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Is chorioamnionitis associated with neurodevelopmental outcomes in preterm infants? A systematic review and meta-analysis following PRISMA

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Abstract

Background: The relationships between chorioamnionitis (CA) and neurodevelopmental outcomes in preterm infants remain controversial. The meta-analysis aims to evaluate the associations between CA and neurodevelopmental deficits in preterm infants.

Methods: All studies exploring the associations between CA and neurodevelopmental deficits in preterm infants were retrieved from the following databases: PubMed, Embase, OVID, EBSCO, ProQuest, CDSR, and CENTRAL. The NOS was used to evaluate the quality of the studies, RevMan was adopted to analyze the data.

Results: Twelve studies involving 4267 preterm infants were included. The ORs across studies was 0.95 ($P = .77$, $I^2 = 51\%$) for cognitive deficits, 1.09 ($P = .44$, $I^2 = 10\%$) for psychomotor deficits, 1.21 ($P = .08$, $I^2 = 25\%$) for language deficits, 2.34 ($P = .02$, $I^2 = 0\%$) for performance intelligence quotient impairment and 2.81 ($P = .03$, $I^2 = 0\%$) for verbal intelligence quotient impairment. Subgroup analyses based on the severity of cognitive deficits indicated that CA might be correlated with severe cognitive deficits ($P = .01$, $I^2 = 0\%$) but not with mild cognitive deficits ($P = .40$, $I^2 = 19\%$). In terms of the CA category, clinical CA may be related to overall psychomotor deficits ($P = .01$, $I^2 = 25\%$) and overall language deficits ($P < .00001$, $I^2 = 23\%$) other than histological CA.

Conclusion: In preterm infants, CA might be a risk factor for performance and verbal intelligence quotient impairment and severe cognitive deficits, and clinical CA might be a risk factor for overall psychomotor and language deficits.

Abbreviations: BW = birth weight, CA = chorioamnionitis, Ca-Co = case-control study, CCA = clinical chorioamnionitis, CDSR = the Cochrane Database of Systematic Reviews, CENTRAL = the Cochrane Central Register of Controlled Trials, CI = confidence interval, CP = cerebral palsy, Des = clinical or histological description, GA = gestational age, HCA = histological chorioamnionitis, IQ = intelligence quotient, IVH = intraventricular hemorrhage, MDI = the Bayley Scales of Infant Development-II, Mental Developmental Index, MeSH = medical subject headings, NICE = The National Institute for Health and Clinical Excellence, NoDes = no description, NOS = Newcastle-Ottawa Quality Assessment Scale, ORs = odds ratio, PDI = the Bayley scales of infant development-II, psychomotor developmental index, PIQ = performance intelligence quotient, PPROM = preterm premature rupture of membranes, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses, PVL = periventricular leukomalacia, Ref = Literature citation, VIQ = verbal intelligence quotient, VLBW = very low birth weight, VLGA = very low gestational age, WISC-III = the Wechsler Intelligence Scale for Children-III, WPPSI-R = the Wechsler Preschool and Primary Scale of Intelligence-Revised.

Keywords: chorioamnionitis, meta-analysis, neurodevelopmental outcomes, preterm infants

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1. Introduction

Chorioamnionitis (CA) is one of the most severe complications during pregnancy; it is defined as intrauterine infection/inflammation and the invasion of polymorphous-clear leukocytes into the membranes, the umbilical cord and/or the chorionic plate.[1] CA is generally subclinical; the diagnosis is based on the accumulation of neutrophils in the placenta and membranes and often cannot be made before delivery. Occasionally, it produce clinical presentations such as maternal fever, uterine tenderness, malodourous amniotic fluid, maternal or foetal tachycardia, maternal leucocytosis and/or elevated C-reactive protein.[1]

Previous studies have reported that CA could lead to significant morbidity and mortality.[2–5] Specifically, it is a frequent cause of preterm birth with very low gestational age (VLGA)/very low birth weight (VLBW),[1,6–9] nearly 50% of cases of spontaneous preterm birth are linked to intrauterine infection.[6,10] For preterm infants born to mothers exposed to CA, an increased risk of severe intraventricular haemorrhage (IVH)[11–16] and/or periventricular leukomalacia (PVL)[12,13,17,18] was observed. Another negative consequence is cerebral palsy (CP), whose relationship with intrauterine infection was verified by the U.K.'s National Institute for Health and Clinical Excellence (NICE) guidelines for children with CP in 2017.[19]

Recently, more emphasis has been placed on exploring the relationships between CA and other neurodevelopmental areas in preterm infants, such as cognition, psychomotor skills, language, and intelligence quotient (IQ). However, the results remain controversial due to heterogeneous evidence. Although some studies have identified CA as an independent risk factor related to adverse neurodevelopmental outcomes in preterm infants,[20] the other studies did not present such an association.[15,21–29] Even more interestingly, histological chorioamnionitis (HCA) has been reported to be correlated with a decrease in neurodevelopmental deficits.[30–33] These conflicting results make it difficult for doctors to make proper medical decisions for the newborn.

This meta-analysis aims to explore the associations between CA and certain neurodevelopmental deficits in VLGA/VLBW preterm birth infants, differentiating between clinically apparent and subclinical processes, mild and severe neurodevelopmental deficits, and short-term, mid-term and long-term adverse neurodevelopmental outcomes.

2. Methods

All analyses were based on previously published studies; thus, ethical approval and patient consent were not necessary. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines were followed to perform this meta-analysis.[34]

2.1. Study selection

All the studies were screened and selected by two reviewers working independently (GYW and RQC). The pre-specified eligibility criteria were as follows:

(i) types of studies: cohort and case-control studies that explored the associations between CA and neurodevelopmental deficits in preterm infants;
(ii) types of participants: preterm infants; we accepted each individual trial's inclusion and exclusion criteria for participants;

(iii) types of CA: HCA, clinical chorioamnionitis (CCA), both HCA and CCA;
(iv) control groups: no CA;
(v) outcomes: cognitive deficits, psychomotor deficits, language deficits, performance intelligence quotient (PIQ) and verbal intelligence quotient (VIQ) impairment of the exposed and non-exposed groups must be evaluated (regardless of the measure used);
(vi) type of journal: published in peer-reviewed journals; and
(vii) publication language: English only. When duplicate publications were identified, we used the most relevant publication. We excluded retracted studies. After assessment, we resolved disagreements between the two reviewers through discussion with a third reviewer (YH).

2.2. Search method

We developed and conducted a comprehensive search of published and unpublished studies using a wide range of scientific medical databases, including PubMed (1966- September 2018), Embase (1980-September 2018), OVID (1966-September 2018), EBSCO (1966-September 2018), ProQuest (1971-September 2018), CDSR (the Cochrane Database of Systematic Reviews, 2018) and CENTRAL (the Cochrane Central Register of Controlled Trials, 2018). The search terms consisted of medical subject headings (MeSH) terms and keywords (chorioamnionitis OR intrauterine infection OR prenatal infection OR antenatal infection) AND (neurodevelopmental disorders OR neurocognitive disorders OR neurological outcomes OR neurochemical development OR risk factors). We also searched the reference lists of original reports, case reports, guidelines, letters to the editor, reviews, and meta-analyses retrieved through electronic searches for additional articles.

2.3. Data extraction and quality assessment

The titles and/or abstracts of the studies retrieved using the abovementioned search strategy and those collected from additional sources were screened independently by two reviewers (GYW and RQC) to identify studies that potentially met the inclusion criteria outlined above. For studies that potentially fulfilled the inclusion criteria, we searched the full texts of the papers, which were assessed independently by the same 2 reviewing authors (GYW and RQC), who used a predesigned data collection form (Microsoft Office Excel 2018, Microsoft, Redmond) to extract all the data. The following information was collected: study design, participants, number of study centers, sample size, mean gestational age (GA) and birth weight (BW) of the infants, CA category, incidence of CA (%), definition of CA, negative neurodevelopmental outcomes, and Newcastle-Ottawa Quality Assessment score (NOS). The data were entered twice into Review Manager (RevMan, Version 5.3.5, The Cochrane Collaboration, London). We defined cognitive deficits as our primary outcome (for any measure used). Because they were defined areas of neurodevelopmental deficits in preterm infants, psychomotor deficits, language deficits, PIQ and VIQ impairment were secondary outcomes. After extraction, all data were checked by another author (YH), and discrepancies were resolved by discussion. We sent letters to the authors of the retrieved studies to clarify missing or unclear data.

Methodological quality was assessed independently by two authors (JHR and JHQ), and disagreements were discussed with

a third author (YH). We adopted the NOS for cohort or case-control studies,[35] which uses a star rating system (range: 0–9 stars) that scores three aspects of the study: selection (0–4 stars), comparability (0–2 stars) and exposure/outcome (0–3 stars). Studies are awarded a star for each criterion they meet, except for the comparability domain (which yields a maximum of 2 stars). The overall score is the total number of stars given. An overall score of 0–4 stars indicates low quality, 5–7 indicates moderate quality, and 8–9 stars indicate high quality.

2.4. Data synthesis and statistical analysis

The 2 reviewing authors (JHR and JHQ) entered their data separately, and we conducted the meta-analysis using RevMan.

Dichotomous data were pooled as odds ratios (ORs) adjusted for potential confounders with 95% confidence intervals (95% CIs), which were extracted from the studies that reported these data. We used forest plots and funnel plots. The funnel plots indicate possible publication bias, evidence of asymmetry, and other small study effects.[36] Because the included studies used different corrected ages of preterm infants for observing the outcomes (short-term: ≤12 months, mid-term: 12–36 months, long-term: ≥36 months), different types of CA (HCA and CCA),

and different severities of cognitive and psychomotor deficits (mild: Mental Developmental Index (MDI) or Psychomotor Developmental Index (PDI) score <85; severe: MDI or PDI score <70), subgroup analyses were conducted to determine whether CA was a risk factor for neurodevelopmental deficits in preterm infants when they were grouped according to the factors mentioned above. A probability value of less than .05 was considered statistically significant.

Statistical heterogeneity was analyzed using Cochran's Q statistic and the I^2 statistic, which is derived from Q and describes the proportion of total variation that is due to heterogeneity beyond chance.[37] The higher the percentage of I^2, the higher the level of heterogeneity.[38] If $P > .10$ and $I^2 < 50\%$, we considered the heterogeneity insufficient, and a fixed effects model was used to pool the data; if $P < .10$ and $I^2 > 50\%$, we considered the heterogeneity substantial, and we used a random effects model to summarize the results.

3. Results

3.1. Search results

We identified appropriate records and ultimately included 12 studies (Fig. 1). All 12 studies were cohort studies and case-
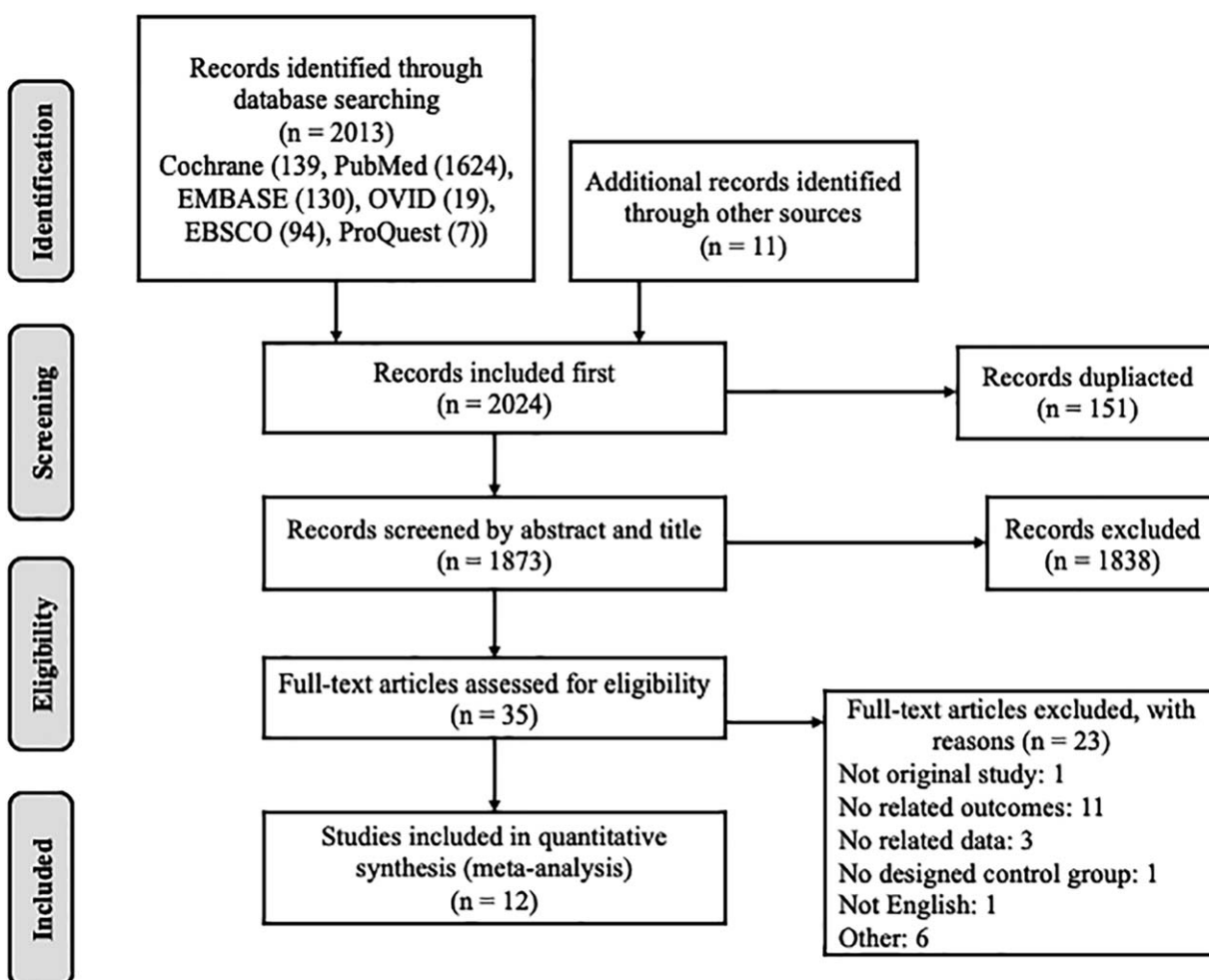

Figure 1. Study flow diagram.

Table 1

Characteristics of the included studies.

Author, published years	Study design	Prosp/ Retro	Participants	Centers	Sample size	Mean BW (g)	Mean GA (w)	CA category	Incidence of CA (%)	Definition of CA	Outcomes	NOS score
Pappas, 2014[33]	Cohort	Retro	Extremely preterm neonates	Multi-centre	1194	NoDes	24.3	HCA CCA	38.1 19.5	Ref	Cognition Language	8
Ylijoki, 2016[42]	Cohort	Retro	Very low birth weight preterm infants	Single	115	1127	NoDes	HCA CCA	38.3 25.2	Des	Cognition Language PIQ VIQ	9
Vander Haar, 2016[39]	Cohort	Retro	Preterm infants	Multi-centre	1574	NoDes	29.4	CCA	12	Des	Cognition Psychomotor	7
Polam 2005[15]	Cohort	Retro	Very low birth weight preterm infants	Single	177	947	26.1	CCA + HCA	57.6	NoDes	Cognition Psychomotor	7
Nasef, 2013[43]	Cohort	Retro	Preterm infants	Single	241	952	27.1	HCA CCA	35 12	Ref	Cognition Psychomotor Language	6
Rovira, 2011[45]	Cohort	Prosp + Retro	Preterm infants	Single	130	1167	29.2	HCA CCA	49.2 30.0	Ref	Language	6
Dexter, 1999[40]	Cohort	Prosp + Retro	Very low birth weight preterm infants	Single	186	1050	NoDes	HCA + CCA	21.5	Ref	Cognition Psychomotor	7
Hendson, 2011[30]	Cohort	Prosp + Retro	Very low birth weight infants	Single	500	899.3	26.1	HCA	48	Des	Cognition	6
Suppiej, 2009[44]	Cohort	Prosp	Premature babies	Single	69	1060	27.5	HCA	39.4	Des	Language	7
Mu, 2007[41]	Cohort	Prosp + Retro	Very low birth weight preterm infants	Single	67	10	27.9	HCA + CCA	56.8	Ref	Cognition Psychomotor	7
Dexter, 2000[21]	Cohort	Prosp + Retro	Very low birth weight 8preterm infants	Single	167	919.5	26.5	HCA	57.1	Des	Cognition Psychomotor	6
van Vliet, 2012[31]	Cohort	Prosp	Very preterm infants	NoDes	66	1111.9	27.7	HCA	27.3	Des	Cognition Psychomotor PIQ VIQ	8

BW = birth weight, CA = chorioamnionitis, CCA = clinical chorioamnionitis, Des = clinical or histological description, GA = gestational age, HCA = histological chorioamnionitis, NoDes = no description, NOS = Newcastle-Ottawa Quality Assessment Scale, PIQ = performance intelligence quotient, Prosp = prospective, Ref = literature citation, Retro = retrospective, VIQ = verbal intelligence quotient.

control studies that included a total of 4267 preterm infants in the quantitative synthesis; of these, 1420 and 2847 infants were allocated to the exposed (mother with CA) and non-exposed (mother without CA) groups, respectively. All the included studies were reviewed by an institutional ethics committee before observation began.

3.2. Study characteristics

All the participants in the included 12 studies were preterm infants with VLGA/VLBW. Of these, 9 studies[15,21,30,31,39–43] identified cognitive deficits as the main outcome. Four[21,30,31,44] of the 12 studies identified only HCA as the exposure factor, while one study[39] identified only CCA as the exposure factor, and the other seven studies[15,33,40–43,45] identified both HCA and CCA as exposure factors. All the included studies used preterm infants born to mothers without CA (non-exposed patients) as their control group. In terms of assessment measures, all nine of the included studies[15,21,30,31,39–43] adopted the Bayley Scales of Infant Development-II, MDI to assess cognitive deficits. For psychomotor deficits, all seven of the studies that examined this outcome[15,21,31,39–41,43] did so using the Bayley Scales of Infant Development-II, PDI. PIQ and VIQ impairment were evaluated using the same instruments; Ylijoki[42] adopted the Wechsler Preschool and Primary Scale of Intelligence-Revised (WPPSI-R) for these evaluations, while van Vliet[31] used the Wechsler Intelligence Scale for Children-III (WISC-III). The characteristics of the recruited studies are presented in Table 1.

3.3. Quality assessment and publication bias

The quality of each study according to NOS is summarized in Table 1. All the studies included in this meta-analysis earned at least 6 stars, indicating moderate to high quality. The funnel plot for the primary outcome "cognitive deficits" (Fig. 2) did not appear to be totally asymmetrical, but because the number of trials included was insufficient, the assessment of publication bias may be inaccurate.

3.4. Cognitive deficits

Nine studies[15,21,30,31,39–43] involving 3083 patients (861 in the exposed group and 2222 in the non-exposed group) reported a non-significant association between CA and cognitive deficits (adjusted OR 1.08, 95% CI 0.88 to 1.31, $P = .47$; heterogeneity: $I^2 = 48\%$, $P = .05$) (Fig. 3).

3.5. Subgroup analyses of cognitive deficits

We defined the cognitive outcome observed in preterm infants at corrected ages of under 12 months as the short-term outcome, and those observed at 12 to 36 months as the mid-term outcome. None of the pooled results showed statistically significant differences in the short-term outcome[40,41] (adjusted OR 1.00, 95% CI 0.53 to 1.90, $P = .99$; heterogeneity: $I^2 = 0\%$, $P = .94$) or the mid-term outcome[15,21,30,31,39,41–43] (adjusted OR 1.07, 95% CI 0.88 to 1.30, $P = .52$; heterogeneity: $I^2 = 55\%$, $P = .03$) between the CA and no CA groups (Fig. 4).
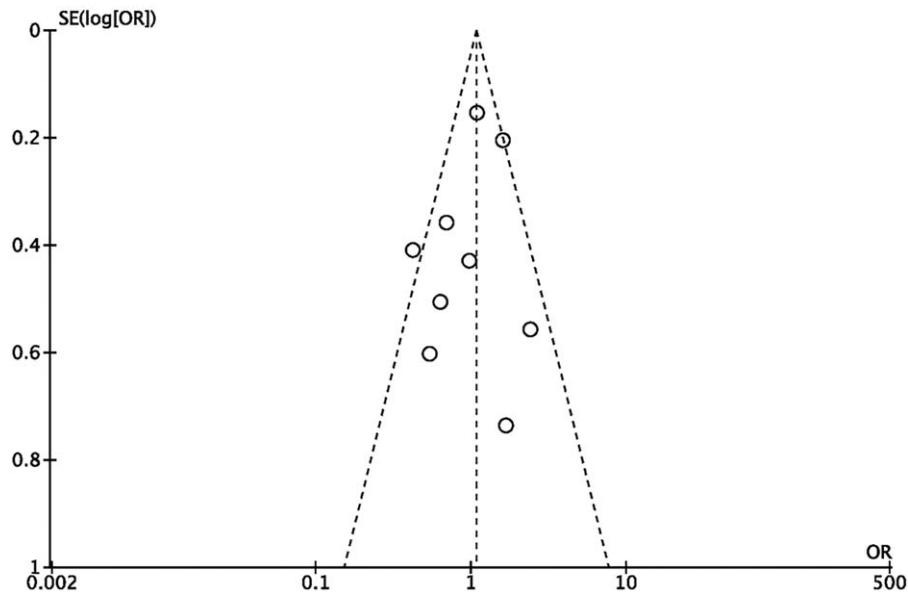
Figure 2. Funnel plot of comparison: chorioamnionitis vs no chorioamnionitis, outcome: cognitive defects. SE = standard error, OR = odds ratio.

Similarly, regardless of whether the CA was histological (adjusted OR 1.16, 95% CI 0.85 to 1.57, $P=.35$; heterogeneity: $I^2=49\%$, $P=.10$) or clinical (adjusted OR 1.20, 95% CI 0.90 to 1.59, $P=.21$; heterogeneity: $I^2=63\%$, $P=.07$), the combined results showed no statistically significant differences between the exposed and non-exposed groups (Fig. 5).

However, as Figure 6 shows, when the patients were divided into subgroups based on the severity of cognitive deficits, there was a significant association between CA and severe cognitive deficits (MDI score < 70; adjusted OR 1.38, 95% CI 1.08 to 1.78, $P=.01$; heterogeneity: $I^2=0\%$, $P=.41$), whereas no such significant relationship could be found between CA and mild cognitive deficits (MDI score < 85, adjusted OR 0.90, 95% CI 0.72 to 1.14, $P=.40$; heterogeneity: $I^2=19\%$, $P=.28$).

3.6. Psychomotor deficits

Seven studies[15,21,31,39–41,43] involving 2467 patients (586 in the CA group and 1881 in the no CA group) reported no significant

association between CA and psychomotor deficits (adjusted OR 1.14, 95% CI 0.91 to 1.43, $P=.26$; heterogeneity: $I^2=0\%$, $P=.59$) (Fig. 7).

3.7. Subgroup analyses of psychomotor deficits

As we did for the examination of cognitive deficits, we divided the preterm infants by their corrected age at observation into short-term, mid-term and long-term groups (observed at 36 months or later). As Figure 8 shows, none of the differences between the exposed and non-exposed groups were statistically significant for any of the subgroups (short-term[40,41]: adjusted OR 1.05, 95% CI 0.56 to 1.96, $P=.89$, heterogeneity: $I^2=40\%$, $P=.20$; mid-term[15,21,31,39,41,43]: adjusted OR 1.19, 95% CI 0.93 to 1.50, $P=.16$, heterogeneity: $I^2=0\%$, $P=.62$; long-term[31]: adjusted OR 1.44, 95% CI 0.33 to 6.31, $P=.63$, heterogeneity: not applicable).

The subgroup analysis revealed a statistically significant difference between the exposed and non-exposed groups when

Figure 3. Forest plot of comparison: chorioamnionitis vs no chorioamnionitis, outcome: odds ratio for cognitive defects. CI = confidence interval.
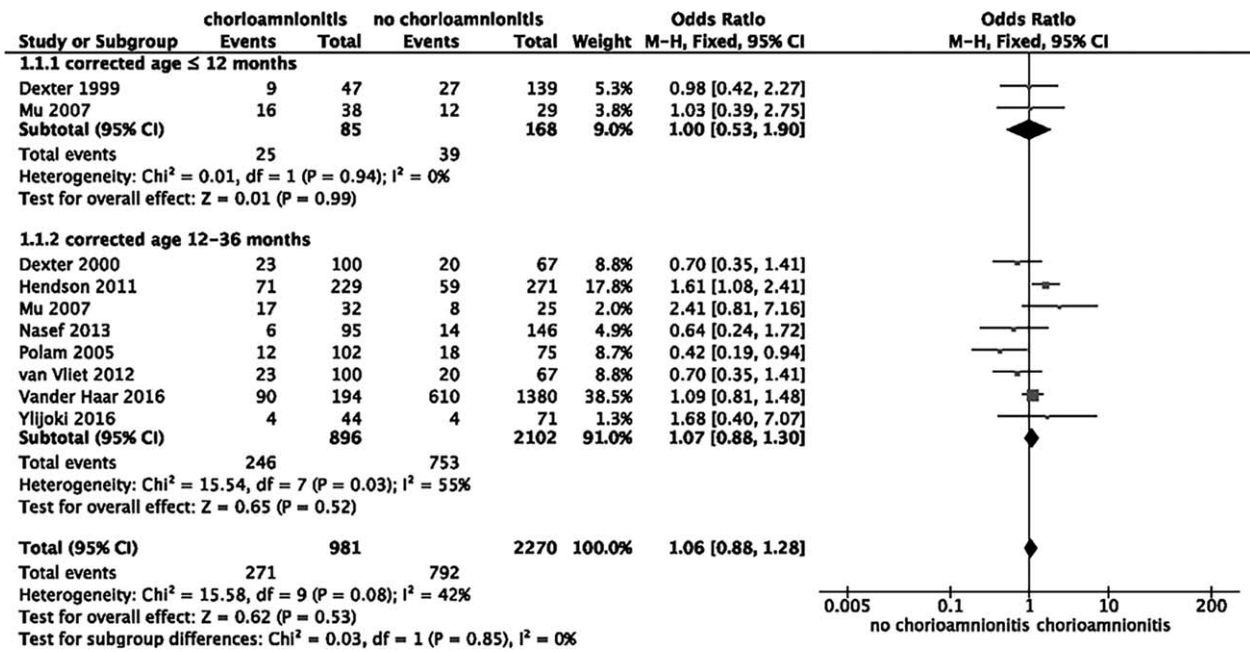
Figure 4. Forest plot of comparison: chorioamnionitis vs no chorioamnionitis, outcome: odds ratio for cognitive defects by subgroup analysis (term). CI = confidence interval.

the mothers of the included infants were exposed to CCA[39,43] (adjusted OR 1.47, 95% CI 1.09 to 1.98, $P = .01$; heterogeneity: $I^2 = 25\%$, $P = .25$), but not when they were exposed to HCA[21,31,43] (adjusted OR 0.97, 95% CI 0.60 to 1.59, $P = .92$; heterogeneity: $I^2 = 0\%$, $P = .94$) (Fig. 9).

In the subgroup analysis based on the severity of psychomotor deficits, the pooled results reported no significant associations between CA and severe[21,39–41] (PDI score <70, adjusted OR 1.01, 95% CI 0.72 to 1.42, $P = .96$; heterogeneity: $I^2 = 0\%$,

$P = .88$) or mild[15,21,31,39,40,43] (PDI score <85, adjusted OR 1.14, 95% CI 0.90 to 1.44, $P = .28$; heterogeneity: $I^2 = 0\%$, $P = .46$) psychomotor deficits (Fig. 10).

3.8. Language deficits

Five studies[33,42–45] involving 1540 patients (700 in the exposed group and 840 in the non-exposed group) evaluated the association between CA and language deficits in preterm infants, and the pooled
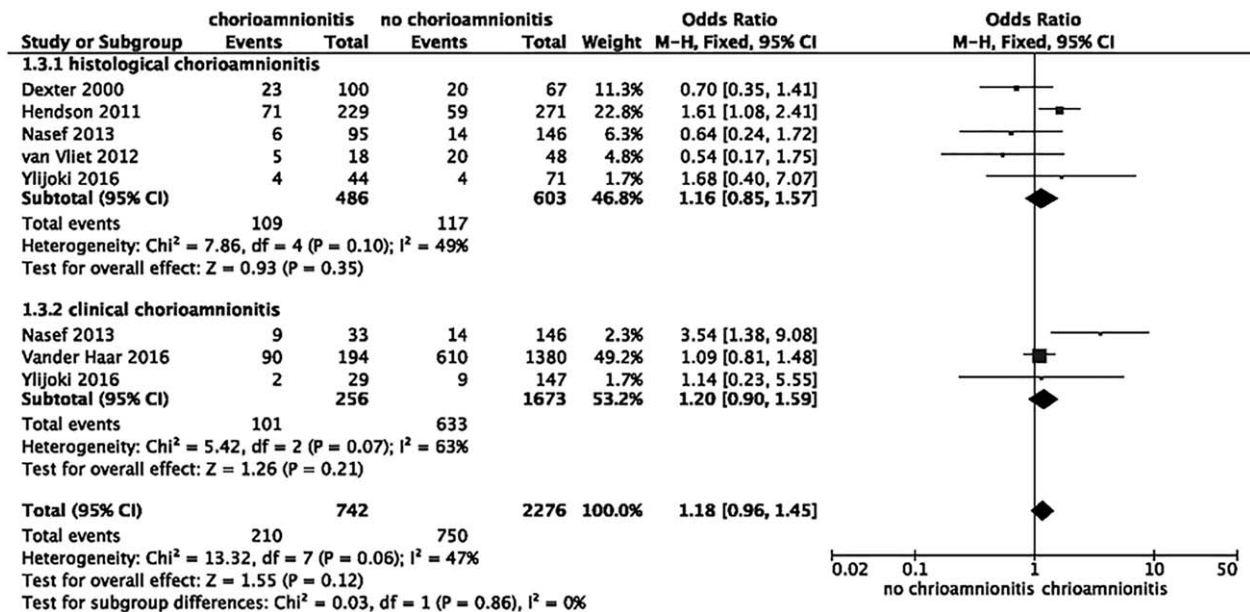
Figure 5. Forest plot of comparison: chorioamnionitis vs no chorioamnionitis, outcome: odds ratio for cognitive defects by subgroup analysis (type). CI = confidence interval.
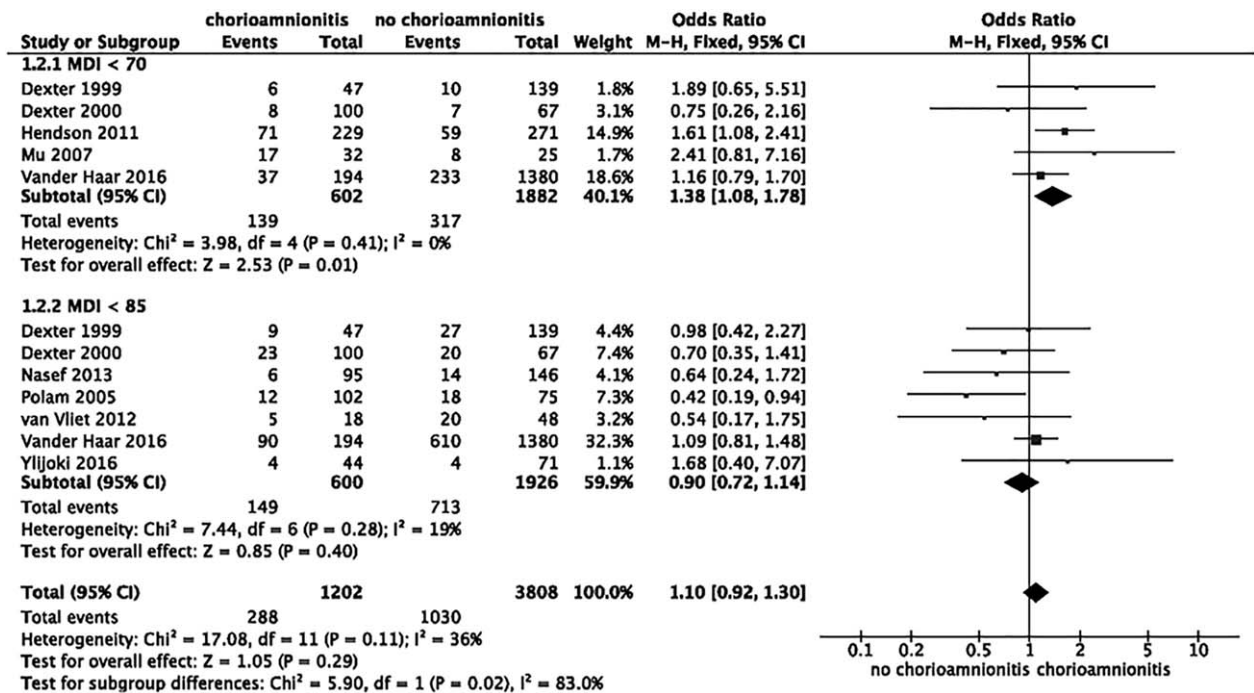
Figure 6. Forest plot of comparison: chorioamnionitis vs no chorioamnionitis, outcome: odds ratio for cognitive defects by subgroup analysis (severity). CI= confidence interval.

results indicated no statistically significant difference between CA and no CA groups (adjusted OR 1.21, 95% CI 0.98 to 1.50, $P = .08$; heterogeneity: $I^2 = 25\%$, $P = .25$) (Fig. 11).

3.9. Subgroup analyses of language deficits

As shown in Figure 12, there was no significant association between HCA[33,42–45] and language deficits (adjusted OR 1.32, 95% CI 0.95 to 1.85, $P = .10$; heterogeneity: $I^2 = 25\%$, $P = .25$). However, among preterm infants born to mothers who were exposed to CCA, there was a significant association between CCA[42,43,45] and language deficits (adjusted OR 4.29, 95% CI 2.30 to 7.99, $P < .00001$; heterogeneity: $I^2 = 23\%$, $P = .27$).

3.10. Intelligence quotient impairment

In this meta-analysis, the IQ includes PIQ and VIQ in this meta-analysis. Two studies[31,42] involving 160 patients (57 in the

exposed group and 103 in the non-exposed group) reported the association between CA and IQ impairment and showed a significant positive association between CA and PIQ impairment[31,42] (adjusted OR 2.34, 95% CI 1.12 to 4.86, $P = .02$; heterogeneity: $I^2 = 0\%$, $P = .33$) (Fig. 13A) and VIQ impairment[31,42] (adjusted OR 2.81, 95% CI 1.13 to 7.00, $P = .03$; heterogeneity: $I^2 = 0\%$, $P = .69$) (Fig. 13B).

4. Discussion

4.1. Summary of results

To our knowledge, this meta-analysis is the first evidence-based study to examine the associations between CA and some areas of neurodevelopmental deficits in preterm infants, including cognitive deficits, psychomotor deficits, language deficits, PIQ and VIQ impairment, although there are some systematic reviews and meta-analyses exploring the effects of CA on certain types of
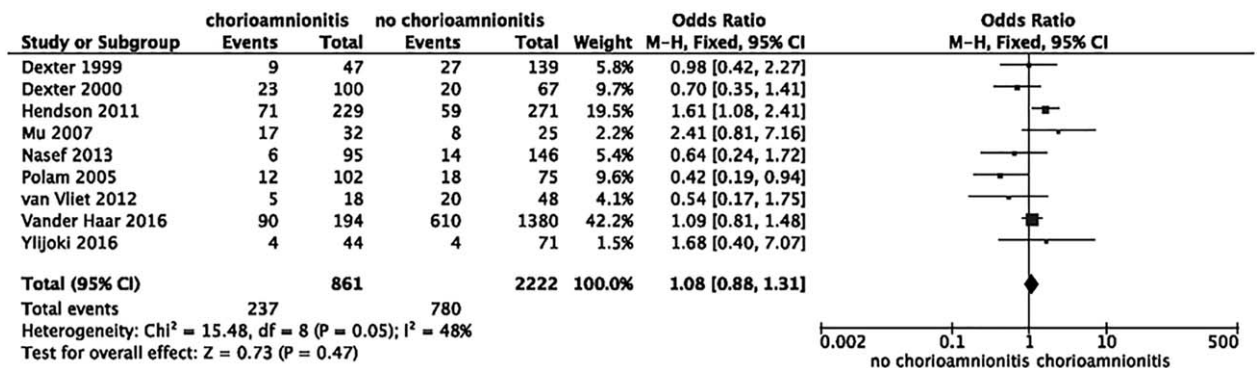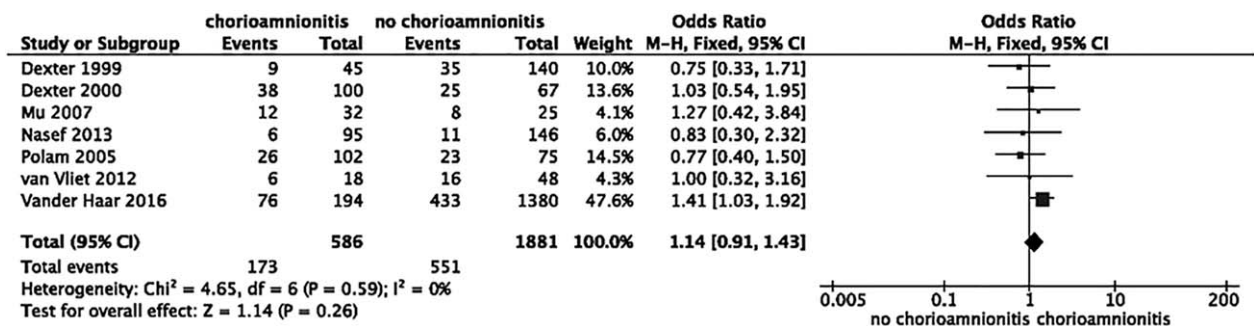

Figure 7. Forest plot of comparison: chorioamnionitis vs no chorioamnionitis, outcome: odds ratio for psychomotor defects. CI=confidence interval.

| Study or Subgroup	chorioamnionitis Events	Total	no chorioamnionitis Events	Total	Weight	Odds Ratio M–H, Fixed, 95% CI	Odds Ratio M–H, Fixed, 95% CI
2.2.1 corrected age ≤ 12 months							
Dexter 1999	9	45	35	140	9.4%	0.75 [0.33, 1.71]	
Mu 2007	15	38	8	30	3.7%	1.79 [0.64, 5.07]	
Subtotal (95% CI)		83		170	13.1%	1.05 [0.56, 1.96]	
Total events	24		43				
Heterogeneity: Chi² = 1.66, df = 1 (P = 0.20); I² = 40%							
Test for overall effect: Z = 0.14 (P = 0.89)							
2.2.2 corrected age 12–36 months							
Dexter 2000	38	100	25	67	12.8%	1.03 [0.54, 1.95]	
Mu 2007	12	32	8	25	3.9%	1.27 [0.42, 3.84]	
Nasef 2013	6	95	11	146	5.6%	0.83 [0.30, 2.32]	
Polam 2005	26	102	23	75	13.6%	0.77 [0.40, 1.50]	
van Vliet 2012	6	18	16	48	4.0%	1.00 [0.32, 3.16]	
Vander Haar 2016	76	194	433	1380	44.8%	1.41 [1.03, 1.92]	
Subtotal (95% CI)		541		1741	84.8%	1.19 [0.93, 1.50]	
Total events	164		516				
Heterogeneity: Chi² = 3.54, df = 5 (P = 0.62); I² = 0%							
Test for overall effect: Z = 1.40 (P = 0.16)							
2.2.3 corrected age ≥ 36 months							
van Vliet 2012	9	12	25	37	2.1%	1.44 [0.33, 6.31]	
Subtotal (95% CI)		12		37	2.1%	1.44 [0.33, 6.31]	
Total events	9		25				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.48 (P = 0.63)							
Total (95% CI)		636		1948	100.0%	1.17 [0.94, 1.46]	
Total events	197		584				
Heterogeneity: Chi² = 5.40, df = 8 (P = 0.71); I² = 0%							
Test for overall effect: Z = 1.42 (P = 0.16)							
Test for subgroup differences: Chi² = 0.21, df = 2 (P = 0.90), I² = 0%							

Figure 8. Forest plot of comparison: chorioamnionitis vs no chorioamnionitis, outcome: odds ratio for psychomotor defects by subgroup analysis (term). CI = confidence interval.

neurologic damage or brain injury, such as CP and PVL. The results of our study show that there were no consistent associations between CA and neurodevelopmental deficits in preterm infants; that is, CA might be a risk factor for PIQ and VIQ impairment and severe cognitive deficits, but not for overall cognitive deficits or its milder subtype, overall psychomotor deficits or overall language deficits, and CCA might be a risk factor for overall psychomotor and overall language deficits. These findings might provide evidence to help doctors and nurses to potentially prevent some types of neurodevelopmental deficits early in preterm infants. In addition to using cognitive deficits as the primary outcome, we defined other types of neurodevelopmental deficits that preterm infants often develop as secondary outcomes, including psychomotor deficits, language deficits, and

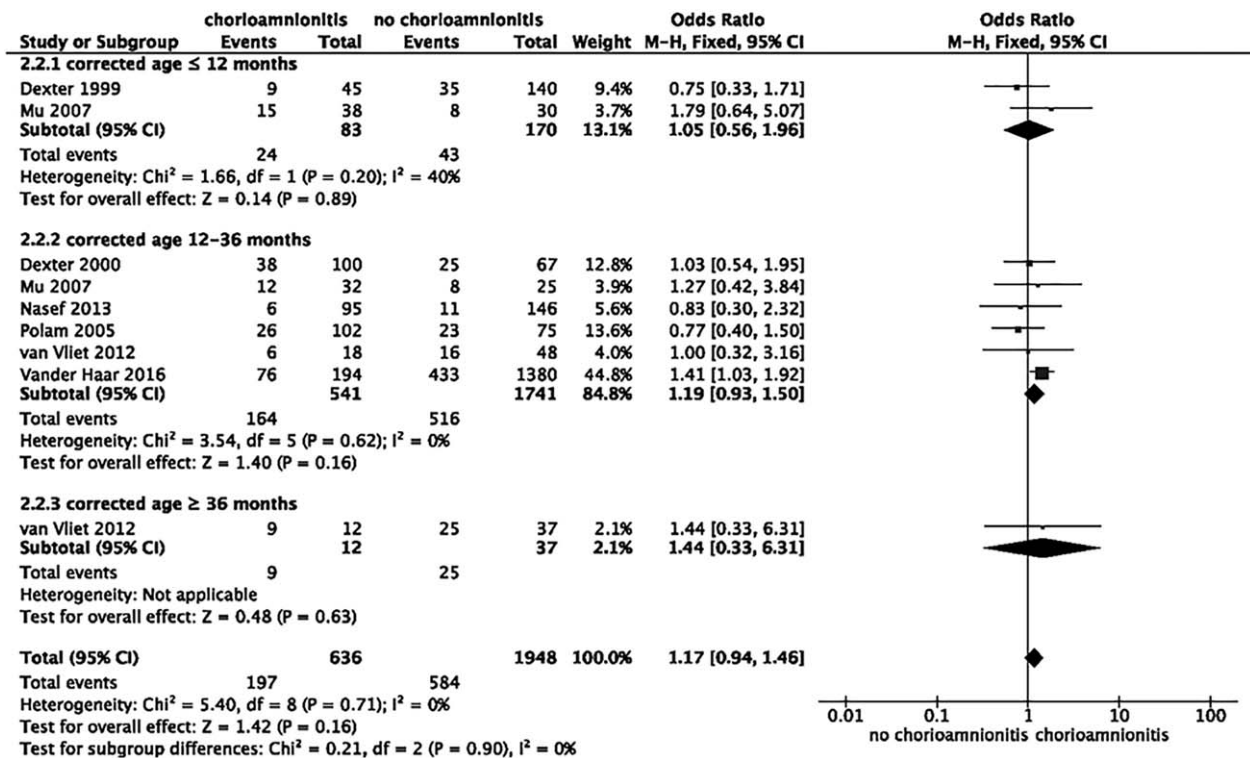| Study or Subgroup	chorioamnionitis Events	Total	no chorioamnionitis Events	Total	Weight	Odds Ratio M–H, Fixed, 95% CI	Odds Ratio M–H, Fixed, 95% CI
2.4.1 histological chorioamnionitis							
Dexter 2000	38	100	25	67	18.4%	1.03 [0.54, 1.95]	
Nasef 2013	6	95	11	146	8.1%	0.83 [0.30, 2.32]	
van Vliet 2012	6	18	16	48	5.8%	1.00 [0.32, 3.16]	
Subtotal (95% CI)		213		261	32.3%	0.97 [0.60, 1.59]	
Total events	50		52				
Heterogeneity: Chi² = 0.13, df = 2 (P = 0.94); I² = 0%							
Test for overall effect: Z = 0.11 (P = 0.92)							
2.4.2 clinical chorioamnionitis							
Nasef 2013	6	33	11	146	3.3%	2.73 [0.93, 8.01]	
Vander Haar 2016	76	194	433	1380	64.4%	1.41 [1.03, 1.92]	
Subtotal (95% CI)		227		1526	67.7%	1.47 [1.09, 1.98]	
Total events	82		444				
Heterogeneity: Chi² = 1.34, df = 1 (P = 0.25); I² = 25%							
Test for overall effect: Z = 2.55 (P = 0.01)							
Total (95% CI)		440		1787	100.0%	1.31 [1.02, 1.69]	
Total events	132		496				
Heterogeneity: Chi² = 3.51, df = 4 (P = 0.48); I² = 0%							
Test for overall effect: Z = 2.09 (P = 0.04)							
Test for subgroup differences: Chi² = 2.00, df = 1 (P = 0.16), I² = 50.0%							

Figure 9. Forest plot of comparison: chorioamnionitis vs no chorioamnionitis, outcome: odds ratio for psychomotor defects by subgroup analysis (type). CI = confidence interval.

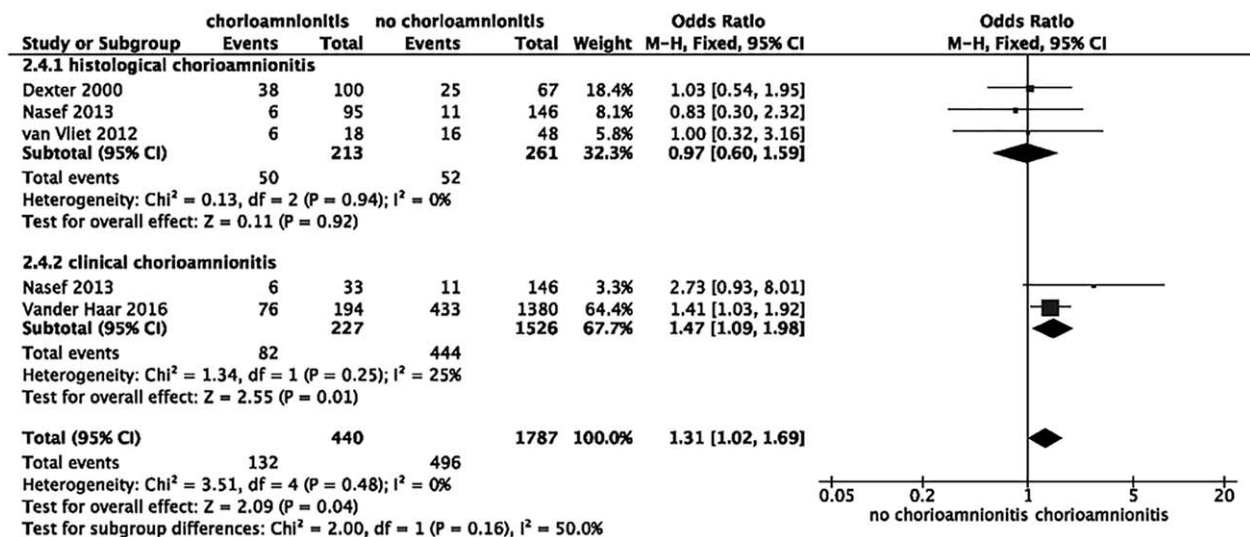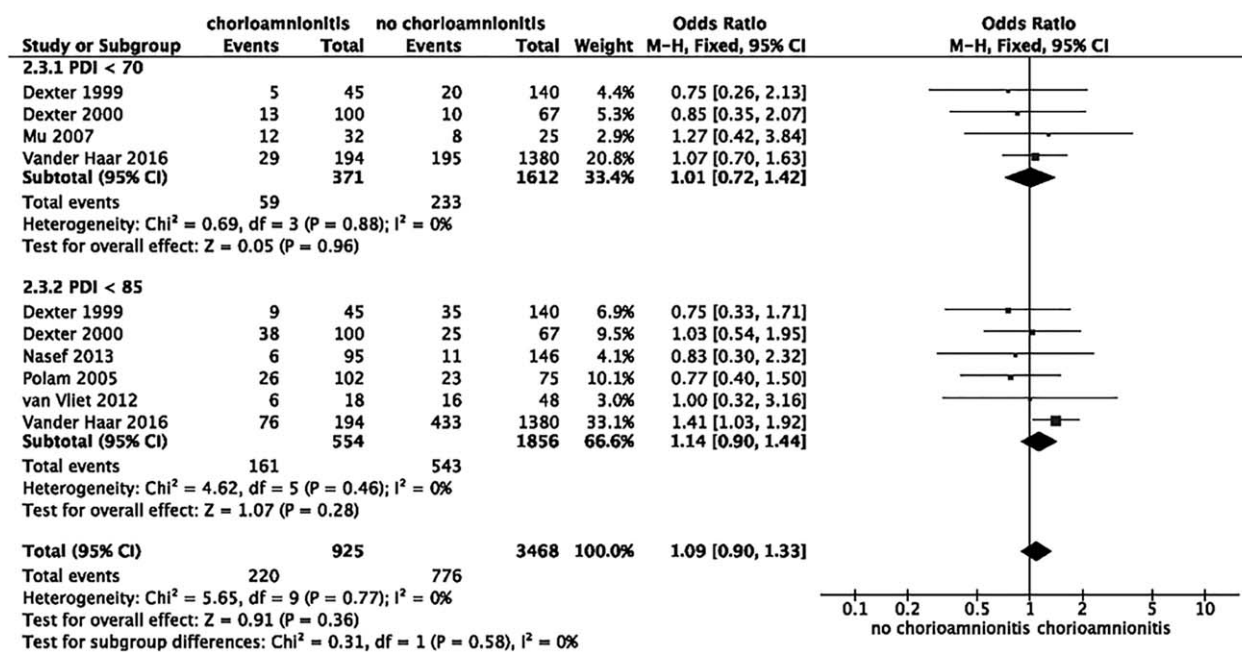| Study or Subgroup	chorioamnionitis Events	Total	no chorioamnionitis Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
2.3.1 PDI < 70							
Dexter 1999	5	45	20	140	4.4%	0.75 [0.26, 2.13]	
Dexter 2000	13	100	10	67	5.3%	0.85 [0.35, 2.07]	
Mu 2007	12	32	8	25	2.9%	1.27 [0.42, 3.84]	
Vander Haar 2016	29	194	195	1380	20.8%	1.07 [0.70, 1.63]	
Subtotal (95% CI)		371		1612	33.4%	1.01 [0.72, 1.42]	
Total events	59		233				
Heterogeneity: Chi² = 0.69, df = 3 (P = 0.88); I² = 0%							
Test for overall effect: Z = 0.05 (P = 0.96)							
2.3.2 PDI < 85							
Dexter 1999	9	45	35	140	6.9%	0.75 [0.33, 1.71]	
Dexter 2000	38	100	25	67	9.5%	1.03 [0.54, 1.95]	
Nasef 2013	6	95	11	146	4.1%	0.83 [0.30, 2.32]	
Polam 2005	26	102	23	75	10.1%	0.77 [0.40, 1.50]	
van Vliet 2012	6	18	16	48	3.0%	1.00 [0.32, 3.16]	
Vander Haar 2016	76	194	433	1380	33.1%	1.41 [1.03, 1.92]	
Subtotal (95% CI)		554		1856	66.6%	1.14 [0.90, 1.44]	
Total events	161		543				
Heterogeneity: Chi² = 4.62, df = 5 (P = 0.46); I² = 0%							
Test for overall effect: Z = 1.07 (P = 0.28)							
Total (95% CI)		925		3468	100.0%	1.09 [0.90, 1.33]	
Total events	220		776				
Heterogeneity: Chi² = 5.65, df = 9 (P = 0.77); I² = 0%							
Test for overall effect: Z = 0.91 (P = 0.36)							
Test for subgroup differences: Chi² = 0.31, df = 1 (P = 0.58), I² = 0%							

no chorioamnionitis chorioamnionitis

Figure 10. Forest plot of comparison: chorioamnionitis vs no chorioamnionitis, outcome: odds ratio for psychomotor defects by subgroup analysis (severity). CI = confidence interval.

PIQ and VIQ impairment, which made our meta-analysis more comprehensive.

4.2. Overall neurodevelopmental deficits

In this meta-analysis, instead of analyzing CP or other brain injuries, we focused on other aspects of neurodevelopmental deficits, including cognitive deficits, psychomotor deficits, language deficits, PIQ and VIQ impairment. In previous studies,[15,20,22–27,29,32,33] the associations between CA and these neurodevelopmental outcomes were controversial. Our meta-analysis confirmed the effects of CA on PIQ and VIQ impairment in preterm infants but simultaneously verified that CA might not be a risk factor for overall cognitive deficits, psychomotor deficits or language deficits. The results indicated that for preterm infants born to mothers exposed to CA, doctors and nurses should be alert to PIQ and VIQ impairment.

The results indicated that the ORs of PIQ and VIQ impairment were 2.34 and 2.81, respectively, which indicated relatively high probabilities of developing PIQ and VIQ impairment in preterm infants born to mothers exposed to CA. This finding shows that we must pay more attention to PIQ and VIQ impairment and adopt more effective interventions for preterm infants born to mothers with CA to prevent intellectual problems in the future. Of course, although CA did not seem to be a direct risk factor for cognitive, psychomotor and language deficits in preterm infants in this meta-analysis, the immature fetal brain and the particular vulnerability of its white matter as a result of prematurity and CA[46] could easily lead to these neurodevelopmental problems, so we should pay close attention to the cognitive, psychomotor and language development of preterm infants, too.

4.3. Subgroup analyses of neurodevelopmental deficits

According to the content of the included studies, we further performed subgroup analyses based on the terms of neurodevelopmental outcomes (short-term: ≤ 12 months of corrected age; mid-term: 12–36 months of corrected age; long-term: ≥ 36 months of corrected age), types of CA (HCA and CCA), severity of neurodevelopmental deficits (mild: MDI or PDI score < 70; severe: MDI or PDI score < 85).

Study or Subgroup	chorioamnionitis Events	Total	no chorioamnionitis Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Nasef 2013	18	95	21	146	9.0%	1.39 [0.70, 2.78]	
Pappas 2014	249	473	257	512	78.0%	1.10 [0.86, 1.42]	
Rovira 2011	15	62	13	68	6.3%	1.35 [0.58, 3.12]	
Suppiej 2009	8	24	4	45	1.2%	5.13 [1.35, 19.42]	
Ylijoki 2016	12	46	14	69	5.5%	1.39 [0.57, 3.35]	
Total (95% CI)		700		840	100.0%	1.21 [0.98, 1.50]	
Total events	302		309				
Heterogeneity: Chi² = 5.35, df = 4 (P = 0.25); I² = 25%							
Test for overall effect: Z = 1.73 (P = 0.08)							

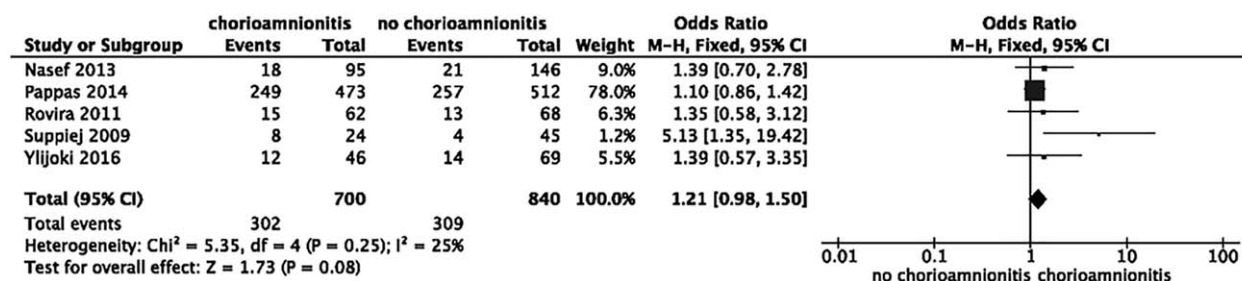no chorioamnionitis chorioamnionitis

Figure 11. Forest plot of comparison: chorioamnionitis vs no chorioamnionitis, outcome: odds ratio for language defects. CI = confidence interval.

Study or Subgroup	chorioamnionitis Events	Total	no chorioamnionitis Events	Total	Weight	Odds Ratio M–H, Random, 95% CI	Odds Ratio M–H, Random, 95% CI
3.2.1 histological chorioamnionitis							
Nasef 2013	18	95	21	146	14.2%	1.39 [0.70, 2.78]	
Pappas 2014	249	473	257	512	18.4%	1.10 [0.86, 1.42]	
Rovira 2011	15	62	13	68	12.6%	1.35 [0.58, 3.12]	
Supplej 2009	8	24	4	45	8.3%	5.13 [1.35, 19.42]	
Ylijoki 2016	12	46	14	69	12.2%	1.39 [0.57, 3.35]	
Subtotal (95% CI)		700		840	65.8%	1.32 [0.95, 1.85]	
Total events	302		309				

Heterogeneity: Tau² = 0.04; Chi² = 5.35, df = 4 (P = 0.25); I² = 25%
Test for overall effect: Z = 1.65 (P = 0.10)

Study or Subgroup							
3.2.2 clinical chorioamnionitis							
Nasef 2013	15	33	21	146	12.8%	4.96 [2.17, 11.34]	
Rovira 2011	13	39	15	91	12.4%	2.53 [1.07, 6.02]	
Ylijoki 2016	7	31	5	145	9.1%	8.17 [2.40, 27.85]	
Subtotal (95% CI)		103		382	34.2%	4.29 [2.30, 7.99]	
Total events	35		41				

Heterogeneity: Tau² = 0.07; Chi² = 2.61, df = 2 (P = 0.27); I² = 23%
Test for overall effect: Z = 4.58 (P < 0.00001)

Total (95% CI)		803		1222	100.0%	2.20 [1.32, 3.66]	
Total events	337		350				

Heterogeneity: Tau² = 0.35; Chi² = 25.84, df = 7 (P = 0.0005); I² = 73%
Test for overall effect: Z = 3.04 (P = 0.002)
Test for subgroup differences: Chi² = 10.66, df = 1 (P = 0.001), I² = 90.6%

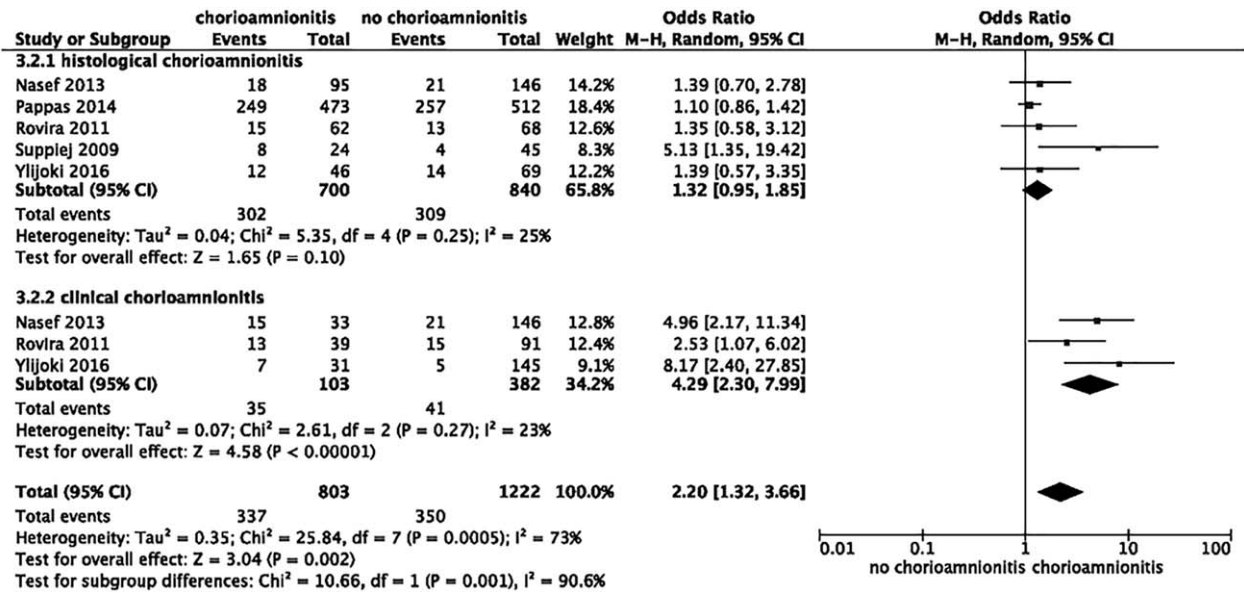Axis: 0.01 0.1 1 10 100
no chorioamnionitis chorioamnionitis

Figure 12. Forest plot of comparison: chorioamnionitis vs no chorioamnionitis, outcome: odds ratio for language defects by subgroup analysis (type). CI= confidence interval.

Most of the subgroup findings were not statistically significant, indicating that these grouping factors did not affect the relationships between CA and neurodevelopmental deficits. Specifically, the effects of CA on short-term, mid-term or long-term cognitive deficits or psychomotor deficits in preterm infants were not significantly different. Thus, the effects of CA on cognitive and psychomotor deficits do not diminish over time, even years after birth. Therefore, continuous screening for cognitive and psychomotor deficits in preterm infants born to mothers exposed to CA should be continued. Meanwhile, the effects of HCA and CCA on cognitive deficits presented no significant difference, indicating that doctors and nurses should be aware that HCA has as important an influence on cognitive development as CCA, despite the absence of clinical symptoms. Moreover, the effects of CA on severe and mild psychomotor deficits were not significantly different. This finding suggests that CA is as likely to cause both mild and severe psychomotor

deficits, and therefore, more attention should be paid to screening for severe deficits.

Some statistically significant and interesting findings should be noted. First, when evaluating the effect of CA on cognitive deficits based on their severity, we found that CA was a potential risk factor for severe cognitive deficits (MDI score < 70) but not for mild cognitive deficits (MDI score < 85). This result indicates that preterm infants born to mothers with CA are more likely to develop severe cognitive deficits than mild ones. Therefore, a high degree of vigilance is highly needed, and more attention should be paid to evaluating the cognitive development of these preterm infants during follow-up. It has been suggested that once a child presents with a mild abnormality of cognitive development, timely measures need to be taken to prevent its progression.

Second, in terms of the association between the type of CA and psychomotor and language deficits in preterm infants, the combined results showed that CCA was positively correlated
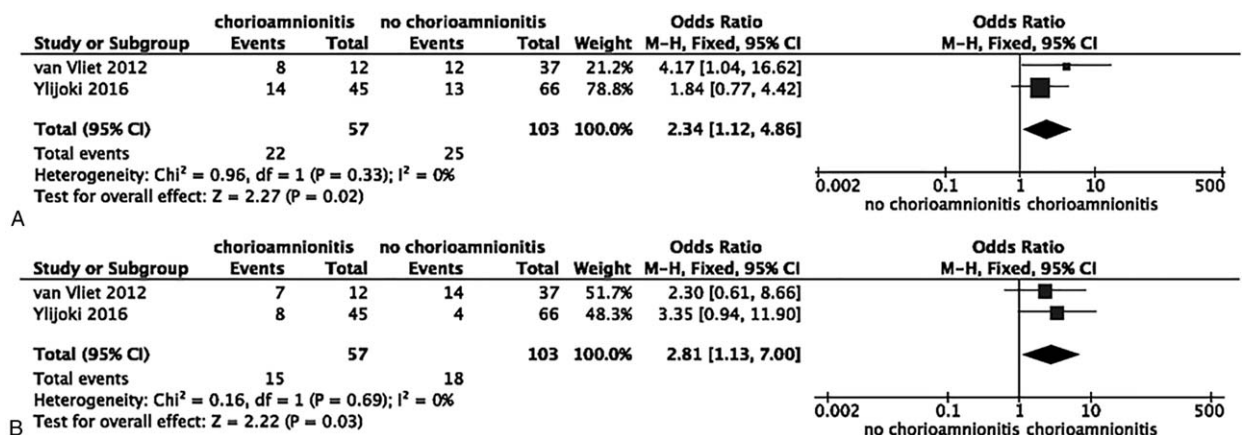
Study or Subgroup	chorioamnionitis Events	Total	no chorioamnionitis Events	Total	Weight	Odds Ratio M–H, Fixed, 95% CI	Odds Ratio M–H, Fixed, 95% CI
van Vliet 2012	8	12	12	37	21.2%	4.17 [1.04, 16.62]	
Ylijoki 2016	14	45	13	66	78.8%	1.84 [0.77, 4.42]	
Total (95% CI)		57		103	100.0%	2.34 [1.12, 4.86]	
Total events	22		25				

Heterogeneity: Chi² = 0.96, df = 1 (P = 0.33); I² = 0%
Test for overall effect: Z = 2.27 (P = 0.02)

Axis: 0.002 0.1 1 10 500
no chorioamnionitis chorioamnionitis

A

Study or Subgroup	chorioamnionitis Events	Total	no chorioamnionitis Events	Total	Weight	Odds Ratio M–H, Fixed, 95% CI	Odds Ratio M–H, Fixed, 95% CI
van Vliet 2012	7	12	14	37	51.7%	2.30 [0.61, 8.66]	
Ylijoki 2016	8	45	4	66	48.3%	3.35 [0.94, 11.90]	
Total (95% CI)		57		103	100.0%	2.81 [1.13, 7.00]	
Total events	15		18				

Heterogeneity: Chi² = 0.16, df = 1 (P = 0.69); I² = 0%
Test for overall effect: Z = 2.22 (P = 0.03)

Axis: 0.002 0.1 1 10 500
no chorioamnionitis chorioamnionitis

B

Figure 13. Forest plot of comparison: chorioamnionitis vs no chorioamnionitis, outcome: odds ratio for intelligence quotient impairment. A: performance intelligence quotient impairment, B: verbal intelligence quotient impairment. CI=confidence interval.

with both psychomotor and language deficits, but HCA was not correlated with these neurodevelopmental deficits, indicating that only CCA was a risk factor for psychomotor and language deficits. The diagnosis of HCA is based on the accumulation of neutrophils in the placenta and membranes and is unobtainable before delivery. CCA arises from HCA when maternal fever, uterine tenderness, malodourous amniotic fluid, maternal or fetal tachycardia, maternal leucocytosis and/or elevated C-reactive protein occur occasionally. Therefore, as HCA progresses, CCA becomes more serious and might have worse outcomes. In addition, we found that the pooled adjusted ORs of the effects of CCA on psychomotor and language deficits were 1.47 and 4.29, respectively, which were relatively high. Therefore, we must be more vigilant about CCA. For preterm infants born to mothers with CCA, we should strengthen monitoring and screening to achieve early detection and effectively prevent the occurrence of psychomotor deficits and especially language deficits.

4.4. Comparison with other published reviews

We retrieved previously published meta-analyses[47,48] that studied the associations between CA and some brain injuries, such as CP and PVL. These studies reported that CA was positively correlated with brain injuries. However, no systematic review or meta-analysis was found that examined the relationships between CA and some areas of neurodevelopmental deficits, including cognitive deficits, psychomotor deficits, language deficits, PIQ and VIQ impairment. In comparison, we included all studies that met the inclusion criteria, and we explored the relationships between CA and these neurodevelopmental outcomes in our analysis. We included not only cognitive deficits but also psychomotor deficits, language deficits, PIQ and VIQ impairment as outcomes to examine the associations between CA and neurodevelopmental deficits more comprehensively.

4.5. Implications for nursing practice

In preterm infants born to mothers with CA, CA might be a risk factor for PIQ and VIQ impairment and severe cognitive deficits, but not for overall cognitive deficits or its mild subtype, overall psychomotor deficits or overall language deficits. CCA might be a risk factor for overall psychomotor and overall language deficits. Therefore, the present meta-analysis provides some initial support for the positive relationships between CA and some neurodevelopmental deficits, and it emphasizes the different roles of HCA and CCA, different risk factors for severe and mild cognitive deficits.

Moreover, given the conclusions of our meta-analysis, doctors and nurses should continuously screen for psychomotor deficits and language deficits because the effects of CA on psychomotor and language deficits do not diminish over time, even years after the birth of preterm infants. Medical staff should be alert to the possibility of cognitive deficits in preterm infants born to mothers with HCA as the effects of HCA and CCA on cognitive deficits were not different. In addition, it is suggested that medical studies should place special emphasis on screening for severe psychomotor deficits given that CA has the same association with severe and mild psychomotor deficits.

4.6. Strengths and limitations

To the best of our knowledge, this meta-analysis is the first evidence-based study that recruited all cohort and case-control studies to evaluate the relationships between CA and some neurodevelopmental deficits (cognitive deficits, psychomotor deficits, language deficits, PIQ and VIQ impairment) in preterm infants through a comprehensive search. In addition, we not only examined cognitive deficits, which is a relatively common neurodevelopmental outcome, but also other areas of neurodevelopmental deficits, including psychomotor deficits, language deficits, PIQ and VIQ impairment. The results are highly relevant to the daily work of doctors and nurses to prevent neurodevelopmental deficits in preterm infants, and they have substantial clinical and social significance. Moreover, we studied the mid-term and long-term effects of CA on some neurodevelopmental deficits in this meta-analysis; this information could tell us more about the long-term relationships between CA and neurodevelopmental outcomes so that doctors and nurses can provide better long-term prevention. It is also worth mentioning that we included studies with negative results, which may help prevent some publication bias.

Nevertheless, several potential limitations should be discussed. First, most of the recruited studies were retrospective studies or retrospective studies with prospective follow-up, the study quality is not as good as prospective research. Therefore, the associations between CA and neurodevelopmental deficits in preterm infants remain to be further examined by more rigorously designed prospective studies. Second, because few of the included studies had a follow-up period longer than 2 years, the longer-term effect of CA on neurodevelopmental deficits in preterm infants still needs to be further evaluated.

5. Conclusions

This meta-analysis is the first evidence-based study that includes all cohort and case-control studies to evaluate the relationships between CA and certain neurodevelopmental deficits in preterm infants. CA might be a risk factor for PIQ, VIQ impairment and severe cognitive deficits to those preterm infants that born to mothers exposed to CA, but not for overall cognitive deficits or its mild subtype, overall psychomotor deficits or overall language deficits, and that CCA might be a risk factor for overall psychomotor and overall language deficits. The results have substantial clinical and social significance because they are highly relevant to the daily work of medical staff and to family and societal interests. However, studies based on more comprehensive and rigorously design are in the process and will be reported in the future papers.

Author contributions

Conceptualization: Yan Huang.
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Formal analysis: Jianhua Ren, Jiahui Qian.
Funding acquisition: Lu Xing.
Investigation: Guoyu Wang, Ruiqi Chen, Jianhua Ren.
Methodology: Guoyu Wang, Ruiqi Chen, Jianhua Ren, Jiahui Qian, Yan Huang.
Resources: Lu Xing, Yan Huang.
Software: Jianhua Ren, Jiahui Qian.
Supervision: Jianhua Ren, Yan Huang.
Visualization: Jiahui Qian.
Writing – original draft: Lu Xing, Guoyu Wang.
Writing – review & editing: Lu Xing, Ruiqi Chen, Yan Huang.

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