

# Vitamin D for COVID-19: real-time meta analysis of 100 studies

Covid Analysis, Aug 23, 2021, Version 83 — corrected Jain (V1 Dec 17, 2020)

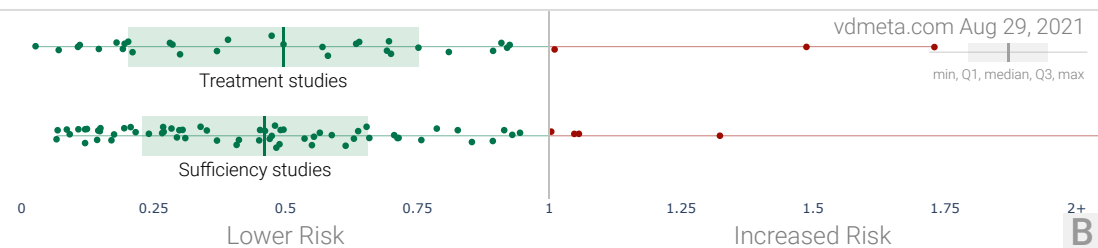
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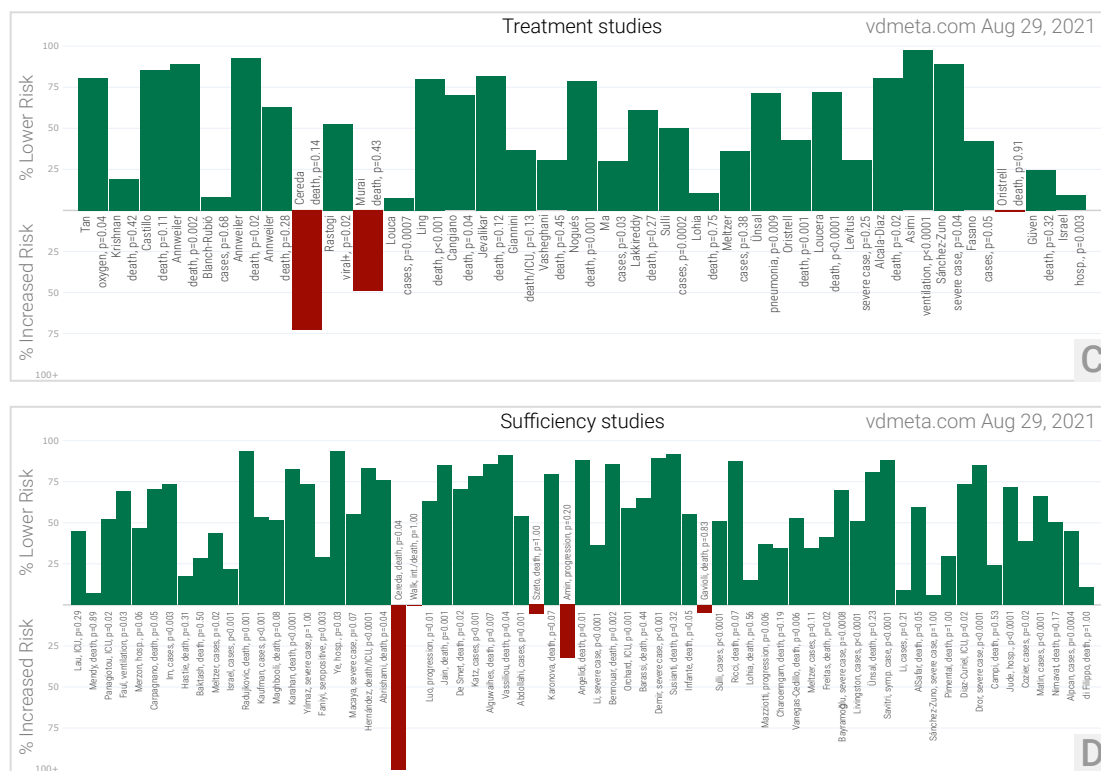
- 91% of 33 vitamin D treatment studies report positive effects (17 statistically significant in isolation).
- Random effects meta-analysis with pooled effects using the most serious outcome reported shows 80% and 42% improvement for early treatment and for all studies (RR 0.20 [0.10-0.37] and 0.58 [0.50-0.67]). Results are similar after restriction to 30 peer-reviewed studies: 83% and 37% (RR 0.17 [0.07-0.42] and 0.63 [0.55-0.72]), and for the 19 mortality results: 78% and 55% (RR 0.22 [0.12-0.43] and 0.45 [0.32-0.64]).
- Late stage treatment with calcifediol/calcitriol shows greater improvement compared to cholecalciferol: 80% versus 39% (RR 0.20 [0.13-0.31] and 0.61 [0.45-0.83]).
- Heterogeneity arises from many factors including treatment delay, patient population, the effect measured, variants, the form of vitamin D used, and treatment regimens. The consistency of positive results across a wide variety of cases is remarkable.
- Sufficiency studies show a strong association between vitamin D sufficiency and outcomes. Meta analysis of the 67 studies with pooled effects using the most serious outcome reported shows 55% improvement (RR 0.45 [0.38-0.53]).
- While many treatments have some level of efficacy, they do not replace vaccines and other measures to avoid infection. Only 9% of vitamin D treatment studies show zero events in the treatment arm.
- Elimination of COVID-19 is a race against viral evolution. No treatment, vaccine, or intervention is 100% available and effective for all current and future variants. All practical, effective, and safe means should be used. Not doing so increases the risk of COVID-19 becoming endemic; and increases mortality, morbidity, and collateral damage.
- All data to reproduce this paper and the sources are in the appendix.

	Improvement	Studies	Authors	Patients
<u>Treatment RCTs</u>	<b>45%</b> [-17-74%]	5	53	482
<u>Treatment studies</u>	<b>42%</b> [33-50%]	33	325	46,860
<u>Cholecalciferol treatment</u>	<b>35%</b> [25-44%]	27	256	39,320
<u>Calcifediol/calcitriol treatment</u>	<b>63%</b> [24-82%]	6	69	7,540
<u>Treatment mortality</u>	<b>55%</b> [36-68%]	19	175	9,760
<u>Sufficiency studies</u>	<b>55%</b> [47-62%]	67	540	34,863

# All 33 vitamin D COVID-19 treatment studies

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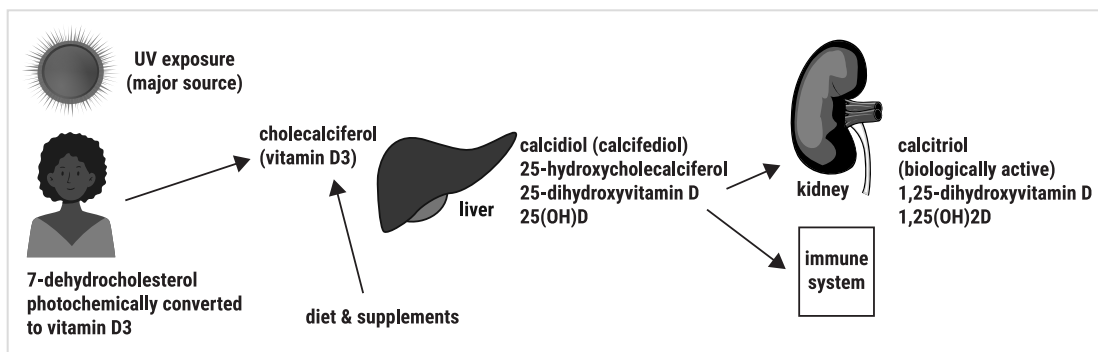


**Figure 1. A.** Random effects meta-analysis of treatment studies. This plot shows pooled effects, analysis for individual outcomes is below, and more details on pooled effects can be found in the heterogeneity section. Effect extraction is pre-specified, using the most serious outcome reported. Simplified dosages are shown for comparison, these are the total dose in the first five days for treatment, and the monthly dose for prophylaxis. Calcifediol or calcitriol treatment is indicated with (c). For details of effect extraction and full dosage information 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.

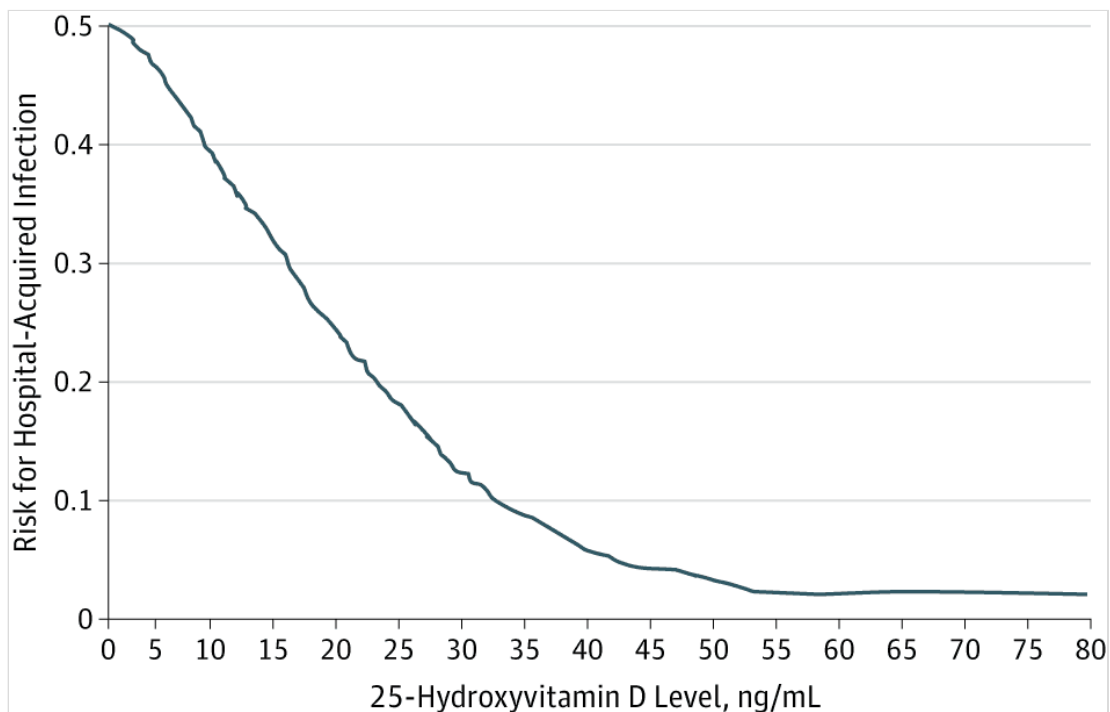
## Introduction

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 [Carlberg, Martens]. For example, [Quraishi] show a strong association between pre-operative vitamin D levels and hospital-acquired infections, as shown in Figure 3. There is a significant delay involved in the conversion from cholecalciferol, therefore calcifediol (calcidiol) or calcitriol may be preferable for treatment.



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

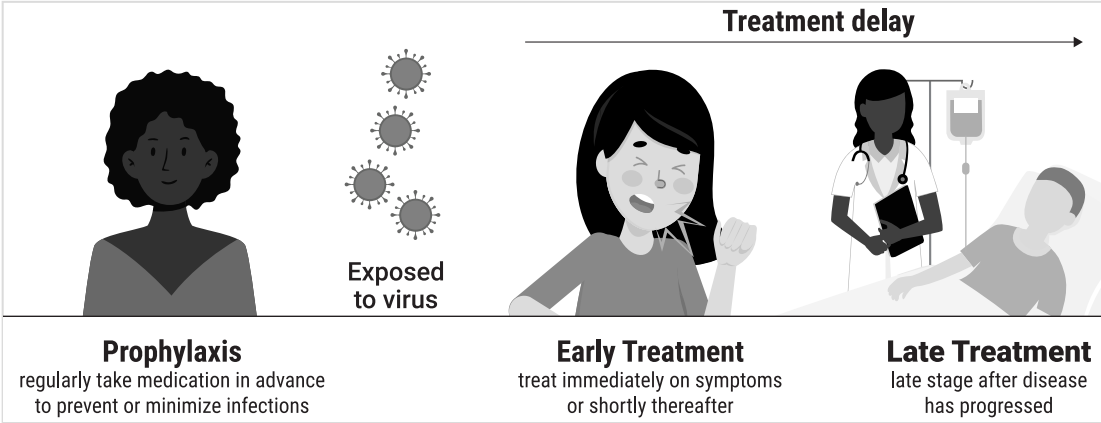


**Figure 3.** Risk of hospital-acquired infections as a function of pre-operative vitamin D levels, from [Quraishi].

**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. We include all sufficiency studies that provide a comparison between two groups with low and high levels. A few studies only provide results as a function of change in vitamin D levels [Butler-Laporte, Raisi-Estabragh], which may not be indicative of results for deficiency/insufficiency versus sufficiency (increasing already sufficient levels may be less useful than going from deficient to sufficient). A few studies show the average vitamin D level for patients in different groups [Al-Daghri, D'avolio, Kerget, Vassiliou], all of which show lower D

levels for worse outcomes. Other studies analyze vitamin D status and outcomes in geographic regions [Jayawardena, Marik, Papadimitriou, Rafailia, Rhodes, Sooriyaarachchi, Walrand, Yadav], all finding worse outcomes to be more likely with lower D levels.

**Treatment.** For studies regarding treatment with vitamin D, we distinguish three stages as shown in Figure 4. **Prophylaxis** refers to regularly taking vitamin D before being infected in order to minimize the severity of infection. Due to the mechanism of action, vitamin D is unlikely to completely prevent infection, although it may prevent infection from reaching a level detectable by PCR. **Early Treatment** refers to treatment immediately or soon after symptoms appear, while **Late Treatment** refers to more delayed treatment.



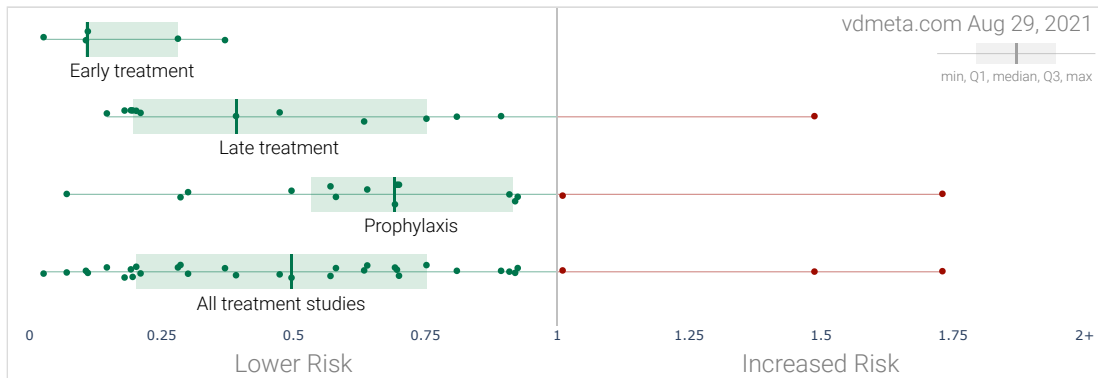
**Figure 4.** Treatment stages.

**Results**

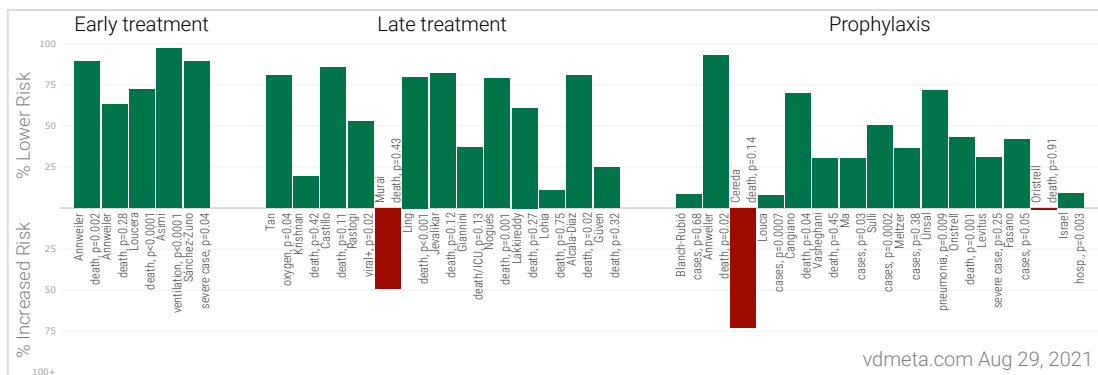
Figure 1 shows the effects reported in sufficiency studies and treatment studies. Figure 5 and 6 show results by treatment stage. Figure 7 shows a forest plot for random effects meta-analysis of sufficiency studies, while Figure 8, 9, 10, 11, 12, 13, 14, and 15 show forest plots for all treatment studies with pooled effects, RCT studies, calcifediol/calcitriol studies, cholecalciferol studies, and for studies reporting mortality, case results, and viral clearance 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	62	67	92.5%	55% improvement RR 0.45 [0.38-0.53] p < 0.0001
Early treatment	5	5	100%	80% improvement RR 0.20 [0.10-0.37] p < 0.0001
Late treatment	12	13	92.3%	53% improvement RR 0.47 [0.32-0.68] p < 0.0001
Prophylaxis	13	15	86.7%	20% improvement RR 0.80 [0.71-0.90] p = 0.00017
All treatment studies	30	33	90.9%	42% improvement RR 0.58 [0.50-0.67] p < 0.0001

**Table 1.** Results.



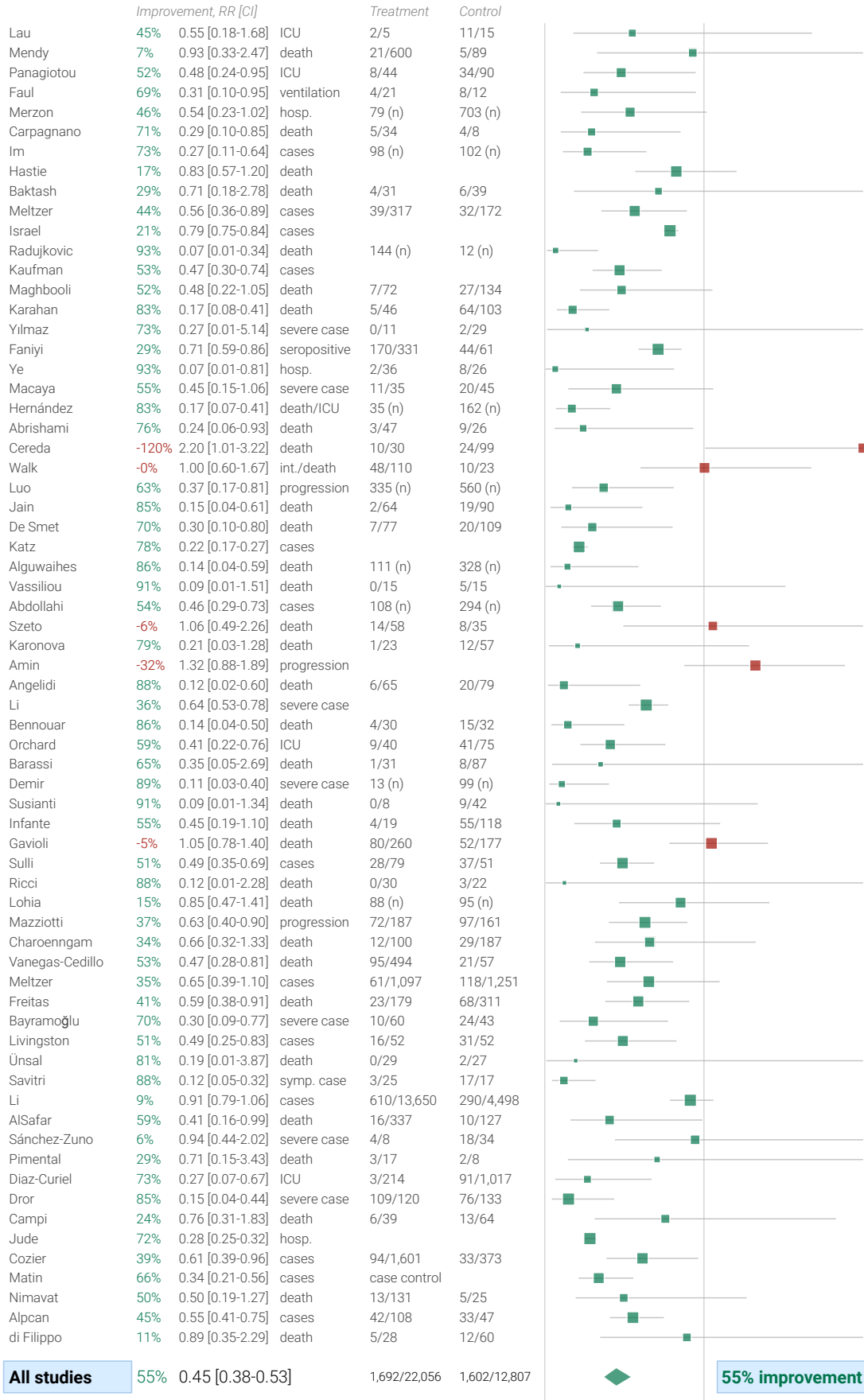
**Figure 5.** Results by treatment stage.

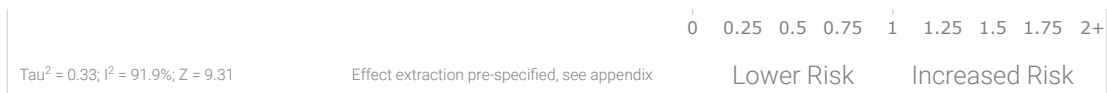


**Figure 6.** Results by treatment stage.

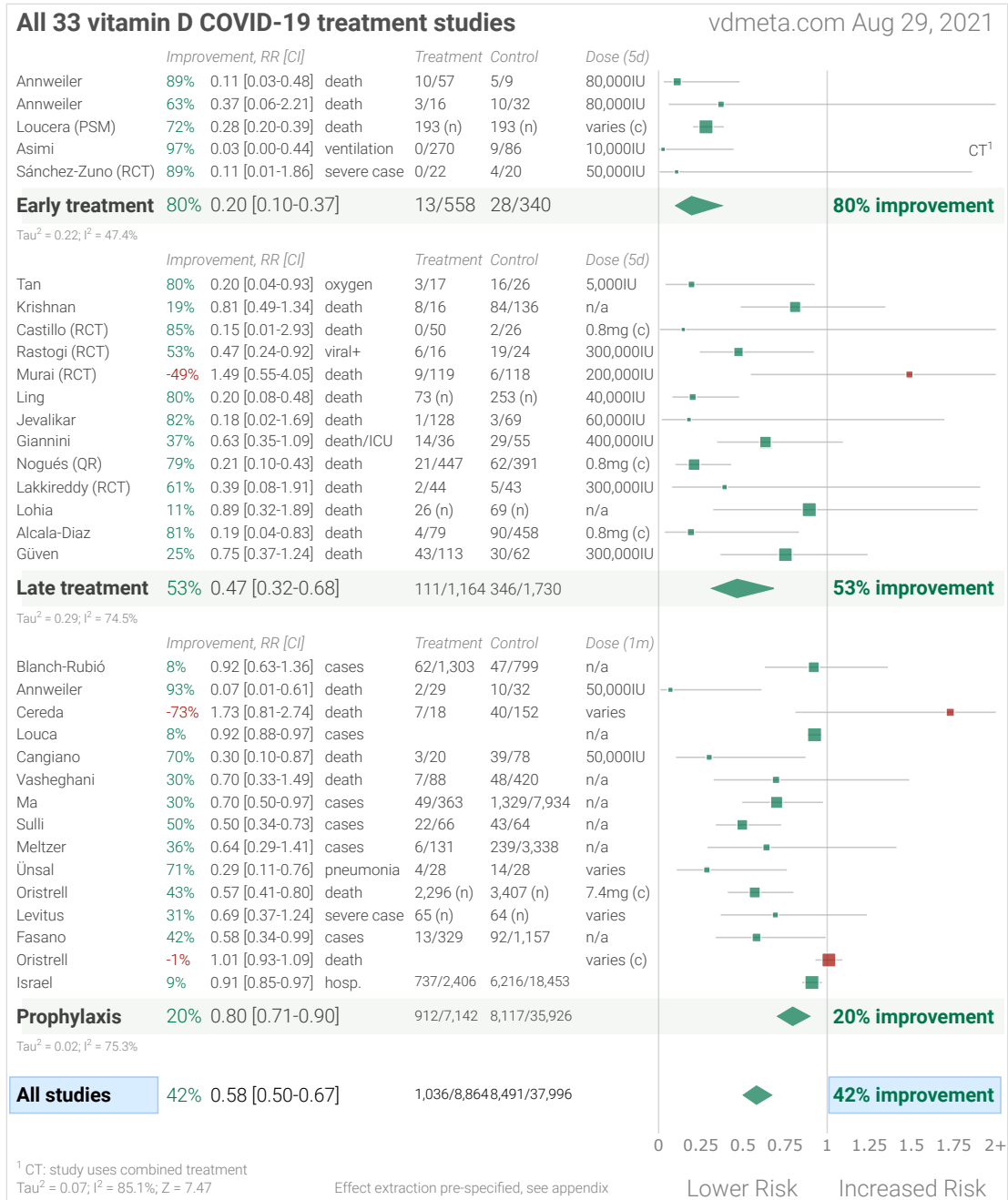
# All 67 vitamin D COVID-19 sufficiency studies

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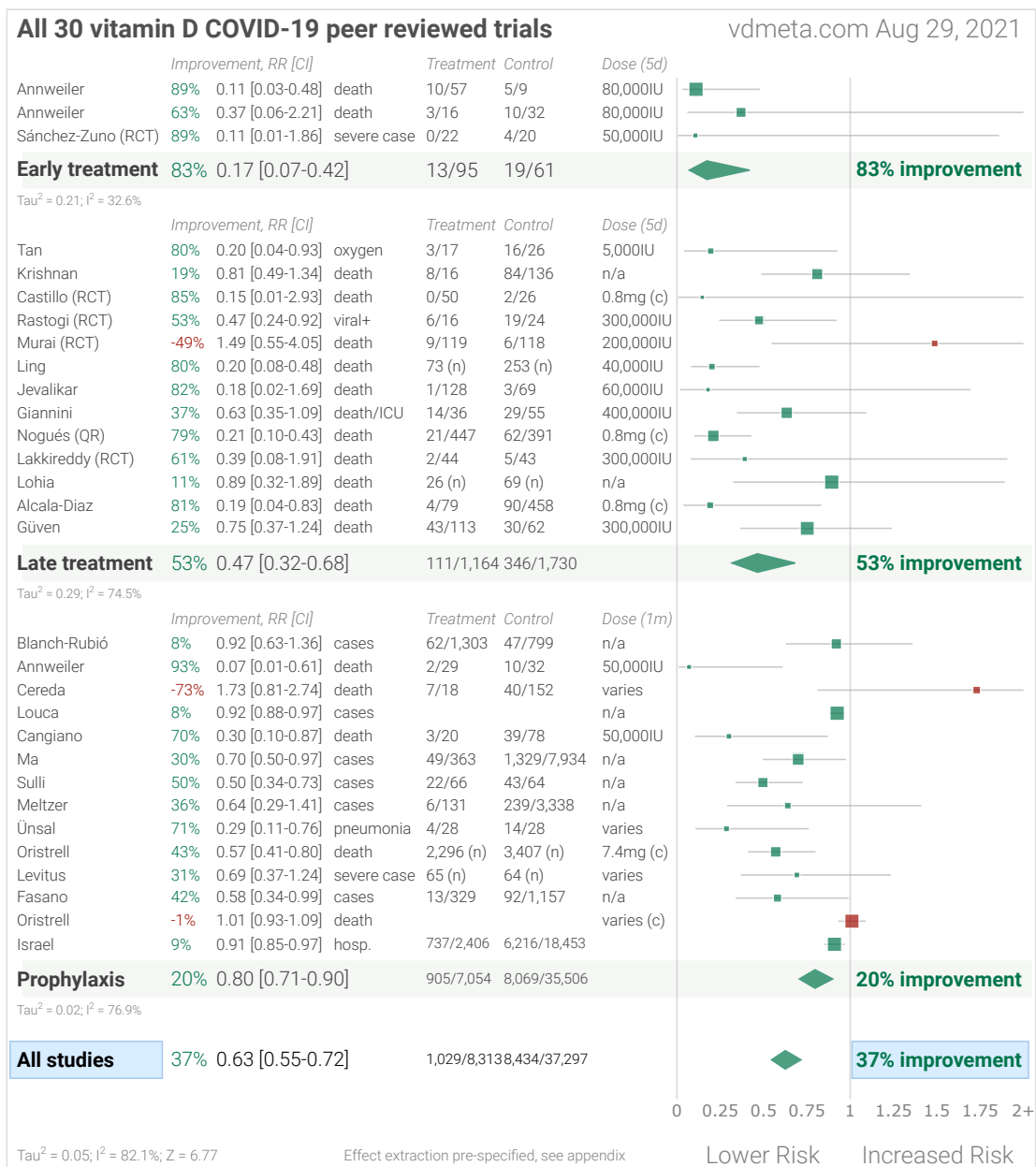


**Figure 7.** Random effects meta-analysis for sufficiency studies. This plot pools studies with different effects and vitamin D cutoff levels, and studies may be within hospitalized patients, excluding the risk of hospitalization. However, the prevalence of positive effects is notable.

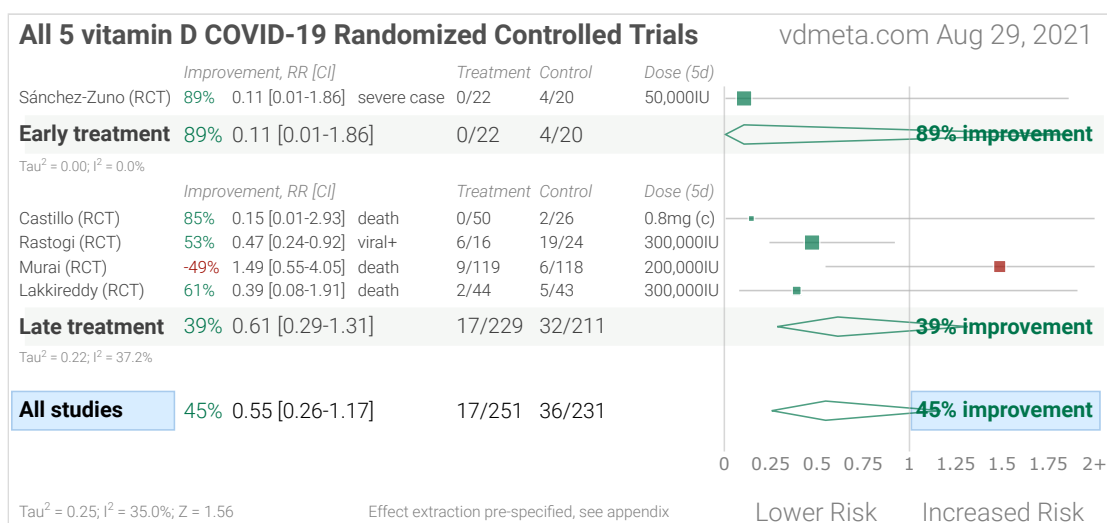


**Figure 8.** Random effects meta-analysis for treatment studies. Effect extraction is pre-specified, using the most serious outcome reported, see the [appendix](#) for details.

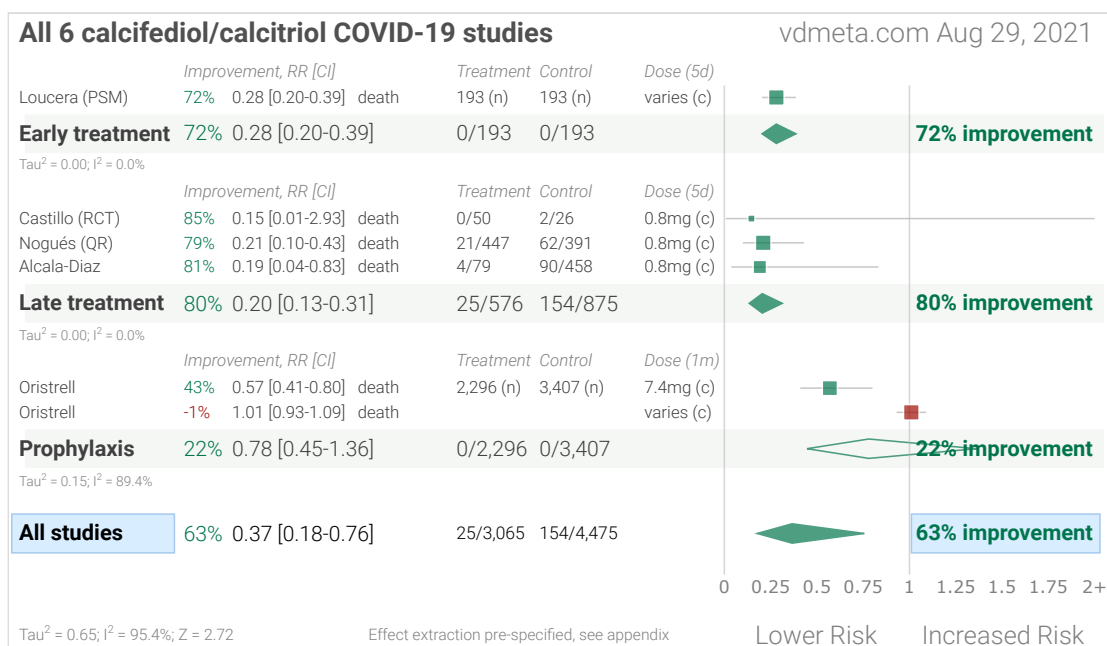




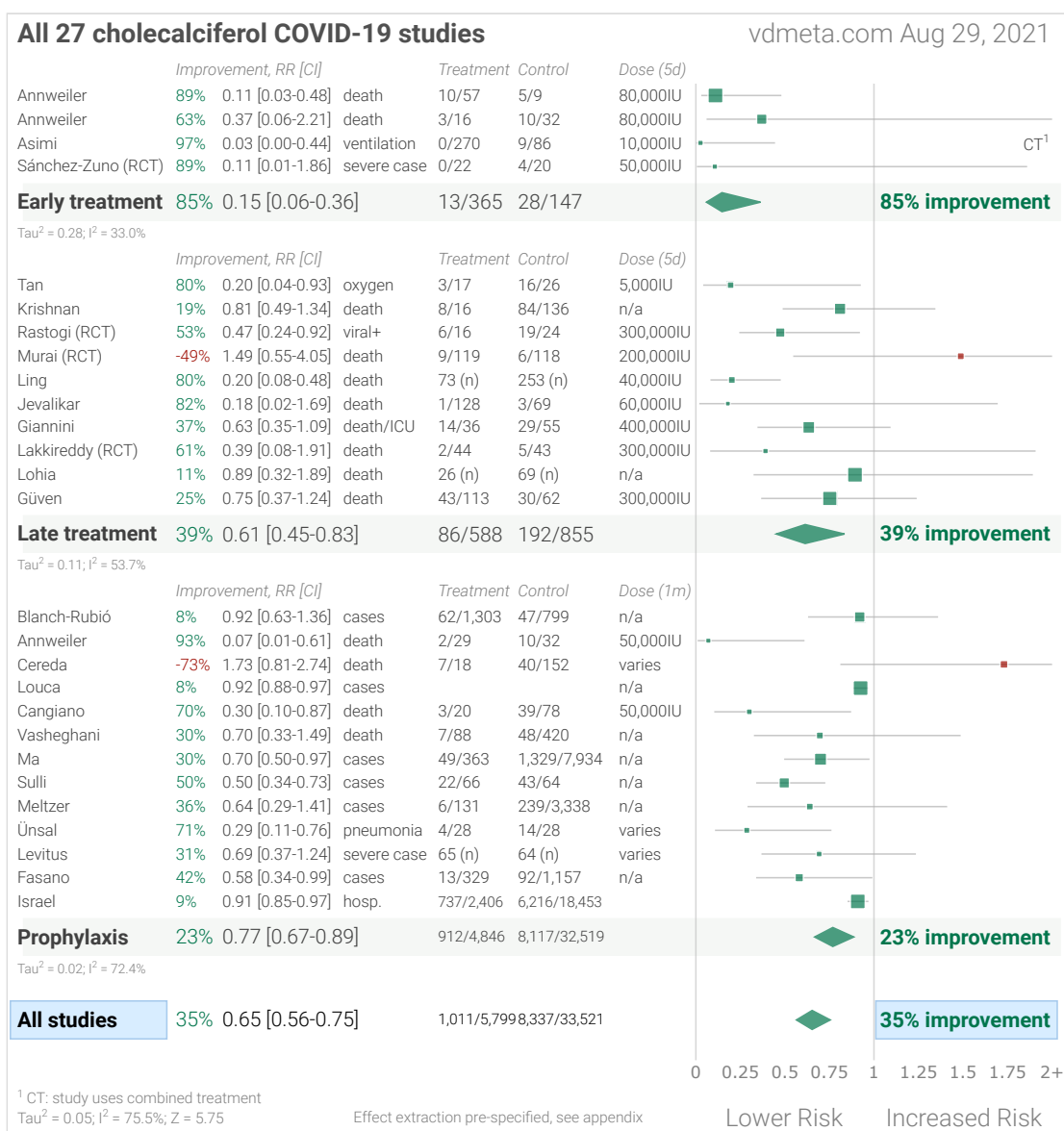
**Figure 9.** Random effects meta-analysis for peer-reviewed treatment studies. Effect extraction is pre-specified, using the most serious outcome reported, see the [appendix](#) for details.



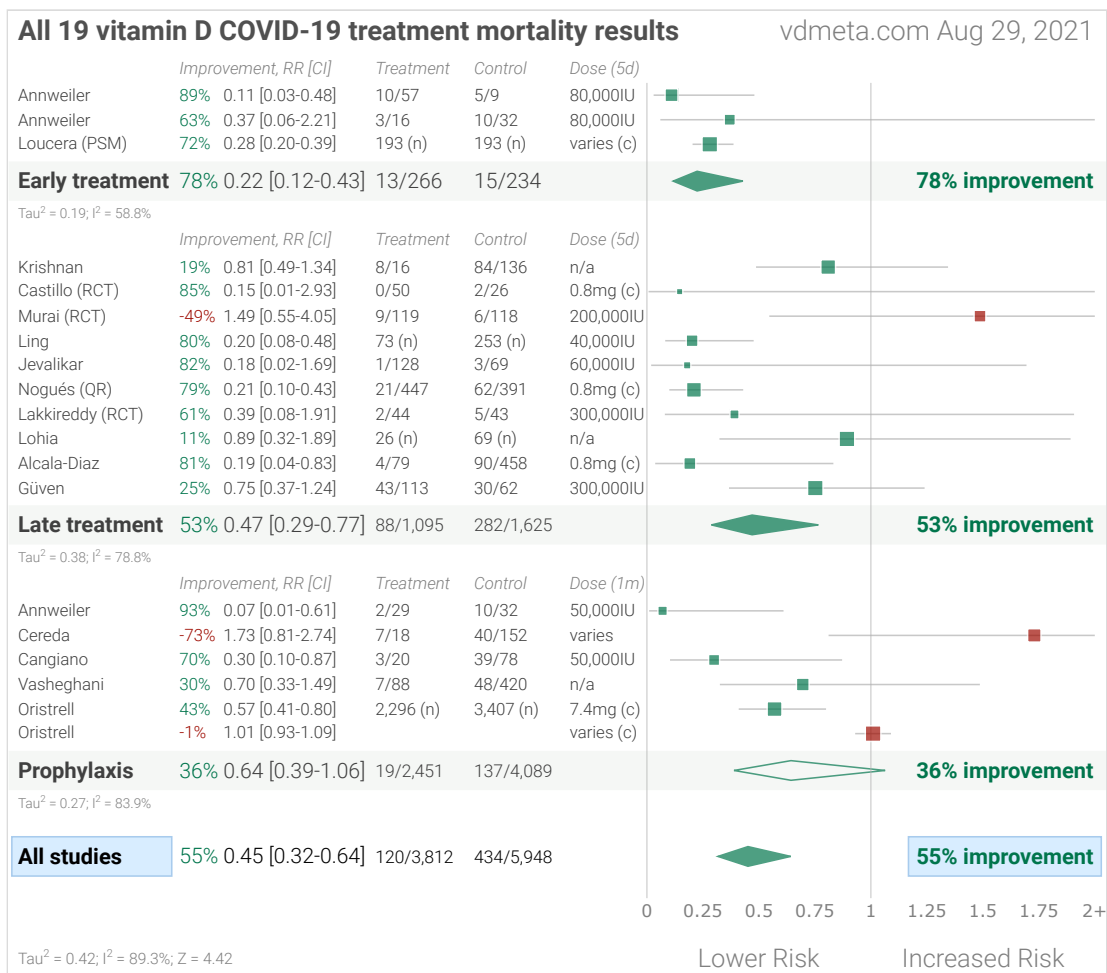
**Figure 10.** Random effects meta-analysis for treatment RCTs. Effect extraction is pre-specified, using the most serious outcome reported, see the [appendix](#) for details.



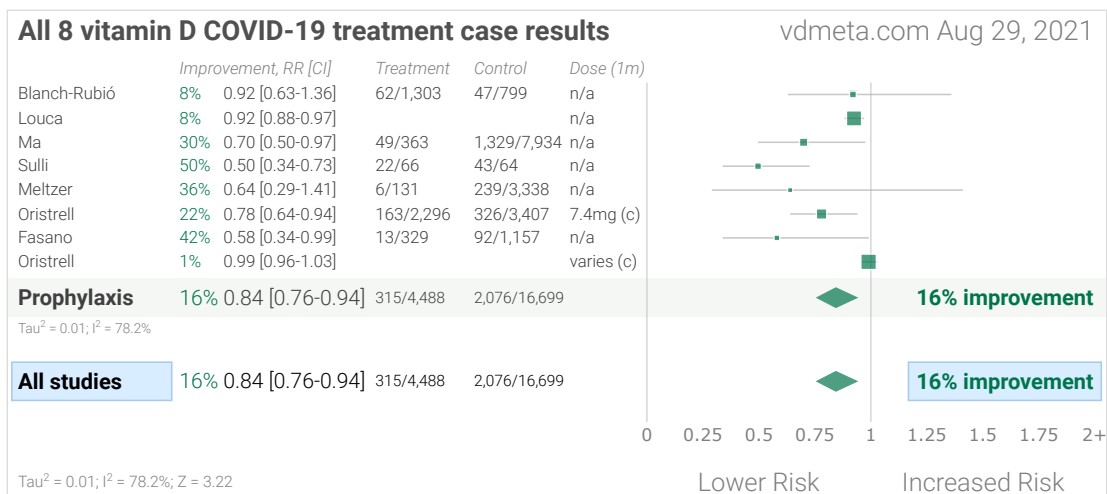
**Figure 11.** Random effects meta-analysis for calcifediol/calcitriol treatment studies. Effect extraction is pre-specified, using the most serious outcome reported, see the [appendix](#) for details.



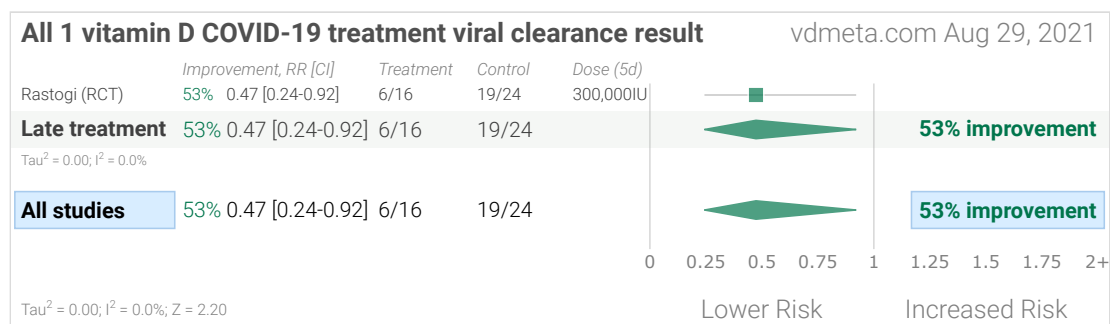
**Figure 12.** Random effects meta-analysis for cholecalciferol treatment studies. Effect extraction is pre-specified, using the most serious outcome reported, see the [appendix](#) for details.



**Figure 13.** Random effects meta-analysis for mortality results only.



**Figure 14.** Random effects meta-analysis for COVID-19 case results only.



**Figure 15.** Random effects meta-analysis for viral clearance results only.

## Exclusions

To avoid bias in the selection of studies, we include all studies in the main analysis, with the exception of *[Espitia-Hernandez]*. This study uses a combined protocol with another medication that shows high effectiveness when used alone. Authors report on viral clearance, showing 100% clearance with treatment and 0% for the control group. Based on the known mechanisms of action, the combined medication is likely to contribute more to the improvement.

Here we show the results after excluding studies with critical issues.

*[Murai]* 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.

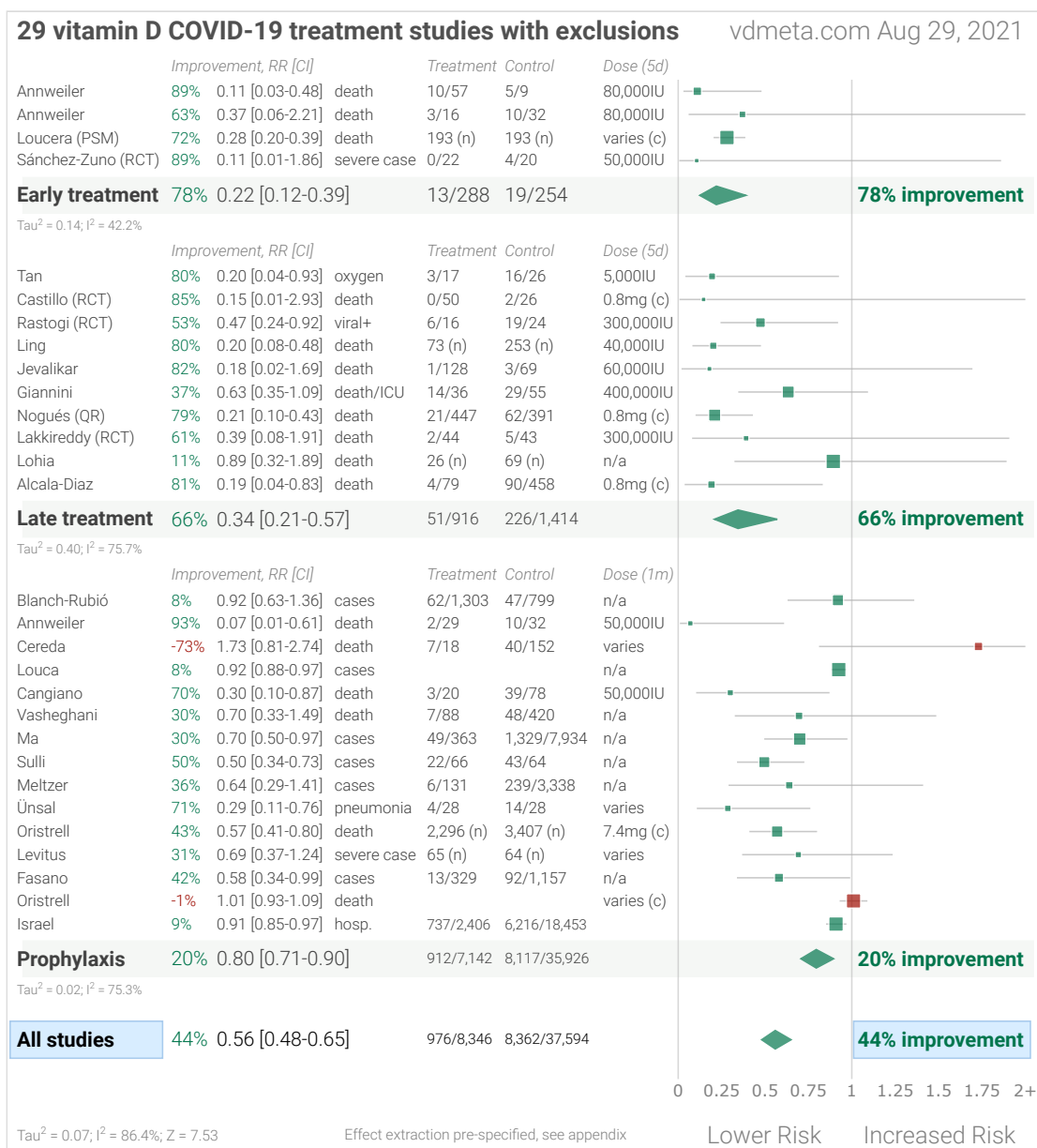
The studies excluded are as follows, and the resulting forest plot is shown in Figure 16.

*[Asimi]*, excessive unadjusted differences between groups.

*[Güven]*, very late stage, ICU patients.

*[Krishnan]*, unadjusted results with no group details.

*[Murai]*, very late stage, >50% on oxygen/ventilation at baseline.

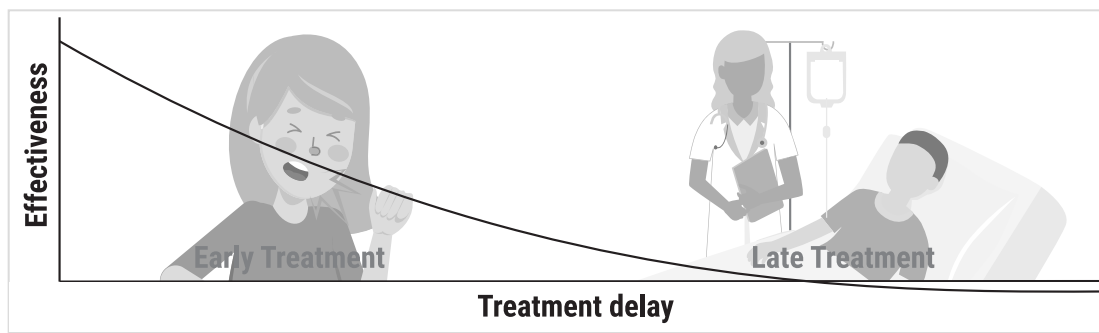


**Figure 16.** Random effects meta-analysis excluding studies with significant issues. Effect extraction is pre-specified, using the most serious outcome reported, see the [appendix](#) for details.

## Heterogeneity

Heterogeneity in COVID-19 studies arises from many factors including:

**Treatment delay.** The time between infection or the onset of symptoms and treatment may critically affect how well a treatment works. For example a medication may be very effective when used early but may not be effective in late stage disease, and may even be harmful. Figure 17 shows an example where efficacy declines as a function of treatment delay. Other medications might be beneficial for late stage complications, while early use may not be effective or may even be harmful.



**Figure 17.** Effectiveness may depend critically on treatment delay.

**Patient demographics.** Details of the patient population including age and comorbidities may critically affect how well a treatment works. For example, many COVID-19 studies with relatively young low-comorbidity patients show all patients recovering quickly with or without treatment. In such cases, there is little room for an effective treatment to improve results.

**Effect measured.** Efficacy may differ significantly depending on the effect measured, for example a treatment may be very effective at reducing mortality, but less effective at minimizing cases or hospitalization. Or a treatment may have no effect on viral clearance while still being effective at reducing mortality.

**Variants.** There are thousands of different variants of SARS-CoV-2 and efficacy may depend critically on the distribution of variants encountered by the patients in a study.

**Regimen.** Effectiveness may depend strongly on the dosage, treatment regimen, and the form of vitamin D used (cholecalciferol, calcifediol, or calcitriol).

**Treatments.** The use of other treatments may significantly affect outcomes, including anything from other supplements and medications, or other kinds of treatment such as prone positioning.

The distribution of studies will alter the outcome of a meta analysis. Consider a simplified example where everything is equal except for the treatment delay, and effectiveness decreases to zero or below with increasing delay. If there are many studies using very late treatment, the outcome may be negative, even though the treatment may be very effective when used earlier.

In general, by combining heterogeneous studies, as all meta analyses do, we run the risk of obscuring an effect by including studies where the treatment is less effective, not effective, or harmful.

When including studies where a treatment is less effective we expect the estimated effect size to be lower than that for the optimal case. We do not *a priori* expect that pooling all studies will create a positive result for an effective treatment. Looking at all studies is valuable for providing an overview of all research, and important to avoid cherry-picking, but the resulting estimate does not apply to specific cases such as early treatment in high-risk populations with a specific form and dosage of vitamin D.

Vitamin D studies vary widely in all the factors above, which makes the consistently positive results even more remarkable. A failure to detect an association after combining heterogeneous studies does not mean the treatment is not effective (it may only work in certain cases), however the reverse is not true — an identified association is valid, although the magnitude of the effect may be

larger for more optimal cases, and lower for less optimal cases. While we present results for all studies in this paper, the individual outcome, form of vitamin D, and treatment time analyses are more relevant for specific use cases.

## 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, and some studies measure risk only within hospitalized patients, which excludes the risk of a serious enough case to be hospitalized, however 62 of 67 studies present positive effects.

30 of 33 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 [Cereda, Murai, Oristrell]. [Murai] is a very late stage study using cholecalciferol. 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. For [Oristrell], benefit was found for cases, severity, and mortality in patients achieving serum vitamin D levels  $\geq 30$ ng/ml.

## Conclusion

Vitamin D is an effective treatment for COVID-19. Random effects meta-analysis of the 33 treatment studies to date results in an estimated reduction of 42% in the effect measured, RR 0.58 [0.50-0.67].

## 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://vdm-meta.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*].

1/15: We added the effect measured for each study in the forest plots.

1/16: We moved the analysis with exclusions to the main text, and added additional commentary.

1/18: We added [*Vasheghani*].

1/19: We added [*Amin*].

1/21: We added [*Bennouar*].

1/22: We added [*Giannini*].

1/30: We added [*Ma*].

1/31: We added [*Demir*].

2/5: We added [*Yilmaz*].

2/7: We added [*Li (B)*].

2/9: We added [*Karahan*].

2/10: We added [*Karonova*].

2/10: We added [*Nogués*].

2/16: We added [*Susianti*].

2/17: We corrected an error in the effect extraction for [*Angelidi*], and we added treatment case and viral clearance forest plots.

2/18: [*Murai*] was updated to the journal version of the paper.

2/20: We added [*Infante*].

2/20: We added [*Gavioli*].

2/25: We added [*Sulli (B)*].

2/26: We added [*Lakkireddy*].

3/6: We added [*Ricci*].

3/10: We added [*Mazziotti*].

3/12: We added [*Charoenngam*].

3/14: We added [*Cereda (B)*].

3/15: We added [*Vanegas-Cedillo*].

3/22: We added [Meltzer].

3/28: We added [Freitas].

3/29: We added [Im].

3/30: We added [Macaya].

3/31: We added [Mendy].

4/4: We added event counts to the forest plots.

4/5: We added [Bayramoğlu, Livingston].

4/9: We added [Ünsal].

4/10: We added [Szeto].

4/12: We added [Barassi].

4/13: We added [Lohia, Oristrell (B)].

4/14: We added [Blanch-Rubió].

4/24: We added analysis restricted to RCT studies and to calcifediol/calcitriol studies. We have excluded [Espitia-Hernandez] in the treatment analysis because they use a combined protocol with another medication that shows high effectiveness when used alone.

4/29: We corrected the treatment group counts for the early treatment group in [Annweiler] (there was no change in the relative risk).

4/30: We added [Loucera].

5/8: We added analysis for treatment studies restricted to peer-reviewed articles.

5/9: We clarified terminology for prophylaxis and added discussion of heterogeneity.

5/10: We added additional information in the abstract.

5/19: We added [AlSafar].

5/20: We updated [Lakkireddy] to the journal version.

5/21: We added [Alcala-Diaz, Li].

5/22: We added analysis restricted to cholecalciferol studies.

5/29: We added [Sánchez-Zuno (B)].

6/7: We added [Diaz-Curiel, Dror].

6/8: We updated [Nogués] to the journal version.

6/9: We added [Fasano].

6/11: We updated [*Oristrell (B)*] to the journal version.

6/12: We added [*Levitus*].

6/16: We added [*Campi*].

6/19: We added [*Jude*].

6/25: We added [*Cereda*].

7/11: We added [*Krishnan*].

7/19: We added [*Oristrell*].

7/21: We added [*Savitri*].

7/24: We added [*Orchard*].

7/25: We added [*Asimi*].

7/26: We added [*Güven*].

7/27: We added [*Cozier*].

7/28: We added [*Israel (B)*].

8/1: We added [*Pimental*].

8/2: We added [*Matin*].

8/10: We added discussion of the immune system and vitamin D.

8/12: We added [*Alpcan*].

8/13: We added [*di Filippo*] and updated [*Louca*] to the journal version of the article.

8/15: We added [*Nimavat*].

8/23: We corrected [*Jain*] to include the mortality outcome.

## 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 a result for vitamin D treatment of COVID-19 patients compared to a control group, and all studies comparing COVID-19 outcomes in groups of patients with low and high vitamin D levels are included. A few studies only provide results as a

function of change in vitamin D levels, which may not be indicative of results for deficiency/insufficiency versus sufficiency (if levels are already sufficient then further increase may be less useful). 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 (the next most serious outcome is used – no studies were excluded). For example, in low-risk populations with no mortality, a reduction in mortality with treatment is not possible, however a reduction in hospitalization, for example, is still valuable. Clinical outcome is considered more important than PCR testing status. When basically all patients recover in both treatment and control groups, preference for viral clearance and recovery is given to results mid-recovery where available (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 (3.9.6) with scipy (1.6.2), pythonmeta (1.23), numpy (1.21.1), statsmodels (0.12.2), and plotly (4.14.3).

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). The forest plots show simplified dosages for comparison, these are the total dose in the first five days for treatment, and the monthly dose for prophylaxis. Calcifediol or calcitriol treatment is indicated with (c). For full dosage details see below.

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. Please submit updates and corrections at <https://vdm-meta.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.

<i>[Abdollahi]</i> , 12/12/2020, retrospective, Iran, Middle East, peer-reviewed, 7 authors.	<b>risk of COVID-19 case, 53.9% lower, RR 0.46, <math>p = 0.001</math></b> , high D levels 108, low D levels 294, >30ng/ml.
<i>[Abrishami]</i> , 10/30/2020, retrospective, Iran, Middle East, peer-reviewed, mean age 55.2, 7 authors.	<b>risk of death, 75.9% lower, RR 0.24, <math>p = 0.04</math></b> , high D levels 3 of 47 (6.4%), low D levels 9 of 26 (34.6%), adjusted per study, >25ng/mL.
<i>[Alguwaihes]</i> , 12/5/2020, retrospective, Saudi Arabia, Middle East, peer-reviewed, 10 authors.	<b>risk of death, 85.7% lower, RR 0.14, <math>p = 0.007</math></b> , high D levels 111, low D levels 328, >12.5 nmol/L.
<i>[Alpcan]</i> , 8/10/2021, retrospective, Turkey, Europe, peer-reviewed, 3 authors.	<b>risk of COVID-19 case, 44.6% lower, RR 0.55, <math>p &lt; 0.001</math></b> , high D levels 42 of 108 (38.9%), low D levels 33 of 47 (70.2%), >20ng/mL.
<i>[AlSafar]</i> , 5/19/2021, retrospective, United Arab Emirates, Middle East, peer-reviewed, 8 authors.	<b>risk of death, 59.3% lower, RR 0.41, <math>p = 0.05</math></b> , high D levels 16 of 337 (4.7%), low D levels 10 of 127 (7.9%), adjusted per study, odds ratio converted to relative risk, >=12ng/mL.
	risk of COVID-19 severe case, 33.2% lower, RR 0.67, $p = 0.005$ , high D levels 337, low D levels 127, adjusted per study, odds ratio converted to relative risk, >=12ng/mL.
<i>[Amin]</i> , 1/7/2021, retrospective, United Kingdom, Europe, peer-reviewed, 2 authors.	<b>COVID-19 severity, 32.3% higher, RR 1.32, <math>p = 0.20</math></b> , odds ratio converted to relative risk, >=50nmol/L vs. <25nmol/L, MR Egger, baseline risk approximated with overall risk.
	risk of COVID-19 case, 7.6% higher, RR 1.08, $p = 0.14$ , odds ratio converted to relative risk, >=50nmol/L vs. <25nmol/L, MR Egger, baseline risk approximated with overall risk.
<i>[Angelidi]</i> , 1/9/2021, retrospective, USA, North America, peer-reviewed, 8 authors.	<b>risk of death, 88.0% lower, RR 0.12, <math>p = 0.01</math></b> , high D levels 6 of 65 (9.2%), low D levels 20 of 79 (25.3%), adjusted per study, >30ng/mL, supplementary table 2, multivariable logistic regression model 5.
<i>[Baktash]</i> , 8/27/2020, prospective, United Kingdom, Europe, peer-reviewed, 8 authors.	<b>risk of death, 28.6% lower, RR 0.71, <math>p = 0.50</math></b> , high D levels 4 of 31 (12.9%), low D levels 6 of 39 (15.4%), adjusted per study, >30nmol/L.
<i>[Barassi]</i> , 1/25/2021, retrospective, Italy, Europe, peer-reviewed, 8 authors.	<b>risk of death, 64.9% lower, RR 0.35, <math>p = 0.44</math></b> , high D levels 1 of 31 (3.2%), low D levels 8 of 87 (9.2%), >20ng/mL.

	<p>risk of mechanical ventilation, 64.9% lower, RR 0.35, <math>p = 0.15</math>, high D levels 2 of 31 (6.5%), low D levels 16 of 87 (18.4%), &gt;20ng/mL.</p>
[Bayramoğlu], 3/31/2021, retrospective, Turkey, Europe, peer-reviewed, 7 authors.	<p><b>risk of moderate/severe case, 69.5% lower, RR 0.30, <math>p &lt; 0.001</math></b>, high D levels 10 of 60 (16.7%), low D levels 24 of 43 (55.8%), adjusted per study, odds ratio converted to relative risk, &gt;12 ng/mL, multivariate logistic regression.</p>
[Bennouar], 1/12/2021, prospective, Algeria, Africa, peer-reviewed, 4 authors.	<p><b>risk of death, 85.5% lower, RR 0.14, <math>p = 0.002</math></b>, high D levels 4 of 30 (13.3%), low D levels 15 of 32 (46.9%), adjusted per study, &gt;30µg/l vs. &lt;10µg/l, proportional Cox regression.</p>
	<p>risk of death, 63.0% lower, RR 0.37, <math>p = 0.10</math>, high D levels 4 of 30 (13.3%), low D levels 14 of 35 (40.0%), adjusted per study, &gt;30µg/l vs. 10-19µg/l, proportional Cox regression.</p>
	<p>risk of death, 23.1% lower, RR 0.77, <math>p = 0.73</math>, high D levels 4 of 30 (13.3%), low D levels 4 of 23 (17.4%), adjusted per study, &gt;30µg/l vs. 20-29µg/l, proportional Cox regression.</p>
[Campi], 6/14/2021, prospective, Italy, Europe, peer-reviewed, 21 authors.	<p><b>risk of death for severe patients, 24.3% lower, RR 0.76, <math>p = 0.53</math></b>, high D levels 6 of 39 (15.4%), low D levels 13 of 64 (20.3%), &gt;20ng/mL.</p>
	<p>risk of ICU for severe patients, 53.1% lower, RR 0.47, <math>p &lt; 0.001</math>, high D levels 12 of 39 (30.8%), low D levels 42 of 64 (65.6%), &gt;20ng/mL.</p>
[Carpagnano], 8/9/2020, retrospective, Italy, Europe, peer-reviewed, 10 authors.	<p><b>risk of death at day 26, 70.6% lower, RR 0.29, <math>p = 0.05</math></b>, high D levels 5 of 34 (14.7%), low D levels 4 of 8 (50.0%), &gt;30 ng/mL.</p>
	<p>risk of death at day 10, 90.0% lower, RR 0.10, <math>p = 0.02</math>, high D levels 2 of 34 (5.9%), low D levels 4 of 8 (50.0%), adjusted per study, &gt;30 ng/mL.</p>
[Cereda (B)], 11/1/2020, prospective, Italy, Europe, peer-reviewed, 13 authors.	<p><b>risk of death, 120.0% higher, RR 2.20, <math>p = 0.04</math></b>, high D levels 10 of 30 (33.3%), low D levels 24 of 99 (24.2%), odds ratio converted to relative risk, &gt;20ng/mL.</p>
	<p>risk of ICU admission, 86.7% lower, RR 0.13, <math>p = 0.59</math>, high D levels 0 of 30 (0.0%), low D levels 5 of 99 (5.1%), continuity correction due to zero event</p>

	(with reciprocal of the contrasting arm).
<i>[Charoenngam]</i> , 3/8/2021, retrospective, USA, North America, peer-reviewed, 6 authors.	<b>risk of death, 34.1% lower, RR 0.66, <math>p = 0.19</math></b> , high D levels 12 of 100 (12.0%), low D levels 29 of 187 (15.5%), adjusted per study, odds ratio converted to relative risk, $\geq 30\text{ng/mL}$ .
	risk of mechanical ventilation, 37.2% lower, RR 0.63, $p = 0.11$ , high D levels 14 of 100 (14.0%), low D levels 34 of 187 (18.2%), adjusted per study, odds ratio converted to relative risk, $\geq 30\text{ng/mL}$ .
	risk of ICU admission, 23.1% lower, RR 0.77, $p = 0.14$ , high D levels 25 of 100 (25.0%), low D levels 56 of 187 (29.9%), adjusted per study, odds ratio converted to relative risk, $\geq 30\text{ng/mL}$ .
	risk of death, 58.1% lower, RR 0.42, $p = 0.01$ , high D levels 7 of 57 (12.3%), low D levels 25 of 79 (31.6%), adjusted per study, odds ratio converted to relative risk, $>65$ years old, $\geq 30\text{ng/mL}$ .
<i>[Cozier]</i> , 7/27/2021, prospective, USA, North America, peer-reviewed, 6 authors.	<b>risk of COVID-19 case, 38.6% lower, RR 0.61, <math>p = 0.02</math></b> , high D levels 94 of 1601 (5.9%), low D levels 33 of 373 (8.8%), adjusted per study, odds ratio converted to relative risk, $>20\text{ng/mL}$ , multivariable.
<i>[De Smet]</i> , 11/25/2020, retrospective, Belgium, Europe, peer-reviewed, 5 authors.	<b>risk of death, 70.1% lower, RR 0.30, <math>p = 0.02</math></b> , high D levels 7 of 77 (9.1%), low D levels 20 of 109 (18.3%), adjusted per study, odds ratio converted to relative risk, $>20\text{ng/mL}$ .
<i>[Demir]</i> , 1/29/2021, retrospective, Turkey, Europe, peer-reviewed, 3 authors.	<b>risk of COVID-19 severe case, 89.3% lower, RR 0.11, <math>p &lt; 0.001</math></b> , high D levels 13, low D levels 99, ratio of the mean number of affected lung segments, $>30\text{ng/mL}$ vs. $\leq 10\text{ng/mL}$ .
	hospitalization time, 87.1% lower, relative time 0.13, $p < 0.001$ , high D levels 13, low D levels 99, $>30\text{ng/mL}$ vs. $\leq 10\text{ng/mL}$ .
	risk of COVID-19 case, 24.2% lower, RR 0.76, $p = 0.18$ , high D levels 13 of 31 (41.9%), low D levels 99 of 179 (55.3%), $>30\text{ng/mL}$ vs. $\leq 10\text{ng/mL}$ .
<i>[di Filippo]</i> , 8/12/2021, retrospective, Italy, Europe, peer-reviewed, 8 authors.	<b>risk of death, 10.7% lower, RR 0.89, <math>p = 1.00</math></b> , high D levels 5 of 28 (17.9%), low D levels 12 of 60 (20.0%), $>20\text{ng/mL}$ .

	<p>risk of ICU admission, 41.6% lower, RR 0.58, <math>p = 0.22</math>, high D levels 6 of 28 (21.4%), low D levels 22 of 60 (36.7%), &gt;20ng/mL.</p> <p>risk of COVID-19 severe case, 39.6% lower, RR 0.60, <math>p = 0.04</math>, high D levels 11 of 28 (39.3%), low D levels 39 of 60 (65.0%), &gt;20ng/mL.</p>
<i>[Diaz-Curiel]</i> , 6/6/2021, retrospective, Spain, Europe, peer-reviewed, 8 authors.	<b>risk of ICU admission, 73.2% lower, RR 0.27, <math>p = 0.02</math></b> , high D levels 3 of 214 (1.4%), low D levels 91 of 1017 (8.9%), odds ratio converted to relative risk, >30ng/mL vs. <20ng/mL.
<i>[Dror]</i> , 6/7/2021, retrospective, Israel, Middle East, preprint, 18 authors.	<b>risk of severe or critical case, 85.1% lower, RR 0.15, <math>p &lt; 0.001</math></b> , high D levels 109 of 120 (90.8%), low D levels 76 of 133 (57.1%), odds ratio converted to relative risk, >40ng/mL vs. <20ng/mL, multivariate logistic regression.
<i>[Faniyi]</i> , 10/6/2020, prospective, United Kingdom, Europe, preprint, 10 authors.	<b>risk of seropositive, 28.8% lower, RR 0.71, <math>p = 0.003</math></b> , high D levels 170 of 331 (51.4%), low D levels 44 of 61 (72.1%), >30nmol/L.
<i>[Faul]</i> , 6/30/2020, retrospective, Ireland, Europe, peer-reviewed, 9 authors.	<b>risk of mechanical ventilation, 69.0% lower, RR 0.31, <math>p = 0.03</math></b> , high D levels 4 of 21 (19.0%), low D levels 8 of 12 (66.7%), adjusted per study, >30nmol/L.
<i>[Freitas]</i> , 3/27/2021, retrospective, Portugal, Europe, preprint, 36 authors.	<b>risk of death, 41.2% lower, RR 0.59, <math>p = 0.02</math></b> , high D levels 23 of 179 (12.8%), low D levels 68 of 311 (21.9%), >20ng/mL.
<i>[Gavioli]</i> , 2/19/2021, retrospective, USA, North America, peer-reviewed, 4 authors.	<b>risk of death, 4.7% higher, RR 1.05, <math>p = 0.83</math></b> , high D levels 80 of 260 (30.8%), low D levels 52 of 177 (29.4%), >20ng/ml.
	risk of death, 44.8% lower, RR 0.55, $p < 0.001$ , high D levels 102 of 376 (27.1%), low D levels 30 of 61 (49.2%), >10ng/ml.
	risk of oxygen therapy, 55.2% lower, RR 0.45, $p < 0.001$ , high D levels 127 of 260 (48.8%), low D levels 116 of 177 (65.5%), adjusted per study, >20ng/ml, multivariate.
	risk of hospitalization, 3.6% lower, RR 0.96, $p = 0.41$ , high D levels 218 of 260 (83.8%), low D levels 154 of 177 (87.0%), >20ng/ml.



[Hastie], 8/26/2020, retrospective, database analysis, United Kingdom, Europe, peer-reviewed, 14 authors.	risk of death, 17.4% lower, RR 0.83, $p = 0.31$ , adjusted per study, >25nmol/L.
	risk of hospitalization, 9.1% lower, 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/ventilation, 83.0% lower, RR 0.17, $p < 0.001$ , high D levels 35, low D levels 162, $\geq 20\text{ng/mL}$ risk of hospitalization * risk of death/ICU/ventilation   hospitalization.
	risk of combined death/ICU/ventilation if hospitalized, 12.0% lower, RR 0.88, $p = 0.86$ , high D levels 35, low D levels 162, $\geq 20\text{ng/mL}$ risk of death/ICU/ventilation   hospitalization.
	risk of hospitalization, 80.6% lower, RR 0.19, $p < 0.001$ , $\geq 20\text{ng/mL}$ .
[Im], 8/11/2020, retrospective, South Korea, Asia, peer-reviewed, 6 authors.	risk of COVID-19 case, 73.1% lower, RR 0.27, $p = 0.003$ , high D levels 98, low D levels 102.
[Infante], 2/18/2021, retrospective, Italy, Europe, peer-reviewed, 11 authors.	risk of death, 54.8% lower, RR 0.45, $p = 0.05$ , high D levels 4 of 19 (21.1%), low D levels 55 of 118 (46.6%), $>20\text{ng/mL}$ .
[Israel], 9/10/2020, retrospective, Israel, Middle East, preprint, 8 authors.	risk of COVID-19 case, 21.3% lower, RR 0.79, $p < 0.001$ , high D levels 2601 of 32712 (8.0%), low D levels 5011 of 39485 (12.7%), adjusted per study, odds ratio converted to relative risk, multivariable $>75\text{ nmol/L}$ vs. $<30\text{ nmol/L}$ .
[Jain], 11/19/2020, prospective, India, South Asia, peer-reviewed, 6 authors.	risk of death, 85.2% lower, RR 0.15, $p = 0.001$ , high D levels 2 of 64 (3.1%), low D levels 19 of 90 (21.1%), $>20\text{ng/mL}$ .
	risk of ICU admission, 95.4% lower, RR 0.05, $p < 0.001$ , high D levels 2 of 64 (3.1%), low D levels 61 of 90 (67.8%), $>20\text{ng/mL}$ .
[Jude], 6/17/2021, retrospective, United Kingdom, Europe, peer-reviewed, 5 authors.	risk of hospitalization, 71.6% lower, RR 0.28, $p < 0.001$ , adjusted per study, odds ratio converted to relative risk, $>25\text{ nmol/L}$ , control prevalence approximated with overall prevalence.
	risk of hospitalization, 57.9% lower, RR 0.42, $p < 0.001$ , adjusted per study, odds ratio converted to relative risk, $>50\text{ nmol/L}$ , control prevalence approximated with overall prevalence.

<b>[Karahan]</b> , 10/5/2020, retrospective, Turkey, Europe, peer-reviewed, 2 authors.	<b>risk of death, 82.5% lower, RR 0.17, <math>p &lt; 0.001</math></b> , high D levels 5 of 46 (10.9%), low D levels 64 of 103 (62.1%), >20nmol/L.
<b>[Karonova]</b> , 12/31/2020, retrospective, Russia, Europe, peer-reviewed, 3 authors.	<b>risk of death, 79.4% lower, RR 0.21, <math>p = 0.07</math></b> , high D levels 1 of 23 (4.3%), low D levels 12 of 57 (21.1%), odds ratio converted to relative risk, >20ng/ml.
	risk of COVID-19 severe case, 71.1% lower, RR 0.29, $p = 0.02$ , high D levels 3 of 23 (13.0%), low D levels 22 of 57 (38.6%), odds ratio converted to relative risk, >20ng/ml.
<b>[Katz]</b> , 12/4/2020, retrospective, USA, North America, peer-reviewed, 3 authors.	<b>risk of COVID-19 case, 78.4% lower, RR 0.22, <math>p &lt; 0.001</math></b> , adjusted per study.
<b>[Kaufman]</b> , 9/17/2020, retrospective, USA, North America, peer-reviewed, median age 54.0, 5 authors.	<b>risk of COVID-19 case, 53.0% lower, RR 0.47, <math>p &lt; 0.001</math></b> , high D levels 12321, low D levels 39190, >55 ng/mL vs. <20 ng/mL.
<b>[Lau]</b> , 4/28/2020, retrospective, USA, North America, preprint, 7 authors.	<b>risk of ICU admission, 45.0% lower, RR 0.55, <math>p = 0.29</math></b> , high D levels 2 of 5 (40.0%), low D levels 11 of 15 (73.3%), >30ng/mL.
<b>[Li]</b> , 5/19/2021, retrospective, USA, North America, peer-reviewed, 4 authors.	<b>risk of COVID-19 case, 8.6% lower, RR 0.91, <math>p = 0.21</math></b> , high D levels 610 of 13650 (4.5%), low D levels 290 of 4498 (6.4%), adjusted per study, odds ratio converted to relative risk, >20ng/mL, Figure 2.
	risk of COVID-19 case, 12.4% lower, RR 0.88, $p = 0.06$ , high D levels 289 of 7272 (4.0%), low D levels 611 of 10876 (5.6%), adjusted per study, odds ratio converted to relative risk, >30ng/mL, Figure 2.
<b>[Li (B)]</b> , 1/11/2021, retrospective, United Kingdom, Europe, peer-reviewed, 6 authors.	<b>risk of COVID-19 severe case, 36.2% lower, RR 0.64, <math>p &lt; 0.001</math></b> , odds ratio converted to relative risk, >25nmol/L.
	risk of hospitalization, 28.8% lower, RR 0.71, $p < 0.001$ , odds ratio converted to relative risk, >25nmol/L.
	risk of COVID-19 case, 29.5% lower, RR 0.71, $p < 0.001$ , odds ratio converted to relative risk, >25nmol/L.
<b>[Livingston]</b> , 4/2/2021, retrospective, United Kingdom, Europe, peer-reviewed,	<b>risk of COVID-19 case, 50.9% lower, RR 0.49, <math>p &lt; 0.001</math></b> , high D levels 16 of 52 (30.8%), low D levels

7 authors.	31 of 52 (59.6%), odds ratio converted to relative risk, >34.4nmol/L.
[Lohia], 3/4/2021, retrospective, USA, North America, peer-reviewed, 4 authors.	<b>risk of death, 14.7% lower, RR 0.85, <math>p = 0.56</math></b> , high D levels 88, low D levels 95, odds ratio converted to relative risk, control prevalence approximated with overall prevalence, >30 ng/mL vs. <20 ng/mL, >30 ng/mL group size approximated.
	risk of mechanical ventilation, 18.9% lower, RR 0.81, $p = 0.48$ , high D levels 88, low D levels 95, odds ratio converted to relative risk, control prevalence approximated with overall prevalence, >30 ng/mL vs. <20 ng/mL, >30 ng/mL group size approximated.
	risk of ICU admission, 28.5% lower, RR 0.72, $p = 0.17$ , high D levels 88, low D levels 95, odds ratio converted to relative risk, control prevalence approximated with overall prevalence, >30 ng/mL vs. <20 ng/mL, >30 ng/mL group size approximated.
[Luo], 11/13/2020, retrospective, China, Asia, peer-reviewed, median age 56.0, 5 authors.	<b>risk of disease progression, 63.0% lower, RR 0.37, <math>p = 0.01</math></b> , high D levels 335, low D levels 560, >30nmol/L.
[Macaya], 10/21/2020, retrospective, Spain, Europe, peer-reviewed, 8 authors.	<b>risk of COVID-19 severe case, 55.0% lower, RR 0.45, <math>p = 0.07</math></b> , high D levels 11 of 35 (31.4%), low D levels 20 of 45 (44.4%), odds ratio converted to relative risk, >20ng/mL.
[Maghbooli], 9/25/2020, retrospective, Iran, Middle East, peer-reviewed, 11 authors.	<b>risk of death, 51.7% lower, RR 0.48, <math>p = 0.08</math></b> , high D levels 7 of 72 (9.7%), low D levels 27 of 134 (20.1%), age >40.
	risk of mechanical ventilation, 31.6% lower, RR 0.68, $p = 0.49$ , high D levels 6 of 77 (7.8%), low D levels 18 of 158 (11.4%).
	risk of ICU admission, 32.0% lower, RR 0.68, $p = 0.33$ , high D levels 11 of 77 (14.3%), low D levels 33 of 158 (20.9%), >30nmol/L.
[Matin], 7/30/2021, retrospective, case control, Iran, Middle East, peer-reviewed, 8 authors.	<b>risk of COVID-19 case, 66.1% lower, RR 0.34, <math>p &lt; 0.001</math></b> , >20ng/mL, RR approximated with OR.
[Mazziotti], 3/5/2021, retrospective, Italy,	<b>risk of acute hypoxemic respiratory failure, 37.0%</b>

Europe, peer-reviewed, 11 authors.	<b>lower, RR 0.63, <math>p = 0.006</math></b> , high D levels 72 of 187 (38.5%), low D levels 97 of 161 (60.2%), odds ratio converted to relative risk, >12ng/mL.
[Meltzer], 3/19/2021, retrospective, database analysis, USA, North America, peer-reviewed, 6 authors.	<b>risk of COVID-19 case, 34.6% lower, RR 0.65, <math>p = 0.11</math></b> , high D levels 61 of 1097 (5.6%), low D levels 118 of 1251 (9.4%), adjusted per study, >40ng/mL vs. <20ng/mL, Table 2, Model 2.
	risk of COVID-19 case, 36.0% lower, RR 0.64, $p = 0.38$ , high D levels 6 of 131 (4.6%), low D levels 239 of 3338 (7.2%), supplementation, $\geq 2,000$ IU/d.
	risk of COVID-19 case, 31.1% lower, RR 0.69, $p = 0.16$ , high D levels 15 of 304 (4.9%), low D levels 239 of 3338 (7.2%), supplementation, $\geq 1,001$ IU/d.
	risk of COVID-19 case, 8.9% lower, RR 0.91, $p = 0.56$ , high D levels 60 of 920 (6.5%), low D levels 239 of 3338 (7.2%), supplementation, $\geq 1$ IU/d.
[Meltzer (B)], 9/3/2020, retrospective, USA, North America, peer-reviewed, 6 authors.	<b>risk of COVID-19 case, 43.5% lower, RR 0.56, <math>p = 0.02</math></b> , high D levels 39 of 317 (12.3%), low D levels 32 of 172 (18.6%), adjusted per study, >20ng/mL.
[Mendy], 6/27/2020, retrospective, USA, North America, preprint, 4 authors.	<b>risk of death, 7.0% lower, RR 0.93, <math>p = 0.89</math></b> , high D levels 21 of 600 (3.5%), low D levels 5 of 89 (5.6%), odds ratio converted to relative risk.
	risk of combined death/ICU, 16.7% lower, RR 0.83, $p < 0.001$ , high D levels 68 of 600 (11.3%), low D levels 23 of 89 (25.8%), odds ratio converted to relative risk.
	risk of ICU admission, 55.3% lower, RR 0.45, $p = 0.008$ , high D levels 47 of 600 (7.8%), low D levels 18 of 89 (20.2%), odds ratio converted to relative risk.
	risk of hospitalization, 15.1% lower, RR 0.85, $p < 0.001$ , high D levels 171 of 89 (192.1%), low D levels 45 of 89 (50.6%), odds ratio converted to relative risk.
[Merzon], 7/23/2020, retrospective, Israel, Middle East, peer-reviewed, 3 authors.	<b>risk of hospitalization, 46.4% lower, RR 0.54, <math>p = 0.06</math></b> , high D levels 79, low D levels 703, odds ratio converted to relative risk, >30ng/mL.
	risk of COVID-19 case, 28.4% lower, RR 0.72, $p <$

	0.001, high D levels 1139, low D levels 6668, odds ratio converted to relative risk, >30ng/mL.
[Nimavat], 8/5/2021, retrospective, India, South Asia, peer-reviewed, 5 authors.	<b>risk of death, 50.4% lower, RR 0.50, <math>p = 0.17</math></b> , high D levels 13 of 131 (9.9%), low D levels 5 of 25 (20.0%), >10ng/mL, within cases.
	risk of COVID-19 severe case, 67.6% lower, RR 0.32, $p = 0.003$ , high D levels 17 of 131 (13.0%), low D levels 10 of 25 (40.0%), >10ng/mL, within cases.
[Orchard], 1/19/2021, retrospective, United Kingdom, Europe, peer-reviewed, 7 authors.	<b>risk of ICU admission, 58.8% lower, RR 0.41, <math>p = 0.001</math></b> , high D levels 9 of 40 (22.5%), low D levels 41 of 75 (54.7%), all hospitalized patients, >50 nmol/L.
	risk of death, 24.1% lower, RR 0.76, $p = 1.00$ , high D levels 1 of 9 (11.1%), low D levels 6 of 41 (14.6%), ICU patients only, >50 nmol/L.
	risk of mechanical ventilation, 8.9% lower, RR 0.91, $p = 0.70$ , high D levels 6 of 9 (66.7%), low D levels 30 of 41 (73.2%), ICU patients only, >50 nmol/L.
[Panagiotou], 6/30/2020, retrospective, United Kingdom, Europe, preprint, 12 authors.	<b>risk of ICU admission, 52.0% lower, RR 0.48, <math>p = 0.02</math></b> , high D levels 8 of 44 (18.2%), low D levels 34 of 90 (37.8%), >50nmol/L.
[Pimental], 5/31/2021, retrospective, Brazil, South America, peer-reviewed, 3 authors.	<b>risk of death, 29.4% lower, RR 0.71, <math>p = 1.00</math></b> , high D levels 3 of 17 (17.6%), low D levels 2 of 8 (25.0%), >20ng/mL.
[Radujkovic], 9/10/2020, prospective, Germany, Europe, peer-reviewed, 6 authors.	<b>risk of death, 93.2% lower, RR 0.07, <math>p = 0.001</math></b> , high D levels 144, low D levels 12, >30nmol/L.
	risk of combined intubation/death, 84.0% lower, RR 0.16, $p < 0.001$ , high D levels 144, low D levels 12, >30nmol/L.
[Ricci], 3/3/2021, retrospective, Italy, Europe, peer-reviewed, 15 authors.	<b>risk of death, 87.6% lower, RR 0.12, <math>p = 0.07</math></b> , high D levels 0 of 30 (0.0%), low D levels 3 of 22 (13.6%), continuity correction due to zero event (with reciprocal of the contrasting arm), >10 ng/mL.
[Savitri], 5/8/2021, retrospective, Indonesia, South Asia, peer-reviewed, 5 authors.	<b>risk of symptomatic case, 88.0% lower, RR 0.12, <math>p &lt; 0.001</math></b> , high D levels 3 of 25 (12.0%), low D levels 17 of 17 (100.0%), >20ng/ml.

[Sulli], 2/24/2021, retrospective, Italy, Europe, peer-reviewed, 10 authors, dosage not specified.	<b>risk of COVID-19 case, 51.1% lower, RR 0.49, <math>p &lt; 0.001</math></b> , high D levels 28 of 79 (35.4%), low D levels 37 of 51 (72.5%), >10ng/mL.
[Susianti], 2/12/2021, retrospective, Indonesia, South Asia, peer-reviewed, 8 authors.	<b>risk of death, 91.5% lower, RR 0.09, <math>p = 0.32</math></b> , high D levels 0 of 8 (0.0%), low D levels 9 of 42 (21.4%), continuity correction due to zero event (with reciprocal of the contrasting arm), >49.92 nmol/L.
	risk of ICU admission, 90.5% lower, RR 0.10, $p = 0.32$ , high D levels 0 of 8 (0.0%), low D levels 8 of 42 (19.0%), continuity correction due to zero event (with reciprocal of the contrasting arm), >49.92 nmol/L.
	risk of disease progression, 81.5% lower, RR 0.19, $p = 0.04$ , high D levels 8, low D levels 42, ISTH DIC>=5, >49.92 nmol/L, bivariate.
	risk of disease progression, 44.4% lower, RR 0.56, $p = 0.03$ , high D levels 8, low D levels 42, increased D-dimer >2 mg/L, >49.92 nmol/L, multivariate.
[Szeto], 12/30/2020, retrospective, USA, North America, peer-reviewed, 7 authors.	<b>risk of death, 5.6% higher, RR 1.06, <math>p = 1.00</math></b> , high D levels 14 of 58 (24.1%), low D levels 8 of 35 (22.9%).
	risk of mechanical ventilation, 39.7% lower, RR 0.60, $p = 0.21$ , high D levels 10 of 58 (17.2%), low D levels 10 of 35 (28.6%).
	risk of no hospital discharge, 26.7% higher, RR 1.27, $p = 0.50$ , high D levels 21 of 58 (36.2%), low D levels 10 of 35 (28.6%).
[Sánchez-Zuno], 5/28/2021, prospective, Mexico, North America, peer-reviewed, 12 authors, dosage 10,000IU days 1-14.	<b>risk of COVID-19 severe case, 5.6% lower, RR 0.94, <math>p = 1.00</math></b> , high D levels 4 of 8 (50.0%), low D levels 18 of 34 (52.9%), >30ng/mL, >4 symptoms.
[Vanegas-Cedillo], 3/14/2021, retrospective, Mexico, North America, preprint, 15 authors.	<b>risk of death, 52.6% lower, RR 0.47, <math>p = 0.006</math></b> , high D levels 95 of 494 (19.2%), low D levels 21 of 57 (36.8%), adjusted per study, >12ng/mL.
[Vassiliou (B)], 12/9/2020, prospective, Greece, Europe, peer-reviewed, 6 authors.	<b>risk of death, 90.9% lower, RR 0.09, <math>p = 0.04</math></b> , high D levels 0 of 15 (0.0%), low D levels 5 of 15 (33.3%), continuity correction due to zero event (with reciprocal of the contrasting arm), >15.2ng/mL.

[Walk], 11/9/2020, retrospective, Netherlands, Europe, preprint, 5 authors.	risk of combined intubation/death, 0.4% higher, RR 1.00, $p = 1.00$ , high D levels 48 of 110 (43.6%), low D levels 10 of 23 (43.5%), >25nmol/L.
[Ye], 10/13/2020, retrospective, China, Asia, peer-reviewed, 18 authors.	risk of severe/critical COVID-19, 93.4% lower, RR 0.07, $p = 0.03$ , high D levels 2 of 36 (5.6%), low D levels 8 of 26 (30.8%), adjusted per study, >50nmol/L.
[Yilmaz], 10/5/2020, retrospective, Turkey, Europe, peer-reviewed, 2 authors.	risk of severe case, 73.4% lower, RR 0.27, $p = 1.00$ , high D levels 0 of 11 (0.0%), low D levels 2 of 29 (6.9%), continuity correction due to zero event (with reciprocal of the contrasting arm), >20ng/ml.
	risk of moderate or severe case, 41.4% lower, RR 0.59, $p = 0.69$ , high D levels 2 of 11 (18.2%), low D levels 9 of 29 (31.0%), >20ng/ml.
[Ünsal], 4/5/2021, retrospective, Turkey, Europe, peer-reviewed, 10 authors.	risk of death, 80.6% lower, RR 0.19, $p = 0.23$ , high D levels 0 of 29 (0.0%), low D levels 2 of 27 (7.4%), continuity correction due to zero event (with reciprocal of the contrasting arm), >=20ng/mL.
	risk of oxygen therapy, 73.4% lower, RR 0.27, $p = 0.07$ , high D levels 2 of 29 (6.9%), low D levels 7 of 27 (25.9%), >=20ng/mL.

### 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, 63.0% lower, RR 0.37, $p = 0.28$ , treatment 3 of 16 (18.8%), 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, 89.0% lower, RR 0.11, $p = 0.002$ , treatment 10 of 57 (17.5%), control 5 of 9 (55.6%), adjusted per study.
[Asimi], 5/22/2021, retrospective, Bosnia and Herzegovina, Europe, preprint, 3	risk of mechanical ventilation, 97.4% lower, RR 0.03, $p < 0.001$ , treatment 0 of 270 (0.0%), control

<p>authors, dosage 2,000IU daily, this trial uses multiple treatments in the treatment arm (combined with zinc and selenium) - results of individual treatments may vary.</p>	<p>9 of 86 (10.5%), continuity correction due to zero event (with reciprocal of the contrasting arm), unadjusted.</p>
	<p>risk of hospitalization, 99.0% lower, RR 0.010, <math>p &lt; 0.001</math>, treatment 0 of 270 (0.0%), control 24 of 86 (27.9%), continuity correction due to zero event (with reciprocal of the contrasting arm), unadjusted.</p>
	<p>risk of COVID-19 severe case, 99.5% lower, RR 0.005, <math>p &lt; 0.001</math>, treatment 0 of 270 (0.0%), control 51 of 86 (59.3%), continuity correction due to zero event (with reciprocal of the contrasting arm), unadjusted.</p>
<p>[<i>Loucera</i>], 4/29/2021, retrospective, propensity score matching, Spain, Europe, preprint, 11 authors, dosage varies (calcifediol).</p>	<p><b>risk of death, 71.9% lower, RR 0.28, <math>p &lt; 0.001</math></b>, treatment 193, control 193, calcifediol, &lt;15 days before hospitalization, Cox model with inverse propensity weighting.</p>
	<p>risk of death, 63.6% lower, RR 0.36, <math>p &lt; 0.001</math>, treatment 210, control 210, calcifediol, &lt;30 days before hospitalization, Cox model with inverse propensity weighting.</p>
	<p>risk of death, 42.9% lower, RR 0.57, <math>p &lt; 0.001</math>, treatment 358, control 358, cholecalciferol, &lt;15 days before hospitalization, Cox model with inverse propensity weighting.</p>
	<p>risk of death, 23.7% lower, RR 0.76, <math>p &lt; 0.03</math>, treatment 416, control 416, cholecalciferol, &lt;30 days before hospitalization, Cox model with inverse propensity weighting.</p>
<p>[<i>Sánchez-Zuno (B)</i>], 5/28/2021, Randomized Controlled Trial, Mexico, North America, peer-reviewed, 12 authors, dosage 10,000IU days 1-14.</p>	<p><b>risk of COVID-19 severe case, 89.4% lower, RR 0.11, <math>p = 0.04</math></b>, treatment 0 of 22 (0.0%), control 4 of 20 (20.0%), continuity correction due to zero event (with reciprocal of the contrasting arm), risk of &gt;3 symptoms at day 14.</p>
	<p>risk of no recovery, 80.8% lower, RR 0.19, <math>p = 0.22</math>, treatment 0 of 22 (0.0%), control 2 of 20 (10.0%), continuity correction due to zero event (with reciprocal of the contrasting arm), risk of fever at day 14, Table S1.</p>

#### 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.

<p><i>[Alcala-Diaz]</i>, 5/21/2021, retrospective, Spain, Europe, peer-reviewed, 17 authors, dosage calcifediol 0.5mg day 1, 0.27mg day 3, 0.27mg day 7, 0.27mg day 14, 0.27mg day 21, 0.27mg day 28.</p>	<p><b>risk of death, 80.8% lower, RR 0.19, <math>p = 0.02</math>,</b> treatment 4 of 79 (5.1%), control 90 of 458 (19.7%), adjusted per study, odds ratio converted to relative risk, day 30, multivariate logistic regression.</p>
<p><i>[Castillo]</i>, 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.</p>	<p><b>risk of death, 85.4% lower, RR 0.15, <math>p = 0.11</math>,</b> treatment 0 of 50 (0.0%), control 2 of 26 (7.7%), continuity correction due to zero event (with reciprocal of the contrasting arm).</p>
	<p>risk of ICU admission, 94.2% lower, RR 0.06, <math>p = 0.001</math>, treatment 50, control 26, odds ratio converted to relative risk.</p>
<p><i>[Giannini]</i>, 1/14/2021, retrospective, Italy, Europe, peer-reviewed, 21 authors, dosage 200,000IU days 1-2.</p>	<p><b>risk of combined death/ICU, 36.6% lower, RR 0.63, <math>p = 0.13</math>,</b> treatment 14 of 36 (38.9%), control 29 of 55 (52.7%), odds ratio converted to relative risk.</p>
<p><i>[Güven]</i>, 7/23/2021, retrospective, Turkey, Europe, peer-reviewed, 2 authors, dosage 300,000IU single dose.</p>	<p><b>risk of death, 24.8% lower, RR 0.75, <math>p = 0.32</math>,</b> treatment 43 of 113 (38.1%), control 30 of 62 (48.4%), odds ratio converted to relative risk.</p>
<p><i>[Jevalikar]</i>, 12/28/2020, prospective, India, South Asia, peer-reviewed, 8 authors, dosage 60,000IU single dose, median total dose.</p>	<p><b>risk of death, 82.0% lower, RR 0.18, <math>p = 0.12</math>,</b> treatment 1 of 128 (0.8%), control 3 of 69 (4.3%).</p>
	<p>risk of ICU admission, 33.7% lower, RR 0.66, <math>p = 0.29</math>, treatment 16 of 128 (12.5%), control 13 of 69 (18.8%).</p>
	<p>risk of oxygen therapy, 31.7% lower, RR 0.68, <math>p = 0.06</math>, treatment 38 of 128 (29.7%), control 30 of 69 (43.5%).</p>
<p><i>[Krishnan]</i>, 7/20/2020, retrospective, USA, North America, peer-reviewed, 13 authors, dosage not specified.</p>	<p><b>risk of death, 19.0% lower, RR 0.81, <math>p = 0.42</math>,</b> treatment 8 of 16 (50.0%), control 84 of 136 (61.8%).</p>
<p><i>[Lakkireddy]</i>, 2/23/2021, Randomized Controlled Trial, India, South Asia, peer-reviewed, mean age 45.5, 9 authors, dosage 60,000IU days 1-8, 8 or 10 days depending on BMI.</p>	<p><b>risk of death, 60.9% lower, RR 0.39, <math>p = 0.27</math>,</b> treatment 2 of 44 (4.5%), control 5 of 43 (11.6%).</p>
	<p>risk of ICU admission, 21.8% lower, RR 0.78, <math>p = 0.74</math>, treatment 4 of 44 (9.1%), control 5 of 43 (11.6%).</p>

	hospitalization time, 7.1% lower, relative time 0.93, $p = 0.90$ , treatment 44, control 43.
[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.	<b>risk of death, 79.8% lower, RR 0.20, <math>p &lt; 0.001</math></b> , treatment 73, control 253, odds ratio converted to relative risk, primary cohort.
	risk of death, 55.5% lower, RR 0.44, $p = 0.02$ , treatment 80, control 443, odds ratio converted to relative risk, validation cohort.
[Lohia (B)], 3/4/2021, retrospective, USA, North America, peer-reviewed, 4 authors, dosage not specified.	<b>risk of death, 10.7% lower, RR 0.89, <math>p = 0.75</math></b> , treatment 26, control 69, odds ratio converted to relative risk, <20 ng/mL, control prevalence approximated with overall prevalence.
	risk of mechanical ventilation, 26.9% lower, RR 0.73, $p = 0.42$ , treatment 26, control 69, odds ratio converted to relative risk, <20 ng/mL, control prevalence approximated with overall prevalence.
	risk of ICU admission, 2.7% lower, RR 0.97, $p = 0.93$ , treatment 26, control 69, odds ratio converted to relative risk, <20 ng/mL, control prevalence approximated with overall prevalence.
[Murai], 11/17/2020, Randomized Controlled Trial, Brazil, South America, peer-reviewed, 17 authors, dosage 200,000IU single dose.	<b>risk of death, 48.7% higher, RR 1.49, <math>p = 0.43</math></b> , treatment 9 of 119 (7.6%), control 6 of 118 (5.1%).
	risk of mechanical ventilation, 47.5% lower, RR 0.52, $p = 0.09$ , treatment 9 of 119 (7.6%), control 17 of 118 (14.4%).
	risk of ICU admission, 24.6% lower, RR 0.75, $p = 0.30$ , treatment 19 of 119 (16.0%), control 25 of 118 (21.2%).
[Nogués], 1/22/2021, prospective quasi-randomized (ward), Spain, Europe, peer-reviewed, 16 authors, dosage calcifediol 0.5mg day 1, 0.27mg day 3, 0.27mg day 7, 0.27mg day 15, 0.27mg day 30.	<b>risk of death, 79.0% lower, RR 0.21, <math>p = 0.001</math></b> , treatment 21 of 447 (4.7%), control 62 of 391 (15.9%), adjusted per study, ITT.
	risk of death, 48.0% lower, RR 0.52, $p = 0.001$ , treatment 500, control 338, adjusted per study, including patients treated later.
	risk of ICU admission, 87.0% lower, RR 0.13, $p < 0.001$ , treatment 20 of 447 (4.5%), control 82 of 391 (21.0%), adjusted per study, ITT.

<i>[Rastogi]</i> , 11/12/2020, Randomized Controlled Trial, India, South Asia, peer-reviewed, 8 authors, dosage 60,000IU days 1-7.	<b>risk of no virological cure, 52.6% lower, RR 0.47, <math>p = 0.02</math></b> , treatment 6 of 16 (37.5%), control 19 of 24 (79.2%).
<i>[Tan]</i> , 6/10/2020, retrospective, Singapore, Asia, peer-reviewed, 14 authors, dosage 1,000IU daily.	<b>risk of oxygen therapy, 80.5% lower, RR 0.20, <math>p = 0.04</math></b> , treatment 3 of 17 (17.6%), control 16 of 26 (61.5%), adjusted per study.

## 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.

<i>[Annweiler (C)]</i> , 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.	<b>risk of death, 93.0% lower, RR 0.07, <math>p = 0.02</math></b> , treatment 2 of 29 (6.9%), control 10 of 32 (31.2%), adjusted per study, regular bolus supplementation.
<i>[Blanch-Rubió]</i> , 10/20/2020, retrospective, Spain, Europe, peer-reviewed, 10 authors, dosage not specified.	<b>risk of COVID-19 case, 8.0% lower, RR 0.92, <math>p = 0.68</math></b> , treatment 62 of 1303 (4.8%), control 47 of 799 (5.9%), adjusted per study.
<i>[Cangiano]</i> , 12/22/2020, retrospective, Italy, Europe, peer-reviewed, 14 authors, dosage 25,000IU 2x per month.	<b>risk of death, 70.0% lower, RR 0.30, <math>p = 0.04</math></b> , treatment 3 of 20 (15.0%), control 39 of 78 (50.0%).
<i>[Cereda]</i> , 11/11/2020, retrospective, Italy, Europe, peer-reviewed, 7 authors, dosage varies.	<b>risk of death, 73.0% higher, RR 1.73, <math>p = 0.14</math></b> , treatment 7 of 18 (38.9%), control 40 of 152 (26.3%), odds ratio converted to relative risk, $\geq 25$ .
	risk of hospitalization, 17.3% higher, RR 1.17, $p = 0.68$ , treatment 7 of 27 (25.9%), control 36 of 170 (21.2%), odds ratio converted to relative risk.
<i>[Fasano]</i> , 6/2/2021, retrospective, Italy, Europe, peer-reviewed, 7 authors, dosage not specified.	<b>risk of COVID-19 case, 42.0% lower, RR 0.58, <math>p = 0.05</math></b> , treatment 13 of 329 (4.0%), control 92 of 1157 (8.0%), odds ratio converted to relative risk.
<i>[Israel (B)]</i> , 7/27/2021, retrospective, Israel, Middle East, peer-reviewed, 10 authors.	<b>risk of hospitalization, 9.1% lower, RR 0.91, <math>p = 0.003</math></b> , treatment 737 of 2406 (30.6%), control 6216 of 18453 (33.7%), odds ratio converted to relative risk, PCR+, cohort 2.
<i>[Levitus]</i> , 5/3/2021, retrospective, USA,	<b>risk of COVID-19 severe case, 30.8% lower, RR</b>

North America, peer-reviewed, 9 authors, dosage varies.	<b>0.69, <math>p = 0.25</math></b> , treatment 65, control 64, odds ratio converted to relative risk, $\geq 1$ .
	risk of COVID-19 severe case, 40.0% lower, RR 0.60, $p = 0.15$ , treatment 65, control 64, odds ratio converted to relative risk, $\geq 5$ .
	risk of COVID-19 severe case, no change, RR 1.00, $p = 0.92$ , treatment 65, control 64, odds ratio converted to relative risk, $\geq 50$ .
<b>[Louca]</b> , 11/30/2020, retrospective, United Kingdom, Europe, peer-reviewed, 26 authors, dosage not specified.	<b>risk of COVID-19 case, 7.5% lower, RR 0.92, <math>p &lt; 0.001</math></b> , odds ratio converted to relative risk, United Kingdom, all adjustment model.
<b>[Ma]</b> , 1/29/2021, retrospective, United Kingdom, Europe, peer-reviewed, 4 authors, dosage not specified.	<b>risk of COVID-19 case, 30.0% lower, RR 0.70, <math>p = 0.03</math></b> , treatment 49 of 363 (13.5%), control 1329 of 7934 (16.8%), adjusted per study, odds ratio converted to relative risk.
<b>[Meltzer (C)]</b> , 3/19/2021, retrospective, database analysis, USA, North America, peer-reviewed, 6 authors, dosage not specified.	<b>risk of COVID-19 case, 36.0% lower, RR 0.64, <math>p = 0.38</math></b> , treatment 6 of 131 (4.6%), control 239 of 3338 (7.2%), $\geq 2,000$ IU/d.
	risk of COVID-19 case, 31.1% lower, RR 0.69, $p = 0.16$ , treatment 15 of 304 (4.9%), control 239 of 3338 (7.2%), $\geq 1,001$ IU/d.
	risk of COVID-19 case, 8.9% lower, RR 0.91, $p = 0.56$ , treatment 60 of 920 (6.5%), control 239 of 3338 (7.2%), $\geq 1$ IU/d.
<b>[Oristrell]</b> , 7/17/2021, retrospective, Spain, Europe, peer-reviewed, 8 authors, dosage varies (calcifediol).	<b>risk of death, 1.0% higher, RR 1.01, <math>p = 0.91</math></b> , calcifediol, univariate.
	risk of death, 4.0% lower, RR 0.96, $p = 0.37$ , cholecalciferol, univariate.
	risk of COVID-19 case, 1.0% lower, RR 0.99, $p = 0.65$ , calcifediol, univariate.
	risk of COVID-19 case, 5.0% lower, RR 0.95, $p = 0.004$ , cholecalciferol, multivariate.
<b>[Oristrell (B)]</b> , 4/6/2021, retrospective, Spain, Europe, peer-reviewed, 10 authors, dosage calcifediol 0.3mg daily, mean daily dose.	<b>risk of death, 43.0% lower, RR 0.57, <math>p = 0.001</math></b> , treatment 2296, control 3407, multivariate, patients with CKD stages 4-5.
	risk of COVID-19 severe case, 43.0% lower, RR

	0.57, $p < 0.001$ , treatment 2296, control 3407, multivariate, patients with CKD stages 4-5.
	risk of COVID-19 case, 22.0% lower, RR 0.78, $p = 0.01$ , treatment 163 of 2296 (7.1%), control 326 of 3407 (9.6%), multivariate, patients with CKD stages 4-5.
[Sulli (B)], 2/24/2021, retrospective, Italy, Europe, peer-reviewed, 10 authors, dosage not specified.	<b>risk of COVID-19 case, 50.4% lower, RR 0.50, <math>p &lt; 0.001</math></b> , treatment 22 of 66 (33.3%), control 43 of 64 (67.2%), vitamin D supplementation.
[Vasheghani], 1/18/2021, retrospective, Iran, Middle East, preprint, 5 authors, dosage not specified.	<b>risk of death, 30.4% lower, RR 0.70, <math>p = 0.45</math></b> , treatment 7 of 88 (8.0%), control 48 of 420 (11.4%), vitamin D supplementation.
	risk of ICU admission, 63.8% lower, RR 0.36, $p = 0.009$ , treatment 13 of 185 (7.0%), control 53 of 323 (16.4%), adjusted per study, vitamin D levels >30ng/mL.
[Ünsal (B)], 4/5/2021, retrospective, Turkey, Europe, peer-reviewed, 10 authors, dosage varies.	<b>risk of pneumonia, 71.4% lower, RR 0.29, <math>p = 0.009</math></b> , treatment 4 of 28 (14.3%), control 14 of 28 (50.0%), average 800-1000IU/day cholecalciferol.

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