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an evaluation of causality

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AIM To explore whether increasing parental education has a causal effect on risk of cerebral palsy (CP) in the child, or whether unobserved confounding is a more likely explanation.
METHOD We used data from Norwegian registries on approximately 1.5 million children born between 1967 and 2011. We compared results from a traditional cohort design with results from a family-based matched case–control design, in which children with CP were matched to their first cousins without CP. In addition, we performed a simulation study to assess the role of unobserved confounding.
RESULTS In the cohort design, the odds of CP were reduced in children of mothers and fathers with higher education (adjusted odds ratio [OR] 0.67, 95% confidence interval [CI] 0.60–0.75 for maternal education, and adjusted OR 0.75, 95% CI 0.67–0.85 for paternal education). In the family-based case–control design, only an association for maternal education remained (adjusted OR 0.80, 95% CI 0.64–0.99). Results from a simulation study suggested that this association could be explained by unobserved confounding.
INTERPRETATION A causal effect of obtaining higher education on risk of CP in the child is unlikely. Results stress the importance of continued research on the role of genetic and environmental risk factors that vary by parents' educational level.

Cerebral palsy (CP) is an umbrella term for a group of conditions characterized by motor impairments with a prevalence of about 2 per 1000 live births.[1] The prevalence of CP has decreased in Europe in recent years, most probably because of better obstetric and neonatal care.[1,2] Still, for most children with CP, the brain damage leading to the disorder cannot be predicted or prevented.[3]

The risk of CP in the child decreases with increasing parental education, but the underlying causal pathways are unknown.[4,5] Norway has low income inequality and offers all pregnant women antenatal care free of charge. Yet, important educational differences in health behaviours and in risk of pregnancy and delivery complications are consistently documented.[6] Increasing parental education may have a causal effect on CP risk through various modifiable factors. For instance, higher education could make the pregnant woman or her partner more informed and better equipped to follow health advice, which could possibly reduce the risk of CP.[7] However, the association could also be due to common causes; that is, environmental and/or genetic factors that affect both parental educational level and the risk of CP. For example, parents who themselves grew up in a family with low socio-economic status are less likely to have attained a higher education, more likely to smoke, be overweight, and have a poor diet as adults,[8] which in turn could affect risk of CP in their offspring.[9] Similarly, a parent with a chronic health condition or a (subclinical) neurodevelopmental disorder has a lower probability of obtaining a higher education,[10,11] and on average has an increased risk of having a child with CP.[12,13]

Traditional cohort studies do not account for unobserved potential confounding factors shared by family members. By using a family-based matched case–control design, environmental, genetic, and social factors shared by first cousins that affect both their own risk of CP and their parents' educational level ('shared confounding') are controlled for.[14] Therefore, if the association between parental education and risk of CP in children is no longer present when using a family-based matched case–control analysis, shared confounding could probably explain the associations found in previous studies. If the association remains, however, increasing parental education may either have a causal effect on risk of CP in the child or unobserved

confounding factors not shared by first cousins may exist ('non-shared confounding').[15]

We explored whether increasing parental education could directly reduce the risk of CP in the child, or whether shared or non-shared confounding are more likely explanations of the observed association. Our approach was to compare overall associations from a cohort design with associations from a family-based matched case–control design. In addition, we performed a simulation study to assess the role of non-shared confounding in the case–control design.

METHOD
Study cohorts
We used data on 2 643 315 live- or stillborn children registered in the Norwegian Medical Birth Registry[16] from 1967 to 2011. Excluding stillborn children who died in the first year of life and all multiple births resulted in a cohort of 2 530 799 singletons (Fig. S1, online supporting information). Since we were interested in the role of shared and non-shared confounding within families, we created two partly overlapping subcohorts: one consisting of children whose mothers were full sisters (the children are maternal first cousins) and one of children whose fathers were full brothers (the children are paternal first cousins), by use of family structure information from the historical event database at Statistics Norway.[17] The cohort design analyses included two subcohorts: one including 1 012 329 maternal first cousins (2508 with CP), the other of 1 010 140 paternal first cousins (2435 with CP). Further, in the maternal first-cousin cohort, we matched each child with CP (2507 children) to their cousins without CP (8333 children), forming 8465 unique maternal first-cousin pairs. In the paternal first-cousin cohort we matched each child with CP (2432 children) to their cousins without CP (8196 children), forming 8312 unique paternal first-cousin pairs. These matched pairs were included in the family-based case–control designs (Fig. S1).

CP status
A person with CP was defined as someone who received a benefit based on a CP diagnosis (International Classification of Diseases, 9th Revision [ICD-9] codes 342–344 or 10th revision [ICD-10] G80–G83) registered in the Norwegian National Insurance Scheme[18] from 1967 to 2013, or who were registered in the Norwegian Patient Registry[19] with a CP diagnosis (ICD-10 G80) from a medical hospital in the period 2008 to 2015 (minimum follow-up time 4y). To ensure higher specificity in the CP diagnoses from the Patient Registry, we conditioned on the diagnosis being registered at least twice.

Parental educational level
Information on educational level of the parents was based on highest attained education at the end of follow-up (1st October 2013) from the national education database at Statistics Norway[20] and categorized as 'low' (primary or lower secondary education), 'intermediate' (upper secondary or short non-tertiary education), and 'high' (bachelor, master, or doctorate degree).

What this paper adds
- Children of higher-educated parents had significantly lower odds of cerebral palsy (CP).
- There was no evidence of difference in risk of CP within first cousins whose mothers or fathers had different educational levels.
- Association between parental education and odds of CP did not reflect a causal effect.

Covariates
Information on maternal and paternal age, parity, year of delivery, and smoking during pregnancy (yes/no, only available for children born in 1999 and onwards) was retrieved from the Medical Birth Registry.

Statistical analyses
We estimated the associations between mothers' and fathers' educational level and the odds of CP in the child using logistic regression models, reporting odds ratios (ORs) and 95% confidence intervals (95% CI). In all analyses we adjusted for year of delivery as a continuous variable and included parental age and parity as quadratic terms. Adjustments were based on a discussion of a directed acyclic graph (Fig. S2, online supporting information). Stata version 15.0 (StataCorp, College Station, TX, USA) was used for the analyses.

In the cohort design, we used a multilevel random intercept logistic regression model to estimate the overall effect of maternal and paternal education on CP risk in children. This model accounts for familial clustering both at the grandparent and parent level by estimating family-specific random intercepts. The intercepts represent unobserved factors shared by children of the same mother/father, and by first cousins, that affect the odds of CP, but that are assumed to be independent of all the covariates in the model, including parental educational level.[21] Hence, this design does not account for any factors shared by first cousins that affect both their risk of CP and the probability that their parents obtained higher education, for example common genetic or environmental factors in the family.

In the matched case–control design, we estimated the associations between parental educational level and risk of CP within cousin pairs using conditional logistic regression.[21] We used robust estimation of variances to account for clustering of pairs of first cousins originating from the same grandparents. When estimating the effect of educational level, only cousin pairs discordant on parental education inform the model (all pairs contribute when estimating the effects of the covariates).[15] The model compares the number of cousin pairs where the case (child with CP) is exposed (parent has intermediate or high education) and the control (child without CP) is unexposed (parent has low education) with the number of pairs where the case is unexposed and the control is exposed.

Unlike the random intercept logistic regression model, the conditional logistic regression model used in the matched case–control design implicitly controls for all factors shared by first cousins. The matched case–control design, however, potentially increases so called 'non-shared confounding' by its very design. When maternal first cousins are discordant on their mothers' educational level, they may also differ more on unobserved non-shared factors.[15] If these non-shared factors affect both maternal educational level and the risk of CP in the child, conditioning on discordance in maternal education (the criteria for selection) can increase bias owing to non-shared confounding. For example, a first-cousin pair could be discordant on their mothers' educational level if one mother had a (subclinical) neurological condition while her sister (mother of the other cousin) did not. Mothers with a neurological condition will, on average, be less likely to have higher education and more likely to have a child with CP.[10,12]

Simulation study

To assess to what extent non-shared confounding could affect the results in the family-based matched case–control design, we performed a simple Monte Carlo simulation study using simstudy in R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria) (Appendix S1, online supporting information). Here, we generated samples of mothers, each with one child, clustered within grandparent groups. In the simulations, we assumed no causal effect of maternal education on risk of having a child with CP. We further assumed that maternal educational level and risk of CP in the child were affected by a grandparent effect – shared between maternal first cousins – and a non-shared unobserved factor. This non-shared unobserved factor was included as a binary variable and its prevalence varied in each simulation from 1% to 25%. The binary factor could represent any environmental or genetic factor – not shared by maternal first cousins – that affects both the probability of the mother taking higher education and the probability of CP in the child. We assessed it to be more likely that any unobserved non-shared confounding would result in an overestimation of the true causal effect rather than an underestimation. Therefore, we further assumed that the binary factor had the same effect on maternal education and CP risk as what we observed for a neurodevelopmental disorder in the mother in a subsample of our data. Other parameter values were based on descriptive statistics in the full cohort. In each simulated data set, we estimated the associations between maternal education and CP in children using the matched case–control design (conditional logistic regression). The aim was to explore how prevalent a non-shared binary factor would have to be to generate ORs similar to what we observed when using real data (Appendix S1).

RESULTS

The characteristics of the children included in the first-cousin cohorts and excluded children (because they did not have a first cousin in the cohort) were similar, although a larger percentage of the excluded children were born early or late in the study period (Table S1, online supporting information). Among the included children, a slightly higher proportion of the children with CP were first-born, and had a mother with low education or who smoked during pregnancy compared with children without CP. In the matched case–control designs, 48% of maternal first-cousin pairs were discordant on maternal education, while 46% of paternal first-cousin pairs were discordant on paternal education (Table 1).

In the cohort of maternal first cousins, the odds of CP were lower in children of mothers with intermediate or higher education than in those of mothers with low education (adjusted OR 0.81, 95% CI 0.73–0.90 for intermediate education, and adjusted OR 0.67, 95% CI 0.60–0.75 for higher education) (Table 2). In the matched case–control analysis, estimating the effect of maternal education within first-cousin pairs, the associations were attenuated (adjusted OR for high vs low education 0.80, 95% CI 0.64–0.99). In the cohort of paternal first cousins, an indication of lower risk was found for children of fathers with higher education (adjusted OR 0.75, 95% CI 0.67–0.85), but this association was no longer present in the matched case–control analysis (adjusted OR 0.96, 95% CI 0.76–1.21).

Simulation study

In the simulation study, we introduced a non-shared binary confounder with an effect on maternal education and CP risk like that of a neurodevelopmental disorder in the mother (observed in a subsample of the data). When assuming no causal effect of maternal education on risk of CP in children, we found that, when present in 10% or more of the mothers, the non-shared binary confounder yielded associations of similar magnitude to what we observed in the matched case–control design (Table 3).

DISCUSSION

In the cohort design, children of mothers with higher education had lower risk of CP, but the effect was somewhat

Table 1: Difference in maternal/paternal educational level among cousin pairs in the case–control designs

Difference in maternal/paternal educational level	Maternal first cousins (n=8465 cousin pairs)		Paternal first cousins (n=8312 cousin pairs)	
	n	%	n	%
Both low	1117	13	850	10
Low vs intermediate	1808	21	1788	22
Low vs high	507	6	317	4
Both intermediate	1668	20	2693	32
Intermediate vs high	1777	21	1628	20
Both high	1498	18	977	12
Missing data	90	1	59	1

Table 2: Odds ratio of cerebral palsy by maternal and paternal education in the cohort and case–control design

	Cohort design				Case–control design			
	Crude OR	95% CI	Adjusted OR[a]	95% CI	Crude OR	95% CI	Adjusted OR[a]	95% CI
Maternal first cousins								
Maternal education								
Low	1.00		1.00		1.00		1.00	
Intermediate	0.84	0.76–0.93	0.81	0.73–0.90	0.98	0.83–1.17	0.96	0.81–1.13
High	0.75	0.67–0.83	0.67	0.60–0.75	0.85	0.68–1.06	0.80	0.64–0.99
p for trend[b]	0.00		0.00		0.15		0.05	
Paternal first cousins								
Paternal education								
Low	1.00		1.00		1.00		1.00	
Intermediate	0.91	0.82–1.01	0.91	0.82–1.01	1.00	0.84–1.20	1.00	0.83–1.19
High	0.77	0.69–0.87	0.75	0.67–0.85	0.97	0.77–1.22	0.96	0.76–1.21
p for trend[b]	0.00		0.00		0.82		0.76	

[a]Adjusted for year of delivery, maternal age, and parity in analysis for maternal education, and adjusted for year of delivery, paternal age, and parity in analysis for paternal education. Only those with full information on educational level and confounders are included in the adjusted analysis. [b]The p-value when including maternal/paternal education as a continuous variable. OR, odds ratio; CI, confidence interval.

Table 3: Odds ratio of cerebral palsy by maternal education by frequency of a binary confounder not shared by maternal first cousins

	Case–control design: maternal first cousins							
	Prevalence of binary non-shared confounder							
	1%		5%		10%		25%	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Maternal education								
Low	1.00		1.00		1.00		1.00	
Intermediate	1.00	0.93–1.08	0.92	0.85–0.99	0.93	0.87–1.00	0.82	0.77–0.88
High	1.01	0.91–1.11	0.93	0.84–1.02	0.82	0.74–0.90	0.76	0.69–0.83

The results are from the simulation study in which we assumed no effect of maternal education on risk of cerebral palsy in children. OR, odds ratio; CI, confidence interval.

attenuated in the case–control design, indicating the presence of shared confounding. The simulation study further indicated that the remaining effect could be due to non-shared confounding. Children of fathers with higher education had a reduced risk of CP in the cohort design, but not when comparing the risk within paternal first cousins. This suggests that the association with the father's education was entirely explained by factors shared within extended families (shared confounding).

The population-based high-quality registry data of approximately 1.5 million children, of whom 3714 had CP, provided new opportunities to explore the relationship between parents' educational level and risk of CP in the child. We compared a traditional cohort design with a matched case–control study that enabled control for shared confounding within extended families. We further expanded on previous analyses by performing a simulation study to explore the role of confounding in the matched case–control design.

A family-based matched case–control design removes some of the potential unmeasured confounding factors that could create bias in the traditional cohort design, but some important limitations still exist. A prerequisite for the family-based case–control design is variation in the exposure within families. For parental education, there is more variation between cousin pairs than within, which reduces sample size. Fewer than 10 000 children contributed to the estimation of the within-family effects of maternal and paternal education, which reduced precision. Further, since the estimate for parental education was based only on first-cousin pairs discordant on parental education level, this could create a selection bias due to non-shared confounding.[15] This would occur if there are unobserved non-shared factors – for example an underlying health problem in the mother of one cousin but not the other – that affect both the mother's educational level and CP risk in the child. First cousins discordant on both CP status and their mothers' educational levels probably differ more with respect to such unobserved factors than two randomly selected cousins from the population. Hence, estimates from the matched case–control design could be more biased than those from the cohort design.[15] Further, the observed effect of education may not be generalizable to cousins concordant on parental education, although we find the lack of substantial differences in distribution of included variables between children in the cohort and case–control designs reassuring.

One limitation of our study was the lack of information on parental education in the year of delivery. If a CP diagnosis in the child affected the mother's chances of taking higher education, this could have resulted in reverse causation and biased our estimates away from the null-value (OR=1). However, a Danish registry-based study on mothers who had a child in the period from 1965 to 1990 found only a short-term adverse effect of having a child with CP on the mother's educational attainment: no effect was observed after 10 years.[22] Further, a previous study including children born in Denmark from 1981 to 2007 found a high correlation between parental education in the year of delivery and at the end of follow-up (Pearson's correlation 0.9) and a similar association between parental education and risk of CP for both measures.[4] Therefore, considerable bias due to reverse causation in our study seems unlikely.

Another limitation was the lack of confirmed CP diagnoses. The CP registry of Norway[23] only includes children born from 1996 onwards. We therefore had to use data on CP diagnoses registered in the Norwegian National Insurance Scheme and the Norwegian Patient Registry. A previous validation study of CP diagnoses in the Insurance Scheme found an underestimation of mild CP cases,[24] while an overestimation of CP diagnoses in the Patient Registry has been found.[25] Whether this misclassification is differential by parental educational level is not known.[4] Overall, however, the prevalence of CP found in our study is in accordance with what has been reported by the CP registry since 1996.[2,25]

We are not aware of previous studies on the association between parental education and risk of CP that have used a family-based matched case–control design. Associations between maternal educational level and other perinatal outcomes strongly associated with CP – preterm birth and small for gestational age[26,27] – have been explored using family-based designs. A registry-based Danish study found no association between maternal education and the risk of preterm birth among maternal first cousins, and the authors therefore concluded that a substantial part of the educational gradient was explained by factors shared by cousins.[28] In the same study, however, the risk of a having a newborn infant who was small for gestational age decreased with higher educational level within maternal first-cousin pairs, but the potential role of non-shared confounding was not assessed. Another Danish registry-based study found that the birthweight of the child increased with the mother's years of schooling when comparing children by mothers who were twins, thereby concluding there could be a causal effect of mothers' education on birthweight.[29]

Despite some indications of a causal effect of maternal education on other perinatal health outcomes,[7] the results from our simulation study indicated that this may not be the most likely explanation for the educational gradient in risk of having a child with CP. In the simulation study, we found that an unobserved non-shared confounder present in 10% or more of the mothers – with the same effect on CP risk as a maternal neurodevelopmental disorder – could explain the associations observed within pairs of maternal first cousins. Given that this unobserved confounder would represent all factors not shared by first cousins affecting both their probability of CP and the probability of their mother taking higher education, it seems likely that non-shared confounding could explain the remaining association.

A family-based design provides an opportunity to pose causal questions related to CP aetiology—an area where we still lack knowledge. A collaborative effort across the Scandinavian countries – all of which have national CP registries with validated diagnoses[30] – would increase the sample size and help levitate the loss of precision seen when using this type of design. The presented simulation study provides an example on how to explore the role of non-shared confounding when using a family-based case–control design.

Compared with parents with low education, we found a lower risk of having a child with CP for parents with higher education. This effect was attenuated when comparing the risks among maternal first cousins, and no longer present among paternal first cousins. Our results indicate that the inverse association between parental education and CP risk is probably to a large extent explained by confounding factors shared within the extended family (environmental, genetic, or both). A simulation study suggested that the remaining association among maternal first cousins could probably be explained by non-shared confounding factors (for example a chronic condition in one child's mother). Hence, we found no convincing evidence of a causal effect of parental education on risk of CP in the child. Our findings, however, need replication using larger samples and other designs.[31] Research efforts aimed at identifying the causal effect of genetic and environmental risk factors for CP that vary by parents' educational level should be expanded and continued.

SUPPORTING INFORMATION
The following additional material may be found online:
   Figure S1: Selection of study samples.
   Figure S2: Directed acyclic graph.
   Appendix S1: Simulation study.
   Table S1: Characteristics of children in the cohorts of maternal and paternal first cousins and among excluded children

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