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## Antenatal corticosteroids in preterm small-for-gestational age infants: a systematic review and meta-analysis

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# Antenatal Corticosteroids in Preterm Small-for-Gestational Age Infants: A Systematic Review and Meta-Analysis

## Condensation

Antenatal corticosteroids reduce neonatal mortality in SGA infants delivered preterm, with no apparent effect on neonatal morbidity.

**Short title:** SGA Infants and Steroids Systematic Review

## AJOG at a Glance

### *A. Why was the study conducted?*

Prior literature offers conflicting evidence guiding antenatal corticosteroid (ACS) administration in small-for-gestational age (SGA) infants given their increased endogenous steroid exposure due to pathologic intrauterine stress. The present study estimates the effect of ACS on neonatal mortality and morbidity in preterm SGA infants through a systematic literature review and meta-analysis.

### *B. What are the key findings?*

ACS administration in preterm SGA infants significantly reduces neonatal mortality, with no apparent effect on neonatal morbidity.

### *C. What does the study add to what is already known?*

The SGA population is one of clinical interest that has not been a population of focus in large-scale randomized trials evaluating ACS administration and neonatal outcomes. Our focused analysis on ACS administration in SGA infants provides the highest level of evidence currently available demonstrating benefit of ACS administration for reducing neonatal mortality in SGA infants delivered preterm.

**Keywords:** small-for-gestational age, fetal growth restriction, antenatal corticosteroids, neonatal morbidity, neonatal mortality

**ABSTRACT**

**Objective:** To estimate the effect of antenatal corticosteroid (ACS) administration on neonatal mortality and morbidity in preterm small-for-gestational age (SGA) infants through a systematic review and meta-analysis.

**Data sources:** A predefined, systematic search was conducted through Ovid Medline, Embase, Scopus, Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of Controlled Trials, World Health Organization International Clinical Trial Registry Portal, and ClinicalTrials.gov yielding 5,324 articles from 1970-2019.

**Study eligibility criteria:** Eligible studies compared neonatal morbidity and/or mortality among SGA infants delivered preterm who received ACS to those who did not.

**Study appraisal and synthesis methods:** The primary outcome was neonatal mortality. Secondary outcomes were respiratory distress syndrome (RDS), necrotizing enterocolitis (NEC), intraventricular hemorrhage and/or periventricular leukomalacia (IVH and/or PVL), bronchopulmonary dysplasia or chronic lung disease of prematurity (BPD or CLD), or neonatal sepsis. We assessed heterogeneity via Higgins  $I^2$  and Cochrane's Q test, and calculated pooled odds ratios (OR) with 95% confidence intervals (CI) using random effects models.

**Results:** Sixteen observational cohort and case-control studies published from 1995-2018 met selection criteria for the systematic review and included 8,989 preterm SGA infants. ACS administration was explicitly reported among 8,376 SGA infants; 4,631 (55.3%) received ACS and 3,741 (44.7%) did not. Thirteen studies including 6,387 preterm SGA infants were then included in the meta-analysis. Neonatal mortality was significantly lower among infants who received ACS compared to those who did not (12 studies: 12.8% vs. 15.1%, pooled odds ratio [OR] 0.63 [95% CI 0.46-0.86]), with significant heterogeneity between studies ( $I^2=55.1\%$ ,

p=0.011). There was no significant difference in RDS (12 studies: OR 0.89 [95% CI 0.69-1.15]), NEC (7 studies: OR 0.93 [95% CI 0.70-1.22]), IVH and/or PVL (10 studies: OR 0.82 [95% CI 0.56-1.20]), BPD or CLD (8 studies: OR 1.11 [95% CI 0.88-1.41]), or neonatal sepsis (6 studies: OR 1.13 [95% CI 0.86-1.49]).

**Conclusions:** These data show that ACS reduces neonatal mortality in SGA infants delivered preterm, with no apparent effect on neonatal morbidity. This supports the use of ACS to reduce neonatal mortality in pregnancies with SGA infants at risk for preterm birth.

**MANUSCRIPT BODY****Introduction**

Small-for-gestational age (SGA) is commonly defined as birthweight less than the tenth percentile. SGA infants can be either constitutionally small or pathologically growth-restricted antenatally.<sup>1-2</sup> Clinically, it can be difficult to differentiate the etiology of FGR (fetal growth restriction). Approximately 3 to 7% of newborns are affected by pathologic FGR, a major risk factor for preterm birth, and the incidence of FGR increases with increasing prematurity.<sup>3-5</sup> FGR in a preterm neonate specifically carries an increased risk of perinatal morbidity and mortality.<sup>5,6</sup>

Administration of antenatal corticosteroids (ACS) has become the standard of care in the setting of anticipated preterm delivery in order to prevent neonatal morbidity and mortality. ACS has been shown to reduce neonatal mortality by 31% in appropriate-for-gestational age (AGA) infants, with efficacy demonstrated specifically in reducing rates of respiratory distress syndrome, intraventricular hemorrhage and necrotizing enterocolitis, among other neonatal outcomes.<sup>7-9</sup> However, large-scale prospective studies evaluating the effect of ACS on preterm birth outcomes have not made small-for-gestational age (SGA) infants a primary population of focus, with data for this population limited to mostly retrospective studies. Furthermore, clinical management related to ACS administration in pregnancies with SGA infants has wide variation largely guided by expert opinion without an evidence-based consensus.

Due to pathologic intrauterine stress, SGA infants may be exposed to higher levels of endogenous corticosteroids at baseline as a result of multiple mechanisms. These mechanisms include increased fetal adrenal cortisol production, compromised ability to remove corticosteroids through the blood brain barrier or placenta, and reduced ability to block the passage of maternal cortisol across the placenta.<sup>10-18</sup> As SGA infants are already exposed to

higher levels of endogenous steroids, the additional administration of exogenous ACS prior to impending preterm delivery may not offer additional benefit. In fact, exposure to single or repeated courses of corticosteroids in utero has been associated with reduced fetal growth; impaired cardiovascular and brain development; and impaired gas exchange and physiologic adaptive mechanisms in the growth-restricted neonate.<sup>10-18</sup> Administration of exogenous ACS may ultimately alter the ability of an SGA infant to compensate for intrauterine stress caused by placental insufficiency.<sup>18</sup> As a result, some researchers have postulated that administration of exogenous steroids may even be detrimental to SGA infants.<sup>2</sup>

### *Objective*

Given limited and conflicting evidence guiding the use of ACS in SGA infants, the present study aims to summarize the totality of evidence on ACS administration in SGA infants at risk for preterm delivery. We performed a systematic literature review and meta-analysis to estimate the effect of ACS on neonatal mortality and morbidity in preterm SGA infants. We hypothesized that administration of ACS in preterm SGA infants would have limited benefit given adaptive physiologic mechanisms in SGA infants.

### **Methods**

We used a predesigned methodology according to guidelines for Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) and Meta-analyses of Observational Studies in Epidemiology (MOOSE).<sup>19,20</sup> The study protocol was registered with PROSPERO (#156264).

## Information Sources and Search Strategy

A medical librarian searched published literature for records discussing ACS (i.e. betamethasone, dexamethasone, alternate drug names and suggested synonyms for dexamethasone and betamethasone), and preterm SGA infants. The librarian created search strategies using a combination of keywords and controlled vocabulary in Ovid Medline (1946-present), Embase.com (1947-present), Scopus (1823-present), Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of Controlled Trials (CENTRAL), World Health Organization International Clinical Trial Registry Portal (WHO ICTRP), and Clinicaltrials.gov (1997-present). Animals were excluded using the OVID human filter recommended in *Cochrane Handbook for Systematic Reviews of Interventions*.<sup>21</sup> The filter was translated to exclude animals in Embase and Scopus. All search strategies were completed initially in June 2019, and a total of 10,139 results were exported to EndNote. 5,204 records were deleted after using the de-duplication processes described by Bramer et al.<sup>22</sup> A total of 4,935 unique records remained in the project library. In addition to these, 35 records were identified in ClinicalTrials.gov, and 24 in World Health Organization International Clinical Trials Registry Portal (WHO ICTRP). A manual search of bibliographies of relevant articles was also performed.

The search was updated in all databases again in May 2020. A total of 10,151 search results were exported from the databases without any date limits and were added to the project Endnote project library (15086). A total of 9,824 duplicates were removed and deleted revealing 330 new citations. Due to the search and site no longer being available, the World Health Organization International Clinical Trials Registry Portal (WHO ICTRP) was not searched in May 2020. All references were exported to an excel workbook for review. Fully reproducible search strategies for each database can be found in the appendix.

*Eligibility Criteria and Study Selection*

Two investigators (SAB and KEB) independently screened abstracts and articles pertaining to ACS administration that reported on neonatal mortality and/or other perinatal outcomes that contribute to overall neonatal morbidity or mortality in SGA infants, and extracted data from each study. Study corresponding authors were contacted via email in attempt to obtain missing data for outcomes of interest. Discrepancies in coding required agreement between authors (SAB, KEB and MT) to be considered resolved.

Studies were included if they reported on SGA infants delivered preterm that received ACS, either betamethasone or dexamethasone, prior to delivery. Included studies reported on neonatal mortality and/or any of the following adverse perinatal outcomes: respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD) or chronic lung disease of prematurity (CLD), necrotizing enterocolitis (NEC), intraventricular hemorrhage (IVH) and/or periventricular leukomalacia (PVL), or neonatal sepsis after delivery.

Studies were excluded if they were a review article; included non-human, animal fetuses; did not report on outcomes distinctly for SGA infants according to ACS administration; analyzed combined effect of surfactant and steroids on perinatal outcomes or compared steroids to an alternative intervention; reported on the effect of repeated or “rescue” doses of steroids; included duplicate data previously reported in another publication by the same author; or included multiple gestations. Additionally, studies were excluded from the meta-analysis if they did not report raw data for the included aforementioned neonatal outcomes.



### *Data Extraction*

The primary outcome was neonatal mortality. Secondary outcomes of interest were RDS, BPD or CLD, IVH and/or PVL, NEC and neonatal sepsis, as defined in Supplementary Table 1.

Long term childhood neurodevelopmental outcomes were also extracted when available.

For each study, when data were available, we extracted mean maternal age, maternal parity, mean gestational age at delivery, mean birth weight, number of infants delivered via Cesarean section, infant sex, number of infants who received surfactant, number of infants affected by chorioamnionitis, and use of surfactant or mechanical ventilation postnatally. Maternal risk factors and co-morbidities were also extracted, including gestational or pre-gestational diabetes mellitus and maternal hypertensive disorders (chronic hypertension, pregnancy-induced hypertension, pre-eclampsia, eclampsia or HELLP syndrome). Each of the aforementioned variables was stratified by the number of SGA infants who did or did not receive ACS.

### *Data Synthesis*

Meta-analysis was performed using the metan add-on program in Stata (Stata 2015 Release 12, StataCorp, Texas, USA). Two-by-two contingency tables were created to compare the presence or absence of neonatal mortality or adverse neonatal outcome stratified by ACS administration. Although the majority of studies were cohort studies, we calculated pooled odds ratios (OR) as one case control study was included. Random effects models were used to account for clinical heterogeneity between studies even when statistical heterogeneity was not evident. To further account for heterogeneity related to varied time periods among included studies, we also performed a subgroup analysis for neonatal mortality among studies that evaluated patients

up to the year 2010 analyzed separately from those that evaluated patients beyond the year 2010. Forest plots were created to visually assess both effect size and identify outliers.

We estimated heterogeneity across studies and tested its significance using the Higgins  $I^2$  statistic and Cochrane's Q test.  $I^2$  of 50% was considered evidence of significant heterogeneity. Publication bias was evaluated visually using funnel plots and asymmetry was tested statistically using Egger's test.

### *Assessment of Risk of Bias*

Quality assessment to determine risk of bias of included studies was also performed using the Downs and Black assessment tool.<sup>23</sup> The checklist is composed of 27 questions, with a total possible score of 28 for randomized and 25 for non-randomized studies. Downs and Black score ranges are given corresponding quality levels: excellent (26–28); good (20–25); fair (15–19); and poor ( $\leq 14$ ). Only randomized studies can achieve a quality level of excellent according to the scoring methodology of the Downs and Black checklist. As all studies were observational and not randomized, the maximum quality level of included studies is “good.”

## **Results**

### *Study Selection*

The search yielded 5,324 articles published from 1970-2019. Sixteen observational cohort and case-control studies published from 1995-2018 met inclusion and exclusion criteria and were selected for the systematic review.<sup>24-39</sup> In aggregate, the 16 studies included in the systematic review included 8,989 preterm SGA infants.

### Study Characteristics

All studies were observational, with fourteen retrospective cohort studies, one prospective cohort study, and one case-control study included (Table 1). ACS administration was explicitly reported among 8,376 SGA infants; 4,631 (55.3%) received ACS and 3,741 (44.7%) did not. Nine studies reported on type of ACS administered, with betamethasone the most commonly used in 8 studies; two studies included infants who received either betamethasone or dexamethasone. Ten studies specified birth weight less than the tenth percentile in their definition for SGA. Additional maternal and neonatal characteristics in the included studies are detailed in Tables 2 and 3, respectively.

Table 4 contains weighted-averages for the primary and all secondary outcomes among SGA infants stratified by ACS administration. Fourteen studies reported on overall neonatal mortality, 14 studies reported on RDS, 8 studies reported on BPD or CLD, 7 studies reported on NEC and 6 studies reported on neonatal sepsis. Among 11 studies that reported on IVH and/or PVL, seven studies reported on IVH alone; 4 studies included grade 3 or 4 IVH and/or PVL as a combined outcome.<sup>26,32,37,38</sup>

Long-term neurodevelopmental outcomes were reported among three studies.<sup>30,31,35</sup> Two studies reported on severe global delay up to three years of age as determined by a development quotient (DQ) less than 70, or more than two standard deviations below the mean DQ of 100, as defined by the Kyoto Scale of Psychological Development test or the Griffiths test for mental developmental scales.<sup>40,41</sup> Among infants with long term follow up data, 16.8% (54/321) of infants that received ACS had severe global delay, while 13.5% (71/525) infants that did not receive ACS had severe global delay. Schaap et al. reported abnormal behavior in long-term

follow-up at school age of surviving infants, with 43% (21/62) of children who received ACS and 45% (19/45) of children who did not receive ACS exhibiting abnormal behavior.<sup>34</sup> However, this study did not report how it classified abnormal behavior.

### *Meta-analysis and Synthesis of Results*

Three studies did not provide raw data for neonatal outcomes according to ACS administration and thus were unable to be included in the meta-analysis. Among these three studies, Griffin et al. reported odds ratios for neonatal mortality; Bernstein et al. reported odds ratios for RDS; and Ley et al. reported odds ratios for neonatal mortality, RDS and IVH and/or PVL (Table 4).<sup>29,36,38</sup> The remaining thirteen studies reported raw data for neonatal outcomes among 6,387 preterm SGA infants and were quantitatively synthesized in the meta-analysis.<sup>24-28,30-35,37,39</sup>

ACS administration was associated with a significant reduction in neonatal mortality (12 studies: 12.8% vs. 15.1%, OR 0.63 [95% confidence interval (CI) 0.46-0.86]). There was significant heterogeneity between studies ( $I^2=55.1\%$  [ $p=0.011$ ]) (Figure 2). There was no evidence of publication bias (Figure 3, Egger's  $p=0.87$ ). In the subgroup analysis by study year, no significant difference in mortality was detected among studies that followed patients up to 2010 (OR 0.93 [95% CI 0.71, 1.21],  $I^2=0.0\%$  [ $p=0.452$ ], 7 studies), but a significant reduction in mortality was found among infants who received ACS among studies that followed patients after 2010 (OR 0.48 [95% CI 0.38, 0.60],  $I^2=5.0\%$  [ $p=0.378$ ]; 5 studies, Figure 4).

Among the secondary outcomes, there was no significant difference in RDS (12 studies: OR 0.89 [95% CI 0.69-1.15],  $I^2=66.7\%$  [ $p=0.001$ ], Supplementary Figure 1), NEC (7 studies: OR 0.93 [95% CI 0.70-1.22],  $I^2=0.0\%$  [ $p=0.447$ ], Supplementary Figure 2), or IVH and/or PVL

(10 studies: OR 0.82 [95% CI 0.56-1.20],  $I^2=53.1\%$  [ $p=0.024$ ], Supplementary Figure 3). Among the 3 studies that reported on individual values for IVH and PVL, only the values for IVH were included in the forest plot for IVH and/or PVL as IVH was more common in these studies.<sup>30-32</sup> Significant heterogeneity was seen in studies reporting RDS and IVH and/or PVL, as reflected by the  $I^2$  statistic. There was no significant difference in risk of BPD or CLD (8 studies: OR 1.11 [95% CI 0.88-1.41],  $I^2=40.2\%$  [ $p=0.111$ ], Supplementary Figure 4) and neonatal sepsis (6 studies: OR 1.13 [95% CI 0.86-1.49],  $I^2=0.0\%$  [ $p=0.583$ ], Supplementary Figure 5).

### *Risk of Bias of Included Studies*

In the quality assessment of included studies, the majority of studies were assessed to be “fair” quality, with two studies determined to be of “good” quality and two studies of “poor” quality (Table 5). Only two studies performed a power calculation and external validity was unable to be determined in most studies. While lack of randomization decreased the quality of all included studies, all studies achieved at least average (e.g. score of 3 or higher) internal validity in both the bias and confounding assessments by using appropriate statistical regression to adjust for potential confounders in the provided analyses.

### **Comment**

#### *Main Findings and Comparison with Existing Literature*

We found that ACS reduces neonatal mortality in SGA infants delivered preterm, with no apparent effect on individual neonatal morbidities. Our results are similar to those of a 2016 systematic review and meta-analysis of 2,846 SGA infants in eight studies conducted up until 2010 that found that administration of ACS to growth-restricted preterm infants did not improve

neonatal morbidity.<sup>42</sup> However, in contrast to our findings, the 2016 meta-analysis was unable to detect a reduction in neonatal mortality with ACS. Our meta-analysis includes five studies with 2,982 SGA infants (46.7% of the study population included in the meta-analysis) followed after 2010, 2,124 (71.2%) of whom received ACS. Our meta-analysis provides a more current and comprehensive update to prior available data and supports ACS administration to SGA infants to reduce neonatal mortality.

Of note, studies in our analysis that followed patients beyond 2010 include data predominately from the 2000s to 2010s, whereas studies that followed patients up to 2010 included patient data also from the 1980s and 1990s. Multiple aspects of medical care and technology have evolved over the past few decades in an effort to reduce infant mortality with improved antenatal interventions, neonatal resuscitation, and other postnatal management among preterm infants. While our subgroup analysis seeks to account for these differences according to study period, it is plausible the reduction in mortality seen in studies that followed patients beyond 2010 could be attributed to other advancements in medical care for SGA infants delivered preterm, not solely due to ACS administration.

### *Strengths and Limitations*

Our study offers several strengths. We included a large representative sample of 8,989 preterm SGA infants, most with birthweight less than the tenth percentile. We used a predefined protocol and comprehensive search strategy to limit selection bias. The SGA population as the specific target in our analysis represents a major strength of our study as SGA infants, albeit an important population of clinical interest, have been either excluded from prior large-scale trials

evaluating ACS administration and neonatal outcomes or not specifically a population of focused analysis in these trials.

As with all meta-analyses, the limitations of the primary studies must be considered. Eleven of the thirteen included studies included in the meta-analysis were retrospective cohort studies, inherently limited in their study design compared to prospective or randomized controlled trials studies. Most studies did not distinguish etiology of SGA infants, whether constitutional versus pathologic, but the benefits and risks of ACS likely vary according to their physiology. As a result of variable definitions for SGA, we were unable to perform a subgroup analysis based on etiology of SGA or to evaluate for differences in the primary or secondary outcomes for more or less severely growth-restricted infants (for example, less than the fifth percentile versus less than the tenth percentile). Missing data for secondary outcomes, and variable ways in which data were reported or outcomes were defined, also limited data synthesis. Gestational age at delivery was highly variable and individual studies included neonates over a broad range of gestational ages, thus limiting our ability to perform subgroup analysis comparing outcomes among very early preterm (less than 28 or 32 weeks' gestation, for example) versus preterm infants at more advanced gestational ages (32 to 34 weeks' gestation). Similarly, heterogeneity in type of steroid used, betamethasone versus dexamethasone, limited subgroup analysis to determine which may be preferential in SGA infants. Few studies reported on what percentage of infants, if any, received a rescue course of ACS, nor did they report on the average time interval from ACS administration to infant delivery, specifically how close the timing of ACS administration was within the optimal window of 48 hours to within seven days of delivery. However, five of the sixteen included studies did exclude infants with suboptimal or partial ACS administration less than 24 hours before birth or greater than 7 days before delivery.

Future studies should further evaluate the effect of ACS administration on SGA infants in the late preterm period from 34 to 37 weeks and in non-singleton pregnancies, as data on ACS use in late preterm and multiple gestations is limited. In fact, the majority of studies excluded multiple gestations. More expansive investigation is also needed to further identify the effect of ACS on long term neurodevelopmental childhood outcomes in SGA infants, outcomes among constitutionally versus pathologically growth-restricted infants who receive ACS, and the benefit or harm of repeated or rescue doses of steroids in SGA infants delivered preterm.

### *Conclusions and Implications*

Despite these limitations, our findings suggest ACS administration among preterm SGA infants could be beneficial in reducing neonatal mortality. Our study provides evidence-based support for the continued clinical use of ACS as the standard of care for reduction of neonatal mortality among infants at risk of preterm birth in the next seven days, including the SGA population, in accordance with current guidance set for by the American College of Obstetricians and Gynecologists.<sup>43</sup> Although a large randomized-controlled trial (RCT) would provide a higher level of evidence and reduce the effect of bias and heterogeneity on study outcomes, an RCT is likely not feasible to evaluate the effect of ACS administration in SGA infants due to both ethical reasons and patient preference for an intervention that is likely to be beneficial. Our meta-analysis of thirteen observational studies provides the highest level of evidence currently available demonstrating benefit of ACS administration for reducing neonatal mortality in SGA infants at risk of preterm delivery.



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**FIGURE LEGENDS****Figure 1. Flow Chart of the Literature Review**

Flow chart demonstrates the literature search, including inclusion and exclusion of selected studies.

**Figure 2. Forest Plots for Neonatal Mortality**

Forest plot demonstrates a significant reduction in neonatal mortality for SGA infants that received ACS.

**Figure 3. Funnel Plot for Publication Bias for Overall Mortality**

Funnel plot demonstrates symmetry for studies that reported overall mortality, suggesting a lack of publication bias.

**Figure 4. Forest Plots for Neonatal Mortality by Study Year**

Forest plot demonstrates a significant reduction in neonatal mortality for SGA infants that received ACS among studies that followed patients after 2010, but no significant difference in mortality among studies that followed patients up to 2010.

**Supplementary Figure 1. Forest Plot for RDS**

Forest plot demonstrates no significant reduction in RDS with ACS administration to SGA infants.

**Supplementary Figure 2. Forest Plot for NEC**

Forest plot demonstrates no significant reduction in NEC with ACS administration to SGA infants.

**Supplementary Figure 3. Forest Plot for IVH and/or PVL**

Forest plot demonstrates no significant reduction in IVH and/or PVL with ACS administration to SGA infants.

**Supplementary Figure 4. Forest Plot for BPD or CLD**

Forest plot demonstrates no significant reduction in BPD or CLD with ACS administration to SGA infants.

**Supplementary Figure 5. Forest Plot for Neonatal Sepsis**

Forest plot demonstrates no significant reduction in neonatal sepsis with ACS administration to SGA infants.

**Table 1. Baseline Study Characteristics**

| Author  | Publication year<br>(study years) | Country              | Study design         | Gestational age at<br>delivery<br>(weeks) | Type of<br>steroid | SGA defined   | Number of SGA<br>infants<br>(n) | Number of SGA<br>infants<br>receiving ACS<br>(n) | Number of SGA<br>infants not<br>receiving ACS<br>(n) |
|---|-----------------------------------|----------------------|----------------------|---|--------------------|---|---------------------------------|--|--|
| Kim   | 2018<br>(2009-2016)               | Korea                | Retrospective cohort | 29-34                                     | D                  | BW <10%ile  | 82                              | 45   | 37   |
| Collaborative Study Group<br>for Respiratory Distress in<br>Preterm Infants<br>(CSGRDSP1) | 2017<br>(2013-2014)               | China                | Retrospective cohort | 24-34                                     | -                  | -   | 602                             | -  | -  |
| Melamed   | 2016<br>(2010-2014)               | Canada               | Retrospective cohort | 24-33w6d                                  | B or D             | BW <10%ile  | 918                             | 698  | 220  |
| Hoellen   | 2016<br>(2000-2011)               | Germany              | Retrospective cohort | 22w5d-29w6d                               | -                  | early onset FGR <32weeks and<br>BW <10%ile  | 92                              | 58   | 23   |
| Riskin-Mashiah  | 2015<br>(1995-2012)               | Israel               | Retrospective cohort | 24-31                                     | -                  | BW <10%ile  | 1771                            | 1246   | 525  |
| Griffin   | 2015<br>(2005-2012)               | United States        | Retrospective cohort | 22-29w6d                                  | -                  | BW <1%ile   | 648                             | 271  | 377  |
| Ishikawa  | 2015<br>(2003-2007)               | Japan                | Retrospective cohort | 22-33w6d                                  | B                  | BW <10%ile  | 1929                            | 719  | 1210   |
| Mitsiakos   | 2013<br>(-)                       | Canada               | Retrospective cohort | 24-31w6d                                  | B                  | BW <10%ile  | 149                             | 87   | 62   |
| van Stralen   | 2009<br>(2001-2005)               | Netherlands          | Retrospective cohort | <34                                       | B                  | BW <3%ile   | 88                              | 54   | 34   |
| Torrance  | 2007<br>(1999-2003)               | Netherlands          | Retrospective cohort | <34                                       | B                  | Abnormal PI, UA or MCA<br>dopplers  | 165                             | 146  | 19   |
| Foix-L'Helias   | 2005<br>(1993-1996)               | France               | Retrospective cohort | 24-31                                     | -                  | FGR antenatally suspected and<br>BW <10%ile   | 151                             | 96   | 55   |
| Schaap  | 2001<br>(1984-1991)               | Netherlands          | Case-control         | 26-31                                     | B                  | fundal height and biometry less<br>than dates; placental dysfunction<br>confirmed on histopathology | 124                             | 62   | 62   |
| Bernstein   | 1999<br>(1991-1996)               | Canada/United States | Retrospective cohort | 25-30                                     | -                  | BW <10%ile  | 1720                            | 937  | 783  |
| Elimian   | 1999<br>(1990-1997)               | United States        | Retrospective cohort | -   | B                  | BW <10%ile  | 220                             | 63   | 157  |
| Ley   | 1997<br>(1985-94)                 | Sweden               | Retrospective cohort | 25-32                                     | -                  | Use of growth curve based on<br>longitudinal EFW on US  | 234                             | 117  | 117  |
| Spinillo  | 1995<br>(1988-1993)               | Italy                | Prospective cohort   | <35                                       | B or D             | BW<10% and AC or HC <10%ile<br>on US  | 96                              | 32   | 64   |

\*SGA=small-for-gestational age, ACS=antenatal corticosteroids, B=betamethasone, D=dexamethasone, BW=birth weight, PI=pulsatility index, UA=umbilical artery, MCA=middle cerebral artery, FGR=fetal growth restriction, EFW=estimated fetal weight, US= ultrasound, AC=abdominal circumference, HC=head circumference

†Blank cells represent missing data



**Table 2. Maternal Characteristics**

| Author<br>(publication year) | Number of<br>SGA infants<br>receiving ACS<br>(n) | Number of SGA<br>infants not<br>receiving ACS<br>(n) | Mean maternal<br>age<br>(years $\pm$ SD) |                | Nulliparity<br>(n, %) |               | Maternal diabetes<br>(n, %) |             | Maternal hypertensive<br>disorder<br>(n, %) |               | Chorioamnionitis <sup>†</sup><br>(n, %)          |  |
|------------------------------|--|--|--|----------------|-----------------------|---------------|-----------------------------|-------------|---|---------------|--|--|
|                              |  |  | +ACS                                     | -ACS           | +ACS                  | -ACS          | +ACS                        | -ACS        | +ACS  | -ACS          | +ACS   | -ACS   |
| Kim<br>(2018)                | 45   | 37   | 34                                       | 33             | 29<br>(64.6)          | 26<br>(70.3)  | 2<br>(4.4)                  | 2<br>(5.4)  | 25<br>(55.6)                                | 18<br>(48.6)  | 0<br>(0.0)                                       | 1<br>(2.7)                                       |
| CSGRDSPi<br>(2017)           | -  | -  | -  | -              | -                     | -             | -                           | -           | -   | -             | -  | -  |
| Melamed<br>(2016)            | 698  | 220  | 32.4 $\pm$ 6.1                           | 30.8 $\pm$ 5.3 | 395<br>(56.6)         | 110<br>(50.0) | 71<br>(10.2)                | 16<br>(7.3) | 489<br>(70)                                 | 94<br>(44)    | 0<br>(excluded)                                  | 0<br>(excluded)                                  |
| Hoellen<br>(2016)            | 58   | 23   | -  | -              | -                     | -             | -                           | -           | -   | -             | -  | -  |
| Riskin-Mashiah<br>(2015)     | 1246   | 525  | -  | -              | -                     | -             | 64<br>(5.1)                 | 23<br>(4.4) | 753<br>(76.8)                               | 227<br>(23.2) | -  | -  |
| Griffin<br>(2015)            | 271  | 377  | -  | -              | -                     | -             | -                           | -           | -   | -             | -  | -  |
| Ishikawa<br>(2015)           | 719  | 1210   | 32.0 $\pm$ 4.9                           | 32.1 $\pm$ 5.0 | 437<br>(60.8)         | 746<br>(61.7) | 8<br>(1.1)                  | 25<br>(2.1) | 318<br>(44.2)                               | 605<br>(50.0) | clinical:<br>43 (6.0)<br>histologic:<br>46 (9.1) | clinical:<br>75 (6.3)<br>histologic:<br>46 (5.5) |
| Mitsiakos<br>(2013)          | 87   | 62   | 30.9 $\pm$ 6.3                           | 29.5 $\pm$ 6.0 | -                     | -             | -                           | -           | 41<br>(47.1)                                | 35<br>(56.4)  | 6 (6.9)  | 2 (3.2)  |
| van Stralen<br>(2009)        | 54   | 34   | 30.0 $\pm$ 5.9                           | 32.8 $\pm$ 5.5 | 22<br>(40.7)          | 8<br>(23.5)   | -                           | -           | 46<br>(85.2)                                | 24<br>(70.5)  | -  | -  |
| Torrance<br>(2007)           | 146  | 19   | -  | -              | -                     | -             | -                           | -           | 99<br>(67.8)                                | 7<br>(36.8)   | -  | -  |
| Foix-L'Hélias<br>(2005)      | 96   | 55   | -  | -              | -                     | -             | -                           | -           | -   | -             | -  | -  |
| Schaap<br>(2001)             | 62   | 62   | 29.0 $\pm$ 5.0                           | 29.0 $\pm$ 5.0 | 37<br>(59.6)          | 40<br>(64.5)  | -                           | -           | 37<br>(59.7)                                | 51<br>(82.3)  | -  | -  |
| Bernstein<br>(1999)          | 937  | 783  | -  | -              | -                     | -             | -                           | -           | -   | -             | -  | -  |
| Elimian<br>(1999)            | 63   | 157  | -  | -              | -                     | -             | -                           | -           | -   | -             | clinical:<br>2 (3.2)<br>histologic:<br>11 (17.5) | clinical:<br>6 (3.8)<br>histologic:<br>34 (21.6) |
| Ley<br>(1997)                | 117  | 117  | -  | -              | -                     | -             | -                           | -           | -   | -             | -  | -  |
| Spinillo<br>(1995)           | 32   | 64   | -  | -              | -                     | -             | -                           | -           | -   | -             | -  | -  |
| <b>Weighted-average</b>      |  |  | <b>32.0</b>                              | <b>31.7</b>    | <b>58.3%</b>          | <b>59.5%</b>  | <b>5.4%</b>                 | <b>3.3%</b> | <b>59.1%</b>                                | <b>48.9%</b>  | <b>clinical: 5.6%<br/>histologic: 7.3%</b>       | <b>clinical: 5.7%<br/>histologic: 5.9%</b>       |

\*SGA=small-for-gestational age, ACS=antenatal corticosteroids, SD=standard deviation, CSGRDSPI=Collaborative Study Group for Respiratory Distress in Preterm Infants, +ACS=infants received antenatal corticosteroids,

-ACS=infants did not receive antenatal corticosteroids

<sup>†</sup> Chorioamnionitis is clinically diagnosed unless otherwise specified

<sup>‡</sup>Blank cells represent missing data

**Table 3. Neonatal Characteristics**

| Author<br>(publication year) | Number of<br>SGA<br>infants<br>receiving<br>ACS<br>(n) | Number of<br>SGA<br>infants not<br>receiving<br>ACS<br>(n) | Mean gestational age<br>(weeks $\pm$ SD) |                | Mean<br>birthweight<br>(g) |            | Cesarean delivery<br>(n, %) |                | Male sex<br>(n, %) |               | Post-natal surfactant<br>(n, %) |              | Mechanical ventilation<br>(n, %)     |                                      |
|------------------------------|--|--|--|----------------|----------------------------|------------|-----------------------------|----------------|--------------------|---------------|---------------------------------|--------------|--------------------------------------|--------------------------------------|
|                              |  |  | +ACS                                     | -ACS           | +ACS                       | -ACS       | +ACS                        | -ACS           | +ACS               | -ACS          | +ACS                            | -ACS         | +ACS                                 | -ACS                                 |
| Kim<br>(2018)                | 45   | 37   | 32.7<br>(-)                              | 34.1<br>(-)    | 1190                       | 1450       | 40<br>(88.9)                | 34<br>(91.9)   | 24<br>(53.3)       | 11<br>(29.7)  | -                               | -            | 23<br>(51.1)                         | 14<br>(37.8)                         |
| CSGRDSPI (2017)              | -  | -  | -  | -              | -                          | -          | -                           | -              | -                  | -             | -                               | -            | -                                    | -                                    |
| Melamed (2016)               | 698  | 220  | 29.8 $\pm$ 2.6                           | 30.7 $\pm$ 2.5 | 959                        | 1061       | 636<br>(91.1)               | 178<br>(80.9)  | 369<br>(52.8)      | 114<br>(51.8) | -                               | -            | 312<br>(44.7%)                       | 106<br>(48%)                         |
| Hoellen<br>(2016)            | 58   | 23   | -  | -              | -                          | -          | -                           | -              | -                  | -             | -                               | -            | -                                    | -                                    |
| Riskin-Mashiah<br>(2015)     | 1246   | 525  | -  | -              | -                          | -          | 1169<br>(72.8)              | 436<br>(27.2)  | 657<br>(69.7)      | 286<br>(30.3) | -                               | -            | -                                    | -                                    |
| Griffin<br>(2015)            | 271  | 377  | -  | -              | -                          | -          | -                           | -              | -                  | -             | -                               | -            | -                                    | -                                    |
| Ishikawa<br>(2015)           | 719  | 1210   | 29.1 $\pm$ 2.6                           | 29.7 $\pm$ 2.7 | 886                        | 959        | 661<br>(91.9)               | 1058<br>(87.4) | 386<br>(53.8)      | 615<br>(50.9) | -                               | -            | -                                    | -                                    |
| Mitsiakos<br>(2013)          | 87   | 62   | 27.5 $\pm$ 2.5                           | 27.8 $\pm$ 2.5 | 779                        | 787        | 73<br>(83.9)                | 53<br>(85.5)   | 34<br>(39.1)       | 615<br>(50.9) | -                               | -            | -                                    | -                                    |
| van Stralen<br>(2009)        | 54   | 34   | 30.0 $\pm$ 1.7                           | 30.4 $\pm$ 1.7 | -                          | -          | 50<br>(92.6)                | 33 (97.1)      | 21<br>(38.9)       | 15<br>(44.1)  | 19<br>(35.2)                    | 13<br>(38.2) | 30<br>(55.6%)                        | 18<br>(52.9%)                        |
| Torrance<br>(2007)           | 146  | 19   | 30.3 $\pm$ 1.9                           | 31.0 $\pm$ 1.6 | 899                        | 903        | 13<br>(95.2)                | 19<br>(100.0)  | 79<br>(54.1)       | 9<br>(47.4)   | 45<br>(30.8)                    | 3<br>(15.8)  | 66<br>(45.2%)                        | 11<br>(57.9%)                        |
| Foix-L'Helias<br>(2005)      | 96   | 55   | -  | -              | -                          | -          | -                           | -              | -                  | -             | -                               | -            | -                                    | -                                    |
| Schaap<br>(2001)             | 62   | 62   | 29.9 $\pm$ 1.3                           | 30.3 $\pm$ 1.0 | 943                        | 987        | 62<br>(100.0)               | 62<br>(100.0)  | 39<br>(62.9)       | 39<br>(62.9)  | 4<br>(6.5)                      | 9<br>(14.5)  | 31<br>(50.0%)                        | 27<br>(43.5%)                        |
| Bernstein<br>(1999)          | 937  | 783  | -  | -              | -                          | -          | -                           | -              | -                  | -             | -                               | -            | -                                    | -                                    |
| Elimian<br>(1999)            | 63   | 157  | -  | -              | -                          | -          | -                           | -              | -                  | -             | 17<br>(27.0)                    | 31<br>(19.7) | -                                    | -                                    |
| Ley<br>(1997)                | 117  | 117  | -  | -              | -                          | -          | -                           | -              | -                  | -             | -                               | -            | -                                    | -                                    |
| Spinillo<br>(1995)           | 32   | 64   | -  | -              | -                          | -          | -                           | -              | -                  | -             | -                               | -            | -                                    | -                                    |
| <b>Weighted-average</b>      |  |  | <b>29.5</b>                              | <b>29.9</b>    | <b>921</b>                 | <b>978</b> | <b>92.6%</b>                | <b>86.4%</b>   | <b>52.6%</b>       | <b>51.2%</b>  | <b>26.2%</b>                    | <b>20.6%</b> | <b>46.0%<br/>(mean<br/>0.8 days)</b> | <b>47.3%<br/>(mean<br/>2.2 days)</b> |

\*SGA=small-for-gestational age, ACS=antenatal corticosteroids, SD=standard deviation, CSGRDSPI=Collaborative Study Group for Respiratory Distress in Preterm Infants, +ACS=infants received antenatal corticosteroids,

-ACS=infants did not receive antenatal corticosteroids

†Blank cells represent missing data

**Table 4. Neonatal Outcomes**

| Author<br>(Publication<br>Year)  | Number<br>of SGA<br>infants<br>receiving<br>ACS<br>(n) | Number<br>of SGA<br>infants<br>not<br>receiving<br>ACS (n) | Neonatal<br>mortality<br>(n, %) |                 | RDS<br>(n, %)                 |                   | BPD or CLD<br>of<br>Prematurity<br>(n, %) |                  | IVH<br>and/or<br>PVL<br>(n, %)                |   | NEC<br>(n, %)     |                  | Neonatal<br>sepsis<br>(n, %) |              |
|----------------------------------|--|--|---------------------------------|-----------------|-------------------------------|-------------------|---|------------------|---|---|-------------------|------------------|------------------------------|--------------|
|                                  |  |  | +ACS                            | -ACS            | +ACS                          | -ACS              | +ACS                                      | -ACS             | +ACS  | -ACS  | +ACS              | -ACS             | +ACS                         | -ACS         |
| Kim<br>(2018)                    | 45   | 37   | 1<br>(2.2)                      | 1<br>(2.7)      | 22<br>(48.9)                  | 11<br>(29.7)      | -   | -                | 4<br>(8.7)                                    | 1<br>(2.7)                                    | 5<br>(11.1)       | 2<br>(5.4)       | 9<br>(20.0)                  | 3<br>(8.1)   |
| CSGRDSPi<br>(2017)               | -  | -  | 13/77<br>(16.9)                 | 17/53<br>(32.1) | 37/77<br>(48.1)               | 42/53<br>(79.2)   | -   | -                | 27/248<br>(10.9)                              | 13/224<br>(5.8)                               | -                 | -                | -                            | -            |
| Melamed<br>(2016)                | 698  | 220  | 48<br>(6.9)                     | 27<br>(12.3)    | 364<br>(52.1)                 | 98<br>(44.5)      | 134<br>(19.2)                             | 30<br>(14.5)     | 35<br>(5.0)                                   | 20<br>(9.1)                                   | 30<br>(4.3)       | 7<br>(1.4)       | -                            | -            |
| Hoellen<br>(2016)                | 58   | 23   | 6<br>(10.3)                     | 10<br>(43.5)    | -                             | -                 | -   | -                | -   | -   | -                 | -                | -                            | -            |
| Riskin-<br>Mashiah<br>(2015)     | 1246   | 525  | 240<br>(19.3)                   | 169<br>(32.2)   | 840/1236<br>(68.0)            | 365/505<br>(72.3) | 225/1009<br>(22.3)                        | 68/363<br>(18.7) | IVH:<br>77/1180 (6.5)<br>PVL:<br>41/992 (4.1) | IVH:<br>49/446 (11.0)<br>PVL:<br>30/347 (8.6) | 101/1235<br>(8.2) | 55/505<br>(10.9) | -                            | -            |
| Griffin <sup>†</sup><br>(2015)   | 271  | 377  | OR 0.16 (0.07-0.34)             |                 | -                             | -                 | -   | -                | -   | -   | -                 | -                | -                            | -            |
| Ishikawa<br>(2015)               | 719  | 1210   | 56<br>(7.8)                     | 92<br>(7.6)     | 341<br>(47.4)                 | 510<br>(42.1)     | 194<br>(27)                               | 250<br>(21)      | IVH:<br>54 (7.5)<br>PVL:<br>11 (1.5)          | IVH:<br>99 (8.2)<br>PVL:<br>28 (2.3)          | 13<br>(1.8)       | 15<br>(1.2)      | 51<br>(7.1)                  | 75<br>(6.2)  |
| Mitsiakos<br>(2013)              | 87   | 62   | 19<br>(21.8)                    | 9<br>(14.5)     | 45<br>(51.7)                  | 36<br>(58.1)      | 16<br>(23.5)                              | 15<br>(28.3)     | IVH:<br>3 (3.4)<br>PVL:<br>1 (1.4)            | IVH:<br>3 (4.8)<br>PVL:<br>1 (1.8)            | 10<br>(11.5)      | 5<br>(8.0)       | 29<br>(33.3)                 | 20<br>(32.3) |
| van Stralen<br>(2009)            | 54   | 34   | 5<br>(9.3)                      | 4<br>(11.8)     | 22<br>(40.7)                  | 17<br>(50.0)      | 6<br>(11.1)                               | 4<br>(11.8)      | 4<br>(7.4)                                    | 1<br>(2.9)                                    | 3<br>(5.6)        | 2<br>(5.9)       | 33<br>(61.1)                 | 24<br>(70.6) |
| Torrance<br>(2007)               | 146  | 19   | 15<br>(10.3)                    | 3<br>(15.8)     | 64<br>(43.8)                  | 8<br>(42.1)       | 34<br>(23.3)                              | 6<br>(31.6)      | -   | -   | -                 | -                | -                            | -            |
| Foix-<br>L'Helias<br>(2005)      | 96   | 55   | 12<br>(12.5)                    | 12<br>(21.8)    | 49<br>(51.0)                  | 35<br>(63.6)      | 25<br>(26.4)                              | 21<br>(37.8)     | -   | -   | -                 | -                | -                            | -            |
| Schaap<br>(2001)                 | 62   | 62   | 9<br>(14.5)                     | 15<br>(24.2)    | 23<br>(37.1)                  | 25<br>(40.3)      | 16<br>(25.8)                              | 19<br>(30.6)     | 8<br>(12.9)                                   | 9<br>(14.5)                                   | -                 | -                | 12<br>(19.4)                 | 12<br>(19.4) |
| Bernstein <sup>†</sup><br>(1999) | 937  | 783  | -                               | -               | OR 0.70                       |                   | -   | -                | -   | -   | -                 | -                | -                            | -            |
| Elimian<br>(1999)                | 63   | 157  | 5<br>(7.9)                      | 11<br>(7.0)     | 17<br>(26.9)                  | 38<br>(24.2)      | -   | -                | 3<br>(4.8)                                    | 8<br>(5.1)                                    | 1<br>(1.6)        | 3<br>(1.9)       | 6<br>(9.5)                   | 9<br>(5.7)   |
| Ley <sup>†</sup><br>(1997)       | 117  | 117  | OR 0.53<br>(95% CI 0.21-1.32)   |                 | OR 1.20<br>(95% CI 0.62-2.34) |                   | -   | -                | OR 0.72<br>(95% CI 0.28-1.84)                 |   | -                 | -                | -                            | -            |
| Spinillo<br>(1995)               | 32   | 64   | -                               | -               | 10<br>(31.3)                  | 30<br>(46.9)      | -   | -                | 2/28<br>(7.1)                                 | 18/58<br>(31.0)                               | -                 | -                | -                            | -            |
| <b>Weighted-<br/>average</b>     |  |  | <b>12.8%</b>                    | <b>15.1%</b>    | <b>55.3%</b>                  | <b>49.0%</b>      | <b>22.6%</b>                              | <b>20.4%</b>     | <b>6.8%</b>                                   | <b>8.8%</b>                                   | <b>5.6%</b>       | <b>4.0%</b>      | <b>13.6%</b>                 | <b>9.2%</b>  |

\*SGA=small-for-gestational age, ACS=antenatal corticosteroids, RDS=respiratory distress syndrome, BPD=bronchopulmonary dysplasia, CLD=chronic lung disease, IVH=intraventricular hemorrhage, PVL=periventricular leukomalacia, NEC=necrotizing enterocolitis, CSGRDSPI=Collaborative Study Group for Respiratory Distress in Preterm Infants, +ACS=infants received antenatal corticosteroids, -ACS=infants did not receive antenatal corticosteroids, OR=odds ratios, CI=confidence interval

<sup>†</sup> Raw data for neonatal outcomes according to ACS administration was not reported for 3 studies; only odds ratios with 95% confidence intervals were reported in these studies comparing SGA infants that received ACS to those that did not receive ACS

<sup>‡</sup> Blank cells represent missing data

**Table 5. Results of the Risk of Bias Assessment using the Downs and Black Assessment Tool**

| <b>Author<br/>(Publication<br/>Year)</b> | <b>Reporting<br/>(11)*</b> | <b>External validity<br/>(3)*</b> | <b>Bias<br/>(7)*</b> | <b>Confounding<br/>(6)*</b> | <b>Power<br/>(1)*</b> | <b>Total<br/>(28)*</b> |
|--|----------------------------|-----------------------------------|----------------------|-----------------------------|-----------------------|------------------------|
| Kim<br>(2018)                            | 10                         | 0                                 | 5                    | 3                           | 0                     | 18                     |
| CSGRDSPi<br>(2017)                       | 5                          | 0                                 | 5                    | 2                           | 0                     | 12                     |
| Melamed<br>(2016)                        | 10                         | 2                                 | 5                    | 3                           | 0                     | 20                     |
| Hoellen<br>(2016)                        | 6                          | 0                                 | 4                    | 2                           | 0                     | 12                     |
| Riskin-<br>Mashiah<br>(2015)             | 9                          | 2                                 | 5                    | 3                           | 0                     | 19                     |
| Griffin<br>(2015)                        | 7                          | 1                                 | 5                    | 3                           | 0                     | 16                     |
| Ishikawa<br>(2015)                       | 10                         | 2                                 | 5                    | 3                           | 0                     | 20                     |
| Mitsiakos<br>(2013)                      | 10                         | 0                                 | 5                    | 3                           | 0                     | 18                     |
| van Stralen<br>(2009)                    | 10                         | 0                                 | 5                    | 3                           | 0                     | 18                     |
| Torrance<br>(2007)                       | 9                          | 0                                 | 4                    | 3                           | 0                     | 16                     |
| Foix-L'Helias<br>(2005)                  | 8                          | 0                                 | 5                    | 3                           | 0                     | 16                     |
| Schaap<br>(2001)                         | 10                         | 0                                 | 5                    | 2                           | 1                     | 18                     |
| Bernstein<br>(1999)                      | 8                          | 1                                 | 4                    | 3                           | 0                     | 16                     |
| Elimian<br>(1999)                        | 10                         | 0                                 | 5                    | 3                           | 1                     | 19                     |
| Ley<br>(1997)                            | 8                          | 2                                 | 4                    | 3                           | 0                     | 17                     |
| Spinillo<br>(1995)                       | 10                         | 0                                 | 5                    | 3                           | 0                     | 18                     |

\*Maximum number can be scored in that criterion.

## APPENDIX

Supplementary Table 1. Study Outcome Definitions

| Study Outcome  | Definition   |
|--|--|
| <i>Neonatal mortality</i>  | The percentage of infants who die either during their hospital stay after delivery or up to three years of life.   |
| <i>Composite neonatal morbidity</i>  | A composite outcome of the percentage of infants affected by any of the included adverse perinatal outcomes: RDS, BPD/CLD, IVH, PVL, NEC or neonatal sepsis.   |
| <i>Respiratory distress syndrome (RDS)</i>   | Defined based on clinical criteria, such as tachypnea, chest wall retractions, grunting, and supplemental oxygen requirement, and based on radiological criteria with poor lung expansion on chest x-ray classified as RDS   |
| <i>Bronchopulmonary dysplasia (BPD)/<br/>chronic lung disease of prematurity (CLD)</i> | Oxygen supplementation required at 36 weeks' postmenstrual age or the presence of chronic respiratory distress and oxygen requirement beyond 28 days of life accompanied by a chest radiograph that showed chronic abnormalities such as persistent streaks of increased density in both lungs interspersed with normal or hyperlucent areas |
| <i>Intraventricular hemorrhage (IVH)</i>   | Bleeding within the ventricular system of the brain as defined by Papile's classification, <sup>21</sup> with the majority of studies including grades 3 and 4   |
| <i>Periventricular leukomalacia (PVL)</i>  | Necrosis of white matter near the lateral ventricles diagnosed by cranial ultrasonography  |
| <i>Necrotizing enterocolitis (NEC)</i>   | Intestines in premature infants become infected causing partial or full-thickness necrosis of the bowel  |
| <i>Neonatal sepsis</i>   | Positive blood cultures and/or need for intravenous antibiotics administration for a minimum of 7 days   |

## Search Strategies

### Ovid Medline

Date Searched: 6/11/2019; 5/13/20

Applied Database Supplied Limits: n/a

Number of Results: 2643; 2783

Search strategy was re-run on May 13, 2020. 140 additional citations found

### Full Search Strategy:

(ACS).ti,ab. OR ((antenatal\* OR prenatal\*) ADJ3 (corticosteroid\* OR corticoid\* OR glucocorticoid\* OR glucorticoid\* OR steroid\* OR CST)).ti,ab. OR ((adrenal cortex) ADJ1 (hormone\*) ADJ2 (prenatal\* OR antenatal\*)).ti,ab. OR ((prenatal\* OR antenatal\*) ADJ2 (Betamethasone OR adbeon OR becasone OR beprogel OR beta methason OR betacortril OR betadexamethasone OR betametasone OR betamethasolone OR betamethazone OR betnasol OR betnelan OR betnesol OR betnovate OR betsolan OR betsolon OR betsoport OR celestan OR celestene OR celeston\* OR cellestoderm OR cidoten OR dermobet OR diprolen OR flubenisolone OR flubenisolonvalerate OR methasone OR rinderon OR walacort)).ti,ab. OR ((prenatal\* OR antenatal\*) ADJ2 (Dexamethasone OR adrecort OR adrenocot OR aroseb dex OR aflucoson\* OR alfalyl OR anaflogistico OR arcodexan\* OR artrosone OR auxison OR azium OR bidexol OR calonat OR cebedex OR cetadexon OR colofoam OR corsona OR cortastat OR cortidex\* OR cortidexason OR cortidrona OR cortidrone OR cortisumman OR dacortina fuerte OR dacortine fuerte OR dalalone OR danasone OR de-sone la OR decacortin OR decadeltosona OR decadeltosone OR decaderm OR decadion OR decadran OR decadron\* OR decaesadril OR decaject OR decameth\* OR decasone OR decaspray OR decasterolone OR decdan OR decilone OR decofluor OR dectancyl OR dekaort OR delladec OR deltafluoren\* OR dergramin OR deronil OR desacort OR desacortone OR desadrene OR desalark OR desameton\* OR desigdrone OR dexam cortisyl OR dexam dabrosan OR dexam korti OR dexam scherosan OR dexam scherozon OR dexam scherozone OR dexam p OR dexacen 4 OR dexachel OR dexacort\* OR dexadabrosan OR dexadecadrol OR dexadrol OR dexagel OR dexagen OR dexahelvacort OR dexakorti OR dexalien OR dexalocal OR dexam OR dexamecortin OR dexameson\* OR dexametason\* OR dexamonozone OR dexam\* OR dexaport OR dexascheroson OR dexascherozon\* OR dexason\* OR dexinoral OR dexionil OR dexmethsone OR dexona OR dexone OR dexpak taperpak OR dextelan OR dextrasone OR dexycu OR dezone OR dibasona OR dexamethasone OR esacortene OR exadion OR exadione OR firmalone OR fluormethyl prednisolone OR fluormethylprednisolon\* OR fluormone OR fluorocort OR fluorodelta OR fluoromethylprednisolone OR fortacortin OR gammacorten\* OR grosodexon\* OR hexadecadiol OR hexadecadrol OR hexadiol OR hexadrol OR isnacort OR isopto\* OR lokalison f OR loverine OR luxazone OR marvidione OR maxidex OR mediamethasone OR megacortin OR mephameson\* OR metasolon\* OR methazon\* OR methylfluorprednisolone OR metisone lafi OR mexasone OR millicorten\* OR mymethasone OR neoforderx OR neofordex OR nisomethasone OR novocort OR oftan dexam OR optacorten OR optacortinol OR oradexan OR oradexon\* OR orgadron OR ozurdex OR pidexon OR policort OR posurdex OR predni f OR prednisolone f OR prodexona OR prodexone OR sanamethasone OR santenson OR santeson OR sawasone OR solurex OR spoloven OR sterasone OR thilodexine OR tobradex OR triamcimetil OR vexamet OR visumethazone OR visumethazone)).ti,ab. OR (((prenatal\* OR antenatal\*).hw. OR ((prenatal\* OR antenatal\* OR fetal OR foetal OR intrauterine OR maternal) ADJ1 (drug exposure)).ti,ab.) AND (exp adrenal cortex hormones/ OR exp glucocorticoids/ OR exp betamethasone/ OR exp dexamethasone/ OR ((adrenal cortex) ADJ1 (hormone\*)).ti,ab. OR (Corticotherap\* OR corticosteroid\* OR corticoid\* OR Glucocorticoid\* OR glucorticoid\* OR Betamethasone OR adbeon OR becasone OR beprogel OR beta methason OR betacortril OR betadexamethasone OR betametasone OR betamethasolone OR betamethazone OR betnasol OR betnelan OR betnesol OR betnovate OR betsolan OR betsolon OR betsoport OR celestan OR celestene

OR celeston\* OR cellederm OR cidoten OR dermobet OR diprolen OR flubenisolone OR flubenisolonvalerate OR methasone OR rinderon OR walacort OR Dexamethasone OR adrecort OR adrenocot OR aroseb dex OR aflucoson\* OR alfaly OR anaflogistico OR arcodexan\* OR artrosone OR auxison OR azium OR bidexol OR calonat OR cebedex OR cetadexon OR colofoam OR corsona OR cortastat OR cortidex\* OR cortidexason OR cortidrona OR cortidrone OR cortisumman OR dacortina fuerte OR dacortine fuerte OR dalalone OR danasone OR de-sone la OR decacortin OR decadeltona OR decadeltonone OR decaderm OR decadion OR decadran OR decadron\* OR decaesadriol OR decaject OR decameth\* OR decasone OR decaspray OR decasterolone OR decdan OR decilone OR decofluor OR dectancyl OR decaort OR delladec OR deltafluoren\* OR dergramin OR deronil OR desacort OR desacortone OR desadrene OR desalark OR desameton\* OR desigdrone OR dexam cortisyl OR dexam dabrosan OR dexam korti OR dexam scherosan OR dexam scherozon OR dexam scherozone OR dexam p OR dexacen 4 OR dexachel OR dexacort\* OR dexadabrosan OR dexadecadrol OR dexadrol OR dexagel OR dexagen OR dexahelvacort OR dexakorti OR dexalien OR dexalocal OR dexam OR dexamecortin OR dexameson\* OR dexametason\* OR dexamonozone OR dexan\* OR dexaport OR dexascherosan OR dexascherozon\* OR dexason\* OR dexinoral OR dexionil OR dexmethsone OR dexona OR dexone OR dexpak taperpak OR dextelan OR dextrasone OR dexycu OR dezone OR dibasona OR dexamethasone OR esacortene OR exadion OR exadione OR firmalone OR fluormethyl prednisolone OR fluormethylprednisolon\* OR fluormone OR fluorocort OR fluorodelta OR fluoromethylprednisolone OR fortacortin OR gammacorten\* OR grosodexon\* OR hexadecadiol OR hexadecadrol OR hexadiol OR hexadrol OR isnacort OR isopto\* OR lokalison f OR loverine OR luxazone OR marvidione OR maxidex OR mediamethasone OR megacortin OR mephameson\* OR metason\* OR methazon\* OR methylfluorprednisolone OR metisone lafi OR mexasone OR millicorten\* OR mymethasone OR neoforderx OR neofordex OR nisomethasona OR novocort OR oftan dexam OR optacorten OR optacortinol OR oradexan OR oradexon\* OR orgadron OR ozurdex OR pidexon OR policort OR posurdex OR predni f OR prednisolone f OR prodexona OR prodexone OR sanamethasone OR santenson OR santeson OR sawasone OR solurex OR spoloven OR sterasone OR thilodexine OR tobradex OR triamcimetil OR vexamet OR visumetazone OR visumethazone).ti,ab.))

AND

(exp Fetal Growth Retardation/ OR exp Infant, Low Birth Weight/ OR exp Obstetric Labor, Premature OR exp Infant, Premature/ OR exp Birth Weight/ OR (birthweight\* OR prematuritas OR small for gestational age).ti,ab. OR ((premature OR preterm\*) ADJ2 (birth\* OR labor\* OR labour\* OR delivery OR deliveries OR infant\* OR neonate\* OR newborn\* OR baby OR babies OR childbirth\* OR fetus\*)).ti,ab. OR ((pre-mature OR pre-term\*) ADJ2 (birth\* OR labor\* OR labour\* OR delivery OR deliveries OR infant\* OR neonate\* OR newborn\* OR baby OR babies OR childbirth\*)).ti,ab. OR ((birth\* OR neonat\* OR newborn OR infant\*) ADJ1 (weight\* OR underweight)).ti,ab. OR ((SGA) ADJ1 (neonate OR infant\* OR fetus\* OR newborn\*)).ti,ab. OR ((small for date) ADJ3 (baby\* OR babies OR infant\* OR neonat\* OR fetus\*)).ti,ab. OR ((small for age) ADJ3 (baby\* OR babies OR infant\* OR neonat\* OR fetus\*)).ti,ab. OR ((fetal OR neonat\* OR infant\* OR fetus OR foetal OR in utero OR intrauterine OR prenatal) ADJ2 (growth) ADJ2 (restrict\* OR retardation OR disorder\*)).ti,ab.) NOT ((exp Animals/) not (exp Animals/ and exp Humans/))

### Embase

Date Searched: 6/11/19, 5/13/20

Applied Database Supplied Limits: n/a

Number of Results: 4184; 4422

Search was re-run on May 13, 2020. Additional 238 results.

Full Search Strategy:

'prematurity'/exp OR 'birth weight'/exp OR 'intrauterine growth retardation'/exp OR 'premature labor'/exp OR 'premature birth'/de OR 'fetal growth retardation'/de OR (birthweight\* OR prematuritas OR 'small for gestational age'):ti,ab OR ((premature OR preterm\*) NEAR/2 (birth\* OR labor\* OR labour\* OR delivery OR deliveries OR infant\* OR neonate\* OR newborn\* OR baby OR babies OR childbirth\* OR fetus\*)):ti,ab OR ((pre-mature OR pre-term\*) NEAR/2 (birth\* OR labor\* OR labour\* OR delivery OR deliveries OR infant\* OR neonate\* OR newborn\* OR baby OR babies OR childbirth\*)):ti,ab OR ((birth\* OR neonat\* OR newborn OR infant\*) NEAR/1 (weight\* OR underweight)):ti,ab OR ((SGA) NEAR/1 (neonate OR infant\* OR fetus\* OR newborn\*)):ti,ab OR (('small for date') NEAR/3 (baby\* OR babies OR infant\* OR neonat\* OR fetus\*)):ti,ab OR (('small for age') NEAR/3 (baby\* OR babies OR infant\* OR neonat\* OR fetus\*)):ti,ab OR ((fetal OR neonat\* OR infant\* OR fetus OR foetal OR 'in utero' OR intrauterine OR prenatal) NEAR/2 (growth) NEAR/2 (restrict\* OR retardation OR disorder\*)):ti,ab

AND

((('antenatal corticosteroid therapy'/de OR ACS:ti,ab OR

((antenatal\* OR prenatal\*) NEAR/3 (corticosteroid\* OR corticoid\* OR glucocorticoid\* OR glucorticoid\* OR steroid\* OR CST)):ti,ab OR (('adrenal cortex') NEAR/1 (hormone\*) NEAR/2 (prenatal\* OR antenatal\*)):ti,ab OR

((prenatal\* OR antenatal\*) NEAR/2 (Betamethasone OR adbeon OR becasone OR beprogel OR 'beta methason'

OR betacortril OR betadexamethasone OR betametasone OR betamethasolone OR betamethazone OR betnasol OR betnelan OR betnesol OR betnovate OR betsolan OR betsolon OR betsoport OR celestan OR celestene OR celeston\*

OR cellestoderm OR cidoten OR dermobet OR diprolen OR flubenisolone OR flubenisolonvalerate OR methasone OR rinderon OR walacort)):ti,ab OR

((prenatal\* OR antenatal\*) NEAR/2 (Dexamethasone OR adrecort OR adrenocot OR 'aeroseb dex' OR aflucoson\* OR alfalyl OR anaflogistico OR arcodexan\* OR artrosone OR auxison OR azium OR bidexol OR calonat OR cebedex OR cetadexon OR colofoam OR corsona OR cortastat OR cortidex\* OR cortidexason OR cortidrona OR cortidrone OR cortisumman OR 'dacortina fuerte' OR 'dacortine fuerte' OR dalalone OR danasone OR 'de-sone la' OR decacortin OR decadeltona OR decadeltona OR decaderm OR decadion OR decadrone OR decadron\* OR decaesadril OR decaject OR decameth\* OR decasone OR decaspray OR decasterolone OR decdan OR decilone OR decofluor OR dectancyl OR decaort OR delladec OR deltafluoren\* OR dergramin OR deronil OR desacort OR desacortone OR desadrene OR desalark OR desameton\* OR desigdrone OR 'dexta cortisyl' OR 'dexta dabrosan' OR 'dexta korti' OR 'dexta scherosan' OR 'dexta scherozon' OR 'dexta scherozone' OR 'dexta p' OR 'dextacen 4' OR dextachel OR dexacort\* OR dexadabrosan OR dexadecadrol OR dexadrol OR dexagel OR dexagen OR dexahelvacort OR dexakorti OR dexalien OR dexalocal OR dexame OR dexamecortin OR dexameson\* OR dexametason\* OR dexamonozone OR dextan\* OR dexapot OR dexascheroson OR dexascherozon\* OR dexason\* OR dextinoral OR dextionil OR dextmethsone OR dextona OR dextone OR 'dextpak taperpak' OR dextelan OR dextasone OR dextycu OR dextone OR dibasona OR dexamethasone OR esacortene OR exadion OR exadione OR firmalone OR 'fluormethyl prednisolone' OR fluormethylprednisolon\* OR fluormone OR fluorocort OR fluorodelta OR fluoromethylprednisolone OR fortacortin OR gammacorten\* OR grosodexon\* OR hexadecadiol OR hexadecadrol OR hexadiol OR hexadrol OR isnacort OR isopto\* OR 'lokalison f' OR loverine OR luxazone OR marvidione OR maxidex OR mediamethasone OR megacortin OR mephameson\* OR metasolon\* OR methazon\* OR methylfluorprednisolone OR 'metisone lafi' OR mexasone OR millicorten\* OR mymethasone OR neoforderx OR neofordex OR nisomethasone OR novocort OR 'oftan dexta' OR optacorten OR optacortinol OR oradexan OR oradexon\* OR orgadrone OR ozurdex OR pidexon OR policort OR posurdex OR 'predni f' OR 'prednisolone f' OR prodexona OR prodexone OR sanamethasone OR santenson OR santeson OR sawasone OR solurex OR spoloven OR sterasone OR thilodexine OR tobradex OR triamcimetil OR vexamet OR visumetazone OR visumethazone)):ti,ab)

OR

((('prenatal drug exposure'/exp OR (prenatal\* OR antenatal\*):de OR ((prenatal\* OR antenatal\* OR fetal OR foetal OR intrauterine OR maternal) NEAR/1 ('drug exposure'))):ti,ab) AND ('corticosteroid therapy'/exp OR 'betamethasone'/exp OR 'dexamethasone'/exp OR (('adrenal cortex') NEAR/1



(hormone\*)):ti,ab OR (Corticotherap\* OR corticosteroid\* OR corticoid\* OR Glucocorticoid\* OR glucorticoid\* OR Betamethasone OR adbeon OR becasone OR beprogel OR 'beta methason' OR betacortril OR betadexamethasone OR betametasone OR betamethasolone OR betamethazone OR betnasol OR betnelan OR betnesol OR betnovate OR betsolan OR betsolon OR betsoport OR celestan OR celestene OR celeston\* OR cellestoderm OR cidoten OR dermobet OR diprolen OR flubenisolone OR flubenisolonvalerate OR methasone OR rinderon OR walacort OR Dexamethasone OR adrecort OR adrenocot OR 'aeroseb dex' OR aflucoson\* OR alfalyl OR anaflogistico OR arcodexan\* OR artrosone OR auxison OR azium OR bidexol OR calonat OR cebedex OR cetadexon OR colofoam OR corsona OR cortastat OR cortidex\* OR cortidexason OR cortidrona OR cortidrone OR cortisumman OR 'dacortina fuerte' OR 'dacortine fuerte' OR dalalone OR danasone OR 'de-sone la' OR decacortin OR decadeltona OR decadeltonone OR decaderm OR decadion OR decadrin OR decatron\* OR decaesadril OR decaject OR decameth\* OR decasone OR decaspray OR decasterolone OR decdan OR decilone OR decofluor OR dectancyl OR dekcort OR delladec OR deltafluoren\* OR dergramin OR deronil OR desacort OR desacortone OR desadrene OR desalark OR desameton\* OR desigdrone OR 'dexa cortisyl' OR 'dexa dabrosan' OR 'dexa korti' OR 'dexa scherosan' OR 'dexa scherozon' OR 'dexa scherozone' OR 'dexa p' OR 'dexacen 4' OR dexachel OR dexacort\* OR dexadabrosone OR dexadecadrol OR dexadrol OR dexagel OR dexagen OR dexahelvacort OR dexakorti OR dexalien OR dexalocal OR dexamone OR dexamecortin OR dexameson\* OR dexametason\* OR dexamonozone OR dexan\* OR dexapot OR dexascherosone OR dexascherozon\* OR dexason\* OR dextrinone OR dexionil OR dexmethasone OR dexona OR dexone OR 'dexpak taperpak' OR dextelan OR dextrasone OR dexycu OR dezone OR dibasone OR dexamethasone OR esacortene OR exadion OR exadione OR firmalone OR 'fluormethyl prednisolone' OR fluormethylprednisolone\* OR fluormone OR fluorocort OR fluorodelta OR fluoromethylprednisolone OR fortacortin OR gammacorten\* OR grosodexon\* OR hexadecadiol OR hexadecadrol OR hexadiol OR hexadrol OR isnacort OR isopto\* OR 'lokalison f' OR loverine OR luxazone OR marvidione OR maxidex OR mediamethasone OR megacortin OR mephameson\* OR metasolone\* OR methazon\* OR methylfluorprednisolone OR 'metisone lafi' OR mexasone OR millicorten\* OR mymethasone OR neoforderx OR neofordex OR nisomethasone OR novocort OR 'oftan dexa' OR optacortin OR optacortinol OR oradexan OR oradexon\* OR orgadron OR ozurdex OR pidexon OR policort OR posurdex OR 'predni f' OR 'prednisolone f' OR prodexona OR prodexone OR sanamethasone OR santenson OR santeson OR sawasone OR solurex OR spoloven OR sterasone OR thilodexine OR tobradex OR triamcimetil OR vexamet OR visumetazone OR visumethazone):ti,ab))) NOT ([animals]/lim NOT [humans]/lim)

## Cochrane

Date Searched: 6/11/19; 5/13/20

Applied Database Supplied Limits: n/a

Number of Results from each database in Cochrane

CDSR: 34; 27

\*0 for last year.

CENTRAL: 497; 498

\*35 found for 2019 -2020 and exported.

Cochrane Protocols : 2

Editorials: 1

Clinical Answers: 1

Search strategy was re-run on May 13, 2020. 8 additional records found (529 total).

#### Full Search Strategy:

1. [mh “fetal growth retardation”] OR [mh “Infant, Low Birth Weight”] OR [mh “Obstetric Labor, Premature”] OR [mh “Infant, Premature”] OR [mh “Birth Weight”] OR (birthweight\* OR prematuritas OR ‘small for gestational age’):ti,ab OR ((premature OR preterm\*) NEAR/2 (birth\* OR labor\* OR labour\* OR delivery OR deliveries OR infant\* OR neonate\* OR newborn\* OR baby OR babies OR childbirth\* OR fetus\*)):ti,ab OR ((pre-mature OR pre-term\*) NEAR/2 (birth\* OR labor\* OR labour\* OR delivery OR deliveries OR infant\* OR neonate\* OR newborn\* OR baby OR babies OR childbirth\*)):ti,ab OR ((birth\* OR neonat\* OR newborn OR infant\*) NEAR/1 (weight\* OR underweight)):ti,ab OR ((SGA) NEAR/1 (neonate OR infant\* OR fetus\* OR newborn\*)):ti,ab OR ((‘small for date’) NEAR/3 (baby\* OR babies OR infant\* OR neonat\* OR fetus\*)):ti,ab OR ((‘small for age’) NEAR/3 (baby\* OR babies OR infant\* OR neonat\* OR fetus\*)):ti,ab OR ((fetal OR neonat\* OR infant\* OR fetus OR foetal OR ‘in utero’ OR intrauterine OR prenatal) NEAR/2 (growth) NEAR/2 (restrict\* OR retardation OR disorder\*)):ti,ab
  
2. ACS:ti,ab OR ((antenatal\* OR prenatal\*) NEAR/3 (corticosteroid\* OR corticoid\* OR glucocorticoid\* OR glucorticoid\* OR steroid\* OR CST)):ti,ab OR ((“adrenal cortex”) NEAR/1 (hormone\*) NEAR/2 (prenatal\* OR antenatal\*)):ti,ab OR ((prenatal\* OR antenatal\*) NEAR/2 (Betamethasone OR adbeon OR becasone OR beprogel OR “beta methason” OR betacortril OR betadexamethasone OR betametasone OR betamethasolone OR betamethazone OR betnasol OR betnelan OR betnesol OR betnovate OR betsolan OR betsolon OR betsopart OR celestan OR celestene OR celeston\* OR cellestoderm OR cidoten OR dermobet OR diprolen OR flubenisolone OR flubenisolonvalerate OR methasone OR rinderon OR walacort)):ti,ab OR ((prenatal\* OR antenatal\*) NEAR/2 (Dexamethasone OR adrecort OR adrenocot OR “aeroseb dex” OR aflucoson\* OR alfaly OR anaflogistico OR arcodexan\* OR artrosone OR auxison OR azium OR bidexol OR calonat OR cebedex OR cetadexon OR colofoam OR corsona OR cortastat OR cortidex\* OR cortidexason OR cortidrona OR cortidrone OR cortisumman OR “dacortina fuerte” OR “dacortine fuerte” OR dalalone OR danasone OR “de-sone la” OR decacortin OR decadeltozona OR decadeltozone OR decaderm OR decadion OR decadran OR decadron\* OR decaesadril OR decaject OR decameth\* OR decasone OR decaspray OR decasterolone OR decdan OR decilone OR decofluor OR dectancyl OR dekaort OR delladec OR deltafluoren\* OR dergramin OR deronil OR desacort OR desacortone OR desadrene OR desalark OR desameton\* OR desigdron OR “dexa cortisyl” OR “dexa dabrosan” OR “dexa korti” OR “dexa scherosan” OR “dexa scherozon” OR “dexa scherozone” OR “dexa p” OR “dexacen 4” OR dexachel OR dexacort\* OR dexadabrosan OR dexadecadrol OR dexadrol OR dexagel OR dexagen OR dexahelvacort OR dexakorti OR dexalien OR dexalocal OR dexame OR dexamecortin OR dexameson\* OR dexametason\* OR dexamonozone OR dexan\* OR dexapot OR dexascheroson OR dexascherozon\* OR dexason\* OR dixinoral OR dexionil OR dexmethsone OR dexona OR dexone OR “dexpak taperpak” OR dextelan OR dextrason OR dexycu OR dezone OR dibasona OR dexamethasone OR esacortene OR exadion OR exadione OR firmalone OR “fluormethyl prednisolone” OR fluormethylprednisolon\* OR fluormone OR fluorocort OR fluorodelta OR fluoromethylprednisolone OR fortacortin OR gammacorten\* OR grosodexon\* OR hexadecadiol OR hexadecadrol OR

hexadiol OR hexadrol OR isnacort OR isopto\* OR “lokalison f” OR loverine OR luxazone OR marvidione OR maxidex OR mediamethasone OR megacortin OR mephameson\* OR metasolon\* OR methazon\* OR methylfluorprednisolone OR “metisone lafi” OR mexasone OR millicorten\* OR mymethasone OR neoforderx OR neofordex OR nisomethasone OR novocort OR “oftan dexta” OR opticorten OR opticortinol OR oradexan OR oradexon\* OR orgadrone OR ozurdex OR pidexon OR policort OR posurdex OR “predni f” OR “prednisolone f” OR prodexona OR prodexone OR sanamethasone OR santenson OR santeson OR sawasone OR solurex OR spoloven OR sterasone OR thilodexine OR tobradex OR triamcimetil OR vexamet OR visumetazone OR visumethazone)):ti,ab

3. (prenatal\* OR antenatal\*):kw OR ((prenatal\* OR antenatal\* OR fetal OR foetal OR intrauterine OR maternal) NEAR/1 (“drug exposure”)):ti,ab
4. ([mh “adrenal cortex hormones”] OR [mh glucocorticoids] OR [mh betamethasone] OR [mh dexamethasone] OR (“adrenal cortex”) NEAR/1 (hormone\*)):ti,ab OR (Corticotherap\* OR corticosteroid\* OR corticoid\* OR Glucocorticoid\* OR glucorticoid\* OR Betamethasone OR adbeon OR becasone OR beprogel OR “beta methason” OR betacortril OR betadexamethasone OR betametasone OR betamethasolone OR betamethazone OR betnasol OR betnelan OR betnesol OR betnovate OR betsolan OR betsolon OR betsopart OR celestan OR celestene OR celeston\* OR cellestoderm OR cidoten OR dermobet OR diprolen OR flubenisolone OR flubenisolonvalerate OR methasone OR rinderon OR walacort OR Dexamethasone OR adrecort OR adrenocot OR “aeroseb dex” OR aflucoson\* OR alfalyl OR anaflogistico OR arcodexan\* OR artrosone OR auxison OR azium OR bidexol OR calonat OR cebedex OR cetadexon OR colofoam OR corsona OR cortastat OR cortidex\* OR cortidexason OR cortidrona OR cortidrone OR cortisumman OR “dacortina fuerte” OR “dacortine fuerte” OR dalalone OR danasone OR “de-sone la” OR decacortin OR decadeltosona OR decadeltosone OR decaderm OR decadion OR decadran OR decadron\* OR decaesadril OR decaject OR decameth\* OR decasone OR decaspray OR decasterolone OR decdan OR decilone OR decofluor OR dectancyl OR dekacort OR delladec OR deltafluoren\* OR dergramin OR deronil OR desacort OR desacortone OR desadrene OR desalark OR desameton\* OR desigdron OR “dexta cortisyl” OR “dexta dabrosan” OR “dexta korti” OR “dexta scherosan” OR “dexta scherozon” OR “dexta scherozone” OR “dexta p” OR “dextacen 4” OR dexachel OR dexacort\* OR dexadabrosan OR dexadecadrol OR dexadrol OR dexagel OR dexagen OR dexahelvacort OR dexakorti OR dexalien OR dexalocal OR dexame OR dexamecortin OR dexameson\* OR dexametason\* OR dexamonozone OR dexan\* OR dexapote OR dexascheroson OR dexascherozon\* OR dexason\* OR dexinoral OR dexionil OR dexmethsone OR dexona OR dexone OR “dexpak taperpak” OR dextelan OR dextrasone OR dexycu OR dezone OR dibasona OR dexamethasone OR esacortene OR exadion OR exadione OR firmalone OR “fluormethyl prednisolone” OR fluormethylprednisolon\* OR fluormone OR fluorocort OR fluorodelta OR fluoromethylprednisolone OR fortocortin OR gammacorten\* OR grosodexon\* OR hexadecadiol OR hexadecadrol OR hexadiol OR hexadrol OR isnacort OR isopto\* OR “lokalison f” OR loverine OR luxazone OR marvidione OR maxidex OR mediamethasone OR megacortin OR mephameson\* OR metasolon\* OR methazon\* OR methylfluorprednisolone OR “metisone lafi” OR mexasone OR millicorten\* OR mymethasone OR neoforderx OR neofordex OR nisomethasone OR novocort OR “oftan dexta” OR opticorten OR opticortinol OR oradexan OR oradexon\* OR orgadrone OR ozurdex OR pidexon OR policort OR posurdex OR “predni f” OR “prednisolone f” OR prodexona OR prodexone OR sanamethasone OR santenson OR santeson OR sawasone OR solurex OR spoloven OR sterasone OR thilodexine OR tobradex OR triamcimetil OR vexamet OR visumetazone OR visumethazone):ti,ab)
5. #3 AND #4
6. #5 OR #2
7. #6 AND #1

Scopus

Date Searched: 6/11/19; 5/13/20

Applied Database Supplied Limits: n/a

Number of Results: 2778, 2911

Search strategy was re-run on May 13, 2020. 133 new results.

Full Search Strategy:

TITLE-ABS(birthweight\* OR prematuritas OR “small for gestational age” OR

((premature OR preterm\*) W/2 (birth\* OR labor\* OR labour\* OR delivery OR deliveries OR infant\* OR neonate\* OR newborn\* OR baby OR babies OR childbirth\* OR fetus\*)) OR

((pre-mature OR pre-term\*) W/2 (birth\* OR labor\* OR labour\* OR delivery OR deliveries OR infant\* OR neonate\* OR newborn\* OR baby OR babies OR childbirth\*)) OR

((birth\* OR neonat\* OR newborn OR infant\*) W/1 (weight\* OR underweight)) OR

((SGA) W/1 (neonate OR infant\* OR fetus\* OR newborn\*)) OR

((“small for date”) W/3 (baby\* OR babies OR infant\* OR neonat\* OR fetus\*)) OR

((“small for age”) W/3 (baby\* OR babies OR infant\* OR neonat\* OR fetus\*)) OR

((fetal OR neonat\* OR infant\* OR fetus OR foetal OR “in utero” OR intrauterine OR prenatal) W/2 (growth) W/2 (restrict\* OR retardation OR disorder\*))

AND

TITLE-ABS(ACS OR

((antenatal\* OR prenatal\*) W/3 (corticosteroid\* OR corticoid\* OR glucocorticoid\* OR glucorticoid\* OR steroid\* OR CST)) OR

((“adrenal cortex”) W/1 (hormone\*) W/2 (prenatal\* OR antenatal\*)) OR

((prenatal\* OR antenatal\*) W/2 (Betamethasone OR adbeon OR becasone OR beprogel OR “beta methason”

OR betacortril OR betadexamethasone OR betametasone OR betamethasolone OR betamethazone OR betnasol OR betnelan OR betnesol OR betnovate OR betsolan OR betsolon OR betsoport OR celestan OR celestene OR celeston\*

OR cellestoderm OR cidoten OR dermobet OR diprolen OR flubenisolone OR flubenisolonvalerate OR methasone OR rinderon OR walacort)) OR

((prenatal\* OR antenatal\*) W/2 (Dexamethasone OR adrecort OR adrenocot OR “aeroseb dex” OR aflucoson\* OR alfalyl OR anaflogistico OR arcodexan\*

OR artrosone OR auxison OR azium OR bidexol OR calonat OR cebedex OR cetadexon OR colofoam OR corsona OR cortastat OR cortidex\* OR

cortidexason OR cortidrona OR cortidrone OR cortisumman OR “dacortina fuerte” OR “dacortine fuerte” OR dalalone OR danasone OR “de-sone la” OR

decacortin OR decadeltona OR decadeltonone OR decaderm OR decadion OR decadrane OR decadron\* OR decaesadril OR decaject OR decameth\* OR

decasone OR decaspray OR decasterolone OR decdan OR decilone OR decofluor OR dectancyl OR decaort OR delladec OR deltafluoren\* OR dergramin

OR deronil OR desacort OR desacortone OR desadrene OR desalark OR desameton\* OR desigdrone OR “dexa cortisyl” OR “dexa dabrosan” OR “dexa

korti” OR “dexa scherosan” OR “dexa scherozon” OR “dexa scherozone” OR “dexa p” OR “dexacen 4” OR dexachel OR dexacort\* OR dexadabrosan OR

dexadecadrol OR dexadrol OR dexagel OR dexagen OR dexahelvacort OR dexakorti OR dexalien OR dexalocal OR dexam OR dexamecortin OR

dexameson\* OR dexametason\* OR dexamonozone OR dexan\* OR dexaport OR dexascheroson OR dexascherozon\* OR dexason\* OR dexinoral OR dexionil

OR dexmethsone OR dexona OR dexone OR “dexpak taperpak” OR dextelan OR dextrason OR dexycu OR dezone OR dibasona OR dexamethasone OR

esacortene OR exadion OR exadione OR firmalone OR “fluormethyl prednisolone” OR fluormethylprednisolon\* OR fluormone OR fluorocort OR  
 fluorodelta OR fluoromethylprednisolone OR fortectortin OR gammacorten\* OR grosodexon\* OR hexadecadiol OR hexadecadrol OR hexadiol OR hexadrol  
 OR isnacort OR isopto\* OR “lokalison f” OR loverine OR luxazone OR marvidione OR maxidex OR mediamethasone OR megacortin OR mephameson\*  
 OR metasolon\* OR methazon\* OR methylfluorprednisolone OR “metisone lafi” OR mexasone OR millicorten\* OR mymethasone OR neoforderx OR  
 neofordex OR nisomethasone OR novocort OR “oftan dexta” OR optecorten OR optecortinol OR oradexan OR oradexon\* OR orgadrone OR ozurdex OR  
 pidexon OR policort OR posurdex OR “predni f” OR “prednisolone f” OR prodexona OR prodexone OR sanamethasone OR santenson OR santeson OR  
 sawasone OR solurex OR spoloven OR sterasone OR thilodexine OR tobradex OR triamcimetil OR vexamet OR visumetazone OR visumethazone))) OR  
 ((KEY(prenatal\* OR antenatal\*) OR  
 TITLE-ABS((prenatal\* OR antenatal\* OR fetal OR foetal OR intrauterine OR maternal) W/1 (“drug exposure”)))  
 AND  
 TITLE-ABS(((“adrenal cortex”) W/1 (hormone\*)) OR  
 Corticotherap\* OR corticosteroid\* OR corticoid\* OR Glucocorticoid\* OR glucorticoid\* OR  
 Betamethasone OR adbeon OR becasone OR beprogel OR “beta methason”  
 OR betacortril OR betadexamethasone OR betametasone OR betamethasolone OR betamethazone OR betnasol OR betnelan OR betnesol OR betnovate OR  
 betsolan OR betsolon OR betsoport OR celestan OR celestene OR celeston\*  
 OR cellestoderm OR cidoten OR dermobet OR diprolen OR flubenisolone OR flubenisolonvalerate OR methasone OR rinderon OR walacort OR  
 Dexamethasone OR adrecort OR adrenocot OR “aeroseb dex” OR aflucoson\* OR alfalyl OR anaflogistico OR arcodexan\* OR artrosone OR auxison OR  
 azium OR bidexol OR calonat OR cebedex OR cetadexon OR colofoam OR corsona OR cortastat OR cortidex\* OR cortidexason OR cortidrona OR  
 cortidrone OR cortisumman OR “dacortina fuerte” OR “dacortine fuerte” OR dalalone OR danasone OR “de-sone la” OR decacortin OR decadeltona OR  
 decadeltonone OR decaderm OR decadion OR decadrone OR decadron\* OR decaesadril OR decaject OR decameth\* OR decasone OR decaspray OR  
 decasterolone OR decdan OR decilone OR decofluor OR dectancyl OR dekaort OR delladec OR deltafluoren\* OR dergramin OR deronil OR desacort OR  
 desacortone OR desadrene OR desalark OR desameton\* OR desigdrone OR “dexta cortisyl” OR “dexta dabrosan” OR “dexta korti” OR “dexta scherosan” OR  
 “dexta scherozon” OR “dexta scherozone” OR “dexta p” OR “dextacen 4” OR dextachel OR dextacort\* OR dextadabrosan OR dextadecadrol OR dextadrol OR  
 dextagel OR dextagen OR dextahelvacort OR dextakorti OR dextalien OR dextalocal OR dextame OR dextamecortin OR dextameson\* OR dextameton\* OR  
 dextamonozone OR dextan\* OR dextapot OR dextascheroson OR dextascherozon\* OR dextason\* OR dextinoral OR dextionil OR dextmethsone OR dextona OR  
 dextone OR “dextak taperpak” OR dextelan OR dextasone OR dextycu OR dextone OR dibasone OR dexamethasone OR esacortene OR exadion OR  
 exadione OR firmalone OR “fluormethyl prednisolone” OR fluormethylprednisolon\* OR fluormone OR fluorocort OR fluorodelta OR  
 fluoromethylprednisolone OR fortectortin OR gammacorten\* OR grosodexon\* OR hexadecadiol OR hexadecadrol OR hexadiol OR hexadrol OR isnacort  
 OR isopto\* OR “lokalison f” OR loverine OR luxazone OR marvidione OR maxidex OR mediamethasone OR megacortin OR mephameson\* OR  
 metasolon\* OR methazon\* OR methylfluorprednisolone OR “metisone lafi” OR mexasone OR millicorten\* OR mymethasone OR neoforderx OR neofordex  
 OR nisomethasone OR novocort OR “oftan dexta” OR optecorten OR optecortinol OR oradexan OR oradexon\* OR orgadrone OR ozurdex OR pidexon OR  
 policort OR posurdex OR “predni f” OR “prednisolone f” OR prodexona OR prodexone OR sanamethasone OR santenson OR santeson OR sawasone OR  
 solurex OR spoloven OR sterasone OR thilodexine OR tobradex OR triamcimetil OR vexamet OR visumetazone OR visumethazone))  
 AND NOT KEY((Animals) AND NOT (Animals AND humans))

[ClinicalTrials.gov](https://clinicaltrials.gov)

Date Searched: 6/11/19 ; 5/13/20

Number of Results: 35 ; 39

search was re-run on May 13, 2020 and 4 additional records were found.

in Expert search:

(Antenatal corticosteroids) **AND** (preterm OR Small for Gestational Age OR birth weight)

[WHO ICTRP](https://www.who.int/clinical-trials/ctpr)

Date Searched: 6/11/19 ; unavailable

Number of Results: 24

From advanced search in search portal:

Antenatal corticosteroid (in title)

AND

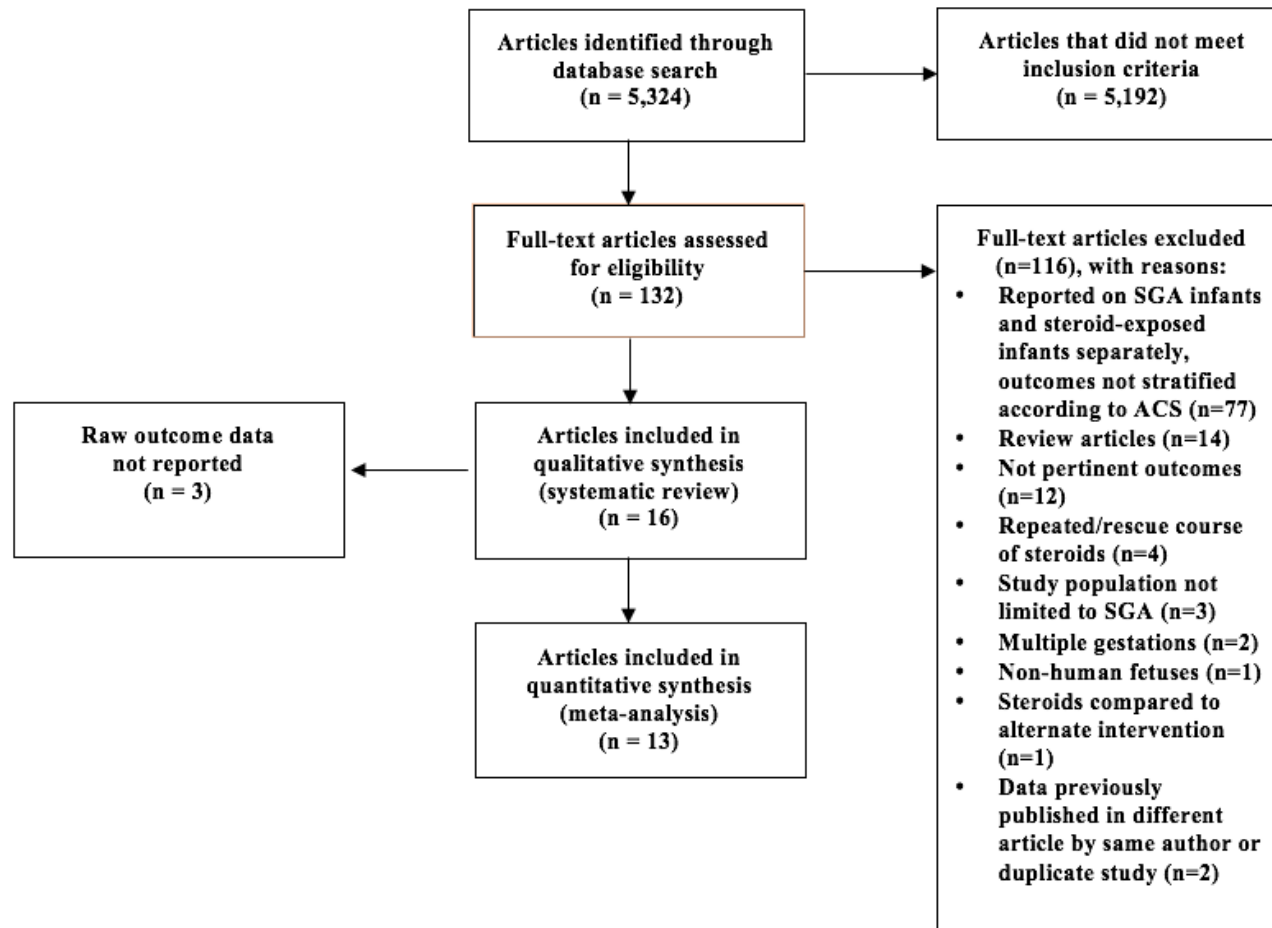
preterm OR small for gestational age OR birth weight (in condition)

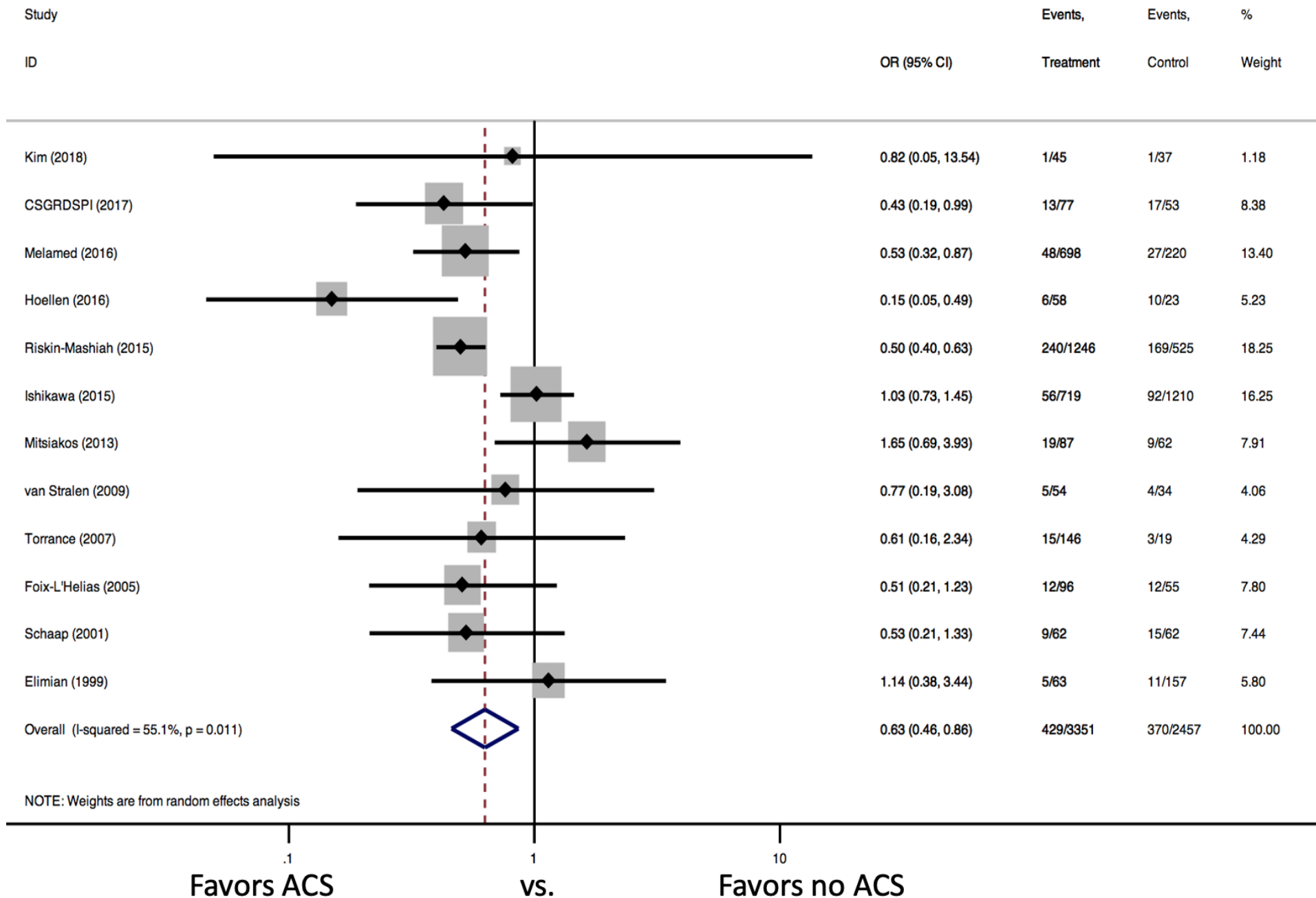
OR

Antenatal corticosteroid (in intervention)

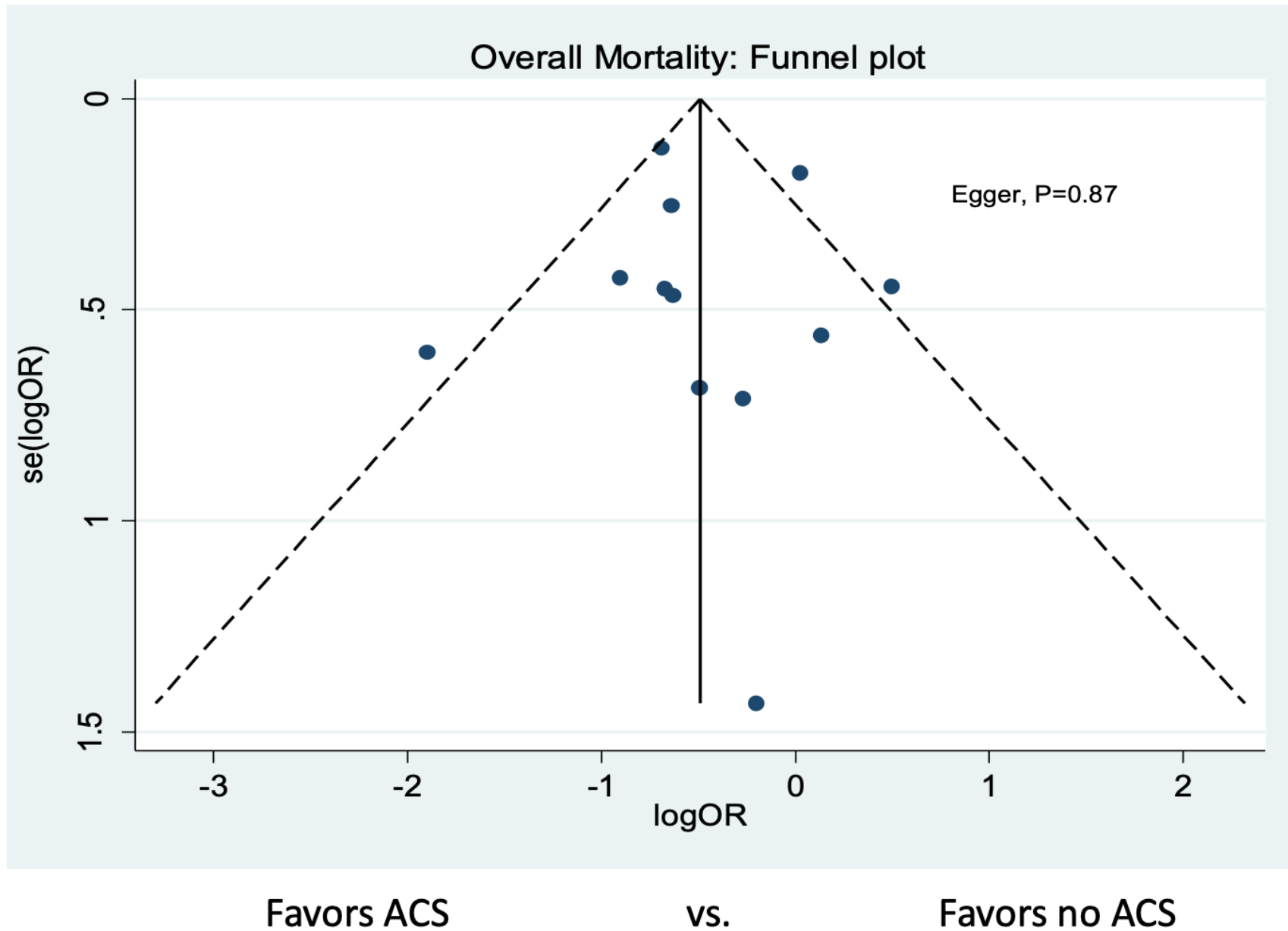
recruitment status : ALL

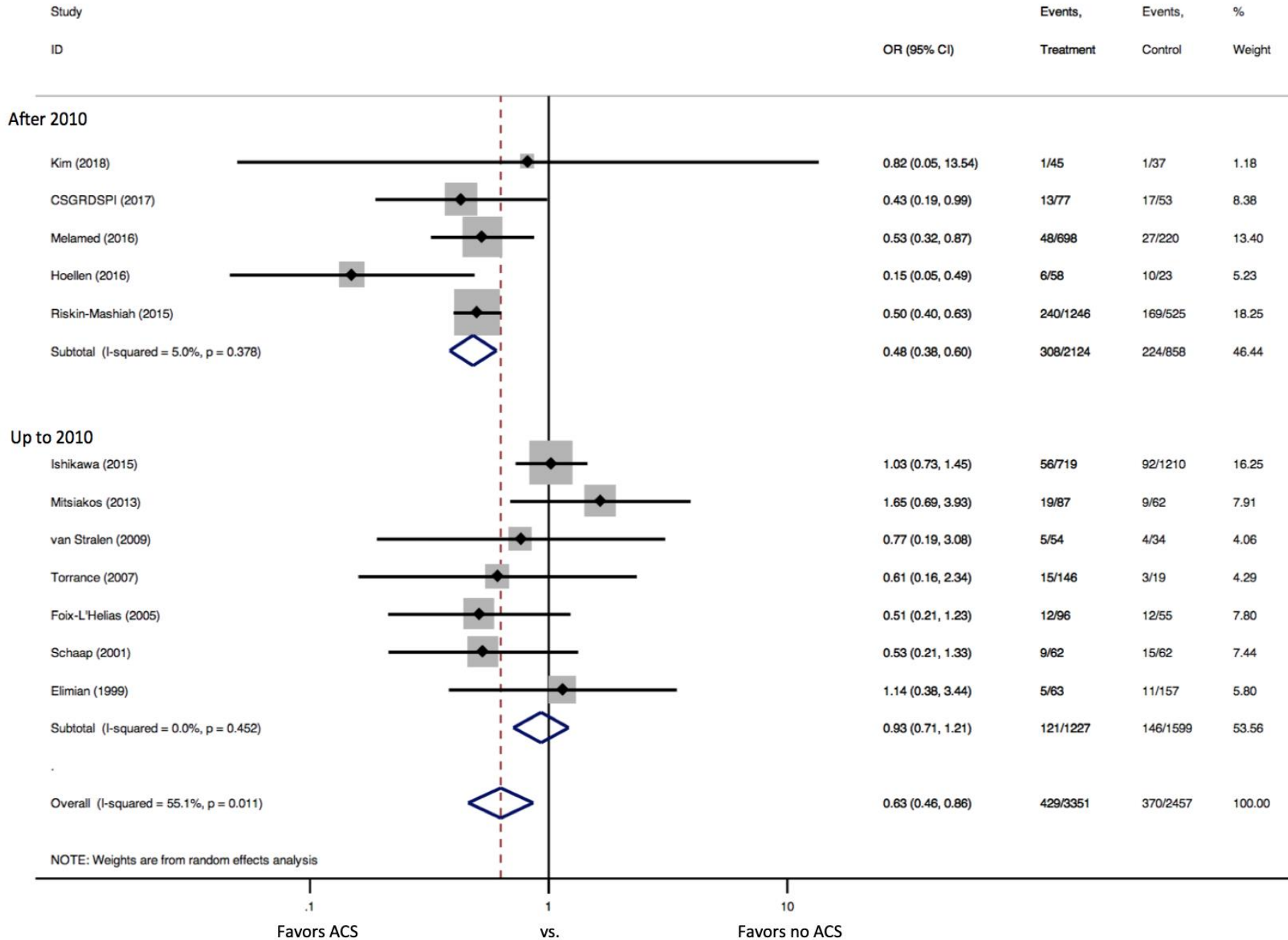
Figure 1. Flow Chart of the Literature Review



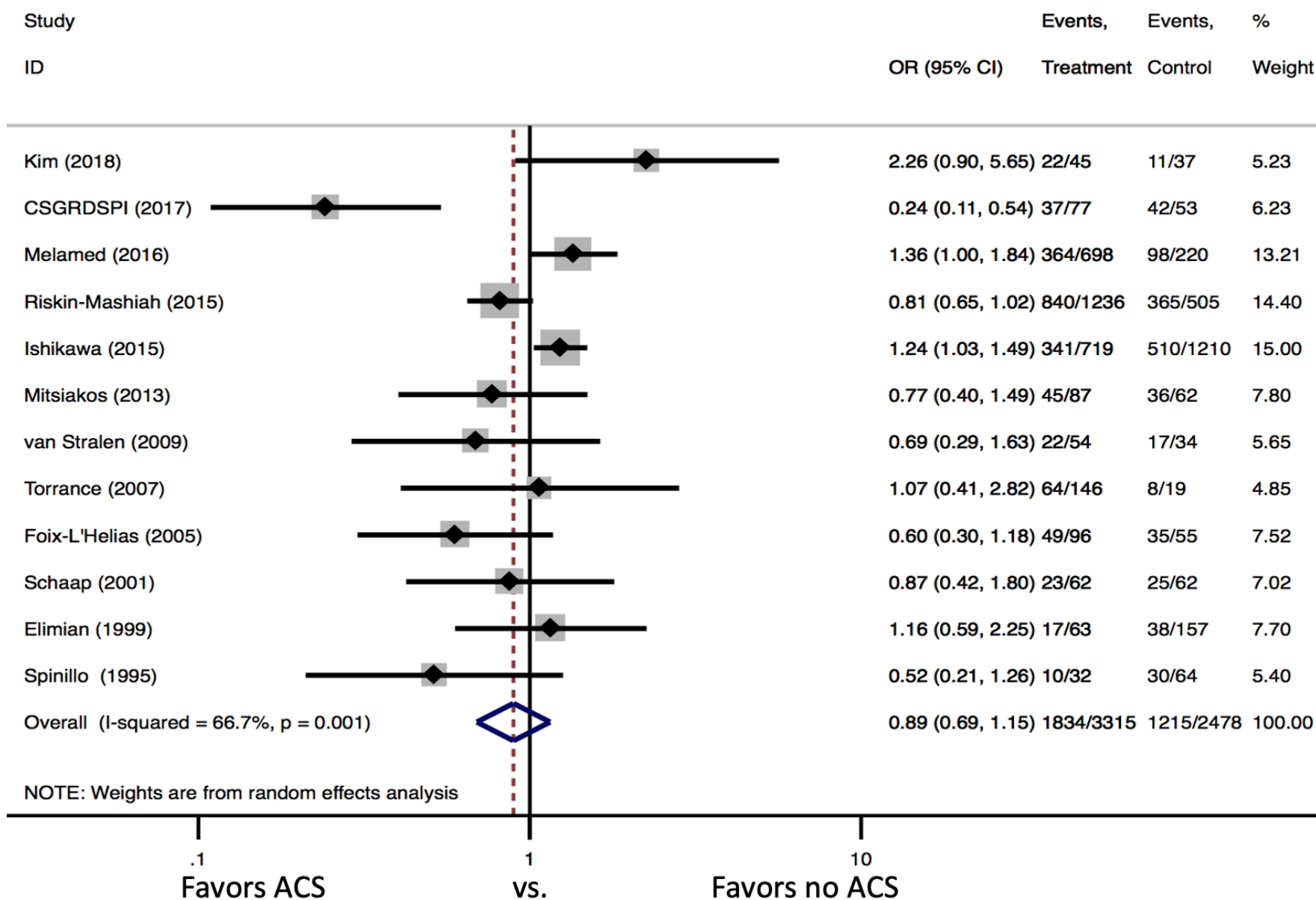
**Figure 2. Forest Plot for Neonatal Mortality**

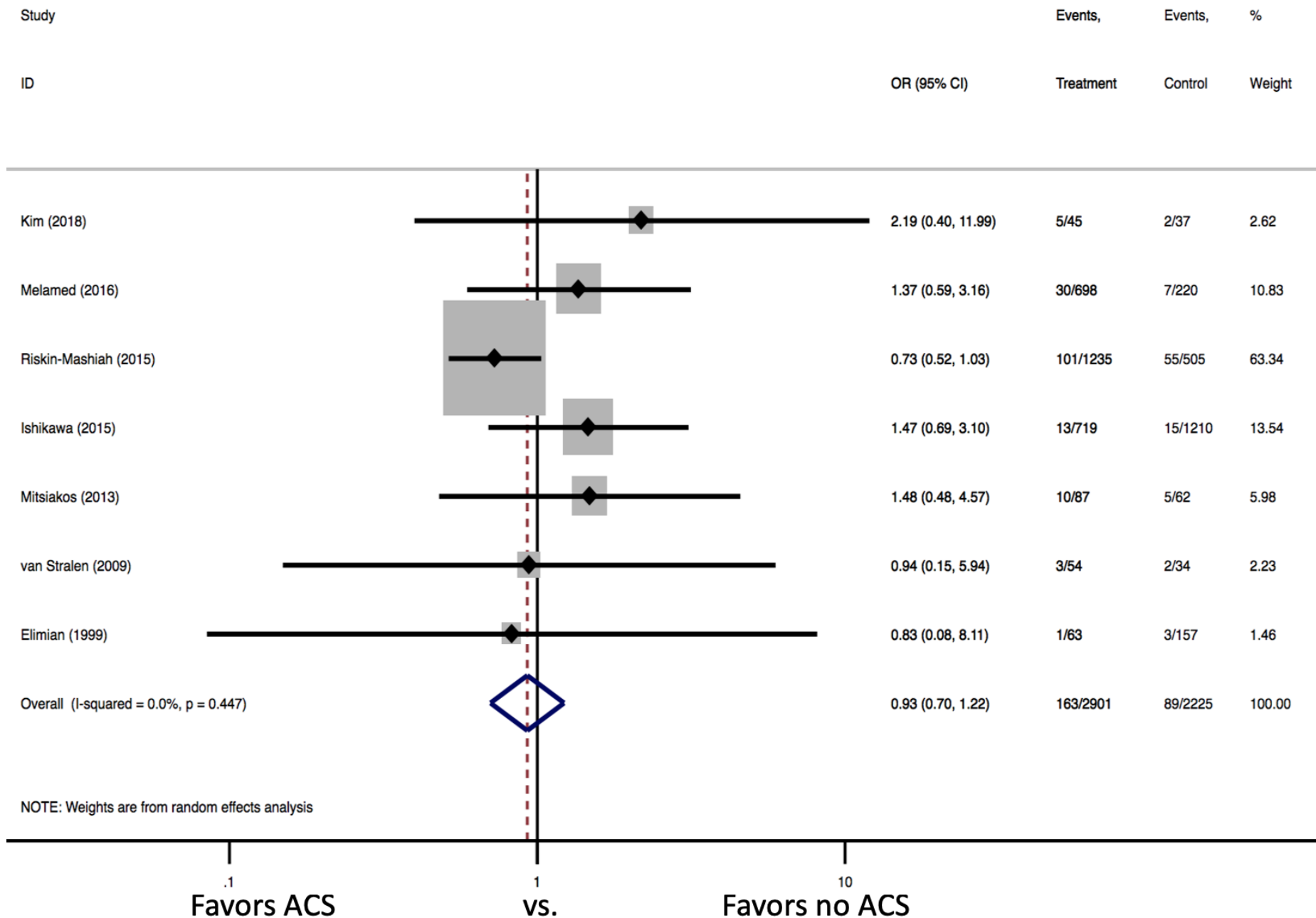


**Figure 3. Funnel Plot for Publication Bias for Overall Mortality**

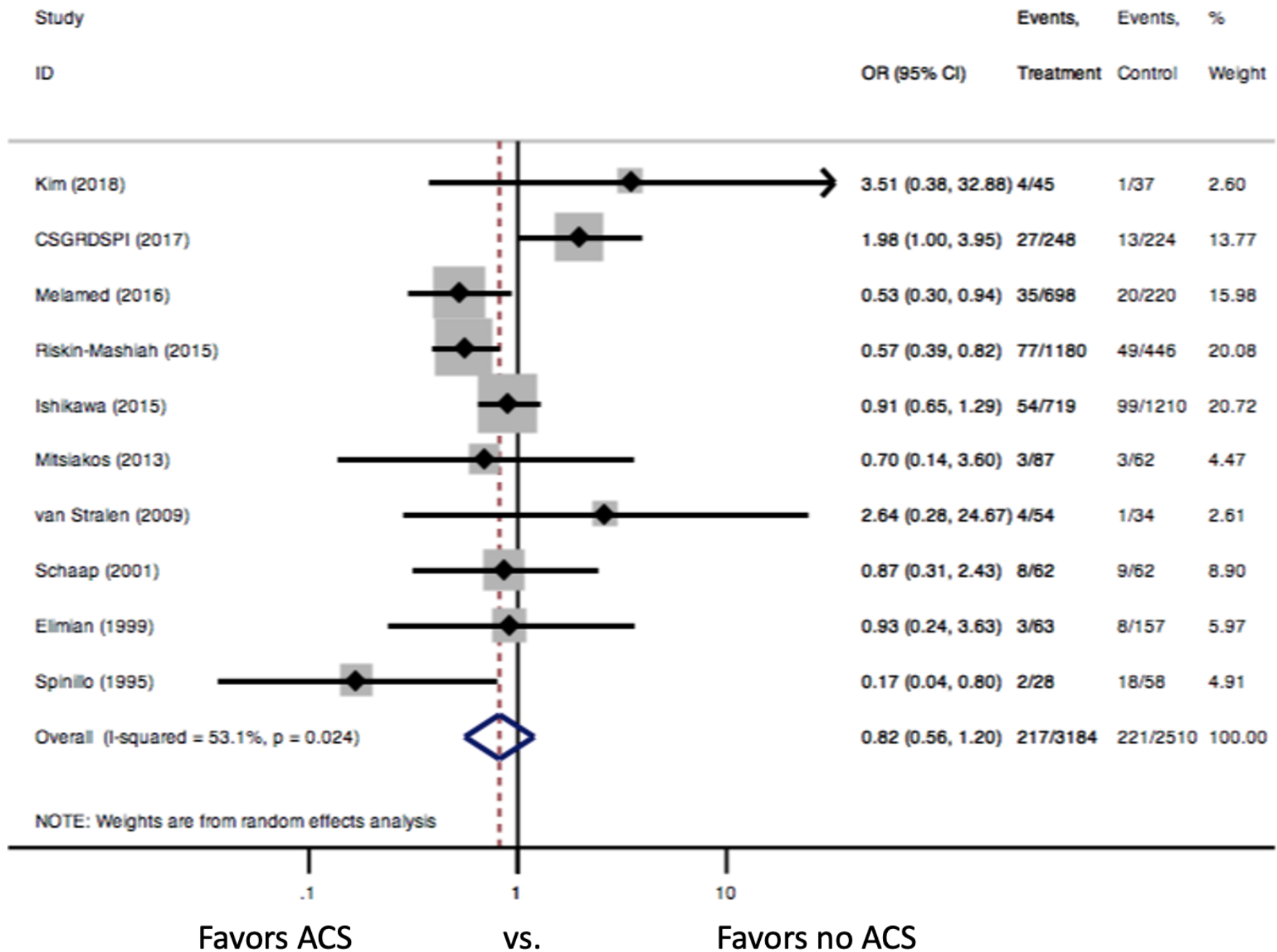
**Figure 4. Forest Plot for Neonatal Mortality by Study Year**

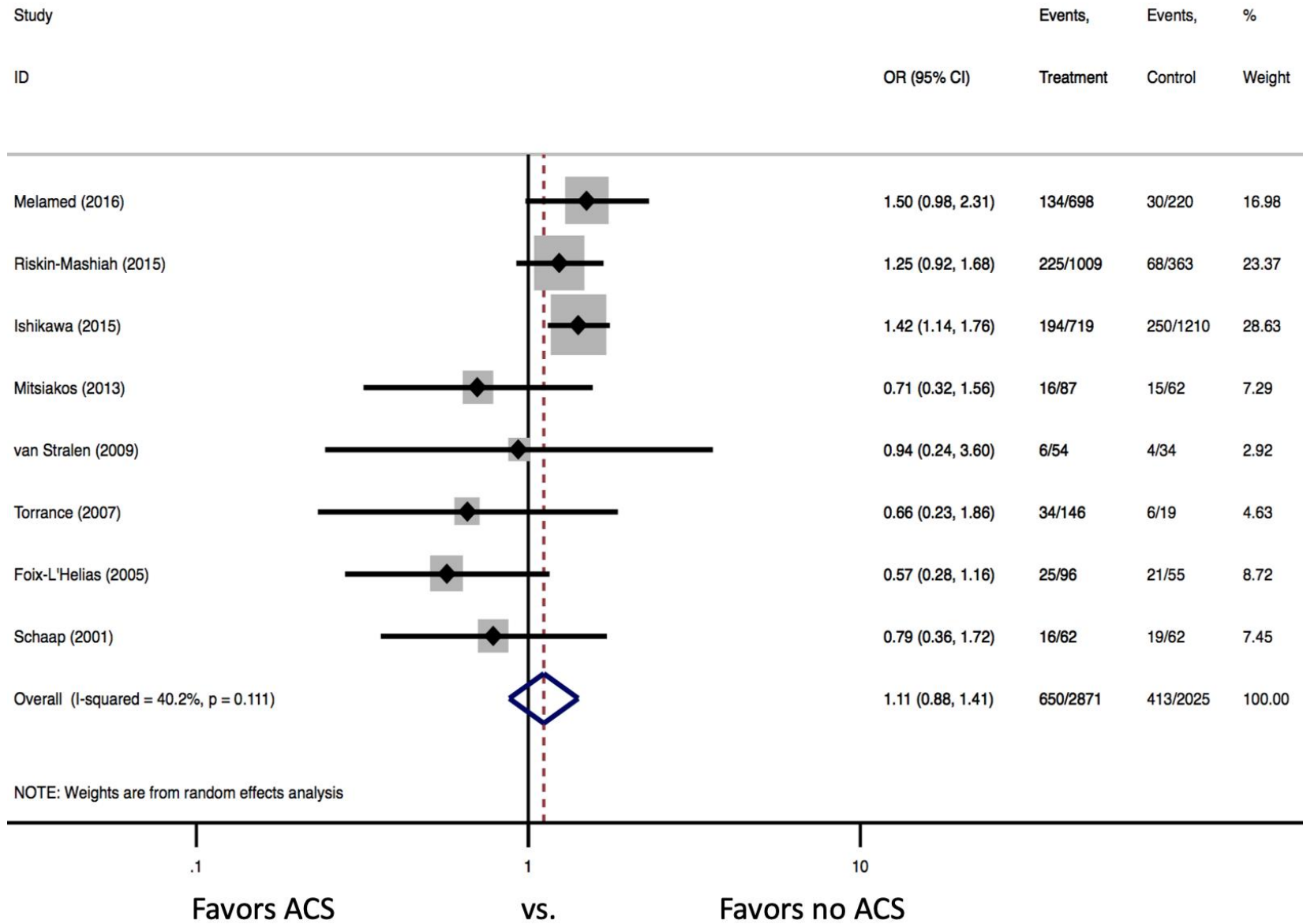
Supplementary Figure 1. Forest Plot for RDS



**Supplementary Figure 2. Forest Plot for NEC**

Supplementary Figure 3. Forest Plot for IVH and/or PVL



**Supplementary Figure 4. Forest Plot for BPD or CLD of Prematurity**

Supplementary Figure 5. Forest Plot for Neonatal Sepsis

