Supplementary Online Content

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

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eTable 1: Definitions of outcomes

Day-28 mortality (Primary outcome)	Defined as the proportion of patients who had died by 28 days after randomization. We used hospital mortality or ICU mortality rates to compute the pooled analysis on 28-day mortality unless actual 28-day mortality rates could be extracted from the published trials or be obtained from study authors.
Day-90 mortality	The proportion of patients who had died by 90 days after randomization.
Hospital mortality	The proportion of patients who had died in hospital after randomization.
ICU mortality	The proportion of patients who had died in ICU after randomization.
SOFA score at day 7	The number of SOFA score at day 7
Shock reversal at day 7	The proportion of patients without hemodynamic instability requiring treatment with vasopressors or inotropes after resolution of the initial episode at day 7
Time to shock reversal	The time from randomization to the attainment of a clinician-prescribed mean arterial pressure target without the use of vasopressors or inotropes.
ICU length of stay	The total duration of stay in ICU
Hospital length of stay	The total duration of stay in hospital
Health-related quality of life	Defined in the included trials
Vasopressor-free days to day 28	The number of days that patients were alive and free of vasopressors at day 28
Ventilation-free days to day 28	The number of days that patients were alive and free of mechanical ventilation at day 28
Any severe adverse event	The proportion of patients experiencing at least one severe adverse event.
Gastroduodenal bleeding	Bleeding of the stomach or/and duodenum
Superinfections	Reinfection or a second infection with a microbial agent
Hyperglycemia	The cut-off was defined in the included trials
Hypernatremia	The cut-off defined in the included trials

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eTable 2: Search strategy

MEDLINE(R)		
1	exp Adrenal Cortex Hormones	378296
2	exp STEROIDS	816471
3	(Adrenal Cortex Hormone* or adrenocortical hormone* or adrenocorticosteroid* or Corticosteroid* or Corticoid* or steroid* or glucocort* or cortisone* or hydrocortisone* or Cortisol or Epicortisol or Cortifair or Cortril or hydroxyhydrocortisone or oxohydrocortisone or tetrahydrocortisol or dexamethason* or baycuten or dexatopic or sofradex or Methylfluorpreordnisolone or Hexadecadrol or Decameth or Decaspray or Dexasone or Dexpak or Maxidex or Millicorten or Oradexon or Decaject or Decaject or Hexadrol or methylprednisolon* or (methyl adj3 prednisolone) or Metipred or Urbason or Medrol or Betamethasone or Flubenisolone or Betadexamethasone or Celestona or Cellestoderm or Celeston or Celestone or prednison* or prednisolon* or hydroxyprednisolone or desonide or Predate or Predonine or Di-Adreson-F or DiAdresonF or triamcinolon*).mp. (	672625
4	exp SEPSIS	112301
5	(Sepsis or septic or Sepses or Py?emia? or Septic?emia? or (blood adj2 poison*) or Bacter?emia? or bacill?emia? or (Lemierre* adj2 (syndrome or disease)) or necrobacillosis or meningococc?emia? or Endotoxemia? or Fung?emia? or Candid?emia? or ((Toxic or Endotox* or bacter*) adj2 Shock) or toxic forward failure or Parasitemia? or Viremia? or urosepsis).mp.	224779
6	(1 or 2 or 3) and (4 or 5)	11388
7	randomized controlled trial.pt.	466885
8	controlled clinical trial.pt.	92588
9	randomized.ab.	419464
10	placebo.ab	191110
11	drug therapy.fs.	2040402
12	randomly.ab.	295667
13	trial.ab.	436805
14	groups.ab.	1824888
15	7 or 8 or 9 or 10 or 11 or 12 or 13 or 14	4263445
16	exp animals/ not humans.sh	4487377
17	15 not 16	3685711
18	6 and 17	4515
Embase		
1	exp corticosteroid/	800954
2	(Adrenal Cortex Hormone* or adrenocortical hormone* or adrenocorticosteroid* or Corticosteroid* or Corticoid* or steroid* or glucocort* or cortisone* or hydrocortisone* or Cortisol or Epicortisol or Cortifair or Cortril or hydroxyhydrocortisone or oxohydrocortisone or tetrahydrocortisol or dexamethason* or baycuten or dexatopic or sofradex or Methylfluorpreordnisolone or Hexadecadrol or Decameth or Decaspray or Dexasone or Dexpak or Maxidex or Millicorten or Oradexon or Decaject or Decaject or Hexadrol or methylprednisolon* or (methyl adj3 prednisolone) or Metipred or Urbason or Medrol or Betamethasone or Flubenisolone or Betadexamethasone or Celestona or Cellestoderm or Celeston or Celestone or prednison* or prednisolon* or hydroxyprednisolone or desonide or Predate or Predonine or Di-Adreson-F or DiAdresonF or triamcinolon*).mp.	1054830

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3	exp SEPSIS/	216562
4	(Sepsis or septic or Sepses or Py?emia? or Septic?emia? or (blood adj2 poison*) or Bacter?emia? or bacill?emia? or (Lemierre* adj2 (syndrome or disease)) or necrobacillosis or meningococc?emia? or Endotoxemia? or Fung?emia? or Candid?emia? or ((Toxic or Endotox* or bacter*) adj2 Shock) or toxic forward failure or Parasitemia? or Viremia? or urosepsis).mp.	330765
5	(1 or 2) and (3 or 4)	485121
6	randomized controlled trial/	53693
7	crossover procedure/	53693
8	double blind procedure/	144960
9	single blind procedure/	30217
10	(random* or factorial* or crossover* or placebo* or assign* or allocat* or volunteer* or (doubl* adj5 blind*) or (singl* adj5 blind*)).mp.	2160682
11	6 or 7 or 8 or 9 or 10	2160682
12	exp animal	22103819
13	human	17796064
14	12 not 13	4307755
15	11 not 14	1950985
16	5 and 15	3716

EBM Reviews - Cochrane Central Register of Controlled Trials

1	exp Adrenal Cortex Hormones/	24875
2	exp STEROIDS/	48557
3	(Adrenal Cortex Hormone* or adrenocortical hormone* or adrenocorticosteroid* or Corticosteroid* or Corticoid* or steroid* or glucocort* or cortisone* or hydrocortisone* or Cortisol or Epicortisol or Cortifair or Cortril or hydroxyhydrocortisone or oxohydrocortisone or tetrahydrocortisol or dexamethason* or baycuten or dexatopic or sofradex or Methylfluorpreordnisolone or Hexadecadrol or Decameth or Decaspray or Dexasone or Dexpak or Maxidex or Millicorten or Oradexon or Decaject or Decaject or Hexadrol or methylprednisolon* or (methyl adj3 prednisolone) or Metipred or Urbason or Medrol or Betamethasone or Flubenisolone or Betadexamethasone or Celestona or Cellestoderm or Celeston or Celestone or prednison* or prednisolon* or hydroxyprednisolone or desonide or Predate or Predonine or Di-Adreson-F or DiAdresonF or triamcinolon*).mp.	72386
4	exp SEPSIS/	3951
5	(Sepsis or septic or Sepses or Py?emia? or Septic?emia? or (blood adj2 poison*) or Bacter?emia? or bacill?emia? or (Lemierre* adj2 (syndrome or disease)) or necrobacillosis or meningococc?emia? or Endotoxemia? or Fung?emia? or Candid?emia? or ((Toxic or Endotox* or bacter*) adj2 Shock) or toxic forward failure or Parasitemia? or Viremia? or urosepsis).mp.	16565
6	(1 or 2 or 3) and (4 or 5)	1678

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eTable 3: Inclusion criteria and exclusion criteria of including trials

Trial	Inclusion criteria	Exclusion criteria
Klastersky 1971	Disseminated cancer Life threatening infection	Not mentioned
Schumer 1976	1. septic history; 2. falling blood pressure 3. positive aerobic or anaerobic blood cultures.	culture was negative
Sprung 1984	1. Systolic BP < 90 mmHg or decrease ≥ 50 mmHg 2. Decreased organ perfusion as evidenced as: altered mental status or oliguria < 20 ml/hour urine production 3. Persistent hypotension despite infusion ≥ 500 ml normal saline. 4. Bacteremia or an identified source of infection	Improvement of blood pressure after 500 ml IS Hypotension secondary to: hemorrhage, AMI, cardiopulmonary arrest, acute pulmonary aspiration
Bone 1987	Clinical evidence of infection, Fever or hypothermia Tachycardia (>90 beats/min) Tachypnea (>20 breaths/min) Inadequate organ perfusion or organ dysfunction	Age >75 Prior CST or steroid allergy Uncontrolled diabetes Vaccination <28 days Burns Pregnancy Peptic ulcer < 6 months TBC or fungal infection Participation in another trial Administration of N
VASSCSG 1987	Clinical suspicion of sepsis and 4 of the following 7 signs within 8-hour period: Shaking chills or fever Tachypneu or hypocapnia Tachycardia Hypotension Abnormal white-cell count Thrombocytopenia Surgical or invasive procedure performed (<48 hours)	CST <2 weeks Cushing disease LE <2 weeks Allergy for CS Body weight >132kg N treatment <4 hours
Luce 1988	For already hospitalized patients: T rise ≥ 1.5° C Decrease in systolic BP ≥ 20 mm Hg For newly admitted patients T > 38.5°C or < 35.5°C Systolic BP < 90 mm Hg	Pregnancy Active peptic ulcer disease < 6 months Allergy to CS Burns HIV Active or prior fungal or TBC infection CST < 24 hours ago Diffuse pulmonary infiltrates
Bollaert 1998	Septic shock MV Vasopressor therapy for > 48 hours	TI LE < 1 week Considered to withhold therapy Gastroduodenal ulcer or GB Prior CST Post corticotropine [cortisol] <18 ugram/kg
Briegel 1999	Septic shock Vasopressor support	Age >75 Pregnancy

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	Cardiac output > 4.0 l/min/m2	TI Treatment with vasopressors for >72 hrs Prior CST Organ transplant recipients Burns Hemorrhagic shock AMI < 6 months
Chawla 1999	Septic shock, exact definition not specified Vasopressor support in order to reach a MAP ≥ 60 mmHg for > 72 hour	Not mentioned
Annane 2002	Documented site or at least strong suspicion of infection T > 38.3°C or < 35.6°C HR < 90 beats per minute Systolic BP < 90 mm Hg Urinary output of less than 0.5 mL/kg of body weight for at least 1 hour or PaO_2/FIO_2 < 280 mm Hg Arterial lactate > 2 mmol/L Need for MV Duration of shock < 3 hours	Pregnancy Acute myocardial infarction Pulmonary embolism AIDS Contraindication for CST
Yildiz 2002	Sepsis, severe sepsis or septic shock Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Chest.1992;101(6):1644-1655.	Pre-existing adrenal disease or adrenalectomy Known malignancies TBC with possible involvement of the adrenal gland CST < 3 months Burns Hemorrhagic shock AMI
Keh 2003	Sepsis Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Chest.1992;101(6):1644-1655.	An age of less than 18 years, glucocorticoid medication within the last 3 months, immunosuppressive therapy, hematologic diseases, pregnancy, a moribund state
Confaloni eri 2005	Minor criteria included (1) respiratory rate greater than 30 breaths per minute at admission; (2) ratios of PaO2 of inspired oxygen (FiO2 to fraction) (PaO2 :FiO2) less than 250; (3) chest radiograph showing bilateral involvement or multilobe involvement; (4) systolic blood pressure less than 90 mm Hg; (5) diastolic blood pressure less than 60 mm Hg. Major criteria included (1) requirement of mechanical ventilation; (2) increase in the size of opacities on chest radiograph of 50% or more at 48 hours; (3) requirement of vasopressors for more than 4 hours; (4) serum creatinine 2 or more mg/dl.	(1) nosocomial pneumonia; (2) severe immunosuppression; (3) acute burn injury; (4)a preexisting medical condition with a life expectancy less than 3 month; (5) pregnancy; (6) a major gastrointestinal bleed within 3 months of the current hospitalization; (7) a condition requiring more than 0.5 mg/kg/day of prednisone equivalent (i.e., acute asthma or chronic obstructive pulmonary disease [COPD])
Oppert 2005	Two or more of the following: hr > 90 bpm, T ≥38.5°C or < 36°C, leukocytosis of ≥12 /nL or >10% immature cells, rr > 20 per minute, mv evidence or strong clinical suspicion of infection.	Pregnancy HIV positive organ transplant receipients CS contra-indicated

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	arterial systolic BP <90 mm Hg for ≥1 hr despite adequate fluid resuscitation CI ≥ 3.5 L/min/m2; need for vasopressor support duration of septic shock < 24 hrs.	CST
Tandan 2005	Septic shock and adrenal insufficiency	Not mentioned
Rinaldi 2006	Severe sepsis according to definition of 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference	Prior illness associated with chronic microalbuminuria Prior or preexisting renal failure CST < 3 months IST Chronic hematologic diseases Pregnancy Septic shock Therapy with endothelial active drugs
Cicarelli 2007	Septic shock exact definition not specified	IST Prior CST active pancreatitis TI LE < 3 months Recent GB
Meduri 2007	Adult intubated patients receiving mechanical ventilation 72 h of study entry diagnostic criteria for ARDS by the American-European Consensus definition (61 patients had sepsis, and the author provided separate data for these participants)	Not mentioned
Aboab 2008	Intensive care unit patients who met the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference criteria for septic shock	Age<18 years nonsinus rhythm, pregnancy, acute myocardial infarction, pulmonary embolism, previous treatment with corticosteroids, known autoimmune disease or immune suppression, chronic cardiovascular, pulmonary or neurologic diseases diabetes mellitus, and any other condition that may be associated with autonomic failure
Sprung 2008	Clinical evidence of infection < 72 hours Systemic response to infection defined by ≥2 of the following < 24 hours: T >38.3°C or < 35.6°C); HR >90 beats/min; RR > 20 breaths/min or PaCO2<32 mmHg or need for invasive mv; white cell count >12 cells/mm3 or <4 cells/mm3 or >10% immature neutrophils. Evidence of shock within the previous 72 hours defined by (both a + b required): Systolic BP < 90 mmHg or decrease in systolic bp > 50 mmHg for ≥1 hour despite adequate fluid replacement OR need for vasopressors ≥1 hour Hypoperfusion or organ dysfunction attributable to sepsis	TI LE < 24 hours IST Long-term CST < 6 months Short-term CST < 4 weeks.

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Hu 2009	Severe sepsis according to definition of 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference	Not mentioned
Arabi 2010	Cirrhosis Septic shock Hypotension duration < 72 hours	Not mentioned
Snijders 2010	Adults with severe community-acquired pneumonia	Not mentioned
Meijvis 2011	1. 18 years or older 2. confirmed community acquired pneumonia	a known congenital or acquired immunodeficiency receipt of chemotherapy any dose of oral corticosteroids, or immunosuppressive medication in the previous 6 weeks haematological malignant disease.
Sabry 2011	Unclear	Not mentioned
Yildiz 2011	Sepsis or septic shock Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Chest.1992;101(6):1644-1655.	Pre-existing adrenal disease or adrenalectomy Known malignancies TBC with possible involvement of the adrenal gland CST < 3 months Burns Hemorrhagic shock AMI
Liu 2012	Adults with ARDS and sepsis, including septic shock	Not mentioned
Rezk 2013	Unclear	Not mentioned
Gordon 2014	adult patients (≥ 16 yr) who had sepsis (2/4 systemic inflammatory response criteria due to known or suspected infection) and who required vasopressors despite adequate IV fluid resuscitation.	Prior IV vasopressor Adrenal insufficiency CST < 3 months ESRD MI, RP, SS AMI LE < 24 hours Pregnancy Enrolment in another trial that might interact with the study drugs, or hypersensitivity to any of the study drugs
Huang 2014	Severe sepsis according to definition of 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference	Not mentioned
Torres 2015	(1) were aged 18 years or older, (2) had clinical symptoms suggesting community-acquired pneumonia (cough, fever, pleuritic chest pain, or dyspnea), (3) had a new chest radiographic infiltrate, (4) met severe community-acquired pneumonia (5) had a C-reactive protein (CRP) level of greater than 150 mg/L at admission	(1) prior treatment with systemic corticosteroids, (2) nosocomial pneumonia, (3) reported severe immunosuppression (4) preexisting medical condition with a life expectancy of less than 3 months, (5) uncontrolled diabetes mellitus, (6) major gastrointestinal bleeding within 3 months, or (7) a condition requiring acute treatment with greater than 1 mg/kg/d of methylprednisolone or its equivalent. (8) pandemic H1N1 influenza A pneumonia
Gordon 2016	Adult patients (≥16 years) who had sepsis (2 of 4 systemic	patients who had received a previous continuous infusion of vasopressors during this ICU

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	inflammatory response criteria due to known or suspected infection and who required vasopressors despite adequate intravenous fluid resuscitation	admission, an ongoing requirement for systemic steroid treatment (ie, known adrenal insufficiency or regular systemic steroid therapy within the last 3months), end-stage kidney failure, known mesenteric ischemia, Raynaud phenomenon, systemic sclerosis or other vasospastic disease, a medical team that was not committed to full active treatment, known pregnancy, enrollment in another interventional trial that might interact with the study drugs, or hypersensitivity to any of the study drugs
Keh 2016	Sepsis Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Chest.1992;101(6):1644-1655.	1. septic shock 2. younger than18years, 3. having known hypersensitivity to hydrocortisone or mannitol (placebo), 4. having a history of glucocorticoid medication
Tongyoo 2016	severe sepsis or septic receiving mechanical ventilation for ARDS aged 18 years or older	1. moribund state 2. advanced malignancy with life expectancy <6 months, pregnancy, immunosuppressive therapy, 3. underlying disease requiring long-term glucocorticoid treatment within the last 6 months or short-term glucocorticoid treatment within the past 4 weeks, 4. difficult-to-control diabetes.
Lv 2017	age 18 years old or older; onset of septic shock within 6 h	Systemic corticosteroid therapy within the last 3 months before septic shock; high-dose steroid therapy; immunosuppression; refusal of the attending staff or patient family.
Annane 2018	hospitalized in intensive care unit for less than 7 days septic shock for less than 24 hours at least one proven site of infection at least 2 organ dysfunctions as defined by a SOFA score =or> to 3 for at least 6 consecutive hours need for vasopressor (dopamine =or>15µg/kg/min or epinephrine/norepinephrine at =or>0,25 µg/kg/min for at least 6 consecutive hours, to maintain systolic arterial pressure at 90 mmHg or more OR mean arterial pressure at 6(mmHg or more informed consent	pregnancy or breath feeding, decision not to resuscitate; underlying disease with an estimated life expectancy of less than 1 month; formal indication for corticosteroids, recent surgery (ie within the past 72 hours) or a surgery at high risk of bleeding; gastro-intestinal bleeding within the past 6 weeks; chronic liver disease (Child C); recent trauma (ie within the past 72 hours) intracranial process; history of stroke, CNS bleeding or traumatic brain injury within the past 3 months; platelet counts of less than 30000 per cubic millimetre; formal indication for curative anticoagulant; prophylactic use of heparin is allowed; any condition of high risk of bleeding as per patient's primary physicians; hypersensitivity of activated drotrecogin alpha or any other component of the drug; no affiliation to a social security
Venkatesh 2018	adults (≥18 years of age) undergoing mechanical ventilation, fulfilled two or more criteria of the systemic inflammatory response syndrome,	1. received treatment with systemic glucocorticoids for an indication other than septic shock, 2. received etomidate during the current hospital admission,

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	patients had been treated with vasopressors or inotropic agents for a minimum of 4 hours up to and at the time of randomization.	3. considered to be likely to die from a preexisting disease within 90 days after randomization or had treatment limitations in place 4. met all the inclusion criteria for more than 24 hours.

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eTable 4: Support for judgement for included trials rated as high risk of bias.

Study	Bias	Support for judgement
Aboab 2010	Other bias	Expected sample size was 150 participants. Due to slow recruitment, trial terminated prematurely after enrolment of 75 participants.
Bollaert 1998	Other bias	Trial terminated prematurely
Briegel 1999	Selective reporting	7-day, 28-day and hospital mortality ere present in protocol but not reported in the article.
Gordon 2014	Blinding of participants and personnel	open-label
	Blinding of outcome assessment	open-label
Hu 2009	Selective reporting	No trial registration
Klastersky 1971	Other bias	Baseline imbalance
Luce 1988	Incomplete outcome data	Only 75/87 participants were included to assess outcomes.
Lv 2017	Selective reporting	90-day mortality were present in protocol but not reported in the article.
	Other bias	Baseline imbalance
Medrui 2007	Selective reporting	Shock at day 7, ventilator free days, ICU free days were present in protocol but not reported in the article.
Oppert 2005	Selective reporting	No trial registration
Rinaldi 2006	Blinding of participants and personnel	open-label
	Blinding of outcome assessment	open-label
	Incomplete outcome data	40 of 52 participants were included to assess outcomes.
Schumer 1976	Random sequence generation	Using card system
	Allocation concealment	Unsealed envelopes
Sprung 1984	Allocation concealment	Not clear how randomization list was kept confidential
	Other bias	Baseline imbalance
Sprung 2008	Incomplete outcome data	All except 1 participants were included to assess primary outcome, but only 466/500 participants were included to assess adverse events.
	Other bias	Expected sample size was 800 participants. Due to slow recruitment, trial terminated prematurely after enrolment of 500 participants;

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eTable 5: Sensitivity analyses

Sensitivity analyses	RR, 95% CI	I^2	P
Excluding studies only reported as abstracts	0.89 [0.81, 0.98]	30%	0.02
Excluding studies published earlier than 2000	0.92 [0.86, 0.98]	0%	0.01
Excluding studies reported ICU or hospital mortality	0.89 [0.80, 0.99]	35%	0.03
Excluding studies with non-low risk of bias	0.90 [0.83, 0.97]	0%	0.005
Excluding trials with <10 events	0.91 [0.83, 0.99]	26%	0.03
Excluding trials with <200 patients	0.90 [0.82, 0.99]	0%	0.04
using fixed-effect models	0.89 [0.83, 0.95]	27%	0.0005
Using adjusted odds/risk/hazard ratios with the generic inverse variance method	0.89 [0.80, 0.98]	30%	0.01

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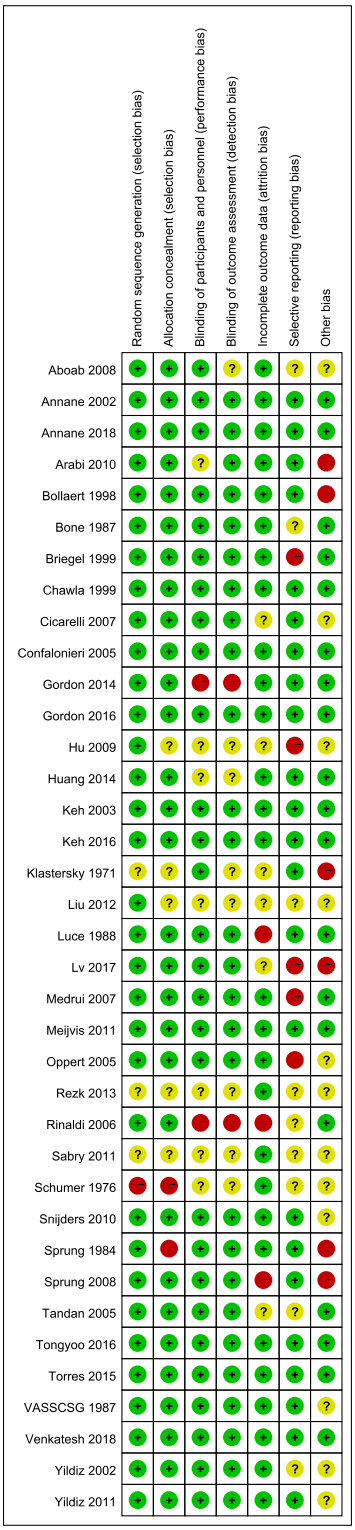
e Figure 1: Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



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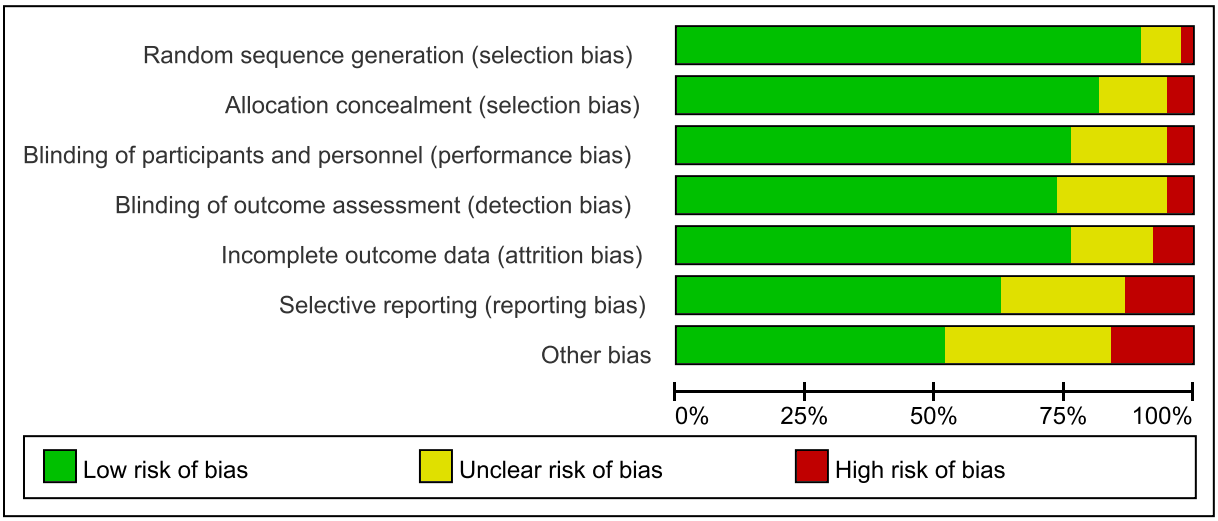
e Figure 2: Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies



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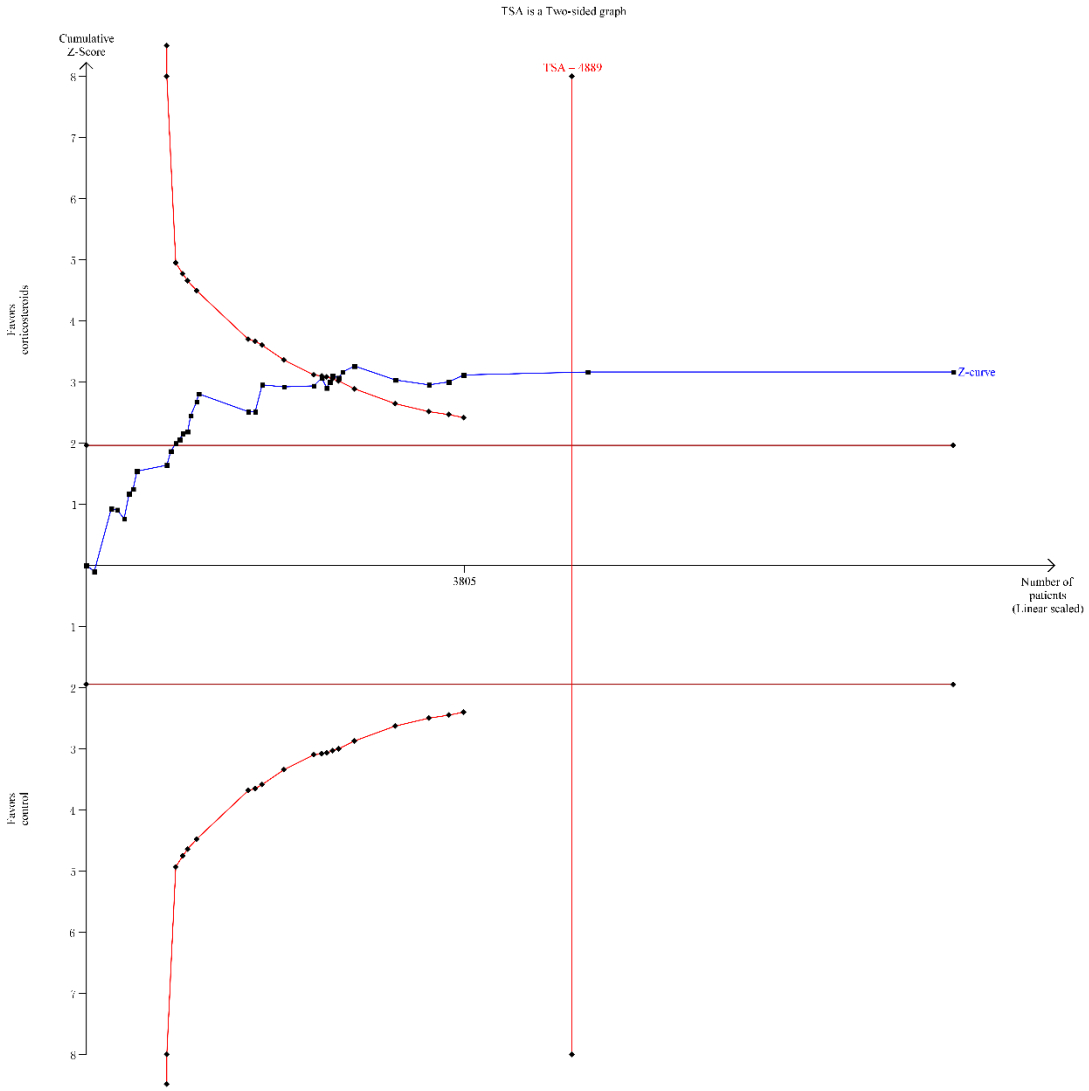
e Figure 3: Trial sequential analysis for 28 days mortality



A DIS of 4899 patients was calculated based on an anticipated RRR of 20% (event proportion of 29% in the control arm, α=0.05 (two-sided), β=0.20 (power 80%)). The blue cumulative z-curve was constructed using a random-effects model and crossed the boundary for futility.

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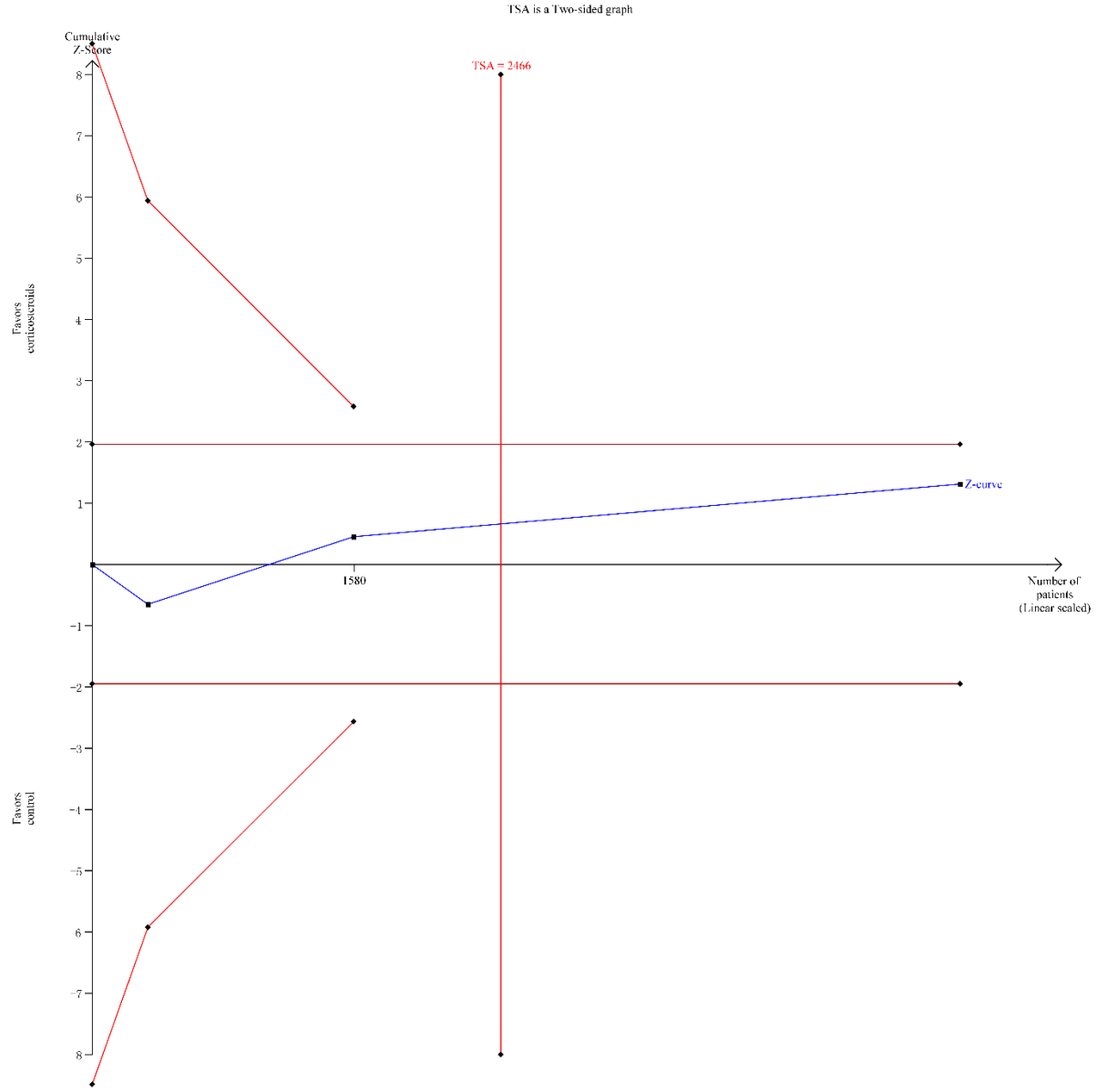
e Figure 4: Trial sequential analysis for 90 days mortality



DIS of 2466 patients was calculated based on an anticipated RRR of 20% (event proportion of 33% in the control arm, α=0.05 (two-sided), β=0.20 (power 80%)). The blue cumulative z-curve was constructed using a random-effects model and crossed the boundary for futility.

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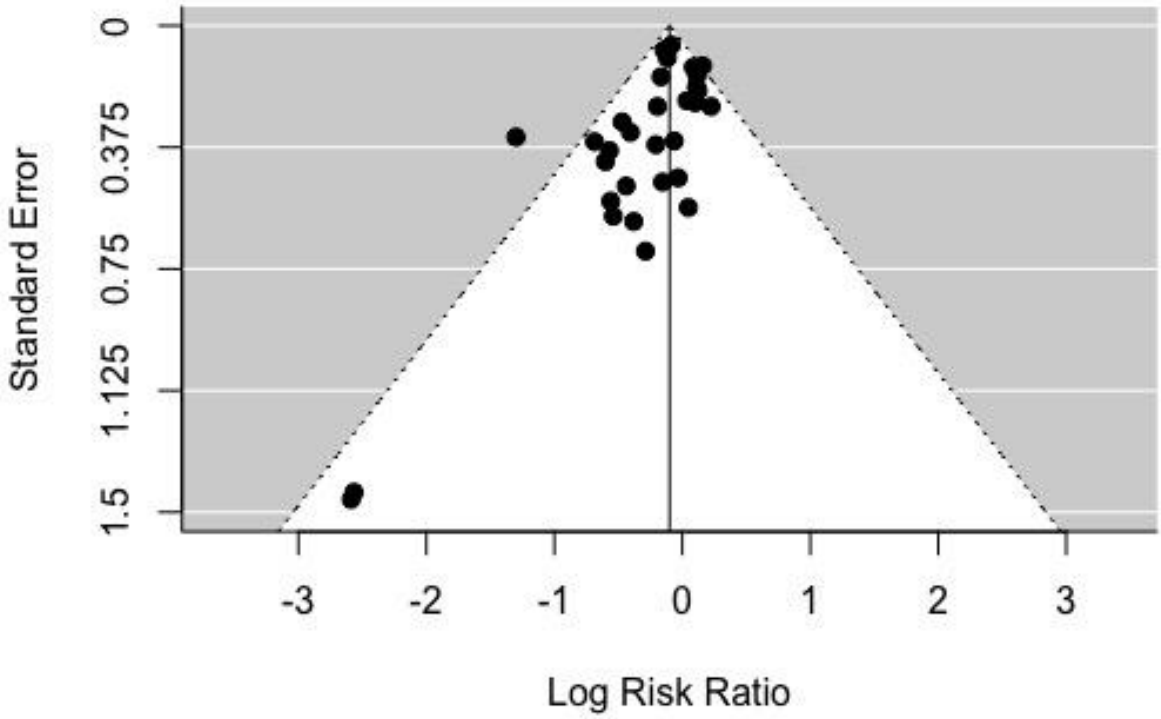
Funnel plot of comparison: 1 Steroids versus control, outcome: 28-Day mortality.



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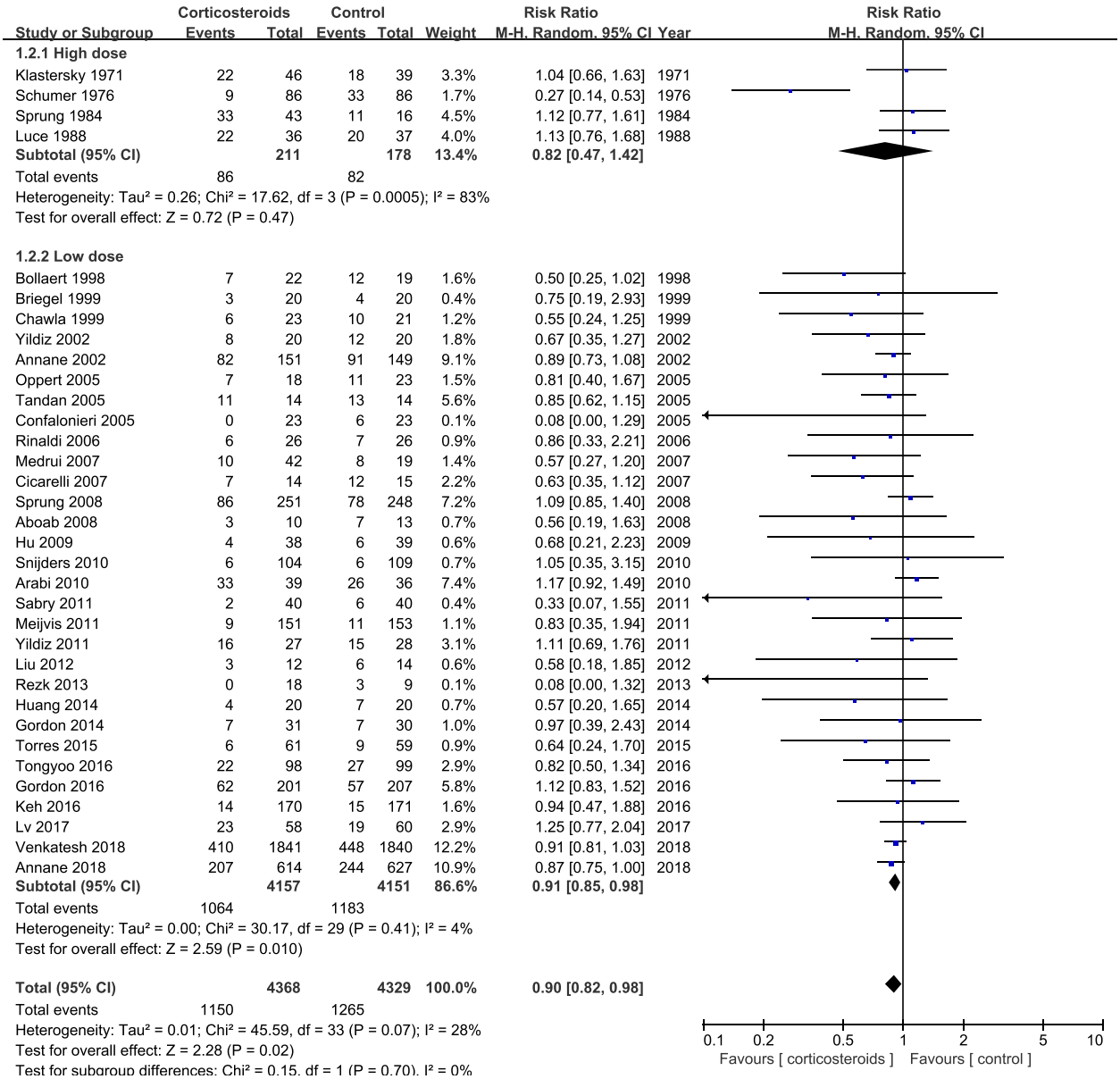
eFigure 6: Subgroup analysis for 28 days mortality –based on dose of corticosteroid. df = degrees of freedom, M-H = Mantel-Haenszel.



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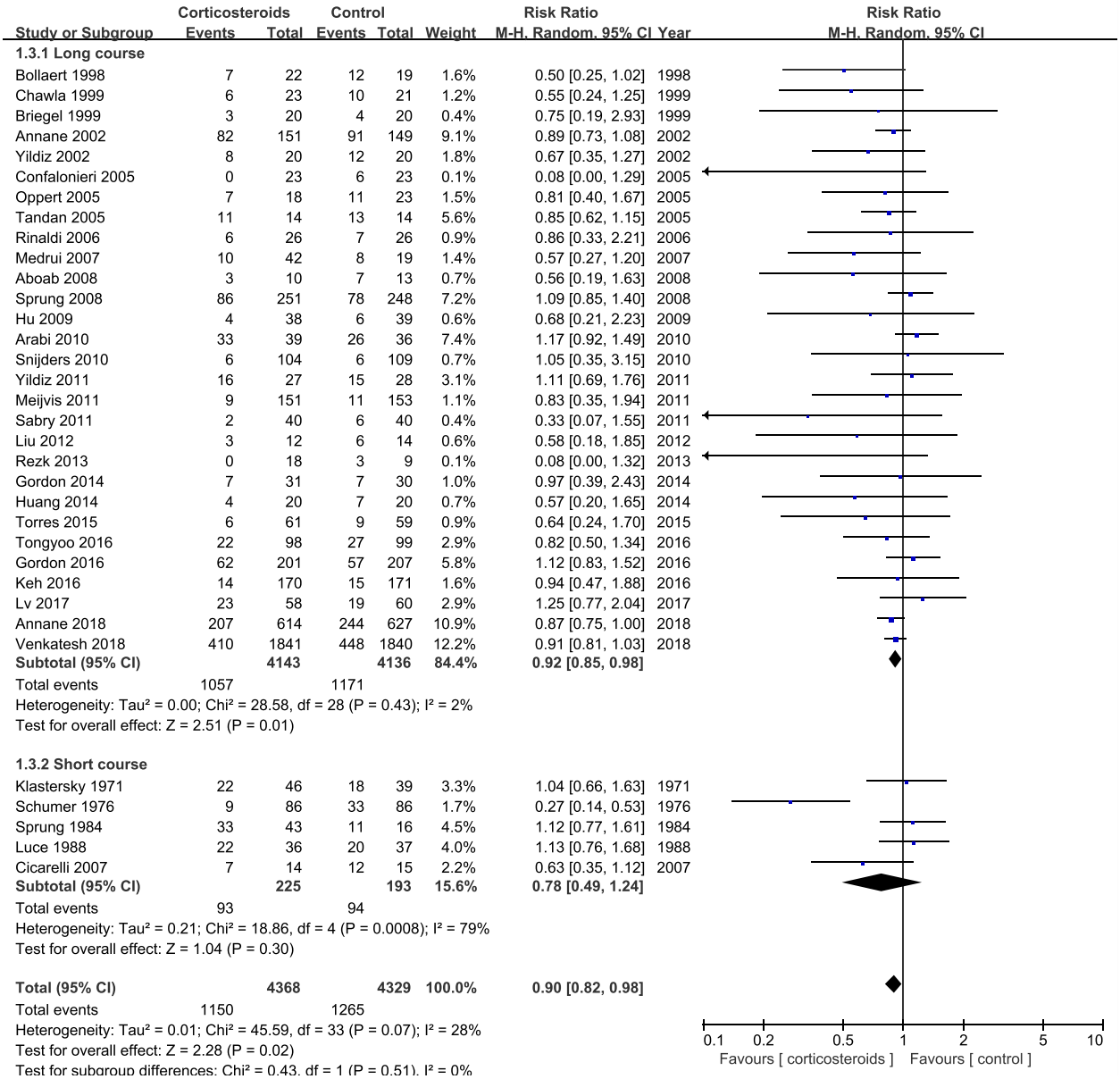
eFigure 7: Subgroup analysis for 28 days mortality –based on treatment duration. df = degrees of freedom, M-H = Mantel-Haenszel.



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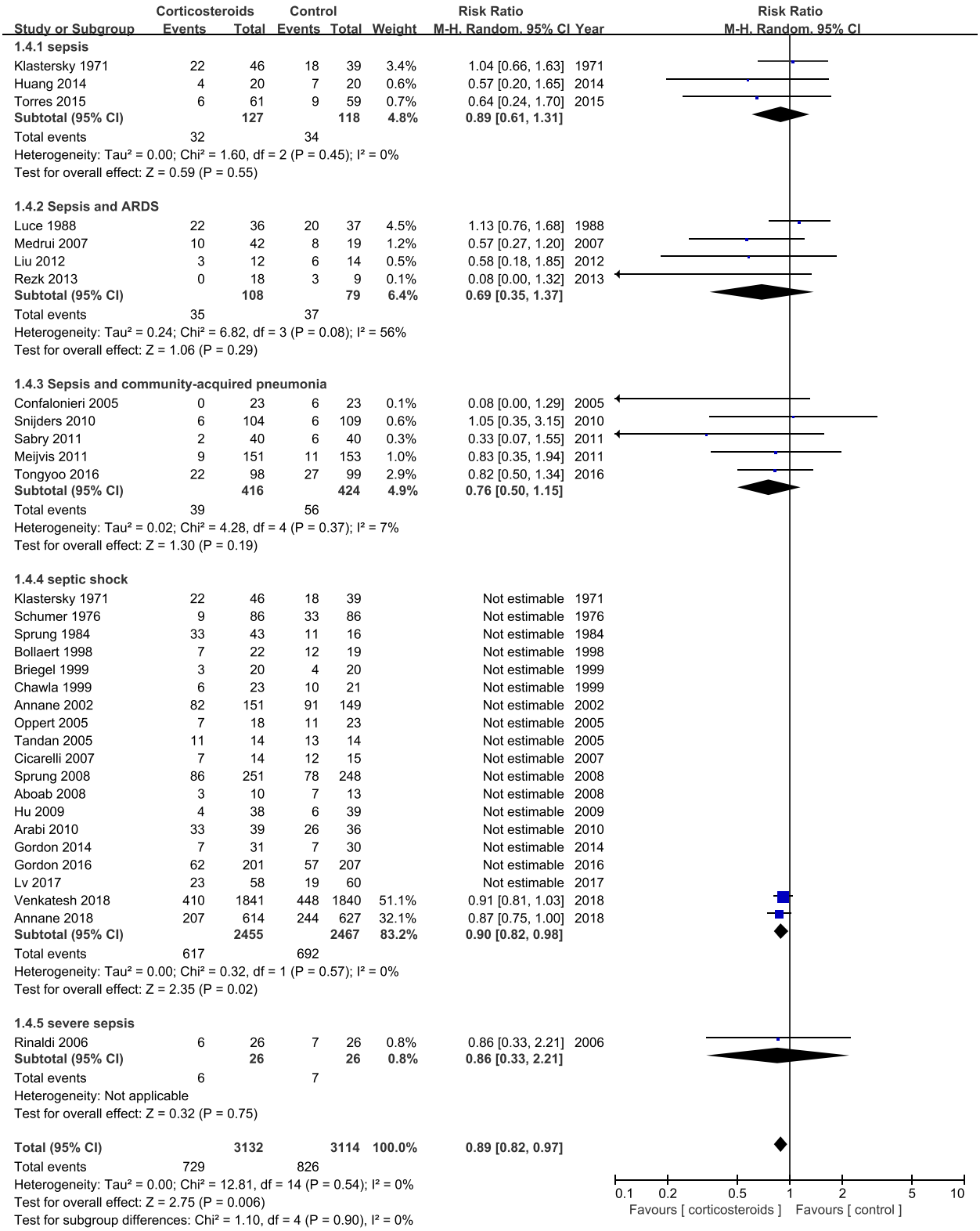
eFigure 8: Subgroup analysis for 28 days mortality –based on sepsis population subtype. df = degrees of freedom, M-H = Mantel-Haenszel.



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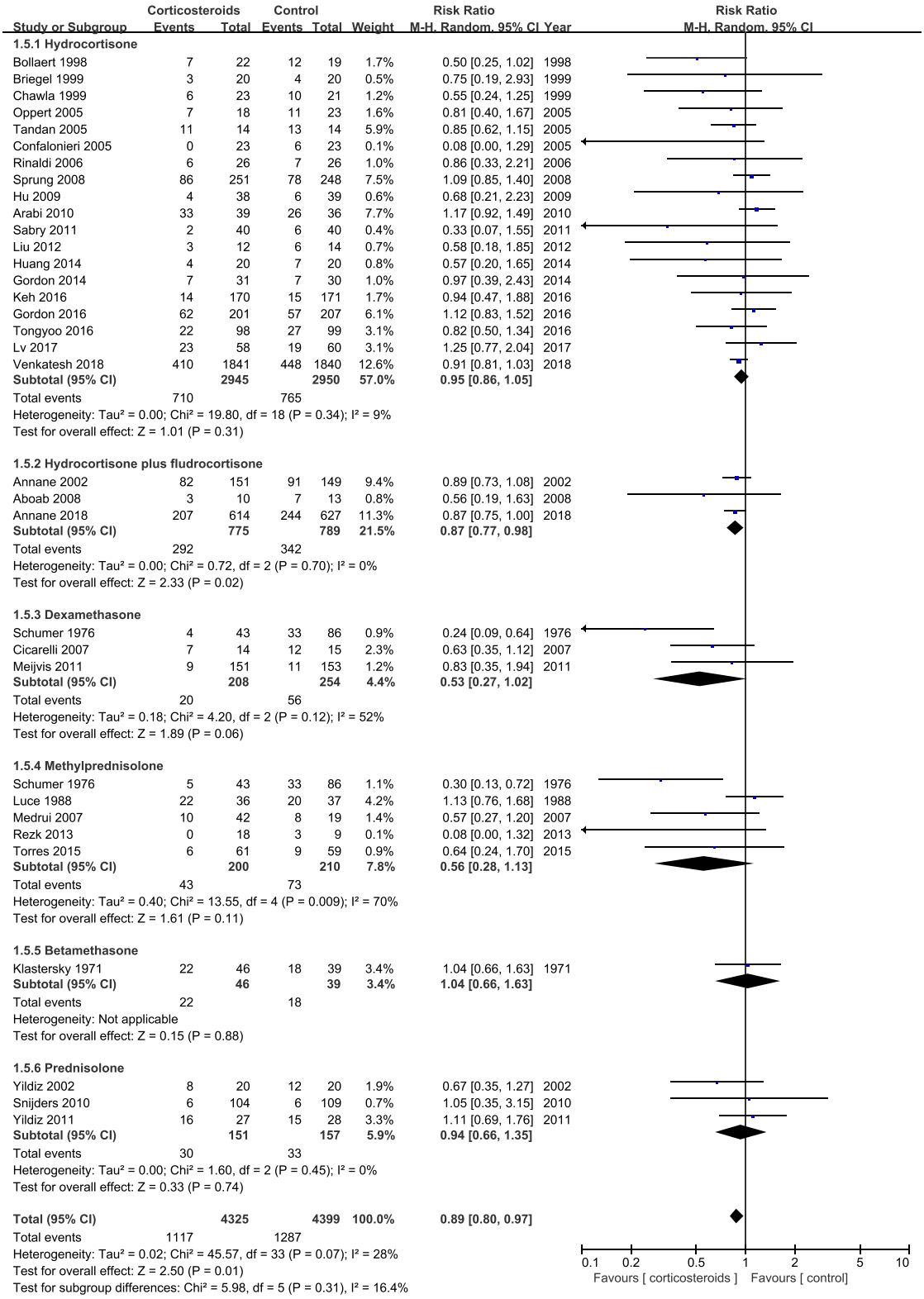
eFigure 9: Subgroup analysis for 28 days mortality –based on type of corticosteroids. df = degrees of freedom, M-H = Mantel-Haenszel.



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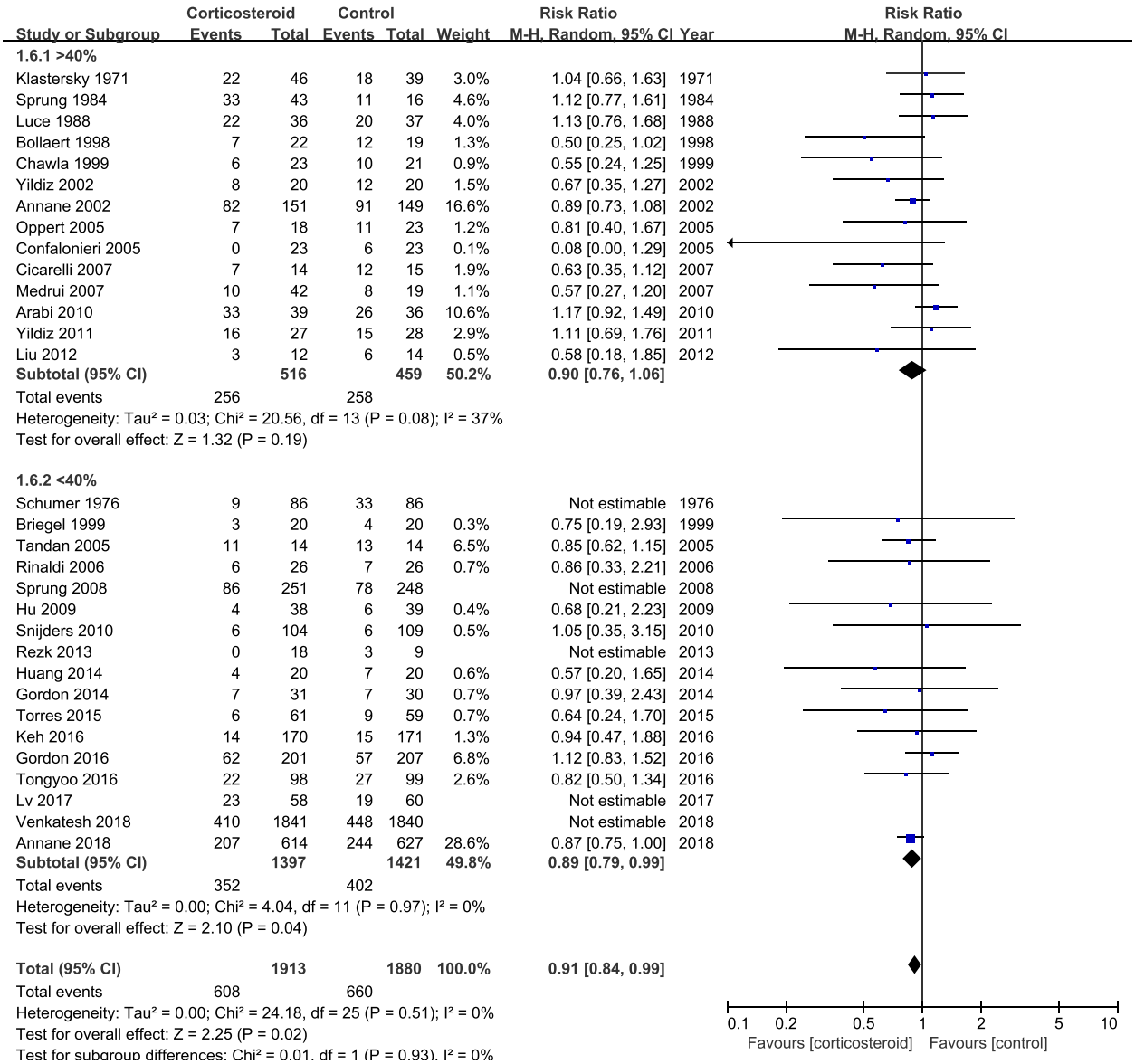
eFigure 10: Subgroup analysis for 28 days mortality –based on control group mortality. df = degrees of freedom, M-H = Mantel-Haenszel.



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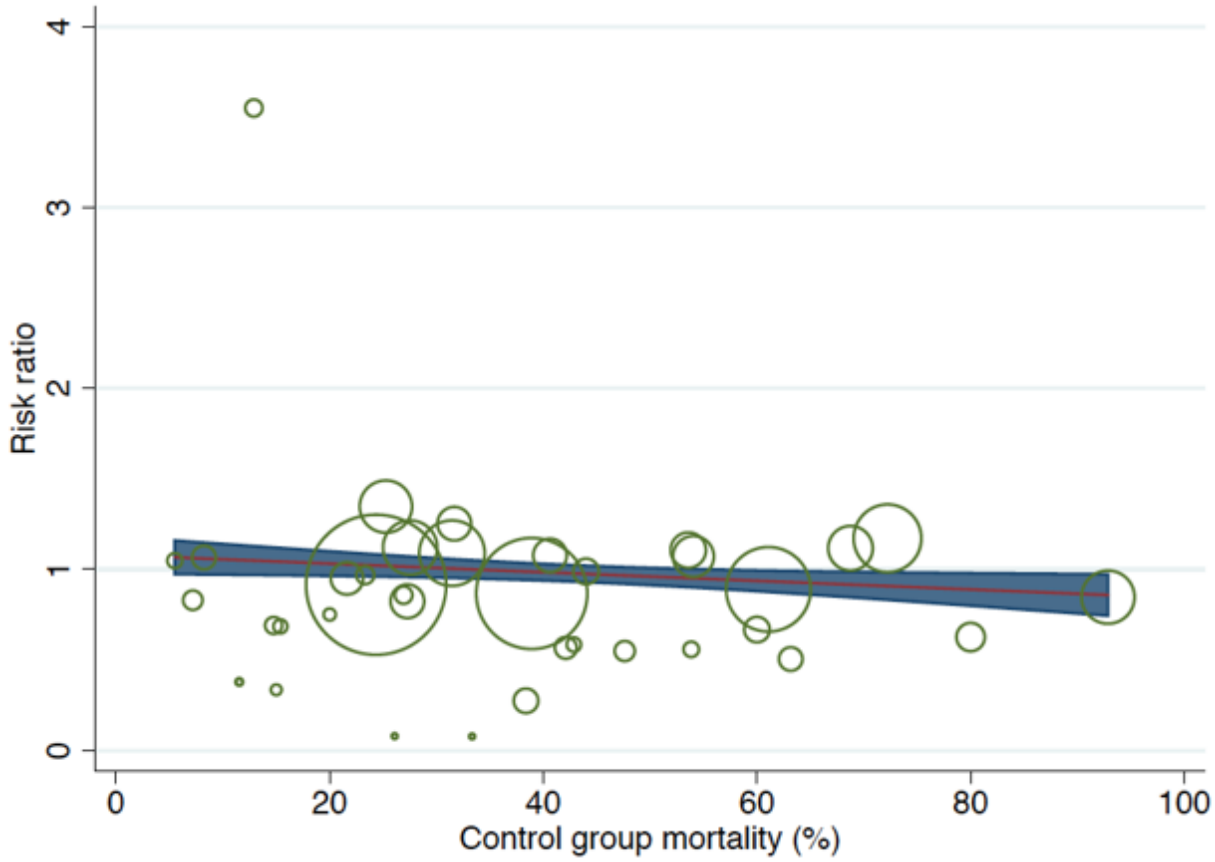
eFigure 11: Meta-regression for 28-day mortality outcome by control group mortality



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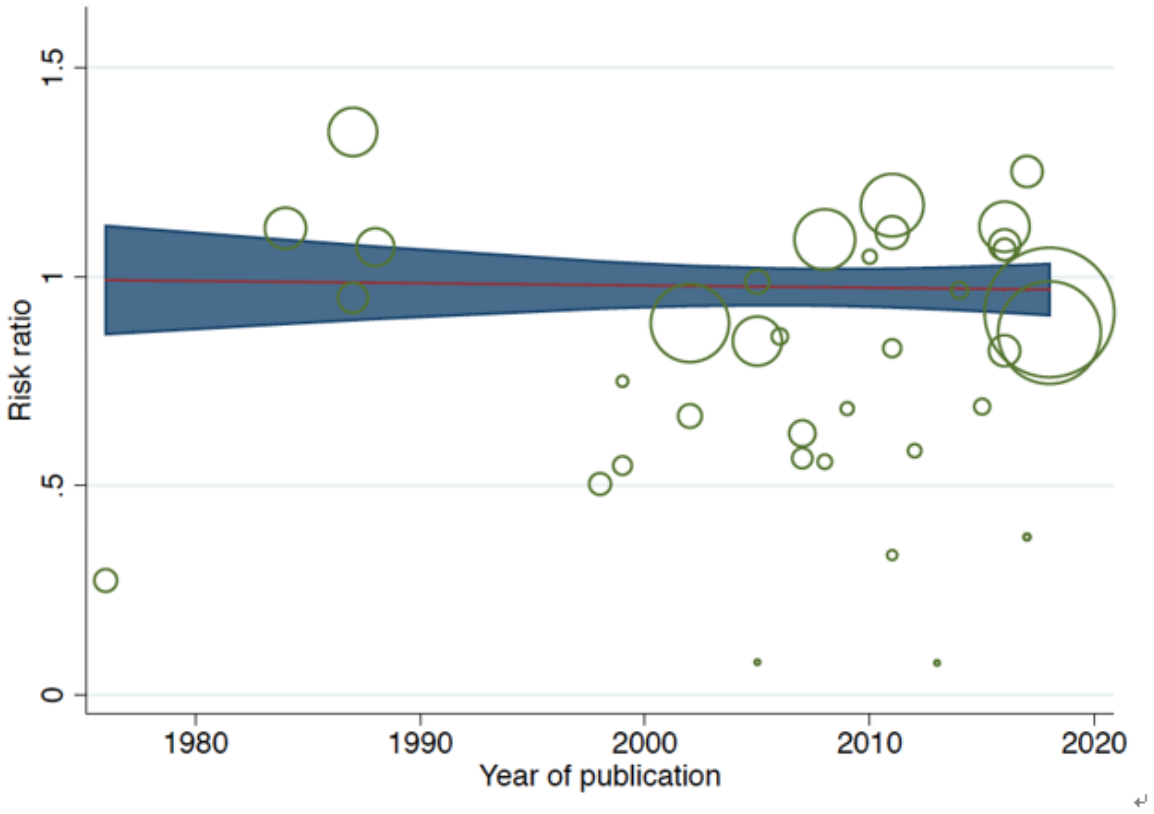
eFigure 12: Meta-regression for 28-day mortality outcome by year of study publication



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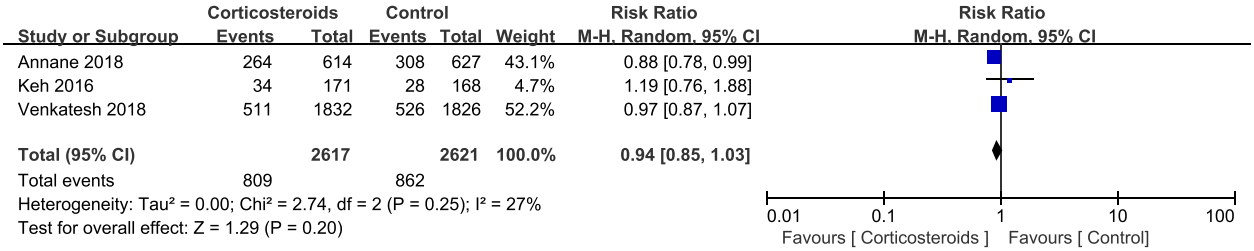
eFigure 13: Forest plot for 90-day mortality. df = degrees of freedom, M-H = Mantel-Haenszel.



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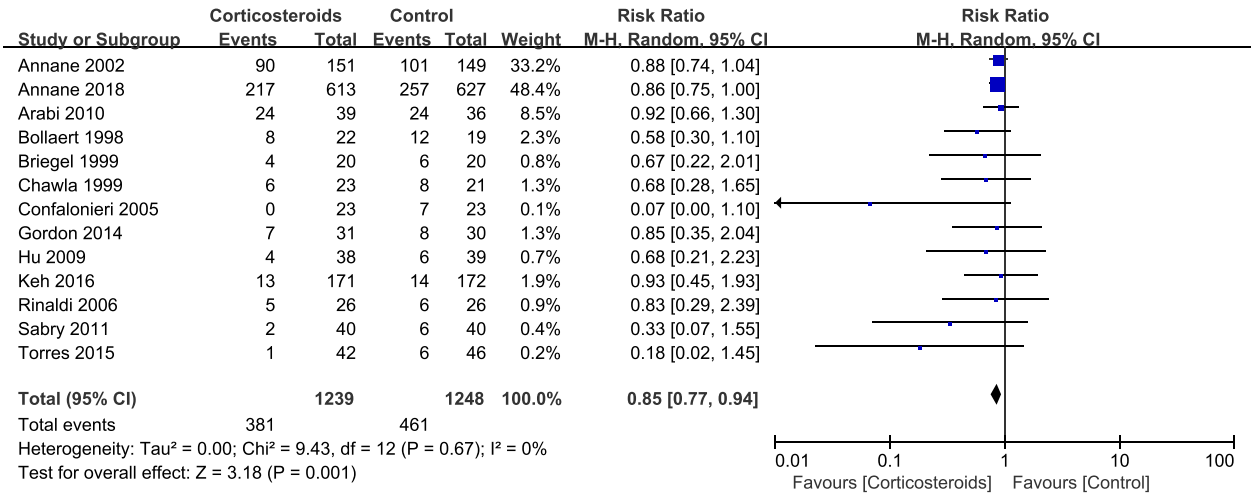
eFigure 14: Forest plot for ICU mortality. df = degrees of freedom, M-H = Mantel-Haenszel.



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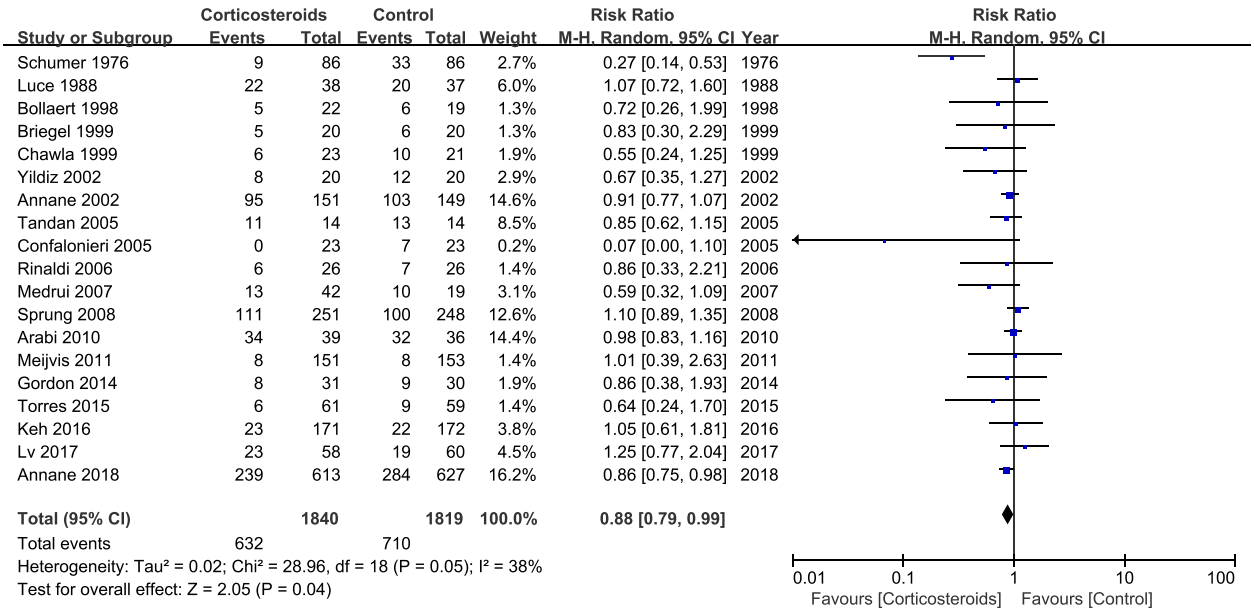
eFigure 15: Forest plot for hospital morality. df = degrees of freedom, M-H = Mantel-Haenszel.



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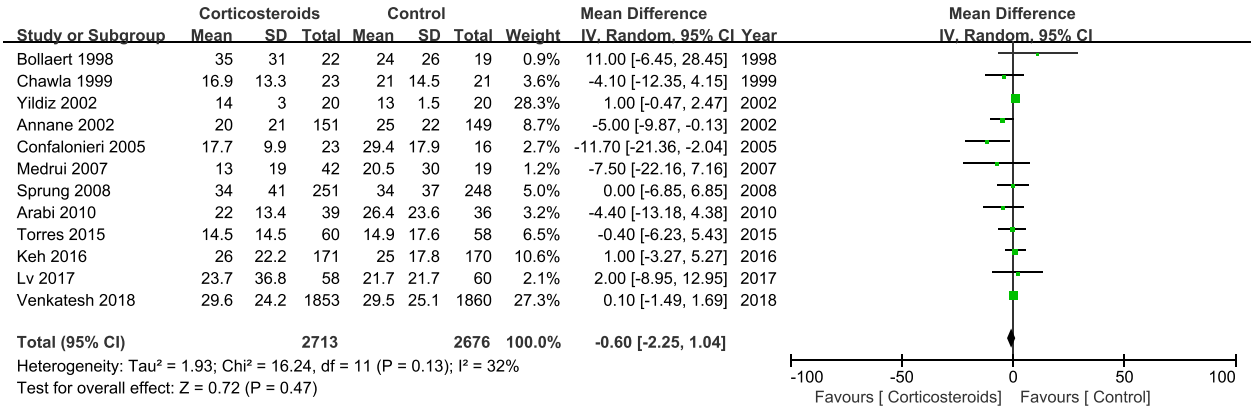
eFigure 16: Forest plot for length of stay in hospital. df = degrees of freedom, M-H = Mantel-Haenszel.



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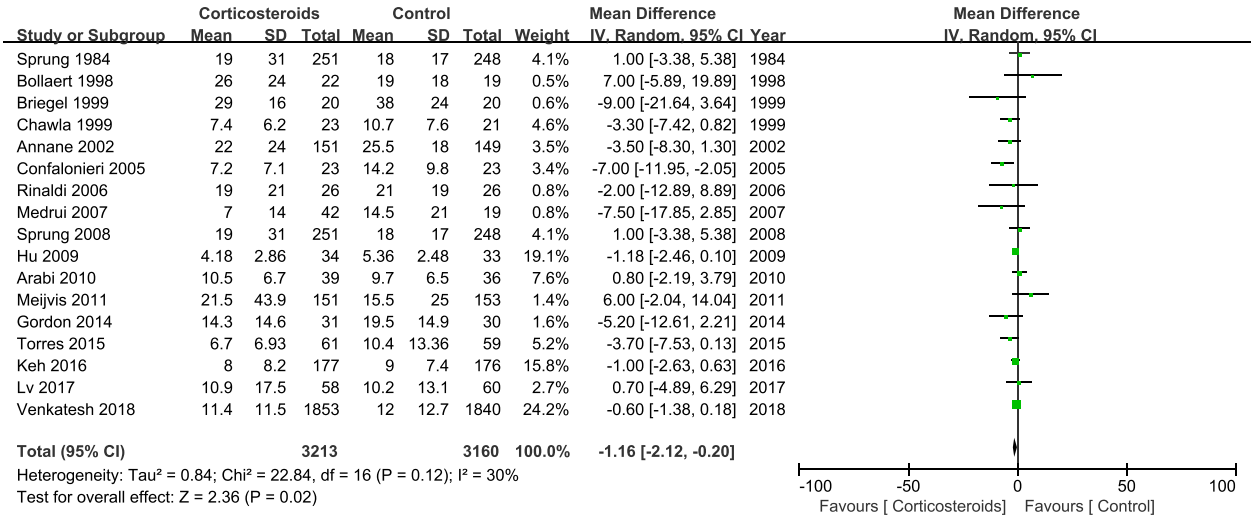
eFigure 17: Forest plot for length of stay in ICU. df = degrees of freedom, M-H = Mantel-Haenszel.



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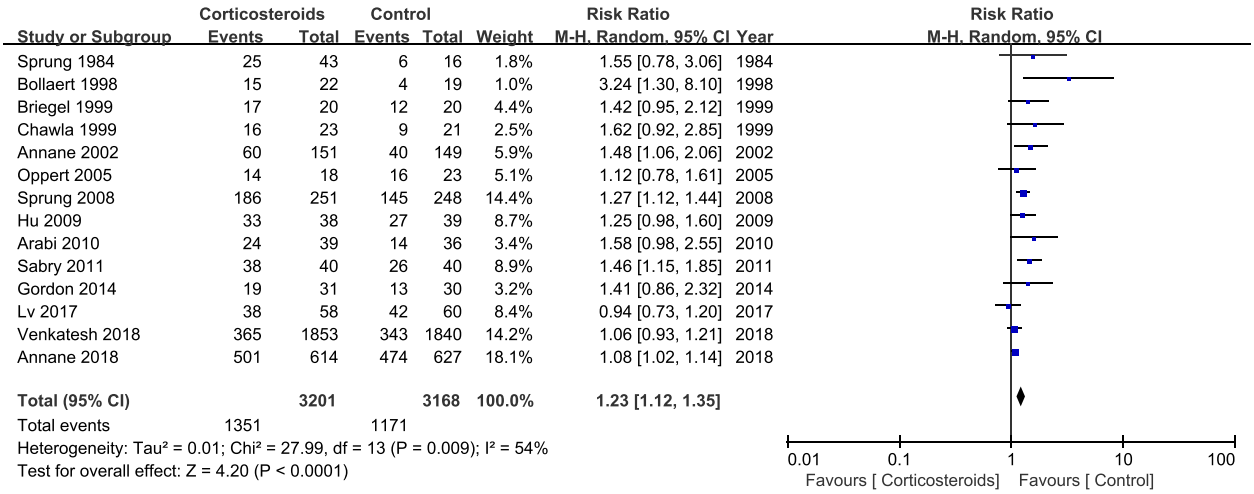
eFigure 18: Forest plot for shock reversal at day 7. df = degrees of freedom, M-H = Mantel-Haenszel.



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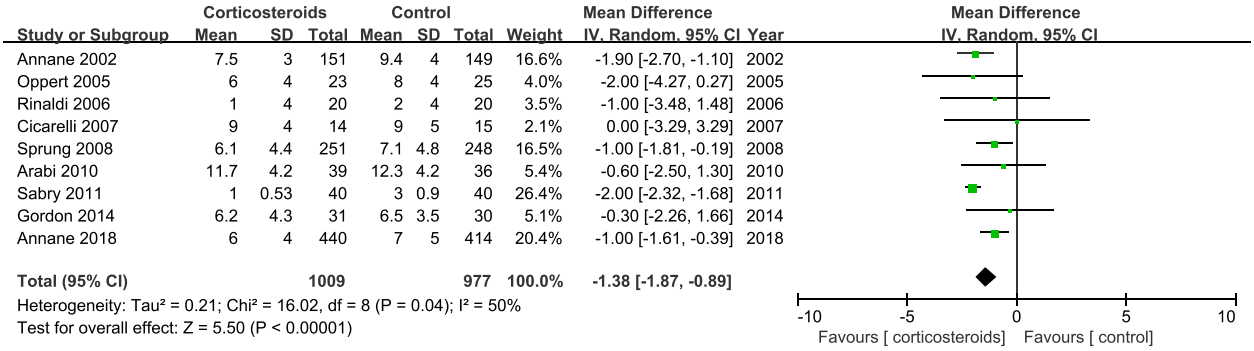
eFigure 19: Forest plot for SOFA score at day 7. df = degrees of freedom, M-H = Mantel-Haenszel.



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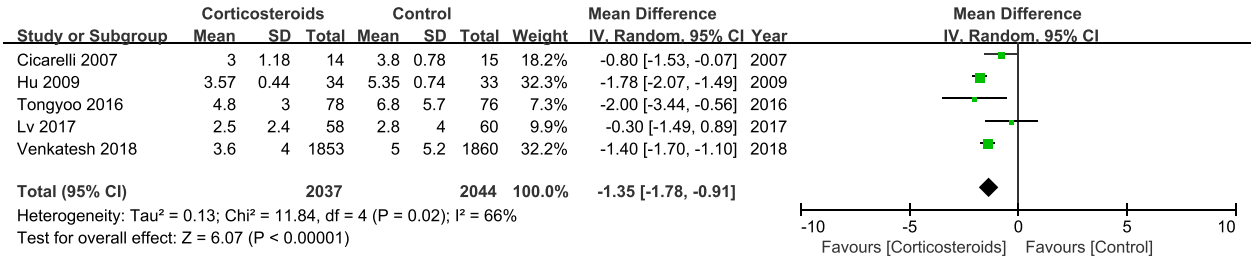
eFigure 20: Forest plot for time to resolution of shock. df = degrees of freedom, M-H = Mantel-Haenszel.



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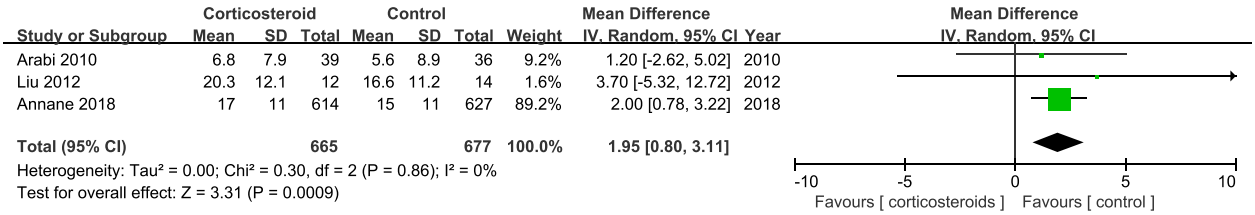
eFigure 21: Forest plot for vasopressor-free day to day 28. df = degrees of freedom, M-H = Mantel-Haenszel.



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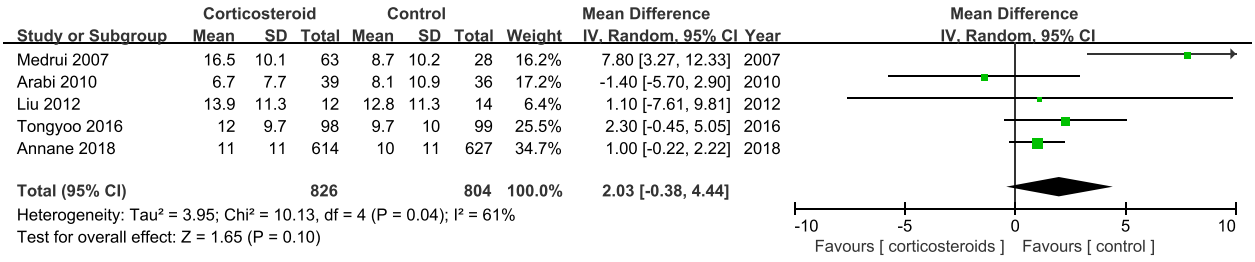
eFigure 22: Forest plot for ventilation-free day to day 28. df = degrees of freedom, M-H = Mantel-Haenszel.



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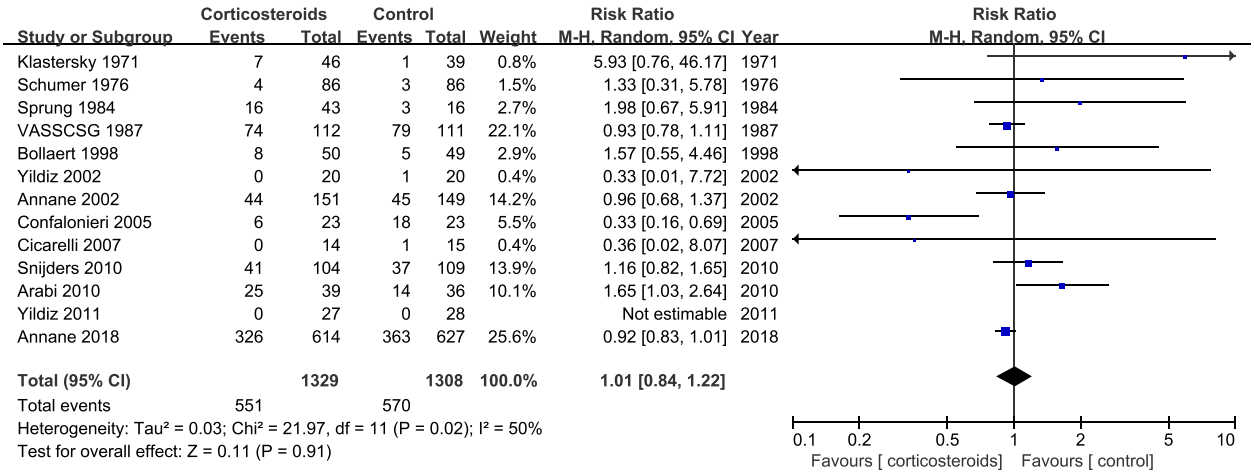
eFigure 23: Forest plot for any severe adverse event. df = degrees of freedom, M-H = Mantel-Haenszel.



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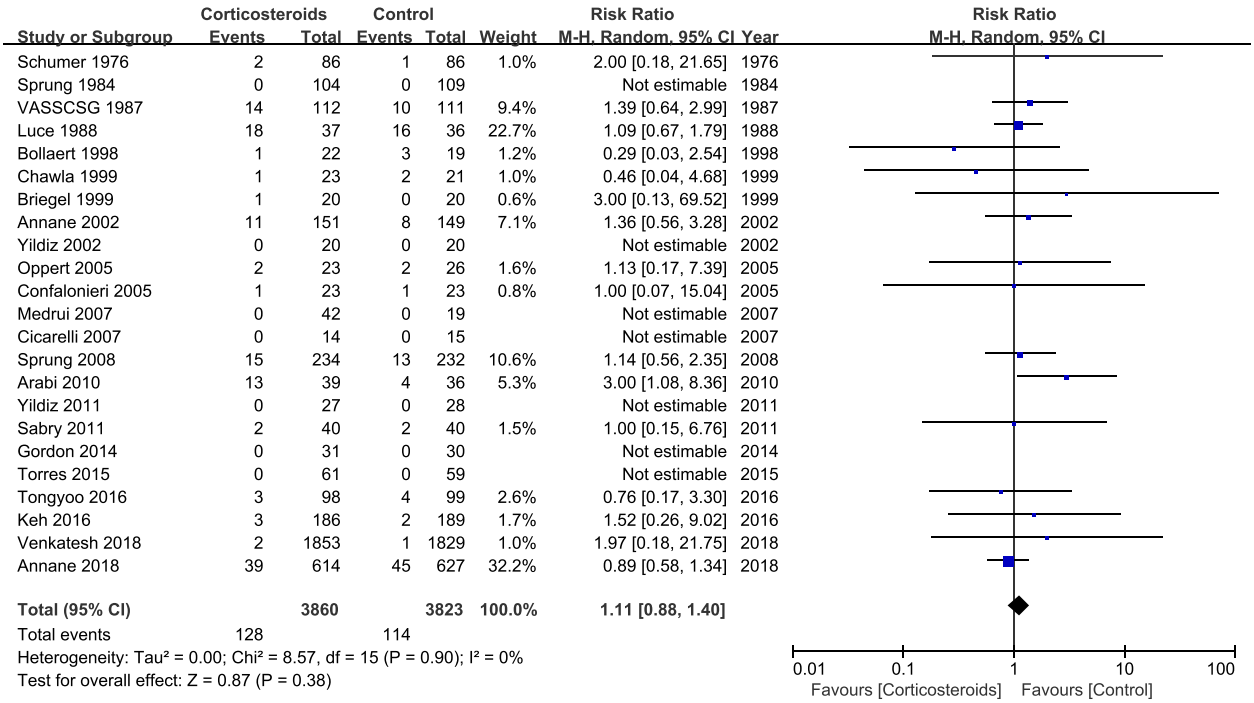
eFigure 24: Forest plot for gastroduodenal bleeding. df = degrees of freedom, M-H = Mantel-Haenszel.



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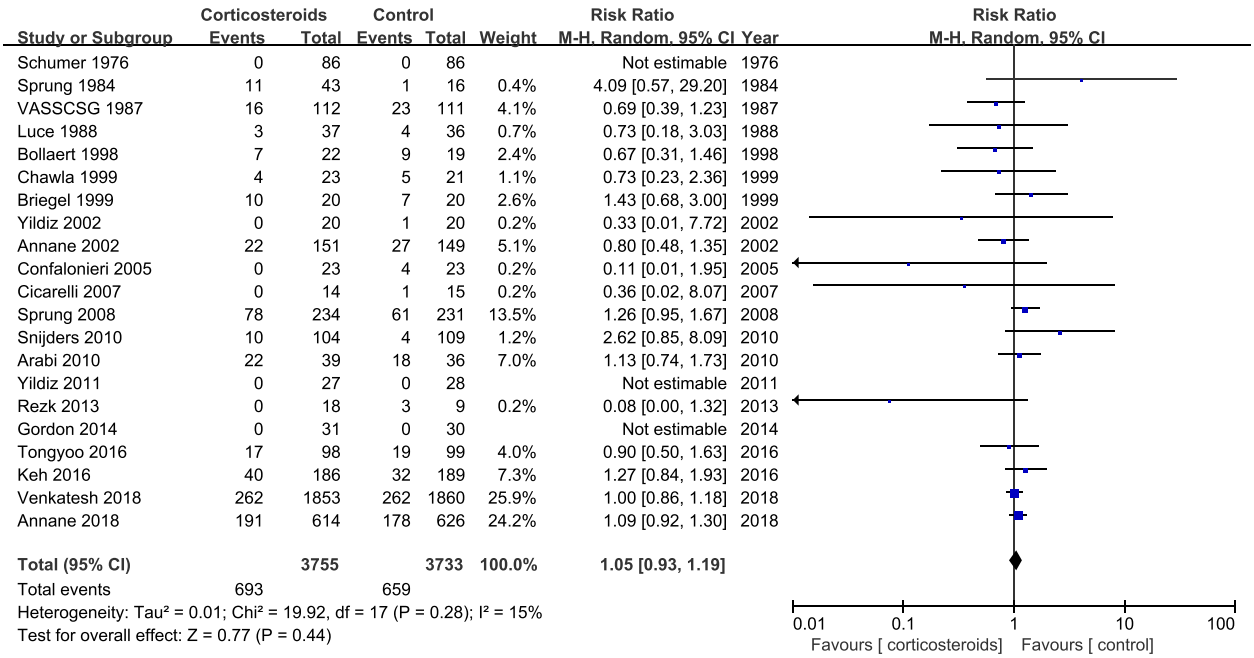
eFigure 25: Forest plot for superinfections. df = degrees of freedom, M-H = Mantel-Haenszel.



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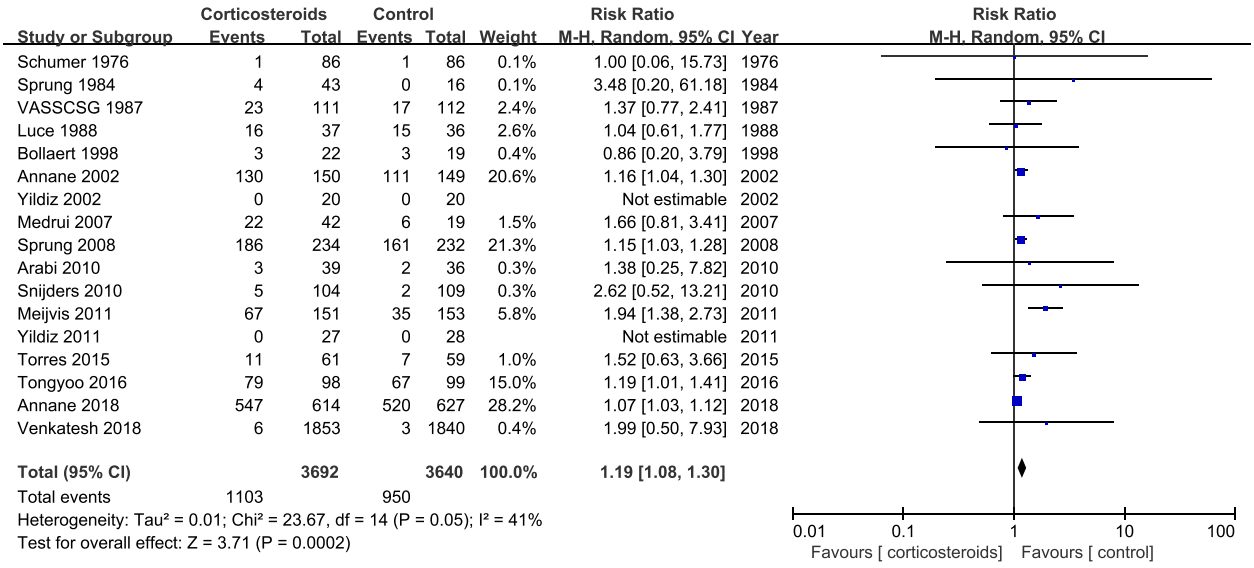
eFigure 26: Forest plot for hyperglycemia. df = degrees of freedom, M-H = Mantel-Haenszel.



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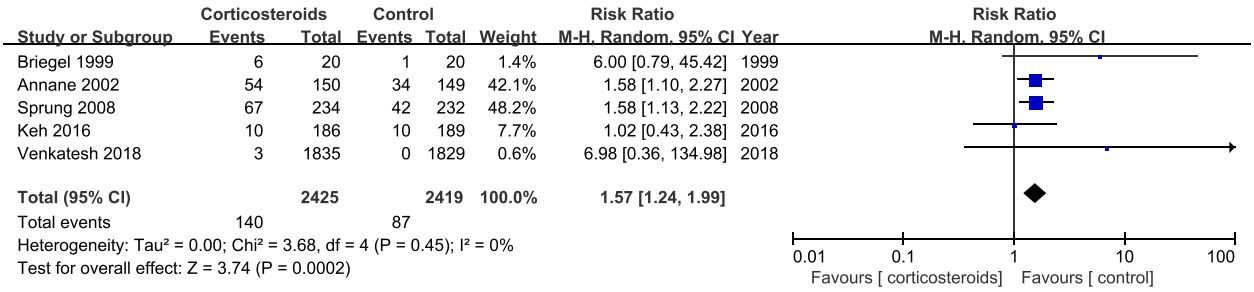
eFigure 27: Forest plot for hypernatremia. df = degrees of freedom, M-H = Mantel-Haenszel.



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