Chorioamnionitis in the Development of Cerebral Palsy: A Meta-analysis and Systematic Review

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abstract

CONTEXT: Chorioamnionitis (CA) has often been linked etiologically to cerebral palsy (CP).

OBJECTIVES: To differentiate association from risk of CA in the development of CP.

DATA SOURCES: PubMed, Cochrane Library, Embase, and bibliographies of original studies were searched by using the keywords (chorioamnionitis) AND ((cerebral palsy) OR brain).

STUDY SELECTION: Included studies had to have: (1) controls, (2) criteria for diagnoses, and (3) neurologic follow-up. Studies were categorized based on: (1) finding incidence of CP in a CA population, or risk of CP; and (2) incidence of CA in CP or association with CP.

DATA EXTRACTION: Two reviewers independently verified study inclusion and extracted data.

RESULTS: Seventeen studies (125 256 CA patients and 5 994 722 controls) reported CP in CA. There was significantly increased CP inpreterm histologic chorioamnionitis (HCA; risk ratio [RR] = 1.34, $P < .01$), but not in clinical CA (CCA). Twenty-two studies (2513 CP patients and 8135 controls) reported CA in CP. There was increased CCA (RR = 1.43, $P < .01$), but no increase in HCA in preterm CP. Increased HCA was found (RR = 4.26, $P < .05$), as well as CCA in term/near-term CP (RR = 3.06, $P < .01$).

CONCLUSIONS: The evidence for a causal or associative role of CA in CP is weak. Preterm HCA may be a risk factor for CP, whereas CCA is not. An association with term and preterm CP was found for CCA, but only with term CP for HCA.

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Cerebral palsy (CP) is the most common motor disability in childhood,[1] with a reported prevalence of 1.5 to 4 per 1000 live births.[2,3] The lifetime cost for all patients with CP is estimated to be $11.5 billion.[4] The etiology of CP is complex and multifactorial. One of the key pathogenetic mechanisms is perinatal inflammation. Chorioamnionitis (CA) is a common manifestation of perinatal inflammation and is treated aggressively in the peripartum period. For this article, we have used CA interchangeably with the new nomenclature of "intrauterine inflammation or infection or both" (triple-I).[5]

As a potentially severe condition in pregnancy, clinical CA (CCA) is a syndrome often diagnosed by the presence of maternal fever (temperature >37.8°C) accompanied by ≥2 of the following criteria: (1) uterine tenderness; (2) malodorous vaginal discharge; (3) fetal tachycardia (heart rate >160 beats per minute); (4) maternal tachycardia (heart rate >100 beats per minute); and (5) maternal leukocytosis (leukocyte count >15 000 cells/mm^3).[6,7] On the other hand, histologic CA (HCA) is a pathologic diagnosis requiring acute morphologic criteria of diffuse infiltration of neutrophils into the chorioamniotic membranes. Although HCA is generally considered to represent the presence of intraamniotic infection, acute HCA can occur with "sterile intraamniotic inflammation" in the absence of detectable microorganisms.[8]

It has long been held that CA is among the key risk factors of CP, and there have been several meta-analyses and systematic reviews showing either CCA or HCA, or both, as risk factors for CP.[9–12] Some have grouped preterm and term gestation cases together for analysis.[9,11] Part of the confusion for clinicians is that some of the included studies restricted the investigation to culture results,[13] or made no mention of CP in CA cases or controls.[14] Confusion also arises from an absence of criteria for the diagnosis of CA,[15,16] the imprecise categorization of patients into CCA and HCA, and combined analysis in different patient cohorts.[10] Previous reviews and meta-analyses have treated studies employing forward and backward approaches with the same weight, namely, determining the rate of CP in patients with CA (forward) as similar to studies describing how many CP patients had a past history of CA (backward).[9–11] Note that the terms "forward" and "backward" are not equivalent to "prospective" and "retrospective," respectively, because one could use a forward approach in a retrospective cohort study, and a prospective study of HCA would be hard to conduct because of the intrinsic delayed nature of diagnosis. In the forward approach, the rate of CP is compared in a cohort of CA with patients without a diagnosis of CA (Fig 1A). In the backward approach, the rate of CA is compared in a cohort of CP with patients without CP (Fig 1A). In addition to taking into consideration that an updated analysis is required (the previous meta-analyses were some years ago[9–11]), this review also focused on the quality of each enrolled study and whether the studies had ruled out defined postnatal etiologic factors (such as child abuse or other injuries and infections that occurred after birth) that contribute to CP, herein labeled as "postnatal causes." This

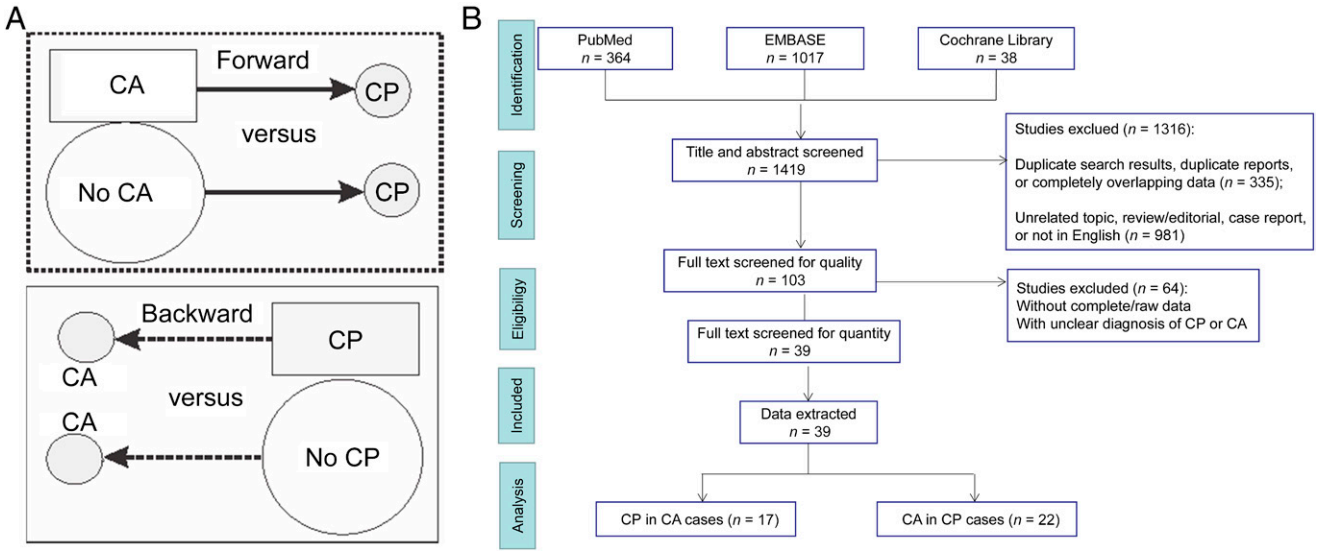

FIGURE 1
A, Comparison between forward (dotted rectangle) and backward approaches (solid rectangle). B, Flow diagram of the current study (based on the PRISMA 2009 flow diagram).

TABLE 1 Characteristics of Enrolled Studies Using a Forward Approach (CP in CA Cases)

Studies Enrolled	Country	Study Period	wk/g	CP/CA, *n*/*N*	Mortality Before Discharge, *n*/*N*	Singleton/ Twin	CP Diagnosed Age, y	Study Type by Original Authors	Study Quality	Notes
CCA preterm										
Bashir et al[25] 2016	Canada	1995–2007	<1250 g	23/130: 37/437	NA	NA	3	Retrospective	Good	Bronchopulmonary dysplasia cohort
Mendez-Figueroa et al[26] 2015	United States	1997–2004	23–36	9/220: 78/2336	16/220: 99/2336	Both	2	Second RCT	Good	Treated with antenatal steroid or $MgSO_4$
Nasef et al[27] 2013-1	Canada	2007–2008	<30	2/23: 9/96	4/33: 25/146	NA	1.5	Retrospective cohort	Good	HCA + CCA included
Botet et al[28] 2011	Spain	2004–2006	<1500 g	5/103: 11/106	NA	Both	2	Case-control	Good	
Allan et al[29] 1997	United States	1989–1992	600–1250 g	10/53: 26/322	NA	Both	1.5	Second RCT	Good	
Gray et al[30] 1997	Australia	1988–1990	24–29	1/12: 8/110	4/16: 58/173	Both	2	Cohort	Good	
CCA mixed gestation										
Bear and Wu[31] 2016	United States	1991–2001	Mixed	642/118 578: 7831/5 899 926	NA	NA	≥5	Retrospective cohort	Good	Postnatally caused CP excluded
Trønnes et al[32] 2014	Norway	1967–2001	23–43	69/4195: 3082/88 125	NA	Both	Unknown, possibly >4	Prospective cohort	Fair	CA + fever or sepsis
HCA preterm										
Huetz et al[33] 2016	France	2008–2011	24–34	4/57: 13/219	6/57: 16/219	Singleton	2	Retrospective cohort	Good	
Miyazaki et al[34] 2016	Japan	2003–2007	22–34	64/661: 101/1522	129/1235: 221/2843	Singleton	3–3.5	Retrospective cohort	Good	
Miyazaki et al[35] 2015: 1	Japan	2003–2007	22–34	21/249: 50/575	32/438: 70/1089	Singleton	3–3.5	Retrospective cohort	Good	Antenatal steroid, data included in ref 34
Miyazaki et al[35] 2015: 2	Japan	2003–2007	22–34	15/194: 72/906	65/402: 173/1645	Singleton	3–3.5	Retrospective cohort	Good	No antenatal steroid, data included in ref 34
Pappas et al[36] 2014: 1	United States	2006–2008	<27	23/473: 23/512	477/910: 423/1014	Both	1.5–2	Retrospective cohort	Good	
Nasef et al[27] 2013: 2	Canada	2007–2008	<30	2/61: 9/96	15/95: 25/146	NA	1.5	Retrospective cohort	Good	HCA + CCA excluded
Soraisham et al[37] 2013	Canada	2000–2006	<29	25/197: 12/187	46/270: 41/259	Both	2.5–3.5	Retrospective cohort	Good	
Watterberg et al[38] 2007: 1	United States	2001–2003	500 g–1 kg	7/55: 8/52	NA	Both	1.5–2	Second RCT	Good	Postnatal saline placebo, ventilated
Watterberg et al[38] 2007: 2	United States	2001–2003	500 g–1 kg	7/57: 6/46	NA	Both	1.5–2	Second RCT	Good	Postnatal steroid, ventilated
Polam et al[39] 2005	United States	1997–2000	22–29	9/102: 5/75	37/186: 38/251	NA	1–2	Case-control	Good	
Kent et al[40] 2005: 1	Australia	1996–2001	<30	3/9: 1/31	4/14: 8/47	NA	1–3	Cohort	Good	No antenatal steroid
Kent et al[40] 2005: 2	Australia	1996–2001	<30	5/49: 5/77	4/58: 8/101	NA	1–3	Cohort	Good	Antenatal steroid
CCA and HCA preterm										
Pappas et al[36] 2014: 2	United States	2006–2008	<27	17/209: 23/512	215/466: 423/1014	Both	1.5–2	Retrospective cohort	Good	
CCA or HCA preterm										
Fung et al[41] 2003	Australia	1997–2001	<28 or <1000 g	3/12: 5/43	34/105: 74/283	NA	2	Prospective cohort	Good	

NA, not available.

TABLE 2 Characteristics of Enrolled Studies Using a Backward Approach (CA in CP Cases)

Studies Enrolled	Country	Study Period	wk/g	CA/CP	Singleton/Twin	CP Diagnosed Age	Study Type by Original Authors	Study Quality	Notes
CCA in preterm CP									
Accordino et al[42] 2016: 1	Italy	2006–2012	24–34	2/26: 6/142	Singleton	1 y	Retrospective	Good	PPROM and PTL
Manuck et al[43] 2014	United States	1997–2004	<34	62/459: 161/1312	Both	2 y	Second RCT	Good	Same cohort as in ref 25
Skrablin et al[44] 2008	Croatia	1999–2001	<37	7/35: 3/35	Both	>2 y	Case-control	Good	
Neufeld et al[45] 2005: 1	United States	1987–1999	<37	33/247: 9/180	Singleton	≤6 y	Case-control	Fair	
Takahashi et al[46] 2005	Japan	1990–1998	22–33	3/30: 17/150	Both	4 y	Retrospective cohort	Good	
Vigneswaran et al[47] 2004: 1	Australia	1984–1994	<1500 g	10/82: 27/207	Singleton	5 y	Case-control	Good	Minimal CP excluded
Nelson et al[48] 2003: 1	United States	1988–1994	<32	20/64: 29/107	Singleton	4 y	Case-control	Good	Postnatally caused CP excluded
Jacobsson et al[49] 2002: 1	Sweden	1983–1990	<37	16/148: 19/296	Both	≥4 y	Case-control	Good	Postnatally caused CP excluded
Gray et al[50] 2001	Australia	1989–1996	24–27	9/30: 26/120	Both	≥2 y	Case-control	Good	
Matsuda et al[51] 2000: 1	Japan	1992–1996	26–30	6/22: 19/170	Singleton	>2 y	Case-control	Fair	Not matched
Redline et al[52] 2000: 1	United States	1983–1991	<1500 g	17/60: 7/59	Singleton	20 mo	Case-control	Good	
Yoon et al[53] 2000: 1	Korea	1993–1995	≤35	2/14: 7/109	Singleton	3 y	Cohort	Good	
Wilson-Costello et al[54] 1998	United States	1983–1991	<1500 g	11/50: 6/50	Singleton	20 mo	Case-control	Good	
O'Shea et al[55] 1998a	United States	1978–1989	500–1500 g	21/160: 10/80	Both	1 y	Case-control	Fair	Postnatally caused CP excluded
O'Shea et al[56] 1998b: 1	United States	1986–1993	500–1500 g	12/52: 11/110	Singleton	1 y	Case-control	Fair	Postnatally caused CP excluded
Yoon et al[57] 1997: 1	Korea	1993–1995	26–35	1/8: 4/75	Singleton	6 mo	Retrospective cohort	Fair	May have PIH
Cooke[58] 1990	United Kingdom	1980–1986	<1501 g	17/81: 6/81	Both	2 y	Case-control	Good	
CCA in term/ near-term CP									
Neufeld et al[45] 2005: 2	United States	1987–1999	≥37	7/395: 25/2675	Singleton	≤6 y	Case-control	Fair	
Wu et al[59] 2003: 1	United States	1991–1998	≥36	15/106: 9/215	Singleton	>15 mo	Case-control	Good	Postnatally caused CP excluded
Grether and Nelson[60] 1997: 1	United States	1983–1985	≥2500 g	5/46: 5/378	Singleton	3 y	Case-control	Good	Postnatally caused CP excluded
HCA in preterm CP									
Accordino et al[42] 2016: 2	Italy	2006–2012	24–34	8/26: 57/142	Singleton	1 y	Retrospective	Good	PPROM and PTL
Huetz et al[33] 2016	France	2008–2011	24–34	4/17: 32/179	Singleton	2 y	Cohort	Good	
Horvath et al[61] 2012	Hungary	2000–2010	<1500 g	7/11: 36/130	NA	>1 y	Cohort	Fair	
Redline et al[62] 2007	United States	1992–1995	<1000 g	8/18: 61/111	Singleton	8 y	Cohort	Good	
Vigneswaran et al[47] 2004: 2	Australia	—	<1500 g	22/54: 56/150	Singleton	5 y	Case-control	Good	
Nelson et al[48] 2003: 2	United States	1988–1994	<32	31/64: 58/107	Singleton	4 y	Case-control	Good	Postnatally caused CP excluded
Jacobsson et al[49] 2002: 2	Sweden	1983–1990	<37	10/28: 6/45	Both	>4 y	Case-control	Good	
Matsuda et al[51] 2000: 2	Japan	1992–1996	26–30	8/22: 61/170	Singleton	>2 y	Case-control	Good	Not matched
Redline et al[52] 2000: 2	United States	1983–1991	<1500 g	37/60: 35/59	Singleton	20 mo	Case-control	Good	
Yoon et al[53] 2000: 2	Korea	1993–1995	≤35	10/12: 44/105	Singleton	3 y	Cohort	Good	
O'Shea et al[56] 1998b: 2	United States	1986–1993	500–1500 g	14/21: 17/28	Singleton	1 y	Case-control	Fair	Postnatally caused CP excluded
Yoon et al[57] 1997: 2	Korea	1993–1995	26–35	6/7: 33/75	Singleton	6 mo	Retrospective cohort	Fair	May have PIH

TABLE 2 Continued

Studies Enrolled	Country	Study Period	wk/g	CA/CP	Singleton/Twin	CP Diagnosed Age	Study Type by Original Authors	Study Quality	Notes
HCA in term/ near-term CP									
Wu et al[59] 2003: 2	United States	1991–1998	≥36	5/19: 1/9	Singleton	>15 mo	Case-control	Good	
Grether and Nelson[60] 1997: 2	United States	1983–1985	≥2500 g	3/46: 3/378	Singleton	3 y	Case-control	Good	Postnatally caused CP excluded
CCA/HCA in preterm CP									
Costantine et al[63] 2007	United States	1993–2002	500 g–1 kg	11/19: 8/38	NA	18–22 mo	Case-control	Good	

PIH, pregnancy-induced hypertension; PPROM, premature rupture of membranes; PTL, preterm labor.

review is aimed at the clinician who would like to know the risk of CP in CA patients separately from the association of CA in CP patients and to determine the risk with categorization of CA as CCA or HCA and gestational age. We found that studies of preterm infants using forward approaches demonstrated that HCA is a risk factor for CP, and the association was also found in studies of near-term/term infants that used a backward approach. No evidence of CCA as a risk factor for CP was borne out from studies using a forward approach, but an association was found in studies of both preterm and term infants using a backward approach.

METHODS

Sources

We searched PubMed, the Cochrane Library, and Embase for relevant case-control or cohort studies to evaluate the relationship between CP and CA. Queries included articles published from January 1, 1960 to September 30, 2016 in peer-reviewed publications (including abstracts). Keywords used were (chorioamnionitis) AND ((cerebral palsy) OR (brain)). We also hand-searched bibliographies of original studies, reviews (including meta-analyses), and relevant conference abstracts and contacted some investigators directly. The last search was conducted on October 8, 2016. No review protocol exists.

Study Selection

Using the methods of Meta-analysis of Observational Studies in Epidemiology (MOOSE)[17] and PRISMA, 2 authors (L.M. and Z.S.) independently selected relevant studies, assessed study quality by means of quality assessment of case-control studies[18] or observational cohort and cross-sectional studies,[19] and extracted data. Questionable studies were confirmed by discussion with a third author (S.T.). Included studies met all of the following criteria: (1) clinical cohort (with a control group) or case-control study investigating the relationship between CA and CP; (2) an explanation of diagnosis and outcomes; (3) had neurologic follow-up information especially for CP; and (4) a quality of good or fair according to published criteria.[18,19] Studies were excluded from consideration if: (1) they did not show all of the above information; (2) had no patient numbers available; and (3) were not written in English.

Data Extraction

We extracted data about study design and methods, inclusion and exclusion criteria, patient (mother, fetus, or newborn) characteristics, treatments (steroids, antibiotics, tocolytics, mechanical ventilation, NICU admission, etc), patient outcomes, and follow-up information. For primary outcomes, we estimated the relationship between CA and CP in term and preterm infants. Statistical analysis was conducted by using Review Manager version 5.0 software (Cochrane Collaboration). The Mantel-Haenszel model was used for dichotomous data. The pooled risk ratios (RRs) and 95% confidence intervals (CIs) were determined by either a fixed-effects or random-effects model, depending on which was most conservative. We used a forest plot to illustrate the relative strength of treatment effects in multiple quantitative scientific studies addressing the same question.[20] Statistical between-study heterogeneity was assessed by I^2 test[21] and χ^2 test. Publication bias was assessed by funnel plot.[22,23] An asymmetric funnel indicated a relationship between treatment effect and study size, suggesting the possibility of either publication bias or a systematic difference between smaller and larger studies

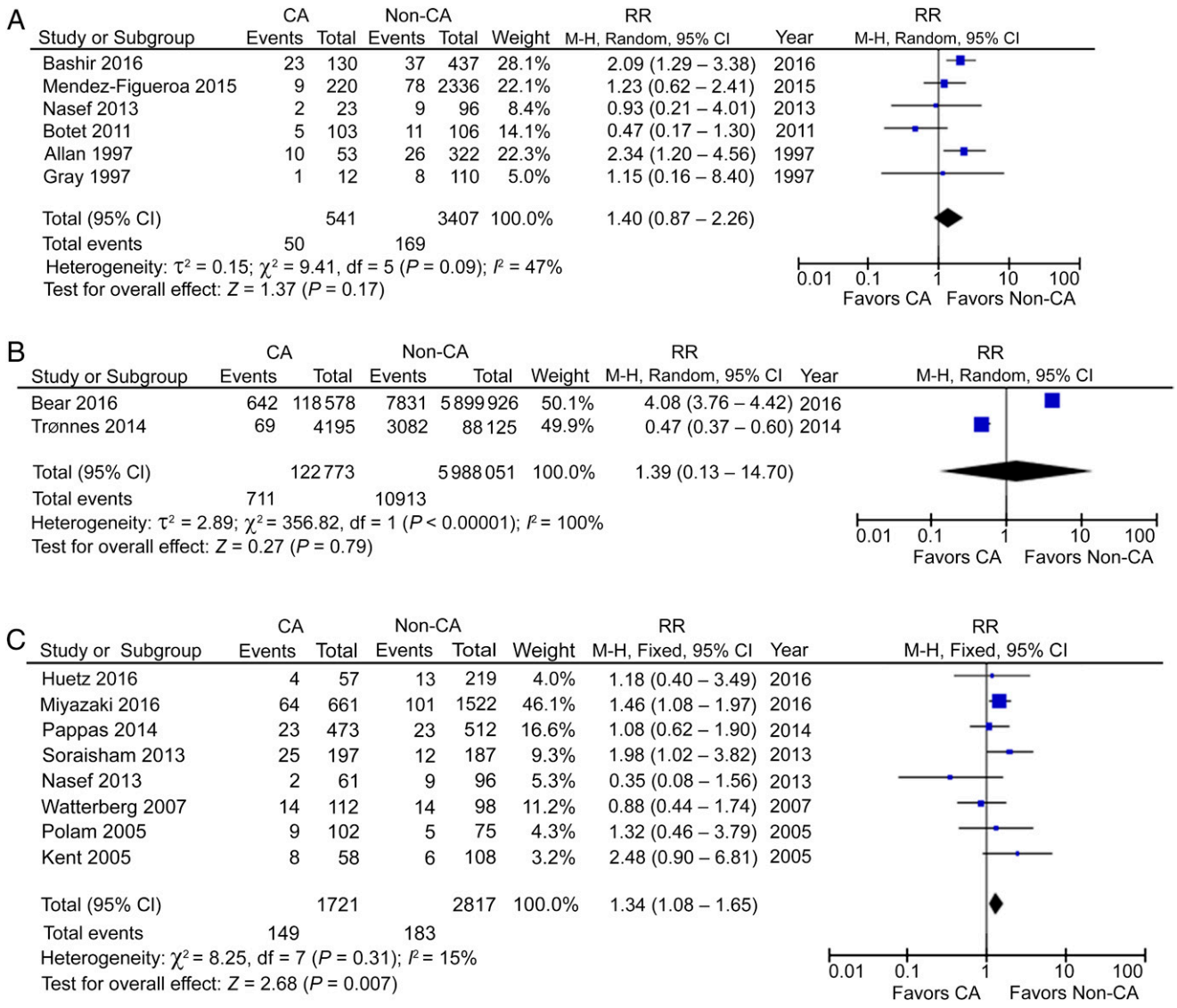

FIGURE 2
A, CP in preterm CCA patients. B, CP in mixed-term CCA patients. C, CP in preterm HCA patients. df, degrees of freedom; M-H, Mantel-Haenszel model.

("small study effects") or the use of an inappropriate effect measure. Differences between groups were assessed on the basis of the χ^2 statistic. For all tests done, statistical significance was achieved if the 2-tailed *P* value was <.05 (for overall effect of CP or CA conditions, or for the heterogeneity test).[24]

RESULTS

Based on our search strategy, 1419 studies were identified. After screening with preset inclusion and exclusion criteria, there were 17 studies analyzing the incidence of CP in the CA population (125 256 CA patients and 5 994 722 controls)[25–41] and 22 studies analyzing the incidence of CA in the CP population (2513 CP patients and 8135 controls)[42–63] (flow diagram in Fig 1B; characteristic information in Tables 1 and 2).

CP in CCA Patients

Using a forward approach, 6 cohort studies reported the incidence of CP in preterm CCA patients, including 541 CCA patients and 3407 non-CCA participants and showed no significantly increased risk.[25–30] The pooled RR (95% CI) was 1.40 (0.87–2.26), with moderate heterogeneity (I^2 = 47%; Fig 2A). Two studies reported CP in a mixed population of preterm and term deliveries in CCA patients, including 122 773 CCA patients and 5 988 051 non-CCA participants,[31,32] again with a nonsignificant RR of 1.39 (95% CI: 0.13–14.70) and with high heterogeneity (I^2 = 100%; Fig 2B). This analysis would suggest that there may be no relationship between CCA and CP when analyzing

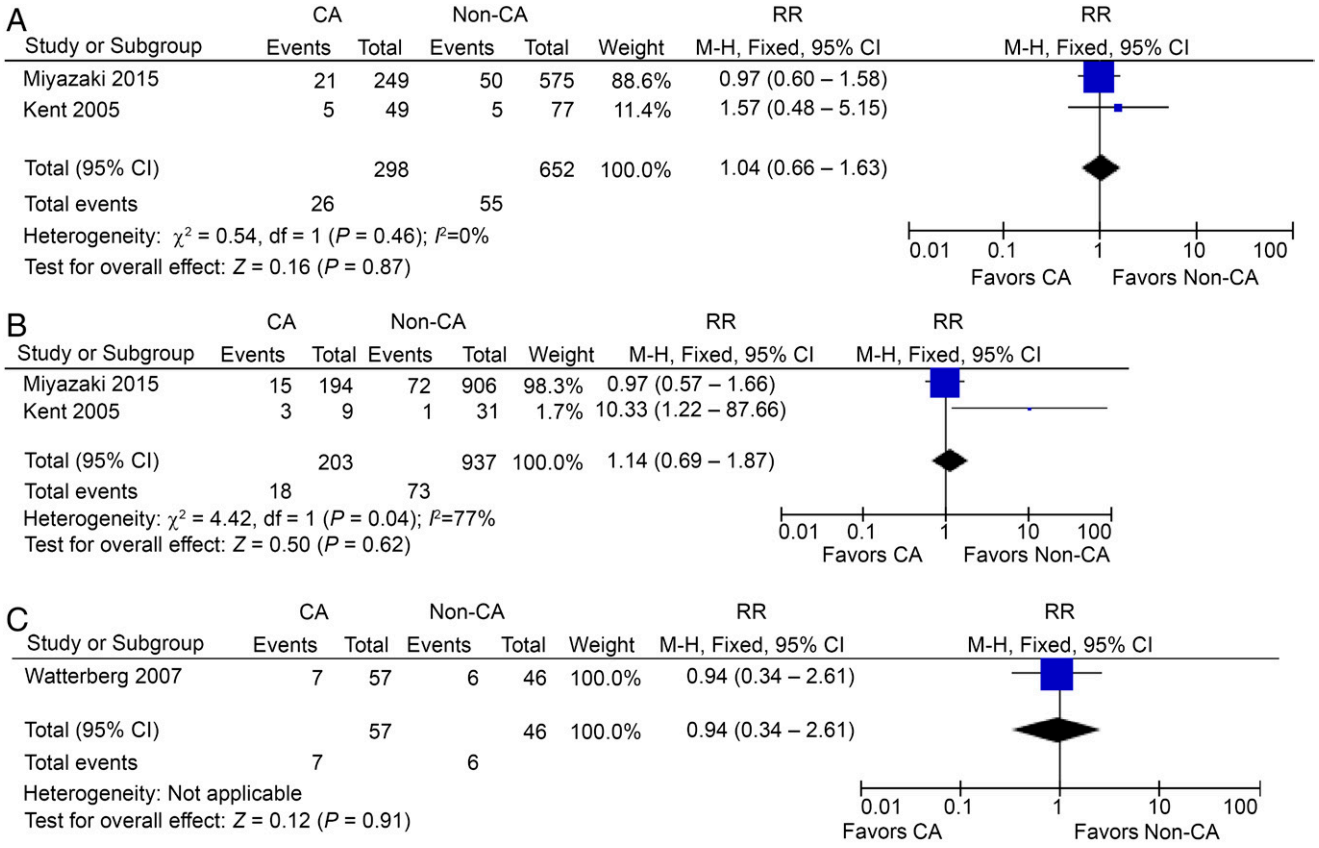

FIGURE 3

A, CP in preterm HCA patients, prenatal steroids used. B, CP in preterm HCA patients, no prenatal steroids used. C, CP in preterm HCA patients, postnatal steroids used. df, degrees of freedom; M-H, Mantel-Haenszel model.

data across all stages of pregnancy and that it is inappropriate to report the CA condition in combined gestational stages, which is shown by the high heterogeneity.

CP in HCA Patients

Eight studies reported CP in preterm HCA patients, including 1721 HCA patients and 2817 non-HCA participants.[27,33,34,36–40] In contrast to CCA, HCA seemed to be a risk factor for CP in preterm gestation, with a RR of 1.34 (95% CI: 1.08–1.65; $P < .01$) and with low heterogeneity ($I^2 = 15\%$; Fig 2C). However, the incidence of CP in HCA patients is small, only 8.7 per 100 preterm infants compared with 6.5 per 100 non-HCA–exposed infants. Interestingly, the use of prenatal or postnatal steroids was reported in 3 studies, but did not lead to a significant decrease of CP in preterm HCA patients (Figs 3 A–C and 4A).[35,38,40]

CP in CCA and/or HCA Patients

One study reported CP in preterm patients with both CCA and HCA, including 209 patients and 512 controls.[36] The RR was borderline at 1.81 (95% CI: 0.99–3.32; $P = .05$; Fig 4B). Thus, there is no strong evidence that a combination of CCA and HCA is associated with CP. One study reported CP in preterm patients with CCA or HCA, including 12 patients and 43 controls.[41] The RR in this case was not significant at 2.15 (95% CI: 0.60–7.74; Fig 4C), again confirming the view that CCA may not be a risk for preterm CP, as well as the need for definitive criteria for diagnosing CA.

CCA in CP Patients

Using a backward approach, 17 cohort studies reported the incidence of CCA in preterm CP patients, including 1568 CP patients and 3283 non-CP participants.[42–58] The RR was significant at 1.43 (95% CI: 1.22–1.68; $P < .01$), with low heterogeneity ($I^2 = 21\%$; Fig 5A). This increased association is in contrast to no significantly increased risk from the analysis using a forward approach. When defined postnatal causes were excluded, we were left with 4 studies with 424 preterm CP patients and 593 controls, which showed a significant increase of CCA in preterm CP patients,[48,49,55,56] with an RR of 1.40 (95% CI: 1.03–1.90; $P < .05$) and low heterogeneity ($I^2 = 9\%$; Fig 5B).

Three studies reported the incidence of CCA in term/near-term CP patients, including 547 CP patients and 3268 non-CP participants.[45,59,60] The RR was significantly high at 3.06 (95% CI: 1.84–5.09; $P < .01$), with medium heterogeneity ($I^2 = 49\%$;

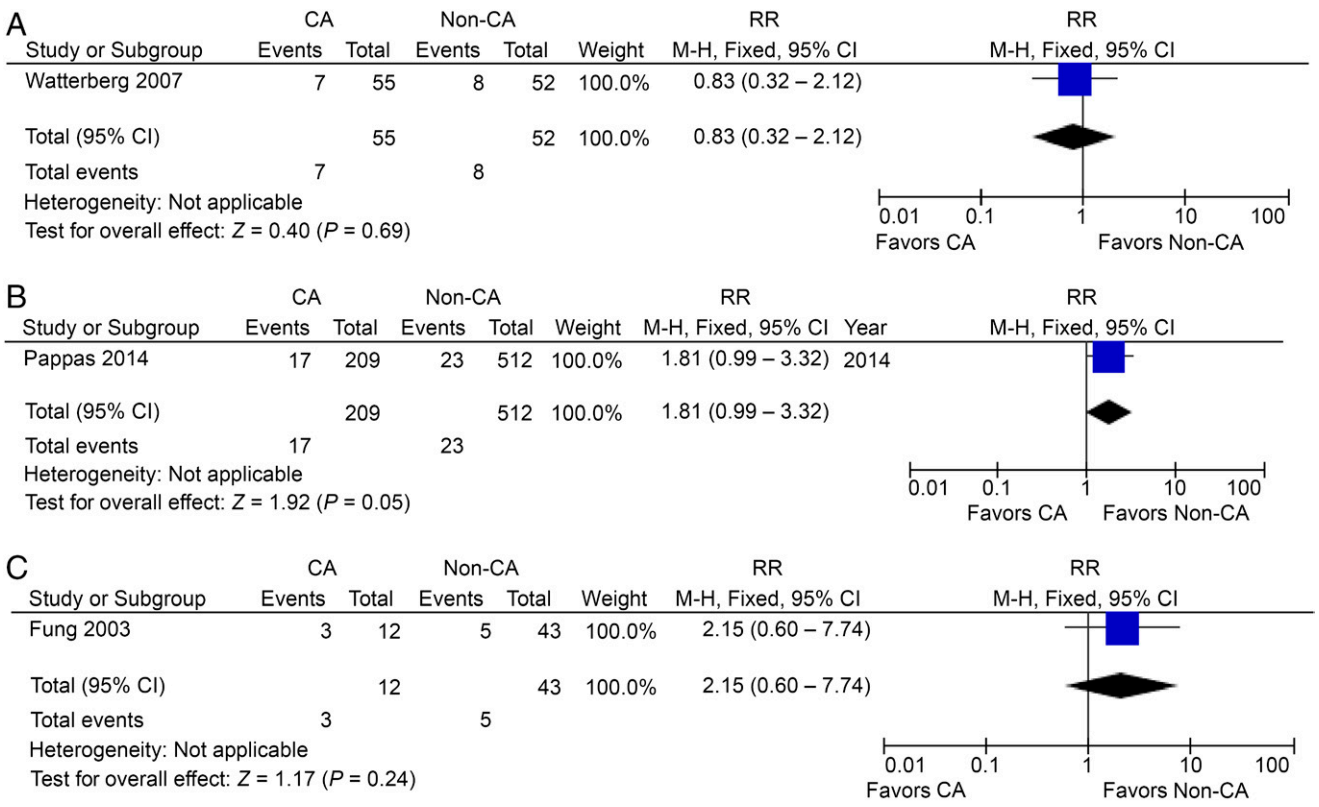

FIGURE 4
A, CP in preterm HCA patients, no postnatal steroids used. B, CP in preterm CCA and HCA patients. C, CP in preterm CCA or HCA patients. M-H, Mantel-Haenszel model.

Fig 6A). Again, when postnatal causes were excluded, 2 studies with 152 term/near-term CP patients and 593 controls showed a significant increase of CCA in term/near-term CP patients,[59,60] with an RR of 4.13 (95% CI: 2.13–7.99; $P < .01$), with medium heterogeneity ($I^2 = 34\%$; Fig 6B).

HCA in CP Patients

Twelve studies reported the incidence of HCA in preterm CP patients, including 340 CP patients and 1298 non-CP participants,[33,42,47–49,51–53,56,57,61,62] but the RR was not significant at 1.12 (95% CI: 0.98–1.28), with high heterogeneity ($I^2 = 67\%$; Fig 6C). The absence of association from studies using a backward approach contradicts the conclusion of increased risk in studies using a forward approach. When postnatal causes were excluded, 2 studies with 85 preterm CP patients and 135 controls[48,56] showed no significant change with an RR of 0.94 (95% CI: 0.73–1.21; Fig 7A). Two studies reported the incidence of HCA in term/near-term CP patients, including 65 CP patients and 387 non-CP participants,[59,60] and the RR in this case was significant at 4.26 (95% CI: 1.25–14.57; $P < .05$), with low heterogeneity ($I^2 = 0\%$; Fig 7B). Again, when postnatal causes were excluded, we were left with 1 study with 46 term/near-term CP patients and 378 controls showing a significant increase of HCA in term/near-term CP patients[60] with an RR of 8.22 (95% CI: 1.71–39.53; $P < .01$; Fig 7C).

CCA or HCA in CP Patients

One study reported CCA or HCA cases in preterm CP patients, including 19 patients and 38 controls,[63] with a significant RR of 2.75 (95% CI: 1.33–5.68; $P < .01$; Fig 7D). One hesitates to come to any conclusion with these small numbers.

DISCUSSION

This meta-analysis reveals the absence of a risk for CP in CCA patients. HCA, on the other hand, seems to be associated with a significant risk for CP, although the incidence of CP in HCA-exposed infants is only 8.6%. This review also points out the less convincing analysis from cohort studies using a backward approach. The fact that there is no increased incidence of CP in CCA patients but a higher incidence of CCA in CP patients perhaps points to another factor (such as prematurity itself) in the causal pathway of CP, perhaps significant only when it coexists with CCA . Statistics derived from a forward approach of studying CA

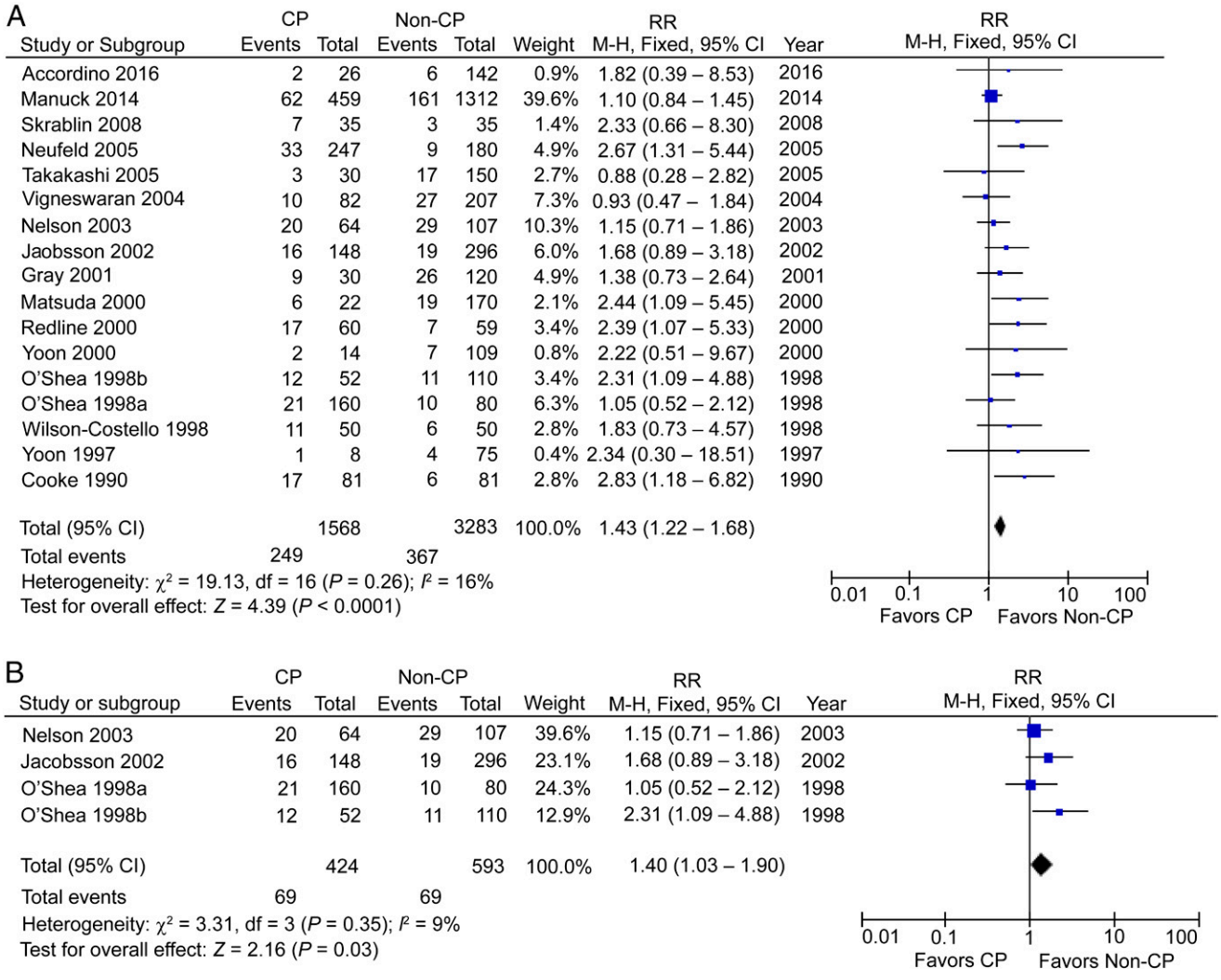

FIGURE 5

A, CCA in preterm CP patients. B, CCA in preterm CP patients, postnatal causes excluded. df, degrees of freedom; M-H, Mantel-Haenszel model.

populations have fewer potential sources of bias and confounding than those obtained from a backward approach of studying a CP population. The statistical power of these 2 strategies differs substantially.[64] HCA seems to show a stronger risk in the studies that used a forward strategy in the preterm population. Although the number of studies is small, an association is found using a backward approach from studies of the near-term/term population, a group that avoids the potential influence of prematurity. The fact that there is no association of HCA with CP in preterm infants suggests that other factors (including prematurity) probably drown out the small contribution of HCA. The perinatal etiologic risk factors for CP include birth asphyxia, inflammation, restricted growth, birth defects, sex, race, and genetics.[65] Treatments in response to CA or preterm labor, such as application of tocolytics, $MgSO_4$, corticosteroids, surfactant, antibiotics, and mode of delivery,[58] as well as complications in the pregnant mother[12] might also affect the pathogenesis of CP.

There are many possible reasons why CCA is not as strong a risk factor as HCA. Wu[10] raised the issue of overdiagnoses of the clinical diagnosis of "chorioamnionitis" in recent years. Maternal fever without maternal inflammation has often been included in the diagnosis of CCA, which then includes a population of fetuses that do not have inflammation. Examples include fever from dehydration and epidural injection. This issue might be solved if all obstetricians followed the recent guidelines of delineating maternal fever alone from triple-I.[5] Even if there is maternal inflammation with evidence of high leukocytes >15 000 and definite pus observed from cervical os and high fever, which constitute the criteria of "suspected" triple-I,[5] the fetus systematically and the fetal brain may not necessarily be affected by inflammation. The previous definitions of HCA

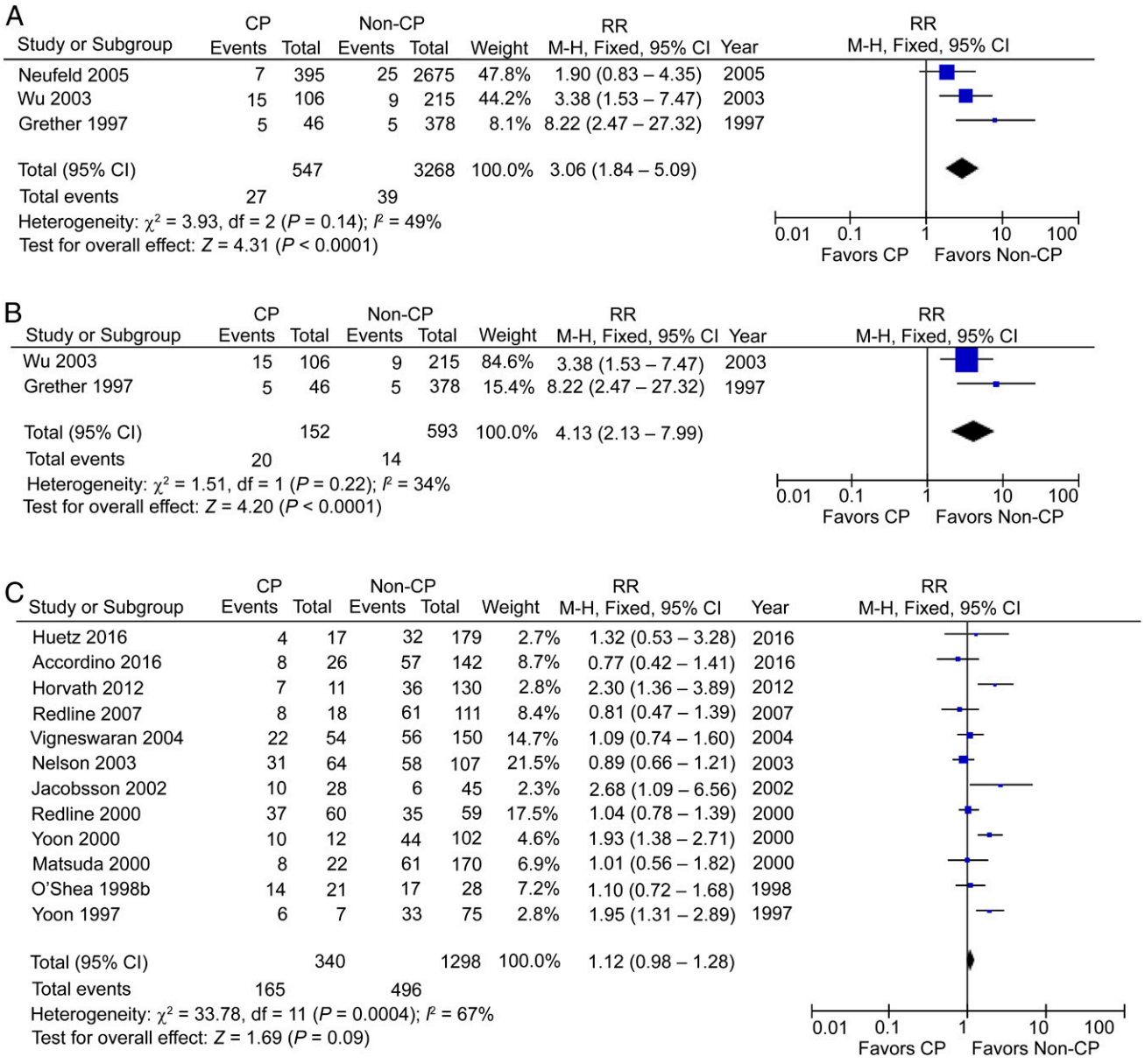

FIGURE 6

A, CCA in term/near-term CP patients. B, CCA in term/near-term CP patients, postnatal causes excluded. C, HCA in preterm CP patients. df, degrees of freedom; M-H, Mantel-Haenszel model.

coinciding with the added criteria constituting "confirmed" triple-I,[5] Gram positivity, positive culture, and low glucose in amniotic fluid, as well as positive placental pathology may still not be enough to confirm the presence of fetal inflammation. One can speculate about the confounding effects of the immunologic responses and specific microbiomes in the mother, placenta, and fetus. Even with the evidence of fetal involvement in the placenta, only the most severe fetal inflammatory response (ie, subacute necrotizing funisitis and chorionic plate vasculitis with thrombosis) was associated with poor developmental outcome, but this was not the case with the milder stages of fetal inflammatory response.[66] Thus, it is possible that with a refined diagnosis of triple-I, clinicians will be able to get a better idea of the risk of CP with inflammation in the mother-infant dyad. It is speculated that the risk of CP is restricted to the population of CA with evidence of severe fetal inflammation and is not present in all cases of confirmed triple-I. Not many hospitals in the United States or Europe have the capability of doing amniotic fluid examination and a quick turnaround of placental pathology. Thus, in the future, there will still be continued confusion about the risk of CP in CCA (now suspected triple-I) and CCA + HCA (confirmed triple-I) populations.

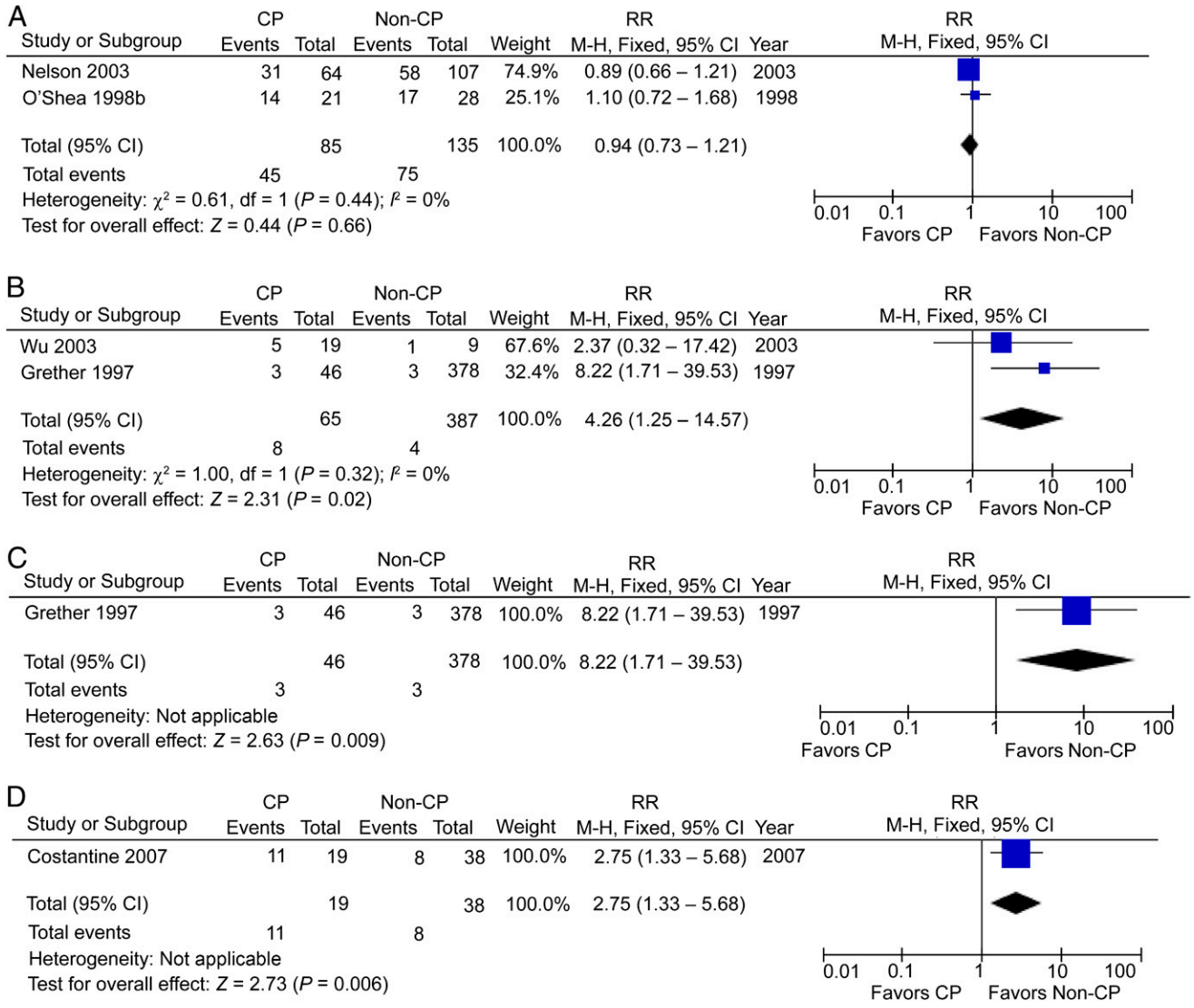

FIGURE 7

A, HCA in preterm CP patients, postnatal causes excluded. B, HCA in term/near-term CP patients. C, HCA in term/near-term CP patients, postnatal causes excluded. D, CCA/HCA in preterm CP patients. df, degrees of freedom; M-H, Mantel-Haenszel model.

The risk of CP in cases of HCA only, without concomitant signs of CCA, is still to be determined.

Other Biases

Most of the studies in Table 1 involved preterm populations of newborns, whereas 7 studies out of the 29 in Table 2 were of term/near-term newborns. According to our analysis, HCA seems to be a risk factor for CP in preterm gestation. However, this is likely due to the large weight in the analysis of the Miyazaki study[34] (46.1%). This study does have limitations, such as a retrospective design and a high rate of exclusions due to incomplete data (6316 excluded out of 10 394 cases). The risk of CP is inversely proportional to gestational age and is 60 times higher at <28 weeks of gestation than at term.[49] The confounding factor to consider in CA is that the risk of prematurity is higher in cases of CA. More than half of CP cases diagnosed at 1 year of age were free of motor handicap at the age of 7 years.[67] A diagnosis made at 2 years of age or later is more reliable than one made before 2 years of age.[68] Twin pregnancy was associated with an increased risk of CP.[69] Thus, studies confined to singleton pregnancies ought to be compared separately from those with twin pregnancies. Exclusion of certain causes of CP also minimizes the bias in the etiologic study of CA, such as CP caused by child abuse, accidents,[31] TORCH (with toxoplasmosis, rubella, cytomegalovirus, and herpes) infection,[48] brain malformation, or even prenatal destructive brain lesions.[60] The discerning reader will notice that the average relative

risk of CP in pooled CCA patients was higher than that of CP in HCA patients. The pooled incidence of CP in preterm CCA was 9.2% vs 5.0% for preterm non-CCA–exposed patients, but the pooled incidence did not reach significance and there was high heterogeneity among enrolled studies, which was not the case for HCA. In any case, the absolute values of CP in both CCA and HCA are still small, suggesting that even HCA constitutes a relatively small risk factor for CP in a preterm infant.

One must also consider the possibility that the incidence of CP may be inversely related to the incidence of death. Investigating the relationship between newborn death and CA from studies with a concomitant report of CP, we found 3 studies that reported the incidence of newborn death before discharge in preterm CCA patients, including 269 CCA patients and 2655 controls,[26,27,30] but the RR was not significant at 1.19 (95% CI: 0.80–1.77) and there was high heterogeneity (I^2 = 52%; Supplemental Fig 14). Seven studies reported the incidence of newborn death before discharge in preterm HCA patients, including 2825 HCA patients and 4880 controls,[27,33,34,36,37,39,40] and in this case, the RR was significant at 1.25 (95% CI: 1.15–1.36; P < .01) and there was low heterogeneity (I^2 = 0%; Supplemental Fig 15). However, the study by Pappas et al[36] contributed 62% of the weight of the analysis. In this study, extremely premature infants were included, and it is well known that the mortality rate for extremely premature infants is much greater than that of preterm infants. Comparing CCA in preterm CP to CCA in term CP, one finds less of an association with preterm CP (RR: 1.43 vs 3.06). One can speculate that if the premature infants who died had somehow survived, then there could have been a higher rate of CP.

The etiology of maternal inflammation may extend beyond CA. Bear and Wu[31] showed that a history of genitourinary and respiratory infections in addition to CCA increases the risk of CP when using a forward approach involving 6 million mother-infant dyads, including preterm and term gestational ages. The RR for CP in 24 414 preterm patients with CCA was 4.1 (95% CI: 3.7–4.5) compared with a RR of 2.01 for 86 335 term CCA patients (95% CI: 1.7–2.4).[31] However, no raw data were shown comparing CP in the preterm CCA or non-CCA populations, nor in the term CCA and non-CCA populations, making this study only applicable for mixed-term analysis. When using a backward approach, Bear and Wu[31] found an association of CP with either CCA, genitourinary or respiratory infections (incidence of maternal infection in CP vs non-CP, 13.7% vs 5.5%, P < .01). Interestingly, it is not known whether maternal infection other than CA occurred specifically in the second and third trimesters, which raises the issue of a susceptibility to infections or inflammation in mother-infant dyads. Thus, it is possible that a subpopulation of mother-infant dyads has an increased chance of fetal inflammation in CCA. This possibility is supported by the increased RR of 7.0 if there was CCA along with a history of other maternal infections. Furthermore, it has been proposed that alterations in the composition of the microbiota might disturb the human immune system, ultimately leading to altered immune responses that may underlie inflammatory disorders.[70]

CONCLUSIONS

HCA is a risk factor for CP in preterm studies using a forward approach. An association of HCA with CP is found only in studies of near-term/term infants but not in studies of preterm infants using a backward approach. The incidence of CP after HCA is still small. The evidence that CCA is a risk factor for CP is not borne out from studies using a forward approach. An association of CP with CCA is found in studies of both preterm and term infants using a backward approach. Future trials of confirmed triple-I with severe fetal inflammatory involvement need to be carried out.

ABBREVIATIONS

CA: chorioamnionitis
CCA: clinical chorioamnionitis
CI: confidence interval
CP: cerebral palsy
HCA: histologic chorioamnionitis
RR: risk ratio
triple-I: intrauterine inflammation or infection or both

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