Antenatal Corticosteroids and Neonatal Outcomes in Twins: A Systematic Review and Meta-analysis

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Short title: Antenatal Corticosteroids in Twins

Precis: Evidence from nonrandomized studies suggests antenatal corticosteroid treatment is associated with lower incidence of neonatal mortality and respiratory distress syndrome in twins.

Abstract

Objective: To assess whether antenatal corticosteroid treatment is associated with improved neonatal outcomes in twins.

Data sources: We searched MEDLINE, PubMed, Embase, and the Cochrane library, from inception through August 12, 2021.

Methods of study selection: Records (n=7,802) were screened in Rayyan by two independent reviewers. We included all nonrandomized studies that compared antenatal corticosteroid treatment vs. no treatment in twins. Our outcomes of interest were neonatal mortality, respiratory distress syndrome, intraventricular hemorrhage, bronchopulmonary dysplasia, necrotizing enterocolitis, periventricular leukomalacia, and retinopathy of prematurity.

Tabulation, integration, and results: We used the ROBINS-I to assess risk of bias. We performed random-effects meta-analyses of estimates from studies without critical risk of bias due to confounding, and reported summary adjusted odds ratios (ORs) and 95% confidence intervals (CIs). Eighteen cohort studies (reporting on 33,152 neonates) met inclusion criteria. Sixteen studies restricted to preterm gestational ages and 11 defined exposed neonates based on an optimal corticosteroid administration-to-birth interval. Limitations due to confounding and selection bias were common concerns for the risk of bias assessments (n=14 at critical or higher), and 11 studies did not account for clustering within twin-pairs in their analyses. All included studies had at least moderate risk of bias. Meta-analysis showed that antenatal corticosteroid administration was associated with lower odds of neonatal mortality (adjusted OR = 0.59, 95% CI = 0.43 to 0.80, I^2 = 69%, five studies, 20,312 neonates) and respiratory distress syndrome

(adjusted OR = 0.70, 95% CI = 0.57 to 0.86, I^2 = 67%, seven studies, 20,628 neonates) in twins. Results were inconclusive for the other outcomes.

Conclusion: Evidence from nonrandomized studies suggests antenatal corticosteroids are associated with lower incidence of neonatal mortality and respiratory distress syndrome in twins.

Systematic Review Registration: PROSPERO, CRD42020205302.

Introduction

Antenatal corticosteroid treatment reduces the incidence of neonatal mortality, respiratory morbidity, and other complications in preterm singleton infants.[1] While twins and higher order multiples are as much as ten times more likely than singletons to be born prematurely,[2] they have routinely been under-represented in randomized trials on antenatal corticosteroids.[1] The most recent Cochrane review of randomized trials on antenatal corticosteroids found subgroup data on multiple gestations from only five trials (884 neonates) and, though effect estimates in multiples were consistent with those in singletons, lacked sufficient power to convincingly demonstrate the effect of antenatal corticosteroids in this group.[1]

Current clinical practice guidelines in the United States and internationally recommend all pregnancies at risk of imminent early-preterm delivery receive antenatal corticosteroids, while also calling for more research focused on multiples.[3–6] However, healthcare practitioners may be more cautious when deciding whether to administer antenatal corticosteroids in multiples.

Future randomized trials on the effect of antenatal corticosteroids in early-preterm twin pregnancies are unfeasible, as practice guidelines recommend treatment at these gestational ages.[3–6] Instead, practitioners may rely on non-randomized studies to inform their recommendations in twin pregnancies at risk of early-preterm delivery. Indeed, in their most recent recommendation, the American College of Obstetricians and Gynecologists cited a 2016 non-randomized study that found an association between antenatal corticosteroids and improved outcomes in twins.[4,7] At the same time, not all non-randomized studies have found an association between antenatal corticosteroids and beneficial outcomes in twins,[8,9] highlighting the need for a comprehensive review of the literature.

We performed a systematic review and meta-analysis of non-randomized studies examining the association between antenatal corticosteroid treatment and adverse neonatal outcomes in preterm twins.

Sources

This study was reported in accordance with PRISMA guidelines.[10] The study protocol was registered prospectively on PROSPERO.[11] Changes to the initial protocol are described in the Appendix 1.

We searched MEDLINE, PubMed, Embase, and the Cochrane library using search terms related to twin pregnancies and antenatal corticosteroids (Appendix 2). We did not search databases of clinical trials (e.g., ClinicalTrials.gov) because our inclusion criteria restricted to non-randomized studies. We included all publications from database inception through August 12, 2021. No language restrictions were applied, non-English abstracts were translated for screening using Google Translate.

Search results were imported into Rayyan (www.rayyan.ai) and duplicates were identified using Rayyan's detect-duplicate feature. Detected duplicates were individually verified by a single reviewer (PS). Titles and abstracts were screened by two independent reviewers (AMG and PS). Full-text of potentially eligible studies were then evaluated by both reviewers independently. Disagreements were resolved by consensus or consultation with a third reviewer (SB).

Study Selection

We included non-randomized studies that compared outcomes among twin neonates that had or had not been exposed to antenatal corticosteroids. No restriction was applied to drug type, dosage, or number of doses.

Our primary outcomes of interest were neonatal mortality and respiratory distress syndrome (RDS), which are strongly linked to antenatal corticosteroid treatment in singletons.[1] Secondary outcomes of interest were other severe neonatal morbidities that have shown a reduction with antenatal corticosteroid treatment in singletons: intraventricular hemorrhage (IVH; grade III or higher), bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC; stage II or higher), periventricular leukomalacia (PVL), and retinopathy of prematurity (ROP; grade III or higher).[1] We also included studies that did not specify or stratify based on severity, but used the high-severity definitions of IVH, NEC, and ROP when possible.

We excluded studies that grouped twins with singletons or higher-order multiple gestations unless the data on twins were reported separately.

Data were extracted in duplicate by two independent reviewers (from AMG, CY, PS, RW) using a standardized data-extraction template. A single reviewer (PS) validated the data by comparing the two independent data extractions and disagreements were resolved by a third review of the data. In the event of missing numerical data (e.g., missing denominators), we contacted the corresponding author by email.

We used the Risk Of Bias In Non-randomised Studies – of Interventions (ROBINS-I)[12] to determine the risk of bias in each study across seven domains: confounding, selection of participants into the study, (mis)classification, deviations from intended treatment, missing data, measurement error, and reporting. The "overall" risk of bias (low, moderate, serious, or critical) was assigned based on the highest risk category across all domains. Two reviewers (AMG and PS) independently assessed each study, and any disagreements were resolved by consensus or consultation with a third reviewer (SB). We visualised the risk of bias assessments using Risk-of-bias VISualization (robvis) tool (mcguinlu.shinyapps.io/robvis). In order to not be rated

critical risk of bias due to confounding, we required that estimates be adjusted for a minimum of a week- or day-based estimate of gestational age at delivery (e.g., using a regression-based adjustment). Studies that only performed a crude adjustment for gestational age, by restricting to infants born before a certain gestational age (e.g., infants born at <34 weeks gestation), were rated as critical risk due to residual confounding (see directed acyclic graph [DAG] in Appendix 3). We recognize that adjusting for gestational age at birth could bias results under certain scenarios (DAG in Appendix 4).[13] However, we propose the risk of bias from adjusting for gestational age at birth is minimal compared with the risk of bias from not adjusting on any measure of gestational age, as gestational age at birth has such a strong influence on infant outcomes.

We synthesized adjusted summary estimates of studies without critical risk of bias in confounding (i.e., studies that adjusted for at least gestational age) as the main analysis. When studies included data from the same source, we excluded the smaller study. We reported summary adjusted odds ratios (ORs) and corresponding 95% CIs for all outcomes in forest plots. We performed all meta-analyses with random-effects models using restricted maximum likelihood method and assessed heterogeneity using I^2. Larger weights were given to more precise (larger) studies.

To further explore the sources of heterogeneity, we performed subgroup analysis stratifying by whether clustering between twin pairs from the same pregnancy was considered, as failure to account for non-independence between twin pairs can cause variance estimates to be artificially low.[14] In addition, we also reported crude ORs for our two primary outcomes (neonatal mortality and RDS) as a sensitivity analysis, using odds (vs. measures of risk) for consistency with the adjusted analyses. To explore treatment effect over time, we performed

post-hoc cumulative meta-analyses for the primary outcomes based on the median value of study period. For all outcomes with five or more studies, we created contour-enhanced funnel plots to assess potential publication bias.[15]

All analyses were performed in Stata version 16.1.

Results

Of the 7,802 records screened, 18 studies **(**reporting on 33,152 neonates) met our inclusion criteria (Appendix 5).[7–9,16–30] Study characteristics are summarized in Table 1. Detailed characteristics are presented in the Supplement (Appendix 6.1-8).

All but one study restricted their analyses to preterm infants (Table 1). Other common inclusion criteria included: admission to the NICU, low birthweight, no chorioamnionitis, no major anomalies, and no twin-to-twin transfusion syndrome (Appendix 6.2). Of the studies that specified the type of drug, six studies reported on betamethasone only, three on dexamethasone only, and five on both betamethasone and dexamethasone (Appendix 6.3). The most common treatment regimens were two doses, 12mg, 24 hours apart for betamethasone; and four doses, 6mg, 12 hours apart for dexamethasone (Appendix 6.3). In ten studies, pregnancies or infants were considered "exposed" if they had experienced an ideal treatment-to-birth interval (e.g., first dose more than 48 hours and less than seven days before delivery) and in seven studies no timing was specified (Table 1).

Risk of bias assessments are presented in Figure 1. For bias due to confounding, eight studies[16,17,19,20,22,23,26,29] were considered at critical risk of bias because of no confounder adjustment (beyond restricting the analysis to preterm births, which was applied in all but one study)[26]. Two additional studies[18,24] appropriately adjusted for confounding for RDS (moderate risk of bias) but did not adjust for confounding for other outcomes of interest (critical risk of

bias). One study[30] was at critical and two studies[9,28] were at serious risk of bias due to confounding for improper confounding control (adjusting for mediator or collider). See Appendix 7 for DAGs illustrating examples of bias from adjusting on mediators or colliders.

For bias due to selection of participants, six studies[7–9,19,20,27] were at serious risk from restricting to infants admitted to NICUs (as admission to NICU is related to antenatal corticosteroids and adverse neonatal outcomes). One study[26] included infants admitted to NICUs *and* restricted to very low birthweight infants (<1500 grams), which we rated as moderate risk of selections bias, as the proportion of very low birthweight infants that are admitted to NICUs is close to 1. See Appendix 8 for DAGs illustrating examples of selection bias.

Risk of bias due to classification and risk of bias due to deviations were low for all studies (Figure 1). The degree of missing data was often not reported, or low (Figure 1). Bias due to measurement and reporting was moderate in most studies (Figure 1). Risk of bias due to reporting was serious in two studies, one with inconsistencies in outcomes between methods and results sections,[30] and one which did not report data on mortality because they were not statistically significant.[17]

One study[21] showed results for gestational ages <34 weeks and gestational ages <37 weeks; where applicable, we used the larger group (<37 weeks) in our analysis. Another study[28] stratified their analysis into subgroups of small for gestational age (in Figures: Riskin-Mashiah 2018a[28]) and not small for gestational age (in Figures: Riskin-Mashiah 2018b[28]). We contacted the authors of two studies, to ask for adjusted ORs in order to pool with all other studies[25] and to clarify the proportion of deaths in the control group.[30] At the time of submission, we had not received new data for either study.

Five studies (three at moderate[7,8,27] and two at serious risk of bias[9,28]) reported adjusted ORs for neonatal mortality and were included in the main analysis for neonatal mortality. Meta-analysis showed antenatal corticosteroid administration was associated with lower odds of neonatal mortality (adjusted OR = 0.59, 95% CI = 0.43 to 0.80; I^2 = 69%; five studies, 20,312 neonates; Figure 2). Subgroup analysis showed that antenatal corticosteroid administration had a larger association with a reduction in neonatal mortality in studies accounting for clustering within twins, compared to those not accounting for clustering (adjusted OR = 0.51, 95% CI = 0.41 to 0.63 vs. adjusted OR = 0.89, 95% CI = 0.69 to 1.14; p for interaction < 0.01). We did not stratify by timing of doses or risk of bias because the number of included studies was small.

Sensitivity analyses based on crude ORs from studies reporting on mortality are shown in Appendix 9. The summary crude OR for mortality was similar to the summary adjusted OR in our main analysis, with wider confidence intervals and higher heterogeneity between studies (crude OR=0.65, 95% CI = 0.39 to 1.06, I^2= 95%, 11 studies, 26,669 neonates). Studies that restricted to early gestational ages resulted in odds ratios that were similar to our main findings (crude OR = 0.54, 95% CI = 0.44 to 0.67; Appendix 9), while the study that did not restrict on gestational age at birth was conflicting (5.61, 95% CI = 3.16 to 9.96; p for interaction <0.001; Appendix 9). Cumulative meta-analysis did not reveal changes of treatment effect over time (Appendix 10).

Seven studies reported adjusted ORs for RDS (five at moderate[7,8,18,21,24] and two at serious risk of bias[9,28]), and one study[25] (moderate risk of bias) reported an adjusted RR. Meta-analysis on adjusted ORs showed antenatal corticosteroid administration was associated with lower odds of RDS (adjusted OR = 0.70, 95% CI = 0.57 to 0.86; I^2 = 67%; seven studies, 20,628 neonates; Figure 3). Results from the study that used RRs conflicted with the summary estimate

for RDS: antenatal corticosteroids were not associated with RDS among infants born at 34 weeks' gestation (RR = 1.01, 95% CI = 0.76 to 1.34) and were associated with greater risk of RDS among infants born through 37 weeks' gestation (RR = 1.22, 95% CI = 1.09 to 1.36).[25] Summary crude ORs did not convincingly demonstrate an association between antenatal corticosteroid treatment and RDS (crude OR = 0.87, 95% CI = 0.68 to 1.10; I^2= 90%; 14 studies, 24,459 neonates) (Appendix 11). Cumulative meta-analysis did not reveal changes of treatment effect over time (Appendix 12).

For the other outcomes, antenatal corticosteroid administration was not convincingly associated with any of our secondary outcome of interest: IVH (adjusted OR = 0.78, 95% CI = 0.55 to 1.13; I^2 = 80%; three studies, 12,497 neonates; Appendix 13), BPD (adjusted OR = 1.08, 95% CI = 0.96 to 1.21; I^2 = 0%; five studies, 19,106 neonates; Appendix 14), NEC (adjusted OR = 1.02, 95% CI = 0.83 to 1.25; I2 = 0%; four studies, 19,773 neonates; Appendix 15), PVL (adjusted OR = 0.77, 95% CI = 0.57 to 1.03; I^2 = 56%; three studies, 11,411 neonates; Appendix 16), or ROP (adjusted OR = 0.96, 95% CI = 0.84 to 1.09; I^2 = 0%; four studies, 18,514 neonates; Appendix 17). While heterogeneity was low for BPD, NEC, and ROP (Appendices 14, 15, 17), this was influenced by a single large study[8] contributing the majority of the weight.

There were no obvious indications of publication bias among outcomes with five or more studies, though the low number of studies limited interpretability (Appendices 18-22).

Discussion

Meta-analyses of non-randomized studies showed that antenatal corticosteroid treatment was associated with decreased odds of neonatal mortality and RDS in preterm twins. The number of studies reporting adjusted estimates was small and findings were inconclusive for IVH, BPD, NEC, PVL, and ROP.

Our findings were in agreement with the 2020 Cochrane meta-analyses of randomized trials in multiples (for neonatal mortality, RR = 0.76, 95% CI = 0.57 to 1.02; for RDS, RR = 0.85, 95% CI = 0.61 to 1.20), but with more precise estimates due to a much larger sample size (e.g., for neonatal mortality, 20,312 vs. 813 neonates).[1] Although studies included in the primary analyses involved participant data spanning from 1990s to 2010s, we did not observe changes in treatment effect over time (Appendices 10, 12).

Our results have several limitations. First, included studies were at risk of residual confounding. While adjusting for confounders was more common in more recent studies, there was a general lack of reporting on why specific confounders were selected, and some studies adjusted for mediators and colliders. There was also disagreement between studies on which confounders to adjust for (other than gestational age at birth). Second, some included studies were at risk of selection bias due restricting to infants that were admitted to NICUs. Third, heterogeneity was moderate to high for neonatal mortality and RDS, though studies were generally in agreement on the direction of the effect (protective). One study[25] (that reported RRs) found that exposure to antenatal corticosteroids was associated with increased risk of RDS among infants >37 weeks gestational age, and, had this study been included in the meta-analysis, would have increased between-study heterogeneity. If outcomes among twins from the same pregnancy are not independent, not accounting for this clustering in the analysis will underestimate the study variance.[14] Including studies with underestimated variance in our meta-analysis may partly explain the high heterogeneity, as the individual studies look more dissimilar than they actually are (increasing between-study variance). There were also slight between-study variations in how some outcomes were assessed and defined (Appendix 6.5-7), but not so different that we expected major heterogeneity in the associations. Fourth, timing, dosage, and

number of dosages likely affect the association between antenatal corticosteroids and our outcomes of interest. We did not stratify by specific intervention type or by risk of bias, because the number of studies in each category was small.

Future randomized trials (such as trials in late-preterm pregnancies) should include twins and, importantly, should provide disaggregated estimates in twins. As multiple gestations are relatively uncommon in the general population, they are often under-presented in clinical research. In addition, given the biological differences in singleton and multiple pregnancies, some clinical research only includes singleton pregnancies and excludes multiple pregnancies. As a result, evidence in multiple gestations is sometimes limited and clinical management in these scenarios often relies on evidence from singletons. However, such a translation may not be always appropriate. For instance, evidence on the effectiveness of progesterone on preterm birth prevention has been demonstrated in high-risk singleton pregnancies, but not in twin pregnancies.[31] While randomized trials on the effect of antenatal corticosteroids may not be justifiable in early-preterm twin pregnancies (when guidelines recommend treatment, and the benefit in singletons is strong), there is currently at least one trial underway to assess the impact of antenatal corticosteroids in late-preterm twins (34 weeks through 36 weeks gestation).[32] Though this trial is insufficiently powered to detect a plausible effect size (i.e., one similar to late-preterm singletons[33]), it may be sufficient when synthesized with other trials that include disaggregated data on late-preterm twins.

Future analyses, including those of randomised trials and subsequent meta-analyses, should consider clustering within twins, since antenatal corticosteroids are delivered at the pregnancy-level and outcomes within twin pairs are not independent. Non-randomized studies would also benefit from transparent rationale for selection of study population and confounders.

Quasi-experimental designs may be particularly useful in addressing the effects of confounding.[34] Future reviews could benefit from a systematic search of non-randomized studies that include higher order multiples, as we identified several studies in multiples that did not provide disaggregated data on twins during our search.[35–40]

Existing guidelines and consensus recommending antenatal corticosteroid administration in twins are based on limited evidence from randomised trials, select observational studies, and extrapolation from studies on singletons. This review showed general agreement among non-randomized studies that antenatal corticosteroids are associated with lower incidence of neonatal mortality and RDS. Pending evidence from randomized trials in late-preterm twins, findings from this review of non-randomized studies may help provide evidence supporting the use of antenatal corticosteroids in twin pregnancies at risk of preterm delivery.

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Table 1. Characteristics of included studies

Study	Location	Time period	Study design	Gestational ages	Treatment timing	Factors adjusted for
Caspi 1981[16]	Israel,* single hospital	1974-1978	Cohort	Admitted for delivery from 28 to 36 weeks	Delivered at least 24 hours after admission	-
Spinillo 1995[17]	Italy, single tertiary hospital	1988-1993	Cohort	Delivered between 24 to 34 weeks	First dose more than 48 hours and less than seven days before delivery	-
Turrentine 1996[18]	USA, single tertiary hospital	1990-1994	Cohort	Delivered between 24 to 34 weeks	First dose more than 48 hours and less than seven days before delivery	Sex, race, birthweight, gestational age, small for gestational age, rupture of membranes, labor, tocolytics, first twin

Al-Yatama 2001[19]	Kuwait, single hospital	1997-1999	Matched cohort	Admitted for delivery from 24 to 34 weeks	No information	-
Hacking 2001[20]	Australia and New Zealand Neonatal Network Database	1995	Cohort	Delivered between 23 to 31 weeks	First dose more than 24 hours and less than eight days before delivery	-
Murphy 2002[21]	UK, single hospital	1990-1997	Cohort	Delivered between 24 to 37 weeks	First dose more than 24 hours before delivery	Gestational age, birth weight, sex, labour, vaginal delivery, infertility, smoker, placental chorionicity
Blickstein 2005[22]	Israeli National Very Low Birth Weight Database	1995-2001	Cohort	Delivered at 24 through 32 weeks	First dose more than 48 hours and less than seven days before delivery	-

Blickstein 2006[23]	Israeli National Very Low Birth Weight Database	1995-2002	Cohort	Delivered at 25 through 32 weeks	First dose more than 48 hours and less than seven days before delivery	-
Kuk 2013[24]	South Korea, single tertiary hospital	1995-2011	Cohort	Delivered between 24 to 34 weeks	Administration-to-delivery intervals: less than two days, two-seven days, more than seven days	Gestational age, indication for preterm birth, chronionicity, gestational diabetes, hypertension, mode of delivery, sex, birth order
Melamed 2016[7]	Canada, Canadian Neonatal Network	2010-2014	Cohort	Delivered at 24+0 through 33+6 weeks	First dose more than 48 hours and less than seven days before delivery	Gestational age, sex, hypertension, outborn status, small for gestational age (<10th percentile), parity, and caesarean birth
Viteri 2016[25]	USA, 14 academic sites	2004-2006	Cohort	Delivered between 24 and 36+6 weeks	Treatment before 34 weeks	Gestational age, maternal age, race, chorionicity, delivery route, birth order, sex, smoking

Braun 2016[26]	Germany, single tertiary hospital	1993-2011	Matched cohort	Exposed to treatment between 23+5 and 33+6 weeks (unexposed matched on gestational age at birth)	Treatment between 23+5 to 33+6 weeks	-
Palas 2018[27]	France, nationwide	2011	Cohort	Delivered between 24 through 31 weeks	Complete course, first dose less than seven days before delivery (or more than seven days since delivery)	*Mortality*: gestational age, small for gestational age, hypertensive diseases, gestational diabetes. *BPD*: gestational age, small for gestational age, hypertensive diseases, smoking status
Riskin-Mashiah 2018[28]	Israeli National Very Low Birth	1995-2012	Cohort	Delivered between 24	Any	Maternal age, ethnicity, infertility treatment, maternal hypertensive disorder, preterm labor, premature

	Weight Database			through 31 weeks		rupture of membranes, amnionitis, gestational age, delivery mode, birth weight z-score, neonatal sex, birth order, delivery room resuscitation, year of birth
Ushida 2020[8]	Neonatal Research Network of Japan	2003-2015	Cohort	Delivered between 24+0 through 31+6 weeks	At least one dose	Maternal age, parity, gestational age, mode of delivery, diabetes mellitus or gestational diabetes mellitus, hypertensive disorders of pregnancy, clinical chorioamnionitis, non-reassuring fetal status, neonatal sex, birth weight, small for gestational age, plurality of pregnancy, chorionicity, birth order, year of delivery

Ben-David 2020[29]	Israel, single tertiary hospital	2016-2018	Cohort	Delivered between 34+0 through 36+6 weeks	First dose after 33+6 weeks gestational age	(None for RDS)
Kong 2020[9]	China, national multicenter	2013-2014	Cohort	Delivered between 25+0 and 35+6 weeks	One or more doses	Gestational age, birth weight, neonatal sex, small for gestational age, delivery mode, Apgar score at 5 min, gestational diabetes mellitus, premature rupture of membranes, Hypertensive disorder complicating pregnancy, placenta abruption and chorioamnionitis.
Gonçalves-Ferri 2021[30]	Brazilian Network of Neonatal Research	2010-2014	Cohort	Delivered between 23+0 and 33+0 weeks	Any	*RDS*: SNAPPE-II and early sepsis. *Mortality and BPD*: SNAPPE-II, early sepsis, surfactant use, mechanical ventilation, enterocolitis. *IVH*:

				SNAPPE-II, early sepsis, mechanical ventilation. *NEC*: SNAPPE-II.

Note: BPD = bronchopulmonary dysplasia, IVH = intraventricular hemorrhage, NEC = necrotizing enterocolitis, RDS = respiratory distress syndrome. SNAPPE-II calculated from mean blood pressure, temperature, PO2/FIO2 ratio, serum pH, multiple seizures, urine output, birthweight, small for gestational age, Apgar score at 5 minutes.

*Presumed, based on author affiliations.

Figure Legends

Figure 1. Risk of bias assessment (ROBINS-I) for included studies. Turrentine 1996 and Kuk 2013 are at moderate risk of bias for respiratory distress syndrome (reported adjusted estimates) and critical risk of bias for all other outcomes (crude estimates only).

Figure 2. Forest plot showing the odds of mortality among twin infants who were exposed vs. unexposed to antenatal corticosteroids. Studies without critical risk of bias due to confounding were included in the meta-analysis. Note: RoB-confounding = risk of bias due to confounding.

Figure 3. Forest plot showing the odds of respiratory distress syndrome among twin infants who were exposed vs. unexposed to antenatal corticosteroids. Studies without critical risk of bias due to confounding were included in the meta-analysis. Note: RoB-confounding = risk of bias due to confounding.

SUPPLEMENTAL INFORMATION

Socha P, McGee A, Bhattacharya S, Young C, Wang R. Antenatal corticosteroids and neonatal outcomes in twins: a systematic review and meta-analysis. 2022.

Contents

Appendix 1

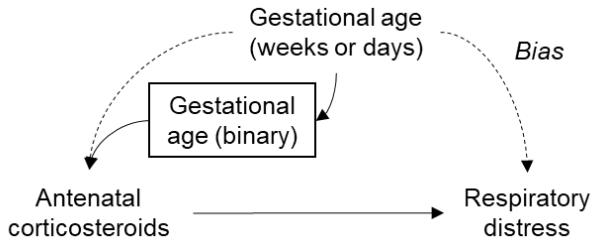
Appendix 1. Changes and clarifications from the registered protocol.

Relevant section	Specification in the protocol[1]	Change or clarification
Inclusion/exclusion criteria	Included studies that compared treatment in twins with other higher order multiple gestations, the number and/or strength of doses, the number and/or timing of courses, or the administration-to-delivery interval	Excluded these studies
Inclusion/exclusion criteria	Excluded studies with low severity intraventricular haemorrhage (less than grade III), necrotising enterocolitis (less than grade II), and retinopathy of prematurity (less than grade III)	Included studies with any severity of intraventricular haemorrhage, necrotising enterocolitis, and retinopathy of prematurity, but used high-severity definitions when possible (i.e., if a study stratified)
Inclusion/exclusion criteria	Included randomized trials	We focused our synthesis on non-randomized studies, as randomized trials of antenatal corticosteroid treatment in multiples have recently been systematically reviewed.[2] During screening, we identified a randomized trial of antenatal corticosteroid treatment in twins that was not included in the 2020 Cochrane review.[3] However, the study had issues with randomization and trial registration (including receiving ethics approval after study initiation).
Risk of bias assessment	Downs and Black checklist[4]	Risk Of Bias In Non-randomised Studies - of Interventions (ROBINS-I)[5]
Meta-analysis	-	Performed two sensitivity analyses: stratifying by whether studies accounted for clustering within twin pairs and pooling crude ORs for our two primary outcomes (mortality and RDS)

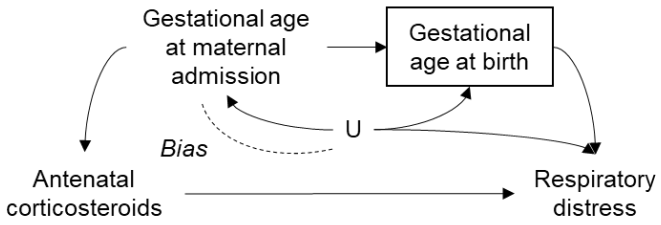
Appendix 2

Search Terms: (corticosteroid* OR steroid* OR adrenal cortex hormone* OR glucocorticoid* OR dexamethasone OR betamethasone) AND (twin pregnancy OR multiple pregnancy OR multiple gestation* OR twin*)

Appendix 3-4

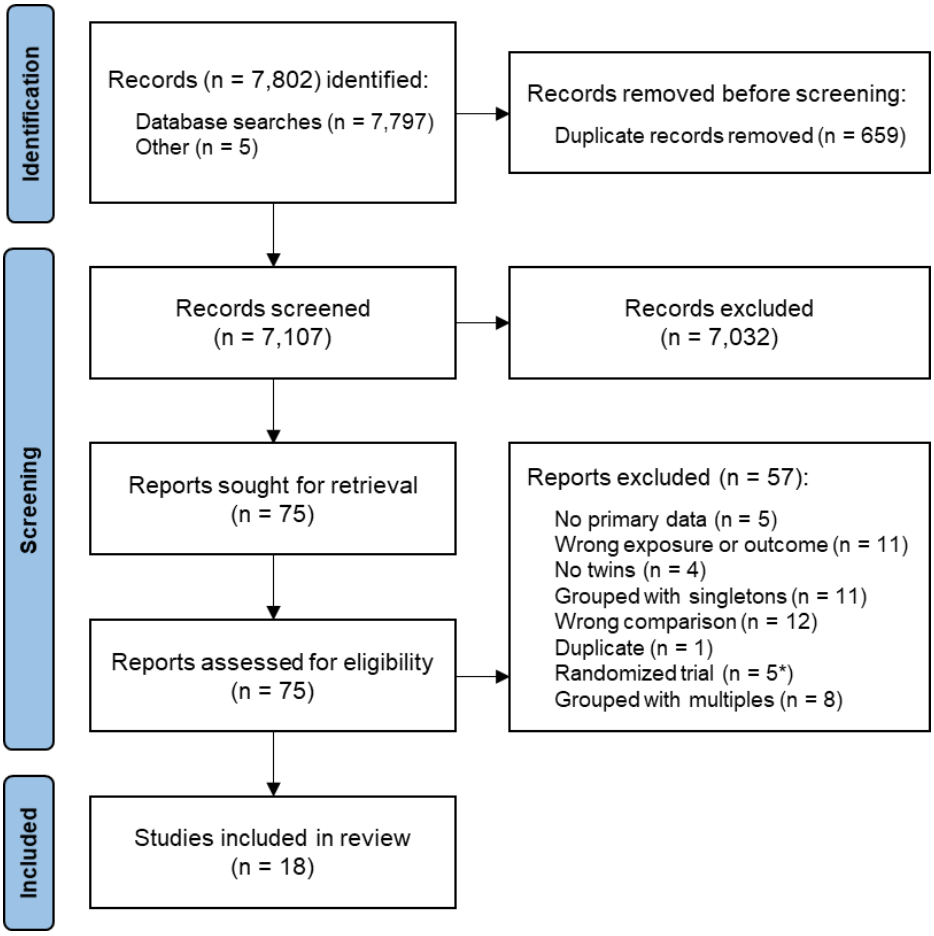


Appendix 3. Directed acyclic graph showing residual confounding (dashed lines) through gestational age, in studies that restrict to premature births (e.g., <37 weeks gestation or <34 weeks gestation) but do not perform any adjustment for week- or day-based gestational age.



Appendix 4. Directed acyclic graph showing risk of bias (dashed line) from adjusting on gestational age at birth. In the presence of an unmeasured variable (U) that confounds the relationship between gestational age at maternal admission and gestational age at birth, and gestational age at birth and respiratory distress, adjusting on gestational age biases the relationship between gestational age at maternal admission and U (opening a backdoor path from antenatal corticosteroids to respiratory distress). There is a trade-off between the strong confounding by gestational age at birth and whether/how strongly U affects gestational age at birth through a "direct" mechanism (i.e., one other than through gestational age at maternal admission). Adjusting on gestational age at maternal admission (where available) should help alleviate this bias; however, this will likely result in residual confounding due to pregnancies that are admitted for delivery, administered corticosteroids, and discharged without delivering (to deliver at a later date).

Appendix 5



Appendix 5. Flow diagram of study search and selection.

Appendix 6

Note: BPD = bronchopulmonary dysplasia, GEE = generalized estimating equations, IVH = intraventricular haemorrhage, NEC = necrotizing enterocolitis, NICU = neonatal intensive care unit, PVL = periventricular leukomalacia, RDS = respiratory distress syndrome, ROP = retinopathy of prematurity.

Appendix 6.1. Details of included studies: setting and design.

Author	Location	Time period	Study design	Selection of controls
Caspi 1981[6]	Israel,[a] single hospital	1974-1978	Cohort	-
Spinillo 1995[7]	Italy, single tertiary hospital	1988-1993	Cohort	-
Turrentine 1996[8]	USA, single tertiary hospital	1990-1994	Cohort	-
Al-Yatama 2001[9]	Kuwait, single hospital	1997-1999	Matched cohort	No information
Hacking 2001[10]	Australia, New Zealand, Australia and New Zealand Neonatal Network Database	1995	Cohort	-
Murphy 2002[11]	UK, single hospital	1990-1997	Cohort	-
Blickstein 2005[12]	Israel, Israeli National Very Low Birth Weight Database[b]	1995-2001	Cohort	-
Blickstein 2006[13]	Israel, Israeli National Very Low Birth Weight Database[b]	1995-2002	Cohort	-
Kuk 2013[14]	South Korea, single tertiary hospital	1995-2011	Cohort	-
Melamed 2016[15]	Canada, Canadian Neonatal Network	2010-2014	Cohort	-
Viteri 2016[16]	USA, 14 academic sites	2004-2006	Cohort	-
Braun 2016[17]	Germany, single tertiary hospital	1993-2011	Matched cohort	Matched on gestational age at delivery
Palas 2018[18]	France, nationwide	2011	Cohort	-
Riskin-Mashiah 2018[19]	Israel, Israeli National Very Low Birth Weight Database[b]	1995-2012	Cohort	-
Ushida 2020[20]	Japan, Neonatal Research Network of Japan	2003-2015	Cohort	-
Ben-David 2020[21]	Israel, single tertiary hospital	2016-2018	Cohort	-
Kong 2020[22]	China, national multicenter	2013-2014	Cohort	-
Gonçalves-Ferri 2021[23]	Brazil, Brazilian Network of Neonatal Research	2010-2014	Cohort	-

[a]Presumed, based on author affiliations.
[b]Data from Riskin-Mashiah 2018 overlaps with the data from in Blickstein 2005 and 2006.

Appendix 6.2. Details of included studies: study population.

Author	Gestational ages	Other inclusion/exclusion criteria
Caspi 1981[6]	Admitted for delivery from 28 to 36 weeks	Excluded: hypertensive disorders of pregnancy, abruptio placentae, obvious placental insufficiency, diabetes mellitus, Ph isoimmunization, stillbirths, chorioamnionitis, unknown gestational age
Spinillo 1995[7]	Delivered between 24 to 34 weeks	Included: planned deliveries for patients with medical complications, undetermined or immature lecithin/sphingomyelin ratio. Excluded: stillborn, malformed, severe abruption, eclampsia
Turrentine 1996[8]	Delivered between 24 to 34 weeks	-
Al-Yatama 2001[9]	Admitted for delivery from 24 to 34 weeks	Excluded: long-term maternal corticosteroid treatment,
Hacking 2001[10]	Delivered between 23 to 31 weeks	Included: admitted to NICU
Murphy 2002[11]	Delivered between 24 to 37 weeks	-
Blickstein 2005[12]	Delivered at 24 through 32 weeks	Included: admitted to NICU, birthweight less than or equal to 1500g. Excluded: lethal malformations, quadruplets or quintuplets
Blickstein 2006[13]	Delivered at 25 through 32 weeks	Included: admitted to NICU, birthweight less than or equal to 1500g. Excluded: lethal malformations, quadruplets or quintuplets
Kuk 2013[14]	Delivered at 24 to 34 weeks	Excluded: twin-to-twin transfusion syndrome, one or more fetal deaths, fetal chromosomal or non-chromosomal major anomalies, placenta previa, placental abruption, serious maternal medical diseases, multiple courses of antenatal corticosteroids
Melamed 2016[15]	Delivered at 24+0 through 33+6 weeks	Included: admitted to NICU. Excluded: birthweight below third percentile, clinical chorioamnionitis, major congenital anomaly, stillbirths, multiples courses of antenatal corticosteroids
Viteri 2016[16]	Delivered between 24 and 36+6 weeks	Excluded: iatrogenic fetal reduction, major fetal anomalies, fetal death of either twin, presumed monoamniotic placenta, suspected twin-to-twin transfusion syndrome, ultrasonographic growth discordance greater that three weeks between fetuses, planned progesterone therapy after 16 weeks gestation, need for cerclage placement, major uterine anomaly, need for anticoagulation, major chronic maternal medical disease
Braun 2016[17]	Exposed to treatment between 23+5 and 33+6 weeks (unexposed matched on gestational age at birth)	Excluded: twin-to-twin transfusion syndrome, intrauterine death, malformations, chromosomal anomalies, fetal or maternal diseases, pathologic umbilical or uterine Doppler findings
Palas 2018[18]	Delivered between 24 through 31 weeks	Included: admitted to NICU. Excluded: delivery-room deaths, twin-to-twin transfusion syndrome, co-twin fetal deaths, manor congenital anomalies
Riskin-Mashiah 2018[19]	Delivered between 24 through 31 weeks	Included: admitted to NICU, birthweight less than or equal to 1500g. Excluded congenital anomalies
Ushida 2020[20]	Delivered between 24+0 through 31+6 weeks	Included: admitted to NICU, birthweight less than or equal to 1500g. Excluded: major congenital anomaly, transfer from other facilities, co-twin fetal death
Ben-David 2020[21]	Delivered between 34+0 through 36+6 weeks	Excluded: one or more stillbirths, clinical chorioamnionitis, suspected fetal anomalies, intra-uterine growth restriction, complications from monochorionicity, twin-to-twin transfusion syndrome, anemia polycythemia
Kong 2020[22]	Delivered between 25+0 and 35+6 weeks	Included: admitted to NICU. Excluded: outborn infants, major congenital anomalies, neonatal death of either twin, monoamniotic placenta, twin-to-twin transfusion syndrome, required discharge for financial reasons
Gonçalves-Ferri 2021[23]	Delivered between 23+0 and 33+0 weeks	Included: admitted to NICU, birthweight 400 to 1499g. Excluded: congenital malformations, death in delivery room, outborns, quadruplets+

Appendix 6.3. Details of included studies: intervention and control groups

Author	Drug	Dosage	Treatment timing	Control
Caspi 1981[6]	No information	4mg, every 8 hours, until delivery (maximum seven days)	Delivered at least 24 hours after admission	No antenatal corticosteroids
Spinillo 1995[7]	Betamethasone or dexamethasone	Two doses, 12mg, 24 hours apart	First dose more than 48 hours/less than seven days before delivery	No antenatal corticosteroids
Turrentine 1996[8]	Betamethasone	Two doses, 12mg, 24 hours apart	First dose more than 48 hours/less than seven days before delivery	No antenatal corticosteroids
Al-Yatama 2001[9]	Dexamethasone	Two doses, 12mg, 12 hours apart	No information	No antenatal corticosteroids
Hacking 2001[10]	No information	Two doses	First dose more than 24 hours/less than eight days before delivery	No antenatal corticosteroids
Murphy 2002[11]	Dexamethasone	Two doses, 12mg, 12 hours apart	First dose more than 24 hours before delivery	No antenatal corticosteroids
Blickstein 2005[12]	Betamethasone or dexamethasone	Two doses, 12mg (betamethasone) or four doses, 6mg (dexamethasone)	First dose more than 48 hours/less than seven days before delivery	Partial, or no antenatal corticosteroids
Blickstein 2006[13]	Betamethasone or dexamethasone	Two doses, 12mg (betamethasone) or four doses, 6mg (dexamethasone)	First dose more than 48 hours/less than seven days before delivery	Partial, or no antenatal corticosteroids
Kuk 2013[14]	Betamethasone or dexamethasone	Two doses, 12mg, 24 hours apart (betamethasone) or four doses, 12 hours apart (dexamethasone)	Administration-to-delivery intervals: less than two days, two-seven days, more than seven days	No antenatal corticosteroids
Melamed 2016[15]	Betamethasone or dexamethasone	Two doses, 12mg, 24 hours apart (betamethasone); or four doses, 6mg, 12 hours apart (dexamethasone)	First dose more than 48 hours/less than seven days before delivery	No antenatal corticosteroids
Viteri 2016[16]	No information	No information	Treatment before 34 weeks	No antenatal corticosteroids
Braun 2016[17]	Betamethasone	16mg or less, 24mg, more than 24mg	Treatment between 23+5 to 33+6 weeks	No antenatal corticosteroids
Palas 2018[18]	Betamethasone	Two doses, 12mg	Complete course, first dose less than seven days before delivery (or more than seven days since delivery)	No antenatal corticosteroids
Riskin-Mashiah 2018[19]	No information	No information	Any	No antenatal corticosteroids
Ushida 2020[20]	Betamethasone	Two doses, 12mg, 24 hours apart	At least one dose	No antenatal corticosteroids
Ben-David 2020[21]	Betamethasone	Two doses, 12mg, 24 hours apart	First dose after 33+6 weeks gestational age	No antenatal corticosteroids
Kong 2020[22]	Dexamethasone	Four doses, 5-6mg, 12 hours apart	One or more doses	No antenatal corticosteroids
Gonçalves-Ferri 2021[23]	Betamethasone	Two doses, 12mg, 24 hours apart[c]	Any	No antenatal corticosteroids

[c]Treatment that was recommended during the time period, but data on actual practice were unavailable.

Appendix 6.4. Details of included studies: assessed outcomes.

Author	Outcomes of interest	Other outcomes
Caspi 1981[6]	Mortality, RDS	-
Spinillo 1995[7]	RDS, IVH	-
Turrentine 1996[8]	RDS, mortality	Fetal deaths
Al-Yatama 2001[9]	RDS	NICU admission
Hacking 2001[10]	Mortality, RDS	Surfactant use
Murphy 2002[11]	RDS	-
Blickstein 2005[12]	RDS	-
Blickstein 2006[13]	IVH	-
Kuk 2013[14]	Mortality, RDS, IVH, BPD, NEC, PVL, ROP	Patent ductus arteriosus, early sepsis, late sepsis
Melamed 2016[15]	Mortality, RDS, BPD, NEC, ROP	Mechanical ventilation, severe neurological injury
Viteri 2016[16]	RDS	NICU admission, mechanical ventilation
Braun 2016[17]	Mortality	RDS or asphyxia, birth weight, body length, head circumference, Ponderal index, Apgar, umbilical artery blood pH, umbilical vein blood pH, base excess, placental weight
Palas 2018[18]	Mortality, BPD	IVH or PVL
Riskin-Mashiah 2018[19]	Mortality, RDS, IVH, BPD, NEC, PVL, ROP	-
Ushida 2020[20]	Mortality, RDS, IVH, NEC, PVL, ROP	Chronic lung disease, sepsis
Ben-David 2020[21]	RDS	TTN, oxygen requirement, CPAP, mechanical ventilation, NICU admission, hypoglycemia, jaundice
Kong 2020[22]	Mortality, RDS, IVH, BPD, NEC, PVL, ROP	Patent ductus arteriosus, sepsis
Gonçalves-Ferri 2021[23]	Mortality, RDS, IVH, BPD, NEC	1 and 5-minute Apgar, need for intubation in delivery room, need for mechanical ventilation, early sepsis, hemodynamic instability

Appendix 6.5. Details of included studies: assessment of primary outcomes of interest.

Author	Morality	Respiratory distress syndrome
Caspi 1981[6]	Early neonatal death	Clinical of Silverman score, typical radiological findings, acid-base balance, and blood gas analysis
Spinillo 1995[7]	-	Physical signs of respiratory distress and required ventilatory support for >48 hours, confirmed radiologically
Turrentine 1996[8]	Neonatal death	Clinical, radiological, and blood gas findings. Severe RDS: an infant with RDS requiring mechanical ventilation
Al-Yatama 2001[9]		Clinical, radiological, and blood gas results; mild to severe
Hacking 2001[10]	Mortality	Increasing respiratory distress or oxygen requirements, or the need for ventilator support from the first 6 hours of life together with a chest radiograph showing a generalized reticulogranular pattern, with or without an air bronchogram
Murphy 2002[11]	-	No information
Blickstein 2005[12]		Characteristic clinical and radiographic findings together with supplementary oxygen or mechanical ventilation.
Blickstein 2006[13]	-	-
Kuk 2013[14]	Neonatal mortality	Radiographic chest findings plus 1 or more clinical signs of respiratory distress including respiratory grunting, retracting, and increased oxygen requirement (fraction of inspired oxygen of greater than 0.4) or the administration of exogenous pulmonary surfactant
Melamed 2016[15]	Death prior to discharge from NICU	Respiratory morbidity, including need for and duration of mechanical ventilation, respiratory distress syndrome, and bronchopulmonary dysplasia, defined as the requirement for oxygen at postmenstrual age of 36 weeks or at the time of transfer to a level II facility
Viteri 2016[16]	-	Clinical diagnosis and oxygen therapy ($PiO_2 \geq 0.40$) for 24 hours or greater
Braun 2016[17]	Morality	-
Palas 2018[18]	Morality	-
Riskin-Mashiah 2018[19]	Death before discharge to home	No information
Ushida 2020[20]	In-hospital death	Clinical manifestations and chest radiography
Ben-David 2020[21]	-	No information
Kong 2020[22]	Death before discharge from NICU	Clinical evidence of respiratory difficulties (tachypnea, retraction, grunting and cyanosis), radiographic appearance of RDS (low volume lungs with a diffuse reticulogranular pattern and air bronchograms)
Gonçalves-Ferri 2021[23]	Death before discharge from NICU	No information

Appendix 6.6. Details of included studies: assessment of secondary outcomes of interest 1/2.

Author	Intraventricular haemorrhage	Bronchopulmonary dysplasia
Caspi 1981[6]	-	-
Spinillo 1995[7]	Grades I-IV. Diagnosed by serial cranial ultrasound examinations	-
Turrentine 1996[8]	-	-
Al-Yatama 2001[9]	-	-
Hacking 2001[10]	-	-
Murphy 2002[11]	-	
Blickstein 2005[12]	-	-
Blickstein 2006[13]	Grades III-IV. Diagnosed using the definition from Papile et al. 1978[24]	-
Kuk 2013[14]	Grades III-IV. Ultrasonographic examination of the neonatal brain, intraventricular bleeding without ventricular dilatation (grade II) or with ventricular dilatation (grade III) or with parenchymal involvement (grade IV)	Need for supplementary oxygen for 28 days or more, or by diagnostic radiographic or histological findings
Melamed 2016[15]	-[d]	Oxygen requirement at postmenstrual age of 36 weeks or at the time of transfer to a level II facility
Viteri 2016[16]	-	-
Braun 2016[17]	-	-
Palas 2018[18]	-	Mechanical ventilator support, continuous positive airway pressure, or ≥30% supplementary oxygen at 36 weeks of gestation and supplementary oxygen for at least 28 days
Riskin-Mashiah 2018[19]	Grades III-IV	No information
Ushida 2020[20]	Grades III-IV. Diagnosed according to Papile et al. 1978[24]	*Chronic lung disease*: need for supplemental oxygen at 36 weeks of corrected gestational age
Ben-David 2020[21]	-	-
Kong 2020[22]	Grades III-IV for crude OR, any grade for adjusted OR. Diagnosed within 28 days of birth using real-time portable cranial ultrasound, grades III-IV according to the Papile et al. 1978[24]	Required mechanical ventilation or supplemental oxygen 28 days after birth. Moderate to severe BPD: still received supplemental oxygen at 36 weeks' postmenstrual age or discharge
Gonçalves-Ferri 2021[23]	Grades III-IV	Oxygen at 36 weeks corrected age

[d]IVH and PVL were aggregated / not reported separately.

Appendix 6.7. Details of included studies: assessment of secondary outcomes of interest 2/2.

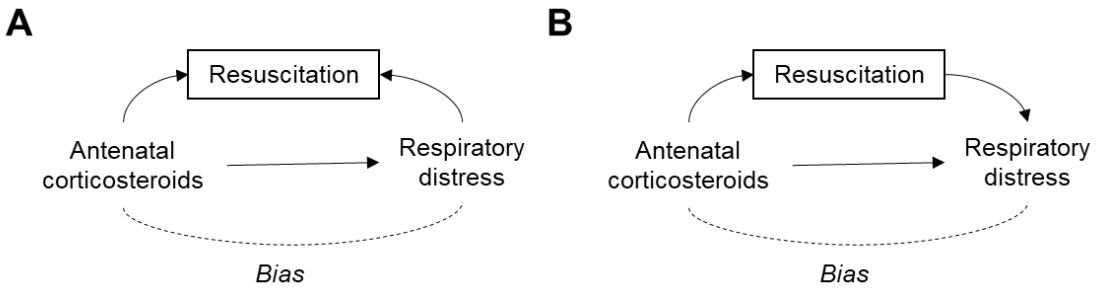
Author	Necrotizing enterocolitis	Periventricular leukomalacia	Retinopathy of prematurity
Caspi 1981[6]	-	-	-
Spinillo 1995[7]	-	-	-
Turrentine 1996[8]	-	-	-
Al-Yatama 2001[9]	-	-	-
Hacking 2001[10]	-	-	-
Murphy 2002[11]	-	-	-
Blickstein 2005[12]	-	-	-
Blickstein 2006[13]	-	-	-
Kuk 2013[14]	Stages II-III. Abdominal distention and feeding intolerance for more than 24 hours with radiological evidence of intramural air, perforation, meconium plug syndrome, or definitive surgical findings	Ultrasonographic examination of the neonatal brain, the presence of an obvious hypoechoic cyst in the periventricular white matter	Grades III-IV. Diagnosed by ophthalmologist, grading based on the International Classification of Retinopathy of Prematurity
Melamed 2016[15]	Stages II-III. According to the criteria of Bell et al. 1978[25]	-[d]	Grades III-IV. According to the international classification of retinopathy of prematurity, or retinopathy of prematurity requiring treatment
Viteri 2016[16]	-	-	-
Braun 2016[17]	-	-	-
Palas 2018[18]	-	-	-
Riskin-Mashiah 2018[19]	Stages II-III	Cystic PVL	Grades III-IV
Ushida 2020[20]	Stages II-III. Defined according to the criteria of Bell et al. 1978[25]	Diagnosed with intracranial ultrasonography or magnetic resonance imaging	Treated ROP
Ben-David 2020[21]	-	-	-
Kong 2020[22]	Stages II-III for crude OR, any stage for adjusted OR. One abdominal sign (bilious gastric aspirate or vomiting, abdominal distention or tenderness, gross or occult blood in the stool) and one radiographic finding (pneumatosis intestinalis, hepatobiliary gas, fixed position loop on serial studies). Stage II according to modified Bell et al. 1978[25]	Diagnosed with intracranial ultrasonography or magnetic resonance imaging	Grades III-IV for crude OR, any grade for adjusted OR. Retinal examination before discharge
Gonçalves-Ferri 2021[23]	Stages II or III	-	-

Appendix 6.8. Details of included studies: analyses.

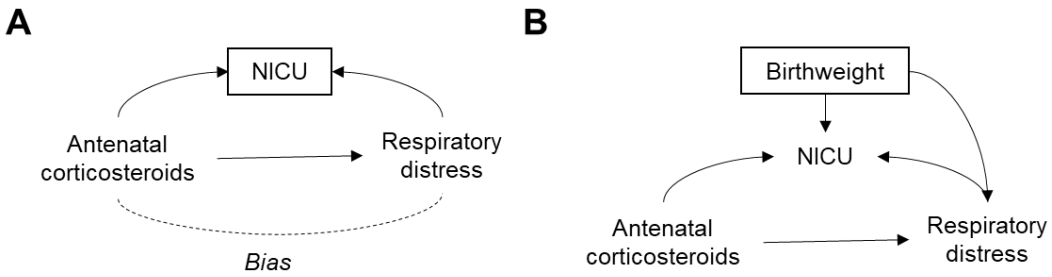
Author	Factors adjusted for	Twin clustering	Strata
Caspi 1981[6]	-	-	-
Spinillo 1995[7]	-	-	-
Turrentine 1996[8]	Sex, race, birthweight, gestational age, small for gestational age, rupture of membranes, labor, tocolytics, first twin	-	-
Al-Yatama 2001[9]	-	-	-
Hacking 2001[10]	-	Unspecified standard error adjustment	-
Murphy 2002[11]	Gestational age, birth weight, sex, labour, vaginal delivery, infertility, smoker, placental chorionicity	Multilevel models	RDS at <34 weeks, RDS at <37 weeks
Blickstein 2005[12]	-	-	-
Blickstein 2006[13]	-	-	-
Kuk 2013[14]	Gestational age, indication for preterm birth, chronionicity, gestational diabetes, hypertension, mode of delivery, sex, birth order	-	-
Melamed 2016[15]	Gestational age, sex, hypertension, outborn status, small for gestational age (<10th percentile), parity, and caesarean birth	GEE	-
Viteri 2016[16]	Gestational age, maternal age, race, chorionicity, delivery route, birth order, sex, smoking	Random effect for sibling pairs	-
Braun 2016[17]	-	(None for mortality)	-
Palas 2018[18]	*Mortality*: gestational age, small for gestational age, hypertensive diseases, gestational diabetes. *BPD*: gestational age, small for gestational age, hypertensive diseases, smoking status	Robust standard errors	-
Riskin-Mashiah 2018[19]	Maternal age, ethnicity, infertility treatment, maternal hypertensive disorder, preterm labor, premature rupture of membranes, amnionitis, gestational age, delivery mode, birth weight z-score, gender, birth order, delivery room resuscitation, year of birth	Potentially, GEE	Small or not small for gestational age
Ushida 2020[20]	Maternal age, parity, gestational age, mode of delivery, diabetes mellitus or gestational diabetes mellitus, hypertensive disorders of pregnancy, clinical chorioamnionitis, non-reassuring fetal status, gender, birth weight, small for gestational age, plurality of pregnancy, chorionicity, birth order, year of delivery	-	-
Ben-David 2020[21]	(None for RDS)	-	-
Kong 2020[22]	Gestational age, birth weight, gender, small for gestational age, delivery mode, Apgar score at 5 min, gestational diabetes mellitus, premature rupture of membranes, Hypertensive disorder complicating pregnancy, placenta abruption and chorioamnionitis.	-	-
Gonçalves-Ferri 2021[23]	*RDS*: SNAPPE-II[e] and early sepsis. *Mortality and BPD*: SNAPPE-II,[e] early sepsis, surfactant use, mechanical ventilation, enterocolitis. *IVH*: SNAPPE-II,[e] early sepsis, mechanical ventilation. *NEC*: SNAPPE-II.[e]	Random effect for pregnancy	-

[e]Calculated from mean blood pressure, temperature, PO2/FIO2 ratio, serum pH, multiple seizures, urine output, birthweight, small for gestational age, Apgar score at 5 minutes.

Appendix 7-8

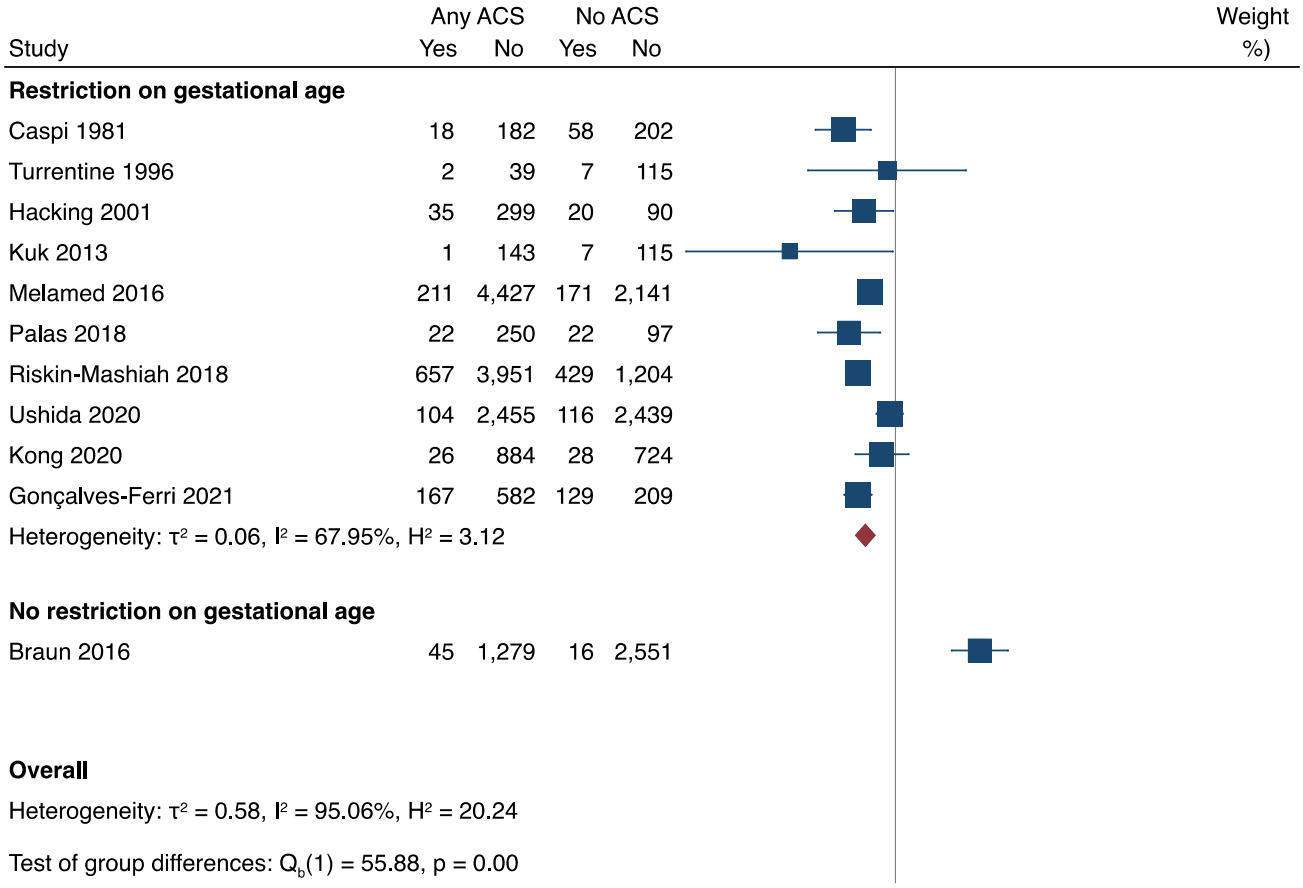


Appendix 7. Directed acyclic graphs showing bias (dashed lines) introduced by adjusting on a collider (A) or mediator (B), as exemplified in Riskin-Mashiah 2018. Here, resuscitation could be conceived as being caused by respiratory distress (A) or the clinical diagnosis of respiratory distress is caused by being resuscitated (B; as is often the case with respiratory distress syndrome). In both cases, conditioning on resuscitation would bias the association between antenatal corticosteroids and respiratory distress.



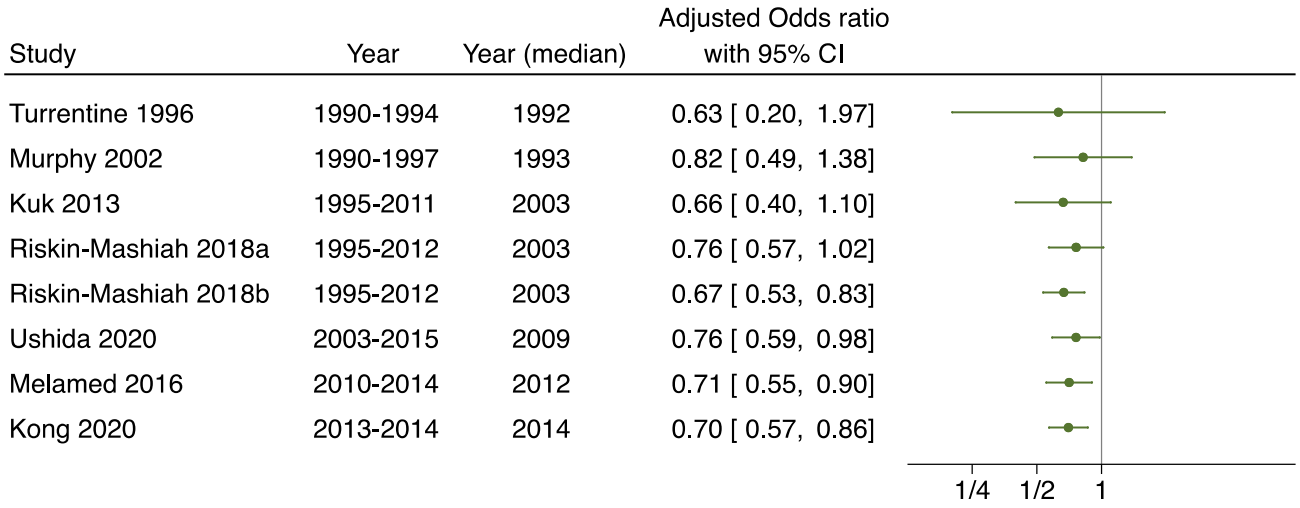
Appendix 8. Directed acyclic graphs showing examples of bias (dashed line) introduced by only including neonates that are admitted to neonatal intensive care units (NICUs). Exemplified in Kong 2020 (A), conditioning on NICU admission could bias the association between antenatal corticosteroids and respiratory distress. Exemplified in Ushida 2020 (B), restricting to infants with birthweight 1500g or less itself does not bias the association between antenatal corticosteroids and respiratory distress, and (since almost all liveborn neonates weighing 1500g or less are admitted to the NICU) conditioning on NICU *and* birthweight *likely* avoids much of the bias associated with restricting to NICUs. However, even if all 1500g infants are sent to the NICU, conditioning on NICUs could still bias results due to delivery-room mortality. When conditioning on birthweight, the primary issue would be generalizability, from very low birthweight infants to higher birthweight infants.

Appendix 9



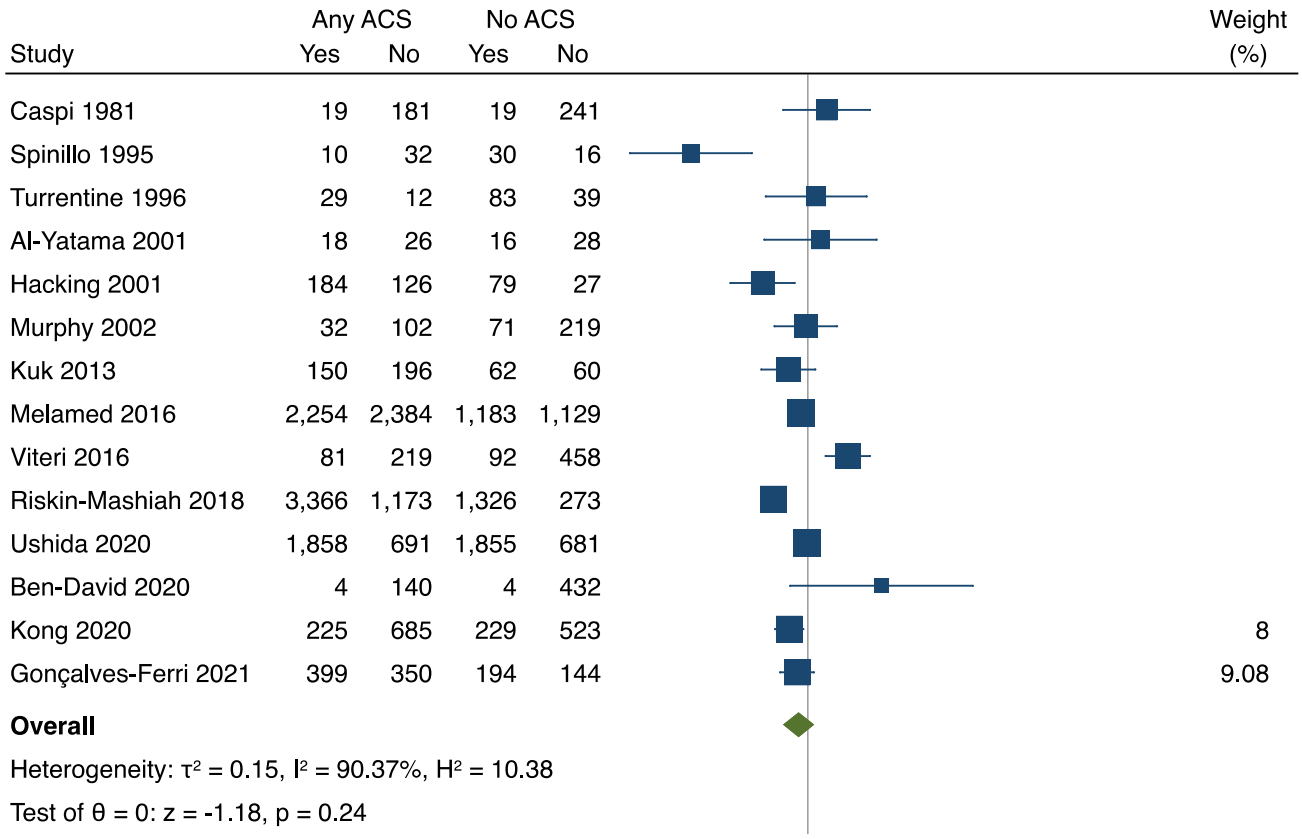
Appendix 9. Forest plot showing the crude, unadjusted odds of mortality among twin infants who were exposed vs. unexposed to antenatal corticosteroids. Note: ACS = antenatal corticosteroids; denominator for Gonçalves-Ferri 2021 were back-calculated from numerators and percentages, there was an error in either the numerator or percentage for mortality and "no ACS" (±1 infant).

Appendix 10



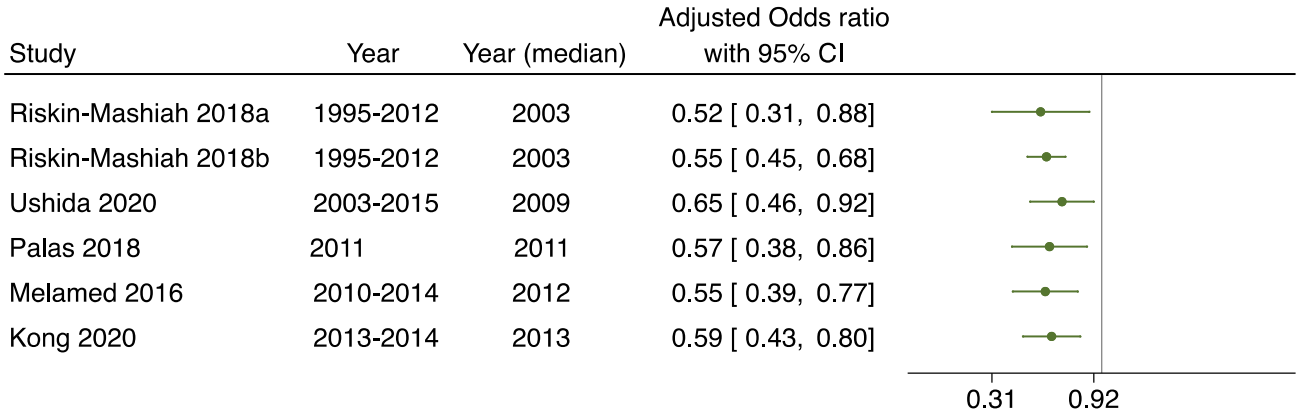
Appendix 10. Cumulative meta-analysis for neonatal mortality (adjusted).

Appendix 11



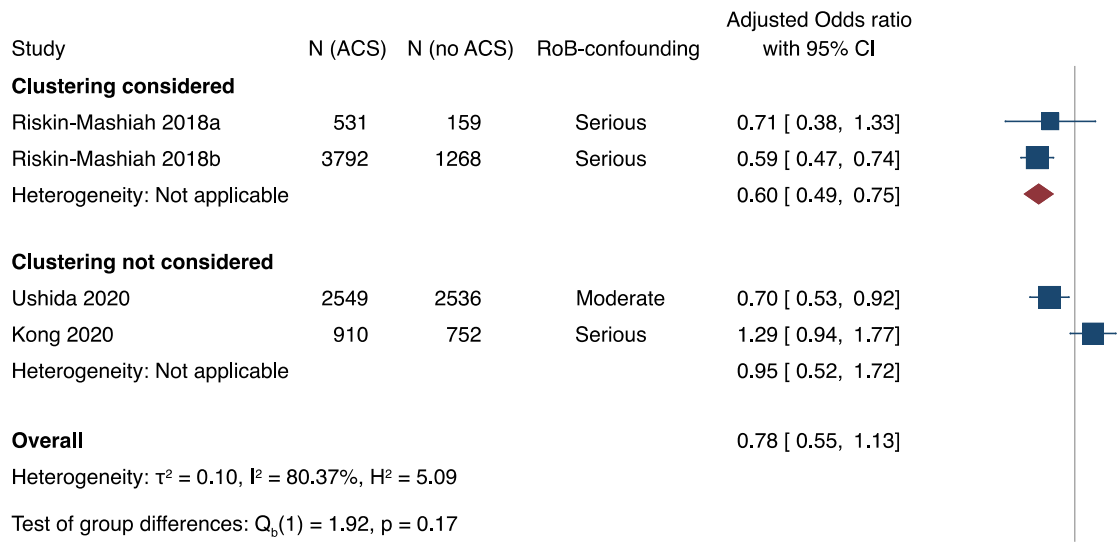
Appendix 11. Forest plot showing the crude, unadjusted odds of respiratory distress syndrome among twin infants who were exposed vs. unexposed to antenatal corticosteroids. All studies restricted to preterm gestational ages. Note: ACS = antenatal corticosteroids.

Appendix 12

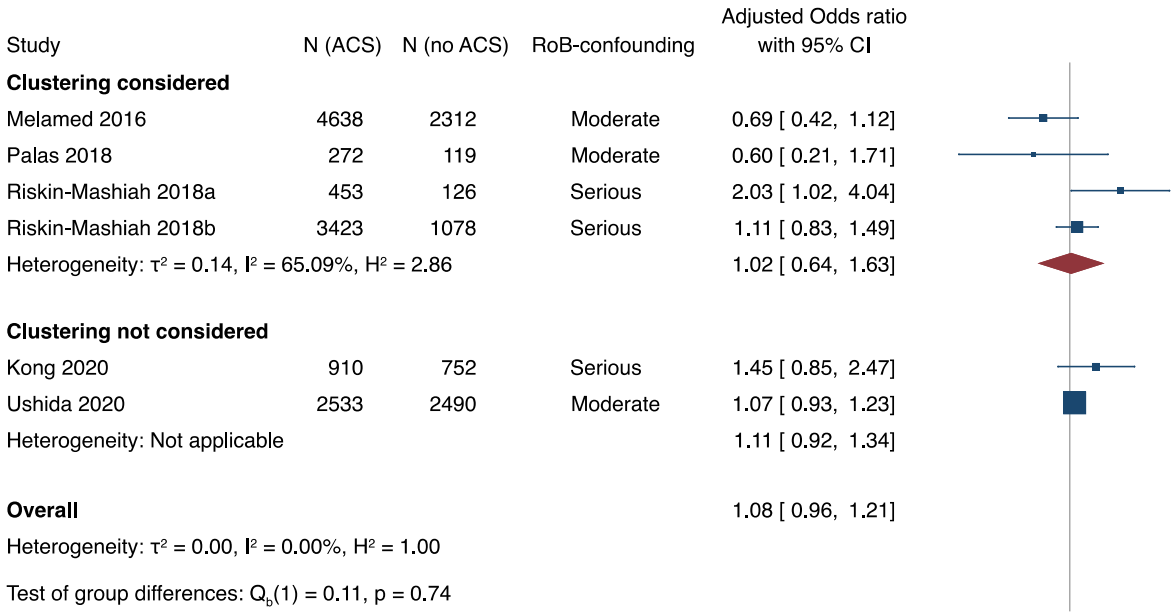


Appendix 12. Cumulative meta-analysis respiratory distress syndrome (adjusted).

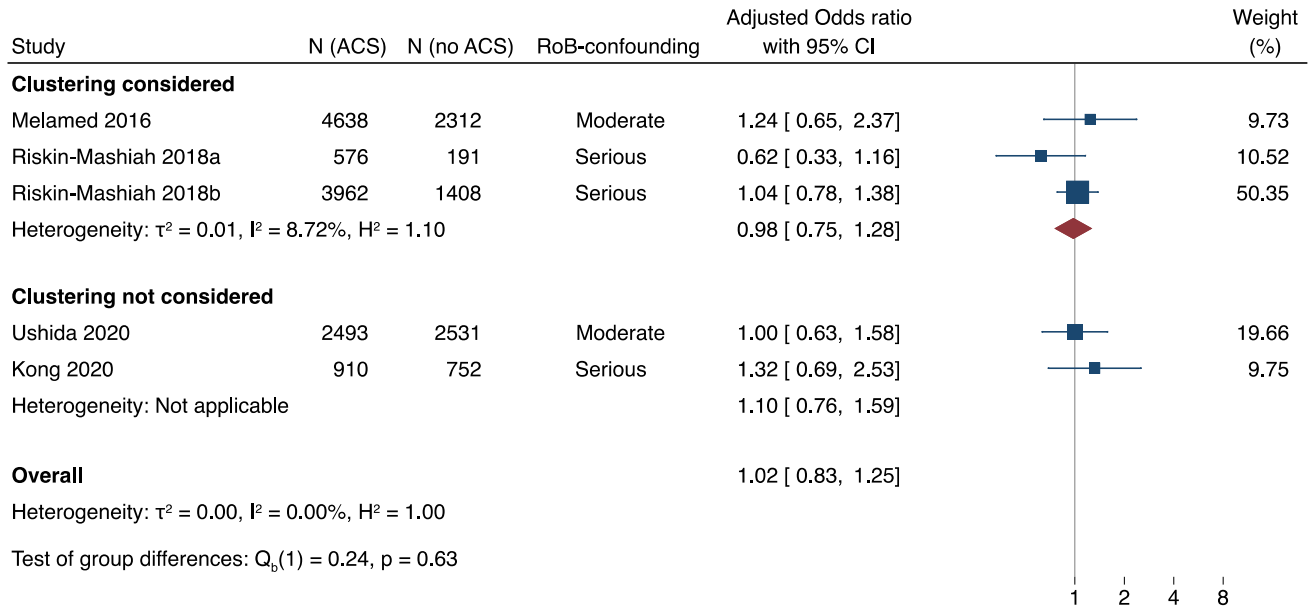
Appendix 13-17



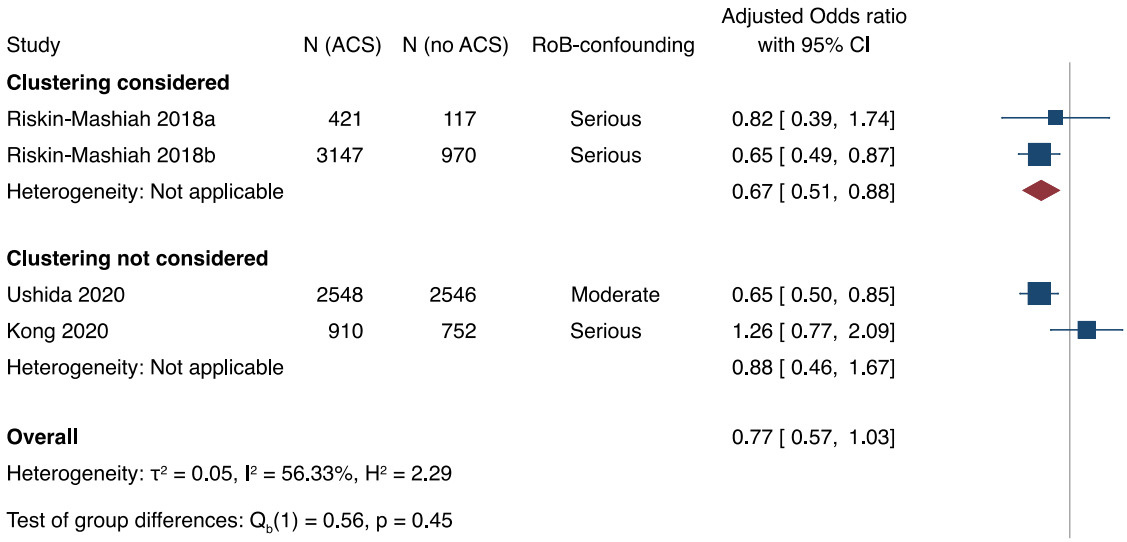
Appendix 13. Forest plot showing the odds of intraventricular haemorrhage among twin infants who were exposed vs. unexposed to antenatal corticosteroids. Studies without critical risk of bias due to confounding were included in the meta-analysis. Note: RoB-confounding = risk of bias due to confounding.



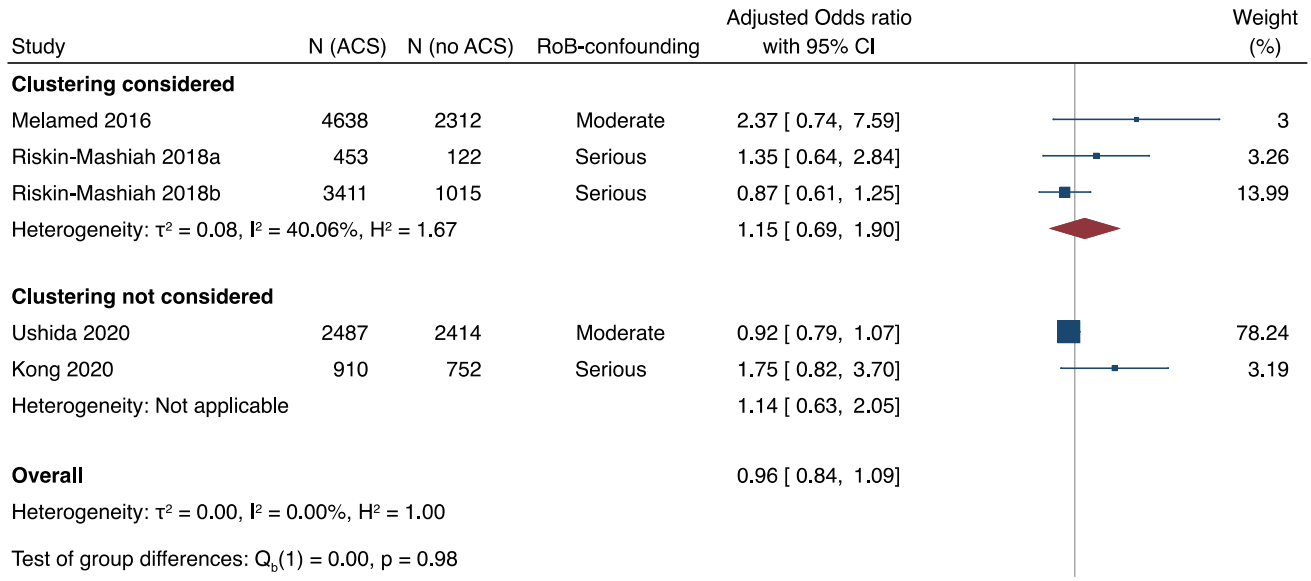
Appendix 14. Forest plot showing the odds of bronchopulmonary dysplasia among twin infants who were exposed vs. unexposed to antenatal corticosteroids. Studies without critical risk of bias due to confounding were included in the meta-analysis. Note: RoB-confounding = risk of bias due to confounding.



Appendix 15. Forest plot showing the odds of necrotising enterocolitis among twin infants who were exposed vs. unexposed to antenatal corticosteroids. Studies without critical risk of bias due to confounding were included in the meta-analysis. Note: RoB-confounding = risk of bias due to confounding.

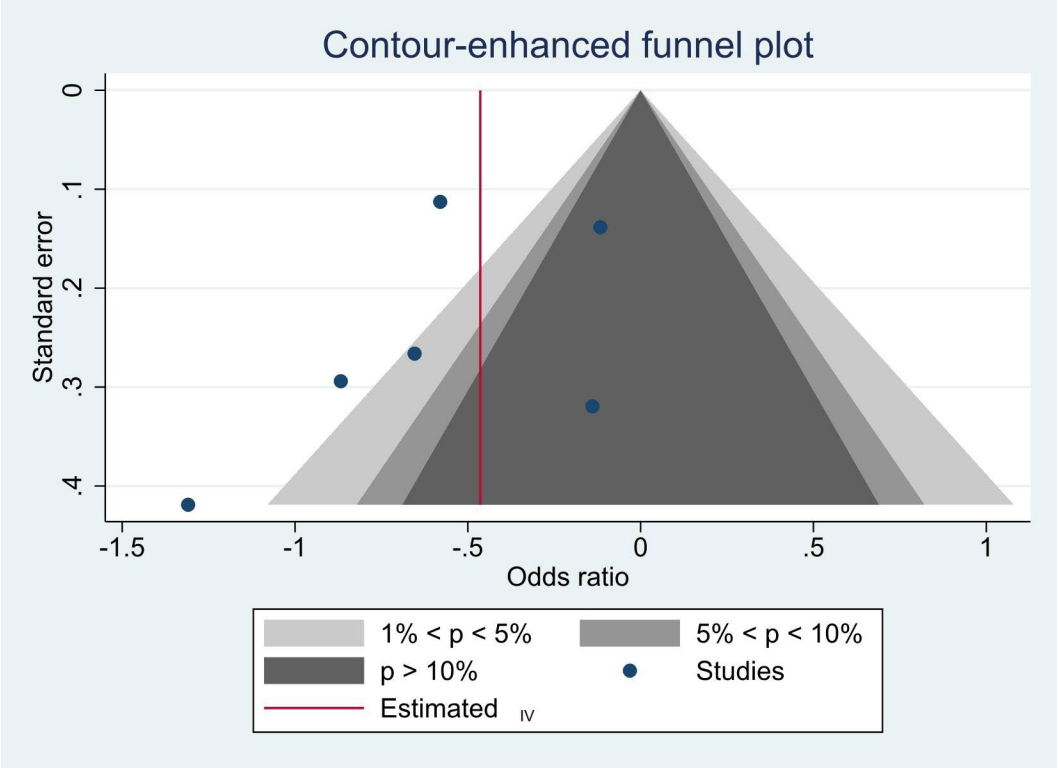


Appendix 16. Forest plot showing the odds of periventricular leukomalacia among twin infants who were exposed vs. unexposed to antenatal corticosteroids. Studies without critical risk of bias due to confounding were included in the meta-analysis. Note: RoB-confounding = risk of bias due to confounding.

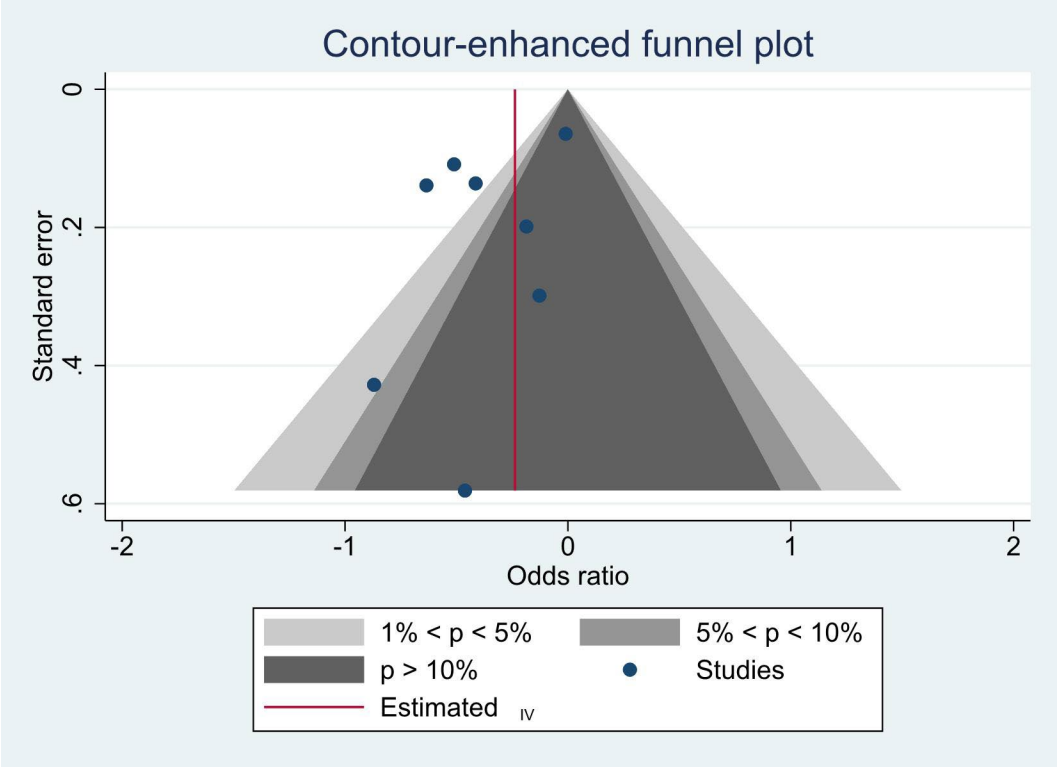


Appendix 17. Forest plot showing the odds of retinopathy of prematurity among twin infants who were exposed vs. unexposed to antenatal corticosteroids. Studies without critical risk of bias due to confounding were included in the meta-analysis. Note: RoB-confounding = risk of bias due to confounding.

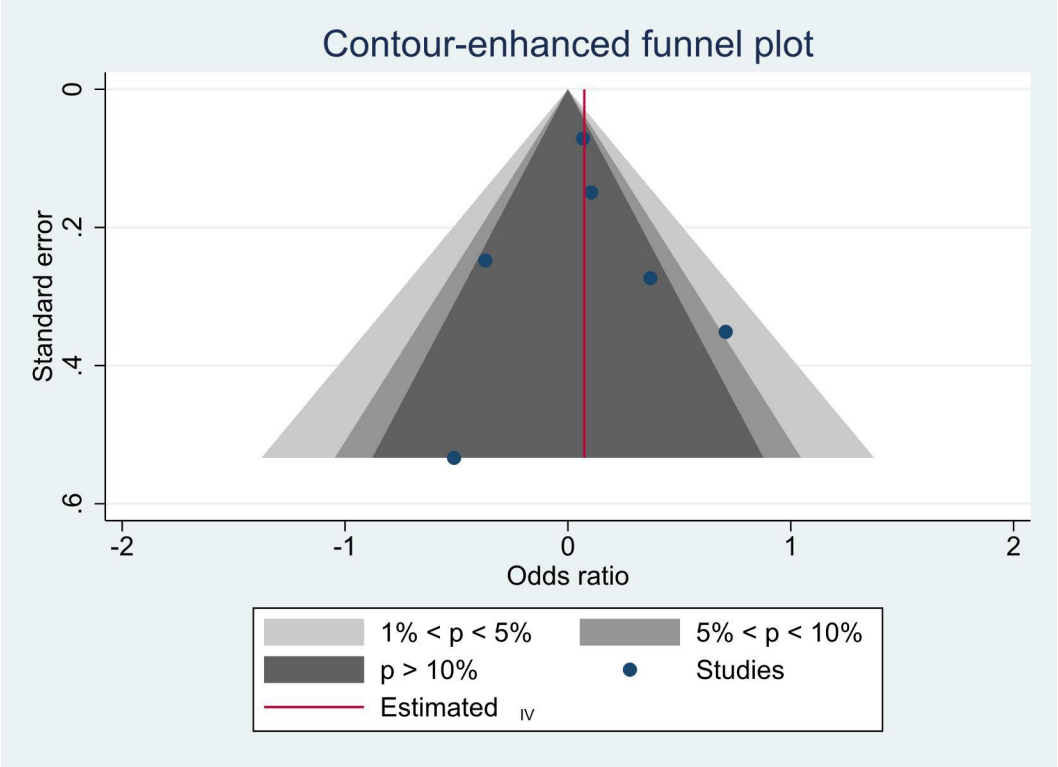
Appendix 18-22



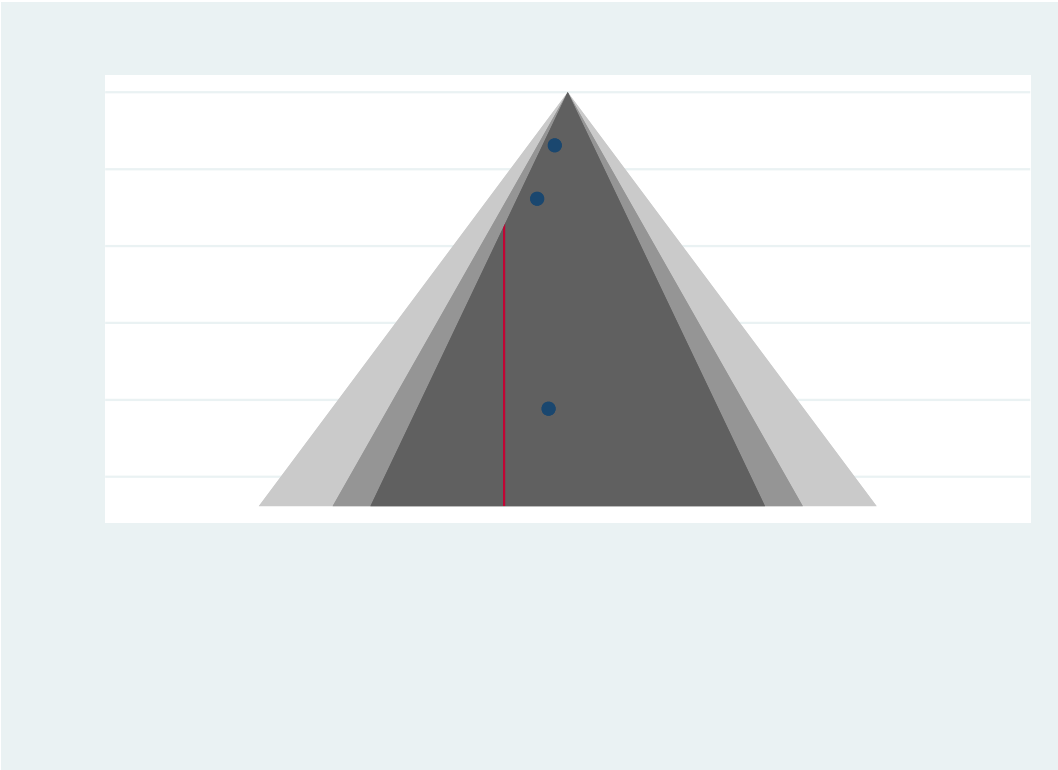
Appendix 18. Funnel plot for neonatal mortality (adjusted).



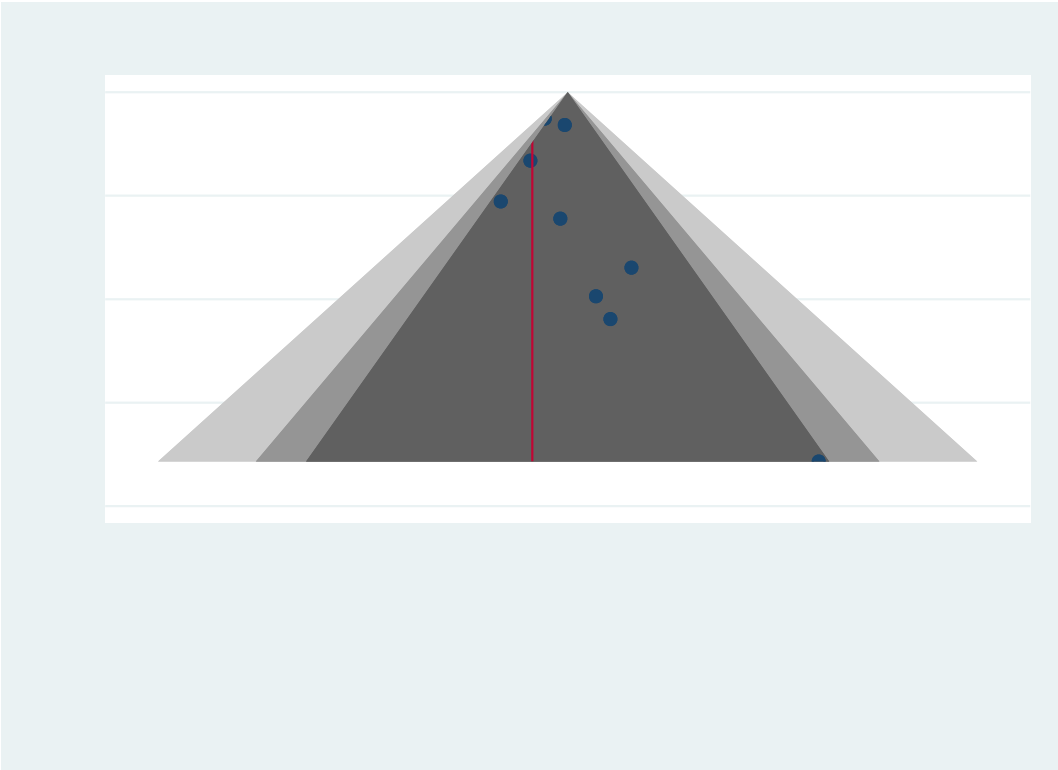
Appendix 19. Funnel plot for respiratory distress syndrome (adjusted).



Appendix 20. Funnel plot for bronchopulmonary dysplasia (adjusted).



Appendix 21. Funnel plot for neonatal mortality (crude).



Appendix 22. Funnel plot for respiratory distress syndrome (crude).

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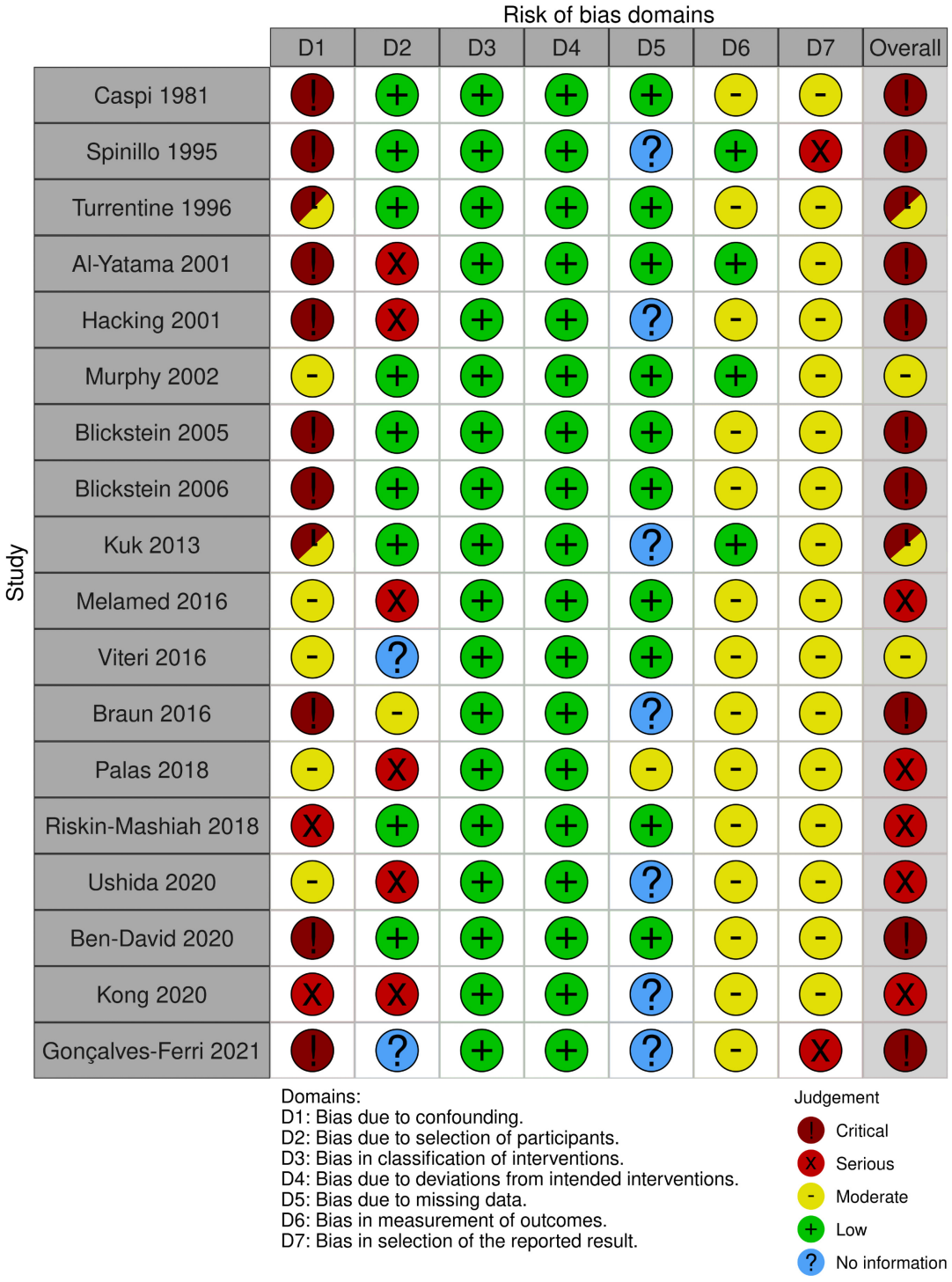
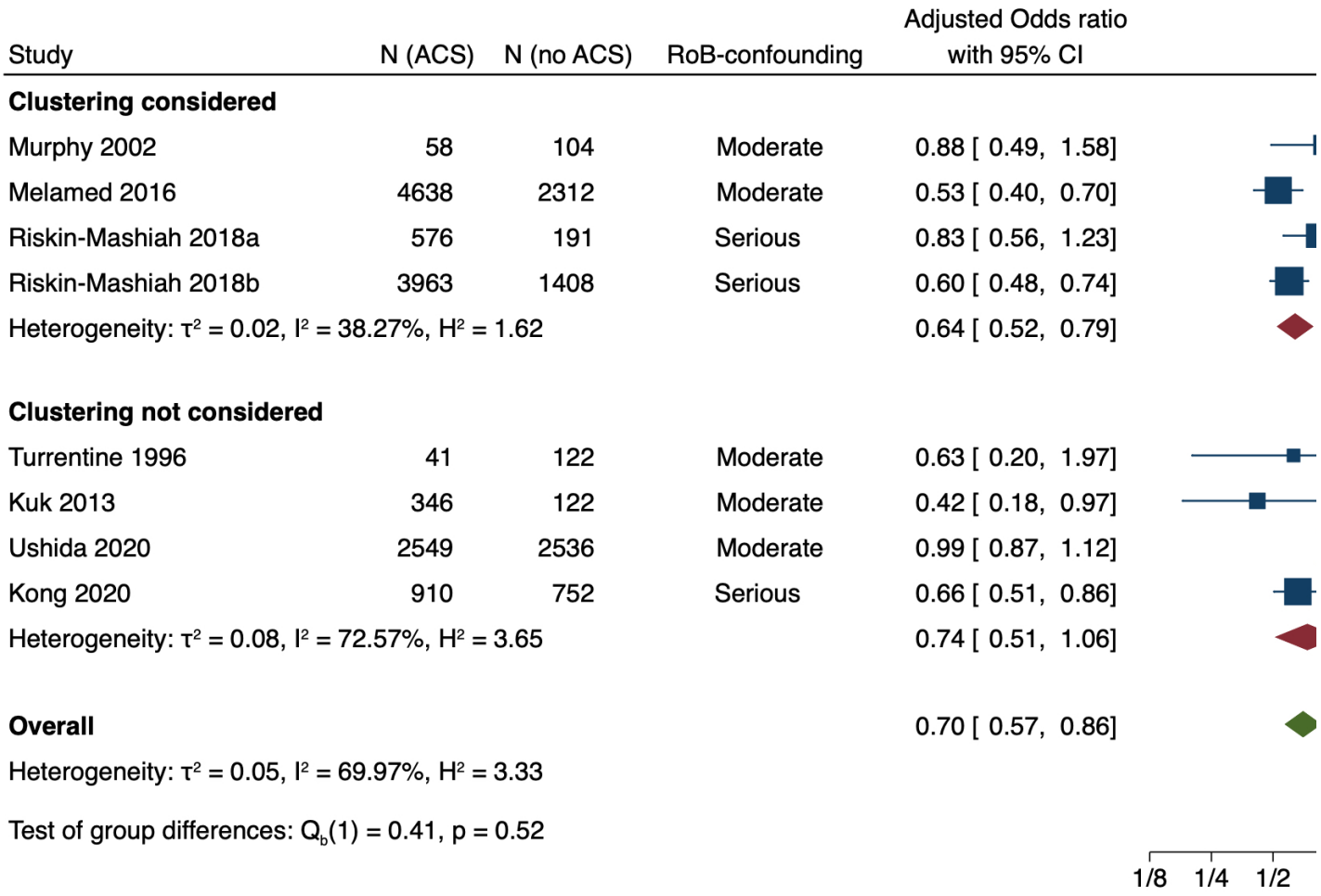

Risk of bias domains
D1
D2
D3
D4
D5
D6
D7
Overall
Study
Caspi 1981
Spinillo 1995
Turrentine 1996
Al-Yatama 2001
Hacking 2001
Murphy 2002
Blickstein 2005
Blickstein 2006
Kuk 2013
Melamed 2016
Viteri 2016
Braun 2016
Palas 2018
Riskin-Mashiah 2018
Ushida 2020
Ben-David 2020
Kong 2020
Gonçalves-Ferri 2021
Domains:
D1: Bias due to confounding.
D2: Bias due to selection of participants.
D3: Bias in classification of interventions.
D4: Bias due to deviations from intended interventions.
D5: Bias due to missing data.
D6: Bias in measurement of outcomes.
D7: Bias in selection of the reported result.
Judgement
Critical
Serious
Moderate
Low
No information

Study	N (ACS)	N (no ACS)	RoB-confounding	Adjusted Odds ratio with 95% CI
Clustering considered				
Melamed 2016	4638	2312	Moderate	0.42 [0.24, 0.75]
Palas 2018	272	119	Moderate	0.27 [0.12, 0.61]
Riskin-Mashiah 2018a	585	199	Serious	0.52 [0.31, 0.88]
Riskin-Mashiah 2018b	3977	1434	Serious	0.56 [0.45, 0.70]
Heterogeneity: τ^2 = 0.01, I^2 = 8.06%, H^2 = 1.09				0.51 [0.41, 0.63]
Clustering not considered				
Ushida 2020	2559	2555	Moderate	0.89 [0.68, 1.17]
Kong 2020	910	752	Serious	0.87 [0.47, 1.63]
Heterogeneity: Not applicable				0.89 [0.69, 1.14]
Overall				0.59 [0.43, 0.80]
Heterogeneity: τ^2 = 0.09, I^2 = 67.10%, H^2 = 3.04				
Test of group differences: $Q_b(1)$ = 11.07, $p < 0.001$				


Study
N (ACS)
N (no ACS)
RoB-confounding
Adjusted Odds ratio with 95% CI
Clustering considered
Murphy 2002 58 104 Moderate 0.88 [0.49, 1.58]
Melamed 2016 4638 2312 Moderate 0.53 [0.40, 0.70]
Riskin-Mashiah 2018a 576 191 Serious 0.83 [0.56, 1.23]
Riskin-Mashiah 2018b 3963 1408 Serious 0.60 [0.48, 0.74]
Heterogeneity: τ² = 0.02, I² = 38.27%, H² = 1.62 0.64 [0.52, 0.79]
Clustering not considered
Turrentine 1996 41 122 Moderate 0.63 [0.20, 1.97]
Kuk 2013 346 122 Moderate 0.42 [0.18, 0.97]
Ushida 2020 2549 2536 Moderate 0.99 [0.87, 1.12]
Kong 2020 910 752 Serious 0.66 [0.51, 0.86]
Heterogeneity: τ² = 0.08, I² = 72.57%, H² = 3.65 0.74 [0.51, 1.06]
Overall 0.70 [0.57, 0.86]
Heterogeneity: τ² = 0.05, I² = 69.97%, H² = 3.33
Test of group differences: Q_b(1) = 0.41, p = 0.52
1/8
1/4
1/2