Sunlight for COVID-19: real-time meta analysis of 4 studies

@CovidAnalysis, November 2023
https://c19early.org/sunmeta.html

- Statistically significant lower risk is seen for mortality and cases. 4 studies from 4 independent teams in 3 countries show statistically significant improvements.

- Meta analysis using the most serious outcome reported shows 41% [20-56%] lower risk.

- 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.

Sunlight for COVID-19 improvement, studies, patients

<table>
<thead>
<tr>
<th>Improvement, Studies, Patients</th>
<th>All studies</th>
<th>4 19,635</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>32%</td>
<td>1 0</td>
</tr>
<tr>
<td>Cases</td>
<td>48%</td>
<td>3 19,635</td>
</tr>
</tbody>
</table>

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

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 57 treatments.
# 4 sunlight COVID-19 studies

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Control</th>
<th>Improvement, RR [CI]</th>
<th>n/a</th>
<th>n/a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cherrie</td>
<td>32%</td>
<td>0.68 [0.52-0.88]</td>
<td>death</td>
<td>n/a</td>
</tr>
<tr>
<td>Ma</td>
<td>29%</td>
<td>0.77 [0.57-0.88]</td>
<td>cases</td>
<td>411/10,393</td>
</tr>
<tr>
<td>Jabbar</td>
<td>63%</td>
<td>0.37 [0.22-0.63]</td>
<td>case control</td>
<td>n/a</td>
</tr>
<tr>
<td>Kalinchuran</td>
<td>58%</td>
<td>0.42 [0.23-0.76]</td>
<td>symp. case</td>
<td>21 (n)</td>
</tr>
</tbody>
</table>

| Prophylaxis | 41%       | 0.59 [0.44-0.80]    | 411/10,414 | 495/9,221 |

**All studies**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Control</th>
<th>Improvement, RR [CI]</th>
<th>n/a</th>
<th>n/a</th>
</tr>
</thead>
<tbody>
<tr>
<td>41%</td>
<td>0.59 [0.44-0.80]</td>
<td>411/10,414</td>
<td>495/9,221</td>
<td></td>
</tr>
</tbody>
</table>

**Efficacy in COVID-19 sunlight studies (pooled effects)**

<table>
<thead>
<tr>
<th>Ivermectin</th>
<th>PVP-I</th>
<th>Quercetin</th>
<th>Melatonin</th>
<th>Sunlight</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Efficacy in COVID-19 studies (pooled effects)**

<table>
<thead>
<tr>
<th>Exercise</th>
<th>Fluvoxamine</th>
<th>Vitamin D</th>
<th>Metformin</th>
<th>Zinc</th>
<th>HCQ</th>
<th>Sotrovimab</th>
<th>Vitamin C</th>
<th>Paxlovid</th>
<th>Molnupiravir</th>
<th>Remdesivir</th>
<th>Ivermectin</th>
<th>PVP-I</th>
<th>Quercetin</th>
<th>Melatonin</th>
<th>Sunlight</th>
<th>Lower risk</th>
<th>Increased risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>variant dependent</td>
<td>independent trials refused</td>
<td>mutagenic/teratogenic</td>
<td>worse w/longer followup</td>
<td>variant dependent</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Effect extraction pre-specified**

Effect extraction pre-specified (most serious outcome, see appendix)

Favors sun exposure

Favors control

**Favorable treatments**

- Sunlight
- Exercise
- Fluvoxamine
- Vitamin D
- Metformin
- Zinc
- HCQ
- Sotrovimab
- Vitamin C
- Paxlovid
- Molnupiravir
- Remdesivir
- Ivermectin
- PVP-I
- Quercetin
- Melatonin

**Unfavorable treatments**

- Acetaminophen
- Cannabidiol
- Vitamin B9
- Conv. Plasma
- Ibuprofen
- Remdesivir
- Paxlovid
- Molnupiravir
- Ivermectin
- PVP-I
- Quercetin
- Melatonin

**Extractions**

- 4 sunlight COVID-19 studies
- Efficacy in COVID-19 sunlight studies (pooled effects)
- Lower risk
- Increased risk

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**November 2023**

[c19early.org](http://c19early.org)
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. 0.7% of 5,722 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

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 and individual outcomes.

Preclinical Research

An In Vitro study supports the efficacy of sunlight. 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 and for specific outcomes. Figure 2, 3, and 4 show forest plots for random effects meta-analysis of all studies with pooled effects, mortality results, and cases.

<table>
<thead>
<tr>
<th>Improvement</th>
<th>Studies</th>
<th>Patients</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>All studies</td>
<td>41% [20-56%]***</td>
<td>4</td>
<td>19,635</td>
</tr>
<tr>
<td>Cases</td>
<td>48% [11-70%] *</td>
<td>3</td>
<td>19,635</td>
</tr>
</tbody>
</table>

Table 1. Random effects meta-analysis for all studies and for specific outcomes. Results show the percentage improvement with treatment and the 95% confidence interval. * p<0.05 *** p<0.001.
4 sunlight COVID-19 studies

<table>
<thead>
<tr>
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Prophylaxis 41% 0.59 [0.44-0.80] per 100kJ m–2 increase

Effect extraction pre-specified (most serious outcome, see appendix)

Favors sun exposure Favors control

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.

1 sunlight COVID-19 mortality result

<table>
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</tr>
</tbody>
</table>

Prophylaxis 32% 0.68 [0.52-0.88]

Effect extraction pre-specified (most serious outcome, see appendix)

Favors sun exposure Favors control

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

3 sunlight COVID-19 case results

<table>
<thead>
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<th>Treatment</th>
<th>Control</th>
</tr>
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<tbody>
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</tr>
</tbody>
</table>

Prophylaxis 48% 0.52 [0.30-0.89]

Effect extraction pre-specified (most serious outcome, see appendix)

Favors sun exposure Favors control

Figure 4. Random effects meta-analysis for cases.
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 5. 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, 39 of the treatments we analyze show statistically significant efficacy or harm, defined as ≥10% decreased risk or >0% increased risk from ≥3 studies. 89% of treatments showing statistically significant efficacy/harm with pooled effects have been confirmed with one or more specific outcomes, with a mean delay of 3.4 months. When restricting to RCTs only, 52% 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.
Figure 5. The time when studies showed that treatments were effective, defined as statistically significant improvement of \( \geq 10\% \) from \( \geq 3 \) 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 and cases. 4 studies from 4 independent teams in 3 countries show statistically significant improvements. Meta analysis using the most serious outcome reported shows 41\% [20-56\%] lower risk.
**Study Notes**

**Cherrie**

### Sunlight for COVID-19 **Cherrie et al. Prophylaxis**

<table>
<thead>
<tr>
<th>Improvement</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>32%</td>
</tr>
<tr>
<td>Mortality, USA</td>
<td>29%</td>
</tr>
<tr>
<td>Mortality, Italy</td>
<td>19%</td>
</tr>
<tr>
<td>Mortality, England</td>
<td>49%</td>
</tr>
</tbody>
</table>

**Is sunlight beneficial for COVID-19?**
Retrospective study in multiple countries (January - April 2020)
Lower mortality with increased sunlight exposure \(p=0.0041\)

c19early.org Cherrie et al., British J. Dermatology, Apr 2021

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

**Jabbar**

### Sunlight for COVID-19 **Jabbar et al. Prophylaxis**

<table>
<thead>
<tr>
<th>Improvement</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case</td>
<td>63%</td>
</tr>
</tbody>
</table>

**Is sunlight beneficial for COVID-19?**
Retrospective 240 patients in Iraq
Fewer cases with increased sunlight exposure \(p=0.00021\)

c19early.org Jabbar et al., Nat. Volatiles & Essent., Dec 2021

**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**

### Sunlight for COVID-19 **Kalichuran et al. Prophylaxis**

<table>
<thead>
<tr>
<th>Improvement</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symp. case</td>
<td>58%</td>
</tr>
</tbody>
</table>

**Is sunlight beneficial for COVID-19?**
Prospective study of 100 patients in South Africa (Sep 2020 - Feb 2021)
Fewer symptomatic cases with increased sunlight exposure \(p=0.0041\)

c19early.org Kalichuran et al., Southern African J., Apr 2022

**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
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.

Appendix 1. Methods and Data

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 c19early.org. Search terms were sunlight, filtered for papers containing the terms COVID-19 or SARS-CoV-2. Automated searches are performed every few hours with notification of new matches. 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 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). If only individual symptom data is available, the most serious symptom has priority, for example difficulty breathing or low $\text{SpO}_2$ is more important than cough. 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. Adjusted primary outcome 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 (3.11.6) with scipy (1.11.3), pythonmeta (1.26), numpy (1.26.1), statsmodels (0.14.0), and plotly (5.17.0).
Forest plots are computed using PythonMeta with the DerSimonian and Laird random effects model (the fixed effect assumption is not plausible in this case) and inverse variance weighting. 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.

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 (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.

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

**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.

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Setting</th>
<th>Study period</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cherrie, 4/8/2021, retrospective, multiple countries, peer-reviewed, 7 authors, study period 22 January, 2020 - 30 April, 2020, per 100kJ m–2 increase.</td>
<td>risk of death, 32.0% lower, RR 0.68, p = 0.004, USA, England, Italy combined.</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>risk of death, 29.0% lower, RR 0.71, p &lt; 0.001, USA.</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>risk of death, 19.0% lower, RR 0.81, p = 0.002, Italy.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>risk of death, 49.0% lower, RR 0.51, p &lt; 0.001, England.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jabbar, 12/31/2021, retrospective, Iraq, peer-reviewed, 4 authors.</td>
<td>risk of case, 62.8% lower, OR 0.37, p &lt; 0.001, higher sunlight exposure 43 of 120 (35.8%) cases, 72 of 120 (60.0%) controls, NNT 4.1, case control OR.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kalichuran, 4/26/2022, prospective, South Africa, peer-reviewed, survey, 4 authors, study period September 2020 - February 2021.</td>
<td>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&lt;1 favor higher sunlight exposure, higher sunlight exposure vs. lower sunlight exposure.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ma, 12/3/2021, retrospective, USA, peer-reviewed, 16 authors, study period May 2020 - March 2021.</td>
<td>risk of case, 23.0% lower, RR 0.77, p &lt; 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.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>risk of case, 23.1% lower, RR 0.77, p &lt; 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.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
References

1. Altman, D., How to obtain the P value from a confidence interval, BMJ, doi:10.1136/bmj.d2304.

2. Altman (B) et al., How to obtain the confidence interval from a P value, BMJ, doi:10.1136/bmj.d2090.

3. c19early.org, c19early.org/timeline.html.


6. Faria et al., Genomics and epidemiology of the P.1 SARS-CoV-2 lineage in Manaus, Brazil, Science, doi:10.1126/science.abh2644.


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