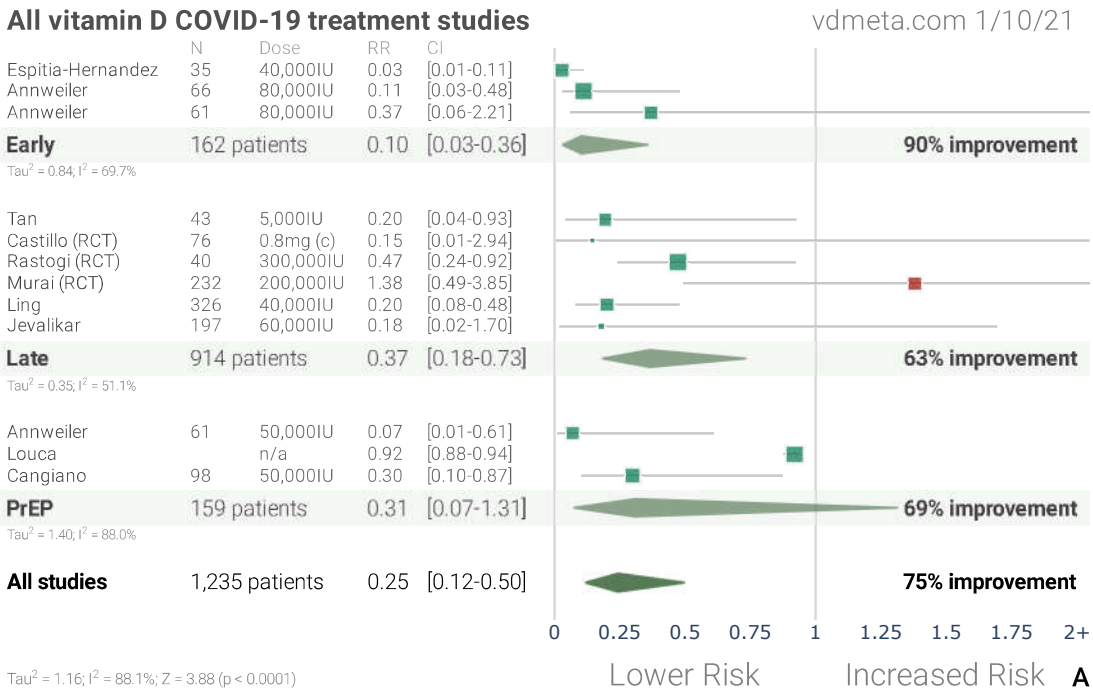
Vitamin D is effective for COVID-19: real-time meta analysis of 37 studies

Covid Analysis, Dec 17, 2020 (Version 9, Jan 10, 2021)
https://vdmeta.com/

- Vitamin D is effective for COVID-19. Random effects meta-analysis of the 12 treatment studies to date shows an estimated reduction of 75% in the effect measured, RR 0.25 [0.12-0.50].
- Sufficiency studies show a strong association between vitamin D sufficiency and outcomes. Meta-analysis of the 25 sufficiency studies shows an estimated reduction of 50%, RR 0.50 [0.41-0.59].

Treatment studies	75% improvement	RR 0.25 [0.12-0.50]
Sufficiency studies	50% improvement	RR 0.50 [0.41-0.59]

Total	37 studies	327 authors	5,876 patients
Treatment	12 studies	126 authors	1,235 patients



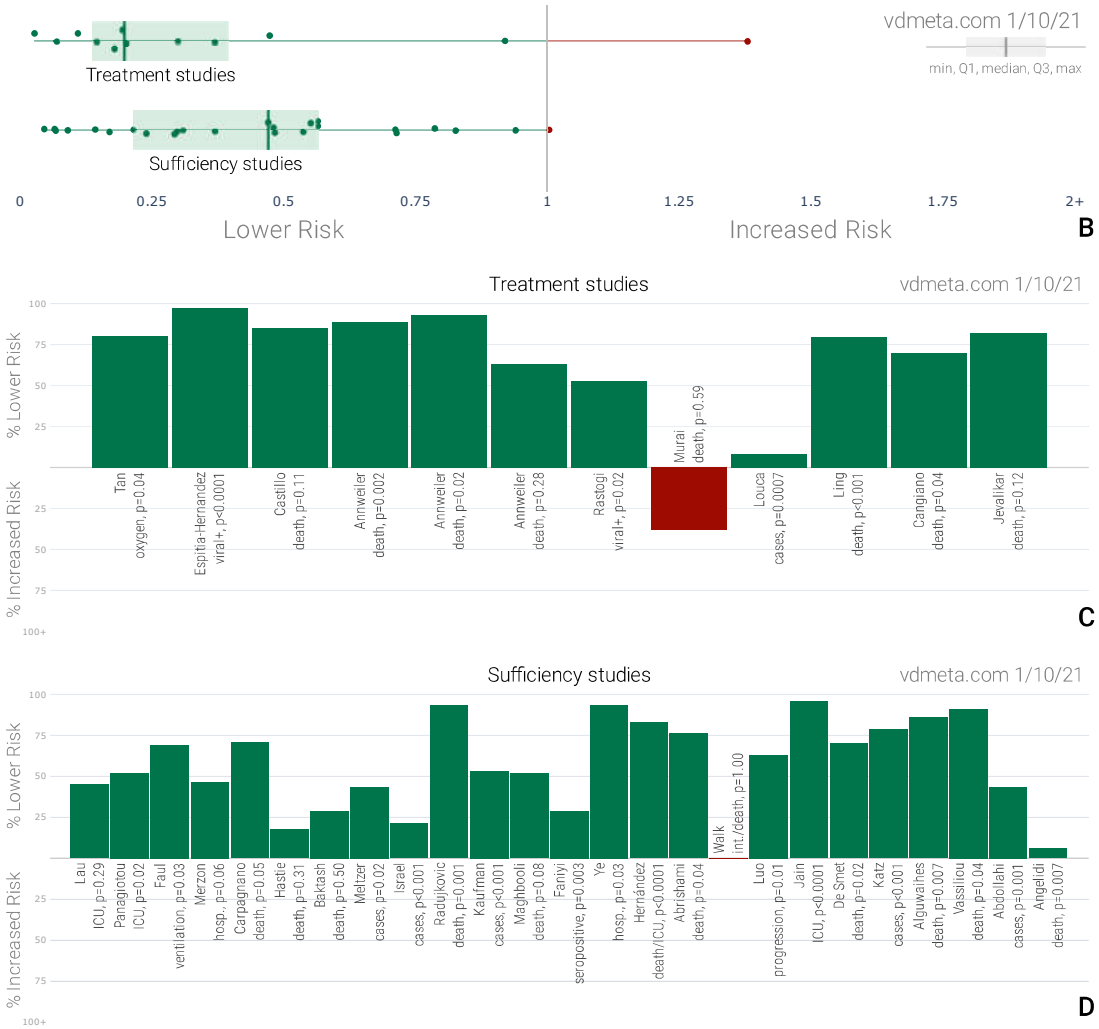


Figure 1. *A. Random effects meta-analysis of treatment studies. Simplified dosages are shown for comparison, these are the total dose in the first five days for treatment, and the monthly dose for prophylaxis. Calcifediol treatment is indicated with (c). For full details see the appendix.* ***B.*** *Scatter plot showing the distribution of effects reported in serum level analysis (sufficiency) studies and treatment studies (the vertical lines and shaded boxes show the median and interquartile range).* ***C and D.*** *Chronological history of all reported effects for treatment studies and sufficiency studies. The 2 studies reporting negative effects both have very low statistical significance.*

Introduction

We analyze all significant studies regarding vitamin D and COVID-19. Search methods, inclusion criteria, effect extraction criteria (more serious outcomes have priority), all individual study data, PRISMA answers, and statistical methods are detailed in Appendix 1. We present random-effects meta-analysis results for studies analyzing outcomes based on sufficiency, for all treatment studies, for mortality results only, and for treatment studies within each treatment stage.

Vitamin D. Vitamin D undergoes two conversion steps before reaching the biologically active form as shown in Figure 2. The first step is conversion to calcidiol, or 25(OH)D, in the liver. The second is conversion to calcitriol, or 1,25(OH)2D, which occurs in the kidneys, the immune system, and elsewhere. Calcitriol is the active, steroid-hormone form of vitamin D, which binds with vitamin D

receptors found in most cells in the body. Vitamin D was first identified in relation to bone health, but is now known to have multiple functions, including an important role in the immune system *[Martens]*. There is a significant delay involved in the conversion from cholecalciferol, therefore calcidiol (calcifediol) may be preferable for treatment.

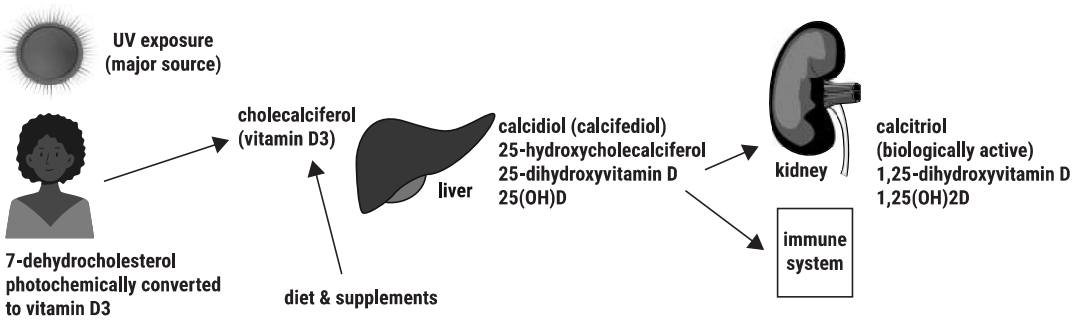


Figure 2. *Simplified view of vitamin D sources and conversion.*

Sufficiency. Many vitamin D studies analyze outcomes based on serum vitamin D levels which may be maintained via sun exposure, diet, or supplementation. We refer to these studies as sufficiency studies, as they typically present outcomes based on vitamin D sufficiency. These studies do not establish a causal link between vitamin D and outcomes. In general, low vitamin D levels are correlated with many other factors that may influence COVID-19 susceptibility and severity. Therefore, beneficial effects found in these studies may be due to factors other than vitamin D. On the other hand, if vitamin D is causally linked to the observed benefits, it is possible that adjustments for correlated factors could obscure this relationship. For these reasons, we analyze sufficiency studies separately from treatment studies.

Treatment. For studies regarding treatment with vitamin D, we distinguish three stages as shown in Figure 3. Pre-Exposure Prophylaxis (PrEP) refers to regularly taking vitamin D before being infected. Early Treatment refers to treatment immediately or soon after symptoms appear, while Late Treatment refers to more delayed treatment.

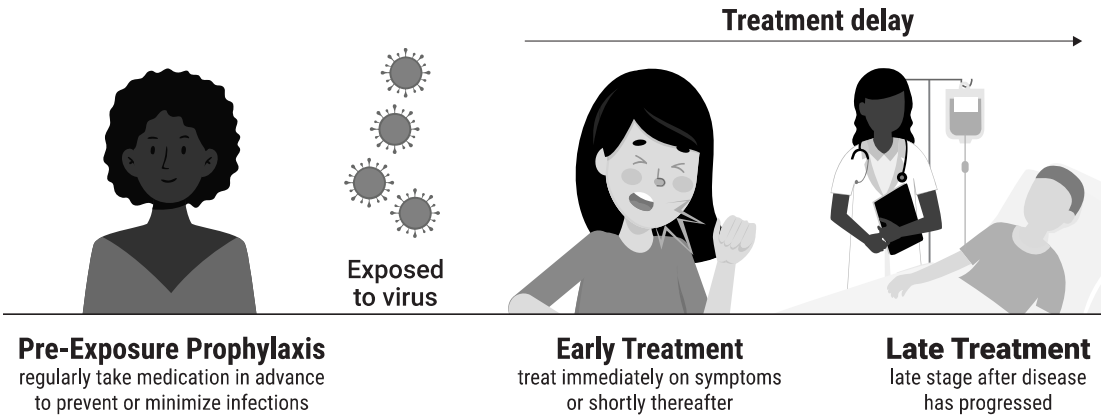


Figure 3. *Treatment stages.*

Results

Figure 1 shows the effects reported in sufficiency studies and treatment studies. Figure 4 and 5 show results by treatment stage. Figure 6 shows a forest plot for random effects meta-analysis of sufficiency studies, while Figure 7 and 8 show forest plots for all treatment studies with pooled effects, and for studies reporting mortality results only. Table 1 summarizes the results.

Study type	Number of studies reporting positive results	Total number of studies	Percentage of studies reporting positive results	Random effects meta-analysis results
Analysis of outcomes based on sufficiency	24	25	**96.0%**	**50%** improvement RR 0.50 [0.41-0.59] p < 0.0001
Early treatment	3	3	**100%**	**90%** improvement RR 0.10 [0.03-0.36] p = 0.00039
Late treatment	5	6	83.3%	**63%** improvement RR 0.37 [0.18-0.73] p = 0.0046
Pre-Exposure Prophylaxis	3	3	**100%**	**69%** improvement RR 0.31 [0.07-1.31] p = 0.11
All treatment studies	11	12	**91.7%**	**75%** improvement RR 0.25 [0.12-0.50] p = 0.00012

Table 1. *Results.*

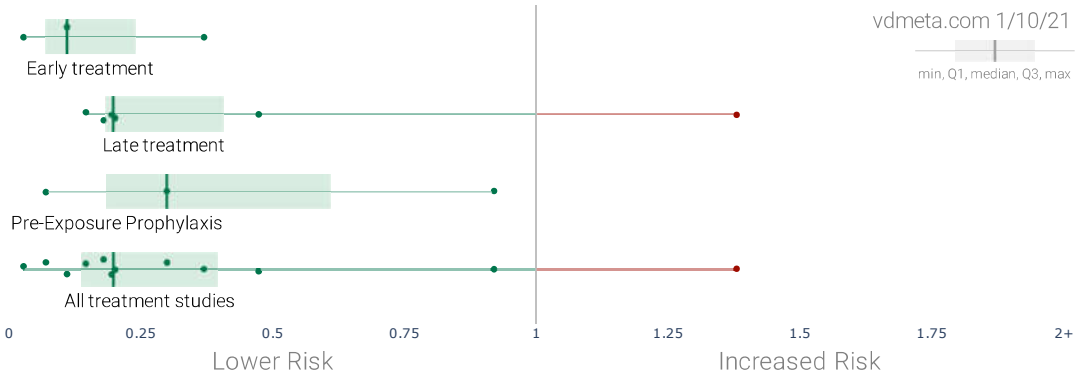


Figure 4. *Results by treatment stage.*

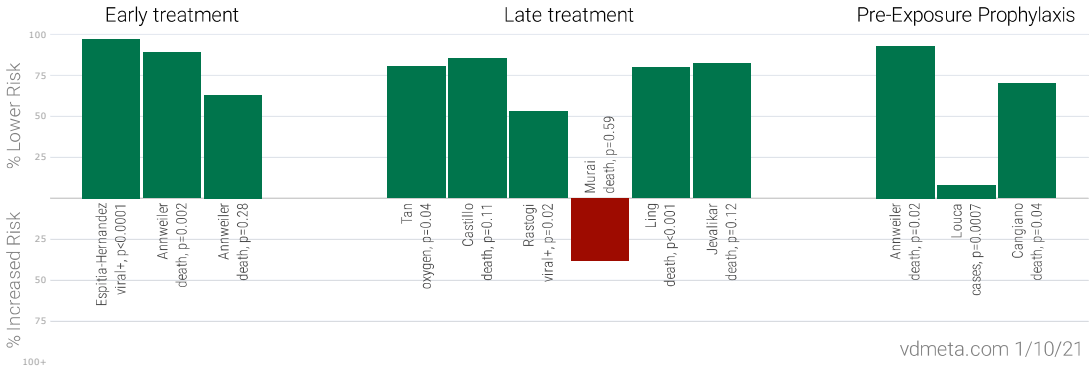


Figure 5. *Results by treatment stage.*

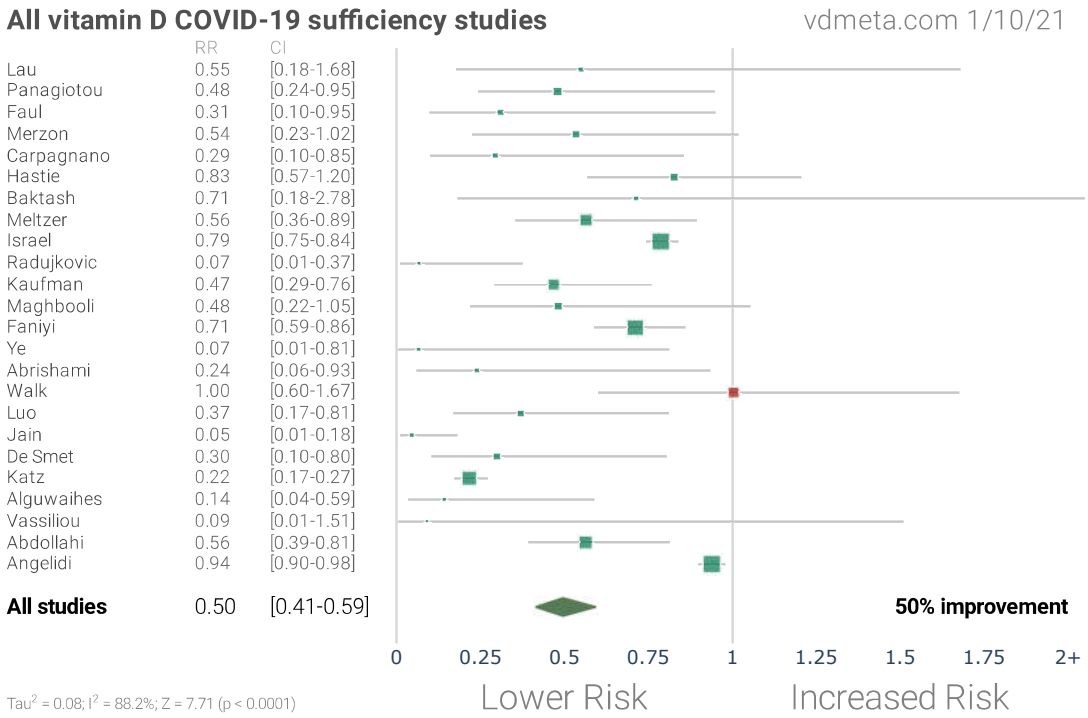


Figure 6. *Random effects meta-analysis for sufficiency studies.*

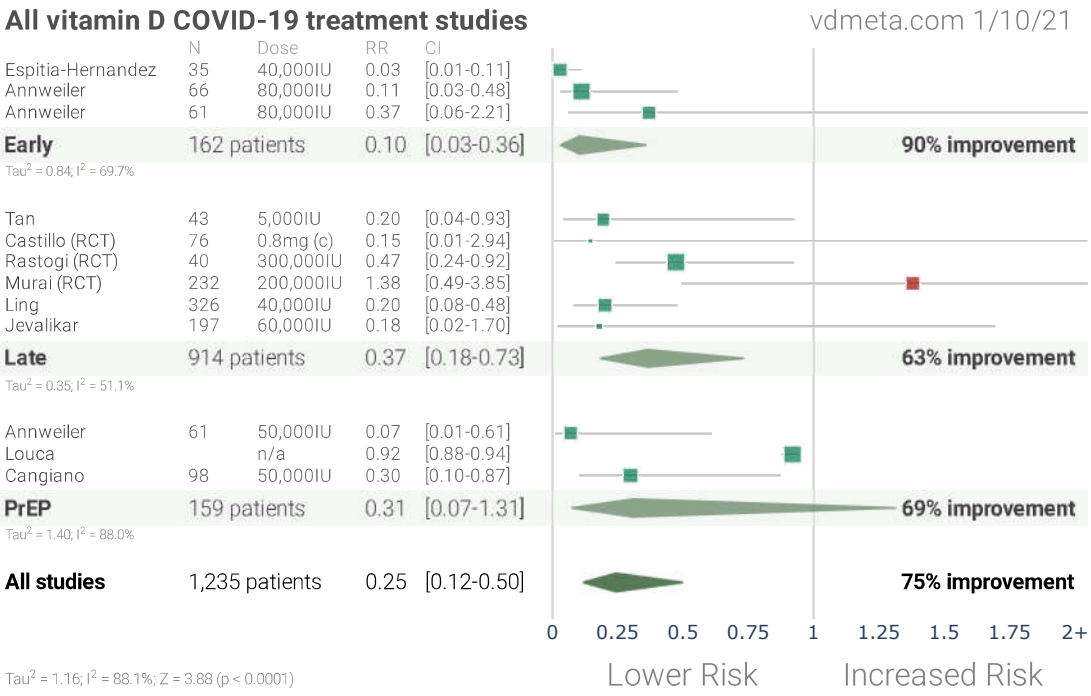


Figure 7. *Random effects meta-analysis for treatment studies.*

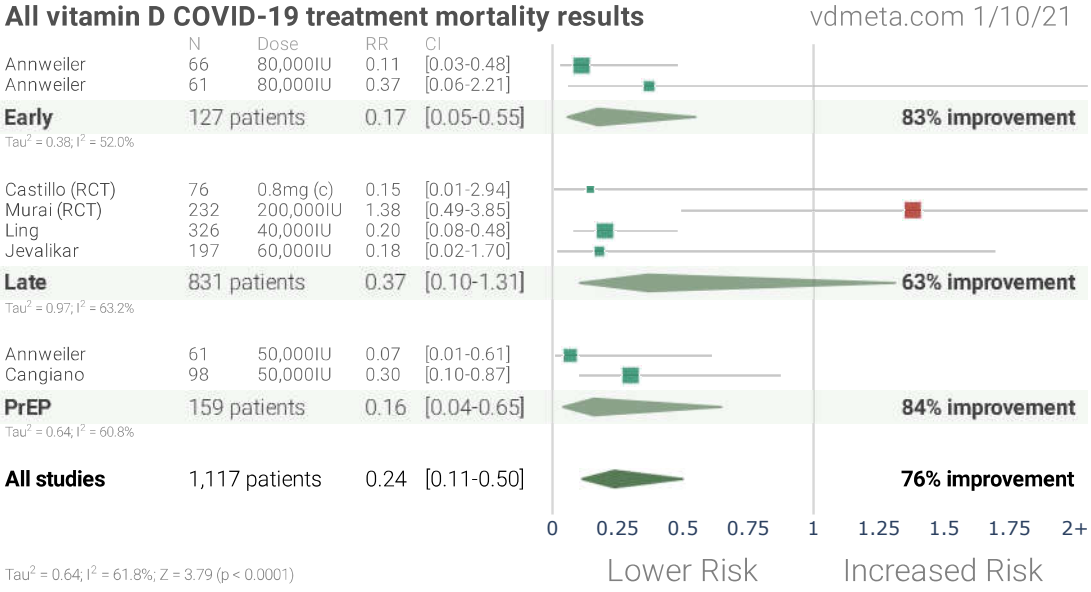


Figure 8. *Random effects meta-analysis for mortality results only.*

Discussion

Typical meta analyses involve subjective selection criteria, effect extraction rules, and study bias evaluation, which can be used to bias results towards a specific outcome. In order to avoid bias we include all studies and use a pre-specified method to extract results from all studies. This provides an overview of all research.

For sufficiency studies, different studies use different levels as the threshold of sufficiency, however 24 of 25 studies present positive effects, the sole exception to date being ***[Walk]***, where the statistical significance of the result is very low.

11 of 12 treatment studies report positive effects. Studies vary significantly in terms of treatment delay, treatment regimen, patients characteristics, and (for the pooled effects analysis) outcomes, as reflected in the high degree of heterogeneity. However treatment consistently shows a significant benefit with the exception of ***[Murai]***. This is a very late stage study (mean 10 days from symptom onset, with 90% on oxygen at baseline), with poorly matched arms in terms of ethnicity, diabetes, and baseline ventilation, all of which favor the control group. Further, this study uses cholecalciferol, which may be especially poorly suited for such a late stage. This result also has very low statistical significance due to the small number of events, and the other reported outcomes of ventilation and ICU admission, which have slightly more events and higher confidence, show benefits for vitamin D. This study is excluded in the analysis in Appendix 2.

Conclusion

Vitamin D is an effective treatment for COVID-19. Random effects meta-analysis of the 12 treatment studies to date results in an estimated reduction of 75% in the effect measured, RR 0.25 [0.12-0.50].

Revisions

This paper is data driven, all graphs and numbers are dynamically generated. We will update the paper as new studies are released or with any corrections. Please submit updates and corrections at https://vdmeta.com/.

12/23: We added ***[Cangiano]***.

12/27: We added the total number of authors and patients.

12/28: We added ***[Jevalikar]***.

12/31: We added additional details about the studies in the appendix.

1/2: We added dosage information and we added the number of patients to the forest plots.

1/5: We added direct links to the study details in the forest plots.

1/7: We added direct links to the study details in the chronological plots.

1/10: We added *[Angelidi]*.

Appendix 1. Methods and Study Results

We performed ongoing searches of PubMed, medRxiv, ClinicalTrials.gov, The Cochrane Library, Google Scholar, Collabovid, Research Square, ScienceDirect, Oxford University Press, the reference lists of other studies and meta-analyses, and submissions to the site c19vitamind.com. Search terms were vitamin D and COVID-19 or SARS-CoV-2. Automated searches are performed every hour with notifications of new matches. All studies that report an effect for vitamin D treatment of COVID-19 patients compared to a control group; and all studies reporting COVID-19 outcomes based on serum vitamin D levels are included. This is a living analysis and is updated regularly.

We extracted effect sizes and associated data from all studies. If studies report multiple kinds of effects then the most serious outcome is used in calculations for that study. For example, if effects for mortality and cases are both reported, the effect for mortality is used, this may be different to the effect that a study focused on. If symptomatic results are reported at multiple times, we used the latest time, for example if mortality results are provided at 14 days and 28 days, the results at 28 days are used. Mortality alone is preferred over combined outcomes. Outcomes with zero events in both arms were not used. Clinical outcome is considered more important than PCR testing status. For PCR results reported at multiple times, where a majority of patients recover in both groups, preference is given to results mid-recovery (after most or all patients have recovered there is no room for an effective treatment to do better). When results provide an odds ratio, we computed the relative risk when possible, or converted to a relative risk according to *[Zhang]*. Reported confidence intervals and *p*-values were used when available, using adjusted values when provided. If multiple types of adjustments are reported including propensity score matching (PSM), the PSM results are used. When needed, conversion between reported *p*-values and confidence intervals followed *[Altman, Altman (B)]*, and Fisher's exact test was used to calculate *p*-values for event data. If continuity correction for zero values is required, we use the reciprocal of the opposite arm with the sum of the correction factors equal to 1 *[Sweeting]*. Results are all expressed with RR < 1.0 suggesting effectiveness. Most results are the relative risk of something negative. If studies report relative times, results are expressed as the ratio of the time for the vitamin D group versus the time for the control group. Calculations are done in Python (3.9.1) with scipy (1.5.4), pythonmeta (1.11), numpy (1.19.4), statsmodels (0.12.1), and plotly (4.14.1). The forest plots are computed using PythonMeta *[Deng]* with the DerSimonian and Laird random effects model (the fixed effect assumption is not plausible in this case). We received no funding, this research is done in our spare time. We have no affiliations with any pharmaceutical companies or political parties.

We have classified studies as early treatment if most patients are not already at a severe stage at the time of treatment, and treatment started within 5 days after the onset of symptoms, although a shorter time may be preferable.

A summary of study results is below. It is easy to propose excluding certain papers for various reasons. To avoid potential bias in evaluation we currently include all studies.

Please submit updates and corrections at https://vdmeta.com/.

Analysis of outcomes based on sufficiency

Effect extraction follows pre-specified rules as detailed above and gives priority to more serious outcomes. Only the first (most serious) outcome is used in calculations, which may differ from the effect a paper focuses on.

[Abdollahi], 12/12/2020, retrospective, Iran, Middle East, peer-reviewed, 7 authors.	**risk of COVID-19 case, RR 0.56, p = 0.001**, treatment 39, control 162, >30ng/ml.
[Abrishami], 10/30/2020, retrospective, Iran, Middle East, peer-reviewed, mean age 55.2, 7 authors.	**risk of death, RR 0.24, p = 0.04**, treatment 3 of 47 (6.4%), control 9 of 26 (34.6%), adjusted per study, >25ng/mL.
[Alguwaihes], 12/5/2020, retrospective, Saudi Arabia, Middle East, peer-reviewed, 10 authors.	**risk of death, RR 0.14, p = 0.007**, treatment 111, control 328, >12.5 nmol/L.
[Angelidi], 1/9/2021, retrospective, USA, North America, peer-reviewed, 8 authors.	**risk of death, RR 0.94, p = 0.007**, treatment 72, control 72, adjusted per study, >30ng/mL multivariable analysis.
[Baktash], 8/27/2020, prospective, United Kingdom, Europe, peer-reviewed, 8 authors.	**risk of death, RR 0.71, p = 0.50**, treatment 4 of 31 (12.9%), control 6 of 39 (15.4%), adjusted per study, >30nmol/L.
[Carpagnano], 8/9/2020, retrospective, Italy, Europe, peer-reviewed, 10 authors.	**risk of death at day 26, RR 0.29, p = 0.05**, treatment 5 of 34 (14.7%), control 4 of 8 (50.0%), >30 ng/mL.
	risk of death at day 10, RR 0.10, p = 0.02, treatment 2 of 34 (5.9%), control 4 of 8 (50.0%), adjusted per study, >30 ng/mL.
[De Smet], 11/25/2020, retrospective, Belgium, Europe, peer-reviewed, 5 authors.	**risk of death, RR 0.30, p = 0.02**, treatment 7 of 77 (9.1%), control 20 of 109 (18.3%), adjusted per study, odds ratio converted to relative risk, >20ng/mL.
[Faniyi], 10/6/2020, prospective, United Kingdom, Europe, preprint, 10 authors.	**risk of seropositive, RR 0.71, p = 0.003**, treatment 170 of 331 (51.4%), control 44 of 61 (72.1%), >30nmol/L.
[Faul], 6/30/2020, retrospective, Ireland, Europe, peer-reviewed, 9 authors.	**risk of ventilation, RR 0.31, p = 0.03**, treatment 4 of 21 (19.0%), control 8 of 12 (66.7%), adjusted per study, >30nmol/L.
[Hastie], 8/26/2020, retrospective, database analysis, United Kingdom,	**risk of death, RR 0.83, p = 0.31**, adjusted per study, >25nmol/L.

Europe, peer-reviewed, 14 authors.	
	risk of hospitalization, RR 0.91, p = 0.40, adjusted per study, >25nmol/L.
[Hernández], 10/27/2020, retrospective, Spain, Europe, peer-reviewed, 12 authors.	**risk of combined death/ICU, RR 0.17, p < 0.001**, >= 20ng/mL risk of hospitalization * risk of death/ICU/ventilation | hospitalization.
	risk of combined death/ICU, RR 0.88, p = 0.86, treatment 216, control 197, >= 20ng/mL risk of death/ICU/ventilation | hospitalization.
	risk of hospitalization, RR 0.19, p < 0.001, >= 20ng/mL.
[Israel], 9/10/2020, retrospective, Israel, Middle East, preprint, 8 authors.	**risk of COVID-19 case, RR 0.79, p < 0.001**, treatment 2601 of 32712 (8.0%), control 5011 of 39485 (12.7%), adjusted per study, odds ratio converted to relative risk, multivariable >75 nmol/L vs. <30 nmol/L.
[Jain], 11/19/2020, prospective, India, South Asia, peer-reviewed, 6 authors.	**risk of ICU admission, RR 0.05, p < 0.001**, treatment 2 of 64 (3.1%), control 61 of 90 (67.8%), >20ng/mL.
[Katz], 12/4/2020, retrospective, USA, North America, peer-reviewed, 3 authors.	**risk of COVID-19 case, RR 0.22, p < 0.001**, adjusted per study.
[Kaufman], 9/17/2020, retrospective, USA, North America, peer-reviewed, median age 54.0, 5 authors.	**risk of COVID-19 case, RR 0.47, p < 0.001**, treatment 12321, control 39190, >55 ng/mL vs. <20 ng/mL.
[Lau], 4/28/2020, retrospective, USA, North America, preprint, 7 authors.	**risk of ICU admission, RR 0.55, p = 0.29**, treatment 2 of 5 (40.0%), control 11 of 15 (73.3%), >30ng/mL.
[Luo], 11/13/2020, retrospective, China, Asia, peer-reviewed, median age 56.0, 5 authors.	**risk of disease progression, RR 0.37, p = 0.01**, treatment 335, control 560, >30nmol/L.
[Maghbooli], 9/25/2020, retrospective, Iran, West Asia, peer-reviewed, 11 authors.	**risk of death, RR 0.48, p = 0.08**, treatment 7 of 72 (9.7%), control 27 of 134 (20.1%), age >40.
	risk of ventilation, RR 0.68, p = 0.49, treatment 6 of 77 (7.8%), control 18 of 158 (11.4%).
	risk of ICU admission, RR 0.68, p = 0.33, treatment 11 of 77 (14.3%), control 33 of 158 (20.9%), >30nmol/L.
[Meltzer], 9/3/2020, retrospective, USA, North America, peer-reviewed, 6 authors.	**risk of COVID-19 case, RR 0.56, p = 0.02**, treatment 39 of 317 (12.3%), control 32 of 172 (18.6%), adjusted per study, >20ng/mL.

[Merzon], 7/23/2020, retrospective, Israel, Middle East, peer-reviewed, 3 authors.	**risk of hospitalization, RR 0.54, p = 0.06**, treatment 79, control 703, odds ratio converted to relative risk, >30ng/mL.
	risk of COVID-19 case, RR 0.72, p < 0.001, treatment 1139, control 6668, odds ratio converted to relative risk, >30ng/mL.
[Panagiotou], 6/30/2020, retrospective, United Kingdom, Europe, peer-reviewed, 12 authors.	**risk of ICU admission, RR 0.48, p = 0.02**, treatment 8 of 44 (18.2%), control 34 of 90 (37.8%), >50nmol/L.
[Radujkovic], 9/10/2020, prospective, Germany, Europe, peer-reviewed, 6 authors.	**risk of death, RR 0.07, p = 0.001**, treatment 144, control 12, >30nmol/L.
	risk of combined intubation/death, RR 0.16, p < 0.001, treatment 144, control 12, >30nmol/L.
[Vassiliou], 12/9/2020, prospective, Greece, Europe, peer-reviewed, 6 authors.	**risk of death, RR 0.09, p = 0.04**, treatment 0 of 15 (0.0%), control 5 of 15 (33.3%), >15.2ng/mL.
[Walk], 11/9/2020, retrospective, Netherlands, Europe, preprint, 5 authors.	**risk of combined intubation/death, RR 1.00, p = 1.00**, treatment 48 of 110 (43.6%), control 10 of 23 (43.5%), >25nmol/L.
[Ye], 10/13/2020, retrospective, China, Asia, peer-reviewed, 18 authors.	**risk of severe/critical COVID-19, RR 0.07, p = 0.03**, treatment 2 of 36 (5.6%), control 8 of 26 (30.8%), adjusted per study, >50nmol/L.

Early treatment

Effect extraction follows pre-specified rules as detailed above and gives priority to more serious outcomes. Only the first (most serious) outcome is used in calculations, which may differ from the effect a paper focuses on.

[Annweiler], 11/2/2020, retrospective, France, Europe, peer-reviewed, 7 authors, dosage 80,000IU single dose.	**risk of death, RR 0.37, p = 0.28**, treatment 2 of 29 (6.9%), control 10 of 32 (31.2%), adjusted per study, supplementation after diagnosis.
[Annweiler (B)], 10/13/2020, retrospective, France, Europe, peer-reviewed, mean age 87.7, 6 authors, dosage 80,000IU single dose, 80,000IU either in the week following the suspicion or diagnosis of COVID-19, or during the previous month.	**risk of death, RR 0.11, p = 0.002**, treatment 10 of 57 (17.5%), control 5 of 9 (55.6%), adjusted per study.
[Espitia-Hernandez], 8/15/2020, retrospective, Mexico, North America, peer-reviewed, 5 authors, dosage 8,000IU daily, 4000IU twice daily for 30 days.	**risk of viral+ at day 10, RR 0.03, p < 0.001**, treatment 0 of 28 (0.0%), control 7 of 7 (100.0%), treatment also with IVM and AZ.

Late treatment

Effect extraction follows pre-specified rules as detailed above and gives priority to more serious outcomes. Only the first (most serious) outcome is used in calculations, which may differ from the effect a paper focuses on.

[Castillo], 8/29/2020, Randomized Controlled Trial, Spain, Europe, peer-reviewed, 7 authors, dosage calcifediol 0.5mg day 1, 0.27mg day 3, 0.27mg day 7, and then weekly until discharge or ICU admission.	**risk of death, RR 0.15, p = 0.11**, treatment 0 of 50 (0.0%), control 2 of 26 (7.7%).
	risk of ICU admission, RR 0.06, p = 0.001, odds ratio converted to relative risk.
[Jevalikar], 12/28/2020, prospective, India, South Asia, preprint, 8 authors, dosage 60,000IU single dose, median total dose.	**risk of death, RR 0.18, p = 0.12**, treatment 1 of 128 (0.8%), control 3 of 69 (4.3%).
	risk of ICU admission, RR 0.66, p = 0.29, treatment 16 of 128 (12.5%), control 13 of 69 (18.8%).
	risk of oxygen therapy, RR 0.68, p = 0.06, treatment 38 of 128 (29.7%), control 30 of 69 (43.5%).
[Ling], 12/11/2020, retrospective, United Kingdom, Europe, peer-reviewed, 7 authors, dosage 40,000IU weekly, regimen varied with 77% receiving a total of 40,000IU/week.	**risk of death, RR 0.20, p < 0.001**, treatment 73, control 253, odds ratio converted to relative risk, primary cohort.
	risk of death, RR 0.44, p = 0.02, treatment 80, control 443, odds ratio converted to relative risk, validation cohort.
[Murai], 11/17/2020, Randomized Controlled Trial, Brazil, South America, preprint, 17 authors, dosage 200,000IU single dose.	**risk of death, RR 1.38, p = 0.59**, treatment 8 of 114 (7.0%), control 6 of 118 (5.1%).
	risk of ventilation, RR 0.49, p = 0.09, treatment 8 of 114 (7.0%), control 17 of 118 (14.4%).
	risk of ICU admission, RR 0.75, p = 0.31, treatment 18 of 114 (15.8%), control 25 of 118 (21.2%).
[Rastogi], 11/12/2020, Randomized Controlled Trial, India, South Asia, peer-reviewed, 8 authors, dosage 60,000IU days 1-7.	**risk of no virological cure, RR 0.47, p = 0.02**, treatment 6 of 16 (37.5%), control 19 of 24 (79.2%).
[Tan], 6/10/2020, retrospective, Singapore, Asia, peer-reviewed, 14 authors, dosage 1,000IU daily.	**risk of oxygen therapy, RR 0.20, p = 0.04**, treatment 3 of 17 (17.6%), control 16 of 26 (61.5%), adjusted per study.

Pre-Exposure Prophylaxis

Effect extraction follows pre-specified rules as detailed above and gives priority to more serious outcomes. Only the first (most serious) outcome is used in calculations, which may differ from the

effect a paper focuses on.

[Annweiler (C)], 11/2/2020, retrospective, France, Europe, peer-reviewed, 7 authors, dosage 50,000IU monthly, dose varies - 50,000 IU/month, or 80,000IU/100,000IU every 2–3 months.	**risk of death, RR 0.07, $p = 0.02$**, treatment 2 of 29 (6.9%), control 10 of 32 (31.2%), adjusted per study, regular bolus supplementation.
[Cangiano], 12/22/2020, retrospective, Italy, Europe, peer-reviewed, 14 authors, dosage 25,000IU 2x per month.	**risk of death, RR 0.30, $p = 0.04$**, treatment 3 of 20 (15.0%), control 39 of 78 (50.0%).
[Louca], 11/30/2020, retrospective, United Kingdom, Europe, preprint, 26 authors, dosage not specified.	**risk of COVID-19 case, RR 0.92, $p < 0.001$**, United Kingdom.
	risk of COVID-19 case, RR 0.76, $p < 0.001$, treatment 19444, control 26313, United States.
	risk of COVID-19 case, RR 0.81, $p < 0.001$, treatment 6722, control 20651, Sweden.

Appendix 2. Analysis with Exclusions

To avoid bias in the selection of studies, we include all studies in the main analysis. Here we show the results after excluding studies with critical bias likely to alter results. The aim here is not to exclude studies on technicalities, but to exclude studies that clearly have major issues that may significantly change the outcome. The studies excluded are as follows, and the resulting forest plot is shown in Figure 9.

[Murai], >50% on oxygen/ventilation at baseline.

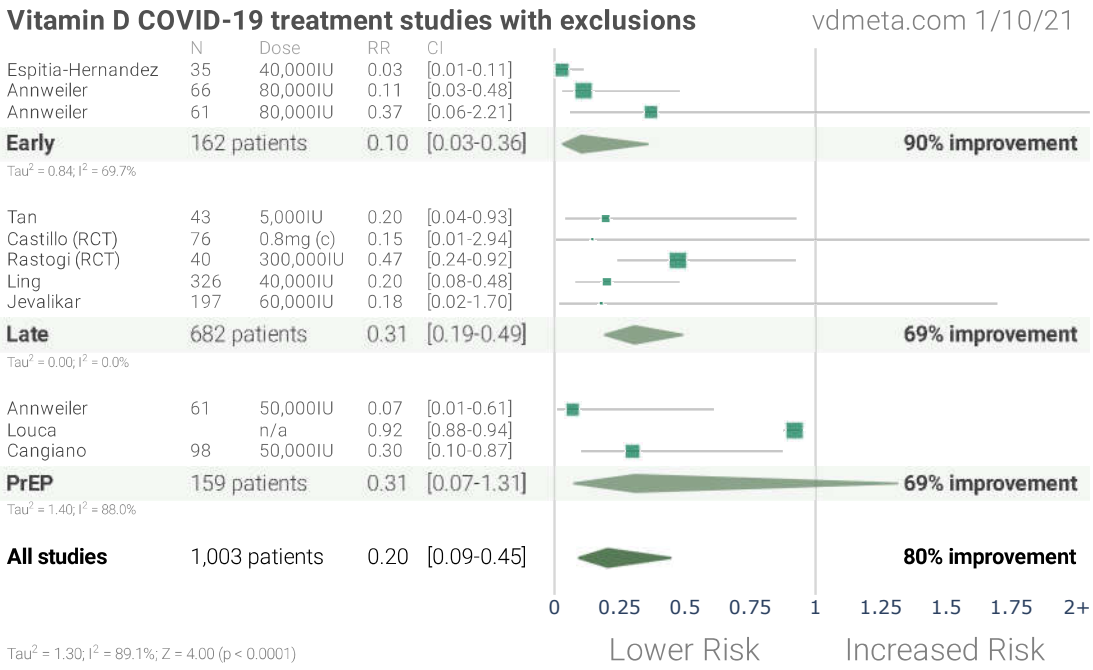


Figure 9. *Forest plot (random effects model) excluding studies with significant issues. (ES) indicates the early treatment subset of a study (these are not included in the overall results).*

References

1. **Abdollahi** et al., Journal of Medical Virology, doi:10.1002/jmv.26726, *The Association Between the Level of Serum 25(OH) Vitamin D, Obesity, and underlying Diseases with the risk of Developing COVID-19 Infection: A case-control study of hospitalized patients in Tehran, Iran*, https://onlinelibrary.wiley.com/doi/abs/10.1002/jmv.26726.

2. **Abrishami** et al., European Journal of Nutrition, doi:10.1007/s00394-020-02411-0, *Possible association of vitamin D status with lung involvement and outcome in patients with COVID-19: a retrospective study*, https://link.springer.com/article/10.1007%2Fs00394-020-02411-0.

3. **Alguwaihes** et al., Cardiovascular Diabetology, doi:10.1186/s12933-020-01184-4, *Diabetes and Covid-19 among hospitalized patients in Saudi Arabia: a single-centre retrospective study*, https://link.springer.com/article/10.1186/s12933-020-01184-4.

4. **Altman**, D., BMJ, doi:10.1136/bmj.d2304, *How to obtain the P value from a confidence interval*, https://www.bmj.com/content/343/bmj.d2304.

5. **Altman (B)** et al., BMJ, doi:10.1136/bmj.d2090, *How to obtain the confidence interval from a P value*, https://www.bmj.com/content/343/bmj.d2090.

6. **Angelidi** et al., Mayo Clinic Proceedings, doi:10.1016/j.mayocp.2021.01.001, *Vitamin D Status is Associated With In-hospital Mortality and Mechanical Ventilation: A Cohort of COVID-19 Hospitalized Patients*, https://www.sciencedirect.com/scie../article/abs/pii/S002561962100001X.

7. **Annweiler** et al., Nutrients, doi:10.3390/nu12113377, *Vitamin D Supplementation Associated to Better Survival in Hospitalized Frail Elderly COVID-19 Patients: The GERIA-COVID Quasi-Experimental Study*, https://www.mdpi.com/2072-6643/12/11/3377.

8. **Annweiler (B)** et al., The Journal of Steroid Biochemistry and Molecular Biology,

doi:10.1016/j.jsbmb.2020.105771, *Vitamin D and survival in COVID-19 patients: A quasi-experimental study*, https://www.sciencedirect.com/science/article/pii/S096007602030296X.

9. **Annweiler (C)** et al., Nutrients, doi:10.3390/nu12113377, *Vitamin D Supplementation Associated to Better Survival in Hospitalized Frail Elderly COVID-19 Patients: The GERIA-COVID Quasi-Experimental Study*, https://www.mdpi.com/2072-6643/12/11/3377.

10. **Baktash** et al., Postgraduate Medical Journal, doi:10.1136/postgradmedj-2020-138712, *Vitamin D status and outcomes for hospitalised older patients with COVID-19*, https://pmj.bmj.com/content/early/../06/postgradmedj-2020-138712?rss=1.

11. **Cangiano** et al., Aging, doi:10.18632/aging.202307, *Mortality in an Italian nursing home during COVID-19 pandemic: correlation with gender, age, ADL, vitamin D supplementation, and limitations of the diagnostic tests*, https://www.aging-us.com/article/202307/text.

12. **Carpagnano** et al., J. Endocrinol. Invest., 2020, Aug 9, 1-7, doi:10.1007/s40618-020-01370-x, *Vitamin D deficiency as a predictor of poor prognosis in patients with acute respiratory failure due to COVID-19*, https://link.springer.com/article/10.1007/s40618-020-01370-x.

13. **Castillo** et al., Journal of Steroid Biochemistry and Molecular Biology, 203, October 2020, doi:10.1016/j.jsbmb.2020.105751, *Effect of calcifediol treatment and best available therapy versus best available therapy on intensive care unit admission and mortality among patients hospitalized for COVID-19: A pilot randomized clinical study*, https://www.sciencedirect.com/science/article/pii/S0960076020302764.

14. **De Smet** et al., American Journal of Clinical Pathology, doi:10.1093/ajcp/aqaa252, *Serum 25(OH)D Level on Hospital Admission Associated With COVID-19 Stage and Mortality*, https://academic.oup.com/ajcp/adva..e/doi/10.1093/ajcp/aqaa252/6000689.

15. **Deng**, H., *PyMeta, Python module for meta-analysis*, http://www.pymeta.com/.

16. **Espitia-Hernandez** et al., Biomedical Research, 31:5, *Effects of Ivermectin-azithromycin-cholecalciferol combined therapy on COVID-19 infected patients: A proof of concept study*, https://www.biomedres.info/biomedi..-proof-of-concept-study-14435.html.

17. **Faniyi** et al., medRxiv, doi:10.1101/2020.10.05.20206706, *Vitamin D status and seroconversion for COVID-19 in UK healthcare workers who isolated for COVID-19 like symptoms during the 2020 pandemic*, https://www.medrxiv.org/content/10.1101/2020.10.05.20206706v1.

18. **Faul** et al., Irish Medical Journal, 113:5, 84, *Vitamin D Deficiency and ARDS after SARS-CoV-2 Infection*, http://imj.ie/vitamin-d-deficiency..d-ards-after-sars-cov-2-infection/.

19. **Hastie** et al., Diabetes and Metabolic Syndrome: Clinical Research and Reviews, 14:4, 561–565, doi:10.1016/j.dsx.2020.04.050, *Vitamin D concentrations and COVID-19 infection in UK Biobank*, https://www.sciencedirect.com/scie../article/abs/pii/S1871402120301156.

20. **Hernández** et al., The Journal of Clinical Endocrinology & Metabolism, doi:10.1210/clinem/dgaa733, *Vitamin D Status in Hospitalized Patients with SARS-CoV-2 Infection*, https://academic.oup.com/jcem/adva..doi/10.1210/clinem/dgaa733/5934827.

21. **Israel** et al., medRxiv, doi:https://www.medrxiv.org/content/10.1101/2020.09.04.20188268v1, *The link between vitamin D deficiency and Covid-19 in a large population*, https://www.medrxiv.org/content/10.1101/2020.09.04.20188268v1.

22. **Jain** et al., Nature, doi:10.1038/s41598-020-77093-z, *Analysis of vitamin D level among asymptomatic and critically ill COVID-19 patients and its correlation with inflammatory markers*, https://www.nature.com/articles/s41598-020-77093-z.

23. **Jevalikar** et al., Research Square, doi:10.21203/rs.3.rs-129238/v1, *Lack of Association of Baseline 25-Hydroxyvitamin D Levels and Cholecalciferol Treatment With Disease Severity and Mortality in Indian Patients Hospitalized for Covid-19*, https://www.researchsquare.com/article/rs-129238/v1.

24. **Katz** el al., Nutrition, doi:10.1016/j.nut.2020.111106, *Increased risk for Covid-19 in patients with Vitamin D deficiency*, https://www.sciencedirect.com/science/article/pii/S0899900720303890.

25. **Kaufman** et al., PLOS One, doi:10.1371/journal.pone.0239252, *SARS-CoV-2 positivity rates associated with circulating 25-hydroxyvitamin D levels*, https://journals.plos.org/plosone/..le?id=10.1371/journal.pone.0239252.

26. **Lau** et al., medRxiv, doi:10.1101/2020.04.24.20075838, *Vitamin D Insufficiency is Prevalent in Severe COVID-19*, https://www.medrxiv.org/content/10.1101/2020.04.24.20075838v1.

27. **Ling** et el., Nutrients, doi:10.3390/nu12123799, *High-Dose Cholecalciferol Booster Therapy is Associated with a Reduced Risk of Mortality in Patients with COVID-19: A Cross-Sectional Multi-Centre Observational Study*, https://www.mdpi.com/2072-6643/12/12/3799.

28. **Louca** et al., medRxiv, doi:10.1101/2020.11.27.20239087, *Dietary supplements during the COVID-19 pandemic: insights from 1.4M users of the COVID Symptom Study app - a longitudinal app-based community survey*, https://www.medrxiv.org/content/10.1101/2020.11.27.20239087v1.

29. **Luo** et al., The Journal of Nutrition, doi:10.1093/jn/nxaa332, *Vitamin D Deficiency Is Inversely Associated with COVID-19 Incidence and Disease Severity in Chinese People*, https://academic.oup.com/jn/advanc..cle /doi/10.1093/jn/nxaa332/5981721.

30. **Maghbooli** et al., PLOS One, doi:10.1371/journal.pone.0239799, *Vitamin D sufficiency, a serum 25-hydroxyvitamin D at least 30 ng/mL reduced risk for adverse clinical outcomes in patients with COVID-19 infection*, https://journals.plos.org/plosone/..le?id=10.1371/journal.pone.0239799.

31. **Martens** et al., Nutrients, doi:10.3390/nu12051248, *Vitamin D's Effect on Immune Function*, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7281985/.

32. **McLean** et al., Open Forum Infect. Dis. September 2015, 2:3, doi:10.1093/ofid/ofv100, *Impact of Late Oseltamivir Treatment on Influenza Symptoms in the Outpatient Setting: Results of a Randomized Trial*, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4525010/.

33. **Meltzer** et al., JAMA network open, 3:9, doi:10.1001/jamanetworkopen.2020.19722, *Association of Vitamin D Status and Other Clinical Characteristics With COVID-19 Test Results*, https://jamanetwork.com/journals /jamanetworkopen/fullarticle/2770157.

34. **Merzon** et al., The FEBS Journal, doi:doi.org/10.1111/febs.15495, *Low plasma 25(OH) vitamin D level is associated with increased risk of COVID-19 infection: an Israeli population-based study*, https://febs.onlinelibrary.wiley.com/doi/full/10.1111/febs.15495.

35. **Murai** et al., medRxiv, doi:10.1101/2020.11.16.20232397, *Effect of Vitamin D3 Supplementation vs Placebo on Hospital Length of Stay in Patients with Severe COVID-19: A Multicenter, Double-blind, Randomized Controlled Trial*, https://www.medrxiv.org/content/10.1101/2020.11.16.20232397v1.

36. **Panagiotou** et al., medRxiv, doi:10.1101/2020.06.21.20136903, *Low serum 25-hydroxyvitamin D (25[OH]D) levels in patients hospitalised with COVID-19 are associated with greater disease severity: results of a local audit of practice*, https://www.medrxiv.org/content/10.1101/2020.06.21.20136903v2.

37. **Radujkovic** et al., Nutrients 2020, 12:9, 2757, doi:10.3390/nu12092757, *Vitamin D Deficiency and Outcome of COVID-19 Patients*, https://www.mdpi.com/2072-6643/12/9/2757/htm.

38. **Rastogi** et al., Postgraduate Medical Journal, doi:10.1136/postgradmedj-2020-139065, *Short term, high-dose vitamin D supplementation for COVID-19 disease: a randomised, placebo-controlled, study (SHADE study)*,

https://pmj.bmj.com/content/early/..1/12/postgradmedj-2020-139065.full.

39. **Sweeting** et al., Statistics in Medicine, doi:10.1002/sim.1761, *What to add to nothing? Use and avoidance of continuity corrections in meta-analysis of sparse data*, https://onlinelibrary.wiley.com/doi/10.1002/sim.1761.

40. **Tan** et al., Nutrition, doi:10.1016/j.nut.2020.111017, *Cohort study to evaluate the effect of combination Vitamin D, Magnesium and Vitamin B12 (DMB) on progression to severe outcome in older COVID-19 patients*, https://www.sciencedirect.com/science/article/pii/S0899900720303002.

41. **Treanor** et al., JAMA, 2000, 283:8, 1016-1024, doi:10.1001/jama.283.8.1016, *Efficacy and Safety of the Oral Neuraminidase Inhibitor Oseltamivir in Treating Acute Influenza: A Randomized Controlled Trial*, https://jamanetwork.com/journals/jama/fullarticle/192425.

42. **Vassiliou** et al., Nutrients, doi:10.3390/nu12123773, *Low 25-Hydroxyvitamin D Levels on Admission to the Intensive Care Unit May Predispose COVID-19 Pneumonia Patients to a Higher 28-Day Mortality Risk: A Pilot Study on a Greek ICU Cohort*, https://www.mdpi.com/2072-6643/12/12/3773/htm.

43. **Walk** et al., medRxiv, doi:10.1101/2020.11.07.20227512, *Vitamin D - contrary to vitamin K - does not associate with clinical outcome in hospitalized COVID-19 patients*, https://www.medrxiv.org/content/10.1101/2020.11.07.20227512v1.

44. **Ye** et al., Journal of the American College of Nutrition, doi:10.1080/07315724.2020.182600, *Does Serum Vitamin D Level Affect COVID-19 Infection and Its Severity? A Case-Control Study*, https://www.tandfonline.com/doi/full/10.1080/07315724.2020.1826005.

45. **Zhang** et al., JAMA, 80:19, 1690, doi:10.1001/jama.280.19.1690, *What's the relative risk? A method of correcting the odds ratio in cohort studies of common outcomes*, https://jamanetwork.com/journals/jama/fullarticle/188182.