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Attention-Deficit/Hyperactivity Disorder in Offspring of Mothers With Inflammatory and Immune System Diseases

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ABSTRACT

BACKGROUND: Prenatal inflammatory mechanisms may play a role in the pathogenesis of psychiatric disorders and could be relevant for attention-deficit/hyperactivity disorder (ADHD). We investigated maternal chronic somatic diseases with immune components as possible risk factors for ADHD in offspring.

METHODS: We performed a population-based nested case-control study by linking data from longitudinal Norwegian registers. We included all individuals born during the period 1967–2008 and alive at record linkage (2012). Individuals receiving ADHD medication during the years 2004–2012 were defined as patients with ADHD (N = 47,944), and all remaining individuals (N = 2,274,713) were defined as control subjects. The associations between maternal diseases and ADHD in offspring were analyzed using logistic regression models.

RESULTS: The following chronic diseases with immune components were related to ADHD in offspring: multiple sclerosis (adjusted odds ratio [OR] = 1.8; 95% confidence interval [CI] = 1.2–2.5), rheumatoid arthritis (adjusted OR = 1.7; 95% CI = 1.5–1.9), type 1 diabetes (adjusted OR = 1.6; 95% CI = 1.3–2.0), asthma (adjusted OR = 1.5; 95% CI = 1.4–1.6), and hypothyroidism (adjusted OR = 1.2; 95% CI = 1.1–1.4). In contrast, chronic hypertension and type 2 diabetes showed no significant associations. Estimates were almost unchanged with additional adjustment for parental ADHD, infant birth weight, and gestational age. Although point estimates for male and female offspring were different for some diseases (e.g., maternal asthma [adjusted OR = 1.7; 95% CI = 1.5–1.8 for female offspring and adjusted OR = 1.5; 95% CI = 1.4–1.6 for male offspring]), none of the associations differed significantly by offspring sex.

CONCLUSIONS: Several maternal somatic diseases with immune components were found to increase the risk of ADHD in offspring. The associations could involve several causal pathways, including common genetic predisposition and environmental factors, and increased insight into the mechanisms behind these relationships could enhance our understanding of the etiology of ADHD.

Keywords: ADHD, Attention-deficit/hyperactivity disorder, Immune disease, Inflammatory disease, Maternal effects, Risk factors

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Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder that affects children and adults worldwide, with prevalence estimates ~5% in children (1) and 3% in adults (2). The prevalence varies among studies; in a Norwegian study of children 8–10 years old, it was estimated to be 1.7% (3). The disorder is two to three times more frequent in boys than girls (4), although the sex distribution becomes more equal with age (5). The etiology of ADHD is complex, involving interactions between genetic and environmental factors, and many risk pathways may lead to its clinical features (6).

Previous studies described several prenatal and perinatal risk factors for ADHD. Low birth weight (7–12), preterm birth (8,9,13–16), and small size for gestational age (8,16) have consistently been related to an increased risk of ADHD or ADHD symptoms. Exposure to maternal smoking (17) and other substances in utero (6) also have been reported to be associated with increased risk of ADHD. Furthermore, associations with ADHD in offspring have been found for some maternal medical conditions, including obesity (18) and epilepsy (8). It has been hypothesized that ADHD may be caused by an exaggerated central nervous system inflammatory response in the fetus caused by maternal inflammation, such as in allergy or autoimmune disease (19). It is difficult to draw conclusions about causal pathways, as associations between maternal diseases and ADHD in offspring can involve several different, partly overlapping, causal pathways. Common genetic predisposition, environmental factors such as maternal medication exposures, and fetal inflammatory response are examples of such causes. Because few studies have

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evaluated maternal immune system diseases, we investigated whether such diseases were associated with ADHD in offspring using data from nationwide registers in Norway. Additionally, we assessed whether these risk factors differed by patient's sex.

METHODS AND MATERIALS

This study was approved by the Norwegian Data Protection Authority, the Norwegian Directorate of Health, and the Regional Committee for Medical and Health Research Ethics (2011/2272). The data were treated anonymously, and so no further consent was required.

We performed a population-based nested case-control study by linking information from the Medical Birth Registry of Norway (MBRN), the Norwegian Prescription Database (NorPD), and the National Educational Database. In a sensitivity analysis, we also included data from the Norwegian Patient Registry.

The nationwide MBRN was established in 1967 and contains information on nearly 2.6 million births up to 2012. The registration is based on compulsory notification and includes information on all live births and fetal losses/stillbirths from 16 weeks of gestation. A standardized form is used to document information on maternal health before and during pregnancy, complications during pregnancy and delivery, and birth outcomes. For the years 1967–1998, information was mainly documented as free text specifications to items such as "Maternal health before pregnancy," "Maternal health during pregnancy," "Complications in relation to birth," and "Infant outcomes." A more detailed documentation form, introduced in 1999, included information on maternal smoking habits and check boxes for specific conditions in addition to free text (20). The NorPD covers all prescribed drugs dispensed to individuals in Norway since 2004. From 2008, NorPD includes diagnostic codes (ICD-10/International Classification of Primary Care, Second edition) for reimbursed drugs (21). The level of education of all Norwegian inhabitants from 16 years of age is registered annually in the National Education Database. The Norwegian Patient Registry provides information on diagnoses of all patients having contact with specialist health services from 2008.

Study Population and Variable Information

Record linkage was established by using the personal identity number unique to every Norwegian resident. This study included all individuals born from 22 weeks of gestation or with birth weight at least 500 g in Norway during the period 1967–2008 who were still alive at record linkage in 2012 (N = 2,322,657).

Cases in this study consisted of all registered individuals in MBRN born during the period 1967–2008 who had been prescribed and dispensed ADHD medications during the years 2004–2012 and were >3 years old at last prescription.

The dispensed and reimbursed ADHD medications methylphenidate (Anatomical Therapeutic Chemical Classification System [ATC] code N06BA04), atomoxetine (ATC code N06BA09), and racemic amphetamine (ATC code N06BA01) were extracted from the NorPD. The use of ADHD medication is restricted in Norway; medical treatment of ADHD is initiated only after thorough assessment of the patient by a specialist in psychiatry or child psychiatry. Dexamphetamine (ATC code N06BA02) was off label in Norway during the study period and is not used as a first-option treatment and therefore was not included in our case definition. Drugs used to treat ADHD may also be used for narcolepsy. Using the reimbursement codes from 2008, we found that 117 individuals (1.4%) were dispensed stimulant medication with the indication narcolepsy, and these were excluded from the case group. Thus, for patients who were dispensed medicine in the period 2004–2008 only, there may be a small number of individuals with narcolepsy left in the case group.

The control group included all registered individuals in MBRN born during the period 1967–2008 and alive at record linkage who had not been dispensed ADHD medication during the period 2004–2012. The 117 individuals who were dispensed stimulant drugs for narcolepsy in the period 2008–2012 were included in the control population (N = 2,274,713). Thus, by design, the control group included people with a diagnosis of ADHD who did not receive ADHD medication or who had used (and stopped using) ADHD medication before 2004 when the NorPD was established.

Maternal educational level was used as a measure for socioeconomic level and grouped in three categories: low (<10 years), medium (10–12 years), and high (>12 years).

Description of Variables

As potential prenatal risk factors for ADHD, we studied the following maternal chronic somatic diseases, all with inflammatory or immune components of pathologic relevance: multiple sclerosis, asthma, rheumatoid arthritis, hypothyroidism, hyperthyroidism, and pregestational type 1 diabetes. Pregestational type 2 diabetes and chronic hypertension were also included. Because we assumed that immunologic/inflammatory mechanisms are less strongly involved in these conditions, they were included to serve as contrasting chronic diseases in the analyses. We chose the diseases included in the analyses using several criteria. Our focus was immune system diseases, and we selected diseases for which the MBRN registration was previously validated (pregestational type 1 and 2 diabetes, rheumatic arthritis, asthma) (20,22), diseases that were previously described in the literature with data from MBRN (multiple sclerosis) (23–25), diseases for which the MBRN notification form from 1999 had specific check boxes (asthma, diabetes type 1 and 2, rheumatic arthritis and chronic hypertension), and diseases for which the MBRN reported significantly increasing time trends in prevalence and for which associations with ADHD in offspring was previously discussed (thyroid disorders) (26–29). The maternal diseases were diagnosed before or during pregnancy for the target individual. Pregestational diabetes, without subtyping, has been registered in the MBRN from 1967 and specified as type 1 and type 2 since 1988 (n = 32,984 cases, n = 1,113,011 controls).

Statistical Analyses

Analyses were performed with PASW Statistics 18 (SPSS Hong Kong, Quarry Bay, Hong Kong) and Stata version 13

Table 1. Sociodemographic Characteristics of Patients With ADHD and Control Subjects in Norway, 1967–2012

	ADHD Patients (N = 47,944), n (%)	Control Subjects (N = 2,274,713), n (%)
Male Sex	31,514 (65.7)	1,158,422 (50.9)
Year of Birth		
1967–1978	6517 (13.6)	675,929 (29.7)
1979–1988	8443 (17.6)	485,773 (21.4)
1989–1998	23,501 (49.0)	556,250 (24.5)
1999–2008	9483 (19.8)	556,761 (24.5)
Marital Status of Mother	(n = 47,314)	(n = 2,246,177)
Single	7588 (16.0)	187,218 (8.3)
Married/cohabiting/partnership	38,535 (81.5)	2,028,282 (90.3)
Divorced/separated/widowed	850 (1.8)	19,479 (.9)
Other/unknown	341 (.7)	11,198 (.5)
Parity	(n = 47,314)	(n = 2,246,177)
Para 0	21,015 (44.4)	925,190 (41.2)
Para 1	15,886 (33.6)	784,852 (34.9)
Para 2+	10,413 (22.0)	536,135 (23.9)
Maternal Age, Years	(n = 47,314)	(n = 2,246,176)
<20	4367 (9.2)	127,279 (5.7)
20–34	39,150 (82.8)	1,882,572 (83.8)
≥35	3797 (8.0)	236,325 (10.5)
Paternal Age, Years	(n = 46,689)	(n = 2,230,886)
<20	1149 (2.5)	28,334 (1.3)
20–39	42,398 (90.8)	2,025,111 (90.8)
≥40	3142 (6.7)	177,441 (8.0)
Educational Level (Mother)[a]	(n = 46,995)	(n = 2,228,246)
Low	15,528 (33.0)	529,358 (23.8)
Medium	20,028 (42.6)	970,395 (43.6)
High	11,439 (24.3)	728,493 (32.7)

ADHD, attention-deficit/hyperactivity disorder.
[a]Maternal educational level: high (>12 years of education), medium (10–12 years of education), and low (≤9 years of education).

(StataCorp LP, College Station, Texas). Data were analyzed using descriptive statistics with χ^2 tests, and we calculated relative risks and crude odds ratios (ORs) for categorical variables. We used logistic regression analyses to calculate ORs adjusting for the following factors: maternal age at delivery, parity, time period of birth (5-year categories), maternal marital status, and maternal educational level. All factors were modeled as categorical variables as specified in the footnotes in Tables 1 and 2 and Supplemental Table S1. We further included one model adding maternal and paternal use of ADHD medication from NorPD (2004–2012) as adjustment variables. This information was used as a proxy for maternal and paternal ADHD. In a final model, we included all the studied maternal diseases in addition to infant birth weight and gestational age. We also included maternal smoking in a subanalysis for individuals born after 1998, when smoking information was available. We stratified analyses by sex and compared associations between male and female offspring. Crude and adjusted ORs were reported with 95% confidence intervals (CIs). We also analyzed mothers with more than one birth by calculating OR with robust standard errors using the mother as the cluster variable.

RESULTS

Sociodemographic Characteristics

Overall, there was a larger male proportion in the ADHD group (65.7%) (Table 1) compared with the control group (50.9%). Mothers of offspring with ADHD were younger, were more often single, and had lower educational level compared with mothers of control subjects. Similarly, fathers of offspring with ADHD were younger and had lower education compared with fathers of control subjects (data not shown).

Association Between Maternal Somatic Diseases and ADHD in Offspring

We found higher frequencies of several immune system diseases among mothers of offspring with ADHD compared with mothers of control subjects (Table 2), with significantly higher overall odds for maternal multiple sclerosis, rheumatoid arthritis, type 1 diabetes, asthma, and hypothyroidism. Maternal chronic hypertension, type 2 diabetes, and hyperthyroidism were not associated with ADHD in offspring.

The associations between maternal immune-related disease and ADHD in offspring did not depend on offspring sex. Figure 1 shows that although the point estimates for the maternal disease–offspring ADHD associations to some extent differ between male and female offspring, CIs overlap. However, for maternal asthma, where the point estimate for ADHD in female offspring was 1.7 and for male offspring was 1.5, the CIs around the estimates overlapped only slightly (95% CI = 1.5–1.8 for female offspring and 95% CI = 1.4–1.6 for male offspring). Furthermore, for maternal multiple sclerosis and ADHD in offspring, where the point estimates were 2.2 for female offspring and 1.6 for male offspring, the CIs were broad, and we may have lacked power to detect a possible true sex difference.

We repeated all analyses with data from 1999 to adjust for maternal smoking habits. The results were not altered noticeably. For example, adjusted OR between maternal asthma and ADHD in offspring was 1.5 (95% CI = 1.4–1.6), and when also adjusting for smoking, OR was 1.7 (95% CI = 1.5–2.0) for female offspring and 1.4 (95% CI = 1.3–1.6) for male offspring.

Although we set the level of significance at $p < .05$, all the above-listed significant results had p values $< .01$. The associations with maternal asthma, rheumatoid arthritis, and type 1 diabetes had p values $< .0001$ (Supplemental Table S1).

Sensitivity Analyses

Because we defined our ADHD cases only on the basis of dispensed ADHD medication, it may be that our cases represent a special subgroup of patients. For the period 2008–2012, we also had available data from the Norwegian Patient Registry. Of the 12,223 individuals registered with an ADHD diagnosis in the Norwegian Patient Registry, only 2040 (17%) individuals did not receive ADHD drugs. Adding these

Table 2. Maternal Chronic Diseases and ADHD in Offspring: Results From Unadjusted and Different Logistic Regression Models

	ADHD Group (N = 47,944), n (%)	Control Group (N = 2,274,713), n (%)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)[a]	Adjusted OR Model Including Maternal and Paternal ADHD[b]	Expanded Model Adjusted OR (95% CI)[c]
Asthma	1857 (3.9)	47519 (2.1)	1.9 (1.8–2.0)	1.5 (1.4–1.6)	1.5 (1.4–1.5)	1.5 (1.5–1.6)
Rheumatoid Arthritis	250 (.5)	5813 (.3)	2.0 (1.8–2.3)	1.7 (1.5–1.9)	1.7 (1.5–1.9)	1.6 (1.4–1.9)
Hypothyroidism	235 (.5)	11,625 (.5)	1.0 (.8–1.1)	1.2 (1.1–1.4)	1.2 (1.0–1.3)	1.2 (1.0–1.4)
Hyperthyroidism	68 (.1)	3070 (.1)	1.1 (.8–1.3)	1.2 (.9–1.5)	1.1 (.9–1.4)	1.2 (.9–1.5)
Type 1 Diabetes[d]	88 (.3)	2825 (.3)	1.1 (.9–1.3)	1.6 (1.3–2.0)	1.7 (1.3–2.1)	1.5 (1.2–1.9)[e]
Type 2 Diabetes[d]	19 (.1)	1135 (.1)	.6 (.4–.9)	1.1 (.7–1.8)	1.2 (.7–1.9)	1.1 (.7–1.8)[e]
Multiple Sclerosis	31 (.1)	880 (0)	1.7 (1.2–2.4)	1.8 (1.2.–2.5)	1.8 (1.3–2.6)	1.8 (1.2–2.6)
Hypertension, Chronic	155 (.3)	6496 (.3)	1.1 (1.0–1.3)	1.1 (.9–1.3)	1.1 (.9–1.3)	1.1 (.9–1.2)

ADHD, attention-deficit/hyperactivity disorder; CI, confidence interval; OR, odds ratio.

[a]Adjusted by year of birth (5-year interval 1967–2008), parity (para 0, para 1, para 2+), mother's age at birth (<20, 20–24, 25–29, 30–34, 35–39, >39 years), mother's educational level (low/medium/high), mother's marital status (married/cohabiting/partnership, single, divorced/separated/widowed, other/unknown).

[b]Adjusted by the same covariates listed in *a* adding maternal and paternal use of ADHD medication.

[c]Model including all risk diseases as covariates listed in *a* in addition to birth weight (5 categories [<1500, 1500–1999, 2000–2499, 2500–4499, ≥4500 kg]) and gestational age (5 categories [22–31 weeks, 32–36 weeks, 37–41 weeks, ≥42 weeks]).

[d]Data from 1989 and later.

[e]All variables, including risk diseases, selected from 1989 and later when analyzing diabetes.

2040 individuals to our case population did not change any results (data not shown).

We also ran several additional models. In one model, we included maternal and paternal use of ADHD medication as possible confounding variables. Overall, the associations were unchanged or only slightly weakened (Table 2). We also looked at overall offspring ADHD including all risk diseases as covariates, with additional adjustment for gestational age and infant birth weight. None of the estimates changed much (Table 2). Results also did not change much when calculating ORs with robust standard errors and the mother as cluster variable (data not shown).

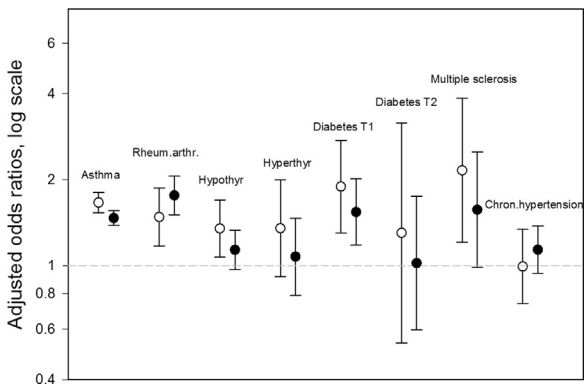

Figure 1. Associations (adjusted odds ratios with 95% confidence intervals) between maternal diseases and attention-deficit/hyperactivity disorder (ADHD) in offspring by sex in Norway, 1967–2012. Female patients with ADHD (white circles); male patients with ADHD (black circles).

As shown in Table 2, the OR for type 1 diabetes increased from 1.1 (95% CI = .9–1.3) in the unadjusted model to 1.6 (95% CI = 1.3–2.0) in the adjusted model. To explore this association further, we performed an additional analysis using data after 1998, when a precoded checkbox for type 1 diabetes was introduced in the MBRN registration form. In this analysis, the unadjusted OR (1.5; 95% CI = 1.2–2.0) was similar to the adjusted OR (1.6; 95% CI = 1.2–2.0). Thus, we consider that the low OR for type 1 diabetes association in the early time period may be an artifact caused by insufficient data collection.

DISCUSSION

This large nationwide register-based study with prospective data showed that several chronic maternal diseases with immune components, including multiple sclerosis, rheumatoid arthritis, asthma, hypothyroidism, and type 1 diabetes were associated with ADHD in offspring. Maternal multiple sclerosis and rheumatoid arthritis were associated with 80% and 70% higher odds of ADHD in offspring, respectively, and maternal asthma was associated with 50% higher odds, independent of maternal smoking. There were no statistically significant sex differences, although we may have lacked power to detect possible true sex differences for some maternal diseases.

This study has several strengths. It is large and includes the entire Norwegian population over a period of 45 years. The genetic homogeneity of the Norwegian population is an advantage when studying other biological risk factors as well as external risk factors. The unique Norwegian personal identity number ensured a valid linkage between the registers involved. The data were prospectively collected with

compulsory notification, minimizing selection and follow-up bias. On one hand, by using the nationwide prescription database to define the case population, thus including only patients who were medicated with reimbursement as cases, we ensured that cases had a valid diagnosis of ADHD. On the other hand, the ADHD cases in this study probably represent the most severely affected patients, as medical treatment is indicated only when substantial loss of function is present. The diagnostic classification system used in Norway is ICD-10. We use data from NorPD during 2004-2012 to define our cases. According to national guidelines published during these years, ADHD should be diagnosed according to ICD-10 criteria, although allowing the inattentive subtype in DSM-IV as sufficient for the diagnosis. Other psychiatric disorders may also be present, as long as the ADHD criteria are fulfilled before the comorbid disorder appears. As some clinicians may have used the more restricted ICD-10 criteria, persons with the inattentive subtype may be underrepresented in our case group. Thus, our results may be most valid for more severe cases of ADHD and the combined subgroup. Moreover, in the Norwegian population, the indications for starting ADHD medication for treating ADHD symptoms could vary slightly from other populations, which may limit to a certain degree the generalizability of our results. Still, our sensitivity analysis showed that only 17% of registered patients during the period 2008–2012 did not receive ADHD medication. Some people included in the control group could have used medication for ADHD before 2004 when NorPD was established; however, this would tend to weaken the associations. Because our control group is very large, the few false-negative ADHD cases should not represent an important source of bias.

We report a robust association between ADHD in offspring and maternal disorders with underlying immune factors, including multiple sclerosis, rheumatoid arthritis, asthma, hypothyroidism, and type 1 diabetes. It has been suggested that maternal diseases with immune components, such as infections, allergy, and autoimmune disease, may cause an exaggerated central nervous system inflammatory response in the fetus (19). Subsequently, this exaggerated inflammatory response could harm the developing brain. Inflammatory mechanisms are believed to play a role in the pathogenesis of psychiatric disorders such as schizophrenia (30) and autism (31), and similar mechanisms may be relevant for the development of ADHD. Altered fetal neurodevelopment has been associated with diverse maternal infections during pregnancy, suggesting the maternal immune response in itself can alter fetal brain development, as shown in a primate model (32).

Ghassabian *et al.* (27) reported that children of mothers with elevated levels of maternal thyroid peroxidase antibodies had more ADHD symptoms. These antibodies could play a part both in the development of autoimmune thyroid disease leading to maternal hypothyroidism and in the fetal neuronal development leading to ADHD.

Patients with ADHD have an increased risk of asthma, the association being highest in female patients (33). However, the present study is the first to show an association between maternal asthma and ADHD in offspring. It was unchanged when adjusting for parental ADHD medication as well as with additional adjustment for maternal smoking and could support shared etiological pathways to ADHD and asthma.

We did not find associations between maternal chronic hypertension or type 2 diabetes and ADHD in offspring. Although it has been proposed that inflammation also may contribute to these disorders (34,35), these chronic conditions are less clearly related to immune system components compared with rheumatoid arthritis and multiple sclerosis, in which the immunopathology is well defined; this indicates that maternal immunological factors could play a role in the pathogenesis of ADHD in offspring.

We controlled for many potential and known confounders. Information on maternal smoking was available only from 1999. However, results using data from 1999 with additional adjustment for smoking were in agreement with the main results. Including maternal and paternal use of ADHD medication in the regression model weakened some of the associations slightly, but they were still in line with the main results.

This study has several limitations. The diagnostic validity of reported diagnosis in the MBRN has not been formally studied for all the studied diseases. The sensitivity of reported rheumatoid arthritis (22) and type 1 diabetes (20) in MBRN is high, estimated to be 88% for rheumatoid arthritis and 90% for type 1 diabetes. For severe asthma, the sensitivity is lower (73%) (20). However, potentially missed maternal cases would most likely attenuate the associations.

The observational design of the study does not allow for definite causal inference. The observed associations could be explained by unmeasured environmental confounding, such as maternal medication use during pregnancy, unmeasured genetic confounding, or an inflammatory response in the fetus; furthermore, these pathways could overlap.

It is known that ADHD is a partially genetic disorder; the heritability has been estimated to .7–.9 (36,37). Environmental factors and the interplay between genetic and environmental factors are also important (38). Analyses of genome-wide genetic markers demonstrated genetic correlations between many traits as well as between somatic and psychiatric disorders (39). Shared genetic susceptibilities could explain some of our findings. For example, the *SLC9A9* gene has been implicated in ADHD and multiple sclerosis (40–42). We did not have data on chronic immune diseases in the fathers in the present data file. However, in a different data set, we had information on prescribed medications of fathers. We used this data set to look at fathers who had been prescribed insulin (2% of the fathers), thyroid replacement drugs (2%), and antiasthmatic drugs (13%) as indications of paternal type 1 diabetes, hypothyroidism, and asthma. Adjusting for the same variables as in the maternal models, we found an adjusted OR for ADHD in offspring related to paternal type 1 diabetes of 1.2 (95% CI = 1.1–1.3), paternal hypothyroidism of 1.1 (95% CI = 1.0–1.2), and paternal asthma of 1.3 (95% CI = 1.3–1.3). In other words, even though there were statistically significant relationships for paternal asthma and type 1 diabetes with ADHD in offspring, the risk estimates were lower than the risk estimates found for maternal chronic immune disease. This finding is an indication that at least some of the relationship between maternal chronic immune disease and ADHD in offspring may be explained by inflammatory mechanisms during pregnancy.

We adjusted for maternal and paternal ADHD, but we had information about parental ADHD only through data registered in the NorPD for parents who had been dispensed ADHD medication during the period 2004–2012. However, before the late 1990s, ADHD was mainly thought of as a childhood disorder, and adults were not given the diagnosis. Therefore, information about parental ADHD is lacking in all data sources until the late 1990s. We cannot exclude residual confounding by shared genetic factors in the present study.

The mechanisms behind our reported findings can also be related to effects of maternal medication use during pregnancy. Acetaminophen used in pregnancy has been associated with an increased risk of hyperkinetic disorder in offspring (43), although the mechanism behind this association is not understood. Acetaminophen may act as a hormone disruptor, interfering with thyroid and reproductive function important for brain development (44). However, it is not completely understood if the association is due to a toxic effect of acetaminophen itself or the underlying causes for women taking these medications during pregnancy. Use of antipsychotics and selective serotonin reuptake inhibitors in pregnancy may affect fetal and infant neurobehavioral development (45,46). It is possible that women with chronic immunological disorders use medications such as acetaminophen and selective serotonin reuptake inhibitors during pregnancy more frequently than women without such disorders. Certain antiasthmatic drugs are associated with an increased risk of birth defects in offspring (47) and could theoretically affect neurodevelopment. However, severe maternal asthma exacerbations are also associated with an increased risk of birth defects in offspring (48). With our data, we could not separate the possible effects of medication taken in pregnancy for the studied diseases from the possible direct effects of the underlying diseases.

Inflammatory response in the fetus can also explain our findings. Abnormal exposure of the fetus to immunomodulatory molecules may play a crucial role in linking adverse pregnancy experiences with altered fetal development. Cytokines are involved in the modulation of the immune system, and elevated cytokine levels resulting from chronic inflammation may affect fetal development in different ways: either directly interfering with neuronal development or by epigenetic mechanisms resulting in altered gene expression (49). This example shows that the activation of the immune system may be a causative agent in the development of neurodevelopmental disorders.

People with chronic illnesses are more frequently in contact with health care services compared with healthy people. Symptoms of ADHD exhibited by their children could be more easily detected and diagnosed than such symptoms in children of mothers without chronic disorders. However, in this case, we would have expected a more uniform increased risk associated with all chronic disorders, including chronic hypertension and type 2 diabetes. In Norway, women of childbearing age with chronic hypertension and type 2 diabetes are closely followed by the family doctor; this would be the natural place to focus on family issues, such as ADHD symptoms in the children.

Besides immunological processes, other disease-related factors may be involved in the association between chronic maternal disease and ADHD in offspring, as ADHD is considered a multifactorial disorder. Although epilepsy is not viewed as an disease with immune components, a clear association was previously reported between maternal epilepsy and ADHD in offspring (8). This association may have several explanations, such as teratogenic effects of antiepileptic medication (49) or fetal hypoxic states caused by maternal seizures. Genetic factors may also be important (50). Thus, different maternal disorders with different pathophysiology may lead to ADHD in the offspring through different underlying pathways.

In conclusion, maternal chronic diseases with immune components as part of the pathogenetic mechanism (multiple sclerosis, type 1 diabetes, hypothyroidism, rheumatoid arthritis, and asthma) were associated with increased risk of ADHD in offspring. The associations did not differ by sex. The etiology of ADHD is probably multifactorial, and the mentioned associations can reflect different causal pathways to ADHD. Maternal disease may impact fetal development through common genetic factors, through environmental factors, or directly through an altered fetal immune response, leading to ADHD in offspring. Further studies are needed to elucidate the mechanisms underlying these relationships, clarifying how genetic vulnerabilities may interact with environmental factors to shape disease risk and clinical presentation. Increased understanding of these pathways could pave the way for new preventive and treatment strategies targeting neurodevelopmental disorders.

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