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REVIEW ARTICLE

The aetiology of preterm birth and risks of cerebral palsy and cognitive impairment: A systematic review and meta-analysis

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Abstract

Aim: The associations between the aetiology of preterm birth and later neurodevelopmental outcomes are unclear. A systematic review and meta-analysis examined the existing evidence.

Methods: The PubMed and Embase databases were searched for papers published in English from inception to 16 December 2020. We included original papers on the causes of preterm birth and the risks of cerebral palsy (CP) and suboptimal cognitive development. Two reviewers independently evaluated the studies and extracted the data.

Results: The literature search yielded 5472 papers and 13 were selected. The aetiology of preterm birth was classified under spontaneous or medically indicated delivery. A meta-analysis was performed, comprising 104 902 preterm infants from 11 papers on CP. Preterm infants born after a medically indicated delivery had a lower CP risk than infants born after spontaneous delivery, with a pooled odds ratio of 0.59 (95% confidence interval 0.40–0.86). This result was robust in the subgroup and sensitivity analyses. Cognitive development was reported in three papers, which suggested that worse outcomes were associated with medically indicated deliveries.

Conclusion: The aetiology of preterm delivery may contribute to the risk of CP and cognitive delay. Further research is needed, using individual-level meta-analyses to adjust for possible confounders, notably gestational age.

KEYWORDS
cerebral palsy, cognitive development, placental insufficiency, PPROM, preterm infant

1 | INTRODUCTION

There are three leading causes of very preterm birth. They are spontaneous preterm delivery with intact membranes, preterm premature rupture of the membranes (PPROM) and medically indicated preterm delivery. The medical indications can include either maternal or foetal causes.[1] The type and duration of foetal exposure vary substantially. In medically indicated preterm delivery, the foetal environment is commonly affected by placental insufficiency, which leads to abnormal foetal blood flow patterns, with or without intrauterine growth

Abbreviations: CP, cerebral palsy; IUGR, intrauterine growth restriction; PPROM, preterm premature rupture of the membranes.

restriction (IUGR).[1] Normal brain growth and cognitive development cannot be sustained, despite foetal compensation through increased blood flow to the brain.[2] The foetal environment is often affected by chorioamnionitis in spontaneous preterm delivery, either with intact membranes or after PPROM. Inflammatory cytokines related to chorioamnionitis can damage the neurons of the central nervous system.[3] It is likely that the foetuses in medically indicated preterm deliveries have been exposed to the pathological condition for an extended period of time before the delivery. In contrast, a spontaneous preterm delivery can be a short process.

It has also been suggested that the existence of differences in the foetal environment in the various aetiologies of very preterm birth was associated with neonatal morbidities.[4–6] One study found that preterm infants who were born following maternal hypertension and IUGR faced an increased risk of bronchopulmonary dysplasia, retinopathy of prematurity and mortality.[6] On the other hand, antenatal infections and inflammation and the spontaneous onset of preterm delivery have been associated with greater risks of brain pathologies.[4,5]

Less is known about how the aetiology of preterm birth affects long-term neurodevelopmental outcomes. Some studies have suggested that the risk of cerebral palsy (CP) was increased after spontaneous onset of preterm delivery, PPROM and chorioamnionitis, but the evidence has been inconsistent.[2,3,7,8] In addition, some studies have suggested that different degrees of placental insufficiency have been associated with impairments in cognitive development.[9–12] The role that the underlying aetiology of preterm birth plays needs to be understood, in order to improve research on the prevention and mitigation of neurodevelopmental impairments in preterm infants.

The aim of this study was to evaluate the effects of the aetiology of preterm delivery on the risk of CP and suboptimal cognitive development, by carrying out a systematic literature review and meta-analysis.

Key Notes

- This systematic review and meta-analysis examined whether the aetiology of preterm birth affected the neurodevelopmental outcomes of preterm infants.
- Medically indicated preterm delivery was associated with a lower risk of cerebral palsy (CP) than spontaneous preterm delivery but was also associated with unfavourable cognitive development outcomes.
- The aetiology of preterm delivery appeared to contribute to the risk of CP and cognitive delay, especially in very preterm infants.

2 | METHODS

2.1 | Search strategy

We performed a database search in PubMed, including a MeSH search, and Embase. Our aim was to identify original papers that looked at the associations between the causes of preterm delivery and the risk of CP and suboptimal cognitive development (Table S1). In addition, we performed a manual search of the reference lists of the included papers. The databases were searched for papers published in English from inception to 16 December 2020.

2.2 | Study selection

We included original studies that evaluated the associations between the cause of preterm birth and the risks of CP or suboptimal cognitive development in preterm infants. We included both cohort and case–control studies. To be included, the aetiology for preterm delivery had to be explicitly determined for all study patients. The main outcome measures were CP and cognitive development, which was assessed using standardised psychological evaluation by a trained psychologist. We excluded studies that only comprised infants born at 37 weeks or more of gestation or mixed groups with both preterm and term-born infants. Papers that were not published in English were also excluded.

The first stage was for the lead author (MY) to select studies based on the titles of the papers, to exclude those that did not meet the search criteria. Then, four authors (MY, MS, JZ, LL) shared the work by independently evaluating the abstracts and full texts that the lead author had selected. Each abstract and full text was evaluated by two of the authors.

2.3 | Data extraction

Two study authors extracted the data from each of the studies that were selected. These included the study design and population, inclusion and exclusion criteria, year of birth, antenatal steroid exposure, aetiological groups and size of the cohort. The outcomes were also extracted, including the age at the time of the evaluation.

2.4 | Assessment of methodological quality

The quality of each included study was also independently assessed by two authors, using the Newcastle–Ottawa quality assessment tool[13] (Appendix A). Disagreements were resolved through discussion with the co-authors.

2.5 | Statistical analyses

We performed a random effects meta-analysis in order to estimate the pooled log-odds ratios (ORs) with 95% confidence intervals

(95% CIs) for the risk for CP for the preterm birth subtypes detailed later. These were spontaneous preterm and medically indicated preterm deliveries. A restricted maximum-likelihood estimator with the Hartung–Knapp–Sidik–Jonkman adjustment[14–16] was used. The heterogeneity in effect sizes between the studies was addressed by estimating Tau^2 statistics. These were defined as the variance of the true effect size and 95% prediction intervals.[14] In addition, we performed subgroup analyses to study the possible moderating effects of various factors on between-study variances in effect sizes. The analysed subgroups included infants born with a very low birth weight of up to1500 g and/or at a very low gestational age of <32 weeks. The groups also included preterm singletons, studies with a minimum of 2 years follow-up and studies performed during the era of systematic active perinatal care for very preterm birth. The singleton subgroup analysis was only performed using studies where singletons could be separated from the full study populations. The era of systematic care for preterm birth was defined as births after the year 2000 or where 70% of the mothers received antenatal steroids. Sensitivity analyses were performed, based on the definition of the mode of onset of delivery, namely labour versus no labour, instead of the aetiology of preterm birth. We also compared cohort versus case–control studies. Finally, we excluded studies that included cases with placental abruption. Publication bias was graphically examined using a funnel plot. A leave-one-out analysis was performed to identify outlier studies.

The analyses were performed with R version 4.2.0 (R Foundation for Statistical Computing, Vienna), using the metafor package version 3.4-0.[17]

This study protocol was registered on the International Prospective Register of Systematic Reviews (CRD42021233866). The review was conducted according to the Preferred Recording Items for Systematic Reviews and Meta-analyses.

3 | RESULTS

The literature search yielded 5472 papers: 180 were selected for the abstract review and 46 for the full-text review (Figure 1). There were 11 studies with CP as an outcome that were eligible for inclusion in the review and meta-analysis.[18–28] We were only able to find three[18–20] eligible papers on cognitive development and only one[24] provided sufficient information for the meta-analysis. The quality of 10 of the 11 studies included in the meta-analysis was high, with a low risk of bias (Appendix A). Even though the quality of one study[27] was not high, we chose to include it due to the low number of papers found for this meta-analysis.

The meta-analysis of the aetiology of preterm delivery and the risk of CP comprised 11 studies with 104 902 preterm infants: seven cohort studies,[18,21–26] one register study[27] and three case–control[28–30] studies (Table 1). The patient population sizes ranged from 100 to

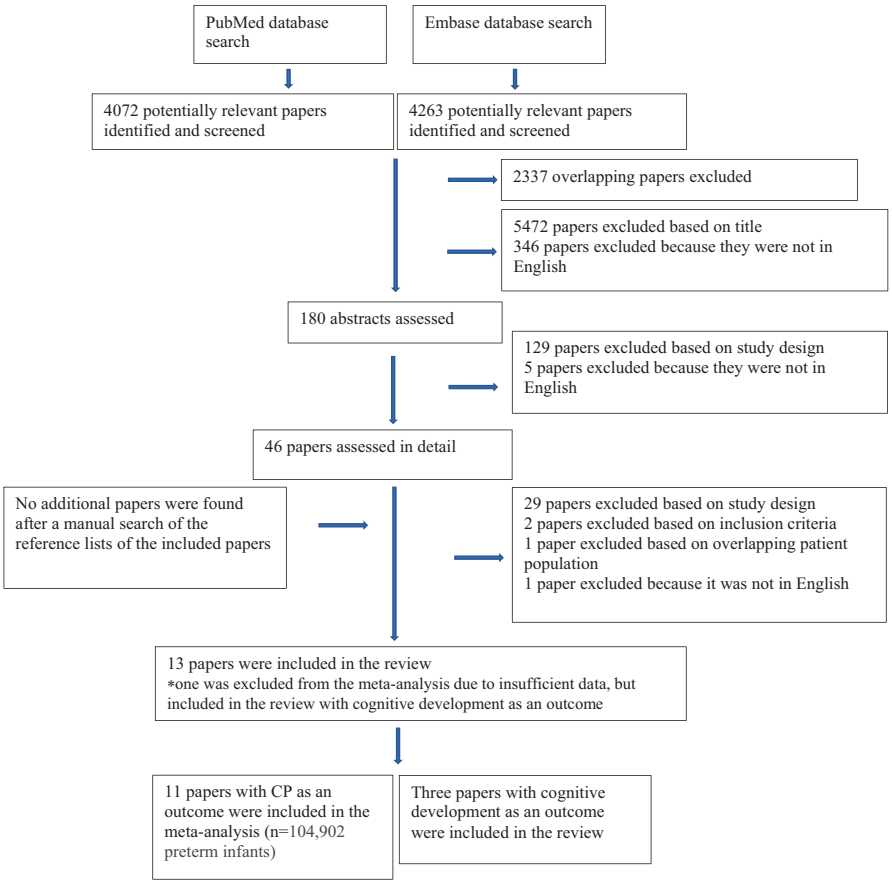

FIGURE 1 Flowchart of the study search and selection.

TABLE 1 A description of the studies included in the meta-analysis on the association of the aetiology of preterm delivery and the risk of cerebral palsy (CP).

			Study design	Inclusion	Antenatal corticosteroid coverage	Age in years at diagnosis of CP	Evaluation method used to diagnose CP	Subgroup analysis				Sensitivity analysis	
Author Reference Year	Number of subjects[a]	Birth year	Cohort/ register study (C/RS) Case–control (CC)	Birth weight and gestational age restrictions in weeks			Neurological evaluation (N), Data from hospital records/register (R)	very low birth weight/ very low gestational age[b]	Singletons[c]	At least 2 years of follow-up[d]	Active perinatal care[e]	Case–control studies excluded[f]	Placental abruptions excluded[g]
McDonald[21] 1963	749	1959	C/RS	≤1800 g	n/a	6–8 years	N	x	x	x		x	
Murphy et al.[30] 1995	293	1984 to 1990	CC	<32 GW	6%	3–5 years	R	x	x	x			
Grey et al.[18] 1997[b]	93	1988 to 1990	C/RS	24–29 GW	n/a	2 years	N	x		x		x	x
Dammann et al.[22] 1998	312	198 to 1986	C/RS	<1500 g	n/a	6 years	N	x		x		x	
Kurkinen-Räty et al.[29] 2000	175	1990 to 1997	CC	24–33 GW	23%	1 year	N		x				
Han et al.[26] 2002	437	1993 to 1994	C/RS	<36 GW	n/a	3 years	N			x		x	
Greenwood et al.[28] 2005	464	1984 to 1993	CC	<32 GW and 33–36 GW	10%	5 years	R	x	x	x			
Livinec et al.[24] 2005	1115	1997	C/RS	<33 GW	75%	2 years	N		x	x	x	x	x
Morken et al.[27] 2007	45 621	1991 to 2001	C/RS	<37 GW	n/a	n/a	R	x	x			x	
McElrath et al.[25] 2009	887	2002 to 2004	C/RS	<28 GW	89%	2	N	x		x	x	x	x
Roberts et al.[23] 2017	54 756	2001 to 2012	C/RS	24–36 GW	n/a	1–6	R		x		x	x	

Abbreviations: n/a, not available.

[a]Number of study subjects with available information on the aetiology of preterm birth and CP.

[b]Studies in subgroup analysis on the association between the aetiology of preterm delivery and the risk of CP in very low birth weight and/or very low gestational infants.

[c]Studies in subgroup analysis on the association between the aetiology of preterm delivery and the risk of CP in preterm singletons.

[d]Studies in subgroup analysis on the association between the aetiology of preterm delivery and the risk of CP after at least 2 years of follow-up.

[e]Studies in subgroup analysis on the association between the aetiology of preterm delivery and the risk of CP during the active perinatal care era (studies with children born after the year 2000 and/or where over 70% of the mothers had received antenatal steroids).

[f]Studies in sensitivity analysis on the association between the aetiology of preterm delivery and the risk of CP, using only data from cohort studies, excluding case–control studies.

[g]Studies in tsensitivity analysis on the association between the aetiology of preterm delivery and the risk of CP, excluding studies that included cases with placental abruption.

more than 50000 patients and they were born between 1959 and 2012. In 7/11 studies,[18,21,22,24–26,29] CP was diagnosed according to clinical assessments, while four studies collected the diagnoses from either hospital, regional or national registers.[23,27,28,30] The age of the patients at the time of evaluation ranged from 1 year of corrected age to 6 years of age, but the age information was missing in one study.[27]

The two subtypes of aetiologies of preterm delivery were formed due to the diverse categories in the original studies (Table 2). Spontaneous preterm delivery included the spontaneous onset of preterm delivery, with or without PPROM and chorioamnionitis, or a delivery caused by an antenatal infection. These cases were included in the spontaneous preterm delivery group, regardless of the mode of delivery. The medically indicated preterm delivery subtype included medical inductions or Caesarean sections for indications such as IUGR, pre-eclampsia, eclampsia and pregnancy-induced hypertension. When the information was available, we excluded multiples births, cases with placental abruption and other unspecified causes of preterm delivery. Table 2 describes the classifications by subtypes, based on the definitions from the original studies and the sample sizes used for the meta-analysis.

The meta-analysis showed that preterm infants born after a medically indicated preterm delivery had a lower risk of CP than children born after a spontaneous preterm delivery: with a pooled OR 0.59 (95% CI 0.40–0.86, $tau^2 = 0.2553$) (Figure 2).

The results of the subgroup analyses (Figure 3) supported the results of the main analysis. Slightly larger pooled effect sizes were found among the studies that were restricted to the populations with a very low birth weight or very low gestation. The pooled OR for these seven studies was 0.48 (95% CI 0.32–0.71). The results were similar for the eight studies with at least 2 years of follow-up, with a pooled OR of 0.46 (95% CI, 0.31–0.66). Similar combined ORs, but with a wider 95% CI, were found in the seven studies in the subgroup that only included singleton births and the three studies in the subgroup that used data from the era of systematic active perinatal care. However, the variance of the true effect was largely reduced when the seven studies on very low birth weight and very

TABLE 2 The aetiology of preterm delivery, based on definitions from the original studies, and the sample sizes for the meta-analysis.

	Spontaneous preterm delivery		Medically indicated preterm delivery		
Authors Reference Year	Original definition (Number in subgroups)	Total *N* (N of CP cases)	Original definition (Number in subgroups)	Total *N* (N of CP cases)	Excluded from the analysis
McDonald[21] 1963	Spontaneous onset	612 (51)	Surgical induction	137 (5)	
Murphy et al.[30] 1995	Spontaneous onset	185 (49)	Caesarean section before labour	108 (10)	
Grey et al.[18] 1997	PROM (44)/Preterm labour ($n=15$)/Chorioamnionitis (12)	71 (7)	Pre-eclampsia	22 (1)	Antepartum haemorrhage ($n=26$), Other complications ($n=3$)
Dammann et al.[22] 1998	Preterm onset of labour and PROM (194)	194 (24)	Pregnancy-induced hypertension (PIH) and other	118 (5)	
Kurkinen-Räty et al.[29] 2000	Spontaneous onset or PROM <24 h ($n=94$)	94 (10)	Caesarean section for maternal or foetal indication	81 (5)	
Han et al.[26] 2002	Spontaneous onset and PROM	282 (17)	Pregnancy-induced hypertension, placenta previa, others	155 (4)	
Greenwood et al.[28] 2005	Spontaneous onset	279 (70)	Induction or elective Caesarean section	185 (38)	
Livinec et al.[24] 2005	Spontaneous preterm labour before rupture of the membranes (285)/ PPROM <24 h (61)/ PPROM >24 h (342)	688 (85)	Maternal hypertension without IUGR ($n=313$)/ All cases with IUGR ($n=114$)	427 (16)	Antepartum haemorrhage (157), Other cases of preterm delivery (56), Twins (529)
Morken et al.[27] 2007	Spontaneous onset	33466 (190)	Iatrogenic	12155 (79)	
McElrath et al.[25] 2009	Preterm labour (474)/ PPROM (231)	705 (89)	Pre-eclampsia (139)/Foetal indication (43)	182 (14)	Abruption ($n=114$), Cervical insufficiency ($n=55$)
Roberts et al.[23] 2017	PPROM (22 209)/ Spontaneous onset (16 495)	38704 (221)	Planned delivery	16052 (112)	

Abbreviations: CP, cerebral palsy; PROM, preterm rupture on membranes; PPROM, preterm premature rupture of the membranes.

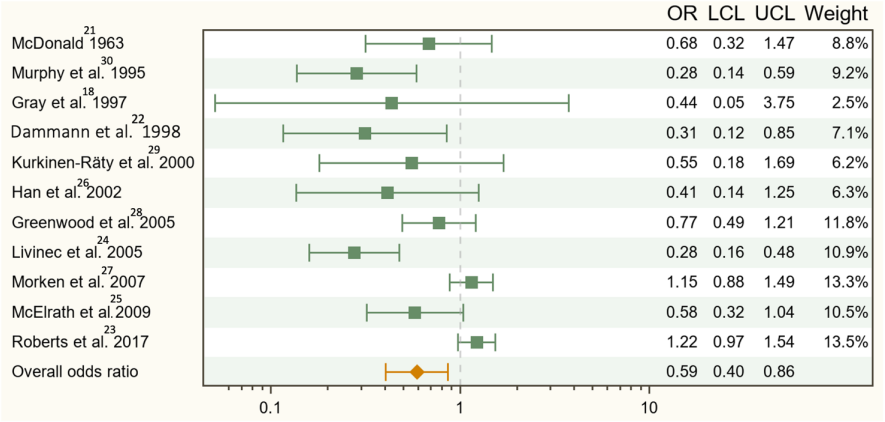

FIGURE 2 Forest plot of the risk of CP associated with medically indicated preterm delivery, compared to spontaneous preterm delivery among infants born preterm. Results from a random effects meta-analysis of 11 studies. Tau^2: 0.2553 (standard error = 0.1705), Tau: 0.5052, I^2: 79.26%. 95% prediction interval: 0.18, 1.91. LCL, lower limit of the 95% confidence interval; OR, odds ratio; UCL, upper limit of the 95% confidence interval.

low gestation age populations were combined (tau^2 = 0.1240), with a narrow 95% prediction interval of 0.30–0.78 (Figure 3).

The sensitivity analyses did not reveal any significant changes in the combined effect size (Figure 3 and Figure S2). The funnel plot revealed that the two largest studies[23,27] were situated on the right side, with an OR of >1 (Figure S2). These two large studies included infants born late preterm and at very low gestational ages. There was no evidence of outlier studies, according to the leave-one-out analysis (Table S3).

Three studies[18–20] examined any associations between the aetiology of preterm delivery and the risk of cognitive impairment (Table 3). The age at the time of the evaluations ranged from 2 to 8 years. The low number of studies and the limitations of the data that were available prevented us from performing a meta-analysis. We were only able to compare the studies to each other by using the aetiologies used in the original studies. Two of the three studies found that spontaneous preterm delivery was associated with a lower risk of cognitive impairment than other aetiologies. These studies had relatively large sample sizes, long follow-up periods and appropriate analyses, which were adjusted for confounding factors and published in 2009 and 2013.[19,20] The third study, published in 1997, reported a univariate analysis that did not find any differences in developmental delay between the groups at 2 years of age.[18]

4 | DISCUSSION

This systematic review and meta-analysis synthesised available evidence on the association of the aetiology of preterm birth with the risks of CP and suboptimal cognitive development. The meta-analysis showed that the risk of CP was lower after a medically indicated preterm delivery than a spontaneous preterm delivery. This finding was consistent in multiple subgroup and sensitivity analyses. On the other hand, a medically indicated preterm delivery seemed to be unfavourable for cognitive outcome, based on a narrative review of three papers.[18–20]

The differences in risk profiles by aetiological subtypes may be explained by different intrauterine exposures. Infants born after medically indicated preterm delivery have often been exposed to the effects of placental insufficiency, which cannot be compensated for by increased blood flow to the brain.[2] This was supported by the finding from our narrative review, which suggested a decreased risk of cognitive delay in the spontaneous preterm delivery subtype. The increased risk of CP after spontaneous preterm delivery may have been caused by the harmful effects of inflammation, which is also more common in deliveries at earlier gestations.[3] Brain injuries in very preterm infants may result from antenatal conditions or prematurity itself. It is also possible that the very preterm infants in the spontaneous preterm delivery group were less likely to have benefitted from antenatal steroids or in utero transfer to a level III hospital, because the delivery progressed so fast. There is also an inherent difference between the aetiological subtypes in the mode of delivery. Medically indicated preterm deliveries mostly happen by Caesarean section, while spontaneous preterm deliveries are more likely to be vaginal deliveries.

One factor that we were not able to take into consideration in our study was an inherent bias towards higher gestational age in indicated preterm deliveries, compared to spontaneous preterm deliveries. This was because preterm deliveries are rarely indicated due to placental insufficiency at very early gestational weeks.[11] Lower gestational age in the spontaneous preterm delivery group could, therefore, have contributed to our results, which showed a higher CP risk. Heterogeneity in classifications and reporting across studies did not permit further exploration of this topic. However, seven[22–27,30] of the 11 papers in the meta-analysis included gestational age in adjusted models. In four papers,[22,24,27,30] the association between spontaneous preterm delivery or PPROM and a higher risk for CP remained in the adjusted models. In contrast, one paper[26] reported that the association seen in the univariate analysis was not seen in the multivariate analysis. Two of the papers[23,25] only reported adjusted models and did not find any associations between preterm birth subtypes and the risk of CP, after adjusting for confounders. Future meta-analyses should aim to obtain individual-level data to permit adjustments for confounding by gestational age.

There is extensive literature regarding the neurodevelopmental outcomes of children born preterm.[31,32] Despite this, we were only able to identify 11 papers that focused on the effects of the

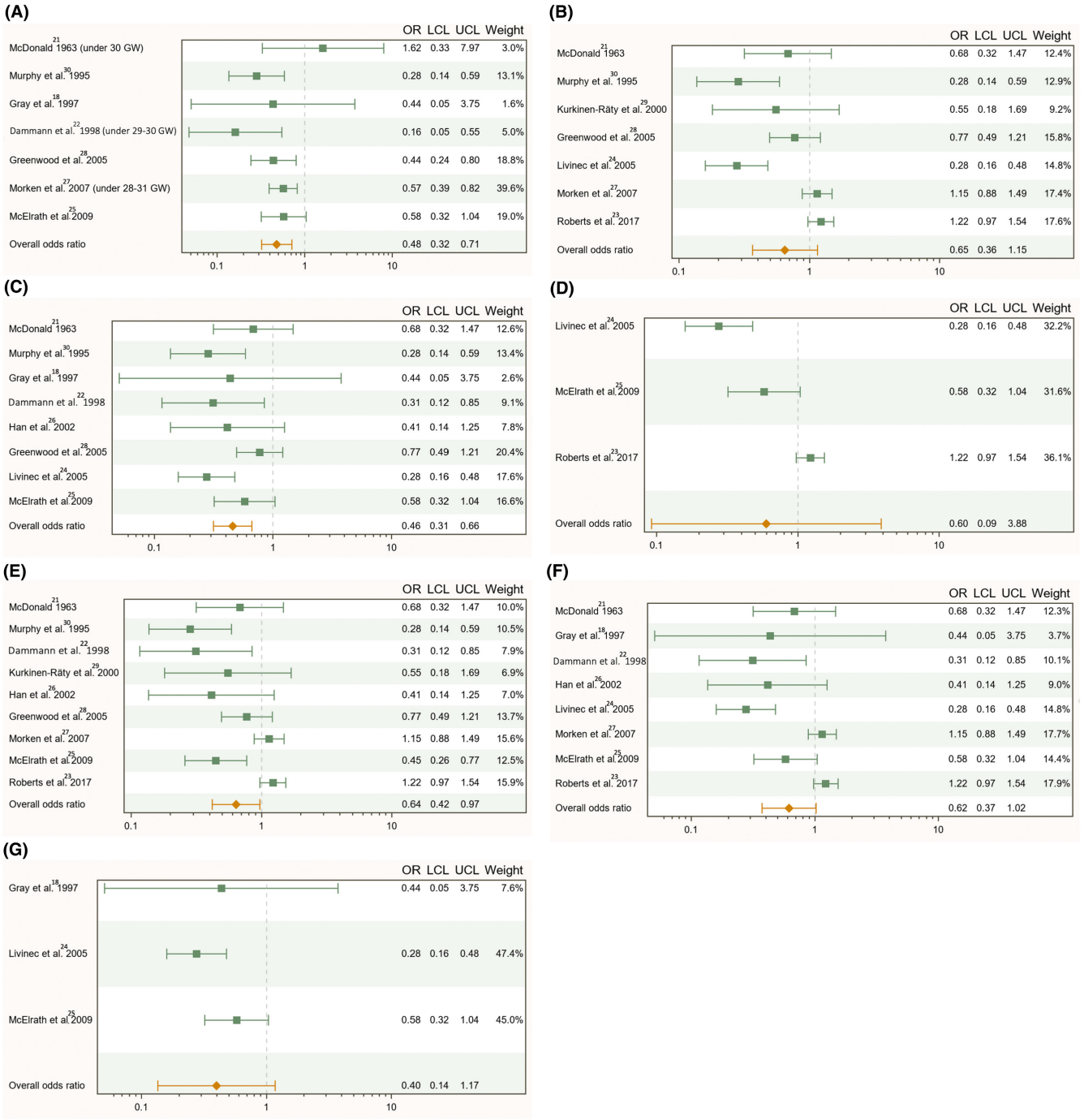

FIGURE 3 Forest plots on the following subgroup analyses: (A) Very low birth weight and/or very low gestational age children, (B) Preterm singletons, (C) After at least 2 years of follow-up, (D) Active perinatal care era (children born after the year 2000 and/or with over 70% of the mothers having received antenatal steroids). In addition, there are plots for sensitivity analyses performed (E) Using labour vs no labour to define the preterm birth subtypes, (F) Using data only from cohort studies, excluding case–control studies and (G) Excluding studies that included cases with placental abruption in their assessment of the association between aetiology of preterm delivery and the risk of CP. (A) Tau^2: 0.0154 (standard error = 0.0721), Tau: 0.1240, I^2: 10.30%. 95% prediction interval: 0.30, 0.78. LCL, lower limit of the 95% confidence interval; OR, odds ratio; UCL, upper limit of the 95% confidence interval. (B) Tau^2: 0.3238 (standard error = 0.2376), Tau: 0.5690, I^2: 87.23%. 95% prediction interval: 0.15, 2.77. LCL, lower limit of the 95% confidence interval; OR, odds ratio; UCL, upper limit of the 95% confidence interval. (C) Tau^2: 0.1130 (standard error = 0.1359), Tau: 0.3362, I^2: 45.94%. 95% prediction interval: 0.19, 1.08. LCL, lower limit of the 95% confidence interval; OR, odds ratio; UCL, upper limit of the 95% confidence interval (D) Tau^2: 0.5235 (standard error = 0.5828), Tau: 0.7235, I^2: 91.07%. 95% prediction interval: 0.04, 8.76. LCL, lower limit of the 95% confidence interval; OR, odds ratio; UCL, upper limit of the 95% confidence interval. (E) Tau^2: 0.2233 (standard error = 0.1653), Tau: 0.4726, I^2: 79.10%. 95% prediction interval: 0.23, 2.01. LCL, lower limit of the 95% confidence interval; OR, odds ratio; UCL, upper limit of the 95% confidence interval. (F) Tau^2: 0.2961 (standard error = 0.2283), Tau: 0.5442, I^2: 82.88%. 95% prediction interval: 0.16, 2.37. LCL, lower limit of the 95% confidence interval; OR, odds ratio; UCL, upper limit of the 95% confidence interval. (G) Tau^2: 0.1370 (standard error = 0.3050), Tau: 0.3701, I^2: 47.22%. 95% prediction interval: 0.10, 1.65. LCL, lower limit of the 95% confidence interval; OR, odds ratio; UCL, upper limit of the 95% confidence interval.

TABLE 3 A description of the studies that evaluated the association between the aetiology of preterm delivery and the risk of cognitive impairment.

Authors Reference Year	N	Study design	Inclusion	Aetiology of preterm delivery	Outcome	Statistical methods	Results
Grey et al.[18] 1997	91	Prospective cohort	24 to 29 GW including multiples	Antepartum haemorrhage/ Pre-eclampsia /PROM/ Preterm labour/ Chorioamnionitis/Other complications	Cognitive development at 2 years of corrected age using Griffiths or McCarthy scores	Univariate analyses only	No association between the aetiology of preterm delivery and developmental delay ($p = 0.82$)
Andrews et al.[19] 2008	261[a]	Prospective cohort	23 to 32 GW, multiples excluded	Spontaneous labour/PROM/ Indicated	Cognitive impairment at 5–8 years using WISC-IV/ DAS	Univariate and multivariate analyses for the risk of IQ < 70	Preterm delivery due to PPROM was associated with a lower risk of IQ <70 (OR 0.2, 95% CI 0.1–0.7)
Mura et al.[20] 2013	890	Prospective cohort	24 to 32 GW, multiples excluded	PPROM/Idiopathic preterm labour/Vascular context/ Other	Cognitive development at 5 years using K-ABC	Univariate and multivariate logistic regression analyses	Preterm delivery due to vascular reasons was associated with an increased risk of cognitive impairment (OR, 1.86; 95% CI, 1.16–2.97)

Note: *N* represents the number of study subjects with available information on preterm birth subtypes and cognitive development for studies 1 and 3.

Abbreviations: DAS, The Differential Ability Scales; GW, gestational weeks; K-ABC, The Kaufman Assessment Battery for Children; NOS, Newcastle–Ottawa scale; WISC-IV, Wechsler Intelligence Scale for Children-IV.

[a]The total number of study patients in study 2, as the number of those with information of cognitive outcomes was unavailable.

aetiology of preterm birth on the risk of CP and three that focused on cognitive development. This may have resulted from a lack of agreement about how to define and measure the aetiology of preterm birth. There may also be a lack of awareness about the possible impact that the aetiology of preterm birth has on child development.

There were significant variations in the classifications of the aetiology of preterm birth. To harmonise the definitions, we had to compromise on the level of data in the classifications. We ended up with two major subtypes: spontaneous preterm delivery and medically indicated preterm delivery. Placental abruption is a rare and distinct aetiology of preterm delivery and the outcomes are often worse than for other aetiologies. It did not fall under either of the two aetiological subtypes used in this study. To eliminate the possible confounding effects of abruptions, we performed a sensitivity analysis without the studies that included preterm birth after abruption. This did not change the main findings. We also performed a subgroup analysis that only included singleton pregnancies. Multiple pregnancies can include several underlying pathologies that contribute to the risk of preterm delivery and, therefore, increase heterogeneity within a preterm birth subtype. This subgroup analysis produced similar findings as the main analysis, but only seven studies could be included.

We chose to include all the relevant studies, regardless of the year of publication, resulting in patient populations born over more than a 50-year time span. The antenatal and neonatal care of preterm infants, and their outcomes, evolved significantly during this period. One major change was the introduction of antenatal corticosteroids. In addition to improving outcomes in very preterm infants,[33] this may have also modified the effects of any inflammation associated with preterm delivery.[34,35] To account for the effect of these advances in perinatal care, we conducted a subgroup analysis that included studies with adequate antenatal corticosteroid coverage and/or a population born after the year 2000. The pooled estimate of the effect was an OR of 0.60 (95% CI 0.09–3.88) in the three studies included in this subgroup analysis,[23–25] which was almost identical to the estimate of the full analysis (pooled OR 0.59, 95% CI 0.40–0.86).

5 | LIMITATIONS

Our review and meta-analysis had a number of limitations, including the heterogenous nature of the studies. This can be explained by the characteristics of the study population, especially the wide gestational age range. The heterogeneity was reduced in the subgroup analysis that only focused on very preterm or very low birth weight infants. There was also a risk of publication bias, as studies without significant results may not have been published.

The number of studies on cognitive development was not sufficient for a meta-analysis. Based on our narrative review of the three papers that were available,[18–20] poor cognitive outcomes seemed more prevalent after indicated preterm deliveries. Further support

for these results was provided by two papers that were not included in this review, as they used different outcome measures.[23,36] Preterm delivery after PPROM was associated with a decreased risk for special needs at a kindergarten[23] and indicated delivery increased the risk for poor psychomotor development in preterm children.[36]

The main limitation of these analyses was the inability to include confounding factors in the meta-analyses, most importantly gestational age. Another potential limitation was the wide gestational age range. To account for this, we performed a subgroup analysis that only included very low birth weight or very low gestational age infants. The association between spontaneous preterm delivery and an increased risk of CP was stronger in this analysis, with less heterogeneity than in the main analysis.

6 | CONCLUSION

Our review and meta-analysis suggest that the aetiologies of preterm birth were associated with distinct developmental risk profiles in children born preterm. The risk of CP was increased among infants born after spontaneous preterm deliveries, especially those born very preterm. Medically indicated preterm delivery, on the other hand, may have been associated with an increased risk of cognitive delay, although the number of studies that investigated cognitive delay was very limited. This difference could be explained by the different foetal growth environment related to each aetiological subgroup of preterm births. However, we were limited in our ability to control for the role of gestational age, which is an important area for further study. More detailed information about the aetiology of preterm delivery should be included in the core outcome sets for research on the consequences of very preterm delivery. This would increase our understanding of this area.

AUTHOR CONTRIBUTIONS

Milla Ylijoki: Methodology; Writing – original draft; Writing - review and editing. **Mariane Sentenac:** Methodology; writing – original draft; writing – review and editing. **Bernd Pape:** Formal analysis; writing – original draft; writing – review and editing. **Jennifer Zeitlin:** Methodology; supervision; writing – original draft; writing – review and editing. **Liisa Lehtonen:** Methodology; supervision; writing – original draft; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

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SUPPORTING INFORMATION

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APPENDIX A

Newcastle–Ottawa scale assessment of included cohort and case–control studies.

	Selection				Comparability	Outcome			
Cohort study	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	Total
McDonald 1963	*		*	*	*	*	*	*	*******
Grey et al. 1997	*	*	*	*		*	*	*	*******
Dammann et al. 1998	*		*		**	*	*	*	*******
Han et al. 2002	*	*	*	*	*	*	*	*	********
Livinec et al. 2005	*	*	*	*	**	*	*	*	*********
Morken et al. 2007	*	*	*	*	*	*		*	*******
Andrews et al. 2008	*	*	*	*	**	*	*	*	*********
McElrath et al. 2009	*	*	*	*	**	*	*	*	*********
Mura et al. 2013	*	*	*	*	**	*	*	*	*********
Roberts et al. 2017	*		*	*	**	*		*	********

	Selection				Comparability	Outcome			
Case–control study	Is the case definition adequate?	Representativeness of the cases	Selection of controls	Definition of controls	Comparability of cases and controls on the basis of the design or analysis	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-response rate	Total
Murphy et al. 1995	*	*	*	*	*	*	*	*	********
Kurkinen-Räty et al. 2000		*		*	*	*	*		*****
Greenwood et al. 2005	*	*	*	*		*	*	*	*******

Note: * represents one score.