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Evaluation of Long-term Outcomes Associated With Preterm Exposure to Antenatal Corticosteroids
A Systematic Review and Meta-analysis

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IMPORTANCE Animal studies have found that antenatal corticosteroids affect many organs across multiple stages of life. However, the long-term outcomes in human children are not well understood.

OBJECTIVE To conduct a systematic review and meta-analysis of long-term outcomes associated with preterm exposure to antenatal corticosteroids compared with no exposure in all children as well as children with preterm and full-term birth.

DATA SOURCES Academic databases were searched for articles published from January 1, 2000, to October 29, 2021, including Ovid MEDLINE, Ovid Embase, PsycInfo, CINAHL (Cumulative Index of Nursing and Allied Health Literature), Web of Science, ClinicalTrials.gov, and Google Scholar. References of articles were also searched for relevant studies.

STUDY SELECTION Randomized clinical trials (RCTs), quasi-RCTs, and cohort studies that assessed long-term neurodevelopmental, psychological, or other outcomes at 1 year or older in those who had preterm exposure to antenatal corticosteroids were included. No language restrictions were set.

DATA EXTRACTION AND SYNTHESIS Two reviewers independently extracted data using a piloted data extraction form. Data on study population, pregnancy characteristics, exposure to antenatal corticosteroids, and outcomes were collected. Preferred Reporting Items for Systematic Reviews and Meta-analyses reporting guidelines were followed, and random-effects models were used for the meta-analysis.

MAIN OUTCOMES AND MEASURES The primary outcome was an author-defined composite of any adverse neurodevelopmental and/or psychological disorder. The secondary outcomes included specific measures of psychological disorders; neurodevelopmental delay; and anthropometric, metabolic, and cardiorespiratory outcomes.

RESULTS A total of 30 studies met the inclusion criteria, and involved more than 1.25 million children who were at least 1 year of age when the outcomes were assessed. Exposure to a single course of antenatal corticosteroids for children with extremely preterm birth was associated with a significant reduction in risk of neurodevelopmental impairment (adjusted odds ratio, 0.69 [95% CI, 0.57-0.84]; I^2 = 0%; low certainty). For children with late-preterm birth, exposure to antenatal corticosteroids was associated with a higher risk of investigation for neurocognitive disorders (n = 25 668 children; adjusted hazard ratio [aHR], 1.12 [95% CI, 1.05-1.20]; low certainty). For children with full-term birth, exposure to antenatal corticosteroids was associated with a higher risk of mental or behavioral disorders (n = 641 487 children; aHR, 1.47 [95% CI, 1.36-1.60]; low certainty) as well as proven or suspected neurocognitive disorders (n = 529 205 children; aHR, 1.16 [95% CI, 1.10-1.21]; low certainty).

CONCLUSIONS AND RELEVANCE Results of this study showed that exposure to a single course of antenatal corticosteroids was associated with a significantly lower risk of neurodevelopmental impairment in children with extremely preterm birth but a significantly higher risk of adverse neurocognitive and/or psychological outcomes in children with late-preterm and full-term birth, who made up approximately half of those with exposure to antenatal corticosteroids. The findings suggest a need for caution in administering antenatal corticosteroids.

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Supplemental content
Editorial

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Antenatal corticosteroids administered in pregnancies at risk for preterm birth decrease the risk of mortality and morbidity in preterm newborns.[1,2] Given these benefits, numerous clinical guidelines advocate the use of antenatal corticosteroids in pregnancies that are at risk for preterm birth.[3,4] Studies in animals have found an association between exposure to antenatal corticosteroids at doses similar to those given to humans and harmful neurological outcomes, including alterations to the hypothalamic-pituitary-adrenal axis,[5,6] diminished cortical surface,[7] loss of essential synaptic proteins,[8] and decreased blood flow in areas of the brain.[9] In full-term animals, preterm exposure to antenatal corticosteroids was associated with harmful neural outcomes, such as decreased hippocampal development.[10] Moreover, in both preterm and full-term animals, there were implications for other organs,[11] including reduced glomerular filtration rate[12]; in full-term animals, the use of antenatal corticosteroids was associated with an increased insulin to glucose ratio.[13] Given these reported harmful outcomes in animals, understanding the long-term implications of preterm exposure to antenatal corticosteroids in children with both preterm and full-term birth is a critical research priority.

We conducted a systematic review and meta-analysis of long-term outcomes associated with (1) preterm exposure to a single course of antenatal corticosteroids (either 24 mg of betamethasone or dexamethasone), or (2) preterm exposure to an unspecified number of courses (although likely 1 course) vs no exposure. Given that approximately half of children who were exposed to antenatal corticosteroids exceeded expectations and were born at or after 35 weeks of gestation,[14] we aimed to conduct a systematic review and meta-analysis of long-term outcomes in all children as well as children with preterm (ie, born before 37 weeks of gestation) and full-term (ie, born at or after 37 weeks of gestation) birth.

Key Points

Question What are the long-term outcomes for children exposed to antenatal corticosteroids?

Findings In this systematic review and meta-analysis of 30 studies involving more than 1.25 million children, exposure to a single course of antenatal corticosteroids was associated with a significant decrease in the adjusted odds of neurodevelopmental impairment in children with extremely preterm birth. In children with late-preterm and full-term birth, antenatal corticosteroid exposure was associated with increased adjusted risks of neurocognitive and/or psychological impairment.

Meaning Findings of this study suggest that caution may be required in administering antenatal corticosteroids given the associated neurocognitive and/or psychological harms for children with late-preterm and full-term birth.

Methods

We followed the *Cochrane Handbook for Systematic Reviews of Intervention*[15] and the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline.[16] The protocol was registered on PROSPERO (CRD42020194167) and updated on December 8, 2021.

Data Sources and Study Eligibility

With the guidance of an information specialist, we searched the following 6 academic databases for articles published from January 1, 2000, through October 29, 2021: Ovid MEDLINE, Ovid Embase, PsycInfo, CINAHL (Cumulative Index of Nursing and Allied Health Literature), Web of Science, and ClinicalTrials.gov; the first 400 results were retrieved from Google Scholar (eAppendix 1 in the Supplement). We also screened the references in articles for relevant studies.

Having set no language restrictions, we considered randomized clinical trials (RCTs), quasi-RCTs, and observational studies (ie, follow-up of RCTs, cohort studies, and case-control studies) that assessed long-term neurodevelopmental, psychological, or other outcomes at 1 year or older in those who had preterm exposure to antenatal corticosteroids. Other types of publications were excluded. Studies involving births occurring in or after 2000 were considered given the implications of recent advances in neonatal care for short-term and long-term outcomes.[17,18]

The primary outcome was an author-defined composite of any adverse neurodevelopmental and/or psychological disorder. Prespecified secondary outcomes included specific measures of visual impairment; auditory impairment; psychological developmental disorders (eg, disorders of speech and language as well as scholastic skills); autism spectrum disorders; attention-deficit/hyperactivity disorder or conduct disorders; mixed disorders of conduct and emotions; emotional, social functioning, or tic disorders; other behavioral and emotional disorders; psychotic, mood, neurotic, stress-related, or somatization disorders; eating disorders; sleep disorders; measures of anxiety-related symptoms or clinical measures of anxiety; measures of anxiety-related symptoms or clinical measures of depression; special educational needs; cerebral palsy; Bayley Scales of Infant and Toddler Development (BSID)-II Mental Developmental Index score less than 70 points; BSID-II Psychomotor Developmental Index score less than 70 points; BSID-III cognitive score less than 85 points; BSID-III language score less than 85 points; IQ scores; intellectual impairment (defined as an IQ or developmental quotient at least 2 SDs below the mean); mild, moderate, or unspecified intellectual disability; and other neurodevelopmental and/or psychological outcomes included in the literature. For the secondary outcomes, we considered long-term anthropometric (ie, weight, height, and head circumference), cardiorespiratory, endocrine, and metabolic outcomes as well as survival in childhood and adulthood.

Furthermore, we reported the proportion of children who were born full term with preterm exposure to antenatal corticosteroids. Because there was not a specific core outcome set for long-term follow-up, all outcomes that were reported at 1 year or older were included.

Data Screening and Extraction

Two of us (K.N. and S.K.L.) independently screened the titles and abstracts for a full-text review. The full-text articles were

assessed, and data were extracted using a piloted data extraction form. Data were collected on pregnancy characteristics, study population, exposure to antenatal corticosteroids, and outcomes included in the review. Discrepancies were resolved through discussion between the 2 reviewers, and although consultation with a third reviewer (S.D.M.) was available for resolving discrepancies, it proved unnecessary.

In addition, 2 of us (K.N. and S.K.L.) planned to independently appraise the quality of RCTs and their follow-up studies using version 2 of the Cochrane risk-of-bias tool.[15] For observational studies, we used the modified Newcastle-Ottawa Scale (NOS) to assess risk of bias across 8 domains, awarding a minimum of one-half star or one-half point (indicating the lowest obtainable score) to a maximum of 9 stars or 9 points (indicating the highest obtainable score).[19] For the comparability domain of the modified NOS, one-half star was awarded for each confounder and 2 stars were awarded if at least 4 of the following 6 key confounders were addressed: use of postnatal steroids, gestational age at birth, intrauterine growth restriction, family or maternal history of neurodevelopmental and psychological problems, socioeconomic status, and maternal substance use. We identified these key confounders on the basis of clinical expertise and review of the literature.

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool was used to rate the certainty of included outcomes in 6 domains (risk of bias, inconsistency, imprecision, indirectness, publication bias, and other considerations). The GRADE ratings were high, moderate, low, or very low certainty.

Data Analysis and Synthesis

Data for all children and the preterm and full-term subgroups were analyzed. Data on the race and ethnicity of children were collected when available.

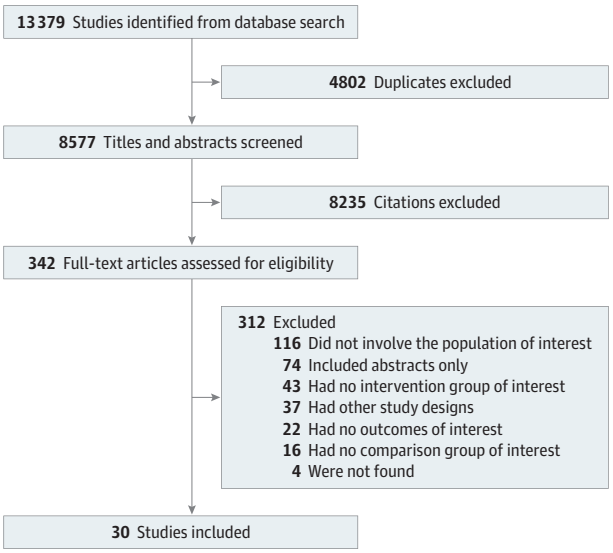
A random-effects meta-analysis was performed for outcomes that could be pooled. Risk ratio (RR), odds ratio (OR), and 95% CIs were identified for binary summary effect sizes, whereas mean differences and 95% CIs were reported for continuous summary effect sizes. The I^2 statistic was used to report heterogeneity. The meta-analysis was performed using Review Manager, version 5.4.1 (Cochrane Community).[20] For studies with overlapping populations, results for each study were presented. However, the largest study was considered for the meta-analysis. Single-study outcomes were also reported.

A 2-sided $P < .05$ was considered to be statistically significant. A priori, we planned to conduct sensitivity analyses limited to higher-quality studies (ie, those rated with at least 6 of 9 stars on the NOS) as well as subgroup analyses to compare outcomes by treatment (betamethasone vs dexamethasone), by sex (male vs female), and by gestational age at administration of antenatal corticosteroids (<28 weeks, 28-33 weeks, or 34-36 weeks).

Results

A total of 13 379 records were retrieved (**Figure 1**). After excluding 4802 duplicate records, we screened 8577 titles and abstracts and assessed 342 full-text articles. A total of 30 cohort studies[21-50] met the final inclusion criteria that, together, involved more than 1.25 million children who were at least 1 year of age when the outcomes were assessed (**Table 1**; eTable 1 in the Supplement); the justifications for excluding other important studies are provided in eAppendix 2 in the Supplement. Race and ethnicity categories were reported in 6 studies[22,27,35,38,40,42] (eTable 1 in the Supplement). A few studies adjusted for race and ethnicity but did not report the adjusted effect sizes of race and ethnicity on long-term outcomes.[22,38,42]

Figure 1. PRISMA Diagram of Study Selection



Of the 30 studies included, 26 focused on neurodevelopmental and/or psychological outcomes[21-37,41-45,47-50] (eTables 2-6 in the Supplement), 3 had data on both neurodevelopmental and/or psychological outcomes and other outcomes[38-40] (eTables 2-7 in the Supplement), and 1 included data on other outcomes[46] (eTable 7 in the Supplement). The duration of participant follow-up ranged from 1 to 10 years (Table 1).

Scores for the cohort studies on the modified NOS ranged from 4.5 to 8.5 points out of a maximum of 9.0 points, with a median NOS score of 5.75 points for studies that compared a single course of antenatal corticosteroids with nonexposure (eTable 8 in the Supplement) and 6.5 points for studies that compared an unspecified number of courses of antenatal corticosteroids with nonexposure. One study[24] addressed at least 4 of the 6 predetermined confounders for scoring the comparability domain of the NOS (eTable 8, eAppendix 3 in the Supplement).

Single Course vs Nonexposure

Ten of 30 studies measured long-term outcomes for children with preterm birth who were exposed to a single course of antenatal corticosteroids compared with those who were unexposed (Table 1).[35-43,46] The use of a single course of antenatal

Table 1. Characteristics of Included Studies

Source and country	Risk-of-bias rating[a]	Recruitment period (timing of follow-up)	Study design	Treatment (dose pattern)
Single antenatal corticosteroid course vs nonexposure				
Children with preterm birth				
Chawla et al,[40] 2013, US	★★★★★★★★	2005-2008 (18-22 mo corrected age)	Retrospective cohort	Betamethasone, 2 doses (NS)
Gover et al,[46] 2012, Canada	★★★★★★★½	2001-2004 (18 mo corrected age)	Prospective cohort	Dexamethasone (two 12 mg once every 12-24 h)
Chawla et al,[38] 2016, US	★★★★★★★	2006-2011 (18-22 mo corrected age)	Prospective cohort study	Betamethasone (two 12 mg once every 24 h) or dexamethasone (four 6 mg once every 12 h)
Lee et al,[42] 2008, US	★★★★★★½	2002-2003 (18-22 mo corrected age)	Retrospective cohort	Betamethasone (two 12 mg once every 24 h) or dexamethasone (four 6 mg once every 12 h)
Agarwal et al,[35] 2018, Singapore	★★★★★★	2010-2011 (mean [SD]: 24 [4] mo corrected age)	Prospective cohort	Dexamethasone (two 12 mg once every 24 h)
Kim et al,[36] 2018, Korea	★★★★★½	2001-2016 (18-22 mo after birth)	Retrospective cohort	Betamethasone (two 12 mg once every 24 h) or dexamethasone (four 6 mg once every 12 h)
Laughon et al,[43] 2009, unspecified	★★★★★½	2002-2004 (24 mo corrected age)	Prospective cohort	Betamethasone (two 12 mg once every 24 h) or dexamethasone (four 6 mg once every 12 h)
McElrath et al,[41] 2009, US	★★★★★½	2002-2004 (approximately 24 mo corrected age)	Prospective cohort	Betamethasone (dose NS; two once every 24 h) or dexamethasone (dose NS; four once every 12 h) administered at least 48 h after the first dose
Lardón et al,[37] 2017, Spain	★★★★½	2008-2013 (during first 2 y of corrected age)	Prospective cohort	Betamethasone (two 12 mg once every 24 h)
Tseng et al,[39] 2016, Taiwan	★★★★½	2007-2010 (2-5 y)	Prospective cohort	Betamethasone (two 12 mg once every 24 h) or dexamethasone (four 6 mg once every 12 h)
Unspecified No. of antenatal corticosteroid courses vs nonexposure				
Children with preterm or full-term birth				
Lamminmäki et al,[45] 2021, Finland	★★★★★★★½	2003-2008 (1.5-8 y)	Retrospective cohort	Betamethasone (two 12 mg once every 24 h)[b]
Räikkönen et al,[21] 2020, Finland	★★★★★★★½	2006-2017 (1-11 y)	Retrospective cohort	Betamethasone (two 12 mg once every 24 h)[b]
Wolford et al,[24] 2020, Finland	★★★★★★★	2006-2010 (6-10 y)	Prospective cohort	Betamethasone (two 12 mg once every 24 h, IM)[b]
Children with preterm birth				
Haslam et al,[27] 2018, Canada	★★★★★★★★½	2009-2011 (18-21 mo corrected age)	Retrospective cohort	Betamethasone (two 12 mg once every 24 h, IM)[b]
Aviram et al,[50] 2021, Canada	★★★★★★★★	2006-2011 (at least 5 y)	Retrospective cohort	Betamethasone (two 12 mg once every 24 h, IM)[b]
Räikkönen et al,[21] 2020, Finland	★★★★★★★½	2006-2017 (1-11 y)	Retrospective cohort	Betamethasone (two 12 mg once every 24 h)[b]
Hutcheon et al,[49] 2020 Canada	★★★★★★★	2000-2013 (5-6 y)	Regression discontinuity	Betamethasone (two 12 mg once every 24 h, IM)[b]
Gentle et al,[22] 2020, US	★★★★★★★	2011-2014 (18-26 mo corrected age)	Prospective cohort	Betamethasone (two 12 mg once every 24 h, IM)[b]
Bulbul et al,[47] 2020, Turkey	★★★★★★½	2011-2014 (18-24 mo corrected age)	Prospective cohort	Antenatal corticosteroids (NS)
Miyazaki et al,[30] 2015, Japan	★★★★★★½	2003-2007 (3 y or 36-42 mo chronological age)	Retrospective cohort	Antenatal corticosteroids (NS)
Ushida et al,[48] 2020, Japan	★★★★★★½	2003-2015 (3 y)	Retrospective cohort	Betamethasone (two 12 mg once every 24 h, IM)[b]
Ushida et al,[23] 2020, Japan	★★★★★★½	2003-2016 (3 y)	Retrospective cohort	Betamethasone (two 12 mg once every 24 h, IM)[b]
Basset et al,[26] 2018, France	★★★★★★	2003-2013 (2 y corrected age)	Prospective cohort	Antenatal corticosteroids (NS)
Ishikawa et al,[29] 2015, Japan	★★★★★½	2003-2007 (3 y or 36-42 mo)	Retrospective cohort	Betamethasone (NS)[b]
Li et al,[25] 2019, China	★★★★★½	2010-2016 (18-24 mo)	Prospective cohort	Betamethasone (12 mg once every 24 h, IM) or dexamethasone (6 mg once every 12 h for 48 h, IM)[b]
Ochiai et al,[33] 2014, Japan	★★★★★½	2000-2009 (3 y)	Retrospective cohort	Betamethasone or dexamethasone (NS)

(continued)

Table 1. Characteristics of Included Studies (continued)

Source and country	Risk-of-bias rating[a]	Recruitment period (timing of follow-up)	Study design	Treatment (dose pattern)
Young et al,[28] 2016, Canada	★★★★★½	2008-2010 (at 2 y and 4 y)	Prospective cohort	Betamethasone (two 12 mg once every 24 h, IM)[b]
Källén et al,[31] 2015, Sweden	★★★★½	2004-2007 (2.5 y corrected age)	Prospective cohort	Betamethasone (NS)
Kiechl-Kohlendorfer et al,[34] 2009, Austria	★★★★½	2003-2006 (1 y corrected age)	Prospective cohort	Antenatal corticosteroids (NS)
Sun et al,[32] 2015, China	★★★★½	2006-2010 (18 mo corrected age)	Retrospective cohort	Antenatal corticosteroids (NS)
Children with full-term birth				
Melamed et al,[44] 2019, Canada	★★★★★★★★	2006-2011 (5 y)	Retrospective cohort	Betamethasone (two 12 mg once every 24 h, IM) or dexamethasone (four 6 mg once every 12 h, IM)[b]
Räikkönen et al,[21] 2020, Finland	★★★★★★★½	2006-2017 (1-11 y)	Retrospective cohort	Betamethasone (two 12 mg once every 24 h)[b]

Abbreviations: IM, intramuscular; NS, not specified.

[a] Each star represents 1 point and half of a star represents one-half point in the modified Newcastle-Ottawa Scale for assessing risk of bias across 8 domains.

[b] Antenatal corticosteroid dose was not stated but assumed on the basis of available guideline recommendations at the time of recruitment and was still classified as unspecified.

corticosteroids vs nonexposure was not associated with significant reductions in odds of visual impairment (3 studies[37,38,42]; adjusted OR [aOR], 1.42 [95% CI, 0.57-3.54]; I^2 = 0%; very low certainty), auditory impairment (3 studies[37,38,42]; aOR, 0.58 [95% CI, 0.33-1.01]; I^2 = 9%; very low certainty), or moderate or severe cerebral palsy (2 studies[38,42]; aOR, 0.82 [95% CI, 0.56-1.19]; I^2 = 0%; low certainty) (**Figure 2**; eTable 6 in the Supplement). For children with extremely premature birth, exposure vs nonexposure was associated with a significantly decreased odds of neurodevelopmental impairment (2 studies[38,42]; aOR, 0.69 [95% CI, 0.57-0.84]; I^2 = 0%; low certainty), cerebral palsy (2 studies[38,42]; aOR, 0.60 [95% CI, 0.43-0.83]; I^2 = 22%; low certainty), and other adjusted adverse neurodevelopmental and/or psychological outcomes (**Table 2**, Figure 2; eTables 2 and 6, eFigure 1 in the Supplement).[38]

Furthermore, Lee et al[42] found that exposure to a single course of betamethasone vs nonexposure was significantly associated with a higher adjusted odds of nonimpairment, which was defined as the absence of cerebral palsy, blindness, deafness, or neurodevelopmental delay (aOR, 2.42 [95% CI, 1.49-3.91]; low certainty) (eTable 2 in the Supplement). Sensitivity analyses did not change the conclusion of these findings (eFigure 2 in the Supplement). Many secondary neurodevelopmental and/or psychological outcomes associated with exposure to a single course of antenatal corticosteroids vs nonexposure were nonsignificant or unadjusted and had few low or very low certainty GRADE ratings (eTables 2 and 3, eFigures 1-3 in the Supplement).

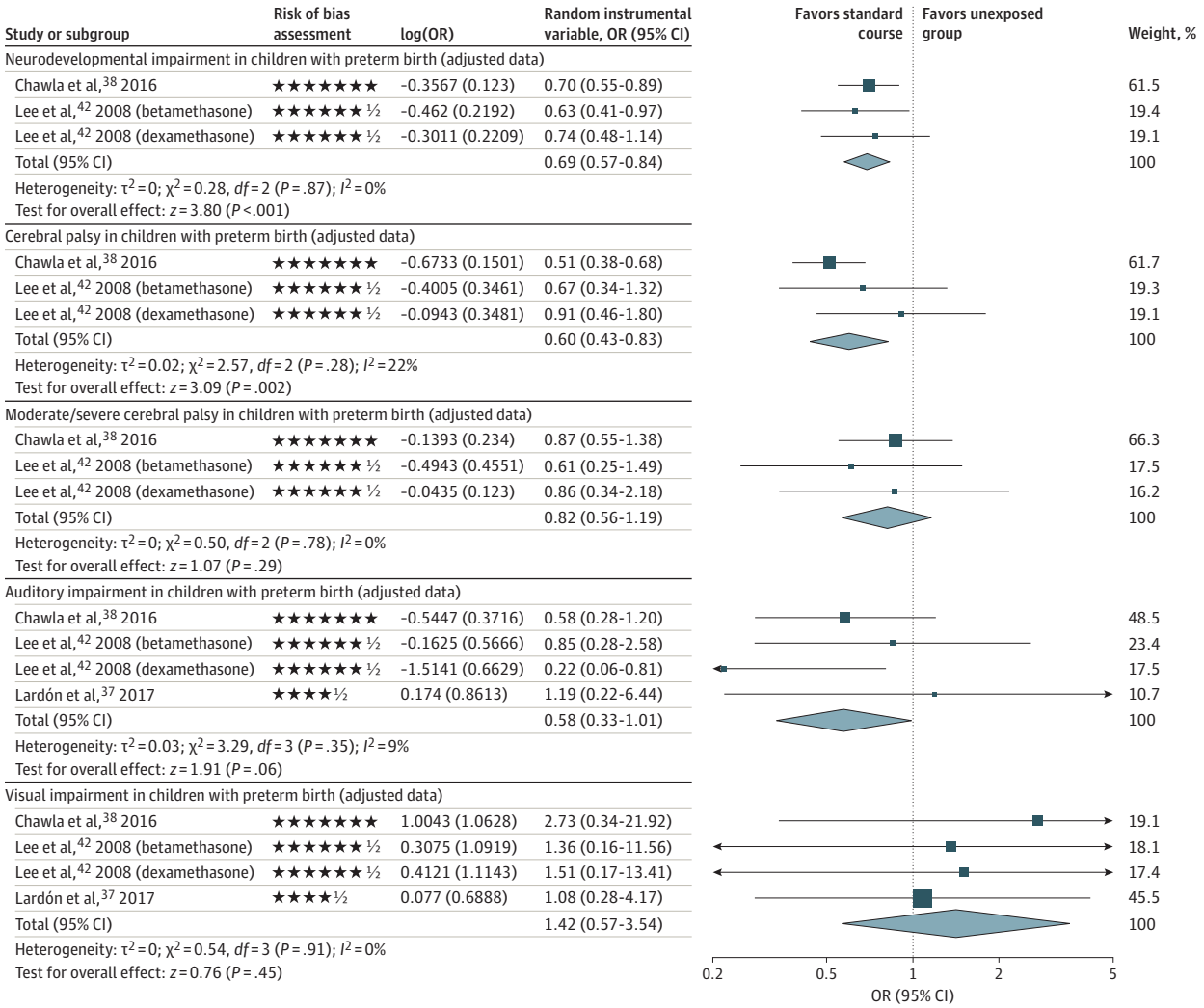
In analyses of other long-term outcomes, a single course of antenatal corticosteroids vs nonexposure was not associated with substantial differences in body weight or head circumference (very low certainty) (eTable 7, eFigure 2 in the Supplement). Tseng et al[39] (cohort study involving 40 children) found a significantly higher unadjusted proportion of children with asthma and allergic disease among those who were exposed to a single course of antenatal corticosteroids (very low certainty) (eTable 7 in the Supplement). Other unadjusted adverse long-term outcomes for the secondary outcome were rated as very low certainty or had nonsignificant associations (eTable 7 in the Supplement).

Unspecified Number of Courses of Antenatal Corticosteroids vs Nonexposure

Twenty of the 30 included studies had long-term outcomes for children who were exposed to an unspecified number of courses of antenatal corticosteroids vs those who were unexposed; however, most of these studies likely included a single course of antenatal corticosteroids because that was the most common clinical scenario during the study period (Table 1; eTables 4 and 5, eFigures 1-3 in the Supplement).[21-34,44,45,47-50] Two studies (Räikkönen et al[21] and Wolford et al[24]) addressed the primary outcome of an author-defined composite of any adverse neurodevelopmental and/or psychological disorder (**Figure 3**), whereas another study (Lamminmäki et al[45]) addressed individual psychological outcomes (eTable 4 in the Supplement). Räikkönen et al[21] reported a significantly elevated risk of any mental or behavioral disorder in children with preterm and full-term birth that was associated with exposure to an unspecified number of courses of antenatal corticosteroids vs nonexposure (670 097 children; adjusted hazard ratio [aHR], 1.33 [95% CI, 1.26-1.41]; low certainty) (Table 2). Furthermore, a subgroup analysis of consecutive sibling pairs who were discordant for treatment exposure demonstrated that the use of antenatal corticosteroids was associated with an increased adjusted risk of any mental or behavioral disorder (241 447 children; aHR, 1.38 [95% CI, 1.21-1.58]; low certainty) (eTable 4 in the Supplement).[21] An unspecified number of courses of antenatal corticosteroids vs nonexposure was associated with increases in risk for 8 of 12 adverse adjusted secondary neurodevelopmental and/or psychological outcomes in children with preterm and full-term birth (eTable 4 in the Supplement).

Sixteen studies[22,23,25-34,47-50] reported on adverse or beneficial neurodevelopmental and/or psychological outcomes specifically in children with preterm birth. In addition, Räikkönen et al[21] reported on outcomes in children with full-term birth and a combination of children with preterm and full-

Figure 2. Primary and Adjusted Long-term Neurodevelopmental and Psychological Outcomes After Exposure to A Single Course of Antenatal Corticosteroids



The forest plots show the comparison between a single course of antenatal corticosteriods and no exposure. Each star represents 1 point and half of a star represents one-half point in the modified Newcastle-Ottawa Scale for assessing risk of bias across domains. Squares represent effect size estimates and the whiskers correspond to the 95% CIs. The diamonds represent the overall effect based on pooled data from all included studies for each outcome. OR indicates odds ratio.

term birth (eTables 4-6 in the Supplement). For children with preterm birth, exposure to an unspecified number of courses of antenatal corticosteroids vs nonexposure was not associated with significant reductions in the risk of neurodevelopmental impairment (5 studies[22,27,30,31,34]; aOR, 0.78 [95% CI, 0.57-1.06]; I^2 = 46%; low certainty) or hearing impairment (2 studies[22,30]; aOR, 0.77 [95% CI, 0.36-1.66]; I^2 = 13%; low certainty) (Figure 3). Young et al[28] reported that exposure to antenatal corticosteroids was associated with decreased cognitive and behavior scores (eTable 4 in the Supplement). Meanwhile, Räikkönen et al[21] reported that exposure was associated with an increased adjusted risk of sleeping disorders (low certainty) and decreased adjusted risk of mild, moderate, or unspecified intellectual disabilities (low certainty) (eTable 4, eFigure 1 in the Supplement). Aviram et al[50] found that exposure was associated with an increased adjusted risk of investigation for neurocognitive disorders in children with late-preterm birth (ie, 34-36 weeks of gestation) (25 668 children; aHR, 1.12 [95% CI, 1.05-1.20]; low certainty) and the use of visual or audiometry testing. No significant associations were observed in other adjusted adverse or beneficial neurodevelopmental and/or psychological outcomes (eTable 4, eFigure 1 in the Supplement). Sensitivity analyses did not change the conclusion of these findings (eFigure 2 in the Supplement).

Two studies reported the proportion of children with full-term birth after preterm exposure to antenatal corticosteroids: 45.3% (6730 of 14 868) in Räikkönen et al[21] and 47.9% (56 of 117) in Wolford et al.[24] Exposure to an unspecified number of courses of antenatal corticosteroids was associated with higher risks of any mental or behavioral disorder (641 487 children; aHR, 1.47 [95%

Table 2. Summary of Findings for the Primary Outcome in Included Studies

Certainty assessment							No./total No. of patients (%)		Effect size (95% CI)			
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Unspecified No. of antenatal corticosteroid courses	Nonexposure	Relative	Absolute	Certainty[a]	Importance
Single antenatal corticosteroid course vs nonexposure												
Children with preterm birth												
Neurodevelopmental impairment												
2 Studies[38,42]	Observational studies	Not serious	Not serious	Not serious	Not serious	None	1009/3376 (29.9)	235/572 (41.4)	aOR, 0.69 (0.57-0.84[b]	<9 per 100 (from <13 to <4)	Low	Important
Unspecified No. of antenatal corticosteroid courses vs nonexposure												
Children with preterm or full-term birth												
Any mental or behavioral disorder												
1 Study[21]	Observational study	Not serious	Not serious	Not serious	Not serious	None	1785/14 868 (12.0)	42 243/655229 (6.4)	aHR, 1.33 (1.26-1.41)[b]	>2 per 100 (from >2 to >3)	Low	Important
Any mental or behavioral disorder												
1 Study[24]	Observational study	Not serious	Not serious	Not serious	Serious[c]	None	24/117 (20.5)	386/4591 (8.4)	aOR, 2.58 (1.50-4.42)[b]	>11 per 100 (from >4 to >20)	Very low	Important
Children with preterm birth												
Any mental or behavioral disorder												
1 Study[21]	Observational study	Not serious	Not serious	Not serious	Not serious	None	1187/8138 (14.6)	2192/20 472 (10.7)	aHR, 1.00 (0.92-1.09)	<0 per 100 (from <1 to >1)	Low	Important
Neurodevelopmental impairment												
5 Studies[22,27,30,31,34]	Observational studies	Not serious	Not serious	Not serious	Not serious	None	NA	NA	aOR, 0.78 (0.57-1.06)	<1 per 100 (from <1 to <1)	Low	Important
Children with full-term birth												
Any mental or behavioral disorder												
1 Study[21]	Observational study	Not serious	Not serious	Not serious	Not serious	None	598/6730 (8.9)	40 051/ 634 757 (6.3)	aHR, 1.47 (1.36-1.60)[b]	>3 per 100 (from <2 to <4)	Low	Important

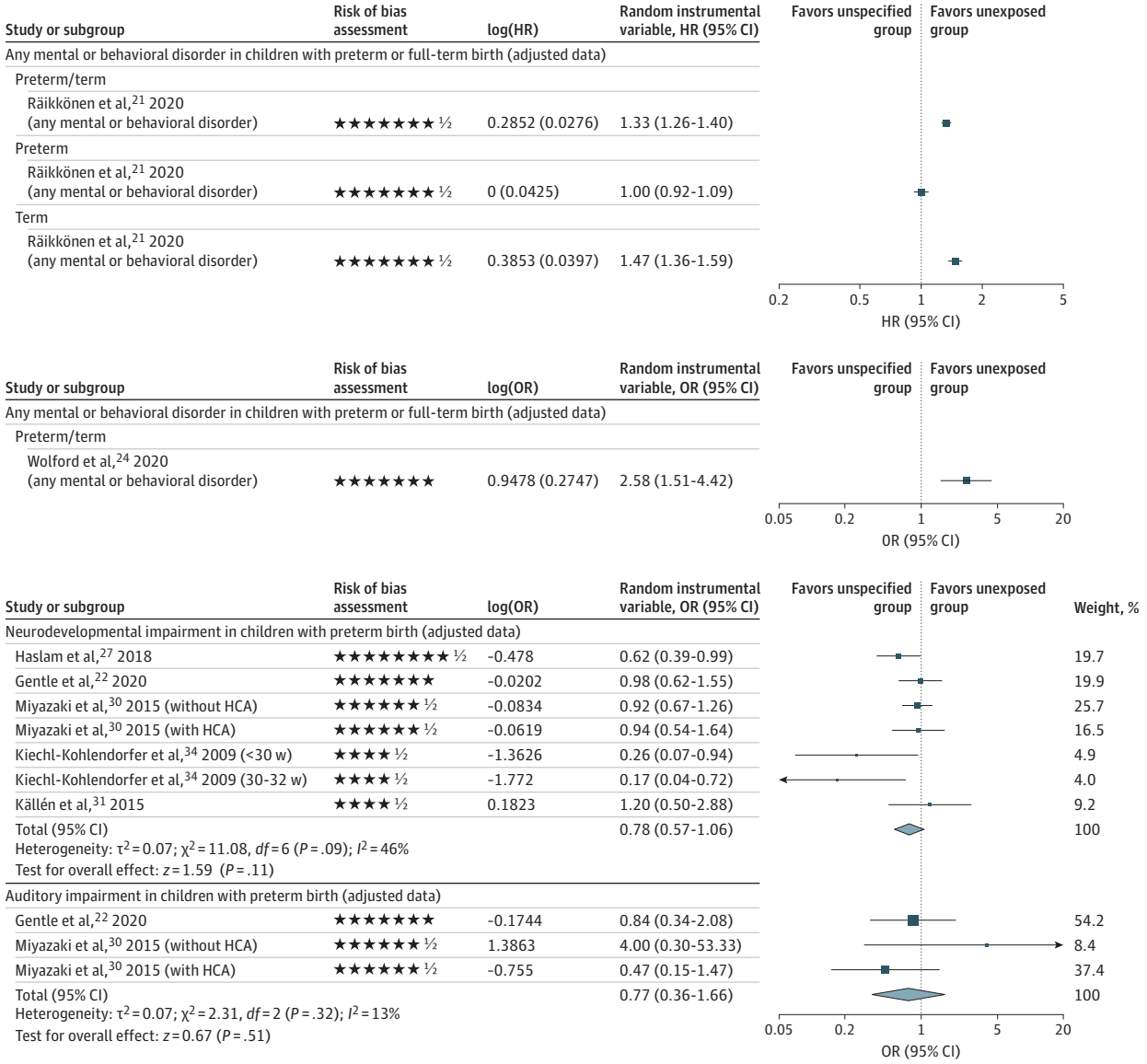
Abbreviations: aHR, adjusted hazard ratio; aOR, adjusted odds ratio; NA, not available.

[a] The Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool was used to rate the certainty of included outcomes as high, moderate, low, or very low.

[b] Statistically significant.

[c] Small number of events that was disproportionate between groups. Wide 95% CIs.

Figure 3. Primary and Adjusted Long-term Neurodevelopmental and Psychological Outcomes After Exposure to an Unspecified Number of Courses of Antenatal Corticosteroids



The forest plots show the comparison between an unspecified number of antenatal corticosteriod courses and no exposure. Each star represents 1 point and half of a star represents one-half point in the modified Newcastle-Ottawa Scale for assessing risk of bias across domains. On each forest plot, squares represent effect size estimates and the whiskers correspond to the 95% CIs. The diamonds represent the overall effect based on pooled data from all included studies for each outcome. HR indicates hazard ratio; OR, odds ratio.

CI, 1.36-1.60]; low certainty)[21] (Figure 3) and with a composite outcome of audiometry testing, visual testing, or proven or suspected neurocognitive disorder (n = 529 205 children; aHR, 1.12 [95% CI, 1.08-1.16]; low certainty) as well as with individual components of that composite outcome, including proven or suspected neurocognitive disorder (aHR, 1.16 [95% CI, 1.10-1.21]; low certainty)[44] (eTable 4, eFigures 1 and 4 in the Supplement). For children with full-term birth, exposure vs no exposure was associated with significant increases in risk for 5 other adjusted adverse neurodevelopmental and/or psychological outcomes (eTable 4 in the Supplement).[21] For the secondary outcomes, no studies reported on outcomes of comparing an unspecified number of courses with no exposure.

Discussion

In this systematic review and meta-analysis of 30 studies on long-term neurodevelopmental, psychological, or other outcomes in more than 1.25 million children, a single course of antenatal corticosteroids vs nonexposure was associated with significantly reduced risk of neurodevelopmental impairment and cerebral palsy

in children with extremely preterm birth (low certainty). For those with late-preterm and full-term birth (the latter group composed approximately half of those with exposure), there were significantly higher risks of adverse neurocognitive and/or psychological outcomes that were associated with exposure to likely 1 course of antenatal corticosteroids compared with children who were unexposed (low certainty).[21,44]

Overall Completeness and Applicability of Evidence

We hypothesized that the difference in findings across gestation (with benefits seen in children with preterm birth and harms seen in those with late-preterm and full-term birth) may be explained by the immature vasculature in children with earlier preterm birth that renders the developing brain susceptible to hemorrhage[51] and, as shown in animal studies, by exposure to antenatal corticosteroids that increases cerebrovascular resistance.[52] This explanation, along with potential blood pressure stabilization,[53] can decrease the risk of intraventricular hemorrhage and potential neurodevelopmental impairment.[38] Furthermore, fetuses approaching term are exposed to maternal[54] and fetal increases[55] in cortisol. This additional exposure to antenatal corticosteroids at this gestational age results in high corticosteroid exposure, which may be associated with altered programming in the developing brain and the hypothalamic-pituitary-adrenal axis.[54] Animal research has suggested that doses of betamethasone that are supraphysiological are at least several times higher and potentially 10 times higher than what is needed.[56] Thus, further study of long-term outcomes after exposure to antenatal corticosteroids is important.

There are concerns about the use of antenatal corticosteroids in later-preterm gestation because of diminishing benefits over the preterm period.[55,57] Future research is warranted on the long-term impacts of the use of antenatal corticosteroids across various gestational age strata and the timing of administration to delivery intervals in the preterm period (which were not well reported in the included studies).

We could not conduct planned subgroup analyses by type of corticosteroid treatment and by sex because of the lack of data in included studies. Lee et al[42] focused on the impact of betamethasone and dexamethasone separately in comparing exposure to a single course of antenatal corticosteroids vs nonexposure in children with preterm birth; these investigators found an association between a significant decrease in neurodevelopmental impairment and use of only betamethasone compared with nonexposure. Further studies comparing the long-term outcomes of betamethasone and dexamethasone use are needed. Robust evidence on the long-term impact of antenatal corticosteroids is important because of the imprecise art of predicting preterm birth[58] and the decrease in the benefits of antenatal corticosteroids in a fetus who remains undelivered 7 days after administration.[59]

Relation to Other Published Reviews on the Topic

The adjusted and unadjusted findings were similar to those reported in another systematic review, which included data before 2000 and found that a single course of antenatal corticosteroids was associated with unadjusted reductions in cerebral palsy compared with nonexposure.[60] The literature search for the previous review concluded in August 2014, and since this time a substantial amount of research has emerged, including 5 studies[35-39] that we included in the present work. In addition, the previous review excluded 12 of 42 studies because their data could not undergo a meta-analysis,[60] rather than considering the studies narratively as performed in the present study.

Strengths and Limitations

This study has some strengths. We included a comprehensive search of multiple academic sources to provide a thorough synthesis of the long-term outcome of antenatal corticosteroids in children with preterm and full-term birth. For relevance to current neonatal care practice, we included studies involving births occurring in or after 2000. To provide a comprehensive view of the long-term impacts of antenatal corticosteroids, we considered both a single course of antenatal corticosteroids and an unspecified number of antenatal corticosteroid courses, which was most likely 1 course as it is the recommended treatment option in many settings.[3,4,61]

This study also has some limitations. Randomized follow-up data were scarce. The use of observational data may involve some degree of bias that affects the quality of the data[62] and may lead to a lower level of certainty with our conclusions. However, when possible, we focused on adjusted data that addressed issues with confounding. Given the paucity of data, the role of race and ethnicity in long-term outcomes after antenatal corticosteroid exposure should be an area for future study. Furthermore, child development scores have different meanings depending on the age at assessment.[63,64] Most pooled studies in the present analysis had similar follow-up ages of assessment (ie, ranging from age 1 to 2 years).

Conclusions

This systematic review and meta-analysis found an association between exposure to a single course of antenatal corticosteroids and a significantly lower risk of neurodevelopmental impairment in extremely preterm birth as well as a significantly higher risk of adverse neurocognitive and/or psychological outcomes in late-preterm and full-term birth. Given that approximately 50% of children who had preterm exposure to antenatal corticosteroids exceeded expectations and were born full term, the timing and dose of antenatal corticosteroid administration should be carefully considered.

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