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ORIGINAL RESEARCH

Association Between Maternal Mood Disorders and Schizophrenia and the Risk of Type 1 Diabetes in Offspring: A Nationwide Cohort Study

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Objective: Our study aimed to determine whether mothers with bipolar disorder, major depressive disorder, schizophrenia, or schizoaffective disorder affected the risk of type 1 diabetes (T1D) in their offspring.

Methods: We conducted a nationwide cohort study by using data from Taiwan's National Health Insurance Research Database and the Maternal and Child Health Database from 2004 to 2018. A total of 2,556,640 mother-child pairs were identified. Cox proportional hazards models were used to compare the risk of T1D between children born to mothers with mood disorders and schizophrenia and those without.

Results: No significant difference in risk of T1D was observed between the offspring of mothers with major psychiatric disorders and those without (adjusted hazard ratio (aHR) of 0.86 with a 95% confidence interval (CI) of 0.58–1.24). In subgroup analysis, we found an aHR of 1.81 with a 95% CI of 0.83–3.82 in the maternal bipolar disorder on the risk of T1D in offspring and an aHR of 0.87 (95% CI: 0.59–1.25) in maternal major depressive disorder. In the schizophrenia/schizoaffective disorder group, aHR cannot be obtained due to lesser than three events in the analysis.

Conclusion: The risk of T1D in offspring of mothers with mood disorders and schizophrenia was not significant. However, children born to mothers with bipolar disorder may have a tendency to develop T1D. The relationship between maternal psychiatric disorders and the risk of T1D in offspring warrants further investigation in studies with longer follow-up periods.

Keywords: type 1 diabetes mellitus, schizophrenia, major depressive disorder, bipolar disorder

Introduction

Type 1 diabetes mellitus (T1D) is a chronic multifactorial disease with onset in early childhood.[1,2] T1D symptoms include hypoglycemia, weight loss, and ketoacidosis, which require continuous treatment and therefore impose a substantial burden on patients' mental health and quality of life.[1,2] Children with T1D are vulnerable to ketoacidosis, which can further impair their cognitive function and school performance.[3] Globally, the incidence of T1D is 15 per 100,000 people, with a prevalence of 0.07–0.12%.[4] Although pathogenesis of T1D is complex and remains to be elucidated, a widely recognized pathology involves the autoimmune destruction of islet β-cells, such as that caused by the aberrant pro-inflammatory pathway induced by T-helper 17 (Th17) cells.[5–7] Due to the young age of T1D onset and lower familial clustering than type 2 diabetes, pathogenesis other than gene should be considered in T1D.[8] As known, maternal immune or cytokine changes can be transferred to the fetus through the placenta, thereby affecting fetal development.[9–11] Thus, maternal immune related diseases could be important in the cause of T1D.

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Major psychiatric disorders, namely schizophrenia, bipolar disorder, and major depressive disorder, have gradually been recognized as disorders of immune and inflammatory dysregulation. Several studies have reported that the Th17 pathway is involved in the pathogenesis of major psychiatric disorders; therefore, this pathway is common in both T1D and major psychiatric disorder pathogenesis.[12–17] Few observational studies evaluating the linkage between psychiatric disorders and T1D risks. Two population-based studies have reported a high prevalence of T1D in patients with schizophrenia or schizoaffective disorder.[18,19] Another population-based cohort study explored the risk of T1D in patients with schizophrenia, and the results revealed an elevated risk with adjusted hazard ratio (HR) of 2.84 (95% confidence interval (CI): 1.18–6.82).[20] Studies on the mood disorders and subsequent T1D risks are scant. A recent Danish nationwide study demonstrated that patients with T1D have an elevated risk of overall psychiatric disorders, including schizophrenia, bipolar disorder, affective disorder, autistic spectrum disorder, and attention deficit/hyperactivity disorder.[21] Despite the use of Danish population-based case-cohort sample, the low sample size of T1D limited the further analysis for stratifying by specific psychiatric disorder. The potential causal relationship between major psychiatric disorders and T1D within individual remains unclear.

During pregnancy, maternal immune changes can have a direct effect on the fetal immune system through the placenta and this effect can persist into the newborn.[9,22] As above mentioned, major psychiatric disorders and T1D share a common immune-related pathogenesis. Thus, the aberrant Th17 immune changes in mothers with major psychiatric disorders may penetrate the placenta and affect Th17 immune pathway in their offspring.

Mothers with major psychiatric disorders might be prescribed antipsychotic medications during pregnancy and antipsychotic medications can also penetrate the placenta.[23] Maternal antipsychotic exposure was found increasing the risk of gestational diabetes (relative risk of 1.30, 95% CI: 1.023–1.660) in a recent systematic review and meta-analysis.[24] There is considerable evidence that intrauterine exposure to diabetes, regardless of the maternal diabetes type, was associated with insulin resistance in offspring. However, the insulin resistance was the core pathogenesis of type 2 diabetes, but not of T1D.[25] Studies have also shown that antipsychotics are associated with type 2 diabetes,[26] but not with T1D. A study by Polcwiartek showed null association between antipsychotic exposure and T1D (odds ratio of 1.38, 95% CI: 0.84–2.29) in the Danish National Patient Register database.[27] Briefly, antipsychotic exposure during pregnancy or gestational diabetes related to antipsychotics did not seem to affect the risk of T1D in offspring. Therefore, our study examined the risk of T1D in the offspring related to maternal major psychiatric disorders, regardless of maternal antipsychotic exposure during pregnancy.

In our review, no studies investigated maternal major psychiatric disorders and their impact on the risk of T1D in offspring. Besides, reverse causality is difficult to avoid in the general population-based cohort study due to the delay of the diagnosis of psychiatric disorders. Mother–infant dyad study can potentially help prevent this reverse causation. Thus, we conducted a nationwide mother–infant dyad study to investigate the association between maternal major psychiatric disorder and the risk of T1D in offspring.

Methods

Data Source

Taiwan's single-payer National Health Insurance (NHI) program was launched on March 1, 1995. The program had enrolled 99.9% of the Taiwan population, according to the official statement in December 2021. Our study used deidentified insurance claim information from the NHI Research Database (NHIRD) between January 1, 2004, and December 31, 2018. We included data on inpatient and outpatient ambulatory services, drug prescriptions, prescription time, and diagnosis codes. We linked the NHIRD data with data from the Taiwan Birth Certificate Registration from January 1, 2004, to December 31, 2017. This registration database provided confirmation of data on live birth, birth date, and gestational age. The linkages between the data sets were utilized to explore the association between maternal major psychiatric disorders and the risk of T1D in offspring. We also retrieved data from the Taiwan Maternal and Child Health Database to obtain complete information on offspring, fathers, and biological mothers from 2004 to 2017.[28]

The NHIRD processed and stored all medical claims as anonymous and encrypted dataset. The data are de-identified and cannot be accessed without proper application for research purposes. To secure the privacy further, the NHIRD

database is only accessible inside a single location, the Data Science Centre, and the raw data are not allowed to be transferred to any portable storage device. This study was approved by the Research Ethics Committee of the Chang Gung Medical Foundation (IRB number: 202000880B0). There was no informed consent required because the dataset was de-identified and anonymous.

Inclusion Criteria for the Study Population and Controls

We included mothers with major psychiatric disorders diagnosed before gestation.[29] The disorders were defined as schizophrenia, schizoaffective disorder, bipolar disorder and major depressive disorder (International Classification of Diseases, Ninth Revision, Clinical Modification [*ICD-9-CM*] codes 295.*296.00, 296.01–06, 296.10–16, 296.81, 296.40–46, 296.50–56, 296.60–62, 296.20–26, and 296.30–36* and *ICD-10* codes F20.*F25.*F30.*F31.*F32.*and F33.*). The diagnoses were ascertained by at least having two times outpatient or one-time inpatient diagnosis.[30–32] We included mothers without major psychiatric disorder before pregnancy as controls.

Outcome Measures

Data on children born to mothers with and without major psychiatric disorders were collected and followed up from birth to December 31, 2018, or death. The primary outcomes were index diagnoses of T1D, which was defined as at least one inpatient or one outpatient diagnosis (*ICD-9-CM* codes 250.01, 250.03, 250.11, 250.13, 250.21, 250.23, 250.31, 250.33, 250.41, 250.43, 250.51, 250.53, 250.61, 250.63, 250.71, 250.73, 250.81, 250.83, 250.91, and 250.93 and *ICD-10* code E10 at any age or E13 before the age of 10 years).[33,34]

Covariates

We included offspring's sex, age, and birth weight, T1D in the father or mother, maternal age, gestational age, enterovirus and cytomegalovirus infection during pregnancy, and maternal smoking status as covariates related to T1D, as described in studies and reviews.[34–36]

Statistical Analysis

We used descriptive analyses to compare the baseline characteristics of the study population, that is, children born to mothers with major psychiatric disorders and those born to mothers without major psychiatric disorders. We also examined the characteristics of children born to mothers with schizophrenia, bipolar disorder, and major depressive disorder individually. The Cox proportional hazard model was applied to estimate the adjusted hazard ratios (aHR) and their 95% confidence intervals for the risk of T1D between children born to mothers with major psychiatric disorders and those born to mothers without any psychiatric disorders. We used child age as the timescale. We also adjusted delivery mode, birth weight, gestational age, maternal viral infection (enterovirus and cytomegalovirus infection), maternal and paternal age at childbirth, maternal thyroid disease history, maternal smoking during pregnancy, and parental history of T1D. Considering the correlation between the outcomes of different children from the same mother, we applied the robust estimation in our Cox proportional hazard model.

In the subgroup analyses, we categorized the exposure cohort on the basis of three different major psychiatric disorders and repeated the analyses. Because the same mother may have more than two major mental illnesses, the three classifications of the mother group in our study are not mutually exclusive. All statistical analyses and processing were performed using the Statistical Analysis Software (SAS) version 9.4.

Results

Characteristics of Children Born to Mothers with or without Major Psychiatric Disorders

There were 2,556,640 mother-child pairings and a total of 76,239 children were born to mothers with major psychiatric disorders, of whom 8322 were classified in the bipolar disorder group, 4014 in the schizophrenia/schizoaffective disorder group, and 71,170 in the major depressive disorder group (Table 1). The total number of distinct or unduplicated mothers

Table 1 Characteristics of Mothers with or without Psychiatric Disorders and Their Offspring

Variable	Mothers with Any Psychiatric Disorder (n= 76,239)	Subgroup			Without Any Psychiatric Disorder (n= 2,480,401)
		Bipolar Disorder (n= 8322)	Schizophrenia/ Schizoaffective Disorder (n = 4014)	Major Depressive Disorder (n= 71,170)	
Offspring covariate					
Child Sex, n (%)					
Male	39,629 (52.0)	4256 (51.1)	2103 (52.4)	37,026 (52.0)	1,291,702 (52.1)
Female	36,610 (48.0)	4066 (48.9)	1911 (47.6)	34,144 (48.0)	1,188,699 (47.9)
Delivery mode, CS, n (%)	34,454 (45.2)	3754 (45.1)	1647 (41.0)	32,432 (45.6)	880,192 (35.5)
Child age, mean (SD), year	8.1 (4.1)	6.7 (3.8)	7.7 (4.1)	7.1 (3.8)	7.1 (3.8)
Gestational age, mean (SD), week	3068.7 (459.7)	3010.8 (495.3)	3017.2 (502.6)	3013.5 (476.8)	3015.6 (478.0)
Birth weight, mean (SD), g	38.3 (1.7)	38.0 (1.9)	38.0 (1.9)	38.0 (1.8)	38.0 (1.8)
Type 1 DM, n (%)	31 (0.04)	7 (0.1)	<3 (<0.1)[a]	29 (0.04)	1214 (0.05)
Age of diagnosis of type 1 DM, mean (SD), years	5.8 (3.5)	5.9 (3.8)	3.2 (0.2)	5.7 (3.4)	6.5 (3.5)
Maternal covariate Maternal age at birth, n (%)					
<35	54,310 (71.2)	5812 (69.8)	2824 (70.4)	50,640 (71.2)	1,962,574 (79.1)
≥35	21,929 (28.8)	2510 (30.2)	1190 (29.6)	20,530 (28.8)	517,827 (20.9)
Virus infection during pregnancy, n (%)	588 (0.8)	84 (1.0)	39 (1.0)	541 (0.8)	11,669 (0.5)
Smoking, n (%)	185 (0.2)	28 (0.3)	18 (0.4)	172 (0.2)	1351 (0.1)
Maternal Type 1 DM, n (%)	178 (0.2)	27 (0.3)	6 (0.1)	164 (0.2)	2452 (0.1)
Thyroid disease, n (%)	4755 (6.2)	571 (6.9)	209 (5.2)	4476 (6.3)	93,724 (3.8)
Paternal covariate					
Paternal age at birth, n (%)					
<35	42,745 (56.1)	4519 (54.3)	2033 (50.6)	40,017 (56.2)	1,514,598 (61.1)
≥35	33,494 (43.9)	3803 (45.7)	1981 (49.4)	31,153 (43.8)	965,803 (38.9)
Type 1 DM, n (%)	108 (0.1)	10 (0.1)	9 (0.2)	101 (0.1)	3444 (0.1)
Family covariate					
Low-income, n (%)	7039 (9.2)	921 (11.1)	736 (18.3)	6406 (9.0)	159,456 (6.4)

Note: [a]Exact case number and proportion cannot be given owing to personal data protection restrictions on publishing cell counts less than 3.
Abbreviations: CS, cesarean section; DM, diabetes mellitus; SD, standard deviation.

and fathers was 1,695,832 and 1,694,879, respectively. The control group included 2,480,401 children whose mothers had never been diagnosed with any psychiatric disorder (Table 1). Approximately 52% of the children in the exposure and control groups were boys. The mean age with standard deviation (SD) was 7.1 ± 3.8 and 8.1 ± 4.1 years for the exposure and control groups, respectively (Table 1). In the exposure group, the age at T1D diagnosis was less than that of the control group, with a mean age and SD of 5.8 ± 3.5 and 6.5 ± 3.5 years, respectively (Table 1). No difference in the incidence of T1D was observed between the exposure and control groups, with the incidence being approximately 0.04%–0.05%; however, a higher incidence of 0.1% was observed in the subgroup of bipolar disorder (Table 1).

Association Between Maternal Major Psychiatric Disorders and the Risk of T1D in Offspring

In the Cox proportional hazard model adjusted for the mode of delivery of the child, birth weight, gestational age, maternal viral infection, maternal and paternal age in childbirth, maternal thyroid disease history, maternal smoking during pregnancy, and parental history of T1D, there was no significant risk (aHR = 0.86 with 95% CI of 0.58–1.24) of developing T1D in offspring with maternal major psychiatric disorders compared to controls (Table 2). In the subgroup analysis, the major depressive disorder group had an aHR of 0.87 (95% CI: 0.59–1.25). The bipolar disorder group had an aHR of 1.81 (95% CI: 0.83–3.82). Both presented with a broader 95% CI covering a null value of 1 due to the rarity of T1D events (prevalence of 0.05%). In the schizophrenia/schizoaffective disorder group, less than three T1D cases were identified and therefore we could not obtain reliable HR estimates in the adjusted Cox proportional-hazards model.

Table 2 Baseline and Adjusted Associations Between Maternal Psychiatric Disorder and Type 1 Diabetes Mellitus Outcomes in Offspring

Mother with Any Psychiatric Disorder		Major Depressive Disorder		Bipolar Disorder		Schizophrenia/Schizoaffective Disorder	
Crude[a]	Adjusted[b]	Crude[a]	Adjusted[b]	Crude[a]	Adjusted[b]	Crude[a]	Adjusted[b]
HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
0.91 (0.64–1.30)	0.86 (0.60–1.23)	0.91 (0.63–1.32)	0.87 (0.60–1.25)	1.97 (0.94–4.14)	1.81 (0.86–3.80)	1.05 (0.26–4.22)	–[c]

Notes: [a]Ref: mother without any psychiatric disorder. [b] Adjusted models controlled for child's delivery mode, birth week and gestational age, maternal viral infection, and maternal and paternal age at childbearing, history of type 1 diabetes mellitus, and maternal smoking during pregnancy, and parental thyroid disease. [c] Estimate cannot be provided because of sparse data problem; data with few counts for diseases.
Abbreviations: CI, confidence interval; HR, hazard ratio.

Discussion

To the best of our knowledge, this study is the first to examine the risk of T1D in children born to mothers with major psychiatric disorders. We observed no significant associations between different maternal major psychiatric disorders and the risk of T1D in offspring. In subgroup analysis, the point estimate of HR of T1D in children born to mothers with bipolar disorder was clinically meaningful (aHR: 1.81), although not statistically significant. The relatively low prevalence of T1D (ie, 0.05%) in our study population and the low fertility rate in mother with bipolar disorders may result in a wide CI and statistically insignificant association between maternal bipolar disorder and the risk of T1D in offspring.[1,3,37,38] On the other hand, no association was observed between maternal major depressive disorder and the risk of T1D in offspring. It was difficult to estimate whether the risk of T1D in offspring was associated with the presence of schizophrenia/schizoaffective disorder in the mother because of the rare event of T1D and the limited sample size of this subgroup.

To our knowledge, only a few studies have investigated the association between bipolar disorder and T1D. Cremaschi et al examined the prevalence of T1D in patients with bipolar disorder by using the case–control study design in Sweden.[39] Their study indicated no difference in the prevalence of T1D between the bipolar disorder and control groups. As mentioned above, we used the mother-child cohort database to avoid reverse causality. Besides, recall bias and lack of adjustment for crucial confounders could have interfered with the results. Their study first identified patients with bipolar disorder from a previous genetic study and contacted them to collect information on T1D. The accuracy of the T1D diagnosis may be thus limited by recall bias and was not confirmed by any physician or laboratory tests. In addition, some crucial confounding factors (eg, gestational week, birth weight, and family history of T1D) were not adjusted for. Another population-based cohort study by Silva et al reported that maternal T1D was not associated with mood disorders in offspring in either an unadjusted or adjusted model.[40] However, the use of less precise bipolar diagnoses, such as the mood disorder, can lead to biased results. As known, depression accounts for a large proportion of mood disorders.[41,42] Moreover, the directionality of their research purpose is different from our research. To fill a gap in knowledge about maternal mood disorders and the risk of T1D in offspring, we conducted a unique mother–infant dyad study to examine the potential causal relationship between bipolar disorder, major depression and T1D in our study.

In contrast, some studies with within-individual association study design, that is, the association between the occurrence of the two disorders during a person's lifetime, have reported high co-occurrence of T1D and depression.[43–45] As known, people with T1D often suffer great emotional stress from enduring chronic illness, which may be one of the important factors leading to depression.[46] Previous within-individual studies reflected the possible association between two disorders, which is often best explained by stress diathesis model. The null association between major depressive disorder and T1D from our results is explained by the different study design. It was not our aim to explore whether emotional stress caused by chronic medical illness could lead to mental illness within individual.

Based on the rare event of the outcome, the point estimate of HR for T1D in children with maternal bipolar disorder was relatively meaningful. Some studies revealed association between bipolar disorder, cognitive impairment, rapid cycling course and insulin-related problems.[47] In our study, the results suggested that children born to mothers with

bipolar disorder may have a tendency to develop T1D, which may be explained by some common immune-related pathogenic mechanisms between T1D and major psychiatric disorders.[5–7,16,17] For example, Th17-mediated inflammation has been observed in major psychiatric disorders.[13,48–52] In stressful environments, IL-17 can cause or accelerate the breakdown of the blood–brain barrier, infiltrate the central nervous system, and cause neuroinflammation.[9] Also, Th17 cells are detected in the placenta, endometrial layer, and maternal peripheral blood during pregnancy and play an essential role in placenta formation and pregnancy maintenance.[10] Therefore, apart from genetic factors, mothers with major psychiatric disorders may have an impact on the fetal immune system through the placenta during pregnancy. On the other hand, Th17 or its surrogate marker IL-17 is highly associated with insulitis.[6,53] The pathogenesis of T1D is characterized by an autoimmune attack on pancreatic islets, which in turn causes insulitis and destroys insulin secretion.[1,2] Our findings, however, did not find significant association between major psychiatric disorders and the risk of T1D. In addition to the rarity of the outcome in our study population, another possible explanation is that the high heterogeneity of mood disorder diagnoses also limits the investigation of exact associations.[54]

Our study has some limitations. First, too few mothers (n = 4014) with schizophrenia and offspring with T1D (n < 3) were identified in the NHIRD; therefore, an analysis could not be performed. Given the low marriage rate of women with schizophrenia and the low birth rate of them, it is understandable that very few mothers with schizophrenia were included despite the use of a nationwide population database.[55] The peaks in T1D onset were 5 to 7 years old and near puberty, that is age 10 to 14 for girls and 12 to 16 for boys.[56] The follow-up duration was 13 years and might not include the T1D patients with their onset near puberty. Underestimation of T1D incidence and results toward null were possible. The future long-term studies may address data scarcity. Second, according to the medical claim database, the diagnoses of major psychiatric disorders and T1D were performed by board-certified psychiatrists and pediatricians. However, because of the nature of the medical claim data, only patients who seek medical help are identified in the NHIRD. Some psychiatric disorders, such as schizophrenia, patients often did not seek help due to stigmatization, lack of insight, poverty, or being homeless.[57,58] Such misclassification may lead to an underestimation of the association between maternal psychiatric disorders and risk of T1D in offspring. In addition, some crucial covariates, such as maternal disease severity, living environment, and stress, cannot be identified in our national databases. Further studies are warranted to examine the effect of these covariates on the risk of T1D in children.

Conclusion

We did not find an association between maternal major psychiatric disorders and the risk of T1D in offspring. Further biological studies or cohort studies with longer follow-up time may be needed to examine the association.

Ethics Approval

This study was approved by the Research Ethics Committee of the Chang Gung Medical Foundation (IRB number: 202000880B0).

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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The authors declare no financial or non-financial conflicts of interests for this work.

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