Neurodevelopmental Disorders or Early Death in Siblings of Children With Cerebral Palsy

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abstract

OBJECTIVES: To explore the presence of shared underlying causes of cerebral palsy (CP) and other neurodevelopmental disorders, by examining risks of other disorders in siblings of children with CP.

METHODS: We used Norwegian national registries to identify 1.4 million pairs of full siblings (singletons) and 28 000 sets of twins born from 1967 to 2006, identify stillbirths and neonatal deaths, and find individuals with CP, epilepsy, intellectual disability, autism spectrum disorders, attention-deficit/hyperactivity disorder, blindness, deafness, schizophrenia, and bipolar disorder. Associations between CP in 1 sibling and neurodevelopmental disorders or early death in other siblings were estimated using logistic regression models.

RESULTS: There were 5707 neonatal survivors (beyond 28 days) with CP (2.5/1000). These children had substantial comorbidity (eg, 29% had epilepsy). Singleton siblings of (singleton) children with CP had increased risks of neurodevelopmental problems, including epilepsy (odds ratio [OR], 1.8 [95% confidence interval (CI), 1.5–2.5]), intellectual disability (OR, 2.3 [95% CI, 1.8–2.9]), autism spectrum disorders (OR, 1.6 [95% CI, 1.1–2.2]), attention-deficit/hyperactivity disorder (OR 1.3 [95% CI, 1.1–1.6]), blindness (OR 2.4 [95% CI, 1.1–5.4]), and schizophrenia (OR 2.0 [95% CI, 1.2–3.2]). There was no increase in risk of bipolar disorder (OR 1.0 [95% CI, 0.6–1.6]). Families with children with CP also had increased risk of losing another child in the perinatal period (stillbirth OR, 1.8 [95% CI, 1.5–2.3]; neonatal death OR, 1.7 [95% CI, 1.3–2.2]). Associations were stronger within sets of twins.

CONCLUSIONS: Siblings of a child with CP were at increased risk for a variety of other neurodevelopmental morbidities, as well as early death, indicating the presence of shared underlying causes.

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DOI: 10.1542/peds.2016-0269

Accepted for publication May 23, 2016

WHAT'S KNOWN ON THIS SUBJECT: Although neurodevelopmental disorders are common, their causes are generally not well understood.

WHAT THIS STUDY ADDS: Siblings of children with cerebral palsy are at increased risk of other neurodevelopmental disorders or early death. This indicates the presence of shared underlying causes. Common causes could be genetic, environmental, or a combination of the two.

To cite: Tollånes MC, Wilcox AJ, Stoltenberg C, et al. Neurodevelopmental Disorders or Early Death in Siblings of Children With Cerebral Palsy. *Pediatrics*. 2016;138(2):e20160269

Cerebral palsy (CP) is the most common cause of physical disability in children, affecting ~2 in 1000 live births.^{1,2} CP originates from nonprogressive damage to the immature brain, but its underlying causes are generally unknown.

A wide range of risk factors in pregnancy and the perinatal period have been identified, of which preterm delivery is one of the strongest; other possible risk factors include multiple fetuses, atypical intrauterine growth, congenital malformations, placental pathology, intrauterine infection, and perinatal stroke.^{3,4} Having a family member with CP is also a risk factor for CP.⁵ Thus far, only a limited number of studies on CP etiology have made use of recent advances in genetic methodology (eg, high-throughput whole-genome or whole-exome sequencing); such investigations indicate that underlying genetic explanatory factors are heterogeneous and complex.^{6,7} Genetic studies in other neurodevelopmental disorders are more abundant. These studies indicate that many phenotypically different disorders may share identical underlying genetic risk factors,^{8,9} and conversely, different genetic factors may lead to phenotypically similar clinical syndromes.¹⁰ Such discoveries challenge traditional diagnostic categories, suggesting that many neurodevelopmental disorders may be part of a continuum of clinical expression rather than distinct conditions. CP is not yet considered among them, even though many children with CP also experience epilepsy, cognitive impairment, autism spectrum disorders, or attention-deficit/hyperactivity disorder (ADHD).^{11–13}

In the present population-based cohort study, our goal was to explore the possibility that CP and other neurodevelopmental disorders share underlying causes by investigating

the risks of such disorders in siblings of children with CP. Because death may be the most severe outcome of brain injury, we also investigated the risk of stillbirth and neonatal death among the siblings.

METHODS

Data Sources

The Medical Birth Registry of Norway was established in 1967 as a compulsory registry of all live births and stillbirths from 16 weeks of gestation.¹⁴ The birth registry includes information on maternal health, pregnancy complications, plurality, gestational age, and the condition of the newborn. It also includes for each delivery the unique national identification numbers of parents and child.

The Norwegian National Insurance Scheme is a data source with records of cash benefits provided to families of children with chronic disease or disability.¹⁵ Benefits are provided if the condition involves significant expenses or extra nursing is needed, irrespective of family income. Later in life, a disability pension may be provided for people unable to support themselves. Benefits require individual application and a physician's diagnosis, coded in accordance with *International Classification of Diseases, Ninth Revision* (ICD-9), or *International Classification of Diseases, 10th Revision* (ICD-10). CP cases identified through the insurance scheme have previously been validated and found to be satisfactory, especially for severe cases.¹⁶ Insurance data were last updated in 2007.

It has been possible to link data from the Norwegian Patient Registry on an individual level since 2008.¹⁷ ICD-10 codes are registered for all hospital visits in addition to all public and private clinic visits. CP diagnoses from the patient registry have been validated against

Norway's consent-based Cerebral Palsy Registry¹⁸ and found to be satisfactory,¹⁹ probably catching the less severe cases to a larger extent than the insurance data. The patient registry data were last updated in 2011.

Our goal was to acquire better coverage of neurodevelopmental disorders by using 2 different sources (insurance data and patient registry data). Siblings were identified in the birth registry as children having the same mother and father (as determined by national identification numbers). Children with the diagnoses of interest were identified through record linkage among the national registries, using each child's unique national identification number.

Study Population and Case Definitions

The study population consisted of 2.3 million singletons, twins, and higher order multiples registered in the Medical Birth Registry between 1967 and 2006 and with a gestational age of ≥ 22 completed weeks (birth weight ≥ 500 g if missing gestational age). By linking births having the same mother and father, 1 422 899 unique pairs of full (singleton) siblings were identified; in a 3-singleton sibship, we identified 3 unique pairs (one-two, one-three, and two-three). For 1 381 347 pairs, both siblings survived for >28 days (neonatal survivors). We similarly identified 28 247 sets of twins, of which 26 485 sets had 2 neonatal survivors.

Stillbirths, neonatal deaths (0–28 days), and post-neonatal deaths (29 days–1 year) were identified through the birth registry. CP cases were defined as those in the National Insurance Scheme with ICD-9 code 343 or ICD-10 code G80 or as those in the patient registry with ICD-10 code G80. Other conditions were defined as follows: autism spectrum disorders, codes 299 and F84; ADHD,

codes 314 and F90; epilepsy, codes 345, G40m, and G41; intellectual disability, codes 317 to 319 and F70 to F79; blindness, codes 369 and H54; deafness, codes 389 and H90; schizophrenia, codes 295 and F20; and bipolar disorder, codes 296 and F31. Schizophrenia and bipolar disorder have been proposed to have neurodevelopmental origins, although they are usually not apparent until later in life.²⁰

In addition, for the purpose of conducting sensitivity analyses, we tried isolating clinical conditions. For example, in considering the risk of epilepsy among the siblings of children with CP, siblings with “epilepsy without CP” were defined as someone registered with an epilepsy diagnosis in either the insurance scheme or the patient registry but who had never been registered with a CP diagnosis either place. Similarly, “CP without epilepsy” was identified in the corresponding way. This approach was used for the other paired outcomes as well.

Statistical Methods

To calculate a measure of association between a CP diagnosis in 1 child and another condition in its sibling,

we used logistic regression models in Stata version 12.1 (Stata Corp, College Station, TX). To account for dependency between sibling pairs by the same parents, robust estimations of variances were used. Crude odds ratios (ORs) were calculated, as well as ORs adjusted for the older sibling’s year of birth (in 5-year categories [eg, 1967–1971, 1972–1976]). There is no biological reason to expect birth order to play a role in the recurrence of neurodevelopmental outcomes among siblings; that is, the occurrence of CP in 1 sibling and a different neurodevelopmental condition in another sibling should be random with regard to which was born first. This theory was tested by calculating 2 ORs. First, we used CP in the older sibling as “exposure” and each condition in the younger sibling as the “outcome.” We then used each condition in the older sibling as “exposure” and CP in the younger sibling as the “outcome.” No statistical evidence of heterogeneity was found between pairs of ORs combined this way, meaning the associations were similar if the child with CP was the older or the younger sibling. For maximum statistical power, we therefore combined the 2 adjusted ORs for each pair of conditions investigated,

using the program “Metan” in Stata, specifying a random effects model meta-analysis. Twins were randomly assigned to “older” or “younger” and handled the same way.

To investigate associations between CP and early death, all available sibling pairs were included. For associations between CP and neurodevelopmental disorders, the cohort was restricted to neonatal survivors (survived for >28 days). For analyses of schizophrenia and bipolar disorder, which are diagnosed later in life, the cohort was further restricted to the earlier births (1967–1990), thus allowing time for more complete follow-up.

Ethical Considerations

This study was approved by the Regional Committees for Medical and Health Research Ethics and the institutions responsible for each registry (the Norwegian Labour and Welfare Administration, the Norwegian Directorate of Health, the Norwegian Institute of Public Health, Statistics Norway, and TaxNorway).

RESULTS

The occurrence of stillbirth, neonatal death, and post-neonatal

TABLE 1 Stillbirth, Neonatal, and Post-Neonatal Death Among All Births (per 1000) and Selected Neurodevelopmental Diagnoses Among Neonatal Survivors (per 1000) According to Year of Birth: Norway, 1967 to 2006

Variable	1967–1976	1977–1986	1987–1996	1997–2006
All births, <i>N</i>	634 134	514 482	596 127	583 378
Stillbirth	12.4	8.7	6.4	4.9
Neonatal death ^a	8.9	4.9	3.6	2.4
Post-neonatal death ^b	3.3	3.4	2.4	1.1
Neonatal survivors, ^c <i>N</i>	620 601	507 495	590 201	579 111
CP	2.0	2.3	2.7	2.9
Epilepsy	7.4	8.8	9.4	8.5
Intellectual disability	6.3	6.2	6.5	4.2
ADHD	7.0	12.7	28.9	21.5
Autism spectrum disorders	1.0	2.6	6.7	6.6
Deafness	8.2	5.4	6.2	8.8
Blindness	0.6	0.5	0.5	0.8
Schizophrenia	4.5	3.8	2.2 ^d	NA
Bipolar disorder	6.5	6.2	4.6 ^d	NA

^a Death from 0 to 28 days.

^b Death from 29 days to 1 year.

^c Liveborn and survived at least 28 days.

^d 1987 to 1990.

TABLE 2 Neurodevelopmental Diagnoses in Neonatal Survivors (Survived >28 Days) With and Without CP, Births in Norway, 1967 to 2006

Variable	Persons With CP (<i>n</i> = 5709), %	Persons Without CP (<i>n</i> = 2 291 699), %
Epilepsy	29.5	0.8
Intellectual disability	25.8	0.5
ADHD	4.1	1.8
Autism spectrum disorders	3.0	0.4
Deafness	3.5	0.7
Blindness	2.1	0.06
Schizophrenia ^a	0.6	0.4
Bipolar disorder ^a	0.8	0.6

Births in Norway, 1967 to 2006.

^a Year of birth 1967 to 1990; includes 2982 neonatal survivors with CP and 1 355 621 without CP.

death has declined in Norway over time (Table 1). In contrast, most neurodevelopmental disorders increased from 1967 to 1996, although some declines have occurred in the final decade. The increases probably reflect more complete registration over time, whereas the decrease in the most recent birth cohorts reflects shorter time for follow-up and detection.

CP was identified among 5707 of 2 297 408 neonatal survivors born from 1967 to 2006 (2.5 per 1000). Epilepsy and intellectual disability were far more common among persons with CP than those without (Table 2). Those with CP were also at increased risk of blindness, deafness, autism spectrum disorders, and ADHD. Persons with CP had

only a slightly higher occurrence of schizophrenia and bipolar disorder.

As we previously reported,⁵ CP is more common among siblings of children with CP (Fig 1, Table 3). In addition, siblings were at increased risk of a wide range of other neurodevelopmental disorders. Siblings of children with CP had roughly twice the risk of being diagnosed with intellectual disability (odds ratio [OR], 2.3 [95% confidence interval, 1.8–2.9]), epilepsy (1.8 [95% CI, 1.5–2.5]), blindness (2.4 [95% CI, 1.1–5.4]), or schizophrenia (2.0 [95% CI, 1.2–3.2]). Siblings of children with CP also had elevated risks of autism spectrum disorders (1.6 [95% CI, 1.1–2.2]) and ADHD (1.3 [95% CI, 1.1–1.6]). For conditions with sufficient numbers of sets of twins,

the associations between CP in 1 twin and another neurodevelopmental disorder in the co-twin were generally even stronger.

Families who had a child with CP had a substantially higher risk of losing another child in the perinatal period (stillbirth OR, 1.8 [95% CI, 1.5 to 2.3]; neonatal death OR, 1.7 [95% CI, 1.3–2.2]) (Fig 2, Table 3). For twins, the association between CP in 1 twin and death of the co-twin was stronger and extended into the post-neonatal period.

One of the most common comorbidities of CP is epilepsy. To exclude the possibility that a recurrence of CP was the only factor contributing to the sibling risk of epilepsy, “outcome” epilepsy cases were restricted to those without CP. The association between CP in 1 sibling and epilepsy in the other was slightly attenuated (OR, 1.6 [95% CI, 1.3–2.1]). When we also restricted index CP cases to those without epilepsy, the association was further attenuated (1.5 [95% CI, 1.1–2.0]). Similar restrictions with other comorbidities led to similarly attenuated associations (Table 4, Supplemental Table 6).

Preterm delivery increases the risk of many neurodevelopmental disorders,

FIGURE 1

Associations between CP in 1 sibling and neurodevelopmental conditions in the other (ORs with 95% CIs): 1 381 347 pairs of singleton full sibling neonatal survivors (survived >28 days) and 26 485 pairs of twin neonatal survivors.

TABLE 3 Associations Between CP in 1 Sibling and Neurodevelopmental Disorders in Other Siblings

Exposure–Outcome	Sibship	Cases/Exposed Younger Sibs	Cases/Unexposed Younger Sibs	Crude OR (95% CI)	Adjusted OR ^a (95% CI)	OR Combined ^b (95% CI)	P for Heterogeneity
CP–CP	Singletons	39/2840	2956/1378507	6.5 (4.7–8.9)	6.4 (4.5–9.2)		
CP–CP	Twins	39/2995	2801/1378352	6.5 (4.7–8.9)	6.4 (4.5–9.2)	6.4 (5.0–8.3)	>0.9
CP–CP		30/181	181726304	29 (19–44)	27 (18–42)		
CP–CP		30/211	151/26274	29 (19–44)	27 (18–42)	27 (20–37)	>0.9
CP–epilepsy	Singletons	38/2840	11472/1378507	1.6 (1.1–2.2)	1.6 (1.1–2.2)		
Epilepsy–CP	Twins	48/11150	2947/1370149	2.0 (1.5–2.7)	2.0 (1.5–2.6)	1.8 (1.5–2.5)	0.4
CP–epilepsy		6/181	223/26304	4.0 (1.8–9.1)	3.9 (1.7–9.0)		
Epilepsy–CP		9/276	202/26209	4.3 (2.2–8.6)	4.4 (2.2–8.6)	4.2 (2.5–7.1)	0.8
CP–intellectual disability	Singletons	33/2840	7864/1378507	2.0 (1.5–2.9)	2.1 (1.4–3.1)		
Intellectual disability–CP	Twins	39/7501	2956/1373846	2.4 (1.8–3.3)	2.4 (1.8–3.4)	2.3 (1.8–2.9)	0.6
CP–intellectual disability		5/181	194/26304	3.8 (1.6–9.4)	3.8 (1.6–9.4)		
Intellectual disability–CP		6/168	205/26317	4.7 (2.1–10.8)	4.6 (2.0–10.6)	4.2 (2.3–7.8)	0.8
CP–ADHD ^c	Singletons	64/2840	21046/1378507	1.5 (1.2–1.9)	1.4 (1.1–1.9)		
ADHD–CP	Twins	56/20157	2939/1361190	1.3 (0.99–1.7)	1.2 (0.9–1.6)	1.3 (1.1–1.6)	0.5
CP–ADHD		12/181	476/26304	3.9 (2.1–7.0)	3.4 (1.9–6.2)		
ADHD–CP		10/476	201/26009	2.8 (1.5–5.2)	2.6 (1.3–4.9)	3.0 (1.9–4.6)	0.5
CP–autism spectrum disorder	Singletons	18/3840	5222/1378507	1.7 (1.1–2.7)	1.6 (0.9–2.6)		
Autism spectrum disorder–CP	Twins	19/5500	2976/1375847	1.6 (1.02–2.5)	1.5 (0.97–2.4)	1.6 (1.1–2.2)	0.9
CP–autism spectrum disorder		3/181	131/26304	3.4 (1.1–10.7)	3.0 (0.9–9.6)		
Autism spectrum disorder–CP		1/123	210/26362	1.0 (0.1–7.3)	0.9 (0.1–6.7)	2.2 (0.8–6.0)	0.3
CP–deafness	Singletons	27/2840	10155/1378507	1.3 (0.9–1.9)	1.3 (0.9–1.9)		
Deafness–CP	Twins	22/9390	2973/1371957	1.1 (0.7–1.6)	1.1 (0.7–1.7)	1.2 (0.9–1.6)	0.6
CP–deafness		6/181	228/26304	3.9 (1.7–8.4)	3.8 (1.7–8.7)		
Deafness–CP		3/210	208/26275	1.8 (0.6–5.7)	1.9 (0.6–6.0)	3.0 (1.5–5.9)	0.3
CP–blindness	Singletons	5/2840	758/1378507	3.2 (1.3–7.7)	3.1 (1.3–7.6)		
Blindness–CP	Twins	2/718	2993/1380629	1.3 (0.3–5.2)	1.3 (0.3–5.2)	2.4 (1.1–5.4)	0.3
CP–blindness		0/181	25/26304	—	—		
Blindness–CP		2/20	209/26465	14.0 (3.2–60)	15.5 (3.5–69)	—	
CP–schizophrenia	Singletons ^c	7/1351	2776/762364	1.4 (0.7–3.0)	1.4 (0.7–3.0)		
Schizophrenia–CP	Twins ^d	14/2949	1529/760766	2.4 (1.4–4.0)	2.4 (1.4–4.0)	2.0 (1.2–3.2)	0.3
CP–schizophrenia		1/68	47/12215	3.9 (0.5–28)	4.4 (0.6–32)		
Schizophrenia–CP		0/56	76/12227	—	—	—	
CP–bipolar disorder	Singletons ^c	6/1351	4358/762364	0.8 (0.3–1.7)	0.8 (0.3–1.7)		
Bipolar disorder–CP	Twins ^d	11/4742	1532/758973	1.1 (0.6–2.1)	1.2 (0.6–2.1)	1.0 (0.6–1.6)	0.4
CP–bipolar disorder		0/68	69/12215	—	—		
Bipolar disorder–CP		0/79	76/12204	—	—	—	

TABLE 3 Continued

Exposure–Outcome	Sibship	Cases/Exposed Younger Sibs	Cases/Unexposed Younger Sibs	Crude OR (95% CI)	Adjusted OR ^a (95% CI)	OR Combined ^b (95% CI)	P for Heterogeneity
CP–stillbirth	Singletons	29/2886	8754/1420013	1.6 (1.1–2.4)	1.7 (1.2–2.5)		
Stillbirth–CP	Twins	67/16825	3307/1406074	1.8 (1.4–2.4)	1.9 (1.5–2.5)	1.8 (1.5–2.3)	0.7
CP–stillbirth	Twins	8/210	579/28037	1.9 (0.9–3.8)	2.3 (1.1–4.7)		
Stillbirth–CP	Twins	10/590	233/27657	2.0 (1.1–3.8)	2.6 (1.3–5.0)	2.5 (1.5–4.0)	0.8
CP–neonatal death ^e	Singletons	17/2886	5519/1420013	1.5 (0.9–2.4)	1.6 (1.02–2.6)		
Neonatal death–CP	Twins	42/11571	3062/1411328	1.7 (1.2–2.3)	1.7 (1.3–2.3)	1.7 (1.3–2.2)	0.9
CP–neonatal death	Twins	21/210	601/28037	5.1 (3.2–8.0)	6.3 (3.9–10.2)		
Neonatal death–CP	Twins	22/659	221/27588	4.3 (2.7–6.7)	5.4 (3.4–8.7)	5.8 (4.2–8.2)	0.7
CP–late neonatal death ^f	Singletons	7/2886	3893/1420013	0.9 (0.4–1.9)	0.9 (0.5–2.0)		
Late neonatal death–CP	Twins	18/6510	3086/1416389	1.3 (0.8–2.0)	1.3 (0.8–2.0)	1.2 (0.8–1.7)	0.5
CP–late neonatal death	Twins	4/210	132/28037	4.1 (1.5–11.2)	4.3 (1.6–11.9)		
Late neonatal death–CP	Twins	4/152	239/28095	3.2 (1.2–8.6)	3.3 (1.2–9.0)	3.8 (1.9–7.7)	0.7

1381/347 pairs of singleton full sibling neonatal survivors (survived >28 days) and 26485 pairs of twin neonatal survivors. Associations between CP in 1 sibling and early death in other siblings. 1422899 pairs of singleton full siblings and 28247 pairs of twins. Norway 1967 to 2006. —, indicates it was not possible to calculate ORs due to zero cases.

^a Adjusted for older sibling's (or twins') year of birth in 5-year categories (eg, 1967–1971, 1972–1976).

^b Adjusted ORs combined with meta-analyses.

^c A total of 763715 pairs of singleton full sibs born between 1967 and 1990.

^d A total of 12283 pairs of twins born between 1967 and 1990.

^e Death 0 to 28 days.

^f Death 29 days to 1 year.

as well as perinatal death.²¹ Thus, a recurrence risk for preterm delivery could contribute to a correlation between CP and other disabilities in siblings. We repeated our analyses after restricting older siblings to those born at term, defined as at least 37 completed weeks for singletons and 36 weeks for twins. (In our cohort, 5.5% of singletons and 28.9% of twins were born preterm.) This analysis had little effect on the results for singletons but yielded a loss of power for twins (Table 5). In addition, the analyses were repeated by using only the 2 first singletons in a sibship, which again generally did not affect the results.

DISCUSSION

Using Norwegian national health registries, we found that siblings of children with CP are at increased risk for a range of neurodevelopmental disorders, including epilepsy, intellectual disability, autism spectrum disorders, ADHD, blindness, and schizophrenia. Families with a child with CP are also at increased risk of losing another child to stillbirth or neonatal death.

Comparison With Other Studies

Comorbidities of CP

It is well established that children with CP are themselves at higher risk of developmental comorbidities. An earlier study from the Norwegian Cerebral Palsy Registry found that 31% of children with CP had intellectual disability, 28% had active epilepsy, 5% had severely impaired vision, and 4% had severely impaired hearing.¹¹ These numbers are comparable to our findings. In a US study (the Autism and Developmental Disabilities Monitoring Program, comprising 4 US centers), 42% of children with CP had epilepsy and ~7% had co-occurring autism spectrum disorders.¹³ Another US study reported that, on average, 52% of 8-year-old children with congenital

Singleton siblings

Twin pairs

FIGURE 2

Associations between CP in 1 sibling and early death in the other (ORs with 95% CIs): 1 422 899 pairs of singleton full siblings and 28 247 pairs of twins.

TABLE 4 Associations Between CP in 1 Sibling and Neurodevelopmental Disorders in Other Siblings

Developmental Disability	Risk in All Siblings of CP Children (OR ^a [95% CI])	Risk in Siblings Without CP Themselves (OR ^a [95% CI])	Risk in Siblings Without CP, and Index CP Child Did Not Have the Disability as Comorbidity (OR ^a [95% CI])
Epilepsy	1.8 (1.5 to 2.2)	1.6 (1.3–2.1)	1.5 (1.1–2.0)
Intellectual disability	2.3 (1.8–2.9)	1.8 (1.4–2.4)	1.3 (0.9–1.9)
ADHD	1.3 (1.1–1.6)	1.3 (1.1–1.6)	1.2 (0.96–1.5)
Autism spectrum disorder	1.6 (1.1–2.2)	1.5 (1.1–2.1)	1.3 (0.9–1.9)
Deafness	1.2 (0.9–1.6)	1.1 (0.8–1.5)	1.0 (0.8–1.4)
Blindness	2.4 (1.1–5.4)	2.0 (0.5–8.6)	1.8 (0.5–6.2)
Schizophrenia ^b	2.0 (1.2–3.2)	1.9 (0.99–3.4)	1.9 (0.99–3.5)
Bipolar disorder ^b	1.0 (0.6–1.6)	1.0 (0.6–1.6)	1.0 (0.6–1.6)

1 381 347 pairs of singleton full sibling neonatal survivors (survived >28 days). Norway, 1967 to 2006.

^a Adjusted for older sibling's year of birth in 5-year categories (eg, 1967–1971, 1972–1976).

^b A total of 763 715 pairs of singleton full sibs born between 1967 and 1990.

spastic CP born from 1985 to 2002 in metropolitan Atlanta had co-occurring intellectual disabilities and 6% had autism spectrum disorders.²² The occurrence of autism spectrum disorders is higher than in our data, perhaps in part due to our inability to fully capture autism spectrum disorder diagnoses in the late and early cohorts. (Those born earlier are less likely to be in the patient registry, whereas the later cohorts have not been followed up long enough to capture all cases.)

Morbidities in Siblings of Children With CP

One previous study investigated the risk of neurologic diseases among siblings of children with CP. In a Swedish population-based registry

study using hospital discharge data, no evidence was found of an association between “CP and other paralytic syndromes” and epilepsy in a sibling.²³ The Swedish study did not have access to diagnoses from outpatient contacts, however, nor did it restrict analysis to CP specifically, which may have contributed to the negative results.

Discussion

The associations between excess risks of a wide range of neurodevelopmental disorders and having a sibling with CP indicate the presence of unmeasured shared causes. Such shared causes may be genetic, or environmental, or a combination of the 2 factors. Several neurodevelopmental disorders

have been found to share genetic risk factors.^{8,9} However, to our knowledge, CP has not been included in such genetic studies. There is considerable complexity and heterogeneity in what is known about genetic risk factors for CP and other neurodevelopmental conditions,^{6,7,10} and we are only beginning to understand the fuller picture. As for possible environmental factors, women may be exposed to persistent harmful factors during subsequent pregnancies due to working conditions, lifestyle, or home environment. In utero exposure to toxins such as lead and mercury has been associated with a wide range of neurodevelopmental deficits.²⁴ Exposure to inflammation during fetal or neonatal life may be a shared cause of various neurodevelopmental disorders, including CP.²⁵ Maternal or fetal genetic predisposition to inflammation could be an example of an interaction between genes and environment contributing to our results.

Given the high degree of comorbidity among the various disorders, it is not surprising that the observed associations were attenuated when restricting the analysis to isolated conditions (eg, “CP without epilepsy” in the index child and “epilepsy without CP” in siblings). Similarly,

TABLE 5 Associations Between CP in 1 Sibling and Neurodevelopmental Disorders in Other Siblings

Exposure–Outcome	Sibship	Cases/Exposed Younger Sibs	Cases/Unexposed Younger Sibs	Crude OR (95% CI)	Adjusted OR ^a (95% CI)	OR Combined ^b (95% CI)	P for Heterogeneity
CP–CP	Singletons	33/2180	2734/1320235	7.4 (5.2–10.5)	7.3 (4.9–11.0)		
CP–CP	Twins	33/2767	2147/1319648	7.4 (5.2–10.5)	7.3 (4.9–11.0)	7.3 (5.5–9.7)	>0.9
CP–CP		3/64	66/19994	14.8 (4.5–49)	15.3 (4.7–50)		
CP–CP		3/69	61/19989	14.8 (4.5–49)	15.3 (4.7–50)	15.3 (6.7–35)	>0.9
CP–epilepsy	Singletons	28/2180	10931/1320235	1.6 (1.1–2.3)	1.6 (1.1–2.3)		
Epilepsy–CP		44/10486	2723/1311929	2.0 (1.5–2.7)	2.0 (1.5–2.7)	1.8 (1.4–2.3)	0.3
CP–epilepsy	Twins	1/64	149/19994	2.1 (0.3–15.3)	2.0 (0.3–14.7)		
Epilepsy–CP		0/187	69/19871	—	—	—	
CP–intellectual disability	Singletons	32/2180	7456/1320235	2.6 (1.8–3.7)	2.7 (1.8–3.9)		
Intellectual disability–CP		34/6879	2733/1315536	2.4 (1.7–3.3)	2.4 (1.7–3.3)	2.5 (2.0–3.2)	0.6
CP–intellectual disability	Twins	1/64	137/19994	2.3 (0.3–16.7)	2.2 (0.3–16.1)		
Intellectual disability–CP		1/111	68/19947	2.7 (0.4–19.3)	2.7 (0.4–19.1)	2.4 (0.6–9.8)	0.9
CP–ADHD	Singletons	51/2180	19995/1320235	1.6 (1.2–2.1)	1.5 (1.1–2.0)		
ADHD–CP		50/19005	2717/1303410	1.3 (0.95–1.7)	1.2 (0.9–1.6)	1.4 (1.1–1.7)	0.3
CP–ADHD	Twins	4/64	329/19994	4.0 (1.4–11.0)	3.5 (1.3–9.7)		
ADHD–CP		1/336	68/19722	0.9 (0.1–6.2)	0.9 (0.1–6.2)	2.3 (0.7–8.1)	0.2
CP–autism spectrum disorder	Singletons	11/2180	4969/1320235	1.3 (0.7–2.4)	1.3 (0.7–2.4)		
Autism spectrum disorder–CP		18/5175	2749/1317240	1.7 (1.05–2.7)	1.6 (1.01–2.5)	1.5 (1.01–2.1)	0.6
CP–autism spectrum disorder	Twins	0/64	94/19994	—	—	—	
Autism spectrum disorder–CP		0/85	69/19973	—	—	—	
CP–deafness	Singletons	22/2180	9682/1320235	1.4 (0.9–2.1)	1.4 (0.9–2.2)		
Deafness–CP		21/8810	2746/1313605	1.1 (0.7–1.8)	1.2 (0.8–1.8)	1.3 (0.9–1.7)	0.6
CP–deafness	Twins	1/64	143/19994	2.2 (0.3–16.0)	2.3 (0.3–16.8)		
Deafness–CP		0/125	69/19953	—	—	—	
CP–blindness	Singletons	4/2180	711/1320235	3.4 (1.3–9.1)	3.4 (1.3–9.0)		
Blindness–CP		0/625	2767/1321790	—	—	—	
CP–blindness	Twins	0/64	17/19994	—	—	—	
Blindness–CP		1/8	68/20050	42 (5–346)	44 (6–347)	—	
CP–schizophrenia	Singletons ^c	3/1077	2656/732204	0.8 (0.3–2.4)	0.8 (0.3–2.4)		
Schizophrenia–CP		13/2808	1412/730473	2.4 (1.4–4.2)	2.4 (1.4–4.1)	1.5 (0.5–4.6)	0.07
CP–schizophrenia	Twins ^d	1/31	40/9841	8.2 (1.1–61.4)	8.5 (1.2–62.4)		
Schizophrenia–CP		0/47	31/9825	—	—	—	
CP–bipolar disorder	Singletons ^c	4/1077	4169/732204	0.7 (0.2–1.7)	0.7 (0.2–1.7)		
Bipolar disorder–CP		10/4522	1415/728759	1.1 (0.6–2.1)	1.1 (0.6–2.1)	1.0 (0.6–1.7)	0.3
CP–bipolar disorder	Twins ^d	0/31	53/9841	—	—	—	
Bipolar disorder–CP		0/60	31/9812	—	—	—	

TABLE 5 Continued

Exposure–Outcome	Sibship	Cases/Exposed Younger Sibs	Cases/Unexposed Younger Sibs	Crude OR (95% CI)	Adjusted OR ^a (95% CI)	OR Combined ^b (95% CI)	P for Heterogeneity
CP–stillbirth	Singletons	15/2206	7762/1345059	1.2 (0.7–2.0)	1.2 (0.7–2.0)		
Stillbirth–CP	Twins	24/7471	2783/1339794	1.5 (1.04–2.3)	1.6 (1.04–2.5)	1.4 (1.03–2.0)	0.4
CP–stillbirth		5/71	188/20542	8.2 (3.3–21)	9.3 (3.6–24)		
Stillbirth–CP		4/218	70/20395	5.4 (2.0–15)	5.9 (2.0–17)	7.6 (3.8–15.5)	0.5
CP–neonatal death ^e	Singletons	11/2206	4731/1345059	1.4 (0.8–2.6)	1.5 (0.8–2.7)		
Neonatal death–CP	Twins	16/5227	2791/1342038	1.5 (0.9–2.4)	1.5 (0.9–2.5)	1.5 (1.03–2.2)	>0.9
CP–neonatal death		2/71	108/20542	5.5 (1.3–23)	5.6 (1.3–24)		
Neonatal death–CP		1/119	73/20494	2.4 (0.3–17)	2.4 (0.3–18)	4.3 (1.3–13.5)	0.5
CP–late neonatal death ^f	Singletons	7/2206	3598/1345059	1.2 (0.6–2.5)	1.2 (0.6–2.6)		
Late neonatal death–CP	Twins	13/5615	2794/1341650	1.1 (0.6–1.9)	1.1 (0.7–1.9)	1.2 (0.8–1.8)	0.8
CP–late neonatal death		2/71	75/20542	7.9 (1.9–33)	7.8 (1.8–33)		
Late neonatal death–CP		0/81	74/20532	—	—	—	

1322415 pairs of singleton full sibling neonatal survivors (survived >28 days) and 20058 pairs of twins neonatal survivors. Associations between CP in 1 sibling and early death in other siblings. 1347265 pairs of singleton full siblings and 20613 pairs of twins. Older sibling born term (gestational age ≥37 completed weeks for singletons and 36 for twins. Norway, 1967 to 2006. —, indicates it was not possible to calculate ORs due to zero cases.

^a Adjusted for older sibling's (or twins') year of birth in 5-year categories (eg, 1967–1971, 1972–1976).

^b Adjusted ORs combined with meta-analyses.

^c A total of 733281 pairs of singleton full sibs born between 1967 and 1990.

^d A total of 9872 pairs of twins born between 1967 and 1990.

^e Death from 0 to 28 days.

^f Death from 29 days to 1 year.

adjustment for shared causal factors would potentially reduce the associations. Our interest was in capturing the full overlap between various neurodevelopmental disorders, thus demonstrating the presence of shared causes. Therefore, restriction to isolated conditions or adjusting for possible shared etiologic factors may not be correct.

If 1 child in a family was diagnosed with CP, there was an increased risk of stillbirth or neonatal death in that child's sibling. This finding again suggests shared underlying causes. Death may be the most serious outcome of a brain injury that would have resulted in CP or another neurodevelopmental disorder had the child survived.

The present study had several major strengths, including the large sample size and population-based design. Both the insurance data and patient registry data have been found to be reasonably valid for CP diagnoses.^{16,19} However, other diagnoses studied here have not yet been validated. Both false-negative and false-positive diagnoses are possible. Affected persons who had not applied for insurance benefits before 2007 (therefore not identified through insurance data) and who were not in contact with the health care system during 2008 to 2011 (thus not identified through the patient registry) would not have been captured as cases. Conversely, mistaken coding, or suspected and later-refuted diagnoses, may result in false-positive cases. In addition, it is a concern that siblings of children with neurodevelopmental diagnoses may come under closer scrutiny by parents, teachers, and physicians and therefore be more readily diagnosed as having neurodevelopmental problems. Such a differential information bias could inflate the observed associations. The fact that bipolar disorder does not follow the pattern of other diagnoses provides some reassurance that surveillance

bias is not the basis for the observed associations. In addition, increased surveillance would not affect registration of perinatal deaths and thus does not explain the increased risk.

Another concern is the limited information available from the national registries. We lacked subtype information for the children with CP, and we also lacked results from imaging or other diagnostic procedures for CP. Such information might have allowed more detailed analyses of the types of CP most strongly related to neurodevelopmental disorders or early death in siblings.

An underlying assumption of our methods is that it is biologically random which sibling has which condition, which may not be true if some disorders are more closely associated with maternal age, for instance. However, we found no statistical evidence to suggest the associations were different if the child with CP was the older or the younger sibling.

The likelihood of being registered with a neurodevelopmental disorder was associated with year of birth (Table 1). This finding may reflect

real changes in incidence rates over time, although changes in diagnostic procedures or classifications are also likely explanations. In addition, many diagnoses cannot be made until later in life. CP in its milder forms cannot be reliably diagnosed until 5 years of age; ADHD is often not apparent before school age; and schizophrenia typically does not appear until late adolescence or early adulthood. Even so, adjusting for year of birth did not affect our results.

We have previously shown that having a first-born child with CP reduces the mother's probability of having a second child by 23%.⁵ If parents of the more serious cases are more likely to stop their reproduction due to the burden of care, and the more serious cases are more strongly related to common causes of neurodevelopmental disorders, our estimates would be biased toward the null, and the "true" underlying associations could be stronger than observed. In addition, our reported associations between CP and other neurodevelopmental disorders may be further underestimated because siblings of children with CP are more likely to be stillborn or die early

before they have the chance to be diagnosed.

CONCLUSIONS

In this large population-based study, CP was associated with an increased risk of other neurodevelopmental disorders in siblings. The associated disorders included autism spectrum disorder, ADHD, epilepsy, intellectual disability, blindness, and schizophrenia. Furthermore, CP was associated with a sibling's stillbirth or neonatal death. These findings suggest the presence of shared causal factors across a range of neurodevelopmental disorders and early death.

ABBREVIATIONS

ADHD: attention-deficit/hyperactivity disorder
CI: confidence interval
CP: cerebral palsy
ICD-9: *International Classification of Diseases, Ninth Revision*
ICD-10: *International Classification of Diseases, 10th Revision*
OR: odds ratio

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

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FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: Supported by grants from the University of Bergen, the Western Norway Regional Health Authority, and by the Intramural Research Program of the National Institute of Environmental Health Sciences, National Institutes of Health. Funded by the National Institutes of Health (NIH).

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

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