Sunlight for COVID-19: real-time meta analysis of 5 studies

@CovidAnalysis, March 2024, Version 4
https://c19early.org/sunmeta.html

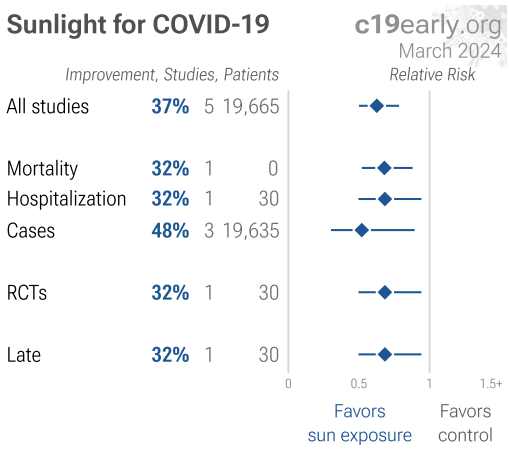
Abstract

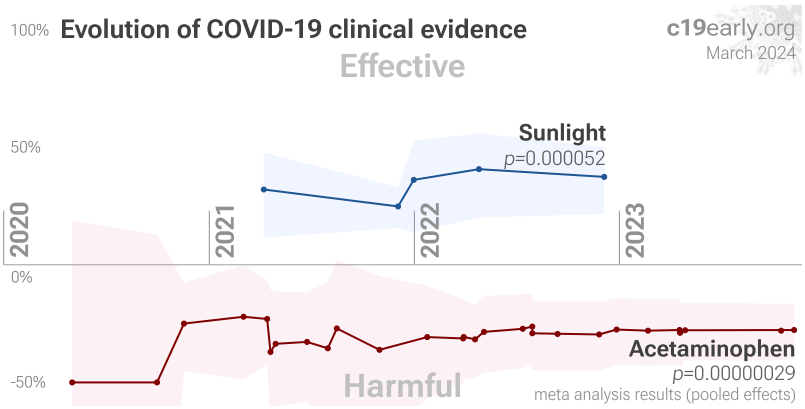
Statistically significant lower risk is seen for mortality, hospitalization, recovery, and cases. 5 studies from 5 independent teams in 4 countries show statistically significant improvements.

Meta analysis using the most serious outcome reported shows 37% [22-50%] lower risk. Results are similar for Randomized Controlled Trials.

No treatment or intervention is 100% effective. All practical, effective, and safe means should be used based on risk/benefit analysis. Multiple treatments are typically used in combination, and other treatments may be more effective. There has been no early treatment studies to date.

All data to reproduce this paper and sources are in the appendix.





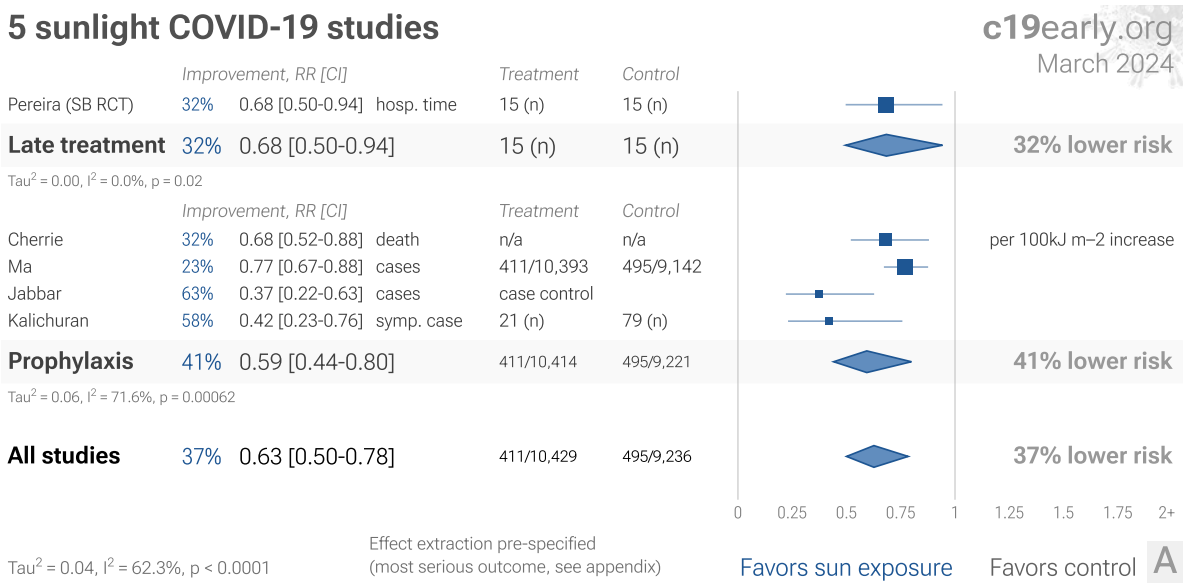
HIGHLIGHTS

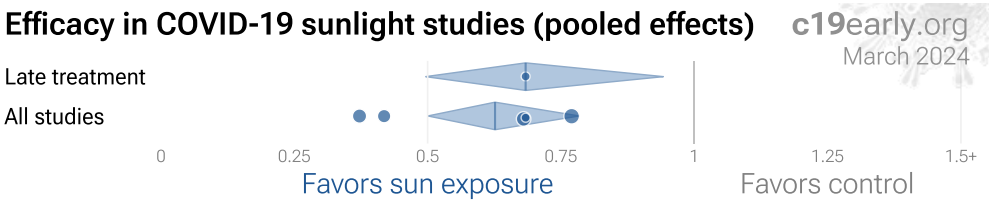
Sunlight reduces risk for COVID-19 with very high confidence for pooled analysis, high confidence for cases, and low confidence for mortality, hospitalization, and recovery.

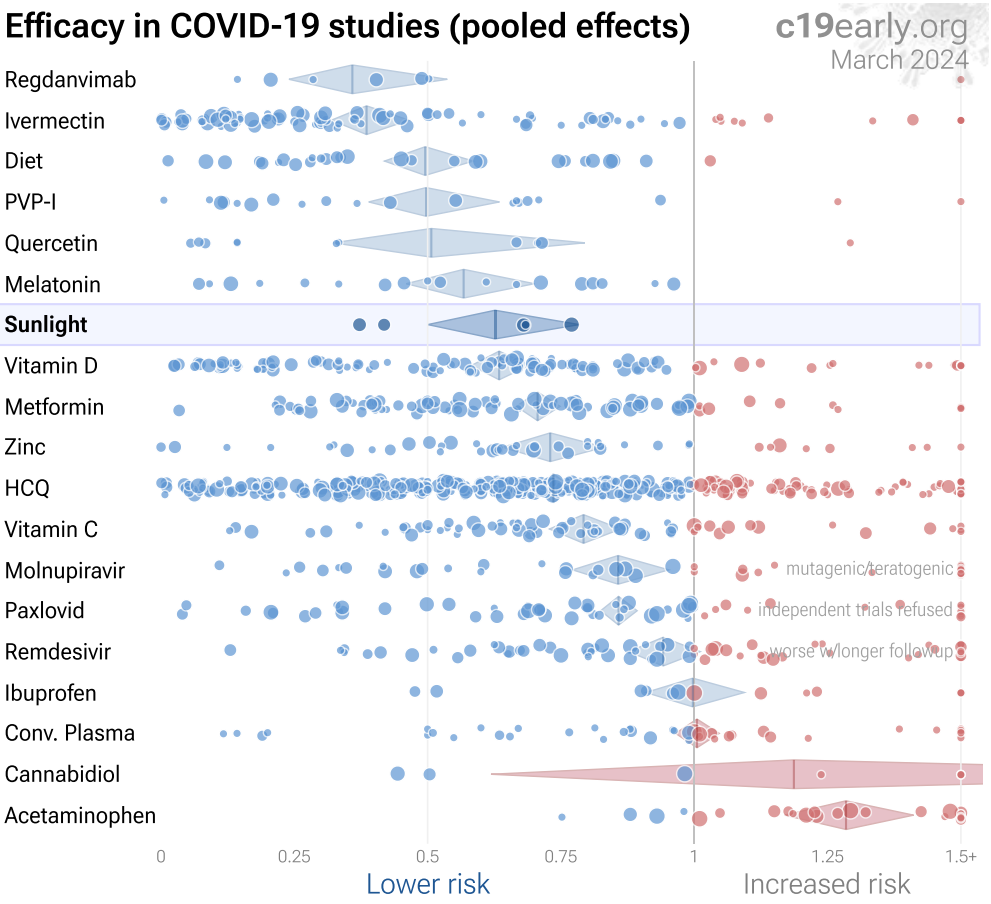
Sunlight was the 32nd treatment shown effective with ≥3 clinical studies in December 2021, now known with p = 0.000052 from 5 studies.

We show traditional outcome specific analyses and combined evidence from all studies, incorporating treatment delay, a primary confounding factor in COVID-19 studies.

Real-time updates and corrections, transparent analysis with all results in the same format, consistent protocol for 66 treatments.


5 sunlight COVID-19 studies
c19early.org
March 2024
Improvement, RR [CI]
Treatment
Control
Pereira (SB RCT) 32% 0.68 [0.50-0.94] hosp. time 15 (n) 15 (n)
Late treatment 32% 0.68 [0.50-0.94] 15 (n) 15 (n) 32% lower risk
Tau² = 0.00, I² = 0.0%, p = 0.02
Improvement, RR [CI]
Treatment
Control
Cherrie 32% 0.68 [0.52-0.88] death n/a n/a per 100kJ m−2 increase
Ma 23% 0.77 [0.67-0.88] cases 411/10,393 495/9,142
Jabbar 63% 0.37 [0.22-0.63] cases case control
Kalichuran 58% 0.42 [0.23-0.76] symp. case 21 (n) 79 (n)
Prophylaxis 41% 0.59 [0.44-0.80] 411/10,414 495/9,221 41% lower risk
Tau² = 0.06, I² = 71.6%, p = 0.00062
All studies 37% 0.63 [0.50-0.78] 411/10,429 495/9,236 37% lower risk
0 0.25 0.5 0.75 1 1.25 1.5 1.75 2+
Tau² = 0.04, I² = 62.3%, p < 0.0001
Effect extraction pre-specified
(most serious outcome, see appendix)
Favors sun exposure
Favors control
A


Efficacy in COVID-19 sunlight studies (pooled effects)
c19early.org
March 2024
Late treatment
All studies
0 0.25 0.5 0.75 1 1.25 1.5+
Favors sun exposure
Favors control
B


Efficacy in COVID-19 studies (pooled effects)
c19early.org
March 2024
Regdanvimab
Ivermectin
Diet
PVP-I
Quercetin
Melatonin
Sunlight
Vitamin D
Metformin
Zinc
HCQ
Vitamin C
Molnupiravir
Paxlovid
Remdesivir
Ibuprofen
Conv. Plasma
Cannabidiol
Acetaminophen
mutagenic/teratogenic
independent trials refused
worse w/longer follow-up
0 0.25 0.5 0.75 1 1.25 1.5+
Lower risk
Increased risk
C

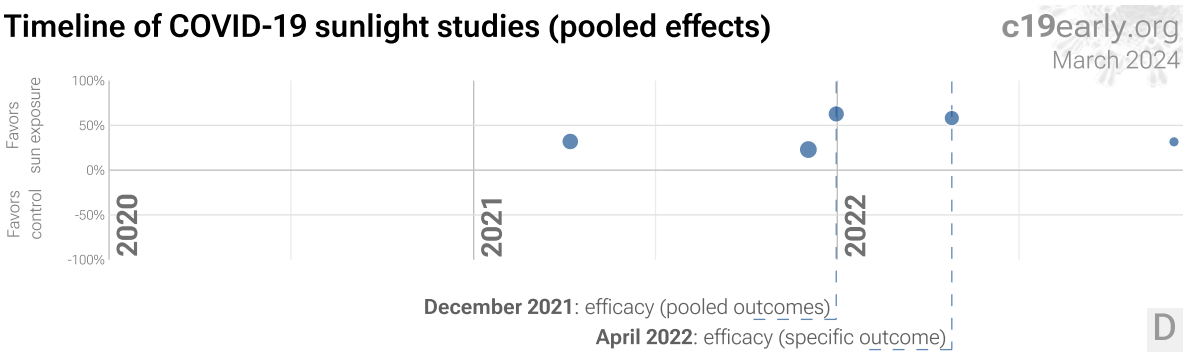


Figure 1. **A. Random effects meta-analysis.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes, and the heterogeneity section for discussion. Effect extraction is pre-specified, using the most serious outcome reported. For details of effect extraction see the appendix. **B. Scatter plot showing the most serious outcome in all studies.** The diamond shows the results of random effects meta-analysis. **C. Results within the context of multiple COVID-19 treatments.** 0.6% of 6,686 proposed treatments show efficacy *c19early.org*. **D. Timeline of results in sunlight studies.** The marked dates indicate the time when efficacy was known with a statistically significant improvement of ≥10% from ≥3 studies for pooled outcomes and one or more specific outcome. Efficacy based on specific outcomes was delayed by 3.8 months, compared to using pooled outcomes.

Introduction

Other infections. Efficacy with sunlight has been shown for influenza *Ruble, Schuit, Slusky*.

Analysis. We analyze all significant studies reporting COVID-19 outcomes as a function of sunlight exposure. 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 all studies, studies within each treatment stage, individual outcomes, and Randomized Controlled Trials (RCTs).

Preclinical Research

2 *In Vitro* studies support the efficacy of sunlight *Aguida, Ratnesar-Shumate*.

Preclinical research is an important part of the development of treatments, however results may be very different in clinical trials. Preclinical results are not used in this paper.

Results

Table 1 summarizes the results for all studies, for Randomized Controlled Trials, and for specific outcomes. Figure 2, 3, 4, 5, and 6 show forest plots for random effects meta-analysis of all studies with pooled effects, mortality results, hospitalization, recovery, and cases.

	Improvement	*Studies*	*Patients*	*Authors*
All studies	37% [22-50%] ****	5	19,665	36
Randomized Controlled Trials	32% [6-50%] *	1	30	5
Cases	48% [11-70%] *	3	19,635	24

Table 1. **Random effects meta-analysis for all studies, for Randomized Controlled Trials, and for specific outcomes.** Results show the percentage improvement with treatment and the 95% confidence interval. * $p<0.05$ *** $p<0.001$.

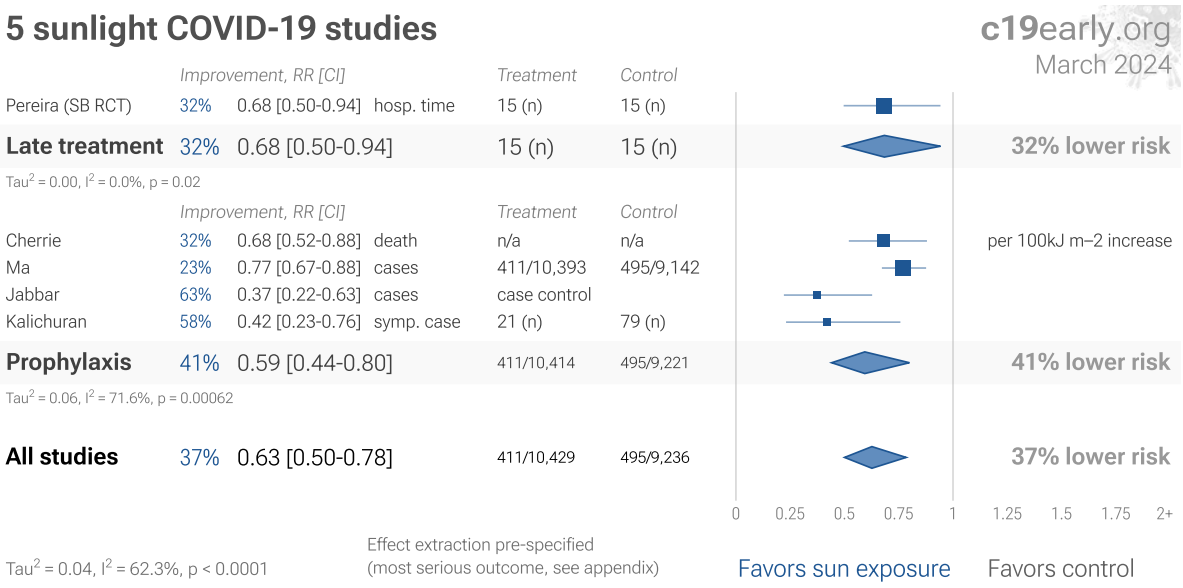


Figure 2. **Random effects meta-analysis for all studies with pooled effects.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes, and the heterogeneity section for discussion. Effect extraction is pre-specified, using the most serious outcome reported. For details of effect extraction see the appendix.

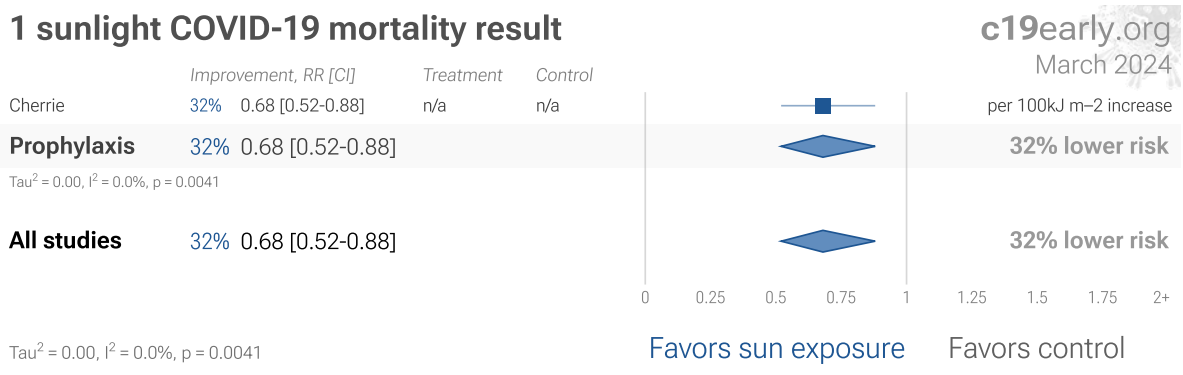


Figure 3. **Random effects meta-analysis for mortality results.**

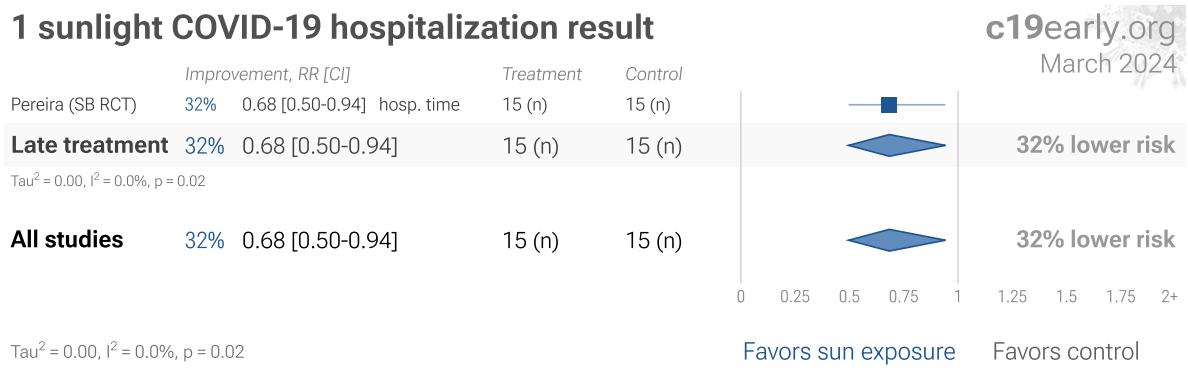


Figure 4. Random effects meta-analysis for hospitalization.

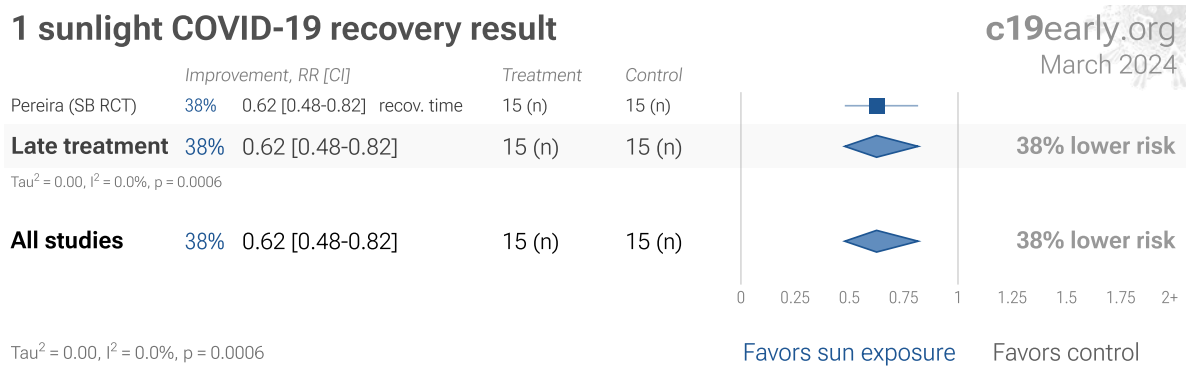


Figure 5. Random effects meta-analysis for recovery.

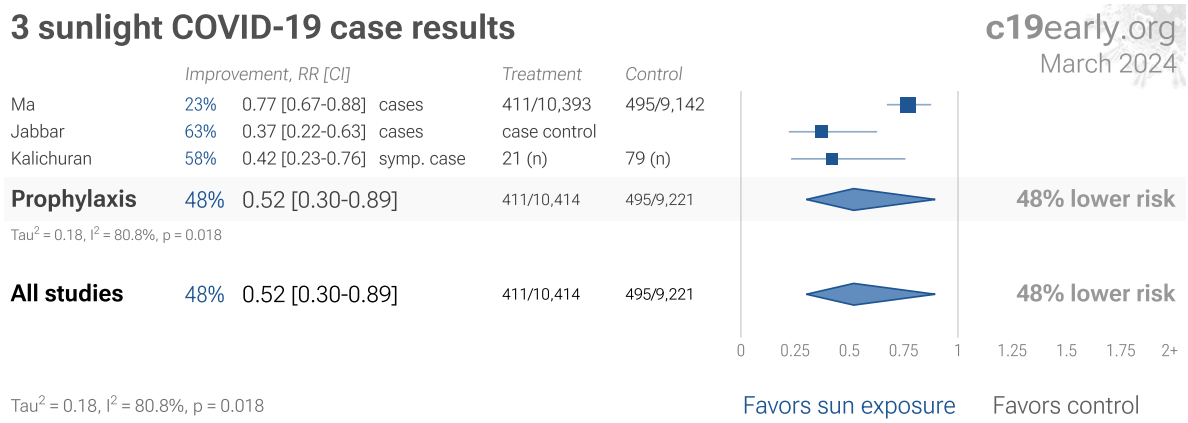


Figure 6. Random effects meta-analysis for cases.

Randomized Controlled Trials (RCTs)

Figure 7 shows a forest plot for random effects meta-analysis of all Randomized Controlled Trials. RCT results are included in Table 1. Currently there is only one RCT.

RCTs have many potential biases. Bias in clinical research may be defined as something that tends to make conclusions differ systematically from the truth. RCTs help to make study groups more similar and can provide a higher level of evidence, however they are subject to many biases *Jadad*, and analysis of double-blind RCTs has identified extreme levels of bias *Gøtzsche*. For COVID-19, the overhead may delay treatment, dramatically compromising efficacy; they may encourage monotherapy for simplicity at the cost of efficacy which may rely on combined or

synergistic effects; the participants that sign up may not reflect real world usage or the population that benefits most in terms of age, comorbidities, severity of illness, or other factors; standard of care may be compromised and unable to evolve quickly based on emerging research for new diseases; errors may be made in randomization and medication delivery; and investigators may have hidden agendas or vested interests influencing design, operation, analysis, and the potential for fraud. All of these biases have been observed with COVID-19 RCTs. There is no guarantee that a specific RCT provides a higher level of evidence.

Conflicts of interest for COVID-19 RCTs. RCTs are expensive and many RCTs are funded by pharmaceutical companies or interests closely aligned with pharmaceutical companies. For COVID-19, this creates an incentive to show efficacy for patented commercial products, and an incentive to show a lack of efficacy for inexpensive treatments. The bias is expected to be significant, for example *Als-Nielsen et al.* analyzed 370 RCTs from Cochrane reviews, showing that trials funded by for-profit organizations were 5 times more likely to recommend the experimental drug compared with those funded by nonprofit organizations. For COVID-19, some major philanthropic organizations are largely funded by investments with extreme conflicts of interest for and against specific COVID-19 interventions.

RCTs for novel acute diseases requiring rapid treatment. High quality RCTs for novel acute diseases are more challenging, with increased ethical issues due to the urgency of treatment, increased risk due to enrollment delays, and more difficult design with a rapidly evolving evidence base. For COVID-19, the most common site of initial infection is the upper respiratory tract. Immediate treatment is likely to be most successful and may prevent or slow progression to other parts of the body. For a non-prophylaxis RCT, it makes sense to provide treatment in advance and instruct patients to use it immediately on symptoms, just as some governments have done by providing medication kits in advance. Unfortunately, no RCTs have been done in this way. Every treatment RCT to date involves delayed treatment. Among the 66 treatments we have analyzed, 63% of RCTs involve very late treatment 5+ days after onset. No non-prophylaxis COVID-19 RCTs match the potential real-world use of early treatments (they may more accurately represent results for treatments that require visiting a medical facility, e.g., those requiring intravenous administration).

RCT bias for widely available treatments. RCTs have a bias against finding an effect for interventions that are widely available — patients that believe they need the intervention are more likely to decline participation and take the intervention. RCTs for sunlight are more likely to enroll low-risk participants that do not need treatment to recover, making the results less applicable to clinical practice. This bias is likely to be greater for widely known treatments, and may be greater when the risk of a serious outcome is overstated. This bias does not apply to the typical pharmaceutical trial of a new drug that is otherwise unavailable.

Non-RCT studies have been shown to be reliable. Evidence shows that non-RCT trials can also provide reliable results. *Concato et al.* found that well-designed observational studies do not systematically overestimate the magnitude of the effects of treatment compared to RCTs. *Anglemyer et al.* summarized reviews comparing RCTs to observational studies and found little evidence for significant differences in effect estimates. *Lee et al.* showed that only 14% of the guidelines of the Infectious Diseases Society of America were based on RCTs. Evaluation of studies relies on an understanding of the study and potential biases. Limitations in an RCT can outweigh the benefits, for example excessive dosages, excessive treatment delays, or Internet survey bias could have a greater effect on results. Ethical issues may also prevent running RCTs for known effective treatments. For more on issues with RCTs see *Deaton, Nichol*.

Using all studies identifies efficacy 5.7+ months faster for COVID-19. Currently, 44 of the treatments we analyze show statistically significant efficacy or harm, defined as ≥10% decreased risk or >0% increased risk from ≥3 studies. Of the 44 treatments with statistically significant efficacy/harm, 28 have been confirmed in RCTs, with a mean delay of 5.7 months. When considering only low cost treatments, 23 have been confirmed with a delay of 6.9 months. For the 16 unconfirmed treatments, 3 have zero RCTs to date. The point estimates for the remaining 13 are all consistent with the overall results (benefit or harm), with 10 showing >20%. The only treatments showing >10% efficacy for all studies, but <10% for RCTs are sotrovimab and aspirin.

Summary. We need to evaluate each trial on its own merits. RCTs for a given medication and disease may be more reliable, however they may also be less reliable. For off-patent medications, very high conflict of interest trials may be more likely to be RCTs, and more likely to be large trials that dominate meta analyses.

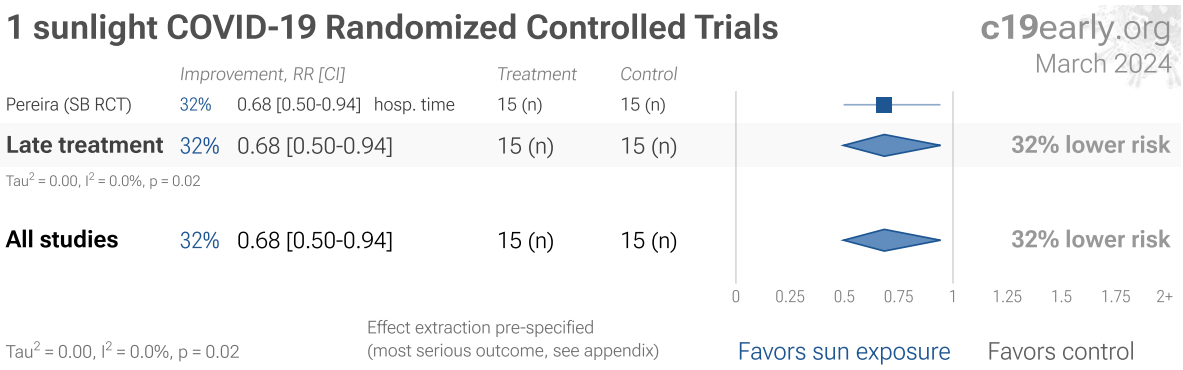


Figure 7. **Random effects meta-analysis for all Randomized Controlled Trials.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes, and the heterogeneity section for discussion. Effect extraction is pre-specified, using the most serious outcome reported. For details of effect extraction see the appendix.

Heterogeneity

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

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 (as in *López-Medina*).

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 many different variants of SARS-CoV-2 and efficacy may depend critically on the distribution of variants encountered by the patients in a study. For example, the Gamma variant shows significantly different characteristics *Faria, Karita, Nonaka, Zavascki*. Different mechanisms of action may be more or less effective depending on variants, for example the viral entry process for the omicron variant has moved towards TMPRSS2-independent fusion, suggesting that TMPRSS2 inhibitors may be less effective *Peacock, Willett*.

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

Pooled outcome analysis. We present both pooled analyses and specific outcome analyses. Notably, pooled analysis often results in earlier detection of efficacy as shown in Figure 8. For many COVID-19 treatments, a reduction in mortality logically follows from a reduction in hospitalization, which follows from a reduction in symptomatic cases, etc. An antiviral tested with a low-risk population may report zero mortality in both arms, however a reduction in severity and improved viral clearance may translate into lower mortality among a high-risk population, and including these results in pooled analysis allows faster detection of efficacy. Trials with high-risk patients may also be restricted due to ethical concerns for treatments that are known or expected to be effective.

Pooled analysis enables using more of the available information. While there is much more information available, for example dose-response relationships, the advantage of the method used here is simplicity and transparency. Note that pooled analysis could hide efficacy, for example a treatment that is beneficial for late stage patients but has no effect on viral replication or early stage disease could show no efficacy in pooled analysis if most studies only examine viral clearance. While we present pooled results, we also present individual outcome analyses, which may be more informative for specific use cases.

Pooled outcomes identify efficacy faster. Currently, 44 of the treatments we analyze show statistically significant efficacy or harm, defined as ≥10% decreased risk or >0% increased risk from ≥3 studies. 88% of treatments showing statistically significant efficacy/harm with pooled effects have been confirmed with one or more specific outcomes, with a mean delay of 3.6 months. When restricting to RCTs only, 50% of treatments showing statistically significant efficacy/harm with pooled effects have been confirmed with one or more specific outcomes, with a mean delay of 6.1 months.

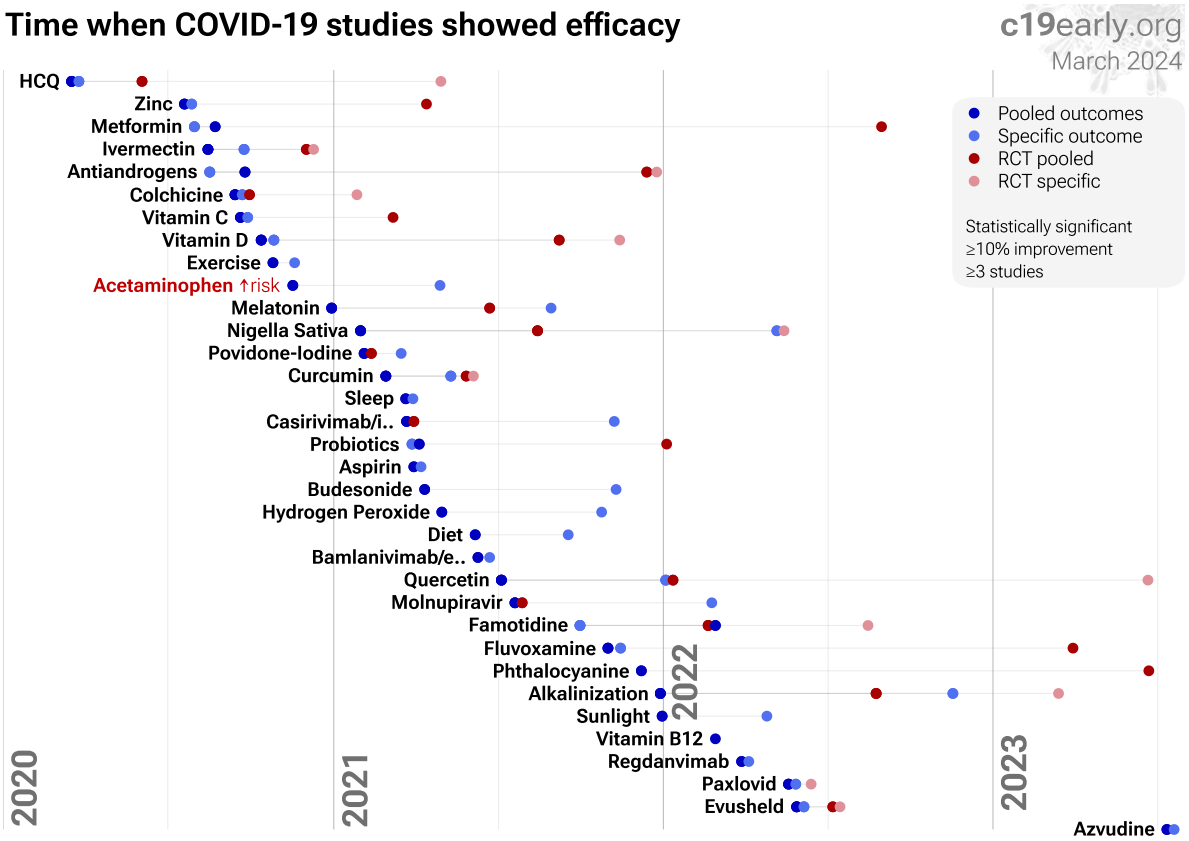


Figure 8. **The time when studies showed that treatments were effective, defined as statistically significant improvement of ≥10% from ≥3 studies.** Pooled results typically show efficacy earlier than specific outcome results. Results from all studies often shows efficacy much earlier than when restricting to RCTs. Results reflect conditions as used in trials to date, these depend on the population treated, treatment delay, and treatment regimen.

Meta analysis. 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 early treatment is very effective. This may have a greater effect than pooling different outcomes such as mortality and hospitalization. For example a treatment may have 50% efficacy for mortality but only 40% for hospitalization when used within 48 hours. However efficacy could be 0% when used late.

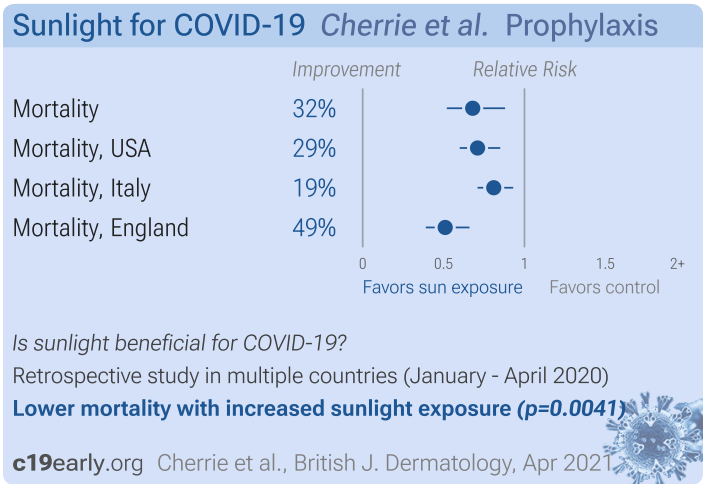
All meta analyses combine heterogeneous studies, varying in population, variants, and potentially all factors above, and therefore may obscure efficacy by including studies where treatment is less effective. Generally, we expect the estimated effect size from meta analysis to be less than that for the optimal case. Looking at all studies is valuable for providing an overview of all research, important to avoid cherry-picking, and informative when a positive result is found despite combining less-optimal situations. However, the resulting estimate does not apply to specific cases such as early treatment in high-risk populations. While we present results for all studies, we also present treatment time and individual outcome analyses, which may be more informative for specific use cases.

Conclusion

Increased sun exposure reduces risk for COVID-19. Statistically significant lower risk is seen for mortality, hospitalization, recovery, and cases. 5 studies from 5 independent teams in 4 countries show statistically significant improvements. Meta analysis using the most serious outcome reported shows 37% [22-50%] lower risk. Results are similar for Randomized Controlled Trials.

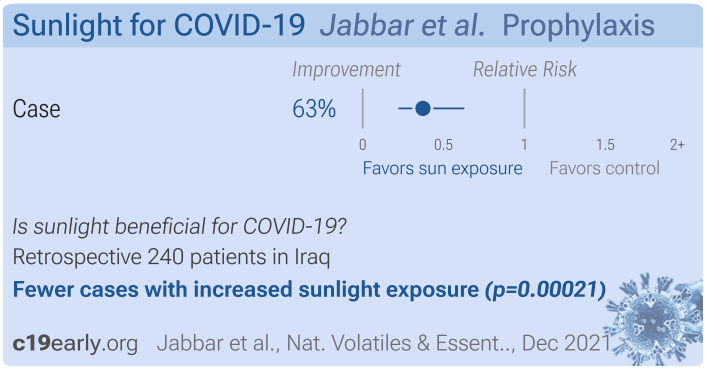
Study Notes

Cherrie



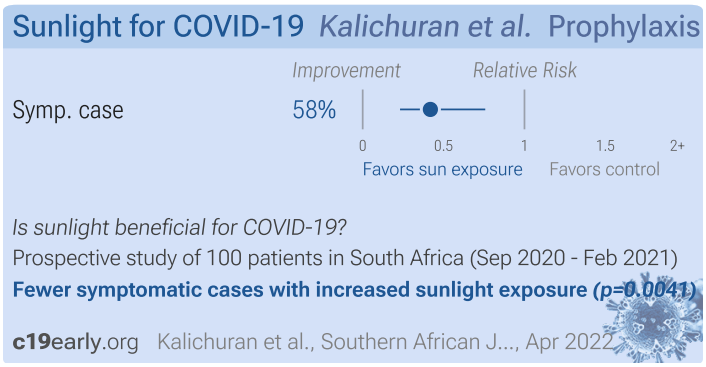
Cherrie: Analysis of UVA exposure and COVID-19 mortality in the USA, England, and Italy, showing increased UVA exposure associated with lower mortality.

Jabbar



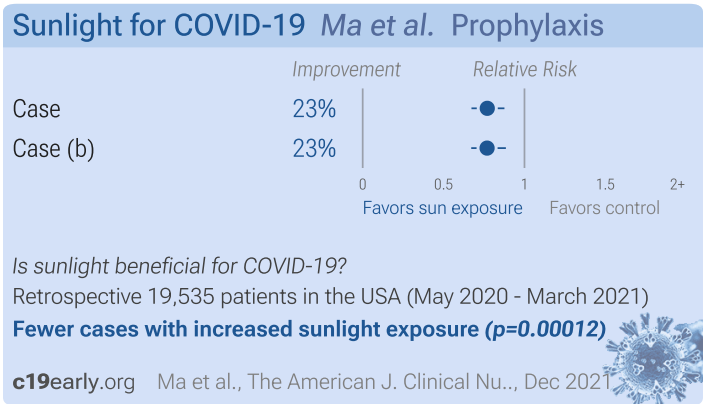
Jabbar: Analysis of 120 COVID-19 and 120 control patients in Iraq, showing lower risk of cases with regular sunlight exposure (3 times/week).

Kalichuran



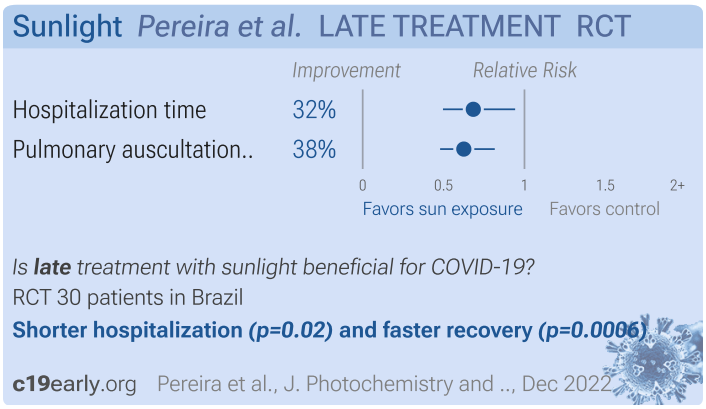
Kalichuran: Prospective study of 100 COVID-19 patients in South Africa, 50 with COVID-19 pneumonia and 50 asymptomatic, showing higher risk of symptomatic COVID-19 with lower exposure to sunlight, and with vitamin D deficiency. Sunlight exposure may be correlated with physical activity and may have additional benefits independent of vitamin D *sciencedirect.com*.

Ma



Ma: Analysis of 39,915 patients with 1,768 COVID+ cases based on surveys in the Nurses' Health Study II, showing higher UVA/UVB exposure associated with lower risk of COVID-19 cases.

Pereira



Pereira: RCT 30 hospitalized COVID-19 patients investigating the effectiveness of photobiomodulation (PBM) using a vest with near-infrared LEDs (simulating part of the sunlight spectrum). The treatment group showed shorter hospitalization, significant improvement in cardiopulmonary function, and improvements in leukocyte, neutrophil, and

lymphocyte counts post-treatment. The treatment group had higher pneumonia severity at baseline.

For more discussion see youtube.com.

Appendix 1. Methods and Data

We perform ongoing searches of PubMed, medRxiv, Europe PMC, ClinicalTrials.gov, The Cochrane Library, Google Scholar, Research Square, ScienceDirect, Oxford University Press, the reference lists of other studies and meta-analyses, and submissions to the site c19early.org. Search terms are sunlight and COVID-19 or SARS-CoV-2. Automated searches are performed twice daily, with all matches reviewed for inclusion. All studies regarding the use of sunlight for COVID-19 that report a comparison with a control group are included in the main analysis. 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 pooled analysis, while other outcomes are included in the outcome specific analyses. 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 have preference. Mortality alone is preferred over combined outcomes. Outcomes with zero events in both arms are not used, the next most serious outcome with one or more events is used. 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 outcomes are considered more important than viral test 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 little or no room for an effective treatment to do better, however faster recovery is valuable. If only individual symptom data is available, the most serious symptom has priority, for example difficulty breathing or low SpO_2 is more important than cough. When results provide an odds ratio, we compute the relative risk when possible, or convert 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 propensity score matching and multivariable regression has preference over propensity score matching or weighting, which has preference over multivariable regression. Adjusted results have preference over unadjusted results for a more serious outcome when the adjustments significantly alter results. 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 expressed with RR < 1.0 favoring treatment, and using the risk of a negative outcome when applicable (for example, the risk of death rather than the risk of survival). If studies only report relative continuous values such as relative times, the ratio of the time for the treatment group versus the time for the control group is used. Calculations are done in Python (3.12.2) with scipy (1.12.0), pythonmeta (1.26), numpy (1.26.4), statsmodels (0.14.1), and plotly (5.19.0).

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) and inverse variance weighting. Results are presented with 95% confidence intervals. Heterogeneity among studies was assessed using the I^2 statistic. Mixed-effects meta-regression results are computed with R (4.1.2) using the metafor (3.0-2) and rms (6.2-0) packages, and using the most serious sufficiently powered outcome. For all statistical tests, a p-value less than 0.05 was considered statistically significant. Grobid 0.8.0 is used to parse PDF documents.

We have classified studies as early treatment if most patients are not already at a severe stage at the time of treatment (for example based on oxygen status or lung involvement), and treatment started within 5 days of the onset of symptoms. If studies contain a mix of early treatment and late treatment patients, we consider the treatment time of patients contributing most to the events (for example, consider a study where most patients are treated early but late treatment patients are included, and all mortality events were observed with late treatment patients). We note that a shorter time may be preferable. Antivirals are typically only considered effective when used within a shorter timeframe, for example 0-36 or 0-48 hours for oseltamivir, with longer delays not being effective *McLean, Treanor*.

We received no funding, this research is done in our spare time. We have no affiliations with any pharmaceutical companies or political parties.

A summary of study results is below. Please submit updates and corrections at https://c19early.org/sunmeta.html.

Late treatment

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

Pereira, 12/5/2022, Single Blind Randomized Controlled Trial, placebo-controlled, Brazil, peer-reviewed, 5 authors.	hospitalization time, 31.6% lower, relative time 0.68, $p = 0.02$, higher sunlight exposure 15, lower sunlight exposure 15.
	pulmonary auscultation improvement time, 37.5% lower, relative time 0.62, $p < 0.001$, higher sunlight exposure 15, lower sunlight exposure 15.

Prophylaxis

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

Cherrie, 4/8/2021, retrospective, multiple countries, peer-reviewed, 7 authors, study period 22 January, 2020 - 30 April, 2020, per 100kJ m–2 increase.	risk of death, 32.0% lower, RR 0.68, $p = 0.004$, USA, England, Italy combined.
	risk of death, 29.0% lower, RR 0.71, $p < 0.001$, USA.
	risk of death, 19.0% lower, RR 0.81, $p = 0.002$, Italy.
	risk of death, 49.0% lower, RR 0.51, $p < 0.001$, England.
Jabbar, 12/31/2021, retrospective, Iraq, peer-reviewed, 4 authors.	risk of case, 62.8% lower, OR 0.37, $p < 0.001$, higher sunlight exposure 43 of 120 (35.8%) cases, 72 of 120 (60.0%) controls, NNT 4.1, case control OR.
Kalichuran, 4/26/2022, prospective, South Africa, peer-reviewed, survey, 4 authors, study period September 2020 - February 2021.	risk of symptomatic case, 58.2% lower, RR 0.42, $p = 0.004$, higher sunlight exposure 21, lower sunlight exposure 79, inverted to make RR<1 favor higher sunlight exposure, higher sunlight exposure vs. lower sunlight exposure.
Ma, 12/3/2021, retrospective, USA, peer-reviewed, 16 authors, study period May 2020 - March 2021.	risk of case, 23.0% lower, RR 0.77, $p < 0.001$, higher sunlight exposure 411 of 10,393 (4.0%), lower sunlight exposure 495 of 9,142 (5.4%), NNT 68, adjusted per study, odds ratio converted to relative risk, UVB, highest quartile vs. lowest quartile, model 3, table 3, multivariable.
	risk of case, 23.1% lower, RR 0.77, $p < 0.001$, higher sunlight exposure 325 of 9,325 (3.5%), lower sunlight exposure 436 of 9,079 (4.8%), NNT 76, adjusted per study, odds ratio converted to relative risk, UVA, highest quartile vs. lowest quartile, model 3, table 3, multivariable.

Supplementary Data

Supplementary Data

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