Supplementary Online Content

The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group. Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19: a meta-analysis. *JAMA*. doi:10.1001/jama.2020.17023

Lists of investigators and steering committee

This supplementary material has been provided by the authors to give readers additional information about their work.

Lists of investigators and steering committee

Efficacy of dexamethasone treatment for patients with ARDS caused by COVID-19 (DEXA-COVID19) trial

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CODEX trial

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RECOVERY trial

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CAPE COVID Trial

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COVID STEROID trial

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Corticosteroids therapy in adult patients with COVID-19 and ARDS (Steroids-SARI) trial

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eTable 1. Summary of assessments of the risk of bias in the estimated effect of corticosteroids on mortality and serious adverse events in each trial, with brief explanation of judgements

	Risk of bias domain (assessments for the effect of assignment to intervention)					
Outcome and study	1. Randomization process	2. Deviations from the intended interventions	3. Missing outcome data	4. Measurement of the outcome	5. Selection of the reported result	**Overall risk of bias**
Results for 28-day mortality						
DEXA- COVID19 (NCT04325061)	Low	Low	Low	Low	Low	**Low**
CoDEX (NCT04327401)	Low	Low	Low	Low	Low	**Low**
RECOVERY (NCT04381936)	Low	Low	Low	Low	Low	**Low**
CAPE_COVID (NCT02517489)	Low	Low	Low	Low	Low	**Low**
COVID STEROID (NCT04348305)	Low	Low	Low	Low	Low	**Low**
REMAP-CAP (NCT02735707)	Low	Low	Low	Low	Low	**Low**
Steroids-SARI (NCT04244591)	Some concerns	Low	Low	Low	Low	**Some concerns**
	Randomization process: Concerns about (i) the fixed block size within centres (which it might have been easy to deduce, despite the blinding) and (ii) the rather informal use of text messages to implement allocations.					
Results for serious adverse events						
DEXA- COVID19 (NCT04325061)	Low	Low	Low	Some concerns	Low	Some concerns
	Outcome measurement: Outcome assessors were not blinded and there was room for subjectivity in how serious adverse events were determined.					
CoDEX (NCT04327401)	Low	Low	Low	Some concerns	Low	Some concerns
	Outcome measurement: The trial was open label and there was room for subjectivity in how serious adverse events were determined.					
CAPE_COVID (NCT02517489)	Low	Low	Low	Low	Low	**Low**
COVID STEROID (NCT04348305)	Low	Low	Low	Low	Low	**Low**
REMAP-CAP (NCT02735707)	Low	Low	Low	Some concerns	Low	**Some concerns**
	Outcome measurement: The trial was open label and there was room for subjectivity in how serious adverse events were determined.					
Steroids-SARI (NCT04244591)	Some concerns	Low	Low	Some concerns	Low	**Some concerns**
	Randomization: Concerns about (i) the fixed block size within centres (which it might have been easy to deduce, despite the blinding) and (ii) the rather informal use of text messages to implement allocations. *Outcome measurement: Outcome assessors were not blinded and there was room for subjectivity in how serious adverse events were determined.*					

eTable 2. Characteristics of the METCOVID trial

	METCOVID
ClinicalTrials.gov identifier	NCT04343729
Planned sample size	420
Eligibility criteria	Hospitalized patients with clinical AND/OR radiological suspicion of COVID-19 (history of fever AND any respiratory symptom, e.g., cough or dyspnea AND/OR ground glass opacity OR pulmonary consolidation on CT scan), aged 18 years or older at the time of inclusion, with SpO2 ≤ 94% at room air OR in use of supplementary oxygen OR under IMV.
Corticosteroid	
Drug name	Methylprednisolone
Dosage and administration	Intravenous (0.5 mg/kg), twice daily, for 5 days
Dose classification	High
Control intervention	Saline solution twice daily, for 5 days
Primary outcome	28-d mortality
Mortality outcome, d	28
Serious adverse event definitions	•Sepsis or positive blood culture collected on day 7 •Insulin due to hyperglycemia
Location	Brazil

eTable 3. Characteristics of patients included in the METCOVID trial

	METCOVID (ITT) (NCT04343729)	
	Steroid	No steroid
Total patients randomized by 16 June 2020 (N)	209	207
PCR-confirmed SARS-COV-2 infection (N, %)	170 (82.5)	162 (78.6)
Mechanical ventilation at time of randomization (if applicable) (N, %)	71 (33.97)	70 (33.82)
Cells below show data for patients who were receiving invasive mechanical ventilation at the time of randomization		
On vasoactive medication at the time of randomization (N, %)	54 (78.3)	59 (84.3)
Female sex (N, %)	20 (28.2)	13 (18.6)
Median (IQR) age (years)	58 [50–68]	65 [56–72]
Treated with any antiviral at the time of randomization[1]	34 (50.1)	33 (47.1)
Treated with remdesivir at the time of randomization (N, %)	0	0
Treated with lopinavir/ritonavir at the time of randomization (N, %)	0	0
Treated with favipravir at the time of randomization (N, %)	0	0
Treated with hydroxychloroquine[2] at the time of randomization (N, %)	19 (26.8)	25 (35.7)
Treated with azithromycin at the time of randomization (N, %)	49 (81.7)	50 (75.8)
Treated with convalescent plasma at the time of randomization (N, %)	0	0

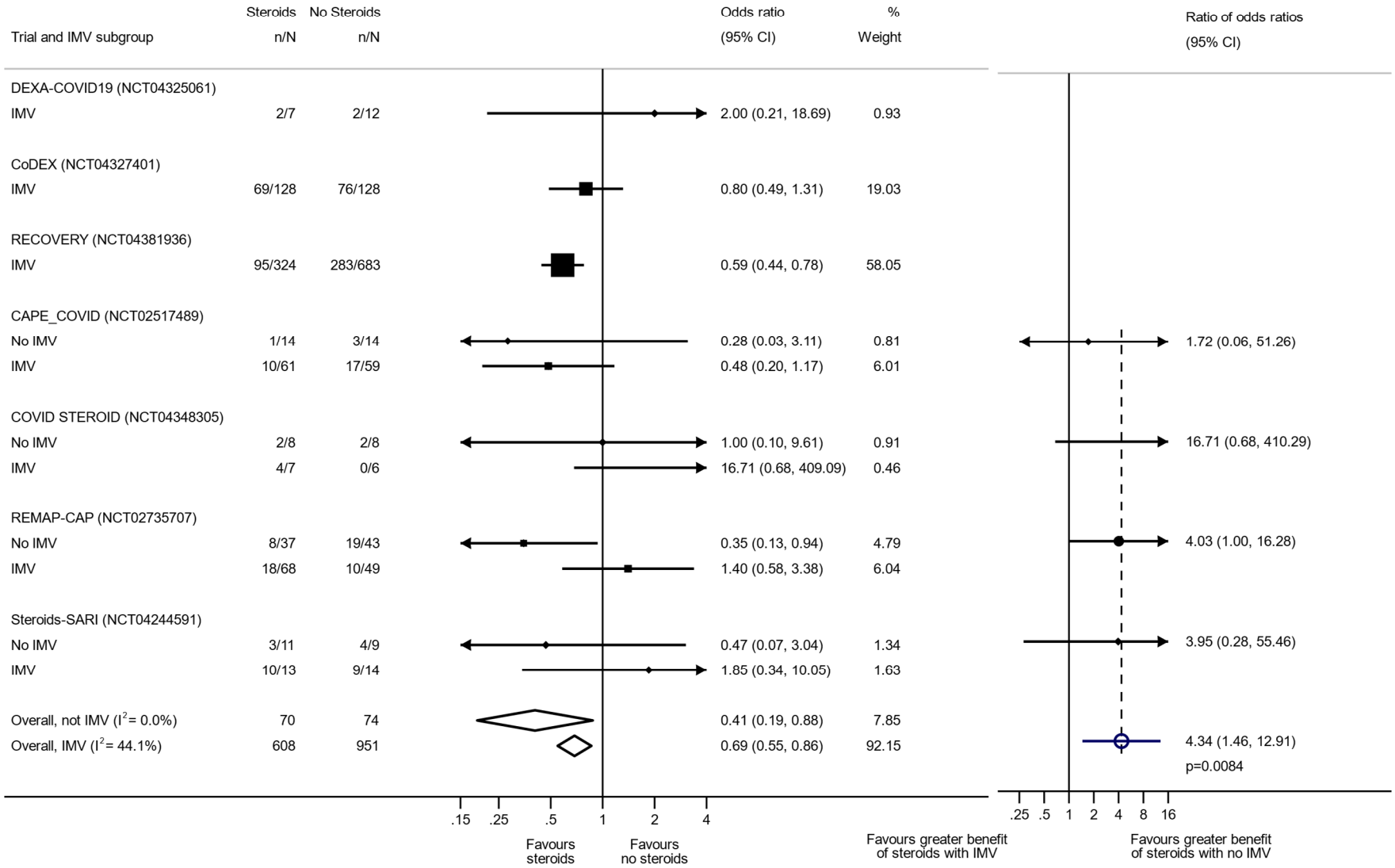
1. Only Oseltamivir was checked
2. Chloroquine or hydroxychloroquine

Information on individual antiviral drugs not available

eTable 4. Summary of assessments of the risk of bias in the estimated effect of corticosteroids on mortality in the METCOVID trial

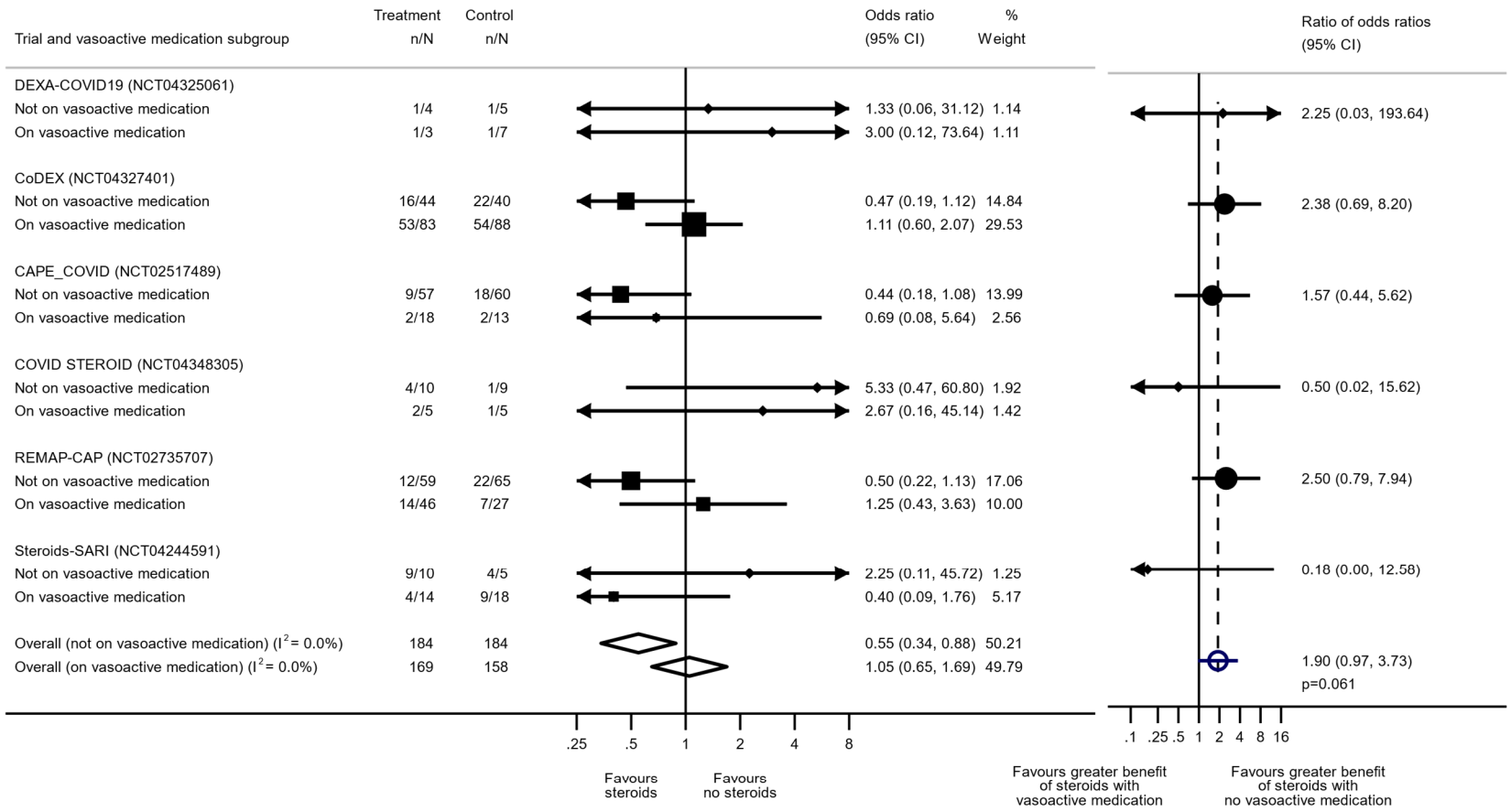
	Risk of bias domain (assessments for the effect of assignment to intervention)					Overall risk of bias
Outcome and study	1. Randomization process	2. Deviations from the intended interventions	3. Missing outcome data	4. Measurement of the outcome	5. Selection of the reported result	
Result for 28-day mortality						
METACOVID (NCT04343729)	Low	Low	Low	Low	Low	**Low**

eFigure 1. Effects of corticosteroids on 28-day mortality according to whether patients received invasive mechanical ventilation (IMV) at the time of randomization Left plot: odds ratio (95% CI) in each subgroup in each trial. Right plot: ratio of odds ratios comparing effects in patients who were and were not invasively mechanically ventilated in each trial, together with a fixed-effect meta-analysis of these ratios of odds ratios. Only trials that recruited critically ill patients who both were and were not invasively mechanically ventilated at the time of randomization contributed to the right plot. See Figure 3 for the effect of Dexamethasone in RECOVERY trial patients who required oxygen with or without non-invasive ventilation but were not invasively mechanically ventilated at randomization.



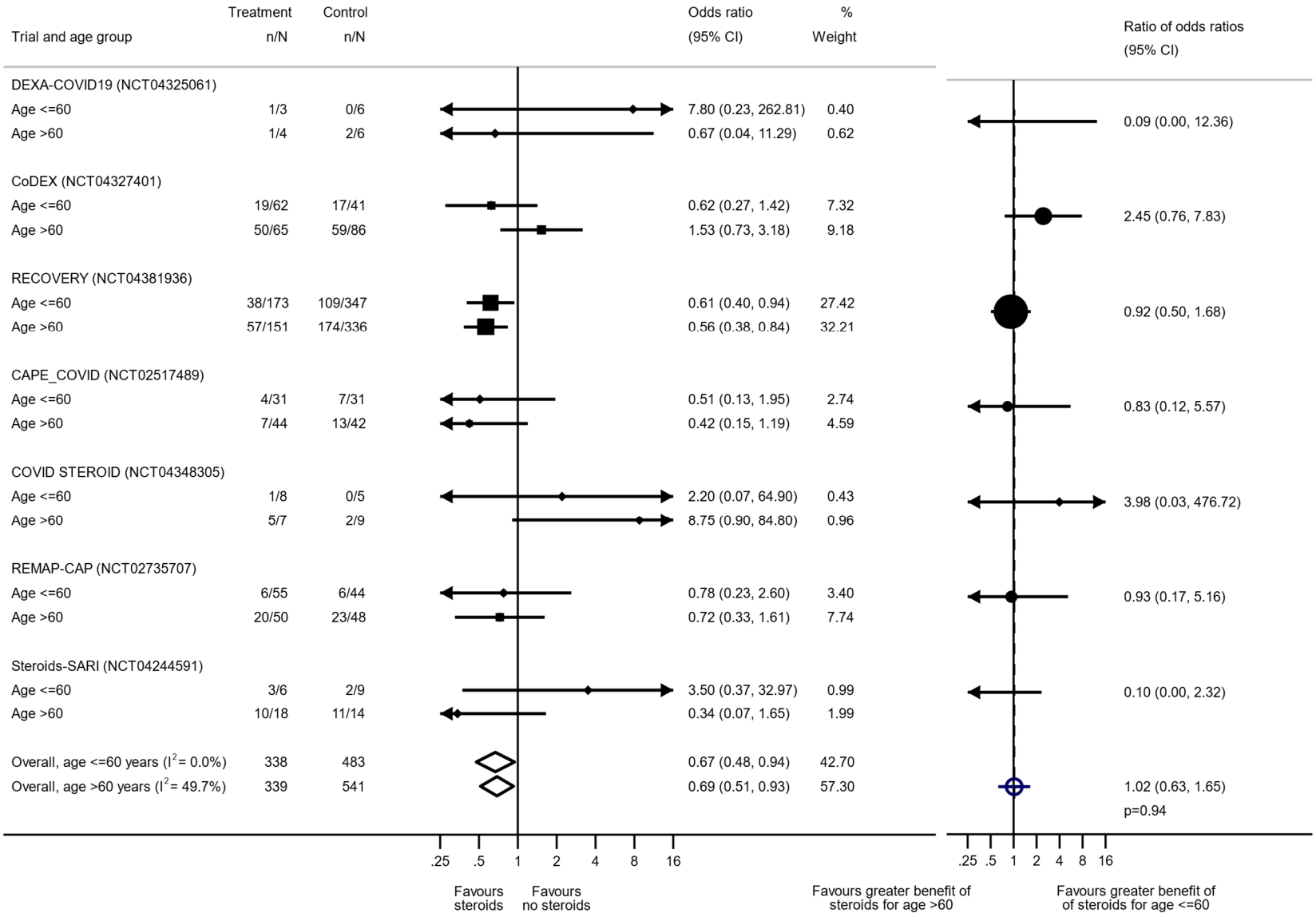
eFigure 2. Effects of corticosteroids on 28-day mortality according to whether patients received vasoactive medication at the time of randomization

Left plot: odds ratio (95% CI) in each subgroup in each trial. Right plot: ratio of odds ratios comparing effects in patients who were and were not receiving vasoactive medication in each trial, together with a fixed-effect meta-analysis of these ratios of odds ratios. The RECOVERY trial did not record whether patients received vasoactive medication at the time of randomization.



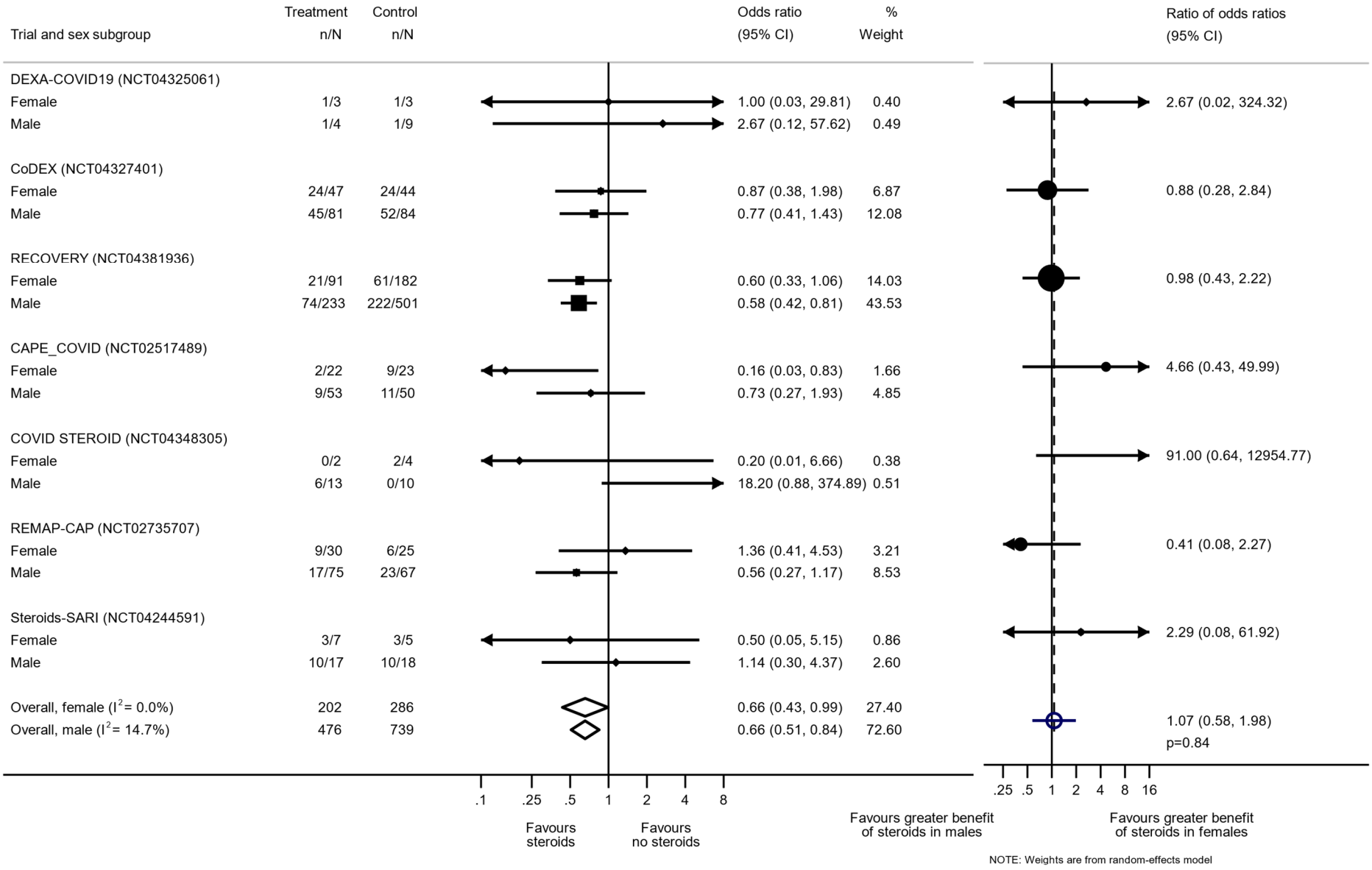
eFigure 3. Effects of corticosteroids on 28-day mortality according to whether patients were aged ≤60 or >60 years at the time of randomization

Left plot: odds ratio (95% CI) in each subgroup in each trial. Right plot: ratio of odds ratios comparing effects in patients who were and were not aged >60 years in each trial, together with a fixed-effect meta-analysis of these ratios of odds ratios.



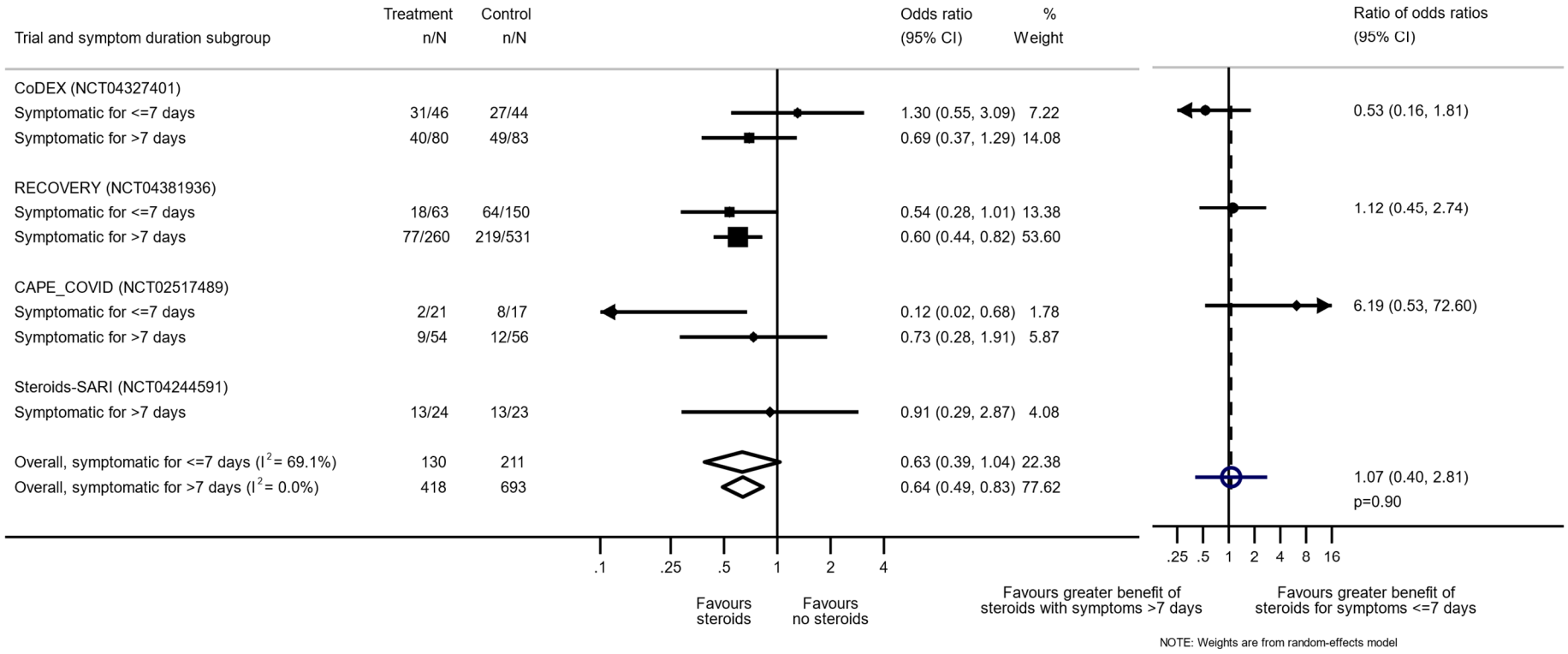
eFigure 4. Effects of corticosteroids on 28-day mortality according to sex. Left plot: odds ratio (95% CI) in females and males in each trial

Right plot: ratio of odds ratios comparing effects in males and females in each trial, together with a fixed-effect meta-analysis of these ratios of odds ratios.

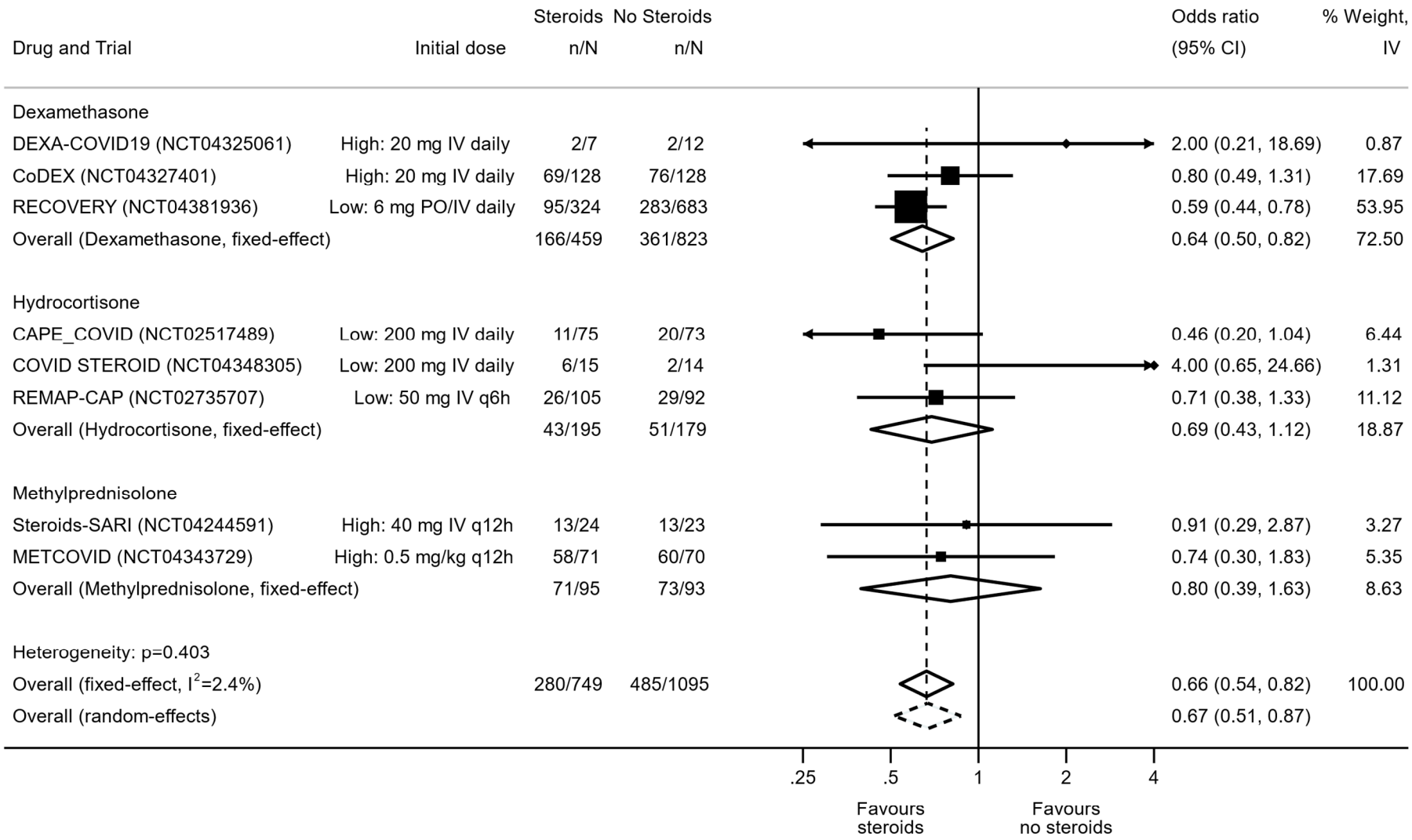


eFigure 5. Effects of corticosteroids on 28-day mortality according to duration of symptoms (≤7 days or >7 days) at the time of randomization, for the four trials that recorded this information

This was a post-hoc analysis based on results reported by the RECOVERY trial. Left plot: odds ratio (95% CI) in each subgroup in each trial. Right plot: ratio of odds ratios comparing effects in patients with >7 days versus ≤7 days duration of symptoms in each trial, together with a fixed-effect meta-analysis of these ratios of odds ratios. The Steroids-SARI trial did not recruit patients with duration of symptoms ≤7 days, so did not contribute to the right plot.



eFigure 6. Additional forest plot showing the association of corticosteroids with all-cause 28-day mortality in each trial including the METCOVID trial*, overall and according to corticosteroid drug



The diamonds shown with solid lines are from fixed-effect meta-analyses (primary analysis). The diamond shown with dashed lines is from a random-effects meta-analysis

* The RECOVERY and METCOVID trial results are for patients who were receiving invasive mechanical ventilation at randomization.