Cannabidiol for COVID-19: real-time meta analysis of 7 studies
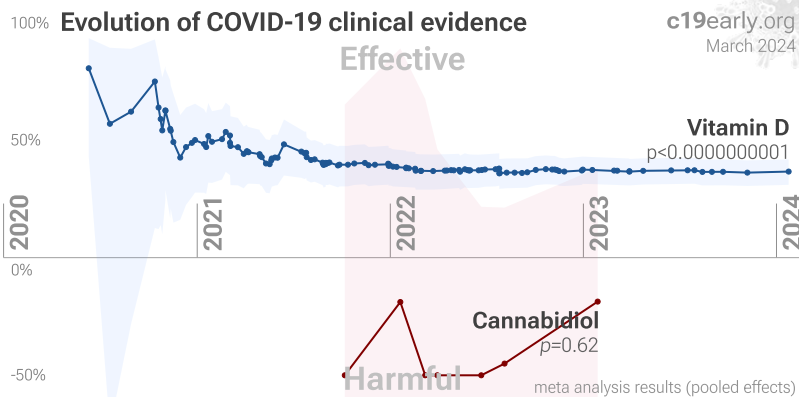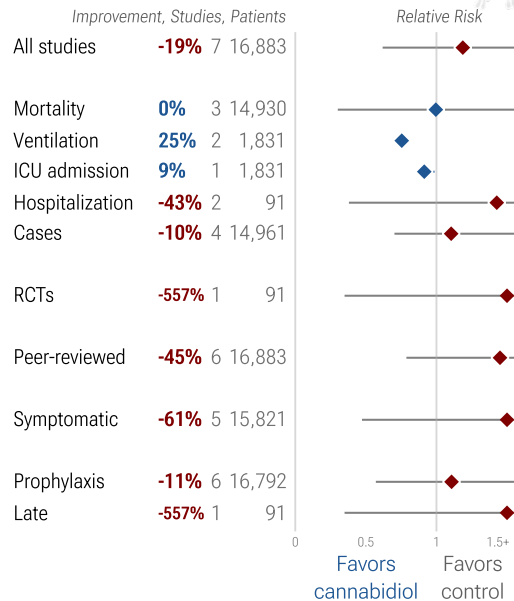
Abstract

Meta analysis using the most serious outcome reported shows 19% [-38-128%] higher risk, without reaching statistical significance.

While non-symptomatic case results show 8% [-14-25%] improvement, symptomatic results show 61% [-53-451%] higher risk.

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

Cannabidiol for COVID-19

c19early.org
March 2024
Relative Risk

Improvement, Studies, Patients

All studies	**-19%**	7	16,883
Mortality	**0%**	3	14,930
Ventilation	**25%**	2	1,831
ICU admission	**9%**	1	1,831
Hospitalization	**-43%**	2	91
Cases	**-10%**	4	14,961
RCTs	**-557%**	1	91
Peer-reviewed	**-45%**	6	16,883
Symptomatic	**-61%**	5	15,821
Prophylaxis	**-11%**	6	16,792
Late	**-557%**	1	91

0   0.5   1   1.5+

Favors cannabidiol   Favors control

Evolution of COVID-19 clinical evidence

c19early.org
March 2024

Effective

Vitamin D
p<0.0000000001

2020   2021   2022   2023   2024

Cannabidiol
p=0.62

Harmful

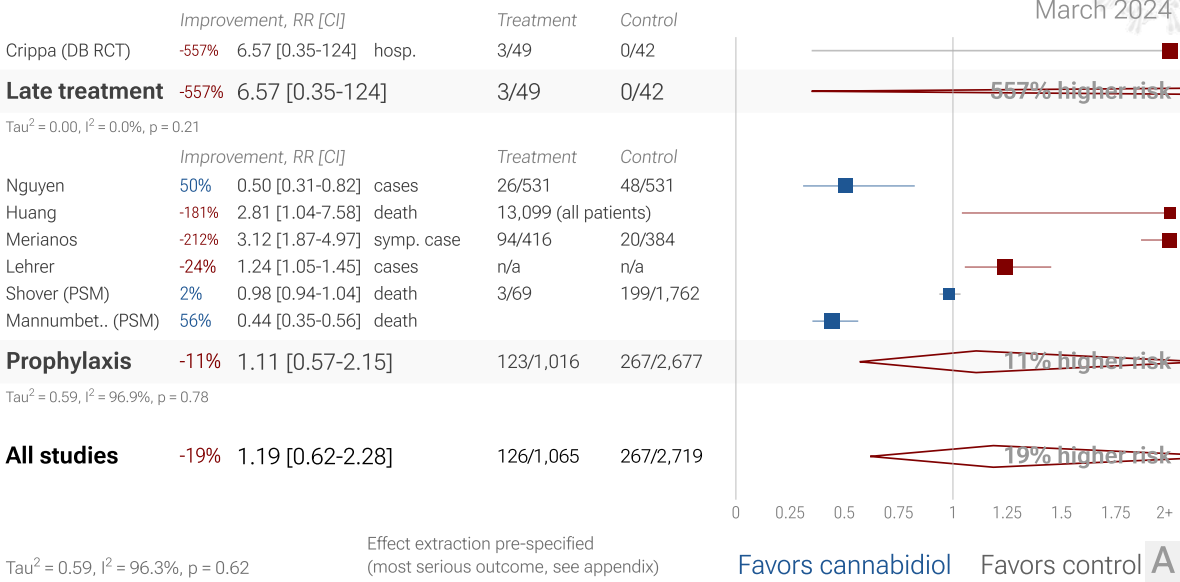meta analysis results (pooled effects)

HIGHLIGHTS

Cannabidiol reduces risk for COVID-19 with low confidence for ventilation, however increased risk is seen with very low confidence for hospitalization, cases, and in pooled analysis.

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.
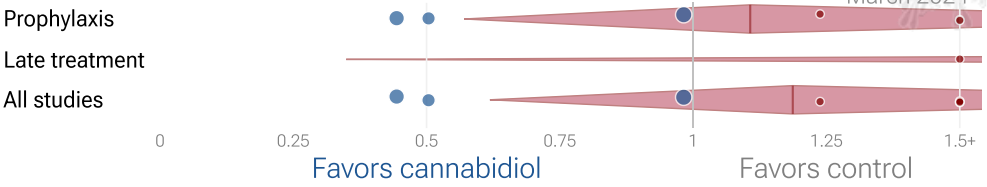
7 cannabidiol COVID-19 studies

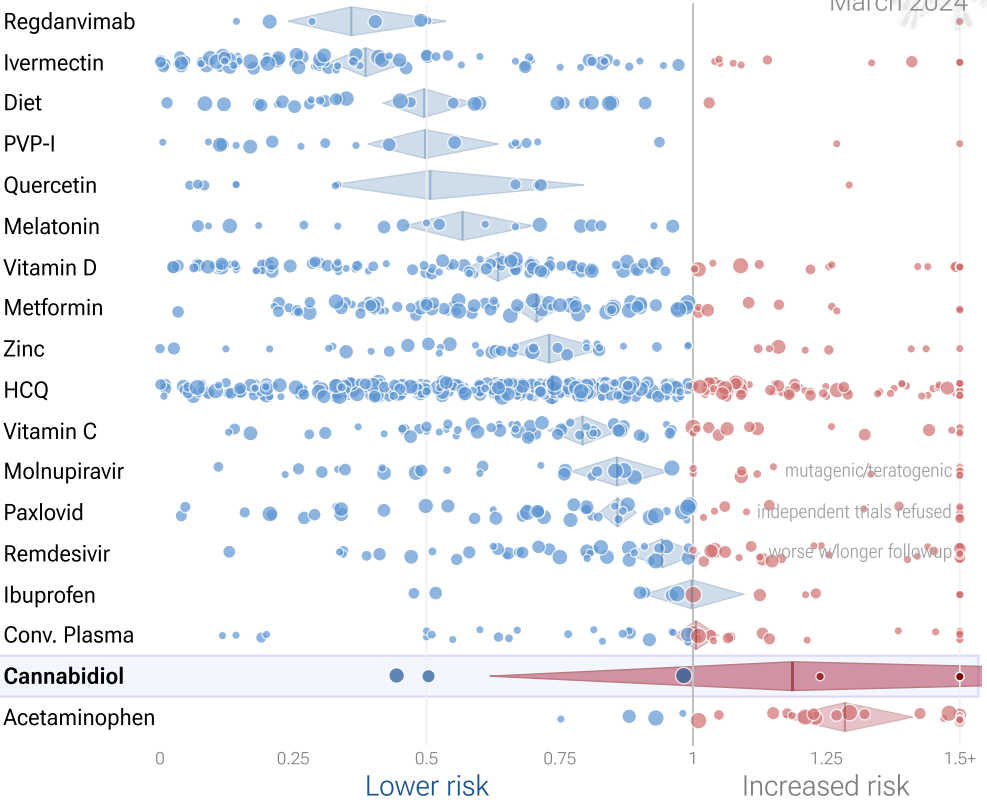|	Improvement, RR [CI]		Treatment	Control
Crippa (DB RCT)	-557%	6.57 [0.35-124]	hosp.	3/49	0/42
Late treatment	**-557%**	**6.57 [0.35-124]**		**3/49**	**0/42**

Tau² = 0.00, I² = 0.0%, p = 0.21

	Improvement, RR [CI]		Treatment	Control
Nguyen	50%	0.50 [0.31-0.82]	cases	26/531	48/531
Huang	-181%	2.81 [1.04-7.58]	death	13,099 (all patients)	
Merianos	-212%	3.12 [1.87-4.97]	symp. case	94/416	20/384
Lehrer	-24%	1.24 [1.05-1.45]	cases	n/a	n/a
Shover (PSM)	2%	0.98 [0.94-1.04]	death	3/69	199/1,762
Mannumbet.. (PSM)	56%	0.44 [0.35-0.56]	death		
Prophylaxis	**-11%**	**1.11 [0.57-2.15]**		**123/1,016**	**267/2,677**

Tau² = 0.59, I² = 96.9%, p = 0.78

				Treatment	Control
All studies	**-19%**	**1.19 [0.62-2.28]**		**126/1,065**	**267/2,719**

Tau² = 0.59, I² = 96.3%, p = 0.62

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

557% higher risk

11% higher risk

19% higher risk

Favors cannabidiol   Favors control   A

Efficacy in COVID-19 cannabidiol studies (pooled effects)

- Prophylaxis
- Late treatment
- All studies

Favors cannabidiol   Favors control   B

Efficacy in COVID-19 studies (pooled effects)

- Regdanvimab
- Ivermectin
- Diet
- PVP-I
- Quercetin
- Melatonin
- Vitamin D
- Metformin
- Zinc
- HCQ
- Vitamin C
- Molnupiravir — mutagenic/teratogenic
- Paxlovid — independent trials refused
- Remdesivir — worse w/longer followup
- Ibuprofen
- Conv. Plasma
- **Cannabidiol**
- Acetaminophen

Lower risk   Increased risk   C

Timeline of COVID-19 cannabidiol studies (pooled effects)
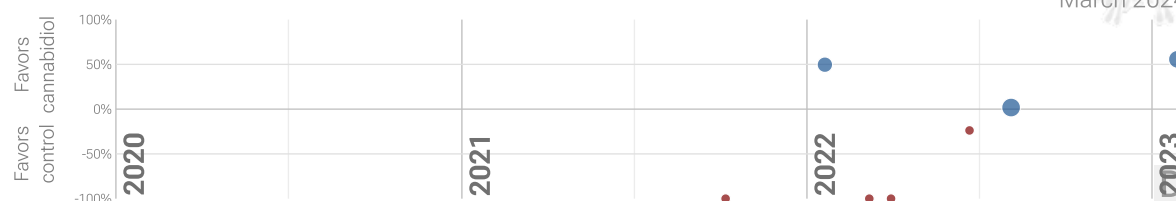
Figure 1. A. Random effects meta-analysis. This plot shows pooled effects, see the specific outcome analyses for individual outcomes, and the heterogeneity section for discussion. Effect extraction is pre-specified, using the most serious outcome reported. For details of effect extraction see the appendix. **B. Scatter plot showing the most serious outcome in all studies, and for studies within each stage.** Diamonds 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 cannabidiol studies.**

Introduction

Immediate treatment recommended. SARS-CoV-2 infection primarily begins in the upper respiratory tract and may progress to the lower respiratory tract, other tissues, and the nervous and cardiovascular systems, which may lead to cytokine storm, pneumonia, ARDS, neurological issues *Scardua-Silva, Yang*, cardiovascular complications *Eberhardt*, organ failure, and death. Minimizing replication as early as possible is recommended.

Many treatments are expected to modulate infection. SARS-CoV-2 infection and replication involves the complex interplay of 50+ host and viral proteins and other factors *Note A, Malone, Murigneux, Lv, Lui*, providing many therapeutic targets for which many existing compounds have known activity. Scientists have predicted that over 6,000 compounds may reduce COVID-19 risk *c19early.org (B)*, either by directly minimizing infection or replication, by supporting immune system function, or by minimizing secondary complications.

Analysis. We analyze all significant controlled studies of cannabidiol for 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 all studies, studies within each treatment stage, individual outcomes, peer-reviewed studies, and Randomized Controlled Trials (RCTs).

Treatment timing. Figure 2 shows stages of possible treatment for COVID-19. **Prophylaxis** refers to regularly taking medication before becoming sick, in order to prevent or minimize infection. **Early Treatment** refers to treatment immediately or soon after symptoms appear, while **Late Treatment** refers to more delayed treatment.
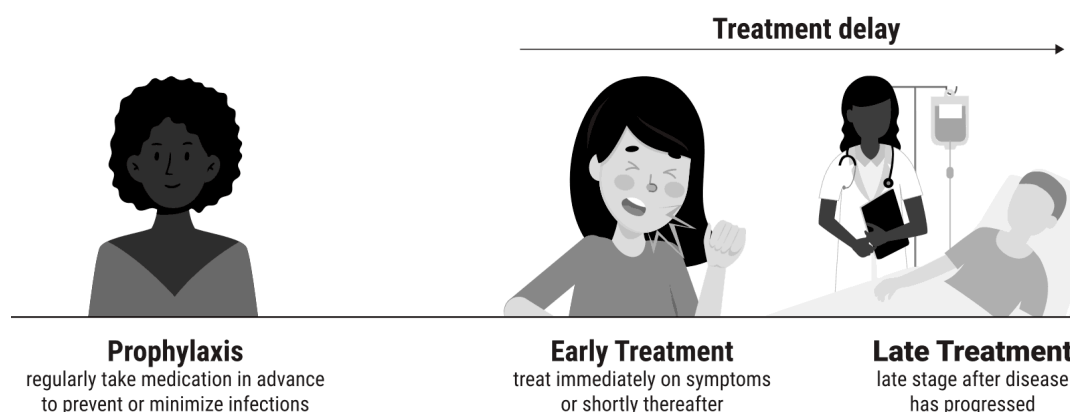
Figure 2. Treatment stages.

Preclinical Research

An *In Vitro* study supports the efficacy of cannabidiol [van Breemen].

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 stages combined, for Randomized Controlled Trials, for peer-reviewed studies, and for specific outcomes. Table 2 shows results by treatment stage. Figure 3, 4, 5, 6, 7, 8, 9, 10, and 11 show forest plots for random effects meta-analysis of all studies with pooled effects, mortality results, ventilation, ICU admission, hospitalization, recovery, cases, peer reviewed studies, and non-symptomatic vs. symptomatic results.
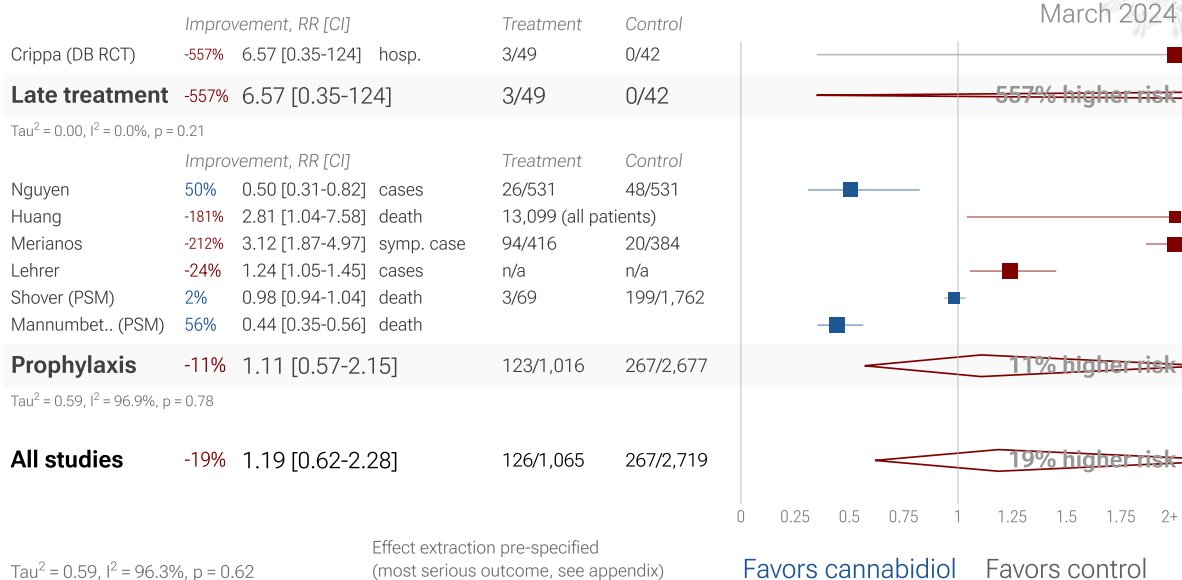
	Improvement	Studies	Patients	Authors
All studies	**-19%** [-128-38%]	7	16,883	92
Peer-reviewed studies	**-45%** [-167-21%]	6	16,883	85
Randomized Controlled Trials	**-557%** [-12269-65%]	1	91	32
Mortality	**0%** [-229-70%]	3	14,930	17
Ventilation	**25%** [19-30%] ****	2	1,831	14
Hospitalization	**-43%** [-436-62%]	2	91	39
Cases	**-10%** [-74-30%]	4	14,961	46

Table 1. Random effects meta-analysis for all stages combined, for Randomized Controlled Trials, for peer-reviewed studies, and for specific outcomes. Results show the percentage improvement with treatment and the 95% confidence interval. *** *p*<0.001 **** *p*<0.0001.

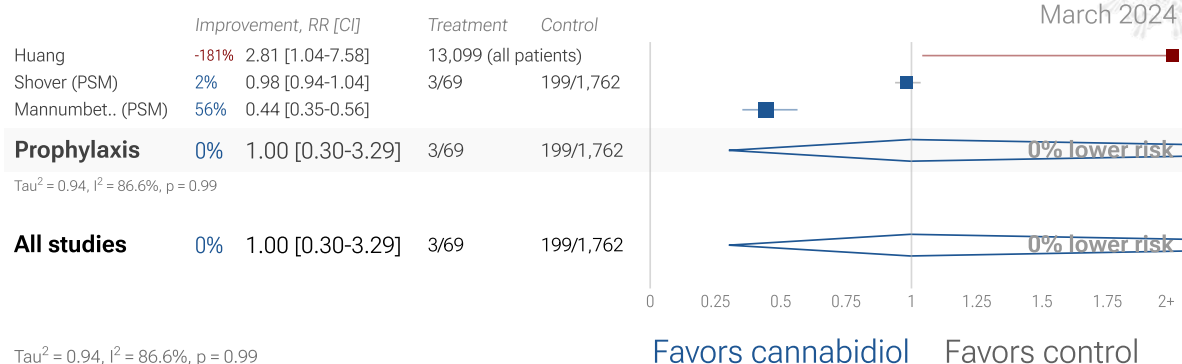|	Late treatment	Prophylaxis
All studies	**-557%** [-12269-65%]	**-11%** [-115-43%]
Peer-reviewed studies	**-557%** [-12269-65%]	**-37%** [-155-27%]
Randomized Controlled Trials	**-557%** [-12269-65%]	
Mortality		**0%** [-229-70%]
Ventilation		**25%** [19-30%] ****
Hospitalization	**-557%** [-12269-65%]	**-6%** [-10--2%] ***
Cases		**-10%** [-74-30%]

Table 2. Random effects meta-analysis results by treatment stage. Results show the percentage improvement with treatment, the 95% confidence interval, and the number of studies for the stage. *** *p*<0.001 **** *p*<0.0001.

7 cannabidiol COVID-19 studies

	Improvement, RR [CI]		Treatment	Control
Crippa (DB RCT)	-557% 6.57 [0.35-124]	hosp.	3/49	0/42
Late treatment	-557% 6.57 [0.35-124]		3/49	0/42

Tau² = 0.00, I² = 0.0%, p = 0.21

	Improvement, RR [CI]		Treatment	Control
Nguyen	50% 0.50 [0.31-0.82]	cases	26/531	48/531
Huang	-181% 2.81 [1.04-7.58]	death	13,099 (all patients)	
Merianos	-212% 3.12 [1.87-4.97]	symp. case	94/416	20/384
Lehrer	-24% 1.24 [1.05-1.45]	cases	n/a	n/a
Shover (PSM)	2% 0.98 [0.94-1.04]	death	3/69	199/1,762
Mannumbet.. (PSM)	56% 0.44 [0.35-0.56]	death		
Prophylaxis	-11% 1.11 [0.57-2.15]		123/1,016	267/2,677

Tau² = 0.59, I² = 96.9%, p = 0.78

All studies	-19% 1.19 [0.62-2.28]		126/1,065	267/2,719

Tau² = 0.59, I² = 96.3%, p = 0.62

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

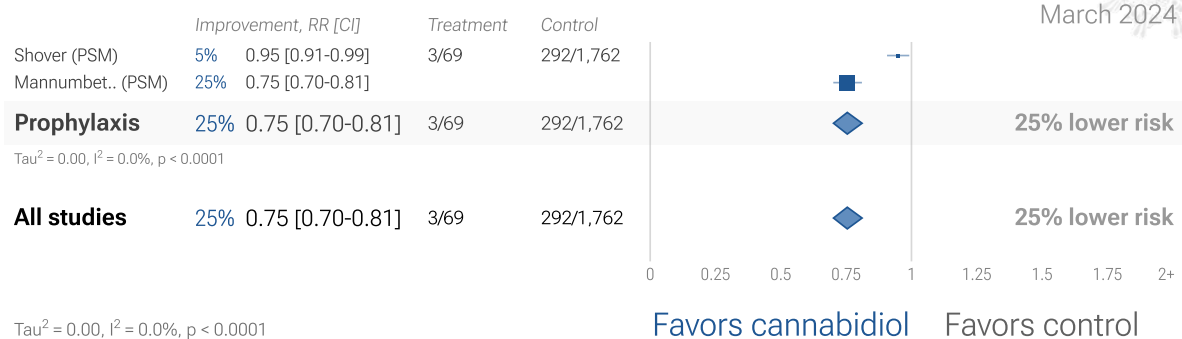Favors cannabidiol   Favors control

Figure 3. 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.

3 cannabidiol COVID-19 mortality results

	Improvement, RR [CI]	Treatment	Control
Huang	-181% 2.81 [1.04-7.58]	13,099 (all patients)	
Shover (PSM)	2% 0.98 [0.94-1.04]	3/69	199/1,762
Mannumbet.. (PSM)	56% 0.44 [0.35-0.56]		
Prophylaxis	0% 1.00 [0.30-3.29]	3/69	199/1,762

Tau² = 0.94, I² = 86.6%, p = 0.99

All studies	0% 1.00 [0.30-3.29]	3/69	199/1,762

Tau² = 0.94, I² = 86.6%, p = 0.99

Favors cannabidiol   Favors control

Figure 4. Random effects meta-analysis for mortality results.

2 cannabidiol COVID-19 mechanical ventilation results

	Improvement, RR [CI]	Treatment	Control
Shover (PSM)	5% 0.95 [0.91-0.99]	3/69	292/1,762
Mannumbet.. (PSM)	25% 0.75 [0.70-0.81]		
Prophylaxis	25% 0.75 [0.70-0.81]	3/69	292/1,762

Tau² = 0.00, I² = 0.0%, p < 0.0001

All studies	25% 0.75 [0.70-0.81]	3/69	292/1,762

Tau² = 0.00, I² = 0.0%, p < 0.0001

Favors cannabidiol   Favors control

Figure 5. Random effects meta-analysis for ventilation.
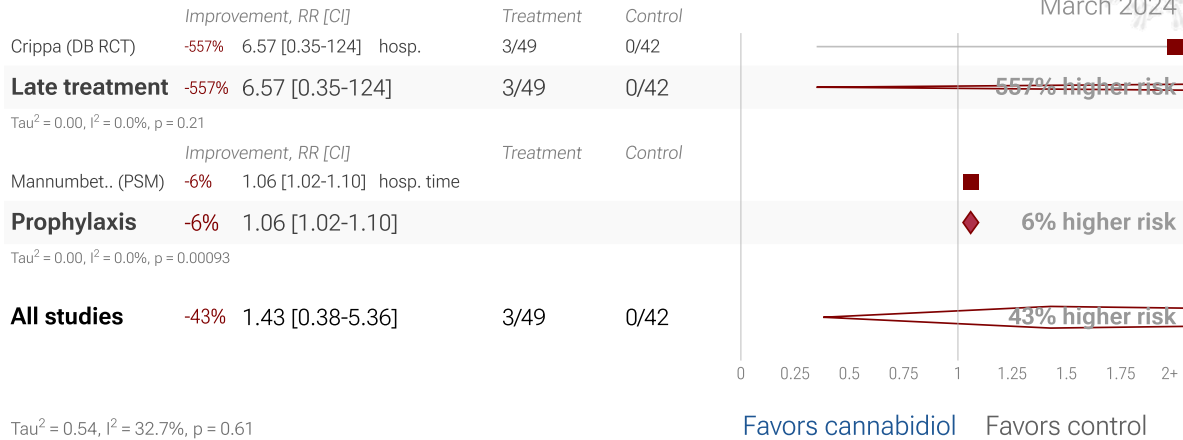
1 cannabidiol COVID-19 ICU result

	Improvement, RR [CI]		Treatment	Control		
Shover (PSM)	9%	0.91 [0.85-0.99]	8/69	543/1,762		
Prophylaxis	9%	0.91 [0.85-0.99]	8/69	543/1,762		9% lower risk
Tau² = 0.00, I² = 0.0%, p = 0.8						
All studies	9%	0.91 [0.85-0.99]	8/69	543/1,762		9% lower risk

Tau² = 0.00, I² = 0.0%, p = 0.8

Favors cannabidiol   Favors control
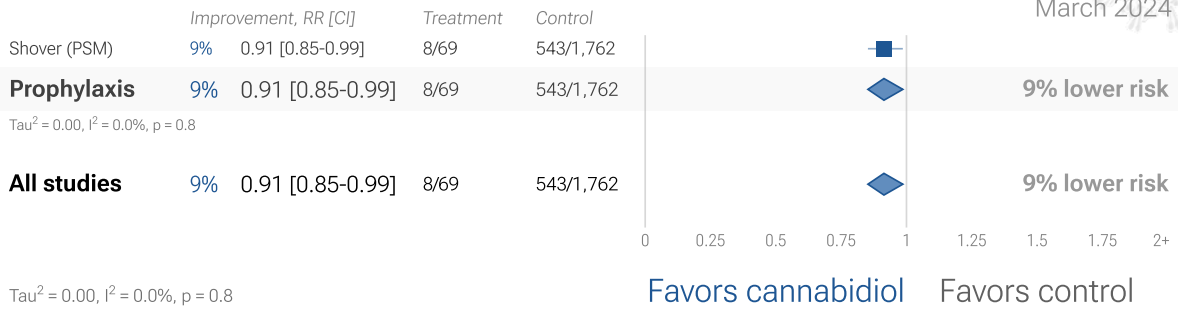
Figure 6. Random effects meta-analysis for ICU admission.

2 cannabidiol COVID-19 hospitalization results

	Improvement, RR [CI]		Treatment	Control		
Crippa (DB RCT)	-557%	6.57 [0.35-124] hosp.	3/49	0/42		
Late treatment	-557%	6.57 [0.35-124]	3/49	0/42		557% higher risk
Tau² = 0.00, I² = 0.0%, p = 0.21						
	Improvement, RR [CI]		Treatment	Control		
Mannumbet.. (PSM)	-6%	1.06 [1.02-1.10] hosp. time				
Prophylaxis	-6%	1.06 [1.02-1.10]				6% higher risk
Tau² = 0.00, I² = 0.0%, p = 0.00093						
All studies	-43%	1.43 [0.38-5.36]	3/49	0/42		43% higher risk

Tau² = 0.54, I² = 32.7%, p = 0.61

Favors cannabidiol   Favors control

Figure 7. Random effects meta-analysis for hospitalization.

1 cannabidiol COVID-19 recovery result

	Improvement, RR [CI]		Treatment	Control		
Crippa (DB RCT)	-33%	1.33 [0.86-2.08] recov. time	49 (n)	42 (n)		
Late treatment	-33%	1.33 [0.86-2.08]	49 (n)	42 (n)		33% higher risk
Tau² = 0.00, I² = 0.0%, p = 0.2						
All studies	-33%	1.33 [0.86-2.08]	49 (n)	42 (n)		33% higher risk

Tau² = 0.00, I² = 0.0%, p = 0.2

Favors cannabidiol   Favors control
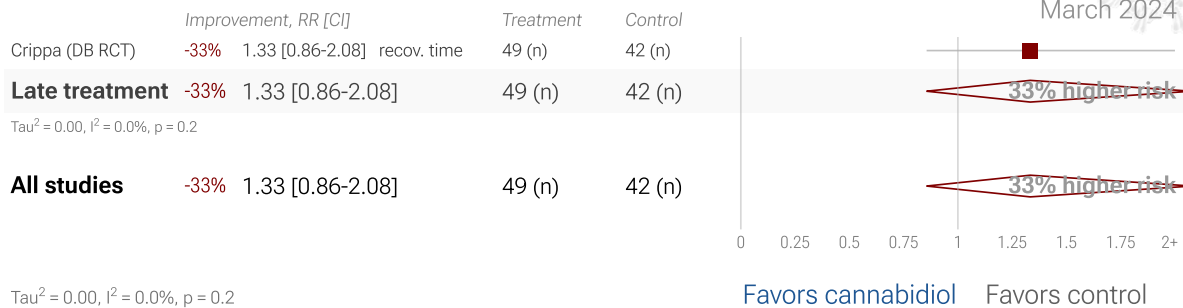
Figure 8. Random effects meta-analysis for recovery.

4 cannabidiol COVID-19 case results

	Improvement, RR [CI]			Treatment	Control
Nguyen	50%	0.50 [0.31-0.82]	cases	26/531	48/531
Huang	19%	0.81 [0.73-0.90]	cases	13,099 (all patients)	
Merianos	-212%	3.12 [1.87-4.97]	symp. case	94/416	20/384
Lehrer	-24%	1.24 [1.05-1.45]	cases	n/a	n/a
Prophylaxis	-10%	1.10 [0.70-1.74]		120/947	68/915

Tau² = 0.19, I² = 94.2%, p = 0.68

All studies	-10%	1.10 [0.70-1.74]		120/947	68/915

Tau² = 0.19, I² = 94.2%, p = 0.68

Favors cannabidiol   Favors control
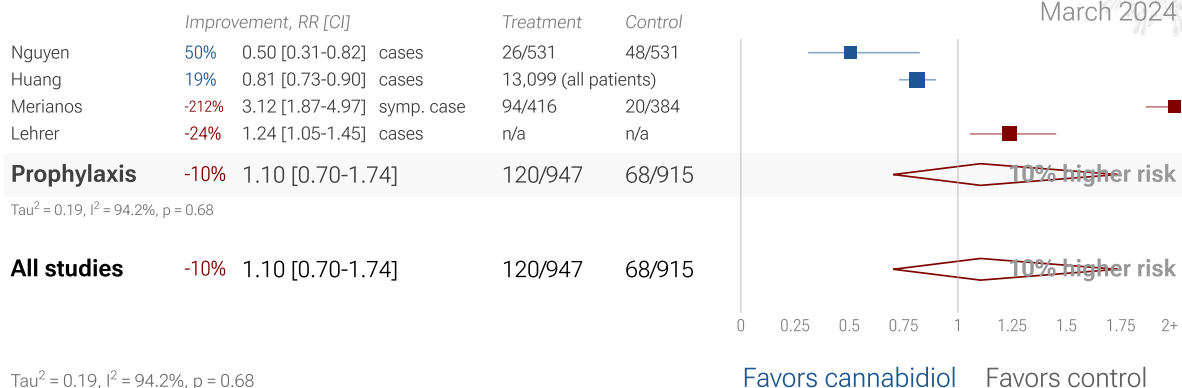
Figure 9. Random effects meta-analysis for cases.

6 cannabidiol COVID-19 peer reviewed studies

	Improvement, RR [CI]			Treatment	Control
Crippa (DB RCT)	-557%	6.57 [0.35-124]	hosp.	3/49	0/42
Late treatment	-557%	6.57 [0.35-124]		3/49	0/42

Tau² = 0.00, I² = 0.0%, p = 0.21

	Improvement, RR [CI]			Treatment	Control
Nguyen	50%	0.50 [0.31-0.82]	cases	26/531	48/531
Huang	-181%	2.81 [1.04-7.58]	death	13,099 (all patients)	
Merianos	-212%	3.12 [1.87-4.97]	symp. case	94/416	20/384
Lehrer	-24%	1.24 [1.05-1.45]	cases	n/a	n/a
Shover (PSM)	2%	0.98 [0.94-1.04]	death	3/69	199/1,762
Prophylaxis	-37%	1.37 [0.73-2.55]		123/1,016	267/2,677

Tau² = 0.39, I² = 87.8%, p = 0.33

All studies	-45%	1.45 [0.79-2.67]		126/1,065	267/2,719

Tau² = 0.39, I² = 85.2%, p = 0.24

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

Favors cannabidiol   Favors control

Figure 10. Random effects meta-analysis for peer reviewed studies. Effect extraction is pre-specified, using the most serious outcome reported, see the appendix for details. *Zeraatkar et al.* analyze 356 COVID-19 trials, finding no significant evidence that preprint results are inconsistent with peer-reviewed studies. They also show extremely long peer-review delays, with a median of 6 months to journal publication. A six month delay was equivalent to around 1.5 million deaths during the first two years of the pandemic. Authors recommend using preprint evidence, with appropriate checks for potential falsified data, which provides higher certainty much earlier. *Davidson et al.* also showed no important difference between meta analysis results of preprints and peer-reviewed publications for COVID-19, based on 37 meta analyses including 114 trials.

	Improvement, RR [CI]			Treatment	Control
Crippa (DB RCT)	-557%	6.57 [0.35-124]	hosp.	3/49	0/42
Huang	-181%	2.81 [1.04-7.58]	death	13,099 (all patients)	
Merianos	-212%	3.12 [1.87-4.97]	symp. case	94/416	20/384
Shover (PSM)	2%	0.98 [0.94-1.04]	death	3/69	199/1,762
Mannumbet.. (PSM)	56%	0.44 [0.35-0.56]	death		
Symptomatic	**-61%**	**1.61 [0.47-5.51]**		100/534	219/2,188

Tau^2 = 1.60, I^2 = 95.0%, p = 0.45

	Improvement, RR [CI]			Treatment	Control
Nguyen	50%	0.50 [0.31-0.82]	cases	26/531	48/531
Huang	19%	0.81 [0.73-0.90]	cases	13,099 (all patients)	
Merianos	-3%	1.03 [0.96-1.09]	cases	367/416	317/384
Lehrer	-24%	1.24 [1.05-1.45]	cases	n/a	n/a
Cases	**8%**	**0.92 [0.75-1.14]**		393/947	365/915

Tau^2 = 0.04, I^2 = 90.6%, p = 0.46

				Treatment	Control
All studies	**-2%**	**1.02 [0.73-1.44]**		493/1,481	584/3,103

Tau^2 = 0.19, I^2 = 96.6%, p = 0.89

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

Favors cannabidiol   Favors control

Figure 11. Random effects meta-analysis for non-symptomatic vs. symptomatic results. Effect extraction is pre-specified, using the most serious outcome reported, see the appendix for details.

Randomized Controlled Trials (RCTs)

Figure 12 shows a forest plot for random effects meta-analysis of all Randomized Controlled Trials. RCT results are included in Table 1 and Table 2. 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).

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.

1 cannabidiol COVID-19 Randomized Controlled Trials

	Improvement, RR [CI]		Treatment	Control
Crippa (DB RCT)	-557% 6.57 [0.35-124] hosp.		3/49	0/42
Late treatment	-557% 6.57 [0.35-124]		3/49	0/42
Tau^2 = 0.00, I^2 = 0.0%, p = 0.21				
All studies	-557% 6.57 [0.35-124]		3/49	0/42

Tau^2 = 0.00, I^2 = 0.0%, p = 0.21

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

Favors cannabidiol   Favors control
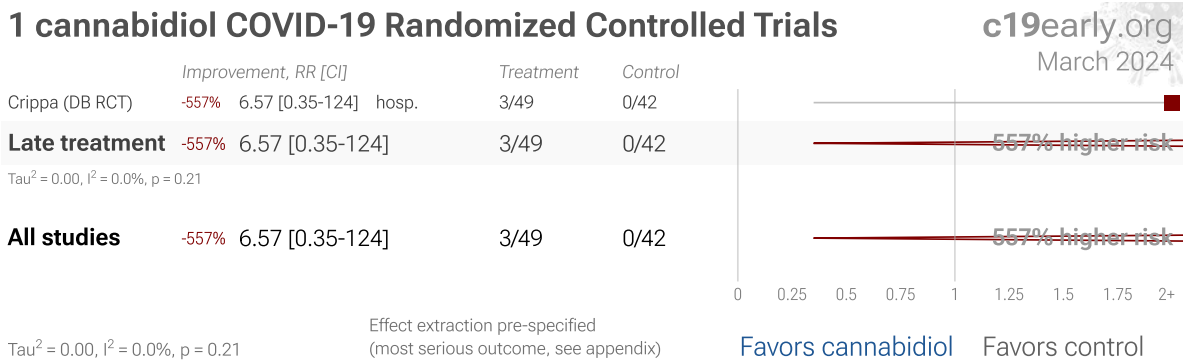
Figure 12. Random effects meta-analysis for all Randomized Controlled Trials. This plot shows pooled effects, see the specific outcome analyses for individual outcomes, and the heterogeneity section for discussion. Effect extraction is pre-specified, using the most serious outcome reported. For details of effect extraction see the appendix.

Heterogeneity

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

Treatment delay. The time between infection or the onset of symptoms and treatment may critically affect how well a treatment works. For example an antiviral may be very effective when used early but may not be effective in late stage disease, and may even be harmful. Oseltamivir, for example, is generally only considered effective for influenza when used within 0-36 or 0-48 hours *McLean, Treanor*. Baloxavir studies for influenza also show that treatment delay is critical — *Ikematsu* report an 86% reduction in cases for post-exposure prophylaxis, *Hayden* show a 33 hour reduction in the time to alleviation of symptoms for treatment within 24 hours and a reduction of 13 hours for treatment within 24-48 hours, and *Kumar* report only 2.5 hours improvement for inpatient treatment.

Treatment delay	Result
Post exposure prophylaxis	**86% fewer cases** *Ikematsu*
<24 hours	**-33 hours symptoms** *Hayden*
24-48 hours	**-13 hours symptoms** *Hayden*
Inpatients	**-2.5 hours to improvement** *Kumar*

Table 3. Studies of baloxavir for influenza show that early treatment is more effective.

Figure 13 shows a mixed-effects meta-regression for efficacy as a function of treatment delay in COVID-19 studies from 66 treatments, showing that efficacy declines rapidly with treatment delay. Early treatment is critical for COVID-19.

Efficacy by treatment delay in COVID-19 studies

c19early.org
March 2024

p<0.00000000001
mixed-effects meta-regression, most serious sufficiently powered outcome
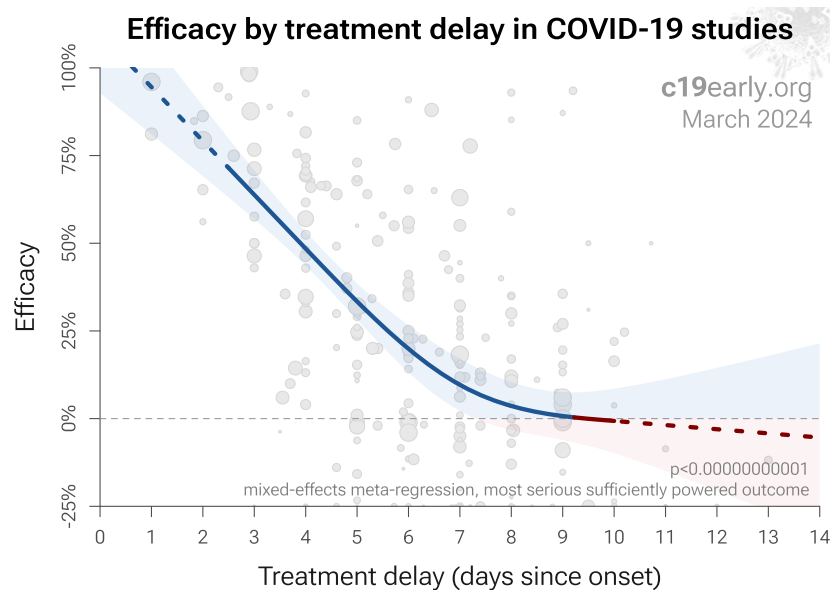
Figure 13. Early treatment is more effective. Meta-regression showing efficacy as a function of treatment delay in COVID-19 studies from 66 treatments.

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*.

Regimen. Effectiveness may depend strongly on the dosage and treatment regimen.

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.

Medication quality. The quality of medications may vary significantly between manufacturers and production batches, which may significantly affect efficacy and safety. *Williams* analyze ivermectin from 11 different sources, showing highly variable antiparasitic efficacy across different manufacturers. *Xu* analyze a treatment from two different manufacturers, showing 9 different impurities, with significantly different concentrations for each manufacturer.

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 14. 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.
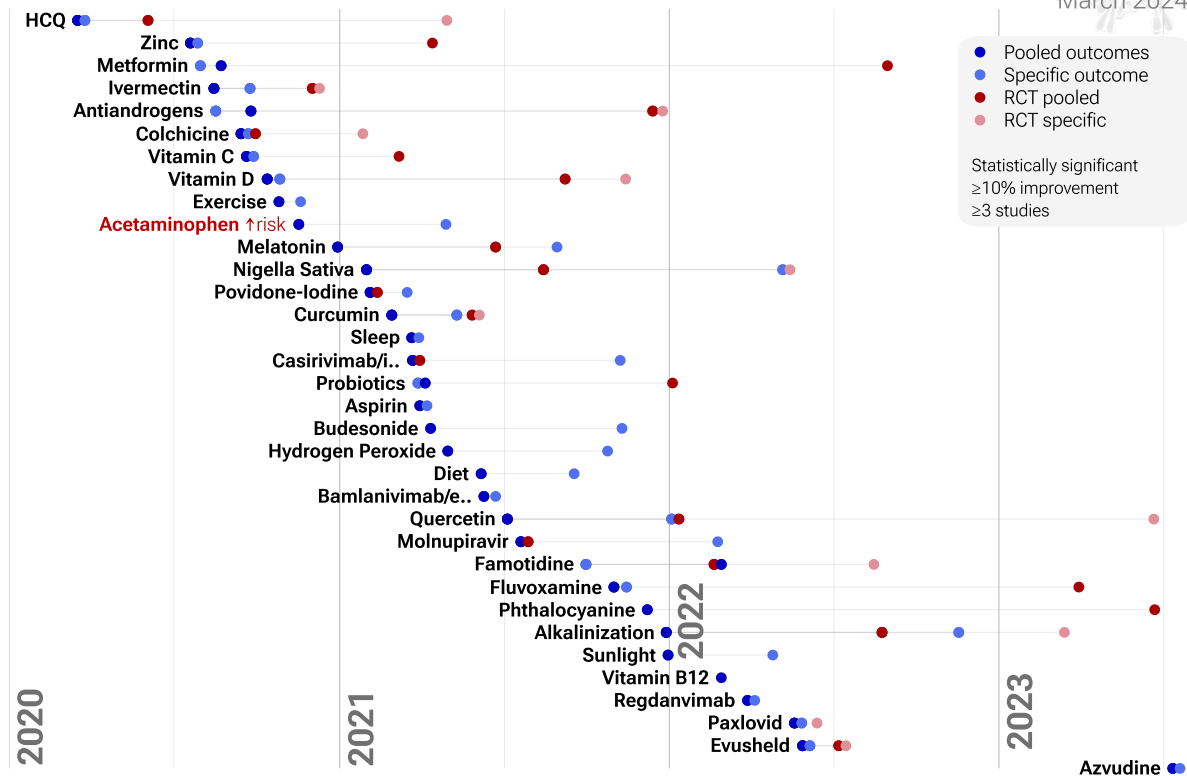
Figure 14. The time when studies showed that treatments were effective, defined as statistically significant improvement of ≥10% from ≥3 studies. Pooled results typically show efficacy earlier than specific outcome results. Results from all studies often shows efficacy much earlier than when restricting 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.

Discussion

Publication bias. Publishing is often biased towards positive results. Trials with patented drugs may have a financial conflict of interest that results in positive studies being more likely to be published, or bias towards more positive results. For example with molnupiravir, trials with negative results remain unpublished to date (CTRI/2021/05/033864 and CTRI/2021/08/0354242). For cannabidiol, there is currently not enough data to evaluate publication bias with high confidence.

Funnel plot analysis. Funnel plots have traditionally been used for analyzing publication bias. This is invalid for COVID-19 acute treatment trials — the underlying assumptions are invalid, which we can demonstrate with a simple example. Consider a set of hypothetical perfect trials with no bias. Figure 15 plot A shows a funnel plot for a simulation of 80 perfect trials, with random group sizes, and each patient's outcome randomly sampled (10% control event probability, and a 30% effect size for treatment). Analysis shows no asymmetry (p > 0.05). In plot B, we add a single typical variation in COVID-19 treatment trials — treatment delay. Consider that efficacy varies from 90% for treatment within 24 hours, reducing to 10% when treatment is delayed 3 days. In plot B, each trial's treatment delay is randomly selected. Analysis now shows highly significant asymmetry, *p* < 0.0001, with six variants of Egger's test all showing p < 0.05 *Egger, Harbord, Macaskill, Moreno, Peters, Rothstein, Rücker, Stanley*. Note that these tests fail even though treatment delay is uniformly distributed. In reality treatment delay is more complex — each trial has a different distribution of delays across patients, and the distribution across trials may be biased (e.g., late treatment trials may be more common). Similarly, many other variations in trials may produce asymmetry, including dose, administration, duration of treatment, differences in SOC, comorbidities, age, variants, and bias in design, implementation, analysis, and reporting.
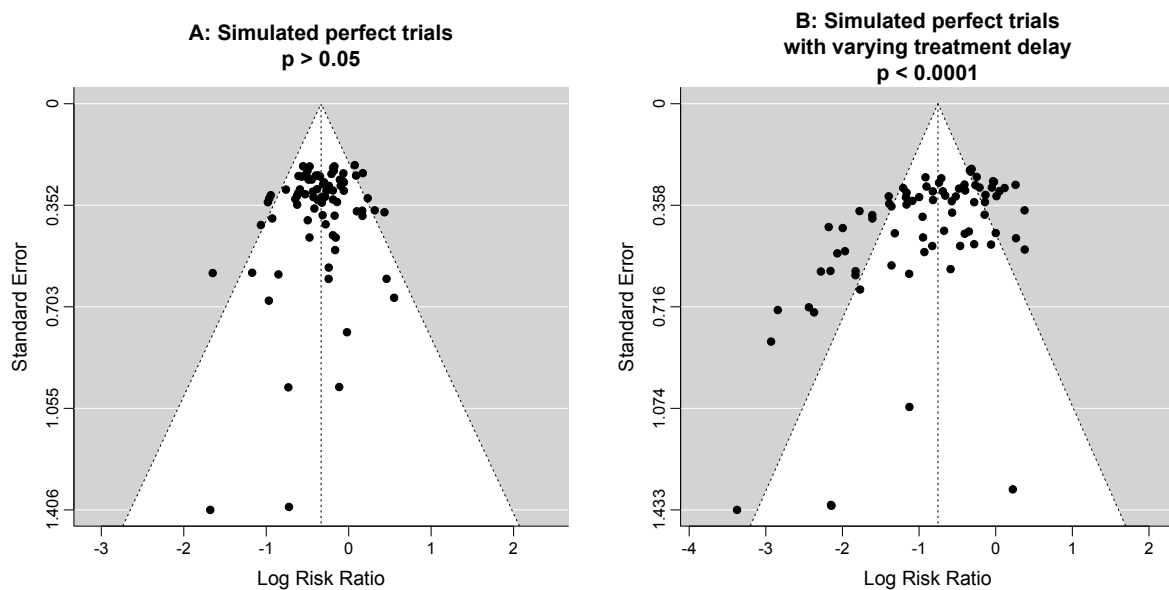
Figure 15. Example funnel plot analysis for simulated perfect trials.

Limitations. Summary statistics from meta analysis necessarily lose information. As with all meta analyses, studies are heterogeneous, with differences in treatment delay, treatment regimen, patient demographics, variants, conflicts of interest, standard of care, and other factors. We provide analyses by specific outcomes and by treatment delay, and we aim to identify key characteristics in the forest plots and summaries. Results should be viewed in the context of study characteristics.

Some analyses classify treatment based on early or late administration, as done here, while others distinguish between mild, moderate, and severe cases. Viral load does not indicate degree of symptoms — for example patients may have a high viral load while being asymptomatic. With regard to treatments that have antiviral properties, timing of treatment is critical — late administration may be less helpful regardless of severity.

Details of treatment delay per patient is often not available. For example, a study may treat 90% of patients relatively early, but the events driving the outcome may come from 10% of patients treated very late. Our 5 day cutoff for early treatment may be too conservative, 5 days may be too late in many cases.

Comparison across treatments is confounded by differences in the studies performed, for example dose, variants, and conflicts of interest. Trials affiliated with special interests may use designs better suited to the preferred outcome.

In some cases, the most serious outcome has very few events, resulting in lower confidence results being used in pooled analysis, however the method is simpler and more transparent. This is less critical as the number of studies increases. Restriction to outcomes with sufficient power may be beneficial in pooled analysis and improve accuracy when there are few studies, however we maintain our pre-specified method to avoid any retrospective changes.

Studies show that combinations of treatments can be highly synergistic and may result in many times greater efficacy than individual treatments alone *Alsaidi, Andreani, De Forni, Fiaschi, Jeffreys, Jitobaom, Jitobaom (B), Ostrov, Said, Thairu, Wan*. Therefore standard of care may be critical and benefits may diminish or disappear if standard of care does not include certain treatments.

This real-time analysis is constantly updated based on submissions. Accuracy benefits from widespread review and submission of updates and corrections from reviewers. Less popular treatments may receive fewer reviews.

No treatment, vaccine, or intervention is 100% available and effective for all current and future variants. Efficacy may vary significantly with different variants and within different populations. All treatments have potential side effects. Propensity to experience side effects may be predicted in advance by qualified physicians. We do not provide medical advice. Before taking any medication, consult a qualified physician who can compare all options, provide personalized advice, and provide details of risks and benefits based on individual medical history and situations.

Reviews. *Scott et al.* present a review covering cannabidiol for COVID-19.

Conclusion

Meta analysis using the most serious outcome reported shows 19% [-38-128%] higher risk, without reaching statistical significance. While non-symptomatic case results show 8% [-14-25%] improvement, symptomatic results show 61% [-53-451%] higher risk.

Study Notes

Crippa

Cannabidiol *Crippa et al.* LATE TREATMENT DB RCT

	Improvement	Relative Risk
Hospitalization	-557%	
Recovery time	-33%	

0   0.5   1   1.5   2+
Favors cannabidiol   Favors control

*Is **late** treatment with cannabidiol beneficial for COVID-19?*
Double-blind RCT 91 patients in Brazil (July - October 2020)
Higher hospitalization (*p=0.25*) and slower recovery (*p=0.21*), not sig.

c19early.org   Crippa et al., Cannabis and Cannabinoi.., Oct 2021

Crippa: RCT 105 patients recruited in an ER in Brazil, 49 treated with CBD, showing no significant differences with treatment. 300mg CBD for 14 days.
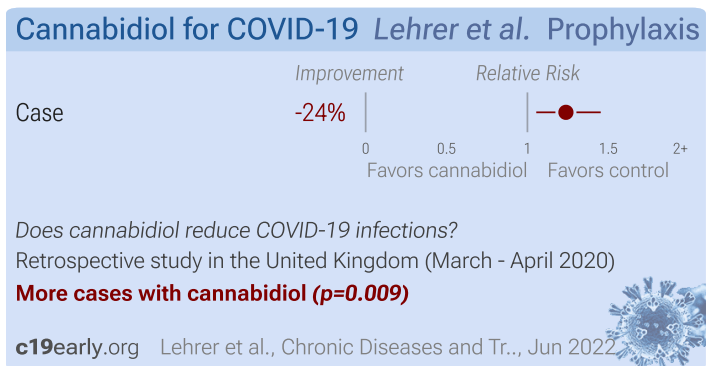
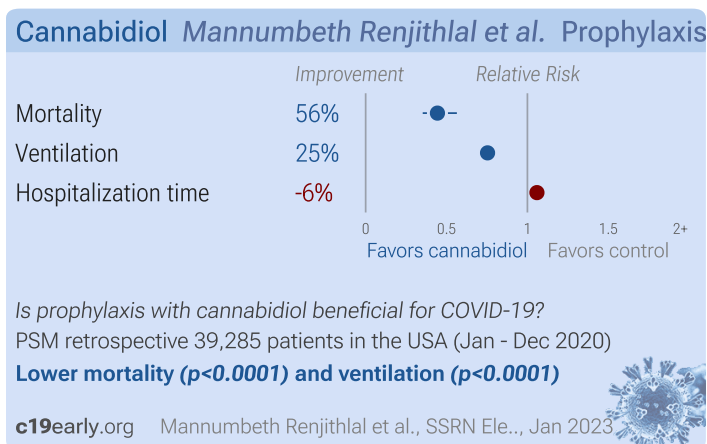For discussion see *liebertpub.com*.

Huang
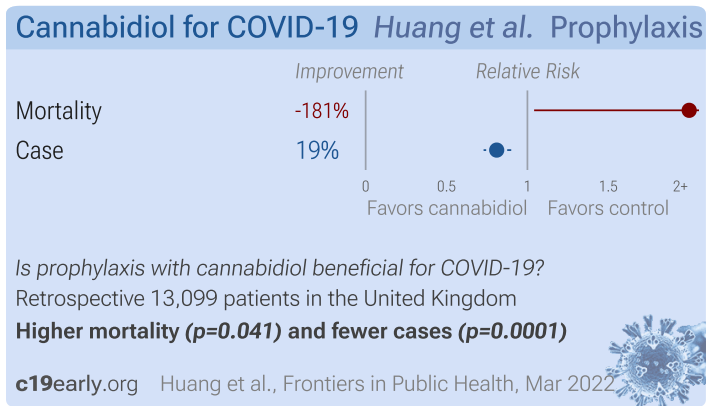
Huang: UK Biobank retrospective with 13,099 cannabis users, showing a lower risk of COVID-19 infection, however regular users had a significantly higher risk of mortality.
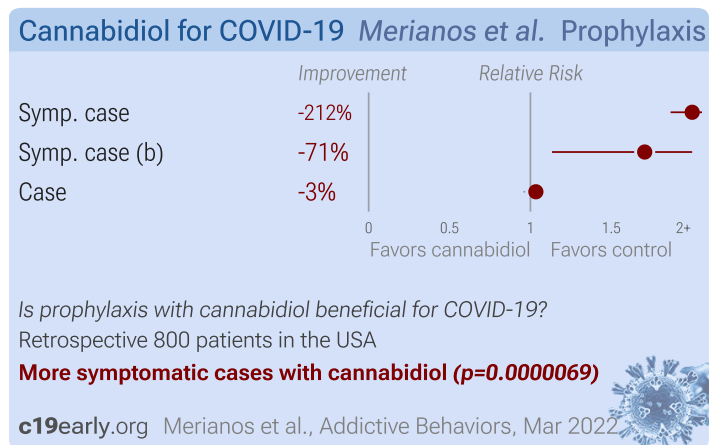
Lehrer

Lehrer: UK Biobank retrospective showing a higher risk of COVID-19 cases with a history of cannabis use.
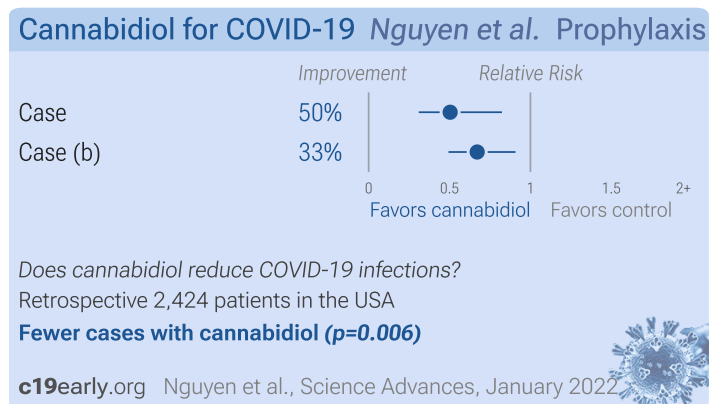
Mannumbeth Renjithlal

Mannumbeth Renjithlal: Retrospective 1,657,800 COVID-19 hospitalizations in the USA including 13,095 patients with cannabis use disorder, showing lower risk of mortality with cannabis use disorder. The text and Table S2 have conflicting results for mortality: 0.45 [0.36-0.57] versus 0.43 [0.34-0.55].

Merianos

Cannabidiol for COVID-19 *Merianos et al.* Prophylaxis

	Improvement	Relative Risk
Symp. case	-212%	
Symp. case (b)	-71%	
Case	-3%	

0 0.5 1 1.5 2+
Favors cannabidiol   Favors control

Is prophylaxis with cannabidiol beneficial for COVID-19?
Retrospective 800 patients in the USA
More symptomatic cases with cannabidiol *(p=0.0000069)*

c19early.org Merianos et al., Addictive Behaviors, Mar 2022

Merianos: Retrospective 800 e-cigarette users in the USA, showing higher risk of COVID-19 diagnosis and symptoms with cannabis use.

Nguyen

Cannabidiol for COVID-19 *Nguyen et al.* Prophylaxis

	Improvement	Relative Risk
Case	50%	
Case (b)	33%	

0 0.5 1 1.5 2+
Favors cannabidiol   Favors control

Does cannabidiol reduce COVID-19 infections?
Retrospective 2,424 patients in the USA
Fewer cases with cannabidiol *(p=0.006)*

c19early.org Nguyen et al., Science Advances, January 2022

Nguyen: Retrospective 1,212 patients in the USA with a history of seizure-related conditions, showing patients treated with CBD100 had significantly lower incidence of COVID-19 cases compared to a matched control group.

In Vitro study showing CBD inhibits SARS-CoV-2 with Vero E6 and Calu-3 cells. Mouse study showing CBD significantly inhibited viral replication in the lung and nasal turbinate.

Authors note that CBD does not inhibit ACE2 expression or the main viral proteases, inhibition occurs after viral entry. Authors stress several limitations for use at this time, including purity, quality, and the formulation of products, and potential lung damage based on administration method.

Authors recommend clinical trials, but do not mention the existing RCT by Crippa et al.

Shover

Cannabidiol for COVID-19 *Shover et al.* Prophylaxis

	Improvement	Relative Risk
Mortality	2%	
Ventilation	5%	
ICU admission	9%	
Oxygen therapy	3%	

0   0.5   1   1.5   2+
Favors cannabidiol   Favors control

Is prophylaxis with cannabidiol beneficial for COVID-19?
Retrospective 1,831 patients in the USA (February 2020 - February 2021)
Lower ventilation *(p=0.017)* and ICU admission *(p=0.018)*

c19early.org Shover et al., J. Cannabis Research, Aug 2022

Shover: Retrospective 1,831 hospitalized COVID-19 patients in the USA, showing lower mechanical ventilation and ICU admission, but no significant difference in mortality.

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 cannabidiol 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 cannabidiol 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 I² 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/cbdmeta.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.

Crippa, 10/7/2021, Double Blind Randomized Controlled Trial, placebo-controlled, Brazil, peer-reviewed, 32 authors, study period 7 July, 2020 - 16 October, 2020.	risk of hospitalization, 557.1% higher, RR 6.57, *p* = 0.25, treatment 3 of 49 (6.1%), control 0 of 42 (0.0%), continuity correction due to zero event (with reciprocal of the contrasting arm).
	recovery time, 33.3% higher, relative time 1.33, *p* = 0.20, treatment 49, control 42.

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.

Huang, 3/8/2022, retrospective, United Kingdom, peer-reviewed, 3 authors.	risk of death, 181.0% higher, HR 2.81, *p* = 0.04, regular users, Cox proportional hazards.
	risk of case, 19.0% lower, OR 0.81, *p* < 0.001, adjusted per study, multivariable, RR approximated with OR.
Lehrer, 6/22/2022, retrospective, United Kingdom, peer-reviewed, mean age 57.0, 3 authors, study period 16 March, 2020 - 26 April, 2020.	risk of case, 23.8% higher, OR 1.24, *p* = 0.009, RR approximated with OR.
Mannumbeth Renjithlal, 1/28/2023, retrospective, propensity score matching, USA, preprint, 7 authors, study period 1 January, 2020 - 31 December, 2020.	risk of death, 55.6% lower, RR 0.44, *p* < 0.001, treatment 380 of 13,095 (2.9%), control 1,430 of 26,190 (5.5%), NNT 39, odds ratio converted to relative risk.

	risk of mechanical ventilation, 24.6% lower, RR 0.75, *p* < 0.001, treatment 925 of 13,095 (7.1%), control 2,455 of 26,190 (9.4%), NNT 43.
	hospitalization time, 5.9% higher, relative time 1.06, *p* < 0.001, treatment mean 7.2 (±12.78) n=13,095, control mean 6.8 (±10.42) n=26,190.
Merianos, 3/31/2022, retrospective, USA, peer-reviewed, survey, 6 authors.	risk of symptomatic case, 211.9% higher, RR 3.12, *p* < 0.001, treatment 94 of 416 (22.6%), control 20 of 384 (5.2%), odds ratio converted to relative risk, COVID-19 symptoms.
	risk of symptomatic case, 70.6% higher, RR 1.71, *p* = 0.008, treatment 77 of 416 (18.5%), control 38 of 384 (9.9%), odds ratio converted to relative risk, COVID-19 diagnosis.
	risk of case, 3.4% higher, RR 1.03, *p* = 0.33, treatment 367 of 416 (88.2%), control 317 of 384 (82.6%), odds ratio converted to relative risk, COVID-19 test.
Nguyen, 1/20/2022, retrospective, USA, peer-reviewed, 34 authors.	risk of case, 49.6% lower, RR 0.50, *p* = 0.006, treatment 26 of 531 (4.9%), control 48 of 531 (9.0%), NNT 24, odds ratio converted to relative risk, active CBD100 users.
	risk of case, 32.9% lower, RR 0.67, *p* = 0.009, treatment 75 of 1,212 (6.2%), control 108 of 1,212 (8.9%), NNT 37, odds ratio converted to relative risk, all CBD100 users.
Shover, 8/5/2022, retrospective, USA, peer-reviewed, 7 authors, study period 12 February, 2020 - 27 February, 2021.	risk of death, 1.8% lower, RR 0.98, *p* = 0.56, treatment 3 of 69 (4.3%), control 199 of 1,762 (11.3%), odds ratio converted to relative risk, propensity score matching.
	risk of mechanical ventilation, 5.1% lower, RR 0.95, *p* = 0.02, treatment 3 of 69 (4.3%), control 292 of 1,762 (16.6%), NNT 8.2, odds ratio converted to relative risk, propensity score matching.
	risk of ICU admission, 8.6% lower, RR 0.91, *p* = 0.02, treatment 8 of 69 (11.6%), control 543 of 1,762 (30.8%), NNT 5.2, odds ratio converted to relative risk, propensity score matching.
	risk of oxygen therapy, 2.6% lower, RR 0.97, *p* = 0.27, treatment 35 of 69 (50.7%), control 1,417 of 1,762 (80.4%), NNT 3.4, odds ratio converted to relative risk, propensity score weighting.

Supplementary Data

Supplementary Data

Footnotes

a.   Viral infection and replication involves attachment, entry, uncoating and release, genome replication and transcription, translation and protein processing, assembly and budding, and release. Each step can be disrupted by therapeutics.

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