The effects of adding glucocorticosteroids to standard care for children with sepsis. A systematic review of randomized clinical trials with meta-analysis and Trial Sequential Analysis

Steven Kwasi Korang (steven.korang@ctu.dk)
Copenhagen Trial Unit, Centre for Clinical Intervention Research, The Capital Region of Denmark, Rigshospitalet, Copenhagen University Hospital, Copenhagen

Sanam Safi
Copenhagen Trial Unit, Centre for Clinical Intervention Research, The Capital Region of Denmark, Rigshospitalet, Copenhagen University Hospital, Copenhagen

Christian Gluud
Copenhagen Trial Unit, Centre for Clinical Intervention Research, The Capital Region of Denmark, Rigshospitalet, Copenhagen University Hospital, Copenhagen

Janus C Jakobsen
Copenhagen Trial Unit, Centre for Clinical Intervention Research, The Capital Region of Denmark, Rigshospitalet, Copenhagen University Hospital, Copenhagen

Research Article

Keywords: Sepsis, infants, children, glucocorticosteroids, corticosteroids, dexamethasone, septic shock, systematic review, meta-analysis, Trial Sequential Analysis, GRADE.

Posted Date: March 11th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-275296/v1

Abstract

Background: Glucocorticosteroids are widely used to treat severe sepsis in pediatric intensive care units. However, the evidence on the clinical effects is unclear.

Objective: To assess the benefits and harms of glucocorticosteroids for children with sepsis.

Data Sources: We conducted a systematic review of randomized clinical trials with meta-analysis and Trial Sequential Analysis (TSA) (PROSPERO CRD42017054341). We searched CENTRAL, MEDLINE, Embase, LILACS, SCI-Expanded, and more.

Study Selection: Randomized clinical trials assessing the effects of adding glucocorticosteroids to standard care for children with sepsis.

Data Extraction: Two independent reviewers screened studies and extracted data. Evidence was assessed by GRADE according to our published protocol.

Data Synthesis: We included 24 trials randomizing 3073 participants.

Meta-analyses showed no evidence of an effect of adding glucocorticosteroids for children with sepsis with a mixed focus for any of our outcomes.

Meta-analyses suggested evidence of a beneficial effect of dexamethasone for children with meningitis when assessing serious adverse events (risk ratio (RR) 0.68, 95% confidence interval (CI) 0.53 to 0.86; P = 0.001, very low certainty of evidence) and ototoxicity (RR 0.63, 95% CI 0.45 to 0.88; P = 0.007, low certainty of evidence). TSAs showed that we did not have sufficient data to confirm or reject these results. We found insufficient evidence to confirm or reject an effect on mortality or our other outcomes.

No trials reported quality of life or organ failure. Most trials were at high risks of bias. We found high clinical heterogeneity between participants. None of our TSAs showed benefits, harms or futility.

Conclusions: Generally, we found no evidence of an effect of glucocorticosteroids for children with sepsis without meningitis. Dexamethasone for sepsis in children due to meningitis may decrease serious adverse events and ototoxicity.

Background

Sepsis is a leading cause of death in infants and children worldwide (1). Guidelines suggest that the glucocorticosteroid, hydrocortisone, might be used for children with fluid refractory and vasopressor-resistant septic shock, but the recommendation is based on unclear evidence (2, 3). The use of glucocorticosteroids for sepsis has been controversial for decades (4). A study from the UK suggested that 76% of pediatric intensive care units used steroids for septic shock (5). A worldwide cross-sectional study showed that the use of glucocorticosteroids was at 45% for children with severe sepsis (6).

Glucocorticosteroids seem to slightly reduce 28-day mortality in adults with sepsis (7). Important differences exist between children and adults with regard to sepsis and septic shock (8, 9). There is, therefore, a need to conduct an up-to-date review to address the benefits and harm of treatment with glucocorticosteroids in children with sepsis.

Methods

We detailed our predefined methodology in our pre-published protocol (10, 11) according to international guidelines (12). In accordance with our protocol, we conducted our systematic review based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines (PRISMA) (13), The Cochrane Handbook for Systematic Reviews of Interventions (12), Keus and colleagues (14), and the eight-step assessment suggested by Jakobsen and colleagues for better validation of meta-analytic results in systematic reviews (15). Review Manager 5.3 was used for all meta-analyses (16).

We searched for trials assessing the effects of adding any glucocorticosteroid to standard care versus standard care for hospitalized children (age < 18 years) with a diagnosis of sepsis based on the current international consensus (SIRS) or similar terms (as defined by trialists) (17). We also included participants suspected of or diagnosed with severe/deep-seated infections such as meningitis, osteomyelitis, endocarditis, and necrotizing enterocolitis (11). We searched for eligible trials published before February 2021 in the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, LILACS, Science Citation Index Expanded on Web of Science, BIOSIS, Google Scholar, clinicaltrials.gov, Trip Medical Database (TRIP), EU Clinical Trial Register (EUCTR), and WHO International Clinical Trials Registry Platform (ICTRP). The search strategy can be found in **Supplementary material**. Trials were included irrespective of trial design, setting, publication status, publication year, language, and the reporting of our outcomes.

Two authors (SKK and SS) independently selected relevant trials, extracted data using a standardized data extraction sheet, and systematically assessed risks of bias (12). We contacted trial authors if relevant data were unclear or missing.

Our primary outcomes were all-cause mortality and serious adverse events (10, 11). Our secondary outcomes were quality of life, shock reversal, organ failure, hearing loss or ototoxicity, and adverse events not considered serious. For all outcomes, we used the trial results reported at maximal follow-up.

We planned several subgroup analyses including subgroups based on risk of bias, type of glucocorticosteroids, dose, age, and presence of shock (10, 11).

We used risk ratios (RR) for dichotomous outcomes. We performed both random-effects (Der Simonian-Laird) and fixed-effect (Mantel-Haenszel) meta-analyses and chose the most conservative result as our primary result (11). We used Trial Sequential Analysis (TSA) to control random errors and reported TSA-adjusted confidence interval (CI) if the cumulative Z-curves did not reach the futility area or passed the diversity-adjusted required information size (DARIS) (11, 15, 18–25). We assessed two primary outcomes

and, hence, considered a P-value of 0.033 or less as the threshold for statistical significance for the primary outcomes to account for multiplicity (11, 15). We assessed five secondary outcomes and considered a P-value of 0.05 as the threshold for statistical significance for the secondary outcomes. We used 'best-worst' and 'worst-best' case analyses to assess the potential impact of missing data (15). We calculated Bayes factor to quantify the likelihood of the meta-analysis results being more or less compatible with either the null hypothesis or the anticipated intervention effects (15). We used GRADE to assess the certainty of the body of evidence (26).

Results

Included trials

Our literature search identified a total of 9133 studies. 1929 duplicates were excluded. 7204 studies were excluded based on the title or abstract. 21 studies were excluded based on the full text assessment. 24 trials met our inclusion criteria randomizing 3073 participants (27-50), of which 20 trials randomizing 2866 participants provided data for our predefined meta-analyses (27-43, 45, 47, 48). See **PRISMA flowchart (Figure 1)** for details regarding the literature search and the selection of trials.

The age groups of the randomized participants were infants (< 1 year) (38, 43, 44, 47) and children (age > 1 year and < 12 years) (27-37, 39-42, 45, 47, 48). All the trials assessed glucocorticosteroids as add on therapy of standard care. The glucocorticosteroids included were hydrocortisone (8 trials) (27, 42, 43, 46-50); dexamethasone (15 trials) (28-41, 43); and methylprednisolone (1 trial) (45) (**Table 1**). 18 trials used placebo plus standard care (27-31, 33, 35-37, 40-43, 45, 46, 48, 49) and 6 trials used only standard care as control intervention (16, 25, 32, 34, 38, 47). The follow-up ranged from one to 12 months. 19 trials reported all-cause mortality (27-43, 45, 47, 48); 20 trials reported serious adverse events (27-43, 45, 47, 48); 2 trials reported shock reversal (37, 42); 11 trials reported ototoxicity (29-31, 33-36, 39-41, 43); 9 trials reported adverse events not considered serious (29, 32, 35-37, 42, 43, 45, 48); and 12 trials reported neurological complications (28-34, 36, 38-41). No trials reported quality of life or organ failure. We created a 'Summary of findings' table (**Table 2**) using the prespecified outcomes all-cause mortality, serious adverse events, shock reversal, ototoxicity, and adverse events not considered serious. We also assessed neurological complications as a post-hoc analysis for trials including children with meningitis.

Six trials were assessed to be at overall low risk of bias (30, 36, 39, 41, 47, 48) whereas 18 trials were assessed to be at overall high risk of bias (27-29, 31-35, 37, 38, 40, 42-46, 49, 50) (**Figure 2**). The certainty of evidence according to GRADE ranged from very low to low.

The visual inspection of the forest plot and test for subgroup difference (P = 0.02) in the meta-analysis on our primary outcome serious adverse events showed that the effects of glucocorticosteroids seemed to differ between trials randomising participants with meningitis and trials randomising participants with sepsis of mixed focus (**Figure 3 and 4**). It was therefore not justifiable to pool trials including only children with meningitis with trials including children with difference underlying infections. Hence, we

chose to report results separately for each group of trials (children with mixed focus of infection and children with meningitis). We have attached the results of the overall analyses in **Appendix 1**.

Effects of interventions

Glucocorticosteroids for sepsis with mixed focus

All-cause mortality

A total of 5/9 trials (55.6%), randomizing 358 participants, reported all-cause mortality. In the glucocorticosteroid group, 33/184 (17.9%) participants died compared with 27/174 (15.5%) participants in the control group. Meta-analysis showed no evidence of a difference when assessing all-cause mortality (RR 1.24, 95% CI 0.80 to 1.92; P = 0.34; I^2 = 0%; 358 participants; 5 trials; very low certainty of evidence; **Figure 5**). Neither visual inspection of the forest plot nor tests for statistical heterogeneity (I^2 = 0 %; P = 0.83) showed signs of heterogeneity.

Trial Sequential Analysis showed that we did not have sufficient data to confirm or reject that adding glucocorticosteroids to standard care reduced the risk of death by 20% and that the accrued information was compatible with either a reduced risk of death by 79% or an increased risk of death by 639% (TSA-adjusted CI 0.21 to 7.39) (**Figure 6)**. Bayes factor (4.31) was above the Bayes factor threshold for significance of 0.1. Hence, the result confirmed the meta-analysis result showing no difference. We assessed the risk of bias of this outcome as high risk of bias. There were no missing data, so we did not perform 'best-worst' and 'worst-best' case meta-analyses on this outcome. As we only included five trials, no funnel plot was constructed.

Subgroup analyses

None of the planned subgroup analyses assessing risk of bias, age, type of steroids, and presence of shock showed evidence of a difference (**Figure 7-10).**

Serious adverse events

A total of 5/9 trials (55.5%), randomizing 358 participants, reported serious adverse events. In the glucocorticosteroid group, 37/184 (20.1%) participants experienced one or more serious adverse events compared with 30/174 (17.2%) participants in the control group. The trials including children with sepsis and mixed focus did not report any neurological events. The majority (80%) of these trials administered hydrocortisone (See Table 2). Meta-analysis showed no evidence of a difference when assessing serious adverse events (RR 1.24, 95% CI 0.82 to 1.87; P = 0.31; I^2 = 0%; 358 participants; 5 trials; very low certainty of evidence; **Figure 11**). Neither visual inspection of the forest plot nor tests for statistical heterogeneity (I^2 = 0%; P = 0.96) showed clear signs of heterogeneity. Trial Sequential Analysis showed that we did not have sufficient data to confirm or reject that adding glucocorticosteroids to standard care reduced serious adverse events by 20% and that the accrued information was compatible with either a decrease of serious adverse events by 77% or an increase of serious adverse events by 562% (TSA-adjusted CI 0.23 to

6.62) (**Figure 12)**. Bayes factor (5.20) was above the Bayes factor threshold for significance of 0.1. Hence, the result confirmed the meta-analysis result showing no difference. We assessed the risk of bias of this outcome as high risk of bias. There were no dropouts, so we did not perform 'best-worst' and 'worst-best' case meta-analyses on this outcome. As we only included five trials, no funnel plot was constructed.

Subgroup analyses

None of the planned subgroup analyses assessing risk of bias, age, type of steroids, and presence of shock showed evidence of a difference (**Figure 13-16).**

Secondary outcomes

Shock reversal

A total of 2/9 (22.2%) trials, randomizing 97 participants, reported shock reversal. In the glucocorticosteroid group 23/48 (47.9%) participants experienced shock reversal compared with 28/49 (57.1%) participants in the control group. Meta-analysis showed no evidence of a difference (RR 0.91, 95% CI 0.52 to 1.59; P = 0.74; I^2 = 68%; 97 participants; 2 trials; very low certainty of evidence; **Figure 17**).

Adverse events

A total of 3/9 trials (33.3%), randomizing 159 participants, reported adverse events. In the glucocorticosteroid group 21/78 (26.9%) participants experienced one or more adverse events compared with 32/81 (39.5%) participants in the control group. Meta-analysis showed no evidence of a difference (RR 0.68, 95% CI 0.45 to 1.04; P = 0.08; I^2 = 0%, 159 participants; 3 trials; very low certainty of evidence; **Figure 18**).

No trials assessed quality of life, organ failure, or ototoxicity. Hence, no meta-analysis was performed.

Dexamethasone for meningitis

Primary outcomes

All-cause mortality

A total of 14/14 trials (100%), randomizing 2449 participants, reported all-cause mortality. In the dexamethasone group, 193/1243 (15.5%) participants died compared with 191/1206 (15.8%) participants in the control group. Meta-analysis showed no evidence of a difference when assessing all-cause mortality (RR 0.97, 95% CI 0.78 to 1.21; P = 0.77; I^2 = 7%; 2449 participants; 14 trials; low certainty of evidence; **Figure 19**). Neither visual inspection of the forest plot nor tests for statistical heterogeneity (I^2 = 0 %; P = 0.58) showed signs of heterogeneity. Trial Sequential Analysis showed that we had did not have sufficient data to confirm or reject that adding glucocorticosteroids to standard care reduced the risk of death by 20% and that the accrued information was compatible with either a reduced risk of death by

41% or an increased risk of death by 58% (TSA-adjusted CI 0.59 to 1.58) (**Figure 20)**. Bayes factor (4.23) was above the Bayes factor threshold for significance of 0.1. Hence, the Bayes factor result confirmed the meta-analysis result showing no difference. We assessed the risk of bias of this outcome as high risk of bias. The 'best-worst' and 'worst-best' case meta-analyses showed that incomplete outcome data bias did not have the potential to influence the results (**Figure 21** and **Figure 22**). Visual inspection of the funnel plots showed no clear signs of asymmetry (**Figure 23**).

Subgroup analyses

None of the planned subgroup analyses assessing risk of bias, age, and dose showed evidence of a difference (**Figure 24-26).**

Serious adverse events

A total of 14/14 trials (100%), randomizing 2379 participants, assessed serious adverse events. In the dexamethasone group, 370/1210 (30.6%) participants experienced one or more serious adverse events compared with 435/1169 (37.2%) participants in the control group. The trials primarily reported neurological complications, hearing loss/ ototoxicity, or a combination of both (see **Table 1**). Meta-analysis showed evidence of a difference when assessing serious adverse events (RR 0.68, 95% CI 0.53 to 0.86; P = 0.001; I^2 = 64%; 2379 participants; 14 trials; very low certainty of evidence; **Figure 27**). There were signs of statistical heterogeneity (I^2 = 64%; P = 0.0006), however, visual inspection of the forest plot did not show clear signs of heterogeneity. Trial Sequential Analysis showed that we did not have sufficient data to confirm or reject that adding glucocorticosteroids to standard care reduced serious adverse events by 20% and that the accrued information was compatible with either a decrease of serious adverse events by 75% or an increase of serious adverse events by 80% (TSA-adjusted CI 0.25 to 1.80) (**Figure 28)**. Bayes factor (0.02) was under the Bayes factor threshold for significance of 0.1. Hence, the result confirmed the meta-analysis result suggesting a difference. We assessed the risk of bias of this outcome as high risk of bias. The 'best-worst' and 'worst-best' case meta-analyses showed that incomplete outcome data bias did not have the potential to influence the results (**Figure 29** and **Figure 30**). Visual inspection of the funnel plots showed clear signs of asymmetry (**Figure 31**) confirmed by Harbord test (P=0.0009).

Subgroup analyses

None of the planned subgroup analyses assessing risk of bias, age, and dose showed evidence of a difference in intervention effects (**Figure 32-34).**

Secondary outcomes

Hearing loss or ototoxicity

A total of 11/14 (78.6%), randomizing 1825 participants, reported hearing loss or ototoxicity. In the dexamethasone group 130/941 (13.8%) participants experienced ototoxicity compared with 174/884

(19.7%) participants in the control group. Meta-analysis showed evidence of a beneficial effect of adding dexamethasone to standard care (RR 0.63, 95% CI 0.45 to 0.88; P = 0.007; I^2 = 44%; 1825 participants; 11 trials; low certainty of evidence; **Figure 35**). Trial Sequential Analysis showed that we did not have sufficient data to confirm or reject that adding glucocorticosteroids to standard care reduced serious adverse events by 20% and that the accrued information was compatible with either a reduced the risk of ototoxicity by 84% or an increased the risk of ototoxicity by 148% (TSA-adjusted CI 0.16 to 2.48) (**Figure 36**).

Adverse events

A total of 5/14 trials (35.7%), randomizing 582 participants, reported adverse events. In the dexamethasone group 126/293 (43.0%) participants experienced one or more adverse events compared with 97/289 (33.6%) participants in the control group. Meta-analysis showed no evidence of a difference (RR 1.15, 95% CI 0.76 to 1.75; P = 0.52; I^2 = 69%, 582 participants; 5 trials; very low certainty of evidence; **Figure 37**).

No trials assessed quality of life, organ failure or shock reversal. Hence, no meta-analysis was performed.

Post-hoc analysis of neurological complications

The trials including children with meningitis reported many neurological complications as serious adverse events. We therefore decided to analyze that outcome separately as well.

A total of 12/14 (85.7%) trials, randomizing a total of 1866 participants, assessed neurological complications. In the dexamethasone group 123/950 (12.9%) participants experienced neurological complications compared with 140/916 (15.3%) participants in the control group. Meta-analysis showed no evidence of a difference (RR 0.79, 95% CI 0.58 to 1.05; P = 0.12; I^2 = 20%; 1866 participants; 12 trials; low certainty of evidence; **Figure 38**).

Discussion

We included 24 trials randomizing a total of 3073 infants or children below 12 years. Six trials were assessed at overall ‘low risk of bias’, and 18 trials were assessed at overall ‘high risk of bias’. The certainty of evidence according to GRADE ranged from very low to low. The trials included a heterogeneous group of children with different underlying infections such as pneumonia, meningitis, and a mix of different foci; the trials were conducted in both high-income countries and low-income countries. The types of glucocorticosteroids were hydrocortisone, dexamethasone, or methylprednisolone. Eighteen trials used placebo and six trials only used standard care as control intervention.

When meta-analyzing the trial results, visual inspection of the forest plots and test for subgroup differences showed that the effects of glucocorticosteroids seemed to differ between trials randomising

participants with meningitis and trials randomising participants with sepsis of mixed focus. Hence, we chose to report results separately for each group of trials.

Meta-analysis showed no evidence of an effect of adding glucocorticosteroids to standard care for children with sepsis with a mixed focus when assessing all-cause mortality, serious adverse events, shock reversal, or adverse events. None of the trials assessed quality of life, ototoxicity, or organ failure for children with sepsis with mixed focus.

Meta-analyses suggested evidence of a beneficial effect of adding dexamethasone to standard care for children with meningitis on serious adverse events and ototoxicity. Bayes factor supported these findings. However, Trial Sequential Analysis showed that we did not have sufficient evidence to confirm that dexamethasone reduced serious adverse events by 20% or more and GRADE assessment indicated of low certainty of evidence. Meta-analyses showed no evidence of an effect of adding dexamethasone to standard care for children with meningitis when assessing all-cause mortality, adverse events, and neurological complications. No trials assessed quality of life, organ failure, or shock reversal for children with meningitis.

Dexamethasone is thought to suppress crucial inflammatory pathways responsible for meningitis (51). Accordingly, it was the glucocorticosteroid chosen in all the trials including only children with meningitis.

Our review has several strengths.
Our methodology was described in detail in a protocol that was published before the literature search was initiated (10, 11). We systematically assessed the risks of systematic errors through bias risk assessments, we conducted Trial Sequential Analyses to guide our GRADE assessments of levels of downgrade for imprecision, and we adjusted our thresholds for statistical significance to control the risks of random errors (15). We systematically used our eight–step procedure to assess if the thresholds for statistical and clinical significance were crossed (15). This added further robustness to our results and conclusions. Furthermore, we included a larger number of both trials and participants than any previous review (52), which gives us increased precision and power. We included enough participants to reject that adding glucocorticosteroids to standard care would reduce the risk of death by 20% or more. Moreover, the two most recent systematic reviews assessing the use of corticosteroids for sepsis among adults and children did not identify enough pediatric trials to perform meta-analysis for the pediatric population (7, 52). One review included participants with community acquired pneumonia that might not have sepsis (53) and excluded trials assessing children with meningitis (7).

Our review also has several limitations.
First, we chose to both include participants with sepsis and meningitis because we hypothesized that the effects of glucocorticosteroids might be similar in these two types of patients (5, 6). However, based on the present results, we reached to the conclusion that pooling trials randomizing children with sepsis and children with meningitis would not be valid since the effects seem to differ. Another limitation is that most trials were at ‘high risk of bias’. For all outcomes, a varying proportion of trials did not report on the patient-relevant outcomes we had prespecified in our protocol (5, 6). This makes our analyses open to

outcome reporting bias (54). The types of participants and choice of glucocorticosteroids differed between the included trials, which leads to a certain degree of clinical heterogeneity. Neither did we distinct between children with different degrees of severity (e.g. PRISM, PIM, PELOD, SOFA scores). We did not reach a sufficient information size for most of our outcomes to confirm or reject a beneficial or harmful effect of glucocorticosteroids. A large ongoing multicenter trial, that is planning to randomize 1032 participants, will likely be an important contribution to the assessment of the effects of glucocorticosteroids, but results are not expected before 2024 (55).

Guidelines suggest that one might use hydrocortisone for children with fluid refractory and vasopressor-resistant septic shock (3), but we found no evidence from randomized clinical trials to support this recommendation. No beneficial effects of glucocorticosteroids were found in children with septic shock, but only few children were randomized. Dexamethasone was the only glucocorticosteroids that seemed to show a beneficial effect for children with meningitis, however, the evidence was of low certainty.

Conclusions

Generally, we found no evidence of an effect of glucocorticosteroids for children with sepsis without meningitis.

Glucocorticosteroids (dexamethasone) seems to reduce serious adverse events and ototoxicity for children with meningitis but does not seem to have any effect on all-cause mortality. The clinical effects of glucocorticosteroids on shock reversal, and adverse events considered non-serious are unclear based on current evidence. No trials assessed quality of life and organ failure.

Based on our results, the guidelines need updating and the use of glucocorticosteroids for sepsis in children should be examined in randomized placebo-controlled clinical trials conducted at low risk of bias and low risk of systematic errors. Such trials ought to be designed according to the SPIRIT statement (56) and reported according to the CONSORT statement (57).

List Of Abbreviations

CI: Confidence interval. DARIS: diversity-adjusted required information size. MD: Mean difference.PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines. RR: Risk ratio. TSA: Trial Sequential Analysis.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interest.

Funding

None of the authors received any specific funding related to the review.

Authors' contributions

Dr. Korang: Drafted the protocol, extracted data, co-ordinated the review, conceived the review, designed the review, analyzed the data, interpreted the data providing a methodological and clinical view, and revised the review.

Acknowledgement

The review author team would like to acknowledge the information specialist Sarah Klingenberg (from the Cochrane Hepato-Biliary Group) for the development of our search strategy and searches.

References

1. Watson RS, Carcillo JA. Scope and epidemiology of pediatric sepsis. Pediatric Critical Care Medicine. 2005;6(3 Suppl):S3-S5.
2. Dellinger RP LM, Rhodes A, Annane D, Gerlach H, Opal SM, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock. Intensive Care Medicine. 2013;39:165-228.
3. Weiss SL, Peters MJ, Alhazzani W, Agus MSD, Flori HR, Inwald DP, et al. Surviving sepsis campaign international guidelines for the management of septic shock and sepsis-associated organ dysfunction in children. Pediatric Critical Care Medicine. 2020;21(2):e52-e106.
4. Aneja R, Carcillo JA. What is the rationale for hydrocortisone treatment in children with infection-related adrenal insufficiency and septic shock? Archives of Disease in Childhood 2007;92(2):165-9.
5. Hildebrandt T, Mansour M, Samsam RA. The use of steroids in children with septicemia: review of the literature and assessment of current practice in PICUs in the UK. Pediatric, Anaesthesia. 2005;15(5):358-65.
6. Weiss SL, Fitzgerald JC, Pappachan J, Wheeler D, Jaramillo-Bustamante JC, Salloo A, et al. Global epidemiology of pediatric severe sepsis: the sepsis prevalence, outcomes, and therapies study. Am J Respir Crit Care Med. 2015;191(10):1147-57.
7. Annane D, Bellissant E, Bollaert PE, Briegel J, Keh D, Kupfer Y, et al. Corticosteroids for treating sepsis in children and adults. The Cochrane Database of Systematic Reviews. 2019;12:CD002243.
8. Aneja R, Carcillo JA. Differences between adult and pediatric septic shock. Minerva Anestesiologica. 2011;77(10):986-92.

9. Zonneveld R, Martinelli R, Shapiro NI, TW K, FB P, CV. C. Soluble adhesion molecules as markers for sepsis and the potential pathophysiological discrepancy in neonates, children and adults. Critical Care (London, England). 2014;18(1):204.
10. PROSPERO: International prospective register of systematic reviews. CRD42017054341. Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42017054341 2017 [
11. Korang SK, Gluud C, Jakobsen JC. Glucocorticosteroids for sepsis in children. A protocol for a systematic review. Acta Anaesthesiologica Scandinavica. 2019;63(6):819-26.
12. Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 51 [updated March 2011] The Cochrane Collaboration, 2011: Available from www.cochrane-handbook.org.
13. Moher D, Liberati A, Tetzlaff J, Altman D. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLOS Medicine. 2009;6(7):e1000097-e.
14. Keus F, Wetterslev J, Gluud C, van Laarhoven CJ. Evidence at a glance: error matrix approach for overviewing available evidence. BMC Medical Research Methodology. 2010;10(90).
15. Jakobsen JC, Wetterslev J, Winkel P, Lange T, Gluud C. Thresholds for statistical and clinical significance in systematic reviews with meta-analytic methods. BMC Medical Research Methodology. 2014;14:120.
16. Review Manager (RevMan). https://training.cochrane.org/online-learning/core-software-cochrane-reviews/revman: The Cochrane Collaboration; 2020.
17. Goldstein B, Giroir B, Randolph A. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. Pediatric Critical Care Medicine: A Journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies. 2005;6(1):2-8.
18. Brok J, Thorlund K, Gluud C, Wetterslev J. Trial sequential analysis reveals insufficient information size and potentially false positive results in many meta-analyses. Journal of Clinical Epidemiology. 2008;61(8):763-9.
19. Brok J, Thorlund K, Wetterslev J, Gluud C. Apparently conclusive meta-analyses may be inconclusive. Trial sequential analysis adjustment of random error risk due to repetitive testing of accumulating data in apparently conclusive neonatal meta-analyses. International Journal of Epidemiology. 2009;38(1):287-98.
20. Thorlund K, Anema A, Mills E. Interpreting meta-analysis according to the adequacy of sample size. An example using isoniazid chemoprophylaxis for tuberculosis in purified protein derivative negative HIV-infected individuals. Clinical Epidemiology. 2010;2:57-66.
21. Thorlund K, Devereaux PJ, Wetterslev J, Guyatt G, Ioannidis JP, Thabane L, et al. Can trial sequential monitoring boundaries reduce spurious inferences from meta-analyses? International Journal of Epidemiology. 2009;38(1):276-86.
22. Thorlund K, Engstrøm J, Wetterslev J, Brok J, Imberger G, Gluud C. User manual for Trial Sequential Analysis (TSA). www.ctu.dk/tsa/files/tsa_manual.pdf2011.

23. Wetterslev J, Thorlund K, Brok J, Gluud C. Trial sequential analysis may establish when firm evidence is reached in cumulative meta-analysis. Journal of Clinical Epidemiology. 2008;61(1):64-75.
24. Wetterslev J, Thorlund K, Brok J, Gluud C. Estimating required information size by quantifying diversity in random-effects model meta-analyses. BMC Medical Research Methodology. 2009;9(86).
25. Copenhagen Trial Unit. TSA- Trial Sequential Analysis. www.ctu.dk/tsa. 2011.
26. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ (Clinical Research Ed). 2008;336:924-6.
27. Group CS. The effectiveness of hydrocortisone in the management of severe infections: a double-blind study. JAMA. 1963;183(6):462-5.
28. Belsey MA, Hoffpauir CW, Smith MH. Dexamethasone in the treatment of acute bacterial meningitis: the effect of study design on the interpretation of results. Pediatrics. 1969;44(4):503-13.
29. Lebel MH, Freij BJ, Syrogiannopoulos GA, Chrane DF, Hoyt MJ, Stewart SM, et al. Dexamethasone therapy for bacterial meningitis. Results of two double-blind, placebo-controlled trials. New England Journal of Medicine. 1988;319(15):964-71.
30. Odio CM, Faingezicht I, Paris M, Nassar M, Baltodano A, Rogers J, et al. The beneficial effects of early dexamethasone administration in infants and children with bacterial meningitis. New England Journal of Medicine. 1991;324(22):1525-31.
31. Schaad UB, Lips U, Gnehm HE, Blumberg A, Heinzer I, Wedgwood J. Dexamethasone therapy for bacterial meningitis in children. Swiss Meningitis Study Group. Lancet. 1993;342(8869):457-61.
32. Ciana G PN, Antonio C, Pivetta S, Tamburlini G, Cuttini M. Effectiveness of adjunctive treatment with steroids in reducing short-term mortality in a high-risk population of children with bacterial meningitis. Journal of Tropical Pediatrics. 1995;41(3):164-8.
33. Kanra GY, Ozen H, Secmeer G, Ceyhan M, Ecevit Z, Belgin E. Beneficial-effects of dexamethasone in children with pneumococcal meningitis. Pediatric Infectious Disease Journal. 1995;14(6):490-4.
34. Kilpi T, Peltola H, Jauhiainen T, Kallio MJ. Oral glycerol and intravenous dexamethasone in preventing neurologic and audiologic sequelae of childhood bacterial meningitis. The Pediatric Infectious Disease Journal. 1995;95(1):21-31.
35. Wald ER, Kaplan SL, Mason Eo Jr, Sabo D, Ross L, Arditi M, et al. Dexamethasone therapy for children with bacterial meningitis. Meningitis Study Group. Pediatrics. 1995;95(1):21-8.
36. Qazi SA, Khan MA, Mughal N, Ahmad M, Joomro B, Sakata Y, et al. Dexamethasone and bacterial meningitis in Pakistan. Archives of Disease in Childhood. 1996;75(6):482-8.
37. Slusher T, Gbadero D, Howard C, Lewison L, Giroir B, Toro L, et al. Randomized, placebo-controlled, double blinded trial of dexamethasone in African children with sepsis. The Pediatric Infectious Disease Journal. 1996;15(7):579-83.
38. Shembesh NM ES, Kashbur IM, Rao BN, Mahmoud KS. Dexamethasone as an adjunctive treatment of bacterial meningitis. Indian Journal of Pediatrics. 1997;64(4):517-22.

39. Molyneux EM, Walsh AL, Forsyth H, Tembo M, Mwenechanya J, Kayira K, et al. Dexamethasone treatment in childhood bacterial meningitis in Malawi: a randomised controlled trial. Lancet. 2002;360(9328):211-8.
40. Peltola H, Roine I, Fernandez J, Zavala I, Ayala SG, Mata AG, et al. Adjuvant glycerol and/or dexamethasone to improve the outcomes of childhood bacterial meningitis: a prospective, randomized, double-blind, placebo-controlled trial. Clinical Infectious Diseases. 2007;45(10):1277-86.
41. Sankar J SP, Bansal A, Ray P, Singhi S. Role of dexamethasone and oral glycerol in reducing hearing and neurological sequelae in children with bacterial meningitis. Indian Pediatrics. 2007;44(9):649-56.
42. Valoor HT, Singhi S, M J. Low-dose hydrocortisone in pediatric septic shock: an exploratory study in a third world setting. Pediatric Critical Care Medicine. 2009;10(1):121-5.
43. Mathur NB, Garg A, Mishra TK. Role of dexamethasone in neonatal meningitis: a randomized controlled trial. Indian Journal of Pediatrics. 2013;80(2):102-7.
44. Mathur NB, Nimesh M. Effect of hydrocortisone in term neonates with vasopressor resistant septic shock. A randomized controlled trial. Intensive Care Medicine. 2013;Conference: 24th annual meeting of the European Society of Paediatric and Neonatal Intensive Care, ESPNIC 2013 Rotterdam Netherlands. :s16.
45. Nagy B, Gaspar I, Papp A, Bene Z, Nagy B Jr, Voko Z, et al. Efficacy of methylprednisolone in children with severe community acquired pneumonia. Pediatric Pulmonology. 2013;48(2):168-75.
46. Branco RG, Amoretti CF, Garcia PCR, Einloft PR, Bruno F, Piva JP, et al. Corticosteroid replacement in sepsis induces lymphopenia: Results of a randomized controlled trial. 2014;Conference: 7th World Congress on Pediatric Intensive and Critical Care, PICC 2014. Istanbul Turkey.:12.
47. El-Nawawy A, Khater D, Omar H, Wali Y. Evaluation of early corticosteroid therapy in management of pediatric septic shock in pediatric intensive care patients: A randomized clinical study. Pediatric Infectious Disease Journal. 2017;36(2):155-9.
48. Menon K, McNally D, O'Hearn K, Acharya A, Wong HR, Lawson M, et al. A randomized controlled trial of corticosteroids in pediatric septic shock: a pilot feasibility study. Pediatric Critical Care Medicine. 2017;18(6):505-12.
49. Amoretti CF, Cabral F, Tonial C, Birck G, Toscan C, Acatrolli A, et al. Corticosteroid replacement in children with septic shock: Randomized double blind placebo controlled trial. Pediatric Critical Care Medicine. 2012;13(5):618.
50. De Graaf H, Ramakrishnan KA, Pappachan J, Nadel S, Levin M, Wolf A, et al. Evaluation of corticosteroid replacement therapy in children with severe septic shock – a randomised intervention trial. Pediatric Critical Care Medicine. 2014;15(4):141.
51. Mogensen TH, Berg RS, Paludan SR, Østergaard L. Mechanisms of dexamethasone-mediated inhibition of Toll-like receptor signaling induced by Neisseria meningitidis and Streptococcus pneumoniae. Infect Immun. 2008;76(1):189-97.
52. Rochwerg B, Oczkowski SJ, Siemieniuk RAC, Agoritsas T, Belley-Cote E, D'Aragon F, et al. Corticosteroids in sepsis: an updated systematic review and meta-analysis. Critical Care Medicine.

2018;46(9):1411-20.

53. Tagarro A, Otheo E, Baquero-Artigao F, Navarro ML, Velasco R, Ruiz M, et al. Dexamethasone for parapneumonic pleural effusion: a randomized, double-blind, clinical trial. J Pediatr. 2017;185:117-23.e6.
54. Chan AW, Hróbjartsson A, Haahr MT, Gøtzsche PC, Altman DG. Empirical evidence for selective reporting of outcomes in randomized trials: comparison of protocols to published articles. JAMA. 2004;291(20):2457-65.
55. Stress Hydrocortisone In Pediatric Septic Shock - Full Text View - ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03401398.
56. Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, et al. SPIRIT 2013 statement: defining standard protocol items for Ccinical trials. Annals of Internal Medicine. 2013;158(3):200-7.
57. Schulz KF, Altman DG, Moher D, Group C. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. BMC Medicine. 2010;8:18.

Tables

Table 1: Characteristics of included trials

	Type of glucocorticosteriod	Focus of infection	Septic shock	Country (income)	Age (infants (age <1 year), children (age >1 year and < 12 years), or adolescents (age > 12 years)
l	Hydrocortisone	Mixed	Yes	Brasil (Upper middle)	Children
	Dexamethasone	Meningitis	No	USA (High)	NA
	Hydrocortisone	Mixed	No	USA (High)	NA
	Hydrocortisone	Mixed	No	Brasil (Middle)	Infants
	Dexamethasone	Meningitis	No	Mosambique (Low)	Infants and children
f	Hydrocortisone	Mixed	Yes	UK (High)	Children
	Hydrocortisone	Mixed	Yes	Egypt (Middle)	Infants
	Dexamethasone	Meningitis	No	Turkey (Upper middle)	Children
	Dexamethasone	Meningitis	No	Finland (High)	Infants and children
	Dexamethasone	Meningitis	No	USA (High)	Children
	Hydrocortisone	Mixed	Yes	India (Lower middle)	Infants
	Dexamethasone	Meningitis	No	India (Lower middle)	Infants
	Hydrocortisone	Mixed	Yes	Canada (High)	Children
x	Dexamethasone	Meningitis	No	Malawi (Low)	NA
	Methylprednisolon	Pneumonia	No	Hungary (High)	Children
	Dexamethasone	Meningitis	No	Costa Rica (Upper middle)	Children
	Dexamethasone	Meningitis	No	Latin America (Middle)	NA
	Dexamethasone	Meningitis	No	Pakistan (Lower middle)	Infants and children
	Dexamethasone	Meningitis	No	India	Children

				(Lower middle)	
	Dexamethasone	Meningitis	No	Scaad (High)	Children
sh	Dexamethasone	Meningitis	No	Libya (Upper middle)	Infants
	Dexamethasone	Mixed	No	Kenya and Nigeria (Lower middle)	Children
	Hydrocortisone	Mixed	Yes	India (Lower middle)	Children
	Dexamethasone	Meningitis	No	USA (High)	Infants

Table 2: Summary of findings table.

Glucocorticosteroids compared with placebo or no intervention for sepsis in children

Patient or population: Children with sepsis

Settings: Hospital

Intervention: Glucocorticosteroids

Comparison: Placebo or no intervention

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Glucocorticosteroids				
All-cause mortality maximum follow-up	**Study population**		**RR** 1.24, (95% CI 0.80 to 1.92)	358 (5)	⊕⊖⊖⊖ **Very low**	Downgraded for bias and imprecision. DARIS: 5810 (RRR 20; alpha 3.33%; beta 10%; Pc 15.5% diversity 0.0%)
	155 per 1000	**192 per 1000** (124 to 295)				
Serious adverse events maximum follow-up	**Study population**		**RR** 1.24 (95% CI 0.82 to 1.87)	358 (5)	⊕⊖⊖⊖ **Very low**	Downgraded for bias, imprecision and indirectness. DARIS: 5143 (RRR 20; alpha 3.33%; beta 10%; Pc 17.2% diversity 0.0%)
	172 per 1000	**213 per 1000** (141 to 322)				
Shock reversal maximum follow-up	**Study population**		**RR** 0.91 (95% CI 0.52 to 1.59)	97 (2)	⊕⊖⊖⊖ **Very low**	Downgraded for bias, indirectness, imprecision, and inconsistency DARIS: 3787
	571 per	**520 per 1000**				

	1000	(297 to 907)				(RRR 20%; alpha 5%; beta 10%; Pc 57.1%; diversity 78.72%)
Adverse events not considered serious maximum follow-up	**Study population**		**RR** 0.68 (95% CI 0.45 to 1.04)	159 (3)	⊕⊖⊖⊖ **Very low**	Downgraded for bias, indirectness, imprecision, and inconsistency DARIS: 1543 (RRR 20%; alpha 5%; beta 10%; Pc 39.5%; diversity 0.0%)
	363 per 1000	**315 per 1000** (210 to 471)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk Ratio **DARIS**: Diversity-adjusted required information size

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Dexamethasone compared with placebo or no intervention for meningitis in children

Patient or population: Children with meningitis

Settings: Hospital

Intervention: Dexamethasone

Comparison: Placebo or no intervention

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Glucocorticosteroids				
All-cause mortality maximum follow-up	Study population		**RR** 0.97, (95% CI 0.78 to 1.21)	2449 (14)	⊕⊕⊖⊖ **Low**	Downgraded for bias and imprecision. DARIS: 9412 (RRR 20%; alpha 3.33%; beta 10%; Pc 15.8%; diversity 39.51%)
	155 per 1000	**150 per 1000** (121 to 188)				
Serious adverse events maximum follow-up	Study population		**RR** 0.68 (95% CI 0.53 to 0.86)	2379 (14)	⊕⊖⊖⊖ **Very low**	Downgraded for bias, publication bias and indirectness. DARIS: 1422 (RRR 20%; alpha 3.33%; beta 10%; Pc 37.2%; diversity 84.48%)
	372 per 1000	**253 per 1000** (197 to 320)				
Ototoxicity maximum follow-up	Study population		**RR** 0.63 (95% CI 0.45 to 0.88)	1825 (11)	⊕⊕⊖⊖ **Low**	Downgraded for bias and imprecision. DARIS: 10515 (RRR 20%; alpha 5.0%; beta 10%; Pc 19.7%;
	197 per 1000	**124 per 1000** (89 to 173)				

						diversity 62.48%)
Adverse events not considered serious maximum follow-up	**Study population**		**RR** 1.15 (95% CI 0.76 to 1.75)	582 (5)	⊕⊖⊖⊖ **Very low**	Downgraded one level for bias, indirectness and two levels for very serious imprecision. DARIS: 7936 (RRR 20%; alpha 5%, beta 10%; Pc 33.6%; diversity 75.25%)
	336 per 1000	**386 per 1000** (255 to 588)				
Neurological complications maximum follow-up	**Study population**		**RR** 0.79 (95% CI 0.58 to 1.05)	1866 (12)	⊕⊕⊖⊖ L**ow**	Downgraded for bias and imprecision. DARIS 10131 (RRR 20%; alpha 5%; beta 10%; Pc 15.3%; diversity 47.38%)
	153 per 1000	**121 per 1000** (89 to 160)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk Ratio **DARIS**: Diversity-adjusted required information size

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Figures

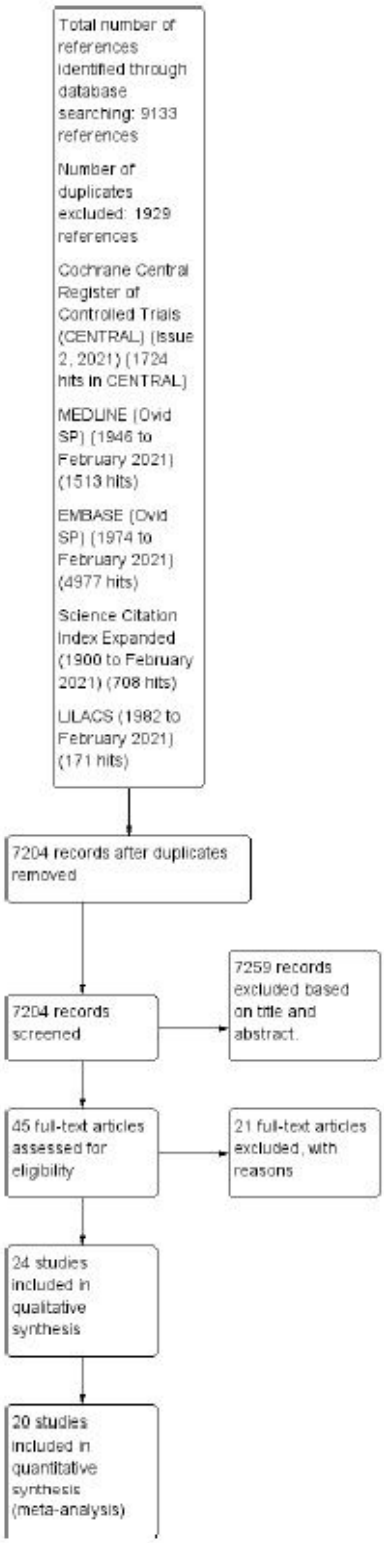


Figure 1

PRISMA flowchart

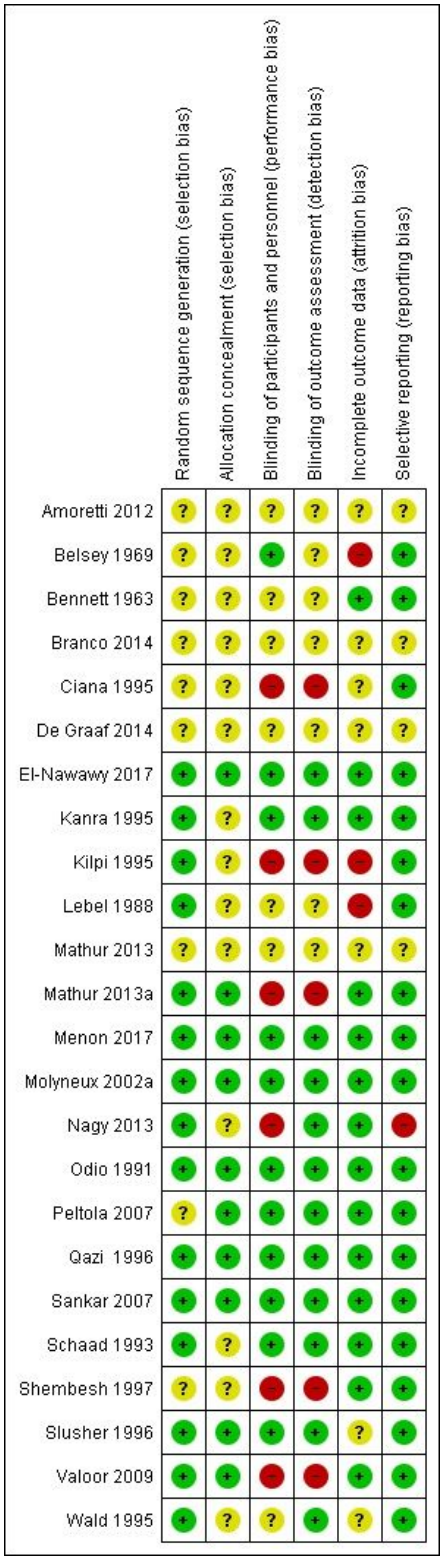


Figure 2

Risk of bias assessment

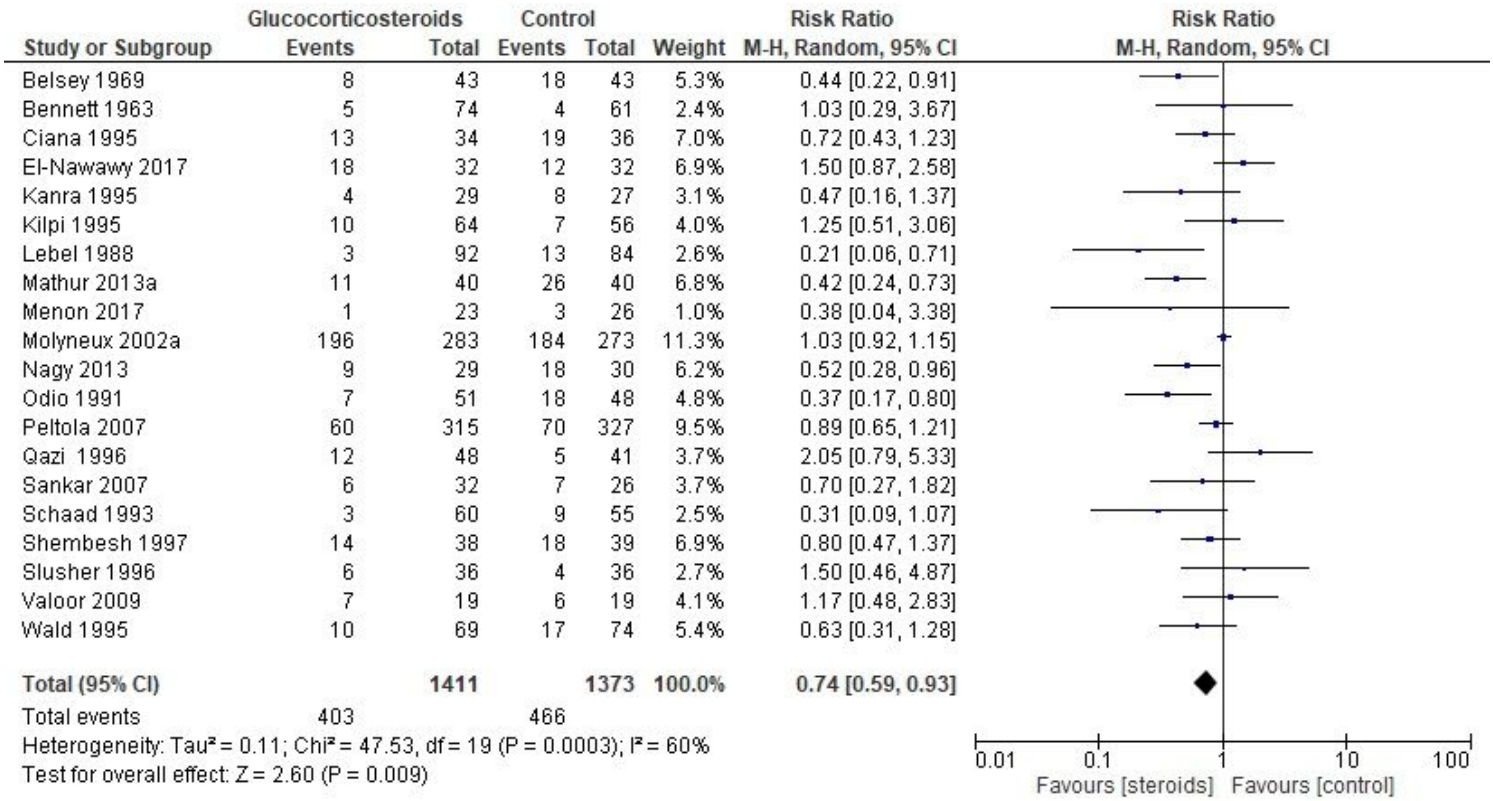


Figure 3

Serious adverse events overall analysis (Random effects model)

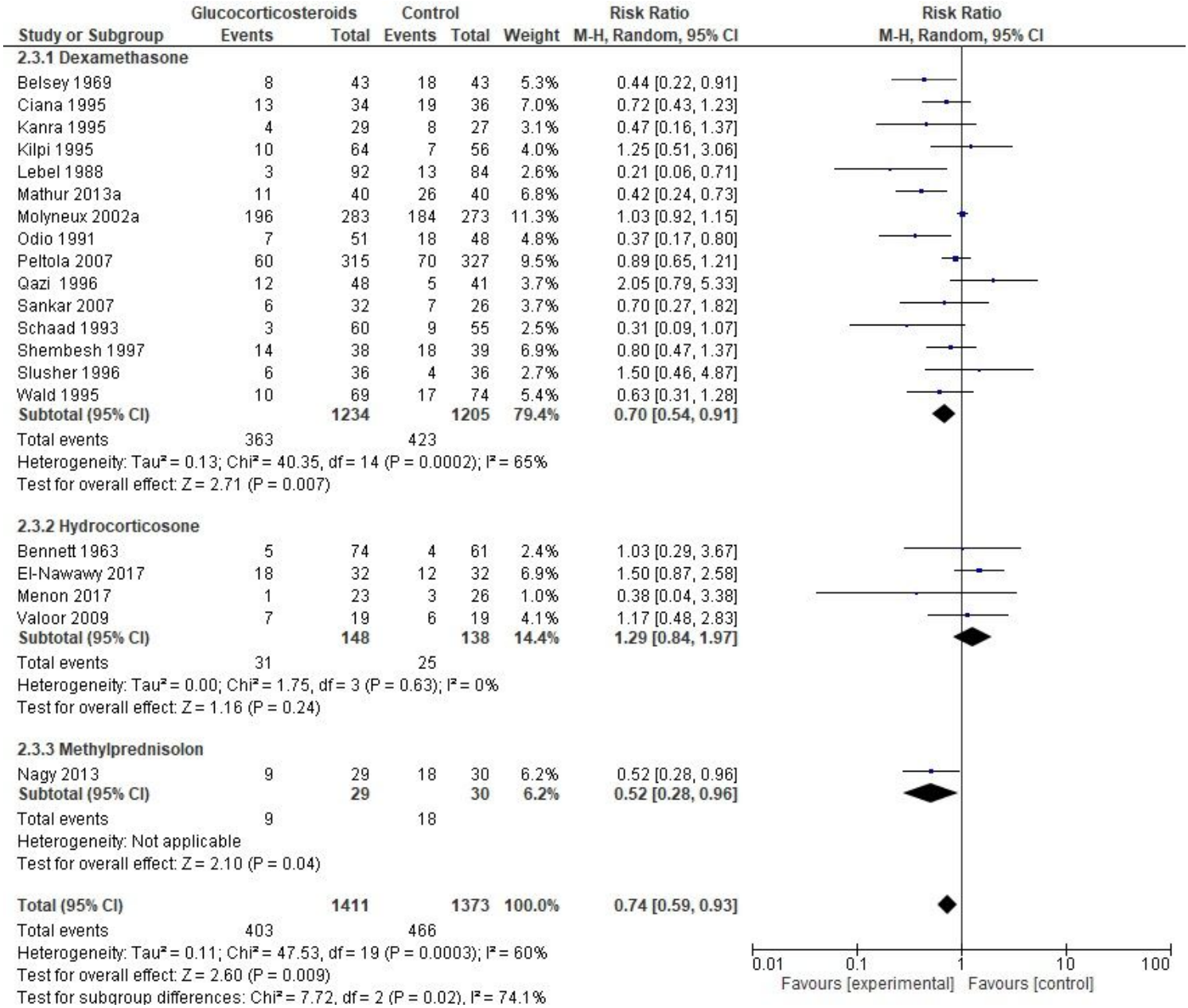


Figure 4

Serious adverse events (overall) - Subgroup based on type of steroid

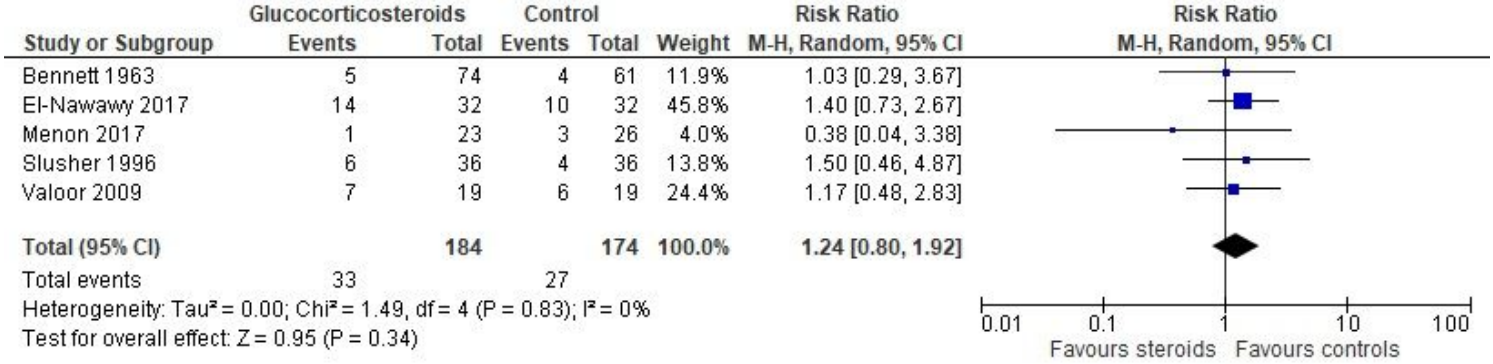


Figure 5

All-cause mortality (Sepsis- mixed focus)

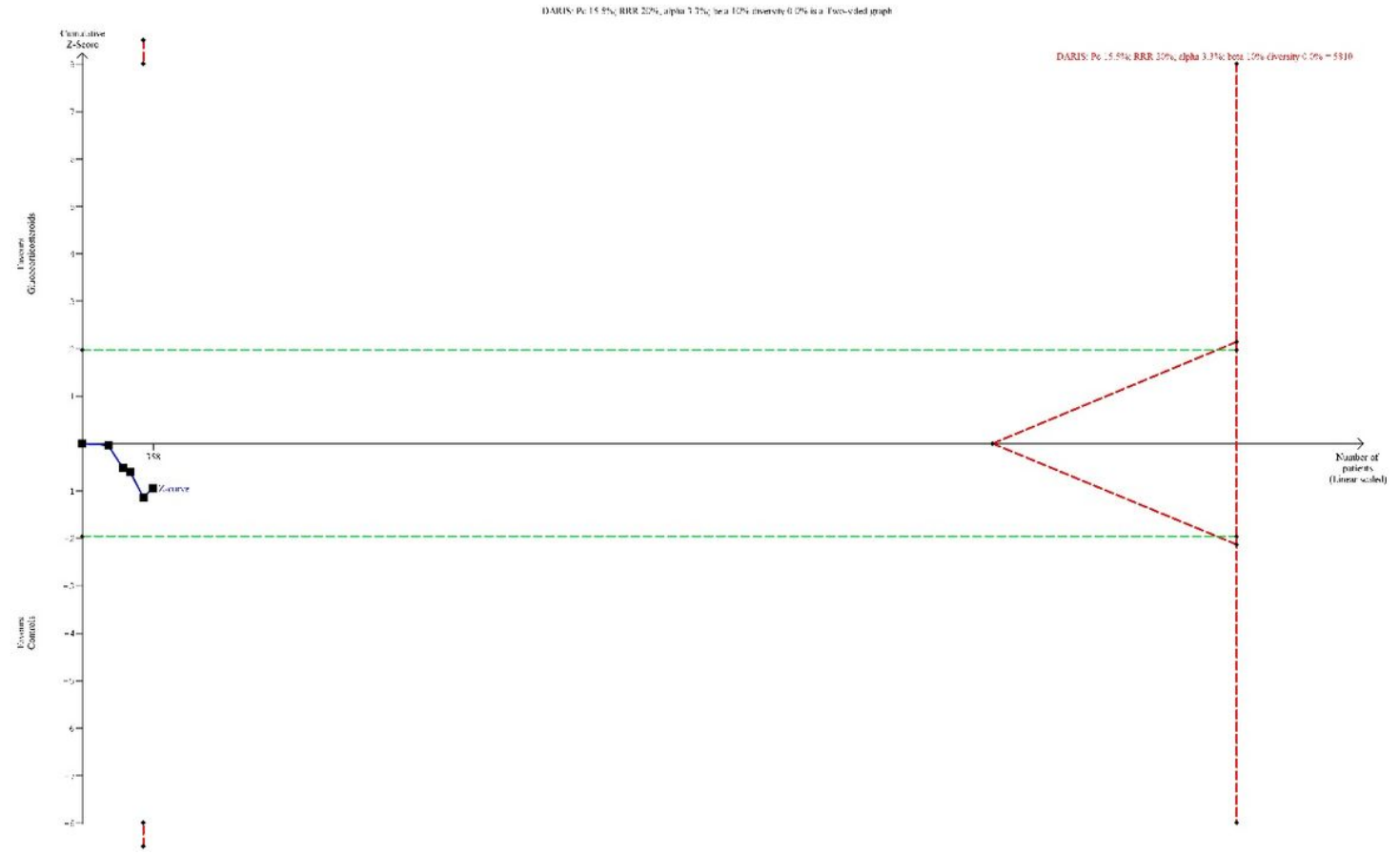


Figure 6

TSA All-cause mortality (Sepsis-mixed focus)

Study or Subgroup	Steroids Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.12.1 Low risk of bias						
El-Nawawy 2017	14	32	10	32	45.8%	1.40 [0.73, 2.67]
Menon 2017	1	23	3	26	4.0%	0.38 [0.04, 3.38]
Subtotal (95% CI)		**55**		**58**	**49.8%**	**1.10 [0.40, 3.03]**
Total events	15		13			
Heterogeneity: Tau² = 0.21; Chi² = 1.32, df = 1 (P = 0.25); I² = 24%						
Test for overall effect: Z = 0.19 (P = 0.85)						
1.12.2 High risk of bias						
Bennett 1963	5	74	4	61	11.9%	1.03 [0.29, 3.67]
Slusher 1996	6	36	4	36	13.8%	1.50 [0.46, 4.87]
Valoor 2009	7	19	6	19	24.4%	1.17 [0.48, 2.83]
Subtotal (95% CI)		**129**		**116**	**50.2%**	**1.21 [0.65, 2.25]**
Total events	18		14			
Heterogeneity: Tau² = 0.00; Chi² = 0.20, df = 2 (P = 0.91); I² = 0%						
Test for overall effect: Z = 0.61 (P = 0.54)						
Total (95% CI)		**184**		**174**	**100.0%**	**1.24 [0.80, 1.92]**
Total events	33		27			
Heterogeneity: Tau² = 0.00; Chi² = 1.49, df = 4 (P = 0.83); I² = 0%						
Test for overall effect: Z = 0.95 (P = 0.34)						
Test for subgroup differences: Chi² = 0.02, df = 1 (P = 0.88), I² = 0%						

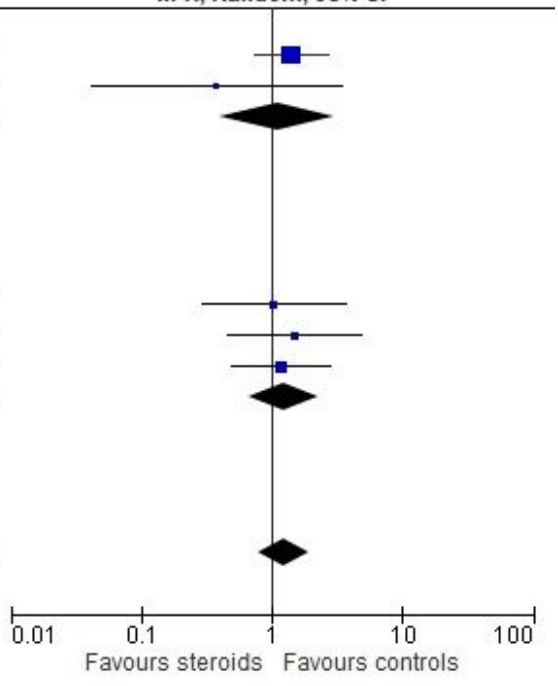


Figure 7

All-cause mortality (Sepsis- mixed focus) – Subgroup based on risk of bias

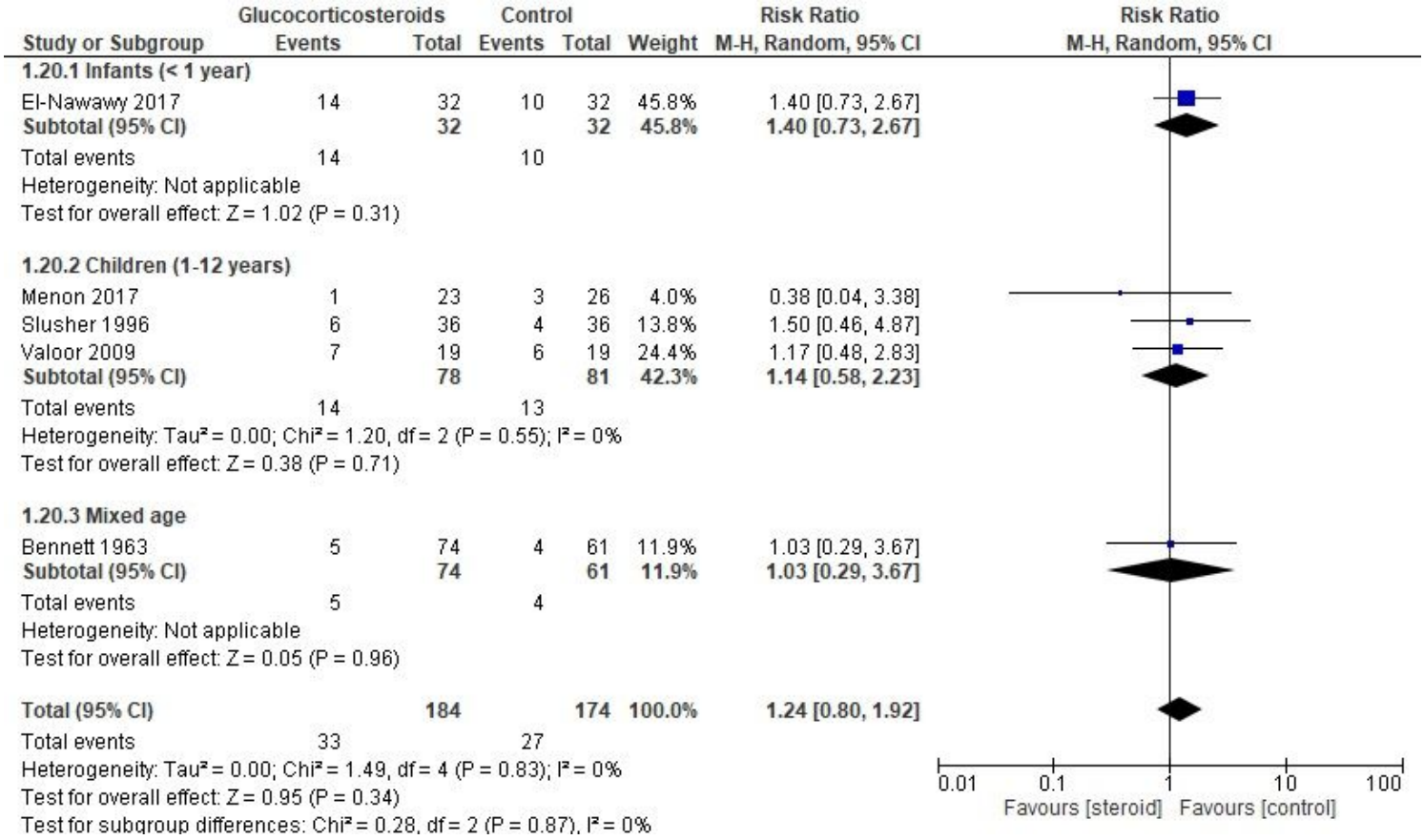


Figure 8

All-cause mortality (Sepsis- mixed focus) – Subgroup based on age

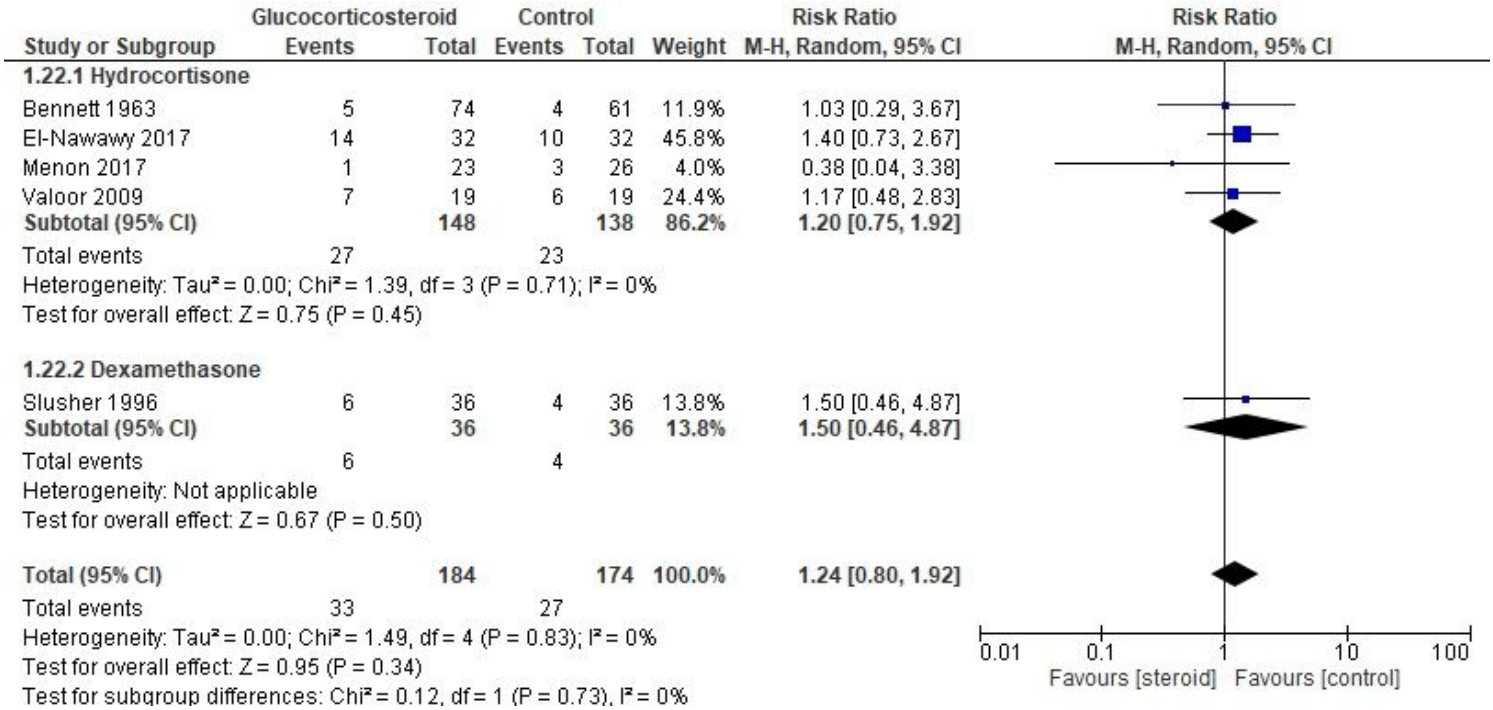


Figure 9

All-cause mortality (Sepsis- mixed focus) – Subgroup based on type of steroid

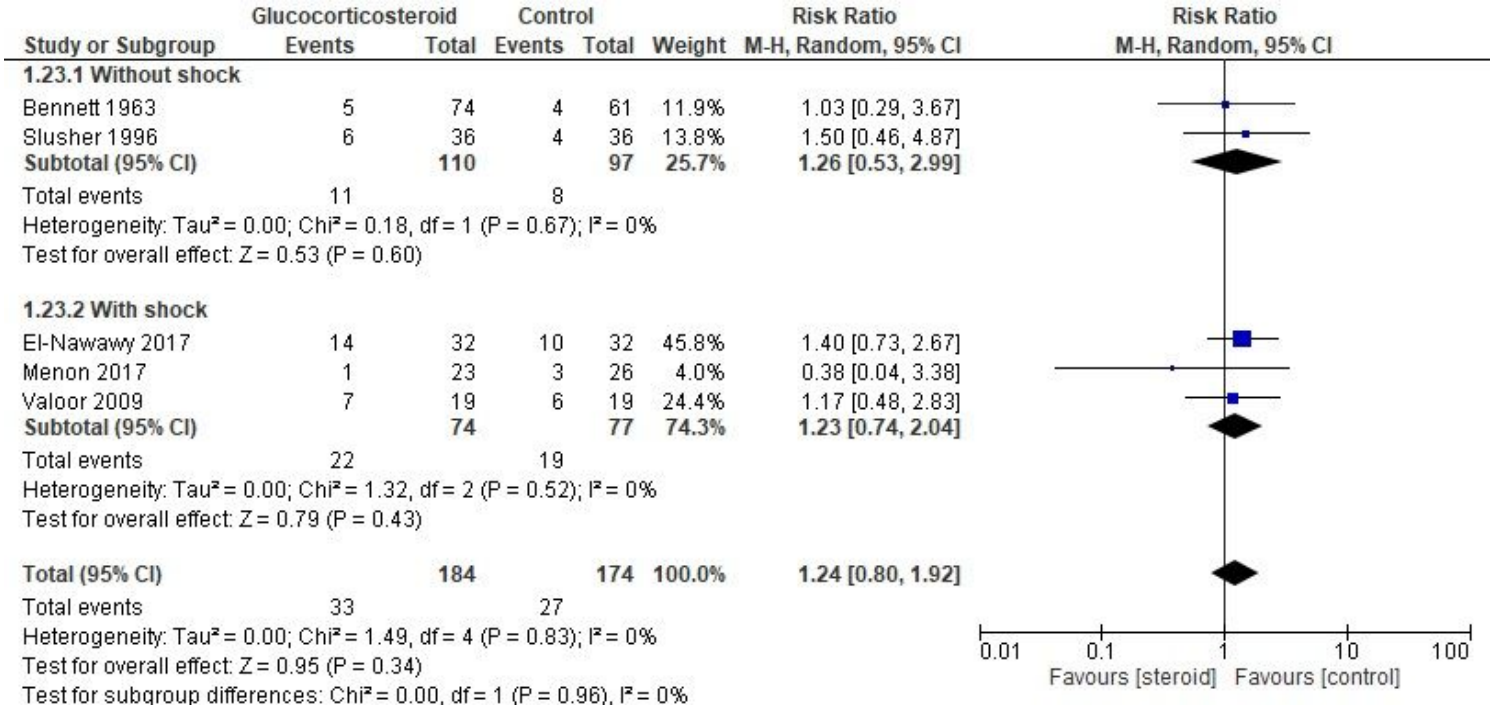


Figure 10

All-cause mortality (Sepsis- mixed focus) – Subgroup based on presence of shock

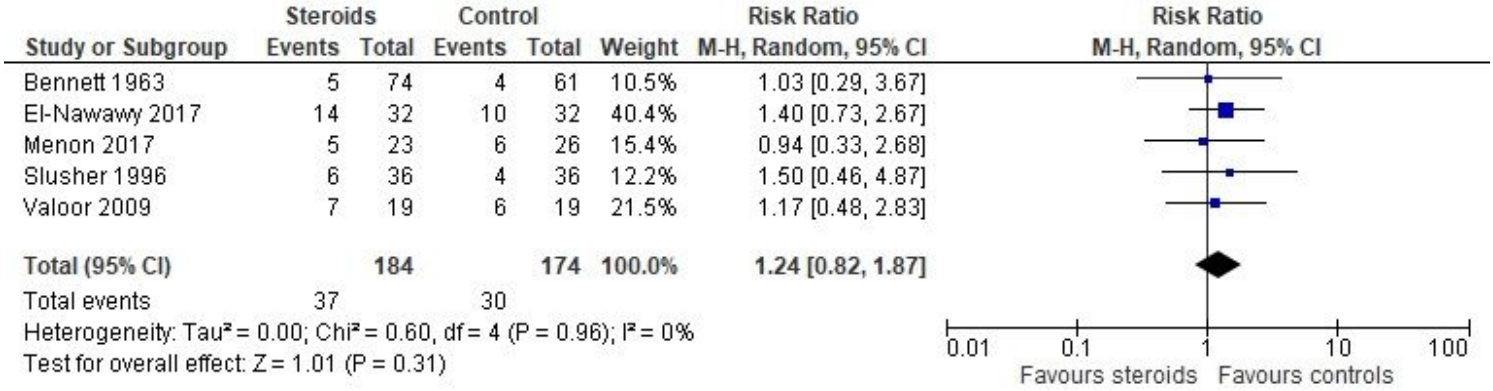


Figure 11

Serious adverse events (Sepsis – mixed focus)

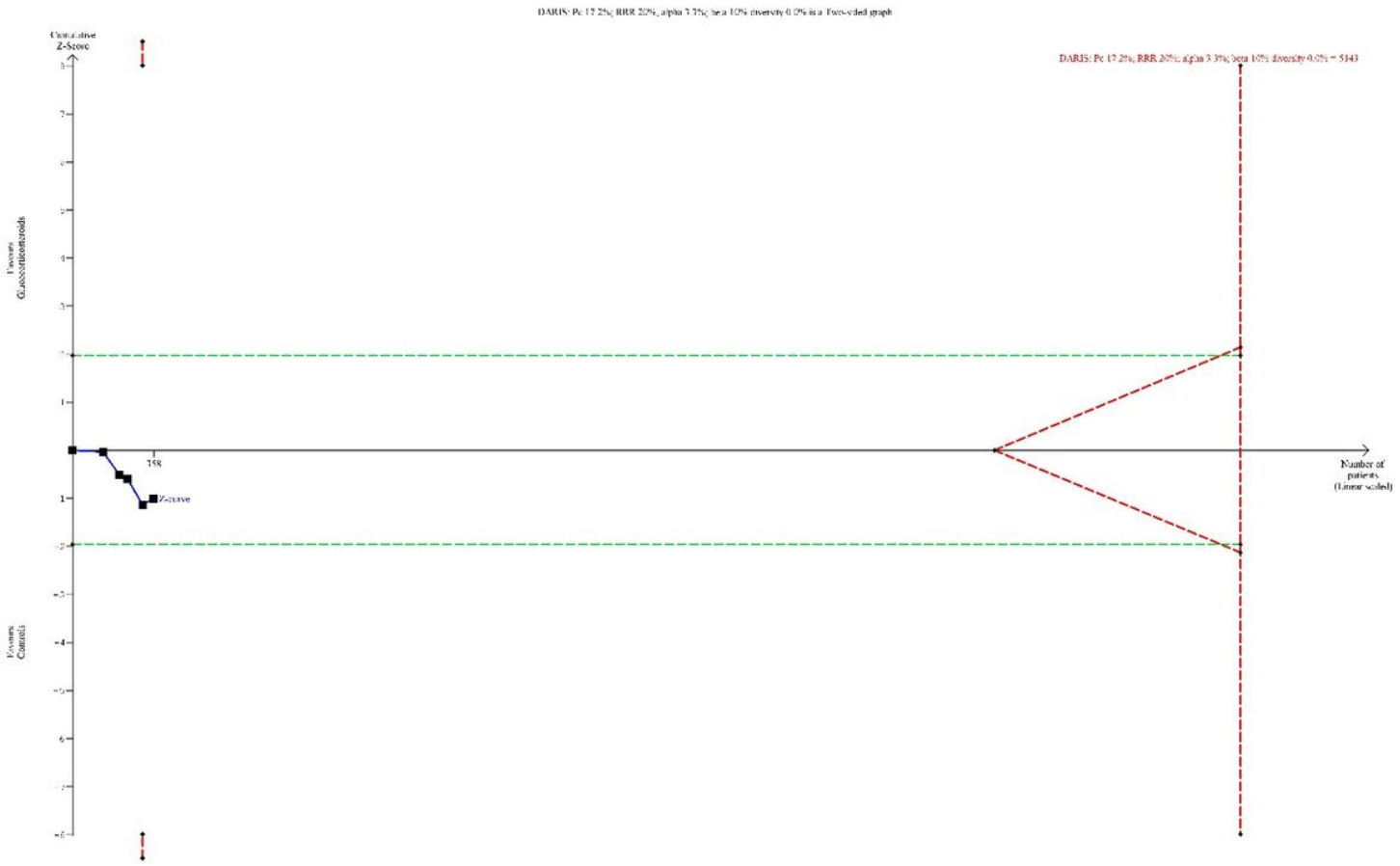


Figure 12

TSA Serious adverse events (Sepsis-mixed focus)

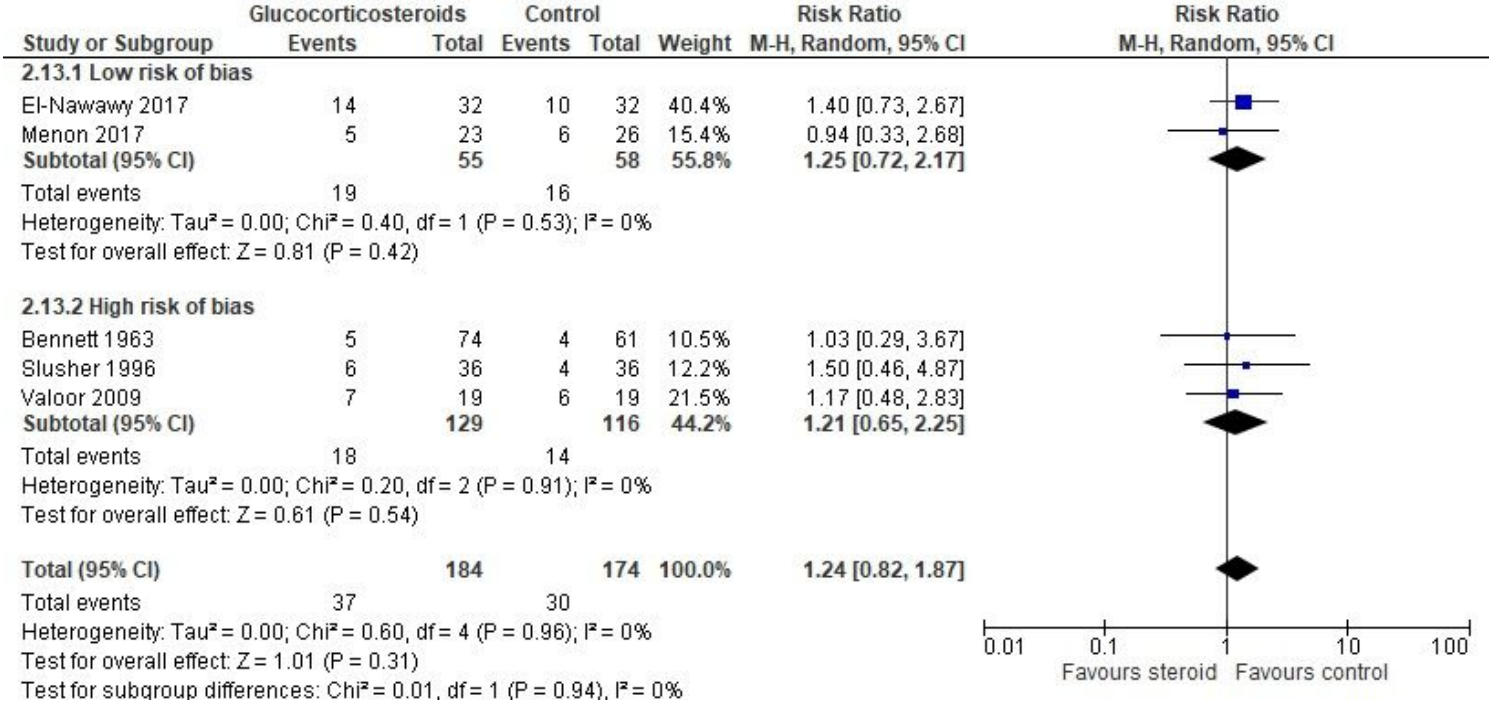


Figure 13

Serious adverse events (meningitis) – Subgroup based on risk of bias

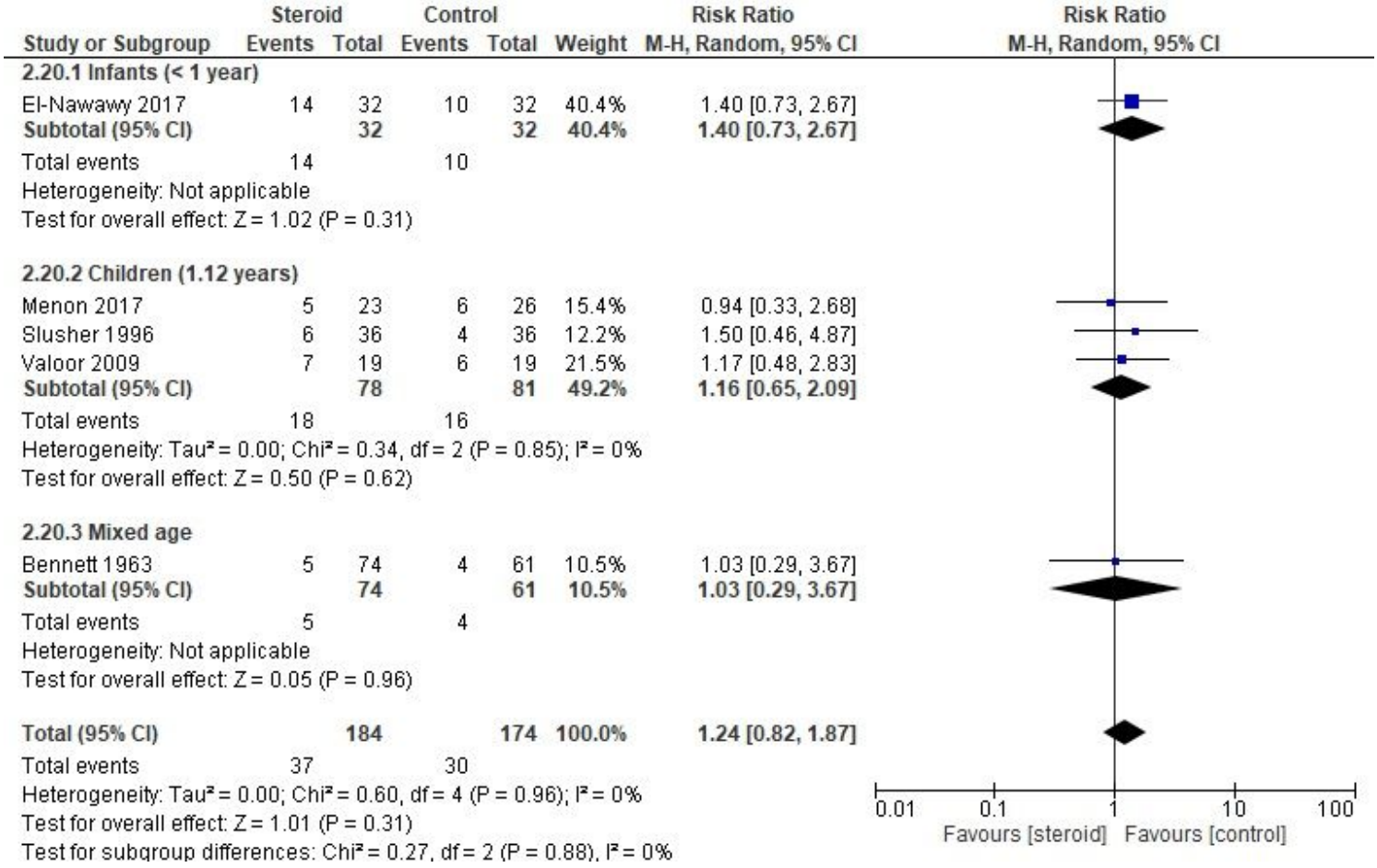


Figure 14

Serious adverse events (Sepsis – mixed focus) – Subgroup based on age

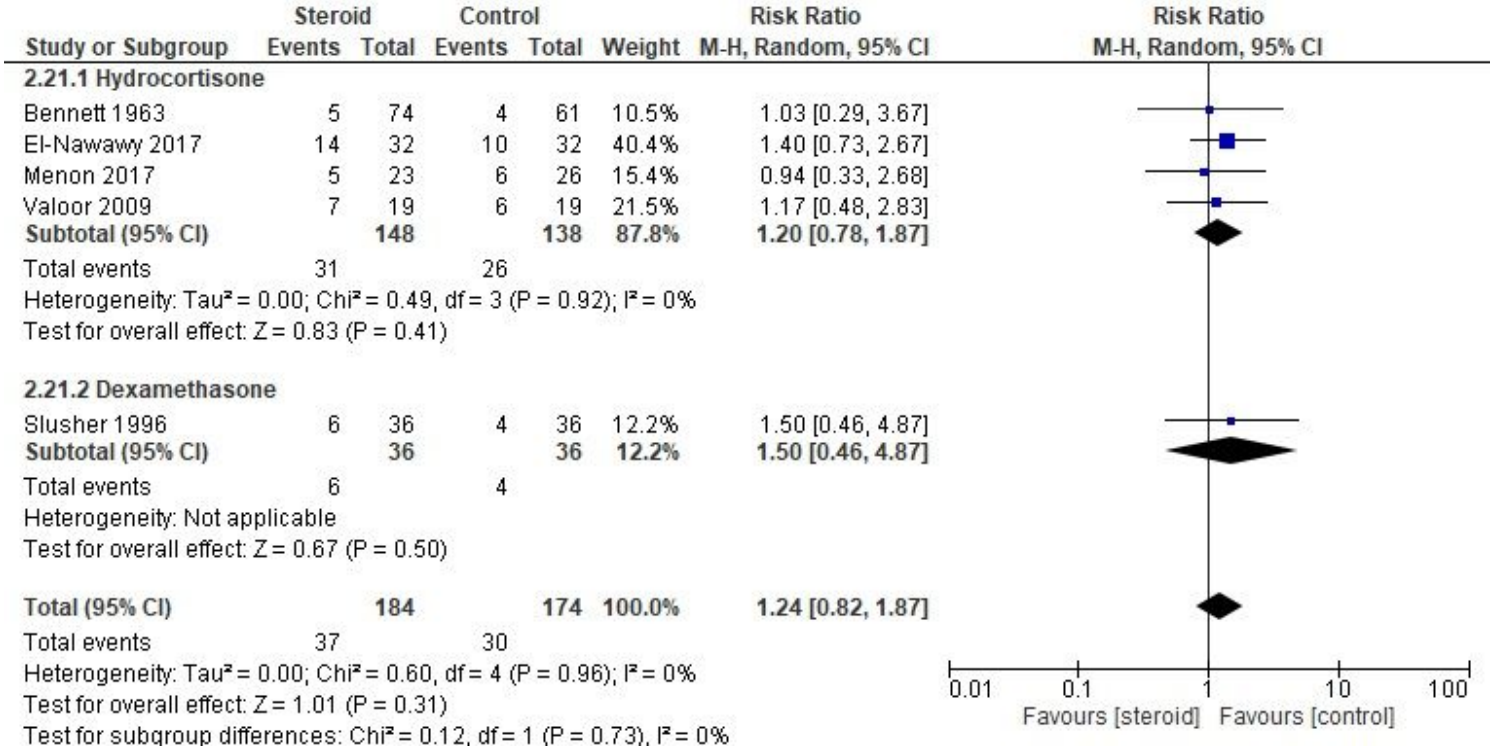


Figure 15

Serious adverse events (Sepsis- mixed focus) – Subgroup based on risk of type of steroid

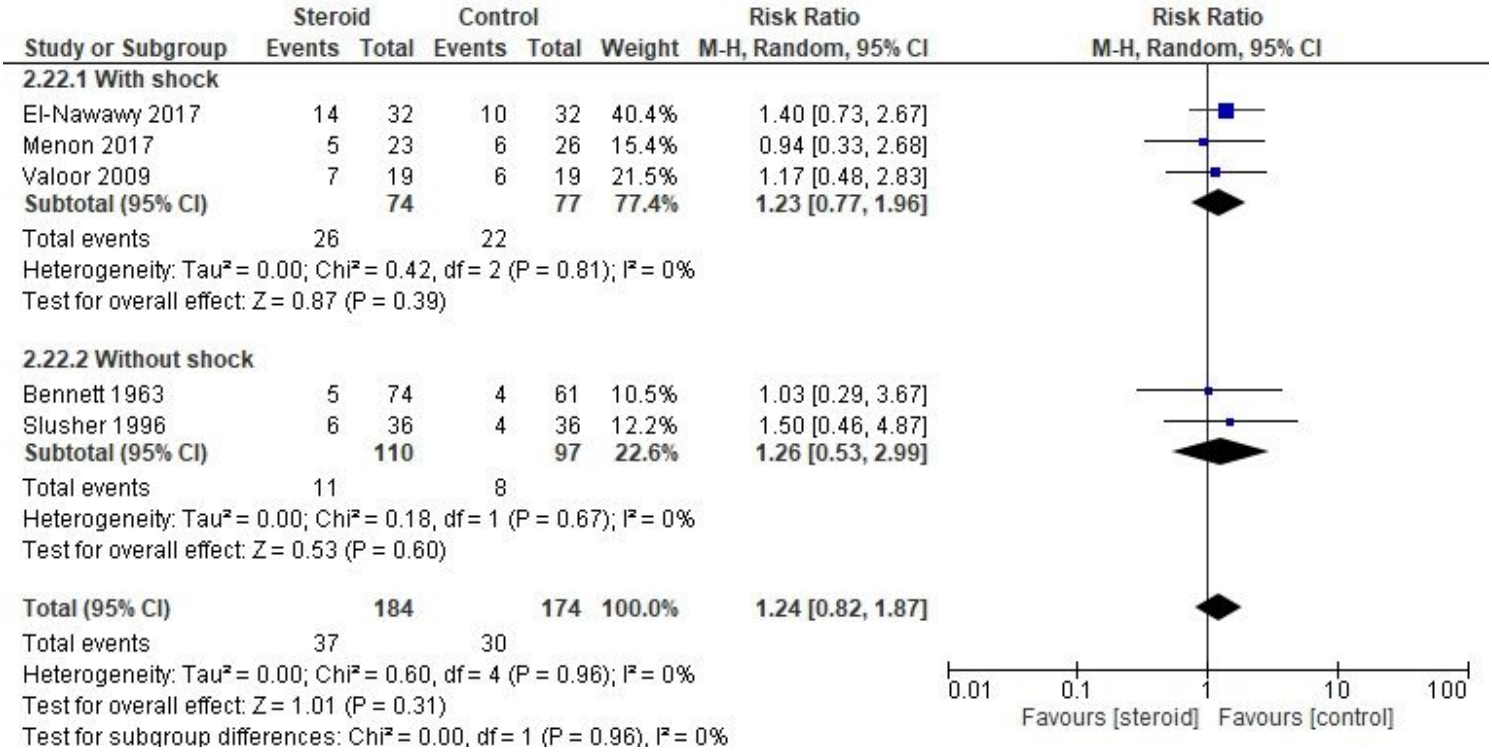
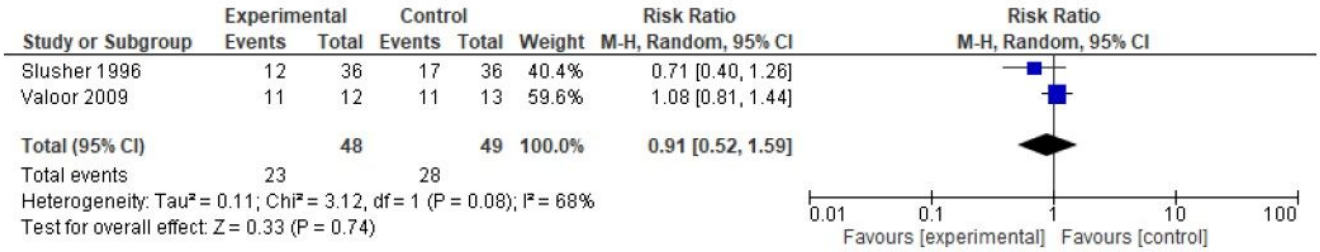


Figure 16

Serious adverse events (Sepsis- mixed focus) – Subgroup based on the presence of shock

A:



B:

Figure 17

Shock reversal (Random effect) mixed focus

Figure 18

Forest plot for adverse events (Sepsis – mixed focus)

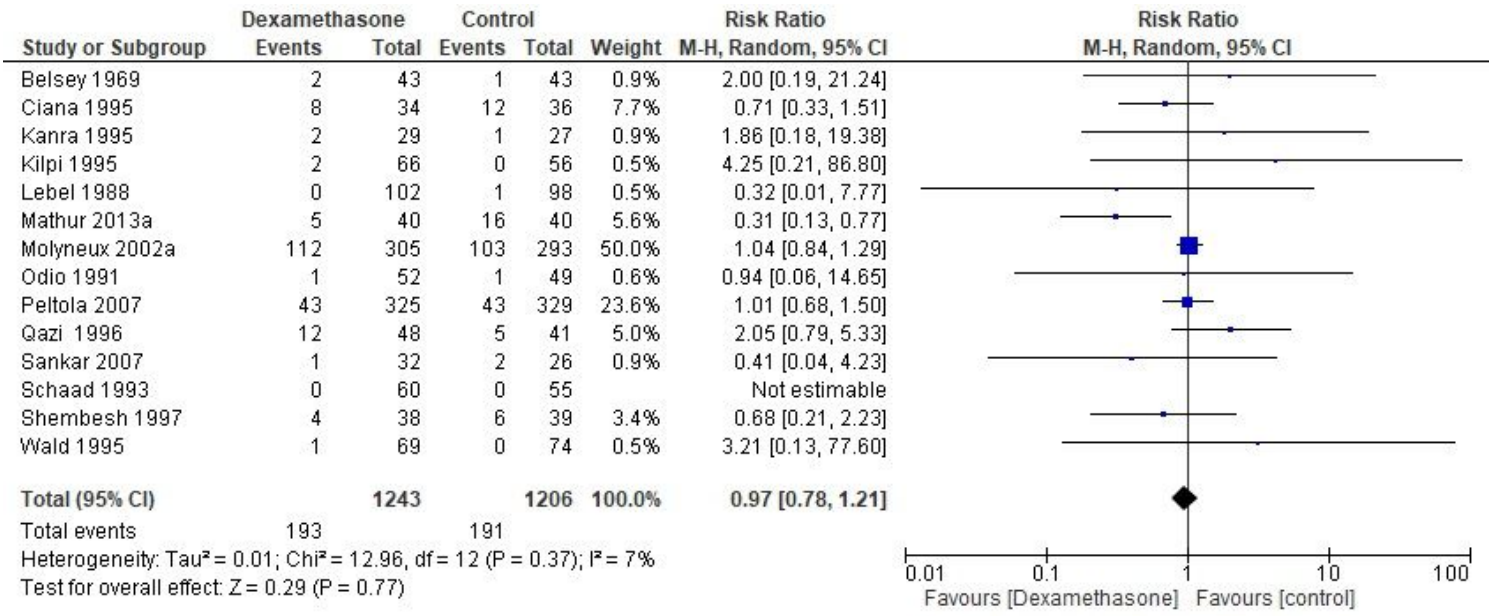


Figure 19

All-cause mortality (meningitis)

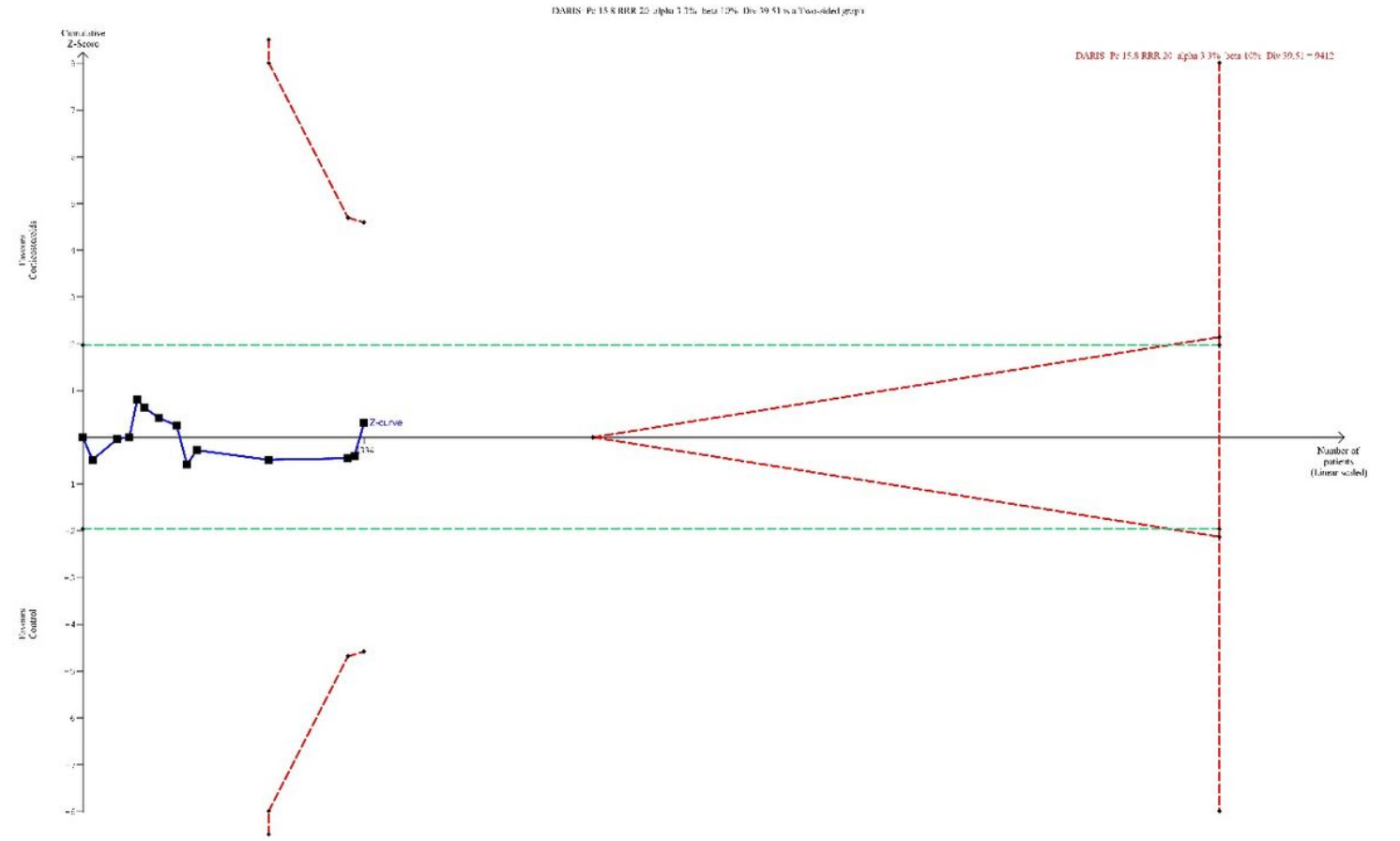


Figure 20

TSA All-cause mortality (meningitis)

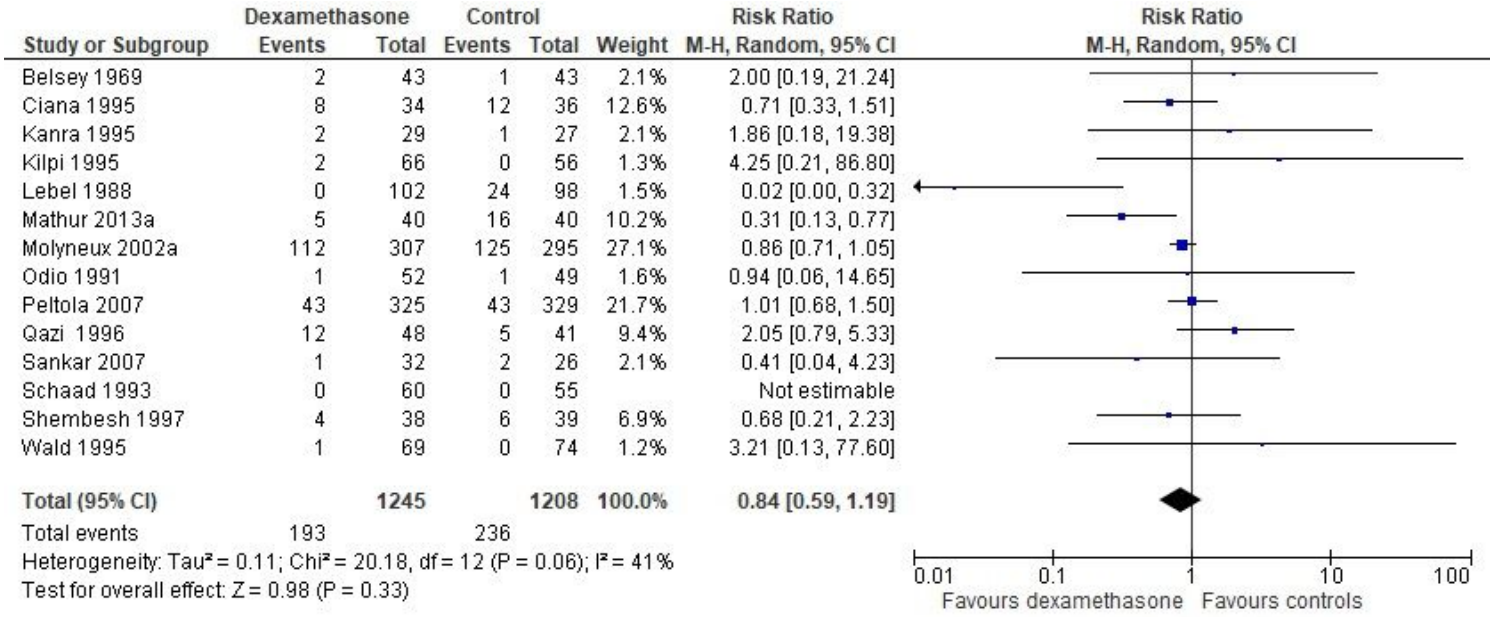


Figure 21

All-cause mortality (meningitis) – Subgroup based on best / worse

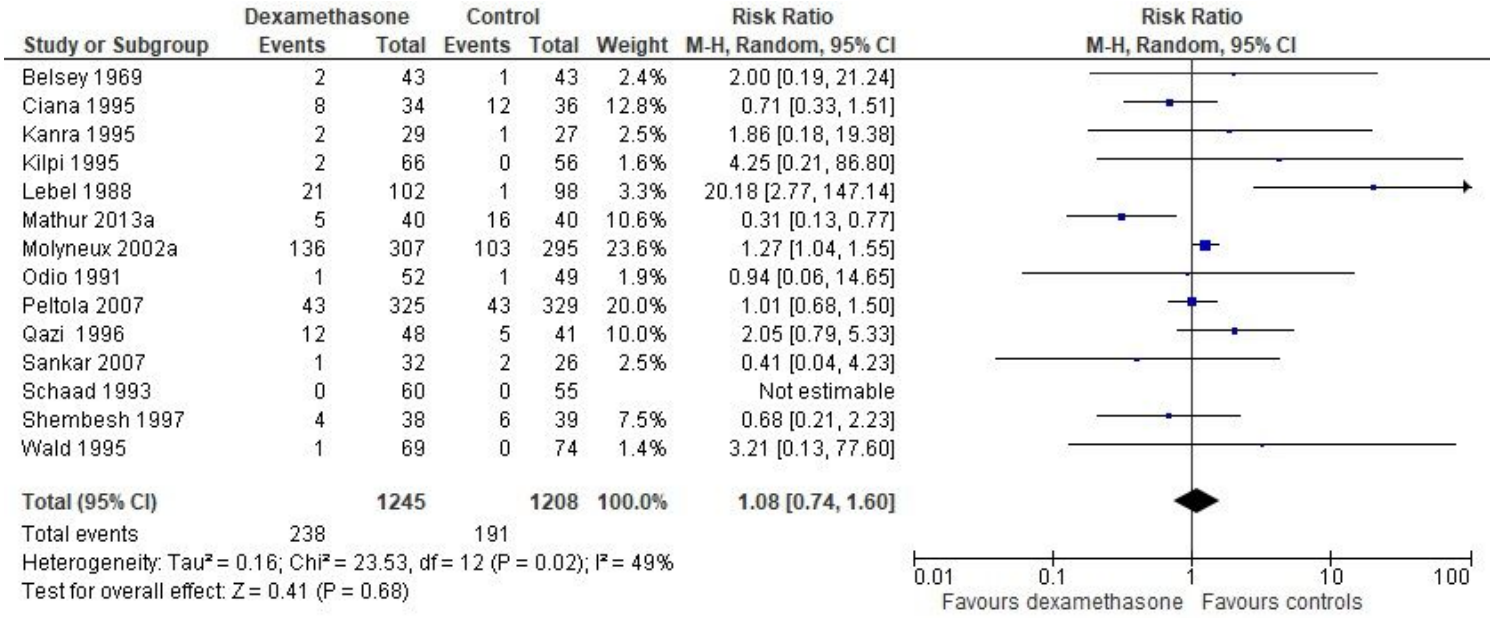


Figure 22

All-cause mortality (meningitis) – Subgroup based on worse - best

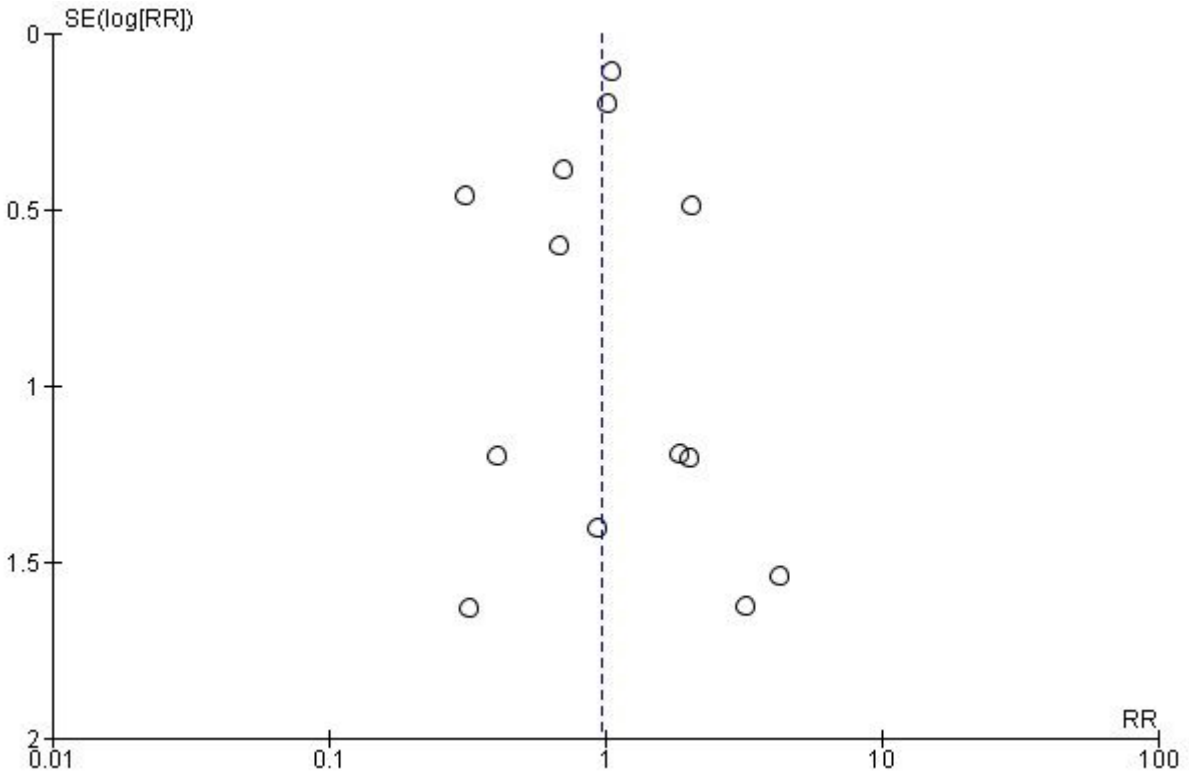


Figure 23

Funnel plot for All-cause mortality (Dexamethasone for meningitis)

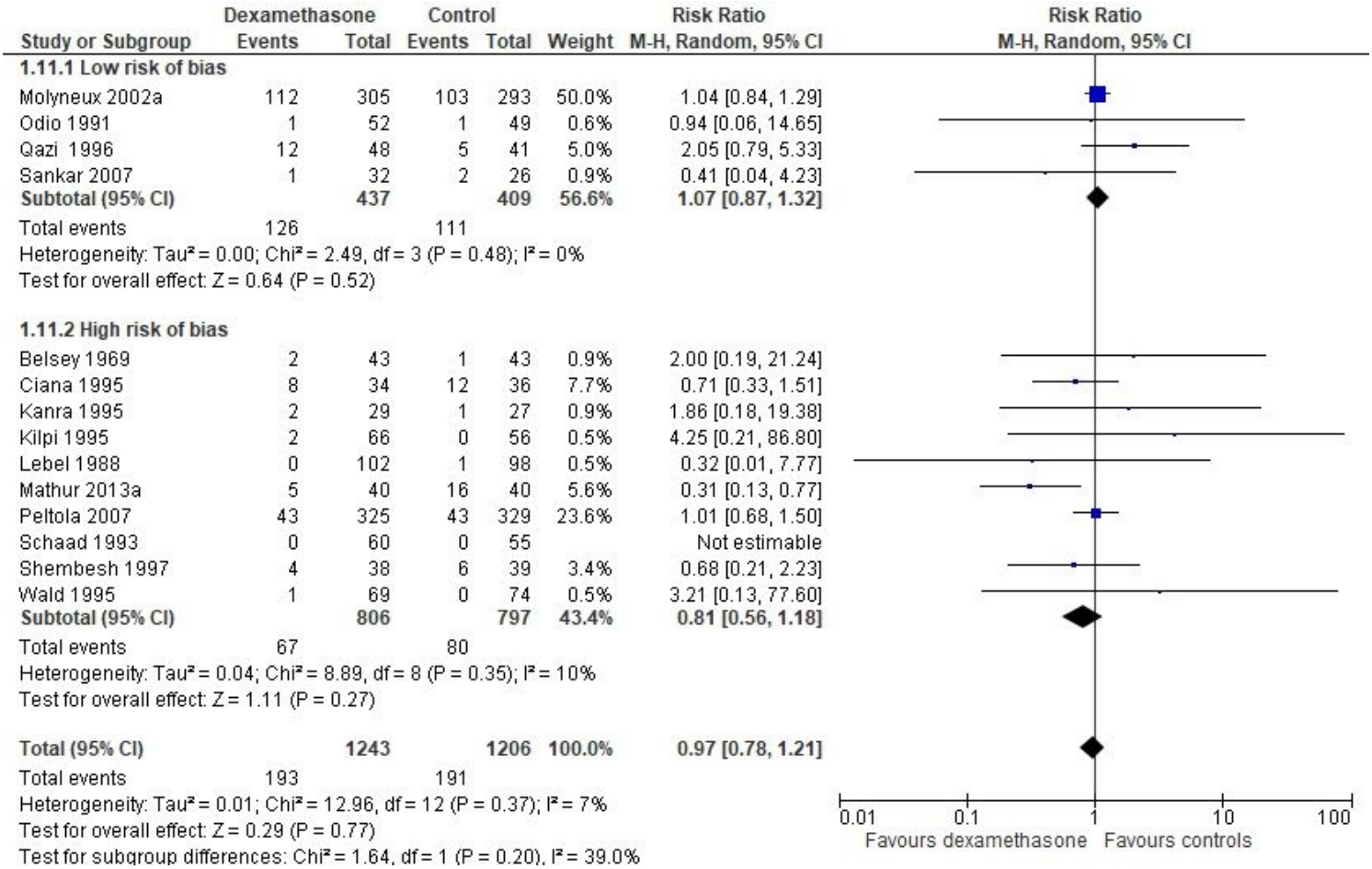


Figure 24

All-cause mortality (meningitis) – Subgroup based on risk of bias

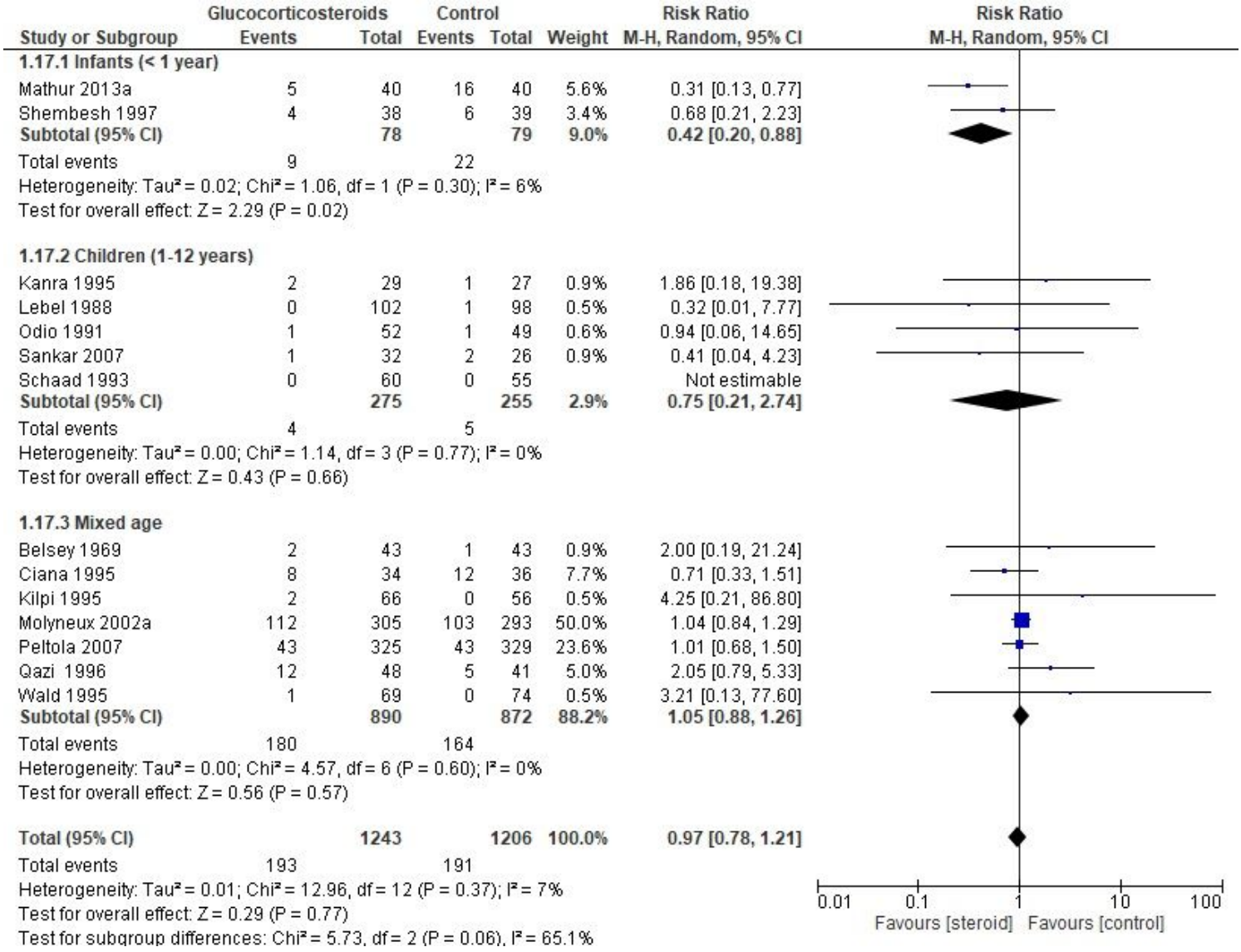


Figure 25

All-cause mortality (meningitis) – Subgroup based on age

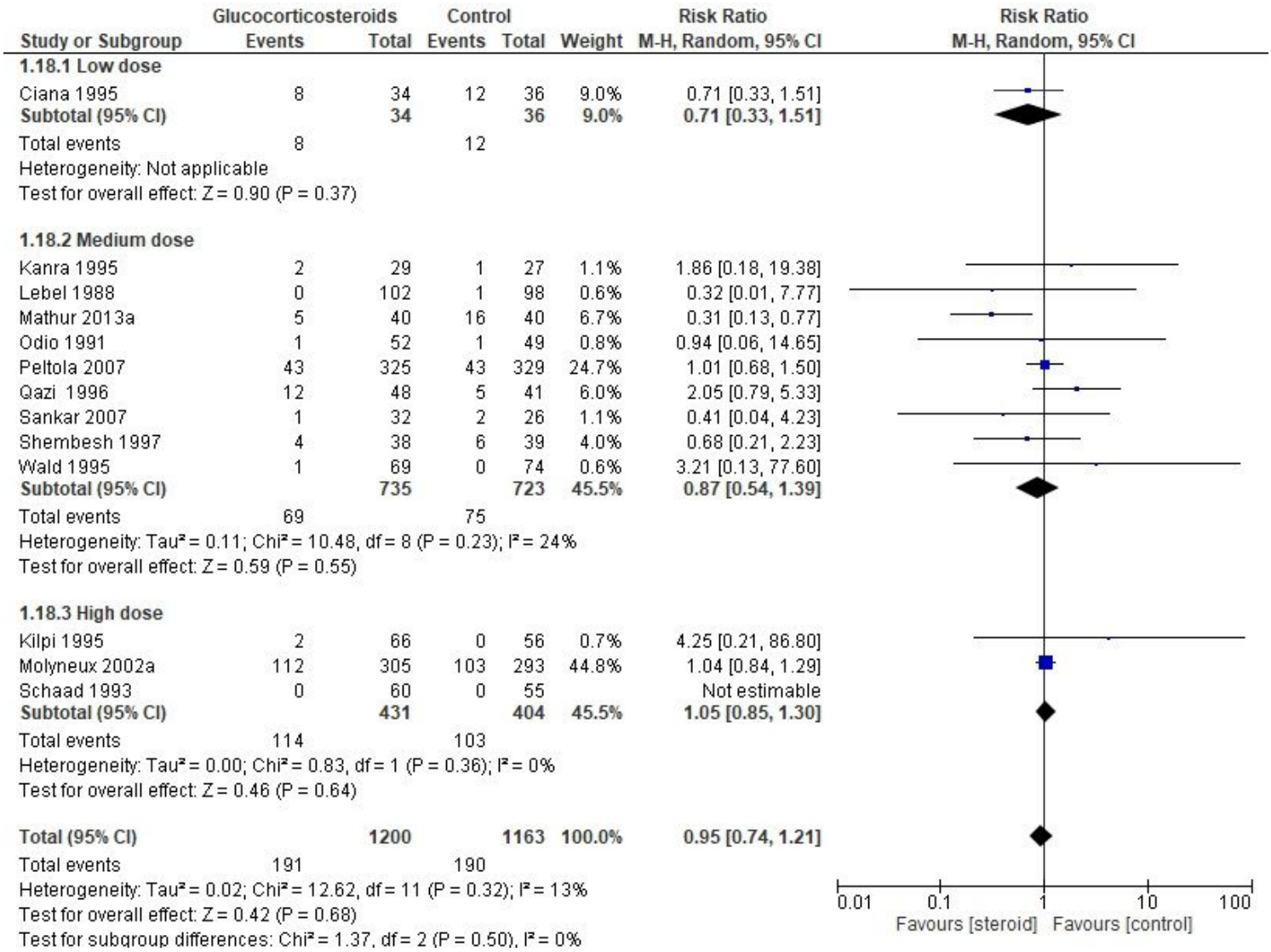


Figure 26

All-cause mortality (meningitis) – Subgroup based on dose

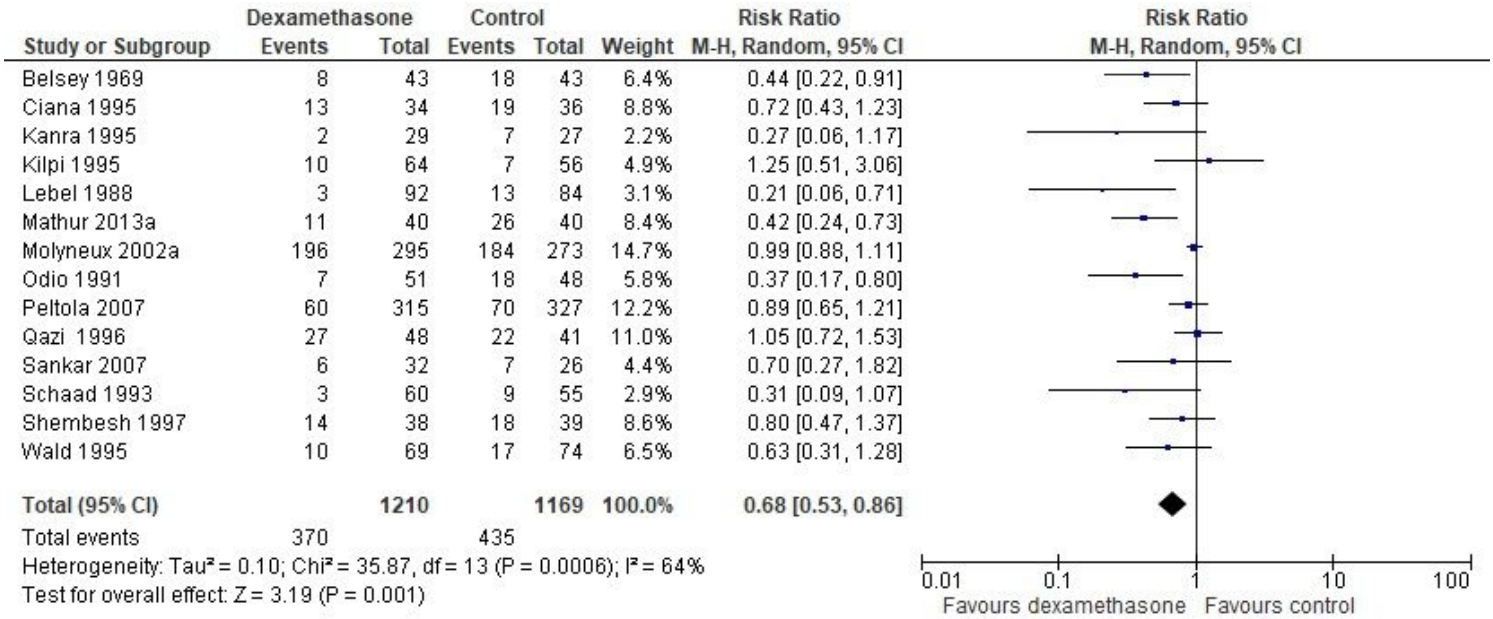


Figure 27

Serious adverse events (Meningitis)

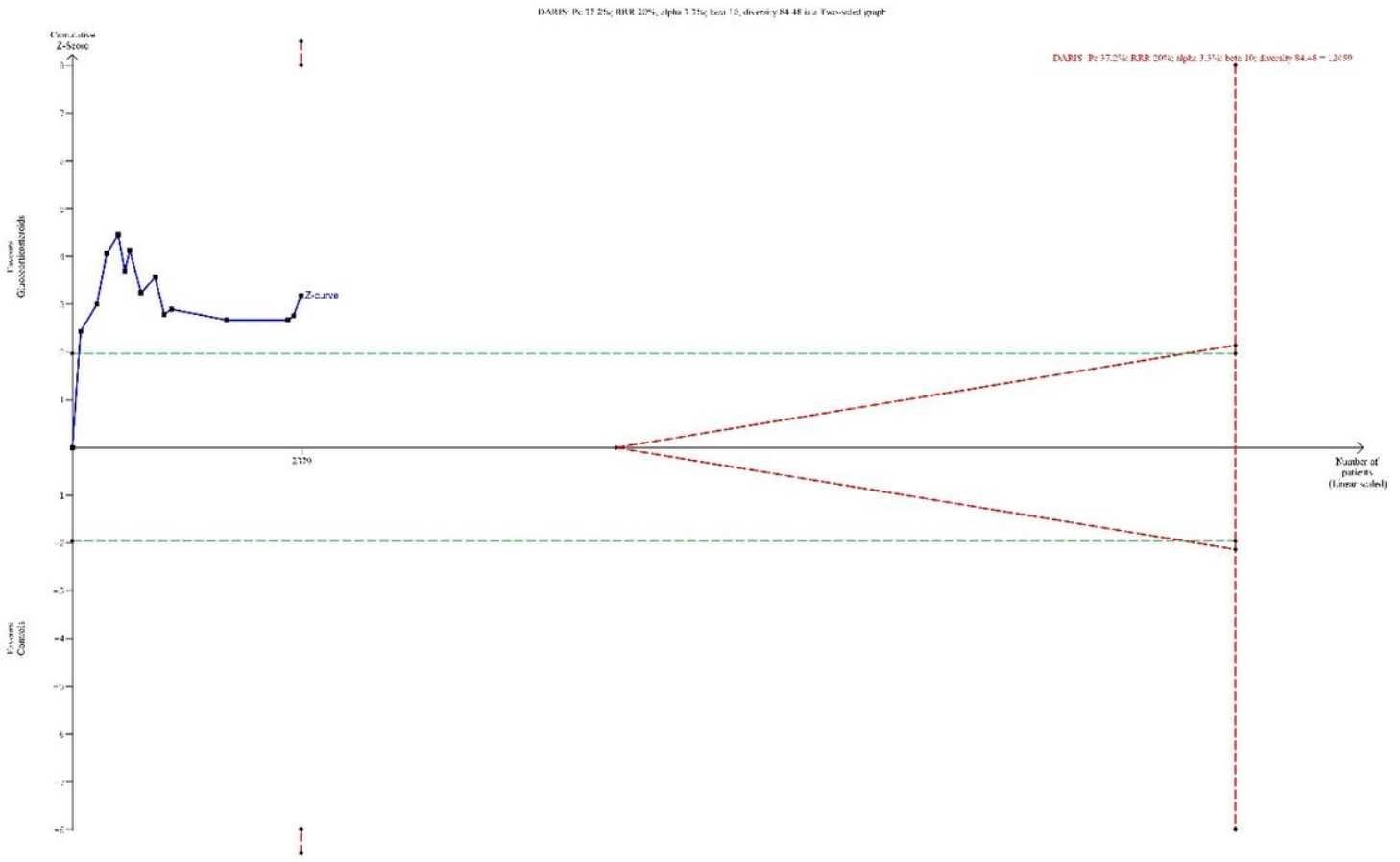


Figure 28

TSA Serious adverse events (meningitis)

Study or Subgroup	Dexamethasone Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Belsey 1969	8	43	18	43	6.6%	0.44 [0.22, 0.91]
Ciana 1995	13	34	19	36	8.7%	0.72 [0.43, 1.23]
Kanra 1995	2	29	7	27	2.4%	0.27 [0.06, 1.17]
Kilpi 1995	10	66	7	56	5.1%	1.21 [0.49, 2.97]
Lebel 1988	3	102	27	98	3.6%	0.11 [0.03, 0.34]
Mathur 2013a	11	40	26	40	8.4%	0.42 [0.24, 0.73]
Molyneux 2002a	198	307	208	295	13.7%	0.91 [0.82, 1.02]
Odio 1991	7	52	19	49	6.1%	0.35 [0.16, 0.75]
Peltola 2007	60	325	72	329	11.7%	0.84 [0.62, 1.15]
Qazi 1996	27	48	22	41	10.7%	1.05 [0.72, 1.53]
Sankar 2007	6	32	7	26	4.7%	0.70 [0.27, 1.82]
Schaad 1993	3	60	9	55	3.2%	0.31 [0.09, 1.07]
Shembesh 1997	14	38	18	39	8.6%	0.80 [0.47, 1.37]
Wald 1995	10	69	17	74	6.7%	0.63 [0.31, 1.28]
Total (95% CI)		**1245**		**1208**	**100.0%**	**0.64 [0.49, 0.82]**
Total events	372		476			

Heterogeneity: Tau² = 0.12; Chi² = 41.15, df = 13 (P < 0.0001); I² = 68%
Test for overall effect: Z = 3.50 (P = 0.0005)

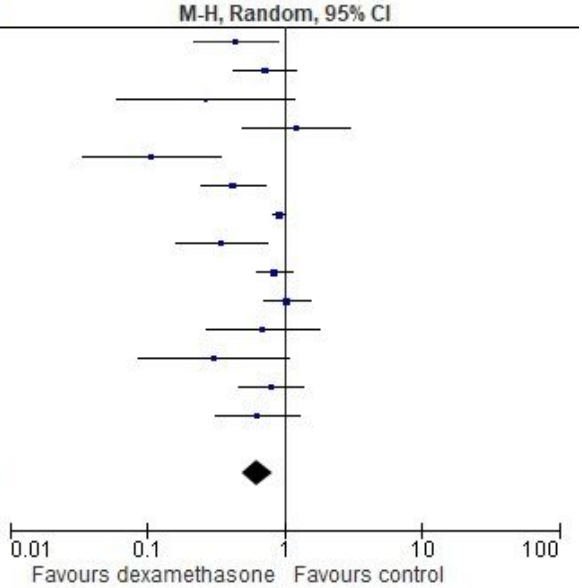


Figure 29

Serious adverse events (Meningitis) – Best-Worst

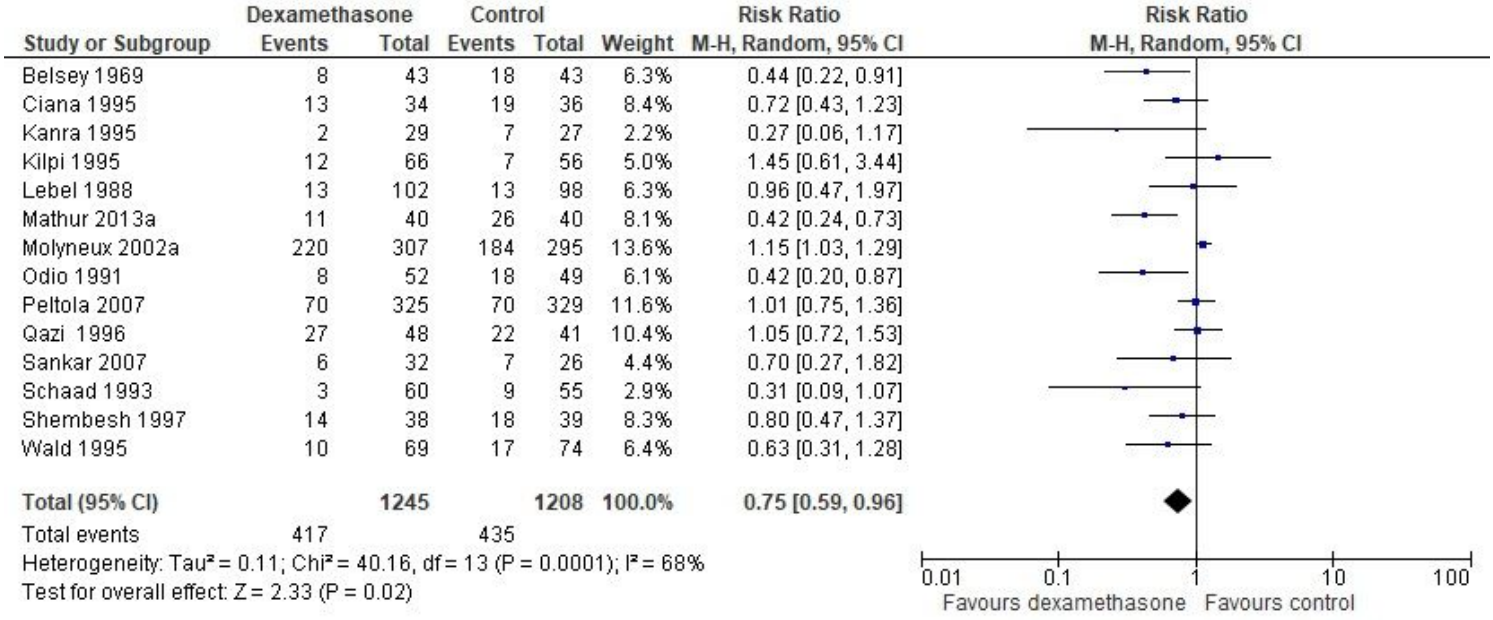


Figure 30

Serious adverse events (Meningitis) – Worst- Best

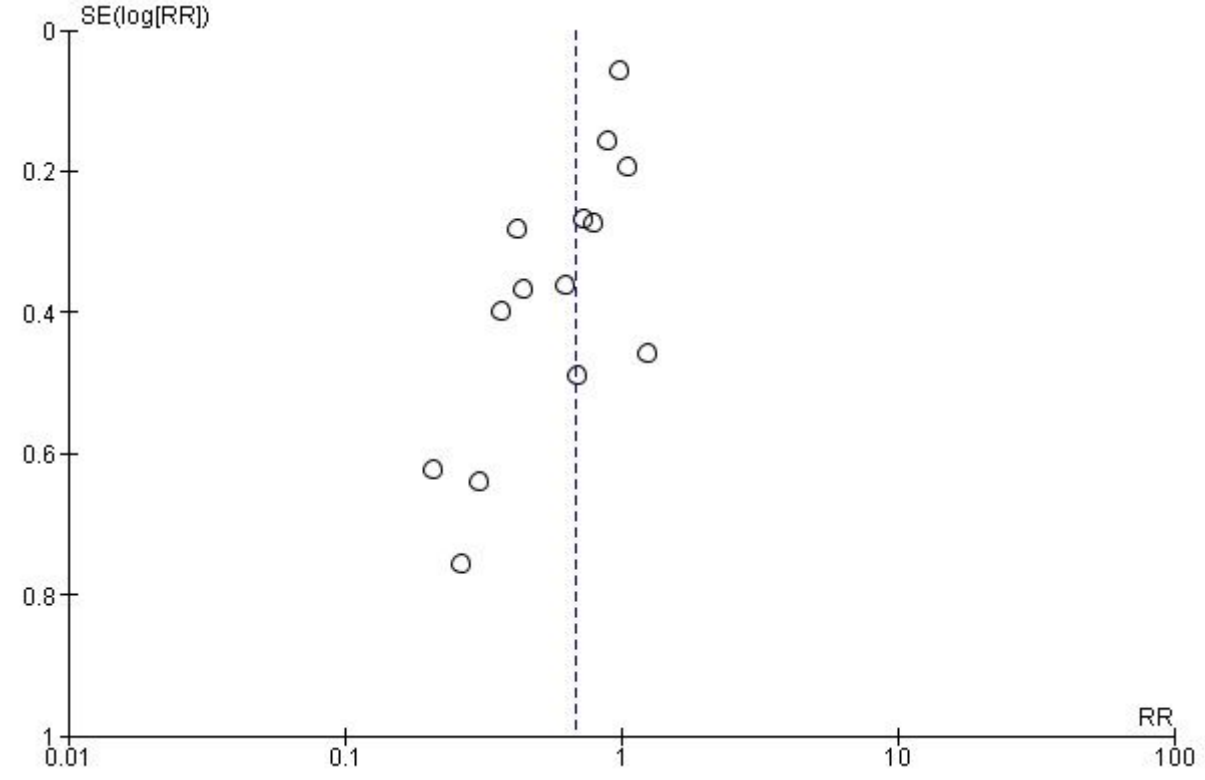


Figure 31

Funnel plot for Serious adverse events (Meningitis)

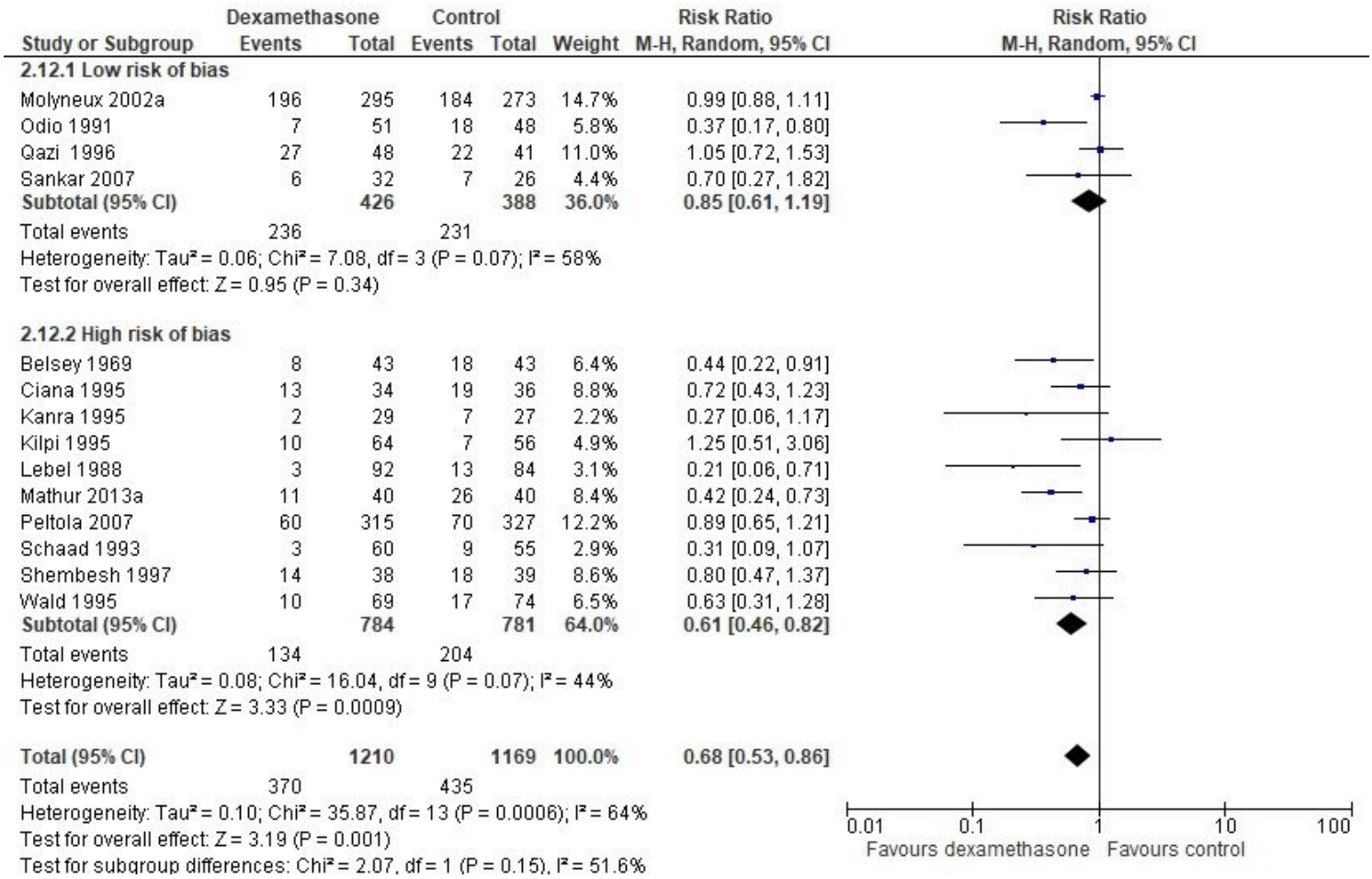


Figure 32

Serious adverse events (meningitis) – Subgroup based on risk of bias

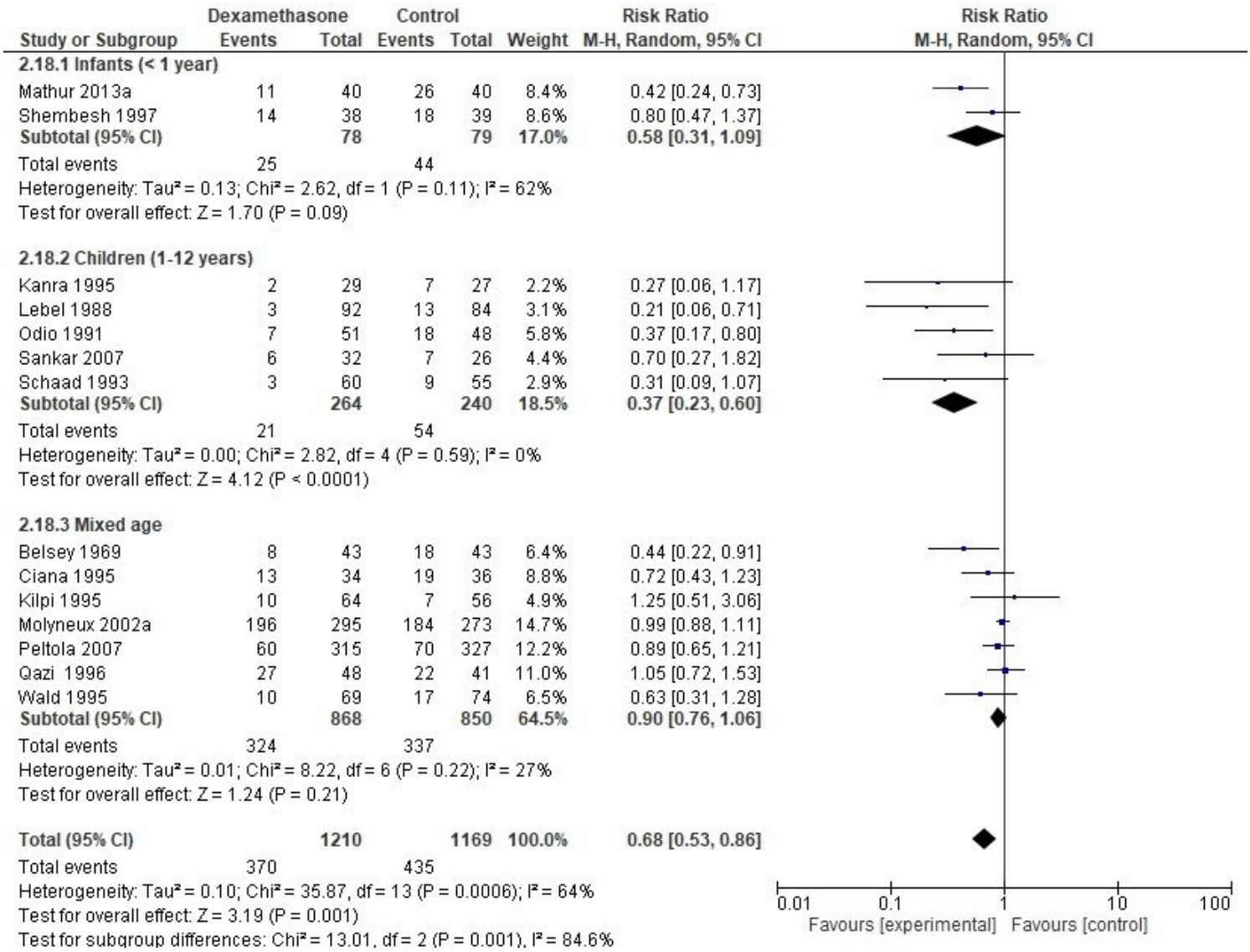


Figure 33

Serious adverse events (meningitis) – Subgroup based on age

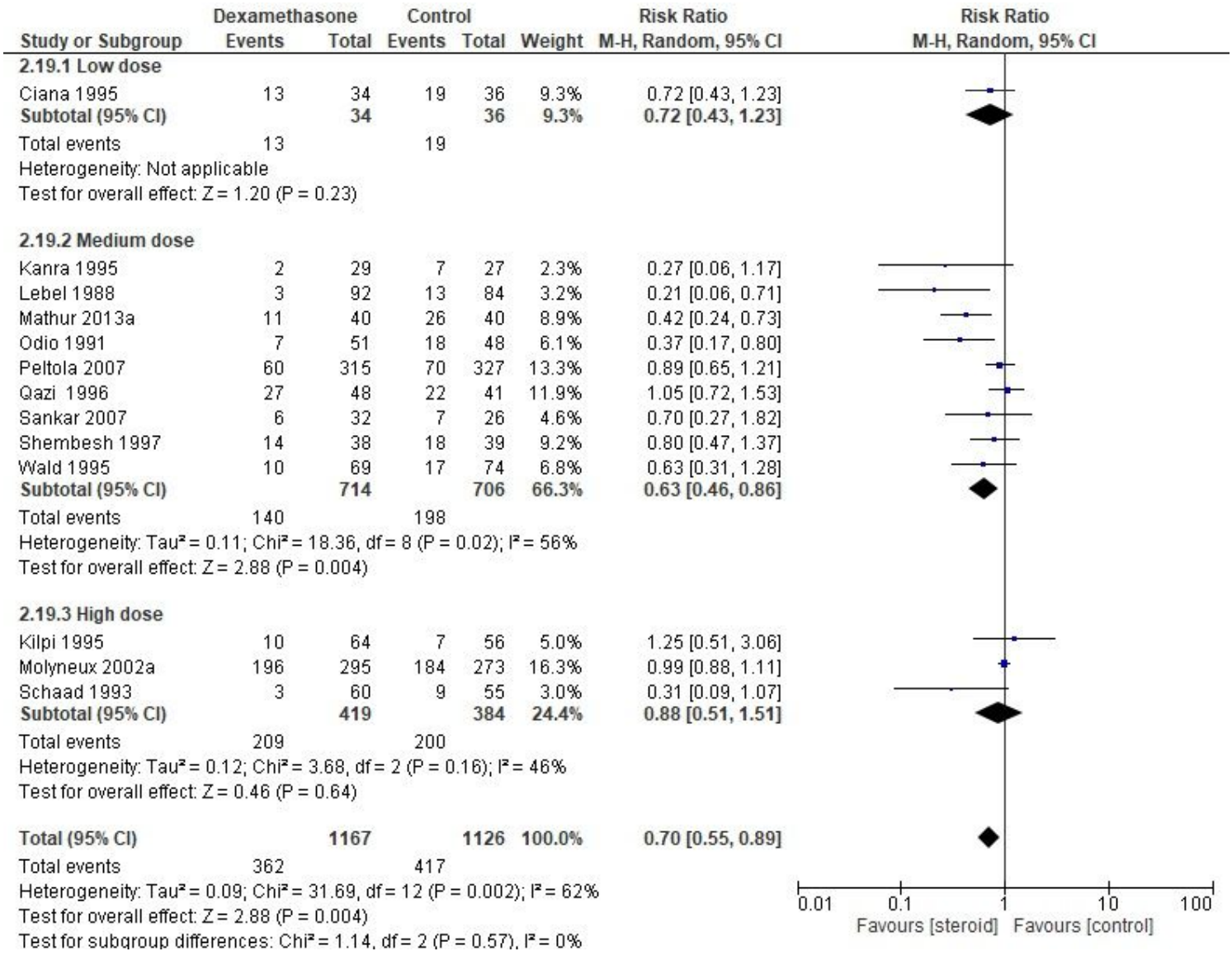


Figure 34

Serious adverse events (meningitis) – Subgroup based on dose

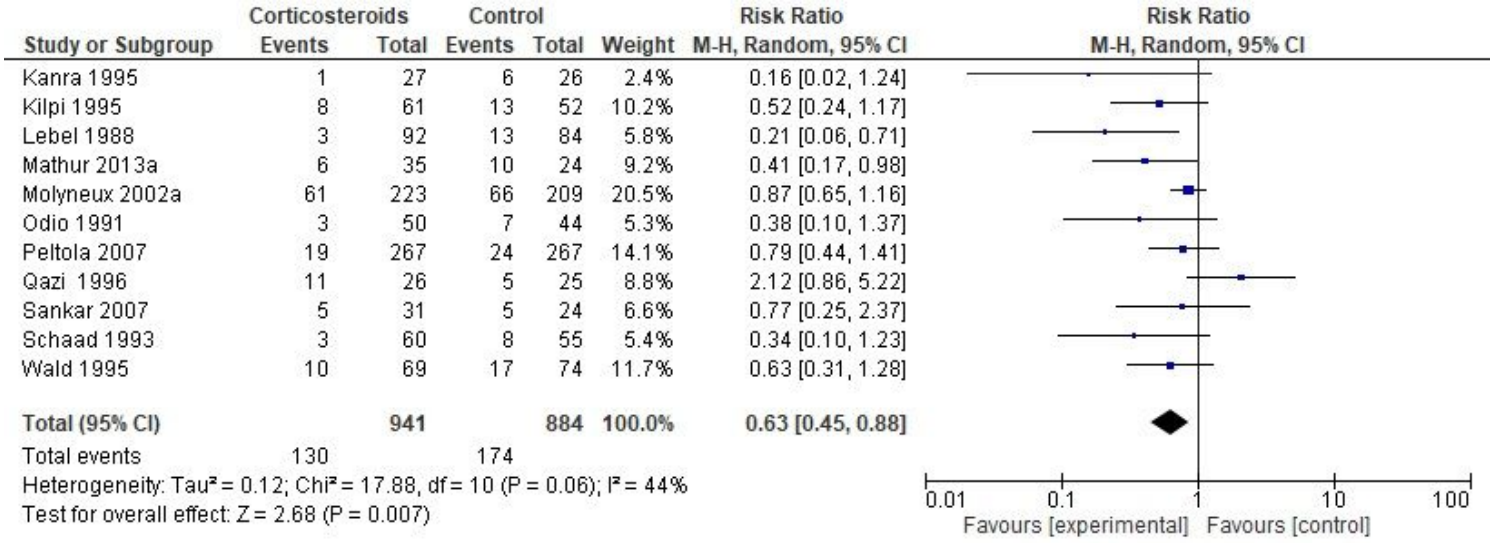


Figure 35

Forest plot of Ototoxicity (Random effects model)

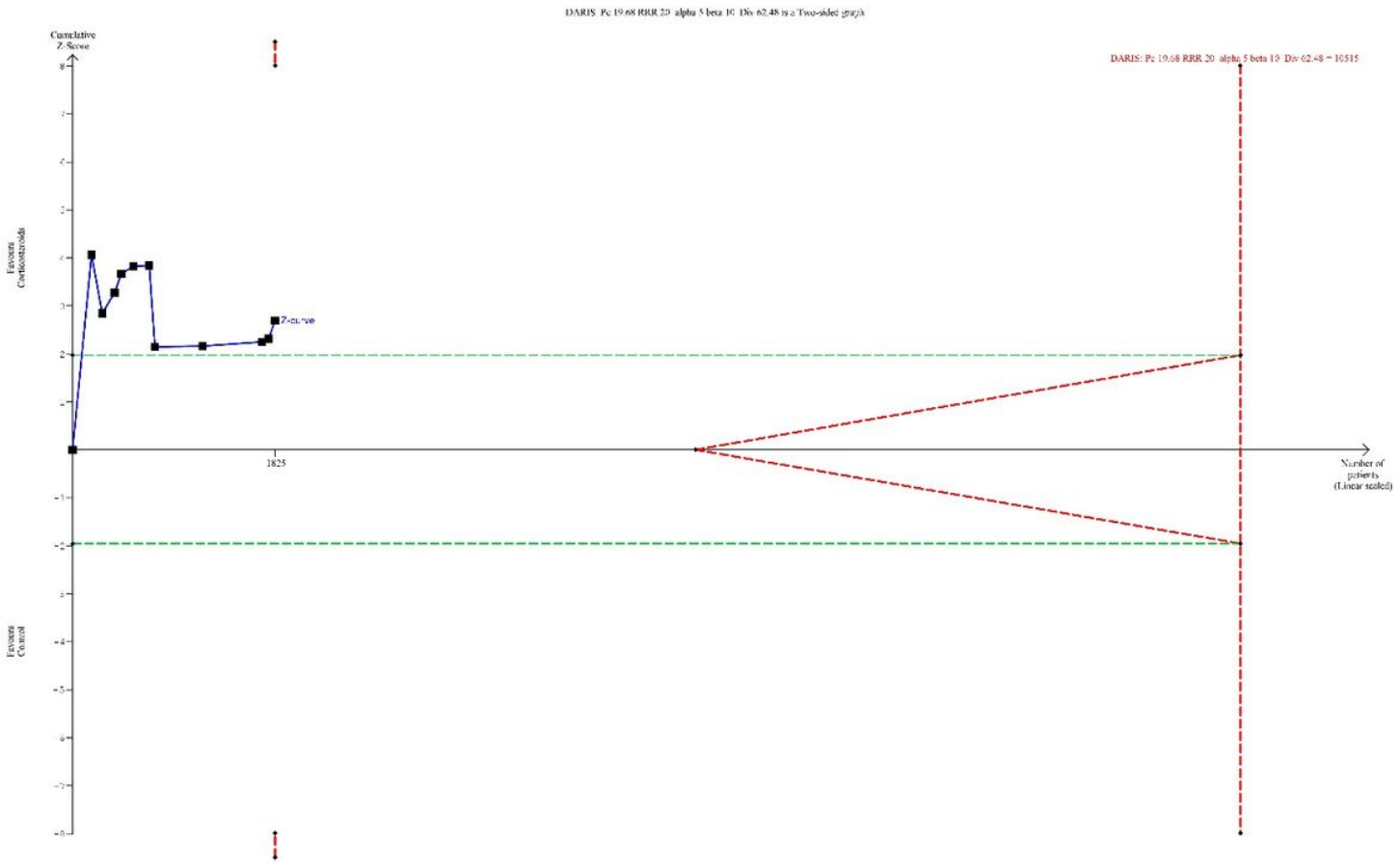


Figure 36

TSA Ototoxicity

Study or Subgroup	Dexamethasone Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Ciana 1995	9	34	6	36	12.5%	1.59 [0.63, 3.99]
Lebel 1988	63	102	34	98	26.9%	1.78 [1.30, 2.43]
Molyneux 2002a	15	40	21	40	21.9%	0.71 [0.43, 1.17]
Qazi 1996	8	48	11	41	14.5%	0.62 [0.28, 1.40]
Wald 1995	31	69	25	74	24.2%	1.33 [0.88, 2.01]
Total (95% CI)		**293**		**289**	**100.0%**	**1.15 [0.76, 1.75]**
Total events	126		97			

Heterogeneity: Tau² = 0.15; Chi² = 12.89, df = 4 (P = 0.01); I² = 69%
Test for overall effect: Z = 0.65 (P = 0.52)

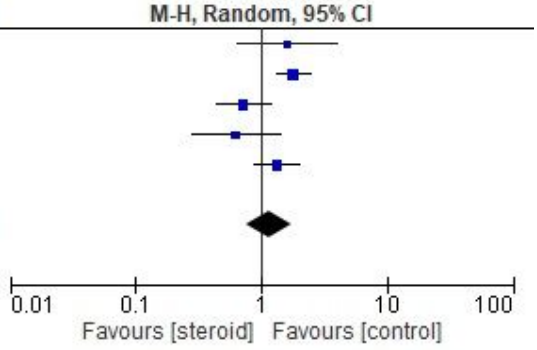


Figure 37

Adverse events (meningitis)

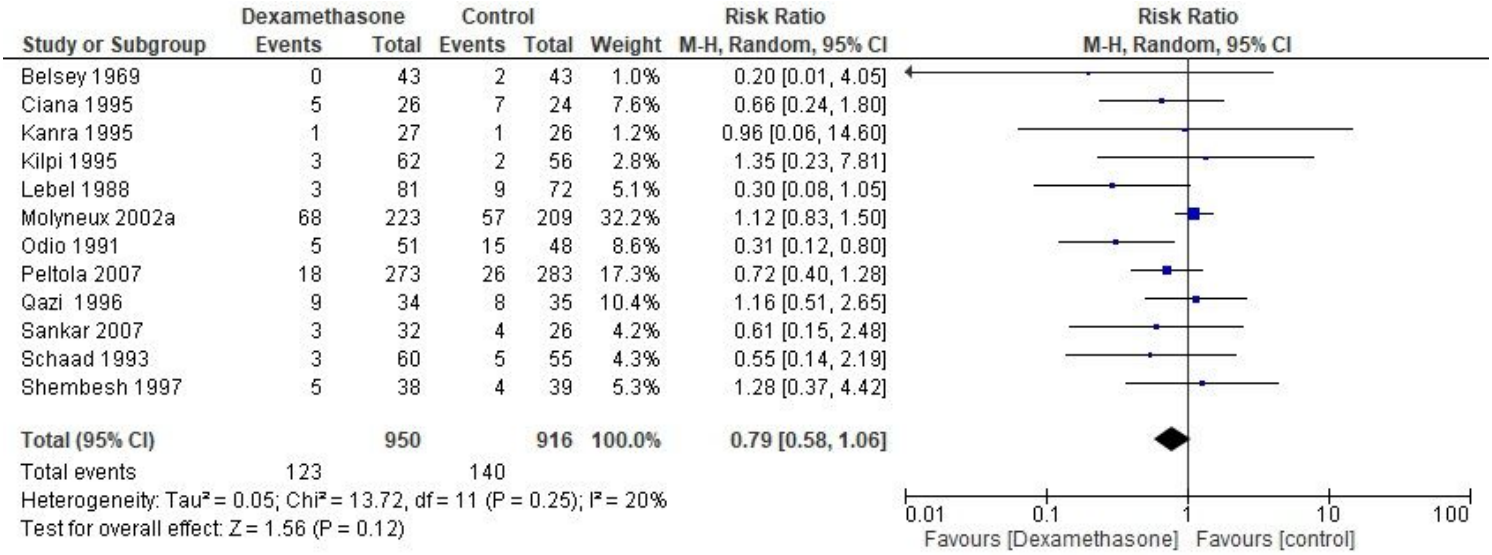


Figure 38

Forest plot of Neurological complications (Random effect)

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- PRISMA2009ChecklistBMC.doc
- SupplementarymaterialSearchstrategies.pdf
- Appendix1.pdf