdoba calcifediol trial suggests strong role for Vitamin D in reducing ICU admissions of hospitalized COVID-19 patients

Irwin Jungreis, Manolis Kellis

- Actual P value for ICU is p = 0.00000077. At the time the trial was published there were 500 COVID-19 RCTs, making it likely to find a trial at P<0.002 due to chance and plausible to find one at P<0.001 due to chance, but it is astronomically unlikely to find one at p = 0.00000077 due to chance.
- 25(OH)D was administered by nurses with other medications to patients, and treating physicians had access to electronic medical records that recorded it. Statisticians, data analysts, and ICU decisions were all blinded. For imperfect blinding to be responsible for the statistical significance at P<0.05 requires 100% of patients and doctors to be conscious of treatment group and for this to lead to a 2-fold increase in misallocation to ICU despite neither having direct control over ICU admission.

Broader application of the Entrenas-Castillo protocol supports the results in observational studies.

- When the protocol was authorized at five out of eight hospital wards, among 838 patients treated in the wards, the treatment was associated with 87% fewer ICU admissions and 70% fewer deaths.
- Among 537 patients in five hospitals, 79 received this treatment and it was associated with 78% fewer deaths.

Nogues, et al. Calcifediol treatment and COVID-19-related outcomes. J Clin Endocrinol Metab. 2021 Jun 7

Alcala-Diaz, et al. Calcifediol Treatment and Hospital Mortality Due to COVID-19: A Cohort Study. Nutrients. 2021 May 21;13(6):1760.

Rapid achievement of 50 ng/mL increases viral clearance in asymptomatic and mild cases.

- 40 individuals who tested positive and were either asymptomatic or mild in symptoms were randomized to receive 60,000 IU D3 per day or placebo.
- If the treated subjects reached 50 ng/mL by day 7, the dose was dropped to once a week. If not, the daily dose was continued through day 14.
- The proportion of subjects who achieved PCR negativity at 3 weeks tripled from 20.8% to 62.5%.

Rastogi, et al. Short term, high-dose vitamin D supplementation for COVID-19 disease: a randomised, placebo-controlled, study (SHADE study). Postgrad Med J. 2020 Nov 12

Mexican RCT provides weak evidence of a weak effect of a weak dose of vitamin D.

- 42 mild patients were randomized to 10,000 IU D3/day or control for 14 days, which increased mean 25(OH)D from 20.2 to 28.2 ng/mL and increased the prevalence of >20 ng/mL from 18.2% to 31.2%.
- At 7 days, 0% of supplemented patients and 20 percent of controls had more than 3 symptoms.

	Baseline			7 Days			
Variable	Supplemented Outpatients *n* = 22	Non-supplemented Outpatients *n* = 20	*p*-Value	Supplemented Outpatients *n* = 22	Non-supplemented Outpatients *n* = 20	*p*-Value	Supplemented Outpatients *n* = 22
Presence of symptoms	21 (95.5)	19 (95.0)	1.00	13 (59.1)	9 (45.0)	0.53	14 (63.6)
>1 symptom a	18 (81.8)	18 (90.0)	0.66	5 (22.7)	6 (30.0)	0.43	6 (27.3)
>2 symptoms a	17 (77.3)	15 (75.0)	1.00	2 (9.1)	4 (20.0)	0.28	4 (18.2)
>3 symptoms a	14 (63.6)	13 (65.0)	1.00	0 (0.0)	4 (20.0)	**0.04**	0 (0.0)

Sánchez-Zuno et al. Vitamin D Levels in COVID-19 Outpatients from Western Mexico: Clinical Correlation and Effect of Its Supplementation. J Clin Med. 2021 Jun; 10(11): 2378.

Very weak evidence that 5,000 IU is superior to 1,000 IU in resolving dry cough and loss of taste.

- 69 Saudi Arabian COVID-19 patients with mild symptoms were randomized to receive 1,000 IU or 5,000 IU per day vitamin D for 2 weeks.
- The dry cough resolved 42% faster (6.2 days vs 9.1 days) in the 5,000 IU group, and the loss of taste resolved 33% faster (11.4 days vs 16.9 days)
- However…

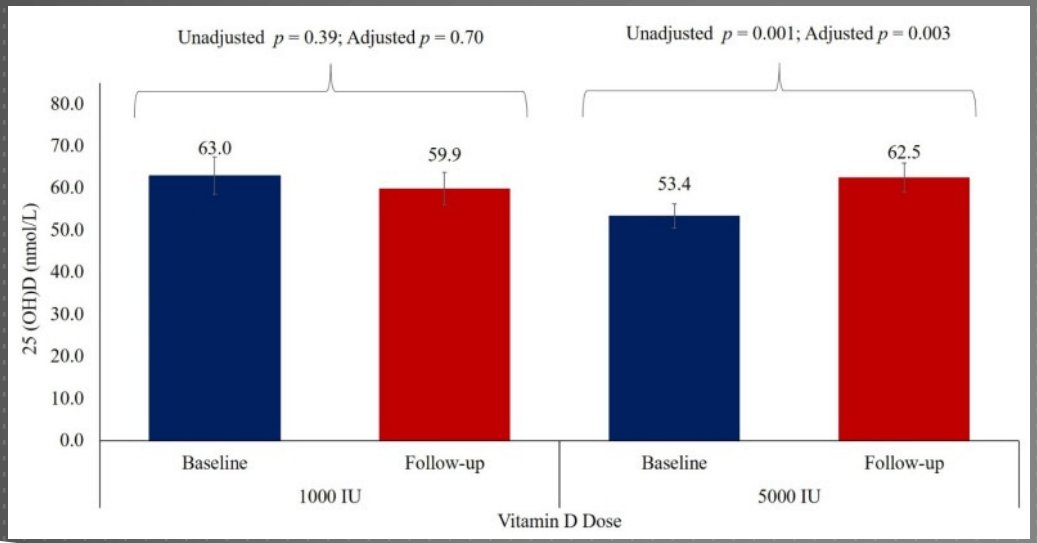


Table 2

Average Days to Resolve Covid-19 Symptoms according to Vitamin D Dose.

Symptoms	1000 IU	5000 IU	*p*-Value
Fever	9.9 ± 1.7	8.5 ± 0.9	0.97
Dyspnea	11.2 ± 1.6	8.9 ± 1.1	0.24
Fatigue	8.9 ± 0.5	7.7 ± 0.8	0.27
Cough	9.1 ± 0.8	6.2 ± 0.8	0.007
Headache	10.6 ± 0.9	8.7 ± 0.8	0.24
GI symptoms	9.7 ± 1.2	7.6 ± 0.7	0.89
Sore throat	9.5 ± 0.6	12.5 ± 0.7	0.15
Body Aches	9.2 ± 0.9	9.6 ± 0.9	0.68
Chills	17.6 ± 1.2	11.2 ± 1.1	0.14
Anosmia	16.3 ± 1.7	11.2 ± 1.1	0.14
Ageusia	16.9 ± 1.7	11.4 ± 1.0	0.035

A study published in Nature Scientific Reports claims to show high-dose D decreases inflammation but actually shows high values regress to the mean.

- 87 subjects in India randomized to 60,000 IU D per day or control. Daily dose given for 8 days if BMI 18-25 and for 10 days if BMI >25.

Variable	Pre (n = 44)		Post (n = 44)		Pre vs Post	
	Mean ± SD or median (IQR)	95% CI of mean/ median	Mean ± SD or median (IQR)	95% CI of mean/ median	t or z statistic	p value
Vit.D (ng/ml)	16 ± 6#	14–17*	89 ± 32#	79–99*	16	< 0.0001
CRP (mg/l)	81 ± 66#	61–101*	16 ± 42#	4–29*	− 6	< 0.0001
LDH (U/l)	369 ± 159#	321–418*	274 ± 115#	240–309*	− 5	< 0.0001
IL6 (pg/ml)	15 (5–57)	9–29	3 (0.9–6)	2–5	4	< 0.0001
Ferritin (ng/ml)	431 (190–836)	262–708	334 (154–508)	203–433	4	0.0004
N/L ratio	5 (3–11)	4–8	3 (2–5)	3–5	4	0.0003

Table 1. Values of various parameters studied in the VD group before and after treatment. *Vit.D* Vitamin D, *CRP* C-reactive protein, *LDH* Lactate dehydrogenase, *Il-6* Interleukin-6, *N/L ratio* Neutrophil/Lymphocyte ratio, *IQR* Interquartile range, #mean ± SD, *95% CI of mean.

Variable	Pre (n = 43)		Post (n = 43)		Pre vs Post	
	Mean ± SD or median (IQR)	95% CI of mean/ median	Mean ± SD or median (IQR)	95% CI of mean/ median	t or z statistic	p value
Vit.D (ng/ml)	17 ± 6#	15–19*	16 ± 7#	14–18*	− 0.1	0.5
CRP (mg/l)	11 (3–43)	5–30	5 (1–9)	2–7	3	0.008
LDH (U/l)	244 (172–298)	189–263	207 (175–251)	190–224	1	0.2
IL6 (pg/ml)	3 (1–9)	1–6	4 (1–11)	1–7	− 0.1	0.9
Ferritin (ng/ml)	169 (63–526)	87–329	196 (54–456)	68–331	2	0.07
N/L ratio	3 (2–5)	2–4	2 (2–4)	2–3	0.3	0.8

Table 2. Values of various parameters studied in the NVD group before and after treatment. *Vit.D* Vitamin D, *CRP* C-reactive protein, *LDH* Lactate dehydrogenase, *Il-6* Interleukin-6, *N/L ratio* Neutrophil/Lymphocyte ratio, *IQR* Interquartile range, #mean ± SD, *95% CI of mean.

Lakkireddy, et al. Impact of daily high dose oral vitamin D therapy on the inflammatory markers in patients with COVID 19 disease. Sci Rep. 2021 May 20;11(1):10641.

Caveats!

- Conclusions may be altered as the 12 additional RCTs completed are published and as the dozens of registered trials are completed and later published.
- Important issues that will unfortunately likely remain neglected are the need to measure PTH and 1,25(OH)2D, and interactions with other important nutrients, especially vitamins A and K, zinc, and magnesium.

Conclusions!

- While the threat of COVID-19 persists, actively maintaining 25(OH)D in the 30-55 ng/mL range is likely to protect against getting infected.
- Maintaining D in this range will also prevent a 5-or-more-day delay in the ability to quickly raise 25(OH)D with vitamin D supplements upon getting sick.
- If the Entrenas-Castillo protocol is converted into daily oral vitamin D3 supplements, it translates to 30,400 IU per day for the first week, followed by a maintenance dose of 7,600 IU per day until symptoms resolve.
- This protocol should be started at the *first* sign of *any possible symptom* and should *not* be delayed until COVID-19 is confirmed. This is needed to raise biological vitamin D activity at the beginning of the infection, rather than waiting until it is a) too late and b) too difficult to raise 25(OH)D in an environment of excessive inflammation.