Supplemental Online Content

Janiaud P, Axfors C, Schmitt AM, et al. Association of convalescent plasma treatment with clinical outcomes in patients with COVID-19: a systematic review and meta-analysis. *JAMA*. doi:10.1001/jama.2021.2747

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eMethods. Literature search strategies

1. PubMed (January 29, 2021)

We used a PRESS-reviewed search strategy (Peer-Reviewed of Electronic Search Strategies). Search terms for PubMed included extensive controlled vocabulary and Medical Subject Headings (MeSH):

#1 corona[ti] OR covid*[ti] OR sars[ti] OR severe acute respiratory syndrome[ti] OR ncov*[ti] OR "severe acute respiratory syndrome coronavirus 2" [Supplementary Concept] OR "COVID-19" [Supplementary Concept] OR (wuhan[tiab] AND coronavirus[tiab]) OR (wuhan[tiab] AND pneumonia virus[tiab]) OR COVID19[tiab] OR COVID-19[tiab] OR coronavirus 2019[tiab] OR SARS-CoV-2[tiab] OR SARS2[tiab] OR SARS-2[tiab] OR "severe acute respiratory syndrome 2"[tiab] OR 2019-nCoV[tiab] OR (novel coronavirus[tiab] AND 2019[tiab]) NOT (animals[mesh] NOT humans[mesh]) AND ("2019/12/01"[EDAT] : "3000/12/31"[EDAT])

#2 ((((plasma[MeSH Terms]) OR (serum[MeSH Terms])) OR (plasma[Title/Abstract])) OR (serum[Title/Abstract])) OR (convalescen*[Title/Abstract])

3 (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR clinical trials as topic[mesh:noexp] OR randomly[tiab] OR trial[ti] NOT (animals[mh] NOT humans [mh]))

#1 AND #2 AND #3

2. Cochrane COVID-19 trial registry (January 31, 2021)

Search terms were “convalescent OR plasma”, and we will use the filter categories “Intervention assignment” (“randomised”), “Study aim” (“Treatment and management”), and “Study type” (“Intervention”).

3. L·OVE Platform – Epistemonikos (January 29, 2021)

We used the filter categories “Prevention and treatment”, “Procedures - convalescent plasma”, and within the primary studies we will select the filters “by reported data - has data” and “by type of study - RCT”.

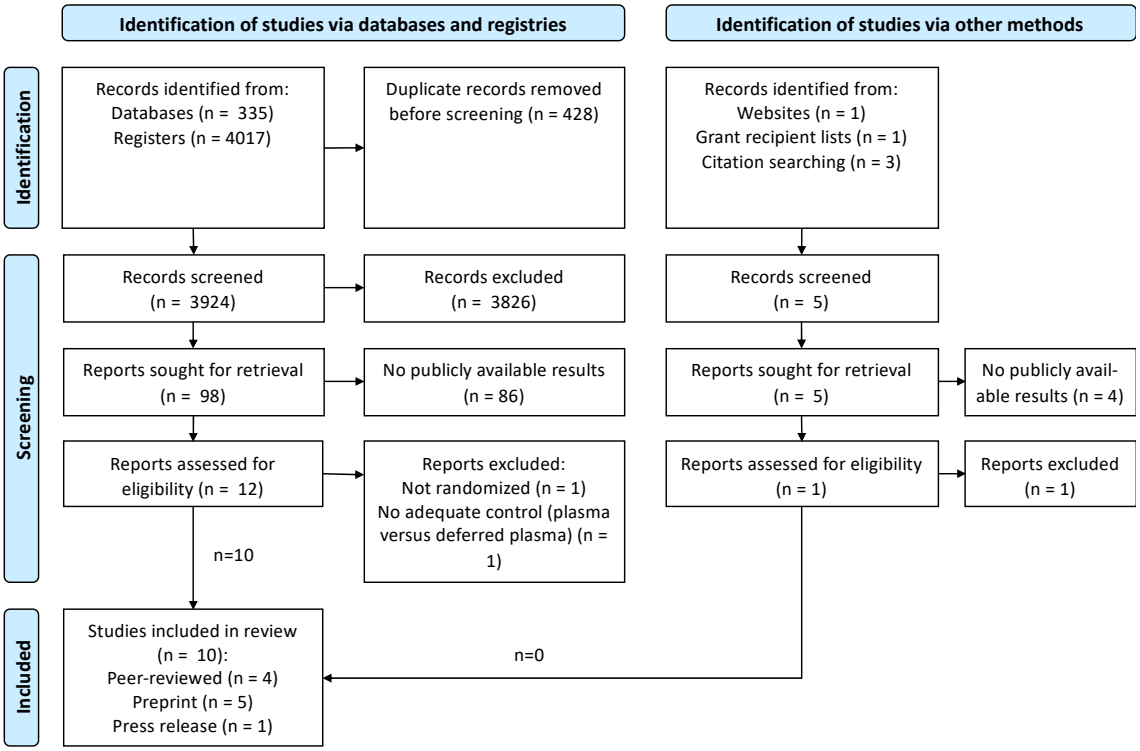
4. Google (January 29, 2021)

We also searched the grey literature using the search string: "convalescent plasma" AND "press release" AND “COVID” on Google. We screened the first 30 hits.

5. Other sources

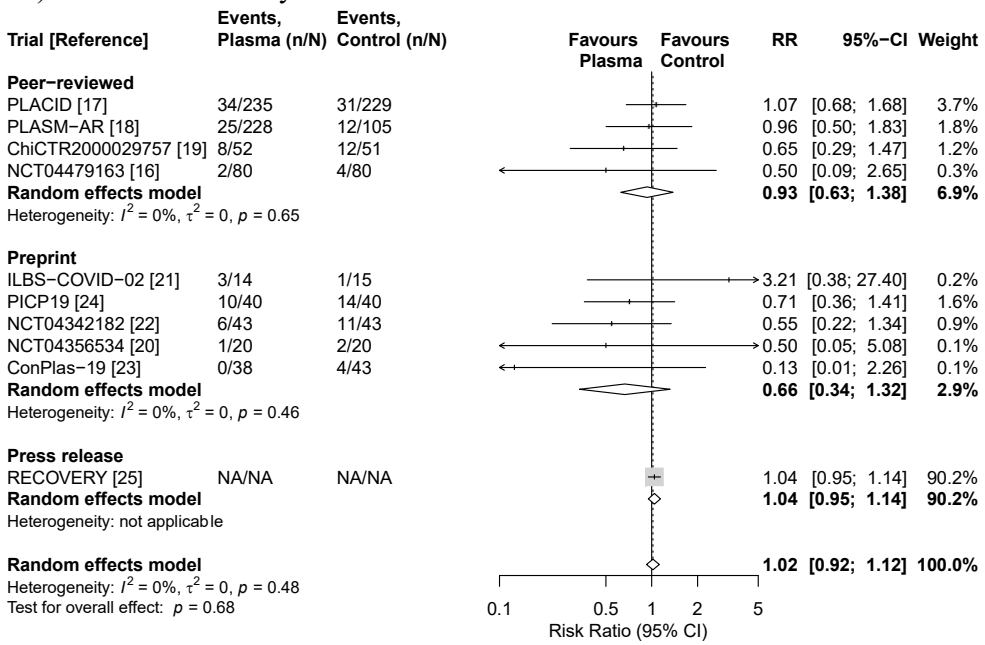
Finally, we complemented our results with trials identified by other published or registered systematic searches as well as personal knowledge.

eFigure 1. Flowchart of the literature search

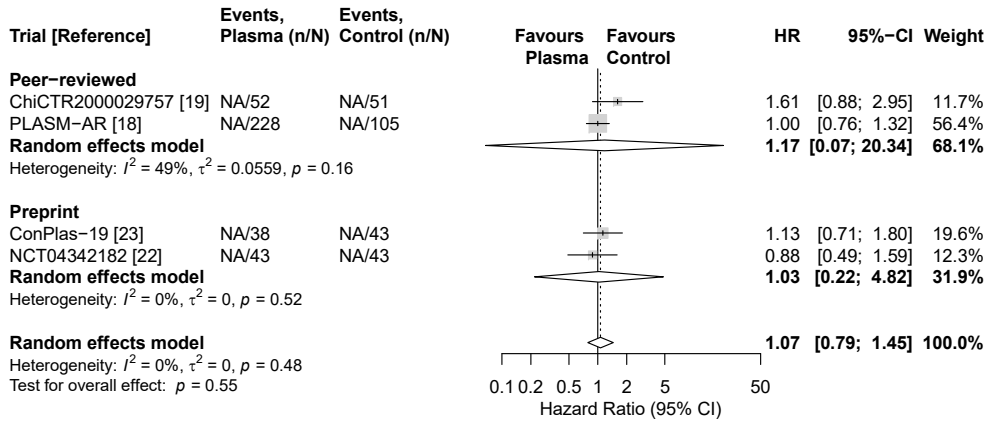


eFigure 2. Forest plots with summary effect sizes per publication type for A) all-cause mortality, B) Length of hospitalization, and C) Mechanical ventilation requirement

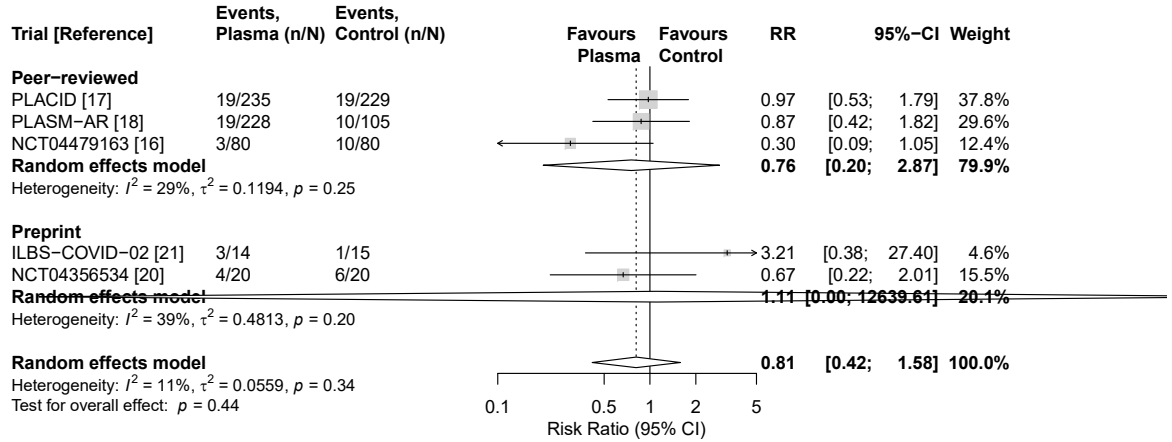
A) All-cause mortality



B) Length of hospitalization

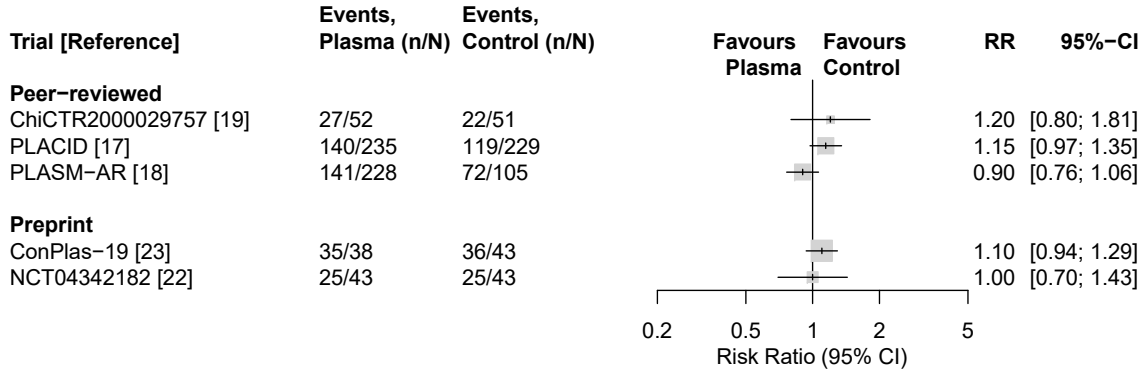


C) Mechanical ventilation requirement

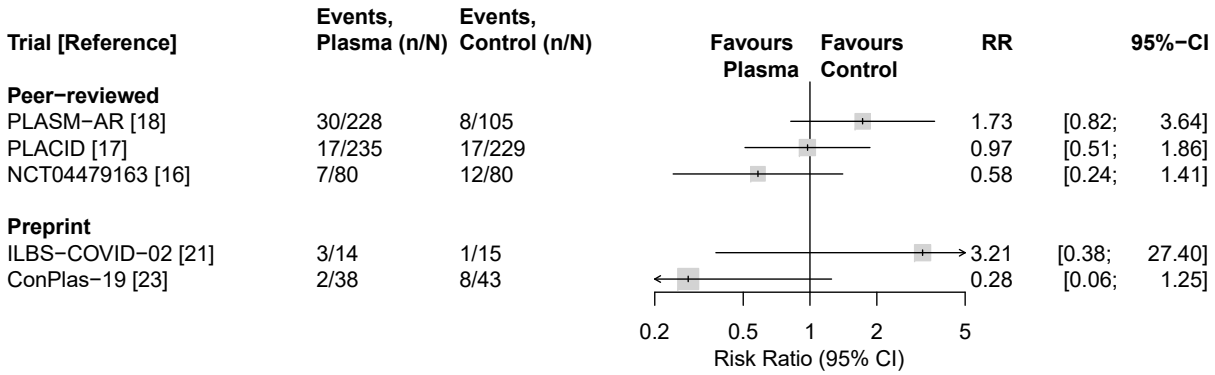


eFigure 3. Association of convalescent plasma with A) study-defined clinical improvement and B) study-defined clinical deterioration for peer-reviewed and preprint trials (no pooling due to heterogeneity of outcome definitions)

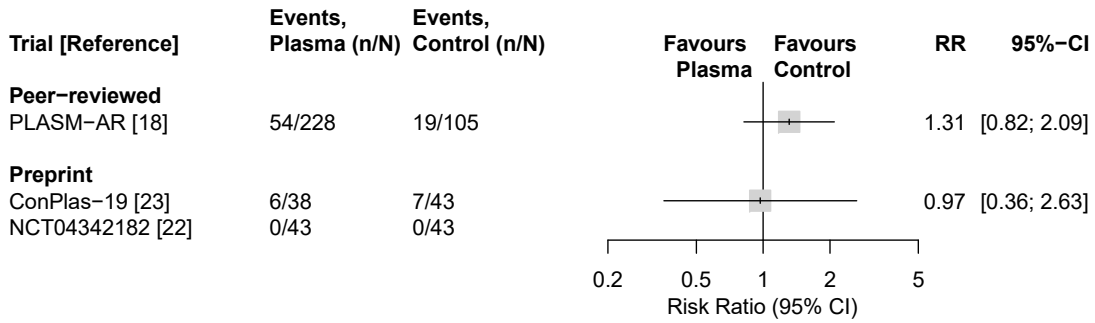
A) Study-defined clinical improvement



B) Study-defined clinical deterioration



eFigure 4. Serious adverse events reported in peer-reviewed and preprint trials (no pooling due to heterogeneity of outcome definitions)[a]



[a]NCT04342182 only reported the plasma-related serious adverse events.

eTable 1. Outcomes reported by trials

Trial	PLASM-AR (NCT04383535)	PLACID (CTRI/2020/04/024775)	ChiCTR2000029757	NCT04479163	NCT04356534	ILBS-COVID-02 (NCT04346446)	NCT04342182	ConPlas-19 (NCT04345523)	PICP19 (CTRI/2020/05/025209)	RECOVERY (NCT04381936)
Publication format	**Journal**	**Journal**	**Journal**	**Journal**	**Preprint**	**Preprint**	**Preprint**	**Preprint**	**Preprint**	**Press release**
Peer-reviewed	**yes**	**yes**	**yes**	**yes**	**no**	**no**	**no**	**no**	**no**	**no**
Trial primary outcome	Ordinal scale of clinical status (from 1/death to 6/recovered) at day 30	Composite of progression to severe disease (pao2/fio2 <100 mm hg) or all-cause mortality at 28 days fio2 <100 mm hg) or all-cause mortality at 28 days post-enrolment	Time to clinical improvement	Severe respiratory disease, defined as a respiratory rate of 30 breaths per minute or more, an oxygen saturation of less than 93% while the patient was breathing ambient air, or both	Requirement for ventilation (invasive and non-invasive)	Proportion of patients remaining free of mechanical ventilation	Mortality	Disease severity scale (proportion of patients in categories 5, 6 or 7 of the covid-19 ordinal scale (death or any kind of ventilation or ECMO))	Mortality	Mortality
Outcome definition										
Mortality	30 days	28 days	28 days	15 and 25 days	NR	28 days	60 days	15 to 29 days	30 days	28 days
Clinical improvement	Discharged with full return to baseline function	Resolution of shortness of breath	Patient discharged alive or reduction of 2 points on a 6-point disease severity scale (ranging from 1 [discharge] to 6 [death]) severity scale (ranging from 1 [discharge] to 6 [death])	NR	NR	NR	WHO Covid-19 severity score at day 15	Time to improvement of one category on the ordinal scale	NA	NR
Clinical deterioration	Discharged without full return to baseline function	Progression to severe disease	NR	Life-threatening respiratory disease, critical systemic illness, or death, alone or in combination	NR	Vasopressor requirement	NR	One-category worsening in any of the daily assessments	NR	NR

Trial	PLASM-AR (NCT04383535)	PLACID (CTRI/2020/04/024775)	ChiCTR2000029757	NCT04479163	NCT04356534	ILBS-COVID-02 (NCT04346446)	NCT04342182	ConPlas-19 (NCT04345523)	PICP19 (CTRI/2020/05/025209)	RECOVERY (NCT04381936)
Mechanical ventilation[a]	Invasive	Invasive or non-invasive	NR	Any, invasive and non-invasive	Any	Invasive	NR	NR	NR	NR
Length of hospitalization	Median IQR and HR	Median IQR	Median IQR and HR	NR	NR	Mean SD	HR	Median 95%CI, HR	Median	NR
Serious adverse events	Common Terminology Criteria for Adverse Events version 5	Death and invasive mechanical ventilation, hemodynamic instability within 6 hours of CP transfusion (no data reported)	NR	NR	Death, life-threatening, requirement of hospitalization or prolonged hospitalization, persistent or significant disability/incapacity, congenital anomaly or birth defect (no data reported)	NR	Death from any cause or a life-threatening transfusion reaction (only data reported for plasma-related serious adverse events)	AE grade 3 and 4 (Medical Dictionary For Regulatory Activities Version 21)	NR	NR

eTable 2. Sensitivity analyses

Outcome	Model	ES (95% CI)[a]	Heterogeneity I^2; tau^2
Peer reviewed only			
Mortality	HKSJ-PM	0.93 [0.63; 1.38]	0.00%; 0.00
	HKSJ-SJ	0.90 [0.59; 1.38]	0.00%; 0.03
	Fixed effect	0.93 [0.67; 1.29]	0.00%; 0.00
	Profile likelihood	1.02 [0.77; 1.12]	NA%; 0.00
Length of hospitalization	HKSJ-PM	1.17 [0.07; 20.34]	49.27%; 0.06
	HKSJ-SJ	1.17 [0.07; 20.37]	49.27%; 0.06
	Fixed effect	1.09 [0.84; 1.40]	49.27%; 0.06
	Profile likelihood	1.07 [0.86; 1.39]	NA%; 0.00
Mechanical ventilation	HKSJ-PM	0.76 [0.20; 2.87]	28.89%; 0.12
	HKSJ-SJ	0.73 [0.18; 2.97]	28.89%; 0.20
	Fixed effect	0.81 [0.52; 1.26]	28.89%; 0.07
	Profile likelihood	0.83 [0.51; 1.25]	NA%; 0.00
Peer reviewed and preprints			
Mortality	HKSJ-PM	1.02 [0.92; 1.12]	0.00%; 0.00
	HKSJ-SJ	0.82 [0.59; 1.14]	0.00%; 0.21
	Fixed effect	1.02 [0.93; 1.11]	0.00%; 0.00
	Profile likelihood	1.02 [0.77; 1.12]	NA%; 0.00
Length of hospitalization	HKSJ-PM	1.07 [0.79; 1.45]	0.00%; 0.00
	HKSJ-SJ	1.09 [0.77; 1.54]	0.00%; 0.03
	Fixed effect	1.07 [0.87; 1.31]	0.00%; 0.00
	Profile likelihood	1.07 [0.86; 1.39]	NA%; 0.00
Mechanical ventilation	HKSJ-PM	0.81 [0.42; 1.58]	11.27%; 0.06
	HKSJ-SJ	0.80 [0.36; 1.78]	11.27%; 0.32
	Fixed effect	0.83 [0.56; 1.24]	11.27%; 0.03
	Profile likelihood	0.83 [0.51; 1.25]	NA%; 0.00

[a]All are risk ratios (RRs) except for length of hospitalization which are hazard ratios (HRs)
HKSJ-PM: Hartung-Knapp adjustment for random effects model, Paule-Mandel estimator for tau^2;
HKSJ-SJ: Hartung-Knapp adjustment for random effects model, Sidik-Jonkman estimator for tau^2;
Fixed effect: inverse variance–weighted fixed-effect model
Profile likelihood: Profile likelihood method with random effects model, likelihood-based confidence intervals

eTable 3. GRADE assessment

A) All-cause mortality

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Convalescent plasma	Control	Relative (95% CI)	Absolute risk difference		
All-cause mortality (peer-reviewed)												
4	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[a]	None	69/595 (11.6%)	59/465 (12.7%)	RR 0.93 (0.63 to 1.38)	-1.21% [-5.29%; 2.88%]	⊕⊕OO LOW	CRITICAL
All-cause mortality (peer-reviewed, preprints, press-release)												
10	randomized trials	no serious risk of bias[b]	no serious inconsistency	no serious indirectness	No serious imprecision	Unpublished data[c]	NA	NA	RR 1.02 (0.92 to 1.12)	NA	⊕⊕⊕O MODERATE	CRITICAL

NA: number of events and total patients in each arm could not be reported as not available for RECOVERY
[a]Imprecision was downgraded by 2 levels because the 95% of the relative risk (RR) was sufficiently wide that the estimate could either include appreciable harm or benefit of the intervention (thresholds: 0.75 and 1.25).
[b]Although there were some concerns for two trials (NCT04356534 and ConPlas-19) and one (PICP19) at high risk of bias, they contributed little to the overall treatment effect estimate.
[c]RECOVERY data come from a press release and so additional data would be warranted to fully assess its potential effect on the overall treatment effect estimate and on the other quality assessment domains.

B) Length of hospitalization

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Convalescent plasma	Control	Relative (95% CI)	Absolute risk difference		
Length of hospitalization (peer-reviewed)												
2	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[a]	None	NA	NA	HR 1.77 (0.07 to 20.34)	NA	⊕⊕OO LOW	CRITICAL
Length of hospitalization (peer-reviewed, preprints)												
4	randomized trials	serious risk of bias[b]	no serious inconsistency	no serious indirectness	very serious[a]	None	NA	NA	HR 1.07 (0.79 to 1.45)	NA	⊕⊕OO LOW	CRITICAL

NA: number of events and total patients in each group could not be reported as only hazard ratios were available for each trial.
[a]Imprecision was downgraded by 2 levels because the 95% of the relative risk (RR) was sufficiently wide that the estimate could either include appreciable harm or benefit of the intervention (thresholds: 0.75 and 1.25).
[b]Some concerns for ConPlas-19 as unclear whether the randomization process was concealed

C) Mechanical ventilation requirement

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Convalescent plasma	Control	Relative (95% CI)	Absolute risk difference		
Mechanical ventilation (peer-reviewed)												
3	randomized trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[a]	None	41/543 (7.5%)	39/414 (9.4%)	RR 0.76 (0.20 to 2.87)	-2.56% [-13.16%; 8.05%]	⊕⊕OO LOW	CRITICAL
Mechanical ventilation (peer-reviewed, preprints)												
5	randomized trials	serious risk of bias[b]	no serious inconsistency	no serious indirectness	very serious[a]	None	48/577 (8.3%)	46/449 (10.2%)	RR 0.81 (0.42 to 1.58)	-2.21% [-8.94%; 4.51%]	⊕⊕OO LOW	CRITICAL

[a]Imprecision was downgraded by 2 levels because the 95% of the relative risk (RR) was sufficiently wide that the estimate could either include appreciable harm or benefit of the intervention (thresholds: 0.75 and 1.25).
[b]Some concerns for NCT04356534 as unclear whether the randomization process was concealed