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Association of placental and umbilical cord characteristics with cerebral palsy: national cohort study

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KEYWORDS: knot; marginal cord insertion; placental abruption; placenta previa; retained placenta; single umbilical artery; umbilical cord entanglement; velamentous cord insertion

CONTRIBUTION

What are the novel findings of this work?
We found that abnormal cord (velamentous insertion, cord knot) and placenta (retained placenta, placental abruption and previa) are associated with an increased risk of cerebral palsy (CP) for the child. Single umbilical artery and cord knot were associated with CP among females while retained placenta was associated with CP among males.

What are the clinical implications of this work?
Placental and cord pathologies seem to account for a small proportion of CP cases, but may be markers of children at increased risk of developing CP.

ABSTRACT

Objectives *Cerebral palsy (CP) is a group of movement disorders usually diagnosed in childhood. A substantial proportion are thought to be caused by antenatal events. Abnormalities of the umbilical cord and placenta are associated with an increased risk of adverse neonatal outcomes, but it is unclear whether these conditions also carry an increased risk of CP. We aimed to determine whether abnormalities of the umbilical cord or placenta are associated with CP and assess if these associations differ by sex of the child or gestational age at birth.*

Methods *We performed a national cohort study by linking data from The Medical Birth Registry of Norway with other national registries. All liveborn singletons born between 1999 and 2017 (*n = *1 087 486) were included and followed up until the end of 2019. Diagnoses of CP were provided by the Norwegian National Insurance Scheme and the Norwegian Patient Register. We used generalized estimating equations and multilevel log binomial regression to calculate relative risks (RR), adjusted for year of birth, and stratified analyses were carried out based on sex and gestational age at birth. Exposures were abnormal umbilical cord (velamentous or marginal insertion, single umbilical artery (SUA), knots and entanglement), and placental abnormalities (retained placenta, placental abruption and previa).*

Results *A total of 2443 cases with CP (59.8% males) were identified. Velamentous cord insertion (adjusted RR (aRR), 2.11 (95% CI, 1.65–2.60)), cord knots (aRR, 1.53 (95% CI, 1.15–2.04)) and placental abnormalities (placenta previa (aRR, 3.03 (95% CI, 2.00–4.61)), placental abruption (aRR, 10.63 (95% CI, 8.57–13.18)) and retained placenta (aRR, 1.71 (95% CI, 1.32–2.22))) carried an increased risk of CP. Velamentous cord insertion was associated with CP regardless of gestational age or sex. A retained placenta was associated with a 2-fold increased risk for CP in males, while the associations of SUA and cord knot with CP were significant only among females.*

Conclusions *The detection of placental and umbilical cord abnormalities may help identify children at increased risk of CP. The associations between placental or umbilical cord abnormalities and the risk of CP do not vary substantially with gestational age at birth or sex of the child.* © *2023 The Authors. Ultrasound in Obstetrics & Gynecology published by John Wiley & Sons Ltd on behalf of International Society of Ultrasound in Obstetrics and Gynecology.*

INTRODUCTION

Cerebral palsy (CP) is a heterogeneous group of non-progressive conditions, mainly affecting movement[1].

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A diversity of largely unknown pathways may contribute to disturbances in brain development, resulting in CP, and a substantial proportion is believed to be caused by antenatal or neonatal adverse events[2,3]. More males than females are diagnosed with CP, and the risk of CP is strongly associated with gestational age at birth[4,5].

Abnormal development of the placenta and umbilical cord is associated with an increased risk of adverse outcome for the fetus[6–9]. Malperfusion of the fetal side of the placenta is associated with neonatal encephalopathy, which is a strong predictor of death and CP[10]. Pregnancies in which the umbilical cord inserts into the amniotic membranes or at the edge of the placenta (velamentous or marginal insertion) and those in which a two-vessel cord (single umbilical artery (SUA)) develops are at increased risk of adverse neonatal outcome[11–13]. In these placentas, signs of fetal malperfusion may be noticed[12]. In addition, cord knots and entanglements are associated with adverse neonatal outcome[14–16]. Disorders involving defective placentation are associated with an increased risk of incomplete detachment of the placenta after birth[17], but whether a retained placenta is associated with CP in the child has not been studied.

Sex differences exist in birth weight, placental weight and incidence of cord complications[8,18], and long-term consequences for health related to placental size and birth weight have sex-specific patterns[19–21]. Whether placental and cord abnormalities show different effects according to sex on the development of CP is unknown.

A systematic review of risk factors for CP in term-born children emphasized placental abnormalities as an important area for further research[2]. Thus, the objectives of this study were to assess whether: (1) abnormalities of the umbilical cord or placenta (abnormal cord insertion, cord knots and entanglement, SUA, placental abruption, placenta previa and retained placenta) are associated with CP in singletons; (2) risks differ between males and females; and (3) these associations vary by gestational age at birth. We also aimed to calculate the proportion of CP cases attributable to placental and cord abnormalities.

METHODS

This was a national cohort study including all singleton live births in Norway that occurred between 1999 and 2017 with a gestational age > 21 weeks and < 45 weeks (or birth weight of 500 g or more if gestational age information was missing), recorded by the Medical Birth Registry of Norway (MBRN). The study was approved by the Norwegian Regional Committee for Medical and Health Research Ethics (REK 2018/1789) and the registry owners. The Strengthening the Reporting of Observational Studies in Epidemiology guidelines were followed[22].

Gestational age was based on ultrasound (97%) or last menstrual period if information based on ultrasound was missing. The cohort was followed until 2019 by linkage to other national databases. Information on CP was obtained from the National Insurance Scheme (NIS) and the Norwegian Patient Registry (NPR). A patient was classified as having CP if this diagnosis (ICD-9: 343 or ICD-10: G80) was recorded at least once by the NIS and/or at least twice by the NPR. Statistics Norway provided information on maternal and paternal immigrant status and level of education. The unique personal Norwegian identification number allowed linkage of individual data from the MBRN with these compulsory registries. All registries were updated throughout 2019. Since the MBRN changed the way it recorded placental and umbilical cord conditions in 1998, birth years from 1999 onwards were included to obtain uniform recordings and, since the diagnosis of CP cannot be made at birth, only birth years until 2017 were included, allowing follow-up ranging from 2 to 21 years.

All data in the MBRN are registered prospectively, and registration with the MBRN is mandatory. The attending midwife or physician performed the examination of the placenta, amniotic membranes, umbilical cord and the neonate and entered the requested information into the registration form shortly after delivery. Information regarding the umbilical cord was labeled as follows: normal, marginal, velamentous, cord-vessel anomaly, entanglement or cord knot. SUA was registered as a cord-vessel anomaly (this variable contains SUA almost exclusively, but other rare vessel anomalies may also be registered[23–25]). All registrations regarding the classification of the umbilical cord and placenta were based on examination of the afterbirth. The attending obstetrician provided the diagnosis of placental abruption, placenta previa and retained placenta (i.e. the need for manual removal of the placenta). Parity was defined as the number of previous deliveries. Pregnancies conceived by assisted reproductive technology were recorded in the registry on a voluntary basis from 1988, and reporting became compulsory in 2001. All neonates were examined by a physician, who recorded the presence of any congenital malformation.

Main exposure variables

Information on the site of cord insertion (velamentous or marginal), SUA and isolated SUA (iSUA, defined as SUA with no other malformations), umbilical cord knot and cord entanglement was provided by the MBRN[26]. An abnormal placenta was defined as placenta previa, placental abruption and retained placenta (abnormal placental detachment after birth with the need of removal).

Outcome measure

Individuals with CP were identified through the NIS[27] and the NPR[28]. In Norway, all residents have compulsory insurance through the NIS[27]. Benefits are granted to individuals with disabilities, involving extra expenses and an attendance benefit if the disabled individual needs special attendance or nursing. The benefits are granted independently of wealth or income, and the causative medical conditions are recorded. In adulthood, the NIS may provide direct pension payments (disability benefit and work assessment allowance). All cases in the cohort had the diagnosis of CP (ICD-9: 343 or ICD-10: G80) as

the medical reason for the benefits granted. Furthermore, we also received information on CP diagnoses from the NPR. This registry holds individual data on visits to specialist care in Norway[28]. In our study, a person was registered with CP if they received benefits or a disability pension based on a CP diagnosis in the NIS or was registered with a CP diagnosis at least twice in the NPR.

Covariates

The following variables were included in the model based on their potential influence on the risk estimates: year of birth, parity, maternal and paternal age, cigarette smoking at the beginning of pregnancy, maternal medical conditions (yes/no), conception by assisted reproductive technology, gestational age, empirical parity- and sex-specific birth-weight percentile based on the study population. Of socioeconomic factors, marital status of the mother, maternal and paternal level of education (five categories) and immigrant status (yes/no) were included. A child was defined as having immigrant parents if both parents had been born abroad. Statistics Norway provided information on the level of education and immigrant status of parents, while the MBRN provided information on the other covariates. Missing data were coded as 0.

Statistical analysis

We used generalized estimating equations analyses and estimated the relative risk (RR) and 95% CI for CP according to exposure (umbilical cord and placental conditions), adjusting for year of birth. Possible confounding variables were included in multilevel log binomial regression using generalized estimating equations, taking the hierarchical data structure into account (births within mothers). Since congenital malformations are associated with both CP and abnormal umbilical cord[29], we repeated the analyses after excluding all children with malformations. Furthermore, we analyzed the population stratified by gestational age at birth (preterm (< 37 weeks), term (37–41 weeks) and post term (≥ 42 weeks)) and by sex of the child.

We used sensitivity analysis to assess the impact of unmeasured confounding on the associations between each exposure and CP using a Bayesian simulation analysis. Additional information is given in Appendix S1 and Table S1.

Population attributable fractions (PAFs) were calculated as: PAF = 100 × (incidence rate in total population – incidence rate in unexposed)/incidence rate in total population, and 95% CIs were calculated for the exposures (placental and cord abnormalities).

Statistical Package for the Social Sciences for Windows version 24 (SPSS, Chicago, IL, USA) and Stata version 17.0 (StataCorp., College Station, TX, USA) were used for statistical analysis.

RESULTS

In the total study population of 1 087 486 singletons, we identified 2443 cases of CP (59.8% males). The occurrence of CP was 2.25 per 1000 live births, with a slight decline in occurrence over time (Table S2). Characteristics of the study population are shown in Table 1.

Velamentous cord insertion was associated with a 2-fold increased risk of CP, while marginal cord insertion was not (Tables 2 and 3). Stratifying births by gestational-age group or sex confirmed an association of velamentous cord with CP in all strata (Table 3). There was no congenital malformation in 82% of cases. Neither SUA nor iSUA appeared to be associated with an increased risk for CP in the overall population (Table 2) or when stratified according to gestational age at birth (Table 3). However, SUA was associated with an increased risk for CP in females (Table 3). Cord knot was associated with CP in the overall group (Table 2). On stratified analysis, this association was significant only among females and preterm cases (Table 3). For SUA, iSUA and cord knot, the RRs for CP in the post-term group were high, but with wide CIs (adjusted RR (aRR), 3.48 (95% CI, 0.86–13.97), 3.80 (95% CI, 0.95–15.27) and 2.54 (95% CI, 0.94–6.85), respectively). Unexpectedly, cord entanglement appeared to be associated with a lower risk of CP in the total population (Table 2). However, by including an unknown confounding factor in the Bayesian sensitivity analysis, this association became marginal (posterior odds ratio, 0.92 (95% CI, 0.86–0.99)).

Placenta previa tripled the risk of CP in the total and sex-stratified analyses (Tables 2 and 3), whereas no such association was found in analyses stratified by gestational age at birth (there were no cases with placenta previa born post-term) (Table 3). Placental abruption was strongly associated with CP, both overall and in gestational-age and sex-specific strata (except for the post-term group, where the CI included 1). Retained placenta was associated with an approximately 70% increased risk of CP (Table 2). This association was attenuated on gestational-age-stratified analyses and remained significant only among males (aRR, 1.90 (95% CI, 1.38–2.60)) when stratified by neonatal sex (Table 3).

The inclusion of parity, maternal age, socioeconomic factors and maternal medical conditions into the models in addition to year of birth (Table 2) or exclusion of cases with malformations (Table S3) did not change the results. After including the assumption of an unknown confounder of all of the exposures in the regression analyses, the associations between the exposures and CP persisted (Table S1).

The population risk of CP attributable to a velamentous cord insertion, cord knot, retained placenta, placenta previa and placental abruption was 1.7%, 0.7%, 1.0%, 0.6% and 3.1%, respectively. By combining the cord and placental abnormalities in this study, these accounted for fewer than 10% of CP cases.

DISCUSSION

In this national cohort study, we found associations between placental and cord abnormalities and a subsequent diagnosis of CP. The finding that velamentous

Table 1 Characteristics of study population of singleton births in Norway between 1999 and 2017, overall and according to presence of cerebral palsy (CP)

Characteristic	*No CP (n = 1 085 043)*	*CP (n = 2443)*	*Total (n = 1 087 486)*
Maternal age			
< 20 years	4126 (0.38)	20 (0.82)	4146 (0.38)
20–24 years	17 887 (1.65)	67 (2.74)	17 954 (1.65)
25–29 years	154 066 (14.20)	338 (13.84)	154 404 (14.20)
30–34 years	353 319 (32.56)	752 (30.78)	354 071 (32.56)
35–39 years	360 842 (33.26)	764 (31.27)	361 606 (33.25)
40–44 years	163 895 (15.10)	410 (16.78)	164 305 (15.11)
45–49 years	29 559 (2.72)	88 (3.60)	29 647 (2.73)
≥ 50 years	1347 (0.12)	4 (0.16)	1351 (0.12)
Missing data	2 (0.00)	0 (0.00)	2 (0.00)
Parity			
0	452 224 (41.68)	1129 (46.21)	453 353 (41.69)
1	390 795 (36.02)	778 (31.85)	391 573 (36.01)
2	171 335 (15.79)	343 (14.04)	171 678 (15.79)
3	47 778 (4.40)	121 (4.95)	47 899 (4.40)
4	22 911 (2.11)	72 (2.95)	22 983 (2.11)
Maternal BMI at beginning of pregnancy*			
< 18.5 kg/m^2	14 701 (4.16)	17 (3.12)	14 718 (4.16)
18.5 to < 25 kg/m^2	218 215 (61.71)	301 (55.23)	218 516 (61.70)
25 to < 30 kg/m^2	78 169 (22.11)	138 (25.32)	78 307 (22.11)
≥ 30 kg/m^2	42 505 (12.02)	89 (16.33)	42 594 (12.03)
Maternal smoking at beginning of pregnancy			
No	795 938 (73.36)	1654 (67.70)	797 592 (73.34)
Sometimes	16 004 (1.47)	46 (1.88)	16 050 (1.48)
Daily	112 109 (10.33)	341 (13.96)	112 450 (10.34)
Not registered	160 992 (14.84)	402 (16.46)	161 394 (14.84)
Maternal marital status			
Not single at birth	1 002 173 (92.36)	2203 (90.18)	1 004 376 (92.36)
Single at birth	82 861 (7.64)	240 (9.82)	83 101 (7.64)
Missing data	9 (0.00)	0 (0.00)	9 (0.00)
Maternal education			
< 8 years	11 047 (1.02)	20 (0.82)	11 067 (1.02)
8–10 years	156 381 (14.41)	458 (18.75)	156 839 (14.42)
11–12 years	22 328 (2.06)	71 (2.91)	22 399 (2.06)
13–17 years	711 334 (65.56)	1598 (65.41)	712 932 (65.56)
≥ 18 years	155 302 (14.31)	258 (10.56)	155 560 (14.30)
Missing data	28 651 (2.64)	38 (1.56)	28 689 (2.64)
Paternal education			
< 8 years	9360 (0.86)	17 (0.70)	9377 (0.86)
8–10 years	171 327 (15.79)	485 (19.85)	171 812 (15.80)
11–12 years	34 971 (3.22)	105 (4.30)	35 076 (3.23)
13–17 years	675 716 (62.28)	1473 (60.29)	677 189 (62.27)
≥ 18 years	151 414 (13.95)	291 (11.91)	151 705 (13.95)
Missing data	42 255 (3.89)	72 (2.95)	42 327 (3.89)
Immigrant			
No	933 362 (86.02)	2146 (87.84)	935 508 (86.02)
Yes	150 871 (13.90)	297 (12.16)	151 168 (13.90)
Missing data	810 (0.07)	0 (0.00)	810 (0.07)
Assisted reproductive technology	25 946 (2.39)	75 (3.07)	26 021 (2.39)
Maternal chronic medical condition	97 947 (9.03)	284 (11.63)	98 231 (9.03)
Neonatal sex			
Male	557 184 (51.35)	1462 (59.84)	558 646 (51.37)
Female	527 731 (48.64)	981 (40.16)	528 712 (48.62)
Not registered	128 (0.01)	0 (0.00)	128 (0.01)
Congenital malformation	45 833 (4.22)	443 (18.13)	46 276 (4.26)
Gestational age at birth			
< 37 weeks	54 637 (5.04)	724 (29.64)	55 361 (5.09)
37–41 weeks	957 627 (88.26)	1557 (63.73)	959 184 (88.20)
≥ 42 weeks	66 784 (6.15)	138 (5.65)	66 922 (6.15)
Missing data	5995 (0.55)	24 (0.98)	6019 (0.55)
Velamentous cord insertion	16 457 (1.52)	77 (3.15)	16 534 (1.52)
Marginal cord insertion	59 607 (5.49)	156 (6.39)	59 763 (5.50)
Umbilical cord knot	13 729 (1.27)	47 (1.92)	13 776 (1.27)
Umbilical cord entanglement	233 535 (21.52)	469 (19.20)	234 004 (21.52)
SUA	4627 (0.43)	16 (0.65)	4643 (0.43)
iSUA	4122 (0.38)	10 (0.41)	4132 (0.38)
Placenta previa	3228 (0.30)	22 (0.90)	3250 (0.30)
Placental abruption	3547 (0.33)	84 (3.44)	3631 (0.33)
Retained placenta	14 916 (1.37)	57 (2.33)	14 973 (1.38)

Data are given as *n* (%). Missing data were coded 0 in analysis. *Percentages for body mass index (BMI) are calculated on a lower denominator because this variable was not recorded from the start of the study and data were missing in almost 70% cases. iSUA, isolated single umbilical artery; SUA, single umbilical artery.

Table 2 Adjusted relative risk (aRR) for cerebral palsy (CP) according to umbilical cord and placental characteristics

Characteristic	*Total* (n)	*CP* (n)	*CP per 1000 cases* (n)	*aRR (95% CI)**	*aRR (95% CI)†*
Velamentous cord insertion	16 534	77	4.7	2.11 (1.65–2.60)	2.06 (1.64–2.58)
Marginal cord insertion	59 763	156	2.6	1.10 (0.94–1.30)	1.11 (0.95–1.31)
SUA	4643	16	3.4	1.54 (0.94–2.51)	1.52 (0.93–2.49)
iSUA	4132	10	2.4	1.08 (0.58–2.00)	1.07 (0.58–1.99)
Umbilical cord knot	13 776	47	3.4	1.53 (1.15–2.04)	1.54 (1.16–2.06)
Umbilical cord entanglement	234 004	469	2.0	0.87 (0.78–0.97)	0.87 (0.79–0.97)
Placenta previa	3250	22	6.8	3.03 (2.00–4.61)	2.98 (1.96–4.53)
Placental abruption	3631	84	23.1	10.63 (8.57–13.18)	10.25 (8.43–12.97)
Retained placenta	14 973	57	3.8	1.71 (1.32–2.22)	1.69 (1.30–2.20)

Reference group comprised cases without any characteristic. *Adjusted for year of birth. †Adjusted for year of birth, maternal age and parity. Other factors did not significantly alter the association between the exposures and outcomes and were not included in the final models. iSUA, isolated single umbilical artery; SUA, single umbilical artery.

Table 3 Adjusted relative risk (95% CI) for cerebral palsy (CP) according to umbilical cord and placental characteristics, stratified by gestational age (GA) at birth and neonatal sex

	GA at birth			*Neonatal sex*	
Characteristic	*Preterm (n = 55 361)**	*Term (n = 959 184)†*	*Post-term (n = 66 922)‡*	*Male (n = 558 646)*	*Female (n = 528 712)*
Velamentous cord insertion	1.56 (1.11–2.22)	1.63 (1.17–2.27)	2.53 (1.04–6.18)	2.17 (1.61–2.91)	1.98 (1.39–2.81)
Marginal cord insertion	1.04 (0.80–1.36)	1.08 (0.88–1.34)	1.03 (0.50–2.09)	1.07 (0.87–1.32)	1.14 (0.89–1.47)
SUA	1.24 (0.59–2.60)	1.11 (0.53–2.32)	3.48 (0.86–13.97)	1.07 (0.51–2.25)	2.02 (1.05–3.89)
iSUA	1.05 (0.39–2.78)	0.69 (0.26–1.84)	3.80 (0.95–15.27)	0.51 (0.17–1.60)	1.74 (0.83–3.67)
Umbilical cord knot	1.73 (1.07–2.78)	1.32 (0.90–1.95)	2.54 (0.94–6.85)	1.31 (0.92–1.89)	1.69 (1.05–2.73)
Umbilical cord entanglement	0.75 (0.60–0.93)	1.01 (0.89–1.15)	1.02 (0.69–1.51)	0.80 (0.70–0.92)	0.83 (0.70–0.99)
Placenta previa	1.24 (0.81–1.90)	0.33 (0.05–2.32)	—§	3.37 (2.03–5.60)	2.54 (1.21–5.34)
Placental abruption	2.80 (2.16–3.64)	8.10 (5.38–12.19)	3.93 (0.55–27.89)	10.58 (8.14–13.77)	9.21 (6.35–13.38)
Retained placenta	1.39 (0.93–2.06)	1.37 (0.94–2.01)	1.50 (0.55–4.04)	1.90 (1.38–2.60)	1.16 (0.73–1.84)

Reference group comprised cases without any characteristic. Analysis was adjusted for year of birth. *< 37 weeks. †37–41 weeks. ‡≥ 42 weeks. §No case with placenta previa was born post-term. iSUA, isolated single umbilical artery; SUA, single umbilical artery.

cord insertion increased the risk of CP in the child persisted after stratifications and adjustments. Stratification by gestational age at birth mostly attenuated the associations. Sex-specific analyses suggested that SUA and cord knot were associated with CP in females, while retained placenta carried an increased risk of CP in males. In our population, placental and umbilical cord abnormalities accounted for fewer than 10% of CP cases.

Prenatal examination of the placenta and umbilical cord using ultrasound is recommended in clinical guidelines[30,31]. However, little is known about the precision and usefulness of the prenatal diagnosis of umbilical cord knots[32,33]. After birth, when classification of the cord and placenta is performed, insights from our study may be useful in order to identify children at risk; the findings support the idea that placental and cord abnormalities contribute to the later development of CP.

Our findings are in line with those of previous studies investigating the associations of cord and placental complications with newborn encephalopathy or CP[4,10,29]. We found that velamentous cord insertion and cord knots, which are both susceptible to vascular stasis, showed associations with CP (Tables 2 and 3). The conditions studied here may increase vulnerability to the development of CP through different mechanisms, and it is plausible that combinations of factors may underlie the development of CP. A velamentous cord indicates an abnormal fetal vascular tree in the placenta, possibly resulting in impaired placental function[34], and increases vulnerability to fetal thrombotic vasculopathy[35]. Fetal vascular malperfusion has been thought to develop during the last weeks of pregnancy and has been observed in placentas with cord abnormalities[36,37]. The higher risk observed for velamentous cord insertion in the post-term group (Table 3) is plausible, considering the physiological changes in the fetoplacental circulation that occur in late pregnancy[38], also supported by experimental work[39]. Our findings are in line with those of a multicenter study and a recent single-center study that found no association between nuchal cord entanglement and later CP[40,41].

Most studies on the association of placental and cord abnormalities with CP or neonatal encephalopathy have been case–control ones, retrospective studies or institution series[13,41,42], although a few population studies exist[4,43]. Our findings are in accordance with those of a study that found an increased risk of CP in pregnancies with placenta previa and placental abruption[4], and with studies showing an association between defective placentation and adverse outcomes[17,44,45]. To our knowledge, no other studies have investigated the association between retained placenta and CP. Our findings support a study

suggesting that iSUA did not carry any risk of long-term neurodevelopmental consequences[46].

The occurrence of CP in our study population declined over time (Table S2). It usually takes some years before a diagnosis of CP is established, and this may in part explain the lower prevalence in the youngest age groups. However, a decreasing prevalence of CP has also been demonstrated in another Norwegian study[47], in which the authors suggest that this may be explained partially by the general improvement in perinatal health in Norway. However, misclassification of milder cases in the youngest children may attenuate the associations.

Umbilical cord compression (in cases with velamentous cord and cord knots) may reduce umbilical blood flow[48], resulting in repeat drops in the fetal heart rate (variable decelerations) during labor[49]. Fetal responses to challenges differ with gestational age[50], and studies of fetal sheep show that compression of the umbilical cord alters the distribution of umbilical and systemic blood flow[51]. Signs of increased apoptosis and frontal cortical gray matter damage have been observed in near-term lamb fetuses exposed to prolonged moderate and intermittent severe hypoxemia[39]. This suggests that cord occlusion near term may potentially cause long-term neurological sequelae, such as CP. We found no strong sex differences in the vulnerability of the fetus to abnormal cord or placenta. This may be unexpected, as male fetuses have higher energy requirements than do females and should, in theory, be more vulnerable to hypoxia[52]. Furthermore, experimental evidence suggests sex-differential mechanisms of protection against perinatal hypoxic–ischemic brain injury[53].

The strengths of this study are the national population design, no loss of follow-up and large sample size. The use of compulsory national registries based on prospective data collection eliminated selection and recall bias, an approach that has been utilized in several studies[54,55]. Validation of the CP diagnosis in the NIS and the NPR revealed high specificity and sensitivity, respectively; thus, a combination of these sources as in the present study should provide reliable identification of cases of CP[56,57]. It is a limitation of our study that not all the variables in the MBRN have been validated. However, many of the variables presented (including placenta and cord characteristics) have been validated[58–61]. Another limitation was the inability to identify cases of CP of postnatal origin, although the proportion of such cases is probably low[5]. Furthermore, we lack information on CP subtypes, which may have different etiologies[5]. There is a possibility of misclassification of milder cases in the youngest in the cohort; however, this misclassification would bias the results towards null.

It is reassuring that after including covariates in the regression models and unknown confounding in our sensitivity analyses, the associations between the exposures and CP persisted, suggesting that the observed associations are robust to confounding.

It is possible that abnormal placentation and umbilical cord and disturbed development of the fetal brain resulting in CP share determinants, or that placental and cord abnormalities are mediators in the causal pathway leading to CP. Our findings suggest that the diagnosis of an umbilical cord or placental abnormality may help identify children at increased risk for CP, although these cases may amount to fewer than 10% of all CP cases. Further studies of placental and cord abnormalities are needed to assess whether CP subtypes may have different associations with umbilical cord or placental complications.

In conclusion, this study shows that placental and cord complications may help to identify children at increased risk of developing CP. The associations between placental or umbilical cord abnormalities and the risk of CP do not vary substantially with gestational age at birth or sex of the child.

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Appendix S1 Further information regarding statistical analysis

Table S1 Sensitivity analysis. Prior- and posterior distributions for exposure coefficients (β) on the outcome (cerebral palsy)

Table S2 Occurrence of cerebral palsy (CP) in study population according to year of birth

Table S3 Relative risk for cerebral palsy (CP) according to umbilical cord and placental characteristic in study population after excluding those with malformations ($n = 2000$)