Maternal Chronic Conditions and Risk of Cerebral Palsy in Offspring: A National Cohort Study

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abstract

BACKGROUND AND OBJECTIVES: Previous studies suggest that children of mothers with certain chronic conditions may be at increased risk of cerebral palsy (CP). We explored possible associations between 17 maternal chronic conditions and CP in offspring.

METHODS: We conducted a prospective cohort study of Norwegian children born in 1990–2012 and surviving to 2 years of age. Information on maternal chronic conditions during pregnancy were extracted from the Medical Birth Registry of Norway (1990–2012). Information on chronic conditions in mothers and fathers recorded in the Norwegian Patient Registry (2008–2014) was available for a subset of children. CP diagnoses were extracted from the National Insurance Scheme (1990–2014) and the Norwegian Patient Registry (2008–2014). We estimated relative risks (RRs) and 95% confidence intervals (CIs) of CP in offspring of parents with chronic conditions compared with the general population using log binominal regression models.

RESULTS: A total of 1 360 149 Norwegian children, including 3575 children with CP (2.6 per 1000 live births), fulfilled the inclusion criteria. The highest risk of CP was among offspring of mothers with type 2 diabetes (RR 3.2; 95% CI 1.8–5.4), lupus erythematosus (RR 2.7; 95% CI 0.9–8.3), type 1 diabetes (RR 2.2; 95% CI 1.4–3.4), and Crohn disease (RR 2.1; 95% CI 1.0–4.1) during pregnancy. No increased risks were seen for offspring of fathers with chronic conditions.

CONCLUSIONS: Several maternal chronic conditions were associated with increased risk of CP in offspring. Maternal autoimmune disorders carried a particular risk.

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WHAT'S KNOWN ON THIS SUBJECT: Most cases of cerebral palsy (CP) occur without known cause. Previous studies suggest that children of mothers with certain chronic conditions may be at increased risk of CP, but this possibility has not been systematically explored.

WHAT THIS STUDY ADDS: Several maternal conditions, particularly autoimmune disorders, were associated with increased risk of CP in offspring. Paternal chronic conditions were not.

ARTICLE

Cerebral palsy (CP) is a nonprogressive movement disorder and a major cause of childhood disability.[1] The etiologies of CP are complex, and only a few prenatal risk factors have been identified.[2] Among these possible risk factors are maternal chronic conditions, although studies are typically underpowered and limited to one or two conditions.[3–7]

A role for maternal chronic conditions in the etiology of CP is not implausible. Inflammation, altered thrombotic state, and placental abnormalities are all features of maternal chronic conditions,[8–10] and all have been linked to CP.[2,11] Maternal chronic conditions are also associated with preterm delivery, reduced Apgar scores, and congenital malformations,[12,13] which are strong predictors of CP.[2,14] There has been no systematic description of maternal chronic conditions and risk of CP in offspring. We used Norwegian national health registries to assess associations between a broad spectrum of maternal chronic conditions and risk of CP in offspring.

METHODS

Study Population

We identified all children born in Norway from 1990 to 2012 who survived to 2 years of age (Fig 1). We also linked the parents of these children to the Norwegian Patient Registry, which provided information on both maternal and paternal diagnoses. Linkage was possible for mothers and fathers born in Norway from 1967 onward (Fig 1).

Data Sources

Data on an individual level were captured through linkage of Norwegian national registries by use of personal identification numbers.[15] We linked persons through 5 registries: the Norwegian Medical Birth Registry (1990–2014),[16] the
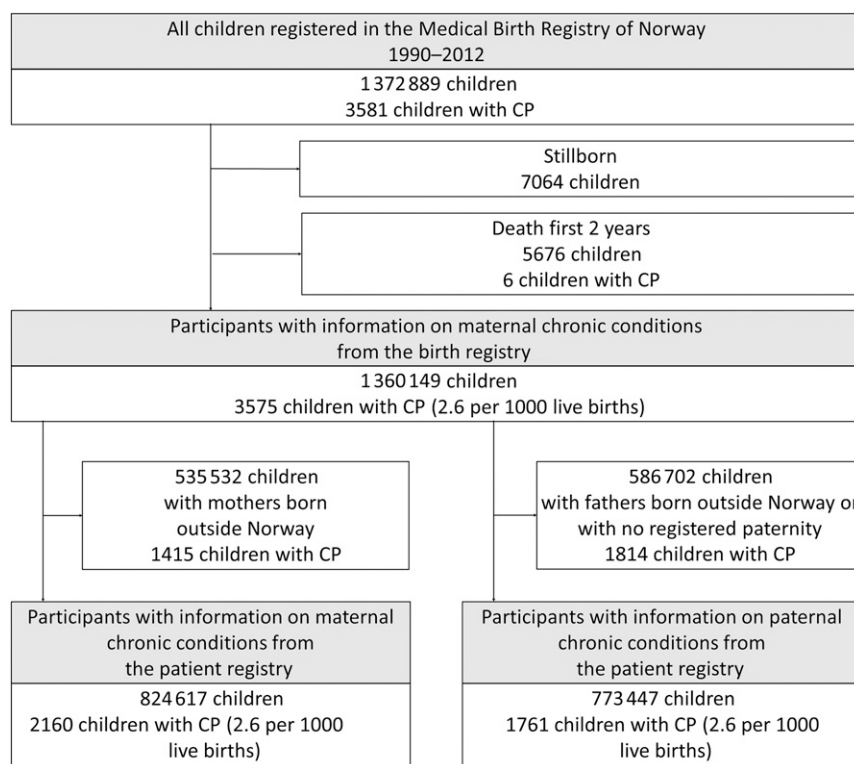

FIGURE 1
Selection of study population.

Norwegian Patient Registry (2008–2014),[17] the Norwegian Insurance Scheme (1990–2014),[18] the Norwegian Cause of Death Registry (1990–2014),[19] and the Norwegian National Education Database (1990–2014).[20]

The birth registry comprises information on all live births and stillbirths from 1967 onward.[16] Information is reported by midwives at the time of delivery on the basis of pregnancy notification forms and hospital records from pregnancy and birth-until-discharge records from hospitals. In December 1998, the birth registry changed registration of conditions from *International Classification of Diseases, Eighth Revision* to *International Classification of Diseases, 10th Revision* (ICD-10) codes and introduced a new notification form. Maternal chronic conditions recorded in the birth registry was the basis for our primary analyses.

Since 2008, the patient registry provides individually identifiable data on diagnoses recorded at visits to specialist care, which does not specifically include the date of first diagnosis.[17]

The insurance scheme pays cash benefits to families of children with chronic diseases irrespective of family income. As disabled children reach adulthood, they are eligible for direct pension payments. The disability must involve significant expenses and need for extra care.[18]

Dates of death were provided by the cause of death registry,[19] and information on parents' education was provided by the education database.[20]

Exposures

We identified chronic medical conditions considered to be clinically relevant for women of childbearing age. Information on the conditions was extracted from the birth registry

by using *International Classification of Diseases* codes (Supplemental Table 4). Conditions for which no mother had a child with CP were excluded. Thyroid disorders were grouped into a single category. Type 1 and type 2 diabetes were distinguished only in the more recent period (ICD-10 codes, 1999–2012). We examined CP risk in offspring for specific maternal conditions, for any chronic condition, and for 1, 2, or ≥3 diagnoses of chronic conditions.

Autoimmune conditions are frequent in women of childbearing age[21] and share underlying biological mechanisms. It was of particular interest to examine these conditions further, but there is not a well-established criterion for this category of disease. We therefore defined "any autoimmune condition" as those identified both by the American Autoimmune Related Association[22] and in a review by Hayter and Cook.[23] These consensus diseases comprised type 1 diabetes, lupus erythematosus, Crohn disease, rheumatoid arthritis, multiple sclerosis, thyroid disorders, ulcerous colitis, and celiac disease (Supplemental Table 4). We also considered risk for mothers with 1 and ≥2 autoimmune diseases.

Although we had no direct measure of disease severity, we did have information on specific complications of advanced disease for some conditions. We classified those mothers with type 1 or type 2 diabetes, lupus, or rheumatoid arthritis who also had hypertension, kidney disease, or heart failure as having severe disease.

It is possible that genetic factors or unmeasured lifestyle or environmental conditions might contribute to maternal disease and also to risk of CP in offspring. To explore this possibility, we assessed the risk of CP among fathers with chronic diseases. To make a proper comparison with mothers, we had to restrict the sample to children of parents linked to the patient registry, which was the only source of chronic disease information that included both mothers and fathers.

Main Outcome

CP diagnoses were obtained from the insurance scheme and the patient registry (1990–2014).[17,18] We defined a person with CP as any person who received a benefit or disability pension on the basis of a CP diagnosis in the insurance scheme or who was registered with a CP diagnosis at least twice in the patient registry. Diagnostic codes for inclusion are presented in Supplemental Table 4.

Covariates

Information on parents' education was obtained from the national education database.[20] Mother's and father's education was categorized as low (primary and lower secondary education), medium (upper secondary and short nontertiary education), and high (college, university, or doctoral degree). Information on year of birth, gestational age, multiple births, parental age, and maternal smoking was available through the birth registry. Single motherhood was defined as unmarried mothers living alone at the time of delivery. Term birth was defined as gestational age ≥37 weeks on the basis of ultrasound measurement on the last menstrual period if the ultrasound measurement was not available. Information on maternal smoking was available from 1999 onward and defined as daily smoking at some time during pregnancy.

Statistical Analysis

Log binominal regression models were used to estimate relative risks (RRs) and corresponding 95% confidence intervals (CIs) for CP by parents' disease status compared with the general population without the disease. We also used logistic and Poisson regression models to check for consistency. Correlations among siblings were taken into account by using robust SE clustering. All analyses were adjusted for year of birth. For maternal disease status in the birth registry, we also adjusted for maternal age, maternal education, and single motherhood. We repeated the analysis for 1999–2012 to allow additional adjustment for maternal smoking.

In sensitivity analyses, we excluded preterm births, children with malformations, multiple births, and mothers registered with >1 condition. Population attributable risk fractions and 95% CIs were calculated for any maternal chronic condition and for any autoimmune condition.

Children missing data for specific variables were excluded. Maternal smoking status was missing for 16% of pregnancies; all other variables had <5% of missing data. Stata version SE 16 (Stata Corp, College Station, TX) and SPSS version 24 (IBM SPSS Statistics, IBM Corporation) were used for the analyses.

Ethical Approval

The Regional Committee for Medical and Health Research Ethics in Norway approved the study (reference number 2010/2949). The approval included a waiver of individual study participant consent.

RESULTS

A total of 1 360 149 Norwegian children fulfilled the inclusion criteria and were followed for a period of 2 to 24 years. These children included 3575 with CP (2.6 per 1000 live births). Information from the patient registry was available on mothers' diagnoses for 824 617 children, including 2160 with CP (2.6 per 1000 live births), and on fathers' diagnoses for 773 447 of the children, including 1761 with CP (2.4 per 1000 live births) (Fig 1). Characteristics of the

TABLE 1 Characteristics of the Study Population

Maternal Disease	Maternal Age, % (No.)		Maternal Education,[a] % (No.)		Single Mother, % (No.)	Gestational Age, % (No.)			Multiple Births, % (No.)	Maternal Smoking,[b] % (No.)
	≤18 y	≥40 y	Low	High		<32 wk	32–36 wk	>42 wk		
Type 2 diabetes[b]	0.2 (4)	7.7 (136)	29.4 (488)	36.6 (607)	7.3 (128)	1.7 (30)	14.1 (249)	1.2 (21)	4.3 (75)	15.4 (271)
Lupus erythematosus	0	3.3 (15)	14.4 (65)	54.5 (246)	7.4 (34)	3.5 (16)	15.2 (70)	1.5 (7)	4.8 (22)	13.1 (51)
Type 1 diabetes[b]	0.8 (27)	3.3 (123)	19.0 (705)	48.7 (1808)	6.8 (258)	2.7 (101)	22.3 (842)	1.2 (46)	3.7 (140)	16.0 (603)
Crohn disease	0.2 (3)	1.7 (27)	13.0 (206)	52.2 (830)	4.7 (75)	1.6 (25)	8.9 (143)	1.9 (30)	3.8 (61)	18.0 (261)
Rheumatoid arthritis	1.1 (55)	3.2 (157)	21.9 (1079)	43.6 (2146)	7.8 (386)	1.1 (55)	7.4 (369)	6.4 (323)	3.9 (194)	16.7 (433)
Multiple sclerosis	0.2 (2)	3.1 (35)	13.6 (148)	56.2 (611)	4.9 (54)	1.0 (11)	6.6 (72)	3.4 (37)	4.1 (45)	14.5 (119)
Migraine	1.0 (124)	2.8 (354)	15.1 (1871)	53.5 (6644)	6.8 (858)	0.9 (109)	5.7 (716)	2.4 (305)	3.3 (416)	13.1 (1408)
Chronic hypertension	0.3 (18)	6.5 (427)	17.0 (1102)	48.3 (3135)	5.0 (327)	3.5 (233)	12.5 (827)	3.4 (222)	3.6 (237)	13.4 (657)
Anemia	1.2 (40)	3.1 (103)	27.8 (861)	39.2 (1213)	7.3 (242)	1.1 (38)	6.3 (210)	6.2 (207)	3.1 (104)	9.6 (178)
Asthma	2.0 (978)	2.3 (1136)	23.1 (11 229)	42.8 (20 801)	10.2 (5024)	0.9 (464)	6.1 (3006)	4.4 (2167)	3.3 (1618)	21.8 (7803)
Thyroid disorder	0.3 (38)	5.0 (766)	13.9 (2063)	57.2 (8503)	5.0 (758)	1.2 (187)	6.7 (1019)	0.3 (43)	4.2 (644)	11.9 (1463)
Epilepsy	1.7 (161)	2.1 (191)	25.4 (2315)	39.1 (3558)	9.4 (871)	1.1 (104)	6.8 (627)	5.7 (524)	3.0 (279)	19.6 (1194)
Ulcerous colitis	0.3 (6)	2.8 (69)	9.5 (230)	62.4 (1504)	4.2 (101)	1.1 (27)	7.1 (172)	2.3 (55)	3.9 (94)	9.6 (206)
Gestational diabetes	0.4 (57)	6.2 (867)	23.7 (3160)	43.0 (5706)	5.5 (759)	1.2 (162)	9.7 (1345)	3.8 (531)	4.6 (630)	13.0 (1400)
Celiac disease	0.6 (17)	2.5 (75)	13.5 (399)	56.8 (1681)	5.5 (165)	0.6 (17)	5.2 (156)	3.9 (117)	3.6 (107)	9.5 (221)
Heart disease	0.6 (44)	3.4 (233)	17.5 (1164)	52.1 (3474)	6.8 (473)	1.2 (81)	7.8 (540)	2.6 (180)	4.0 (275)	13.8 (818)
Chronic kidney disease	1.8 (236)	1.9 (248)	22.1 (2861)	43.9 (5692)	9.0 (1190)	1.3 (177)	7.8 (1021)	6.9 (912)	3.2 (419)	18.8 (1183)
Any autoimmune condition[b]	0.5 (134)	4.0 (1182)	14.2 (4080)	55.9 (16 054)	5.7 (1661)	1.4 (399)	8.7 (2544)	0.2 (60)	4.1 (1195)	15.2 (3842)
Any chronic condition	1.2 (1690)	3.2 (4571)	20.4 (27 623)	46.7 (63 151)	7.9 (10 798)	1.2 (1643)	7.6 (10 228)	1.0 (1338)	3.6 (4956)	3.4 (24 954)
No condition[c]	1.1 (7405)	2.5 (18 101)	16.9 (117 594)	53.1 (370 602)	6.1 (43 495)	0.9 (6362)	5.4 (38 623)	0.3 (2240)	3.4 (24 994)	14.1 (102 254)
Total population	1.3 (17 089)	2.2 (30 081)	18.1 (246 576)	46.8 (638 242)	6.8 (92 314)	0.9 (12 326)	5.3 (72 645)	5.5 (74 557)	3.2 (44 038)	14.4 (118 366)

a Highest education level (low: primary school; high: college, university, or PhD).
b Data available for 1999–2013.
c Children of mothers with none of the diseases listed above.

TABLE 2 RR of CP in Offspring by Maternal Chronic Condition in the Medical Birth Registry of Norway

Maternal Condition	Exposed No.	Exposed With CP No. (per 1000)	aRR (95% CI)[a]
Type 2 diabetes[b]	1765	13 (7.4)	3.2 (1.8–5.4)
Lupus erythematosus	460	3 (6.5)	2.7 (0.9–8.3)
Type 1 diabetes[b]	3771	20 (5.3)	2.2 (1.4–3.4)
Crohn disease	1609	8 (5.0)	2.1 (1.0–4.1)
Rheumatoid arthritis	4977	26 (5.2)	2.0 (1.3–2.9)
Multiple sclerosis	1100	3 (6.5)	1.8 (0.8–4.4)
Migraine	12 590	49 (3.9)	1.6 (1.2–2.2)
Chronic hypertension	6609	23 (3.3)	1.4 (0.9–2.1)
Anemia	3320	12 (3.6)	1.4 (0.8–2.4)
Asthma	49 375	148 (3.0)	1.2 (1.0–1.4)
Thyroid disorder	15 316	44 (2.9)	1.2 (0.9–1.6)
Epilepsy	9258	29 (3.1)	1.2 (0.8–1.7)
Ulcerous colitis	2430	7 (2.9)	1.2 (0.5–2.8)
Gestational diabetes	13 852	36 (2.6)	1.1 (0.8–1.5)
Celiac disease	2989	8 (2.7)	1.1 (0.5–2.2)
Heart disease	6900	16 (2.3)	1.0 (0.6–1.6)
Chronic kidney disease	13 179	32 (2.4)	0.9 (0.6–1.3)
Any autoimmune condition[b]	32 662	117 (3.6)	1.4 (1.1–1.7)
Any chronic condition	138 195	432 (3.1)	1.3 (1.2–1.5)

All analyses are adjusted for year of birth. aRR, adjusted relative risk.
[a] Results are presented in Fig 2.
[b] Data available for 1999–2012.

study population are presented in Table 1.

Overall, mothers with chronic conditions had a 30% increased risk of CP in their offspring (RR 1.3; 95% CI 1.2–1.5). The strongest associations were for type 2 diabetes (RR 3.2; 95% CI 1.8–5.4), lupus erythematosus (RR 2.7; 95% CI 0.9–8.3), type 1 diabetes (RR 2.2; 95% CI 1.4–3.4), and Crohn disease (RR 2.1; 95% CI 1.0–4.1). Increased risk of CP in offspring was also associated with rheumatoid arthritis (RR 2.0; 95% CI 1.3–2.9), multiple sclerosis (RR 1.8; 95% CI 0.8–4.4), and migraine (RR 1.6; 95% CI 1.2–2.2). Weaker and less convincing associations were found for chronic hypertension, anemia, asthma, epilepsy, thyroid disorder, and ulcerous colitis (Table 2, Fig 2). Risk increased from 1.3 (95% CI 1.1–1.4) with any single condition, to 1.6 (95% CI 1.1–2.4) with 2 conditions, and to 3.4 (95% CI 1.5–7.7) with ≥3 conditions (Table 3).

Mothers with any autoimmune disease had a 40% increased risk of CP in their offspring (RR 1.4; 95% CI

1.1–1.6) (Table 2). The RR was 1.4 (95% CI 1.1–1.7) with a single autoimmune diagnosis and 2.7 (95% CI 1.1–6.6) with ≥2 (Table 3). Only a few children had mothers with type 1 or type 2 diabetes, lupus erythematosus, or rheumatoid arthritis complicated by other diseases, but risk estimates were markedly increased for this group (Supplemental Table 5). Overall, the population attributable fraction was 3% for any maternal condition (95% CI 2%–5%) and 1% for autoimmune diseases (95% CI 0%–2%).

Analyses using logistic and Poisson regression models yielded similar results, as did analyses with additional adjustment for parental age, parental education, and single-mother status (Supplemental Table 6). Adjustment for smoking in sensitivity analyses had little effect on the results. Effect estimates were largely unchanged after analyses were restricted to children born at term, with the notable exception of maternal type 1 diabetes, for which there was no association with CP among term births. Similarly,

restricting analyses to children with no malformation, singletons, and mothers registered with only 1 condition did not change effect estimates (Supplemental Table 7).

Compared to associations with maternal conditions recorded at delivery, associations with maternal conditions from the patient registry were generally attenuated. This may reflect the fact that diagnoses from the patient registry could have occurred long after the pregnancy of interest. By using the patient registry data, the highest risk of CP in offspring was for mothers with type 2 diabetes (RR 2.5; 95% CI 1.9–3.3), type 1 diabetes (RR 2.2; 95% CI 1.7–3.0), chronic hypertension (RR 1.8; 95% CI 1.4–2.3), lupus erythematous (RR 1.7; 95% CI 0.7–3.7), and chronic kidney disease (RR 1.5; 95% CI 0.9–2.4). Chronic conditions in fathers revealed no associations (Fig 3, Supplemental Table 8).

DISCUSSION

Using a national registry–based cohort of >1.3 million children, we found that a broad range of maternal chronic conditions were associated with increased risk of CP in offspring. The associations were stronger for diagnoses reported at the time of delivery and especially for mothers with multiple diagnoses. Autoimmune conditions carried a particular risk. We found no increased risk of CP in offspring of fathers with chronic conditions.

Strengths and Weaknesses

Linking individual data across several national health registries allowed for a thorough investigation of chronic conditions in mothers and CP risk in offspring. The quality of maternal diagnoses in the birth registry has been confirmed through validation studies of rheumatoid arthritis, diabetes, asthma, and epilepsy,[24–26] each with high specificity and sensitivity. It is possible that the
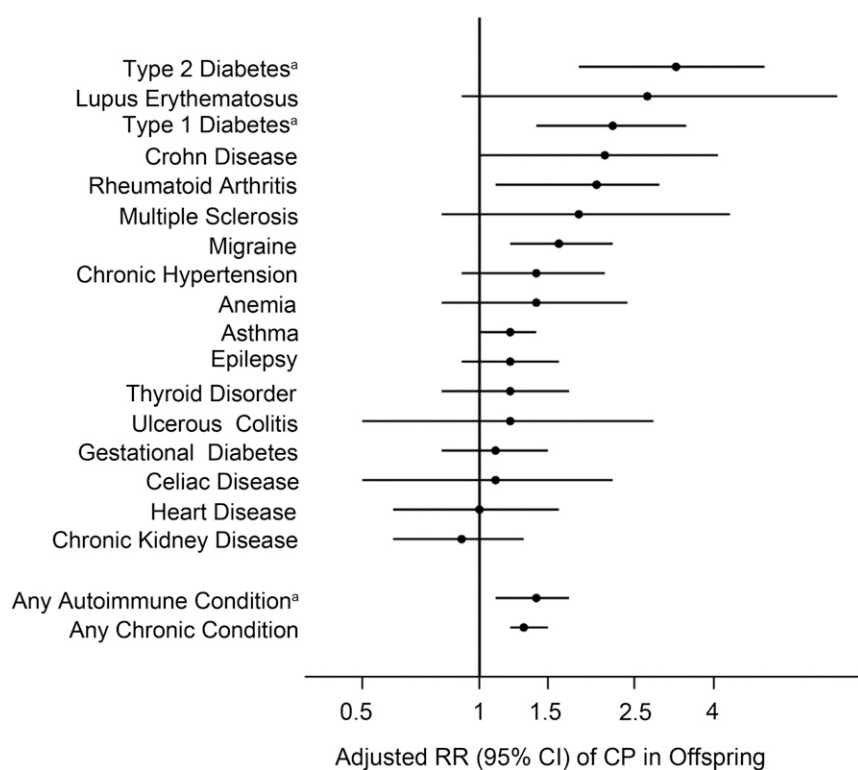
FIGURE 2
RR of CP by maternal chronic condition in the Medical Birth Registry of Norway. Analyses are adjusted for year of birth, and corresponding numbers are presented in Table 2. [a] Data available 1999–2012.

recording of maternal diagnoses in the birth registry is not totally independent of CP risk in offspring. For instance, a difficult delivery might make it more likely that a maternal chronic condition is noted. This concern is somewhat mitigated by the fact that maternal diagnoses recorded in the national patient registry also were linked to CP risk, although those diagnoses are registered independent of pregnancy and delivery.

A validation study of CP diagnoses in the insurance scheme revealed a sensitivity of 70% (underreporting of milder cases) but a specificity of 99%.[14] A validation study of CP diagnoses in the patient registry, using the Cerebral Palsy Registry of Norway, conversely found high sensitivity (98%) but lower specificity (86%).[27] Combining validated CP diagnoses from these 2 sources should provide valid

information. CP cases can nonetheless be missed if affected infants die before diagnosis. Because a diagnosis of CP often cannot be made reliably until the age of at least 2 years,[28] stillbirths and children who died within 2 years of age were not included. Because the risk of being stillborn and dying early is higher for children of mothers with chronic

disease,[12,13] this exclusion could cause RRs to be underestimated.

There is no universally accepted definition for autoimmune diseases. We used a consensus between two authoritative definitions.[22,23] We lacked detailed information on many subcategories of autoimmune diseases, and there may be interesting patterns within specific subgroups of autoimmune diseases that we cannot detect.

Both the outcome (CP in children) and the exposures (chronic conditions in parents) are rare. Thus, although our study population included >1.3 million children, we still lacked power in some strata. We performed multiple analyses, and spurious associations due to multiple testing cannot be excluded. Nonetheless, a number of strong associations were identified. The consistency of these associations across two independent measures of maternal chronic diseases adds to their validity.

Preterm delivery and congenital malformations are potential mediating variables on the causal pathway between maternal illness and CP in offspring.[11,12] Although adjustment for mediating variables (especially preterm delivery) is subject to collider stratification bias,[29,30] we found that excluding these infants from the analysis had no impact on results.

TABLE 3 RR of CP in Offspring by Number of Maternal Chronic Conditions in the Medical Birth Registry of Norway

Maternal Condition	Exposed No.	Exposed With CP No. (per 1000)	aRR (95% CI)
No autoimmune condition[a,b]	1 328 494	3459 (2.6)	Reference
1 autoimmune condition[a,b]	30 809	111 (3.6)	1.4 (1.1–1.7)
>1 autoimmune condition[a,b]	846	5 (5.9)	2.7 (1.1–6.6)
No conditions[c]	1 222 386	3143 (2.6)	Reference
1 condition[c]	128 390	394 (3.1)	1.2 (1.1–1.4)
2 conditions[c]	9054	33 (3.6)	1.6 (1.1–2.2)
>2 conditions[c]	751	5 (6.7)	3.1 (1.4–6.8)

All analyses are adjusted for year of birth. aRR, adjusted relative risk.
[a] Data available for 1999–2012.
[b] Children of mothers with none, 1, or >1 autoimmune condition listed in Table 2.
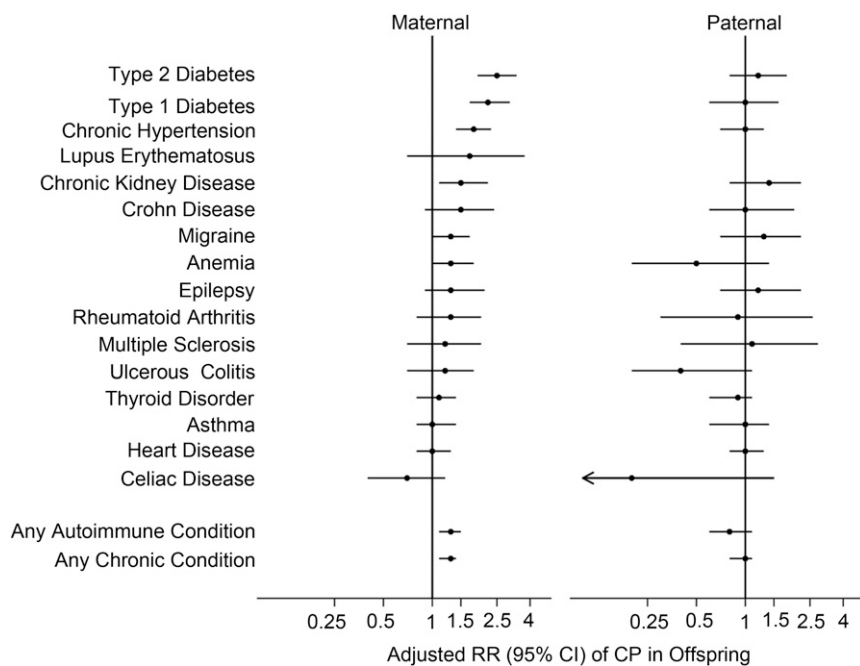[c] Children of mothers with none, 1, 2, or >2 of the conditions listed in Table 2.

FIGURE 3
RR of CP by parental chronic condition in the Norwegian Patient Registry. Analyses are adjusted for year of birth, and corresponding numbers are presented in Supplemental Table 8.

We cannot rule out unmeasured confounding. For example, BMI is associated with many of the chronic conditions[9] as well as with risk of CP.[31] Data on BMI were not available for our study period. More general lifestyle and environmental confounding factors would presumably have produced associations for fathers as well. The absence of associations with fathers' chronic conditions suggests these are not an important concern. Treatment of a chronic disease might contribute to the observed associations. Chronic conditions often require treatment with drugs that might influence the risk of CP by being either directly harmful to neurodevelopment or indirectly harmful through modification of the severity of the disease. Finally, we lacked information on subtypes of CP, date of parental diagnosis, confirmed paternity, and valid indicators of the severity of the diseases, all of which could be informative in understanding the underlying biological mechanisms by which maternal disease might affect offspring risk of CP.

Comparison With Other Studies

Researchers of previous studies exploring these associations have typically considered only 1 or 2 conditions. In a Swedish register–based study, a twofold increase in CP risk with maternal type 1 diabetes was found,[3] consistent with our results. In a retrospective case-control study, a sevenfold higher incidence of CP in offspring of mothers with chronic kidney disease was found,[4] but this may be a function of a small sample size. We found no association with renal disease in the birth registry data and only a 1.5 RR in the patient registry. Maternal thyroid function is known to affect neurodevelopment in offspring, and hypothyroidism, in particular, may be associated with CP.[7] In a recent Danish population–based cohort study, researchers reported an odds ratio of 3.1 for unilateral spastic CP in offspring of mothers with any thyroid disorder in pregnancy.[6] We only found a risk estimate of 1.2 with thyroid disorders overall, but we were unable to assess subtypes of CP.

Interpretation of Results

The role of autoimmune diseases in CP risk (and maternal inflammation specifically) deserves closer attention. Infection is well recognized as a condition associated with CP,[11] but less is known about inflammation in the absence of an infectious agent. There is a linear relationship between BMI and risk of CP in offspring,[32] suggesting a link between inflammation and CP in offspring. Specific cytokines that have elevated levels in autoimmune conditions (such as interleukin 1β, interleukin 6, interleukin 17A, and tumor necrosis factor α) also have elevated levels in children with CP.[33–35] The highest and most consistent risk of CP in our data was in offspring of mothers with diabetes. High glucose levels enhance the expression of inflammatory cytokines,[36] but other factors linked to maternal diabetes, such as neonatal macrosomia and neonatal hypoglycemia,[37] may also contribute. Autoimmune-related autoantibodies, particularly antiphospholipid antibodies, have been suggested to interfere with embryotic implantation, hormonal and cytokine balance, and complement activation, all of which potentially affect fetal neurodevelopment as well.[38] Another pathway could be through placental abnormalities and insufficiency or changes in coagulation status, any of which can predispose to neonatal stroke and thereby affect fetal neurodevelopment. Using studies with larger sample sizes and a more clinical focus, including measures of placental structure and perinatal blood assays, researchers may be able to explore these possible connections between maternal autoimmune diseases and fetal neurodevelopment.

We did not have information on severity or duration of maternal diseases. Type 1 and type 2 diabetes

were more strongly related to CP than gestational diabetes, which may be due to more severe metabolic changes or to the presence of disease earlier in pregnancy, when brain development is more vulnerable to structural damage. Conditions with concurrent complications revealed stronger risk of CP, but numbers were too low to draw firm conclusions (Supplemental Table 5).

If maternal chronic conditions increase the risk of CP, they may also affect other neurodevelopmental problems. In a recent study, authors reported an increased risk of attention-deficit/hyperactivity disorder in the offspring of mothers with a similar range of chronic conditions.[39]

The lack of associations between the father's chronic illness and CP risk supports the interpretation that CP risk in offspring is the direct result of the mother's condition and not genetic predisposition or unmeasured situational factors. Perhaps the largest caveat with the analysis of fathers is that men are less likely to have many of the conditions reported for women,[21] especially autoimmune diseases, which decreases our power to detect associations. Men may also be less likely to seek medical services, but this probably does not affect registration of serious disease. Error in paternity would also suppress associations. Given these limitations, the lack of associations with fathers' conditions does not exclude the possibility of genetic mechanisms that influence fetal neurodevelopment. Both CP and autoimmune conditions are known to cluster within families.[21,40] It would be of interest to explore familial patterns of autoimmune conditions and their possible associations with familial patterns of CP and other neurologic disabilities.

The population fraction of CP attributable to maternal chronic conditions is necessarily small because (fortunately) so few mothers have chronic diseases. We estimate that all chronic conditions together contribute to 3% of CP cases and that autoimmune conditions contribute to just 1% of CP cases. Although these associations do not amount to a heavy public health burden, they do suggest biological pathways that may lead to CP, pathways for which interventions might eventually be possible.

CONCLUSIONS

Several maternal chronic conditions, particularly autoimmune disorders, were associated with increased risk of CP in offspring. Risk was higher if the disease was known to be present during pregnancy and among mothers with multiple chronic conditions.

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ABBREVIATIONS

CI: confidence interval
CP: cerebral palsy
ICD-10: *International Classification of Diseases*, 10th Revision
RR: relative risk

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