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- Closely monitor the mental health of women in the postpartum period

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Postpartum Depression and Psychosis and Subsequent Severe Mental Illnesses in Mothers and Neurodevelopmental Disorders in Children:

A Nationwide Study

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ABSTRACT

Background: The association between postpartum depression and postpartum psychosis and subsequent maternal and offspring mental disorders in Western countries has been established; however, whether the relationship can be generalized to the Asian population is unknown.

Methods: Using the Taiwan National Health Insurance Research Database, this study enrolled 933,745 mother-infant pairs who delivered their first child and had no history of severe mental illness before childbirth from 2001 to 2010. Postpartum depression and postpartum psychosis were assessed in 3 periods between childbirth and 3, 6, or 12 months after childbirth. Subsequent maternal schizophrenia (*ICD-9-CM* code: 295), bipolar disorder (*ICD-9-CM* code: 296 except 296.2x, 296.3x, 296.9x, and 296.82), and depressive disorder (*ICD-9-CM* codes: 296.2x, 296.3x, 300.4, and 311) and offspring autism spectrum disorder (ASD; *ICD-9-CM* code: 299) and attention-deficit/hyperactivity disorder (ADHD; *ICD-9-CM* code: 314) were identified during the follow-up period to the end of 2011.

Results: Both postpartum depression and postpartum psychosis were found to be related to increased risks of schizophrenia, bipolar disorder, and depressive disorder in mothers, with hazard ratios (HRs) ranging between 8.80 (95% CI, 7.95–9.74) and 63.96 (95% CI, 50.39–81.18). Children exposed to maternal postpartum depression and psychosis were more likely to develop ADHD. Only postpartum depression was related to the likelihood of offspring ASD.

Conclusions: Per these findings, clinicians and health care providers should closely monitor the mental health condition of postpartum women and their children.

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Clinical Points

- Postpartum depression and psychosis were related to subsequent schizophrenia and major affective disorders in mothers.
- Postpartum depression and psychosis were associated with the increased risks of offspring attention-deficit/hyperactivity disorder and autism spectrum disorder.
- Close monitoring of the mental health condition of postpartum women and their children is recommended.

Postpartum depression is a serious concern for the mother-infant pair because it is associated with substantial morbidity for mothers and infants, including increased risk of maternal suicide, impaired mother-infant attachment, and infant malnutrition in the early years of life.[1,2] The World Health Organization reported that postpartum depression has a lifetime prevalence of at least 10% in developed countries and a higher risk in low-income countries.[1–3] A Danish register-based cohort study[4] indicated an increased risk for first psychiatric admission up to 3 months postpartum for primiparous women. Compared to postpartum depression, postpartum psychosis is a more severe psychiatric condition that affects 1 to 2 of every 1,000 mothers shortly after childbirth and is characterized by hallucinations and delusions, cognitive disorganization and confusion, severe anxiety, and sleep problems.[5] Postpartum psychosis may be significantly associated with a higher risk of maternal suicide and infanticide.[5]

Increasing evidence suggests that postpartum depression and postpartum psychosis are associated with an increased risk of severe mental illness, especially bipolar disorder,[1,6] in the mother. Iliadis et al[6] revealed that women with postpartum depression, especially those with thoughts of self-harm, were more likely to develop long-term affective disorders, including bipolar disorder or depressive disorder, during the 7-year follow-up period. Munk-Olsen et al[7] reported that approximately 14% of women with the first psychiatric contact during the first postpartum month developed bipolar disorder within the 15-year follow-up period after an initial postpartum episode compared with 4% women with the first psychiatric contact not related to childbirth. Chaudron and Pies[8] indicated that postpartum psychosis, a severe but rare psychiatric emergency, is mostly considered a presentation of bipolar disorder. However, the association between postpartum depression and postpartum psychosis and subsequent schizophrenia has scarcely been investigated.[9]

Furthermore, growing evidence has linked mental disorders, including schizophrenia, bipolar disorder, and major depressive disorder, in mothers to the increased likelihood of autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD) in offspring.[10–14] An Italian birth cohort study of 3,634 children and their mothers[14,15] found that the total ADHD score at age 4 years was associated with maternal lifetime depression. Eriksson et al[15] analyzed the data from the Swedish Medical Birth register and demonstrated that mothers of children with ASD had high rates of depression and antidepressant use. Our previous studies[10–13] also showed that children with ASD or ADHD were more likely to have mothers with schizophrenia, bipolar disorder, or major depressive disorder. In addition, the relationship between postpartum depression and postpartum psychosis and offspring neurodevelopmental disorders, including ASD and ADHD, has been identified in recent decades.[16,17] A longitudinal follow-up study[16] with a wave 1 assessment for maternal depression and a wave 5 assessment for offspring ADHD found that maternal postnatal distress was related to ADHD in the offspring at age 8–9 years, independent of parenting attitude. Vizzini et al[14] revealed that the positive association between maternal depression and offspring ADHD was further enhanced when depressive symptoms were active during pregnancy. Say et al[17] analyzed the prevalence of maternal postpartum depression between mothers of children with ASD and of those with ADHD and suggested that postpartum maternal depression is more specific to ASD. However, the small sample size of the studies may have confounded the results.

We used the Taiwan National Health Insurance Research Database (NHIRD) with total population sampling and a longitudinal study design to investigate the relationship between postpartum depression and postpartum psychosis and subsequent severe maternal mental illnesses and offspring neurodevelopmental disorders. We hypothesized that both postpartum depression and postpartum psychosis are associated with subsequent severe maternal mental illnesses, especially bipolar disorder in mothers, and offspring ADHD and ASD.

METHODS

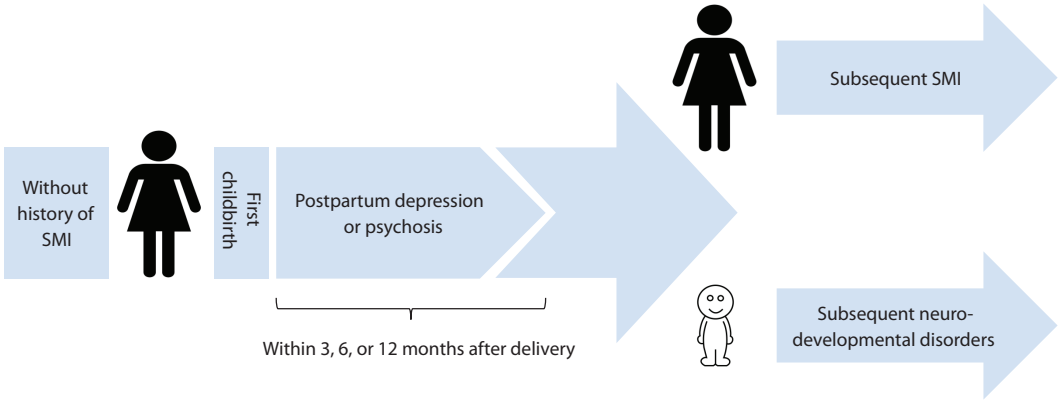
Data Source

In current study, we used the Taiwan NHIRD, which consists of health care data for > 99% of all Taiwan residents and is audited and released by the National Health Research Institute for scientific and study purposes. Individual medical records included in the NHIRD are anonymized to protect patient privacy. Comprehensive information on insured individuals is included in the database, including demographic data, clinical visit dates, and disease diagnoses. In this study, using each resident's unique personal identification number, all of the information was linked. Subsequently, following the method of Chen et al[10] and Cheng et al,[11] family kinships in the NHIRD were used for genealogy reconstruction. The diagnostic codes used were based on the *International Classification of Diseases, 9th Revision, Clinical Modification* (*ICD-9-CM*). The NHIRD has been used extensively in many epidemiologic studies in Taiwan.[11,18–20] This study was approved by the Institutional Review Board of Taipei Veterans General Hospital.

Enrollment of Mother-Child Pairs

Women who delivered their first child and had no history of severe mental illness before childbirth between January

Figure 1. Flow of Assessment of Postpartum Depression or Psychosis and Subsequent Maternal Severe Mental Illness (SMI) or Child Neurodevelopmental Disorders



2001 and December 2010 were enrolled in this study. Severe mental illnesses included schizophrenia (*ICD-9-CM* code: 295) and affective disorders (bipolar and depressive disorders, *ICD-9-CM* codes: 296, 300.4, and 311). Postpartum depression was defined as the *ICD-9-CM* diagnostic codes of depressive disorder (296.2x, 296.3x, 300.4, and 311) given by board-certified psychiatrists. Postpartum psychosis was defined as the exposure to any antipsychotic (Anatomic Therapeutic Chemical Classification System code: N05A except N05AN) because certain diagnostic codes for postpartum psychosis were not available in the *ICD-9-CM* system.[1] Because postpartum depression and psychosis occurred within 4 weeks of giving birth and possibly as late as 30 weeks postpartum,[21] 3 periods were assessed for postpartum depression or psychosis: the periods between childbirth and 3, 6, or 12 months after childbirth (Figure 1).

Outcome Assessment

To clarify the association of postpartum depression or psychosis with subsequent maternal severe mental illnesses, each mother was followed from 12 months after delivery to the end of 2011 for the presence of schizophrenia (*ICD-9-CM* code: 295), bipolar disorder (*ICD-9-CM* codes: 296 except 296.2x, 296.3x, 296.9x, and 296.82), and depressive disorder (*ICD-9-CM* codes: 296.2x, 296.3x, 300.4, and 311). Based on the World Health Organization study,[22] schizophrenia, bipolar disorder, and depressive disorder are the 3 leading mental illnesses that cause global burden as measured by years lived with disability and disability-adjusted life-years. In addition, each child was followed from the birth to the end of 2011 for the diagnoses of ADHD (*ICD-9-CM* code: 314) and ASD (*ICD-9-CM* code: 299). The diagnoses of psychiatric disorders were given by board-certified psychiatrists based on their clinical judgment and comprehensive diagnostic interview. The level of urbanization (from most [level 1] to least [level 5] urbanized)[23] was also assessed in our study.

Statistical Analysis

Descriptive statistics were used for the demographic characteristics of mothers and children and the incidence of postpartum depression, postpartum psychosis, subsequent severe mental illnesses in mothers, and neurodevelopmental disorders in children. Cox regression analyses with adjustment for demographic data (income level and residence) and ages of mothers were conducted to examine the association of postpartum depression or psychosis (between childbirth and 3, 6, or 12 months after delivery) with subsequent severe mental illnesses in mothers. Studies have shown that income level, the urbanization level of residence, and age may be related to the incidence of severe mental disorder.[24,25] Cox regression analyses with additional adjustment for children's sex were used to examine the association of postpartum depression or psychosis with neurodevelopmental disorders in children. Furthermore, Cox regression analyses were also used to investigate the additive effects of postpartum depression or psychosis and subsequent maternal severe mental illnesses in the risks of subsequent offspring ADHD and ASD. The period between childbirth and 6 months after delivery was chosen as the time period of postpartum depression and psychosis in this analysis because the majority of postpartum depression and psychosis occurs within 3 to 6 months after delivery.[2] A 2-tailed P value of $< .05$ was considered statistically significant. All data processing and statistical analyses were performed using Statistical Package for Social Science (SPSS) version 17 (SPSS Inc; Chicago, Illinois) and Statistical Analysis Software (SAS) version 9.1 (SAS Institute; Cary, North Carolina).

Data Availability

As participants did not provide consent for their data to be publicly shared, even anonymized, data will be made available only to potential collaborators with ethical approval after they submit a research proposal to the Bureau of the National Health Insurance (NHI; https://nhird.nhri.org.tw/).

RESULTS

In all, 933,745 mother-child pairs were enrolled in our study. The incidence rates of postpartum depression were 0.16%, 0.33%, and 0.70% in the 3 time periods between

Table 1. Demographic Characteristics and Clinical Data of Mother-Child Pairs[a]

Variable	Value
Mothers (n = 933,745)	
Age at childbirth, mean (SD), y	29.87 (4.95)
Postpartum depression	
In the period between childbirth and 3 mo after delivery	1,510 (0.16)
In the period between childbirth and 6 mo after delivery	3,069 (0.33)
In the period between childbirth and 12 mo after delivery	6,081 (0.65)
Postpartum psychosis	
In the period between childbirth and 3 mo after delivery	562 (0.06)
In the period between childbirth and 6 mo after delivery	1,201 (0.13)
In the period between childbirth and 12 mo after delivery	2,439 (0.26)
Severe mental illnesses during follow-up period of > 12 mo after delivery	
Schizophrenia	1,639 (0.18)
Age at schizophrenia diagnosis, mean (SD), y	33.66 (6.03)
Bipolar disorder	2,864 (0.31)
Age at bipolar disorder diagnosis, mean (SD), y	33.24 (5.82)
Depressive disorder	35,576 (3.81)
Age at depressive disorder diagnosis, mean (SD), y	33.10 (5.70)
Level of urbanization	
1 (most urbanized)	232,952 (24.95)
2	332,179 (35.57)
3	137,948 (14.77)
4	100,659 (10.78)
5 (most rural)	130,007 (13.92)
Income-related insured amount, NTD/mo	
≤ 15,840	162,728 (17.43)
15,841–25,000	422,080 (45.20)
≥ 25,001	348,937 (37.37)
Children (n = 933,745)	
Sex	
Female	440,926 (47.22)
Male	492,819 (52.78)
Neurodevelopmental disorders	
ASD	5,380 (0.58)
Age at ASD diagnosis, mean (SD), y	4.45 (2.06)
ADHD	30,353 (3.25)
Age at ADHD diagnosis, mean (SD), y	6.24 (1.81)

[a]Values are shown as n (%) unless otherwise noted.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, ASD = autism spectrum disorder, NTD = New Taiwan Dollars.

childbirth and 3, 6, or 12 months after delivery, respectively, among mothers who had no history of any severe mental illness (Table 1). The incidence rates of postpartum psychosis varied from 0.06% to 0.26% in the different time periods (Table 1). The incidence rates of subsequent maternal schizophrenia, bipolar disorder, and depressive disorder were 0.18%, 0.31%, and 3.81% in the follow-up period (Table 1). Furthermore, the incidence rates of offspring ASD and ADHD were 0.58% and 3.25%, respectively (Table 1).

Cox regression analyses showed that both postpartum depression and postpartum psychosis in the 3 time periods (between childbirth and 3, 6, or 12 months after delivery, respectively) were related to the increased risks of subsequent schizophrenia (postpartum depression: HRs [95% CIs]: 12.04 [8.69–16.68], 11.54 [9.07–14.69], and 12.00 [10.08–14.28]; postpartum psychosis: 63.96 [50.39–81.18], 52.08 [43.43–62.46], and 54.47 [47.49–62.48]), bipolar disorder (postpartum depression: HRs [95% CIs]: 15.10 [12.01–19.00], 13.77 [11.58–16.37], and 14.29 [12.60–16.20]; postpartum psychosis: 26.47 [20.12–34.84], 24.35 [20.03–29.60], and 25.61 [22.24–29.49]), and depressive disorder (postpartum depression: HRs [95% CIs]: 10.90 [9.98–11.90], 11.58 [10.89–12.31], and 13.81 [13.24–14.41]; postpartum psychosis: 8.72 [7.52–10.12], 8.80 [7.95–9.74], and 9.55 [8.90–10.24]) in mothers (Table 2). In addition, children who were exposed to both maternal postpartum depression (HRs [95% CIs]: 1.74 [1.57–1.93] to 1.78 [1.54–2.05]) and postpartum psychosis (HRs: 1.69 [1.22–2.36] to 1.84 [1.48–2.29]) were more likely to develop ADHD later in life (Table 2). Only postpartum depression (HR = 1.47; 95% CI, 1.13–1.93), but not postpartum psychosis, was related to the likelihood of subsequent offspring ASD (Table 2).

Finally, we found additive effects of postpartum depression or psychosis and subsequent severe mental illnesses, especially postpartum depression or psychosis with subsequent maternal bipolar disorder (postpartum depression: HR [95% CI]: 2.33 [1.38–3.94]; postpartum psychosis: HR [95% CI]: 4.18 [2.63–6.64]) and depressive disorder (postpartum depression: HR [95% CI]: 1.92 [1.53–2.40]; postpartum psychosis: HR [95% CI]: 1.81 [1.25–2.62]), in the risks of offspring ADHD (Table 3). Postpartum psychosis (HR = 2.27; 95% CI, 1.32–3.92), but not postpartum depression, with subsequent schizophrenia was related to the risk of offspring ADHD (Table 3). Only postpartum depression with subsequent depression (HR = 2.40; 95% CI, 1.49–3.86) was associated with the offspring ASD risk (Table 3).

DISCUSSION

Our findings showed that the risk of subsequent bipolar disorder was the highest, followed by schizophrenia and depressive disorder, after postpartum depression, but the risk of subsequent schizophrenia was the highest, followed by bipolar disorder and depressive disorder, after postpartum psychosis. Both postpartum depression and postpartum psychosis were related to the risk of offspring ADHD, but only postpartum depression was associated with the risk of offspring ASD. Based on Chen and colleagues' calculations that ORs of 1.68, 3.47, and 6.71 are equivalent to Cohen *d* values of 0.2 (small), 0.5 (medium), and 0.8 (large), respectively,[26] the ORs of postpartum depression or psychosis with subsequent severe mental disorders in mothers indicated a large effect size, and the ORs of postpartum depression or psychosis with neurodevelopmental disorders in children indicated a small-to-medium effect size in the current study.

Studies have suggested postpartum depression as a clinical marker of subsequent bipolar disorder and postpartum psychosis as a presentation of bipolar disorder.[7,8] Our results validate the association between postpartum

Table 2. Postpartum Depression or Psychosis and Risks of Severe Mental Illnesses in Mothers and Neurodevelopmental Disorders in Children[a]

	Mothers			Children	
Postpartum Depression or Psychosis	Schizophrenia	Bipolar disorder	Depressive disorder	ASD	ADHD
Postpartum Depression (Presence vs Absence)					
In the period between childbirth and 3 mo after delivery	**12.04 (8.69–16.68)**	**15.10 (12.01–19.00)**	**10.90 (9.98–11.90)**	1.58 (0.95–2.63)	**1.75 (1.43–2.15)**
In the period between childbirth and 6 mo after delivery	**11.54 (9.07–14.69)**	**13.77 (11.58–16.37)**	**11.58 (10.89–12.31)**	**1.46 (1.00–2.13)**	**1.78 (1.54–2.05)**
In the period between childbirth and 12 mo after delivery	**12.00 (10.08–14.28)**	**14.29 (12.60–16.20)**	**13.81 (13.24–14.41)**	**1.47 (1.13–1.93)**	**1.74 (1.57–1.93)**
Postpartum Psychosis (Presence vs Absence)					
In the period between childbirth and 3 mo after delivery	**63.96 (50.39–81.18)**	**26.47 (20.12–34.84)**	**8.72 (7.52–10.12)**	0.83 (0.27–2.57)	**1.69 (1.22–2.36)**
In the period between childbirth and 6 mo after delivery	**52.08 (43.43–62.46)**	**24.35 (20.03–29.60)**	**8.80 (7.95–9.74)**	0.79 (0.35–1.76)	**1.84 (1.48–2.29)**
In the period between childbirth and 12 mo after delivery	**54.47 (47.49–62.48)**	**25.61 (22.24–29.49)**	**9.55 (8.90–10.24)**	1.46 (0.96–2.21)	**1.81 (1.55–2.12)**

[a]Values are shown as HR (95% CI). **Bold** type indicates statistical significance ($P < .05$).
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, ASD = autism spectrum disorder, HR = hazard ratio.

Table 3. Maternal Severe Mental Illnesses After Postpartum Depression or Psychosis and Risk of Neurodevelopmental Disorders in Children[a]

	ASD		ADHD	
Postpartum Depression or Psychosis	n (%)	HR (95% CI)	n (%)	HR (95% CI)
Postpartum Depression (Presence vs Absence)				
None (n = 930,676)	5,353 (0.6)	1 (reference)	30,170 (3.2)	1 (reference)
Postpartum depression only (n = 1,808)	8 (0.4)	0.81 (0.40–1.61)	87 (4.8)	**1.62 (1.31–1.99)**
Postpartum depression and subsequent depression (n = 1,057)	17 (1.6)	**2.40 (1.49–3.86)**	77 (7.3)	**1.92 (1.53–2.40)**
Postpartum depression and subsequent bipolar disorder (n = 135)	2 (1.5)	2.04 (0.51–8.17)	14 (10.4)	**2.33 (1.38–3.94)**
Postpartum depression and subsequent schizophrenia (n = 69)	0 (0)	NA	5 (7.2)	1.61 (0.67–3.84)
Postpartum Psychosis (Presence vs Absence)				
None (n = 932,544)	5,374 (0.6)	1 (reference)	30,272 (3.2)	1 (reference)
Postpartum psychosis only (n = 589)	0 (0)	NA	22 (3.7)	1.19 (0.78–1.80)
Postpartum psychosis and subsequent depression (n = 380)	4 (1.1)	1.47 (0.55–3.93)	28 (7.4)	**1.81 (1.25–2.62)**
Postpartum psychosis and subsequent bipolar disorder (n = 105)	2 (1.9)	2.63 (0.66–10.51)	18 (17.1)	**4.18 (2.63–6.64)**
Postpartum psychosis and subsequent schizophrenia (n = 127)	0 (0.0)	NA	13 (10.2)	**2.27 (1.32–3.92)**

[a]**Bold** type indicates statistical significance ($P < .05$).
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, ASD = autism spectrum disorder, HR = hazard ratio, NA = not available.

depression and postpartum psychosis and subsequent affective disorders, especially bipolar disorder, during follow-up after childbirth; moreover, postpartum depression and postpartum psychosis were related to subsequent schizophrenia. The mean time between childbirth and schizophrenia diagnosis was 4.60 years. Munk-Olsen et al[4] suggested that postpartum psychosis increased the risk of non–pregnancy-related psychotic disorders, including affective disorders with psychotic features and schizophrenia spectrum disorders. However, few studies have linked postpartum depression and postpartum psychosis with subsequent schizophrenia spectrum disorders.[4,7,8] Based on the epidemiologic evidence of schizophrenia, women develop schizophrenia several years after men, and the incidence is noticeably higher in women after age 30 years, which is consistent with our findings.[27,28] The definite association between postpartum depression and postpartum psychosis and subsequent schizophrenia and their pathomechanisms needs further investigation.

Furthermore, our findings confirm the relationship between postpartum depression and postpartum psychosis and offspring ADHD and suggest that postpartum depression and postpartum psychosis have additive effects in the development of subsequent severe maternal mental illnesses, especially bipolar disorder, and offspring ADHD risk. Thus, a biological link between postpartum depression or psychosis, maternal bipolar disorder, and offspring ADHD is indicated because a strong relationship between maternal bipolar disorder and offspring ADHD, with postpartum depression or psychosis as a common presentation of bipolar disorder, has been established.[7,29–31] We also found that postpartum depression, especially with subsequent maternal depressive disorder, was associated with ASD risk, which is consistent with findings that suggest an increased risk of ASD and language developmental delay in children exposed to postpartum depression.[17,32] Further studies are needed to elucidate the relationship between postpartum depression or psychosis and offspring ASD risk.

We proposed the pathomechanisms to explain the temporal association of postpartum depression and psychosis with subsequent severe mental disorders in mothers and neurodevelopmental disorders in children. A clinical trial[33]

of 8 women with and 8 without a history of postpartum depression who were administrated the gonadotropin-releasing hormone agonist leuprolide acetate, followed by the adding back of supraphysiologic doses of estradiol and progesterone for 8 weeks and then withdrawal of both steroids in double-blind conditions, found that 5 of the 8 women with a history of postpartum depression and none of the 8 women in the comparison group developed significant mood symptoms during the withdrawal period. The findings of Bloch et al[33] may suggest that a subgroup of women who were differentially sensitive to mood-destabilizing effects of gonadal steroids were more likely to develop postpartum depression or psychosis after the delivery. The subgroup of at-risk women may indirectly indicate genetic vulnerability.[33,34] Evidence has demonstrated shared genetic liability, such as the Val66Met polymorphism of the *BDNF* gene, the Val158Met polymorphism of the *COMT* gene, the BcII polymorphism of the glucocorticoid receptor, the short version of the serotonin-transporter linked polymorphic region genotype, and polymorphisms in the serotonin-2A receptor gene, between postpartum depression and psychosis and other severe mental disorders, including bipolar disorder and major depressive disorder.[34–38] Studies further revealed that delivery abruptly shifts the immune system into a proinflammatory state (ie, increased levels of tumor necrosis factor-α and interleukin-6), which may last for several weeks or even months.[34,39] The concurrent and sustaining vicious interaction between the changes in reproductive hormone concentrations after delivery, the dysregulated immune system, stressful psychosocial adversities, and genetic vulnerability may contribute to the development of postpartum depression and psychosis and further increase the likelihoods of subsequent severe mental disorders in mothers.[5,34,40] The aforementioned genetic vulnerability of mothers may be also associated with the risks of offspring ADHD and ASD.[41,42] Furthermore, the role dysfunction of mothers related to postpartum depression and psychosis, such as the poor emotional bonding between mothers and infants, may be associated with the elevated likelihoods of subsequent ASD and ADHD in children.[17,43–45] In addition, interestingly, the large effect size (ORs between 8 and 64) of postpartum depression and psychosis with subsequent severe mental disorders in mothers may indicate postpartum mothers who were directly exposed to hormonal changes and proinflammatory cytokines, but the small-to-medium effect size (ORs between 1.4 and 1.8) of postpartum depression and psychosis with neurodevelopmental disorders in children may suggest children who were exposed only to the shared genetic vulnerability and psychosocial adversities.

Several study limitations need to be addressed. First, the incidence of postpartum depression and postpartum psychosis and subsequent severe maternal mental illnesses and offspring neurodevelopmental disorders may be underestimated because only those who sought medical help were identified. However, the Taiwan NHI is a low-cost and easily available medical insurance system, which increased the accessibility to medical consultation. Psychiatric disorders were diagnosed by board-certified psychiatrists, thereby improving diagnostic validity. In addition, further community follow-up study with structured interviews would be required to validate our finding. Second, medications were too complicated to be adjusted for well in the regression models. Whether specific medications used in the postpartum period may be related to subsequent severe mental illnesses in mothers and neurodevelopmental disorders in children would need further investigation. Third, some study participants were followed up for 10 years and some for only 1 year because of the enrollment time in our study. Thus, a follow-up time of 1–10 years may not be sufficient to study the association between postpartum conditions and long-term child neuropsychiatric disorders. Further studies with a longer follow-up time up to adolescence and young adulthood would be necessary to validate and expand our findings. Fourth, information on lifestyle choices, dietary habits, marital status, and environmental factors is not available in the database, and we could not assess their effect.

In conclusion, postpartum depression and postpartum psychosis are related not only to subsequent severe maternal mental illnesses, including schizophrenia, bipolar disorder, and depressive disorder, but also to offspring neurodevelopmental disorders, especially ADHD. We recommend that clinicians and health care providers closely monitor the mental health condition of postpartum women and their children. In addition, a mental health program that provides a routine assessment to postpartum women and their children may be recommended for the improvement of mental health of mothers and children. However, the pathomechanisms of postpartum depression and postpartum psychosis, subsequent severe maternal mental illnesses, and offspring neurodevelopmental disorders warrant further investigation.

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REFERENCES

1. Kettunen P, Koistinen E, Hintikka J. Is postpartum depression a homogenous disorder: time of onset, severity, symptoms and hopelessness in relation to the course of depression. *BMC Pregnancy Childbirth*. 2014;14(1):402.
2. Putnam KT, Wilcox M, Robertson-Blackmore E, et al; Postpartum Depression: Action Towards Causes and Treatment (PACT) Consortium. Clinical phenotypes of perinatal depression and time of symptom onset: analysis of data from an international consortium. *Lancet Psychiatry*. 2017;4(6):477–485.
3. Woody CA, Ferrari AJ, Siskind DJ, et al. A systematic review and meta-regression of the prevalence and incidence of perinatal depression. *J Affect Disord*. 2017;219:86–92.
4. Munk-Olsen T, Laursen TM, Pedersen CB, et al. New parents and mental disorders: a population-based register study. *JAMA*. 2006;296(21):2582–2589.
5. Davies W. Understanding the pathophysiology of postpartum psychosis: challenges and new approaches. *World J Psychiatry*. 2017;7(2):77–88.
6. Iliadis SI, Skalkidou A, Ranstrand H, et al. Self-harm thoughts postpartum as a marker for long-term morbidity. *Front Public Health*. 2018;6:34.
7. Munk-Olsen T, Laursen TM, Meltzer-Brody S, et al. Psychiatric disorders with postpartum onset: possible early manifestations of bipolar affective disorders. *Arch Gen Psychiatry*. 2012;69(4):428–434.
8. Chaudron LH, Pies RW. The relationship between postpartum psychosis and bipolar disorder: a review. *J Clin Psychiatry*. 2003;64(11):1284–1292.
9. Jones I, Chandra PS, Dazzan P, et al. Bipolar disorder, affective psychosis, and schizophrenia in pregnancy and the post-partum period. *Lancet*. 2014;384(9956):1789–1799.
10. Chen MH, Hsu JW, Huang KL, et al. Risk and coaggregation of major psychiatric disorders among first-degree relatives of patients with bipolar disorder: a nationwide population-based study. *Psychol Med*. 2019;49(14):2397–2404.
11. Cheng CM, Chang WH, Chen MH, et al. Co-aggregation of major psychiatric disorders in individuals with first-degree relatives with schizophrenia: a nationwide population-based study. *Mol Psychiatry*. 2018;23(8):1756–1763.
12. Chen MH, Pan TL, Huang KL, et al. Coaggregation of major psychiatric disorders in first-degree relatives of individuals with attention-deficit/hyperactivity disorder: a nationwide population-based study. *J Clin Psychiatry*. 2019;80(3):18m12371.
13. Wang HE, Cheng CM, Bai YM, et al. Familial coaggregation of major psychiatric disorders in first-degree relatives of individuals with autism spectrum disorder: a nationwide population-based study [published online ahead of print September 11, 2020]. *Psychol Med*.
14. Vizzini L, Popovic M, Zugna D, et al. Maternal anxiety, depression and sleep disorders before and during pregnancy, and preschool ADHD symptoms in the NINFEA birth cohort study. *Epidemiol Psychiatr Sci*. 2019;28(5):521–531.
15. Eriksson MA, Westerlund J, Anderlid BM, et al. First-degree relatives of young children with autism spectrum disorders: some gender aspects. *Res Dev Disabil*. 2012;33(5):1642–1648.
16. Mulraney M, Giallo R, Efron D, et al. Maternal postnatal mental health and offspring symptoms of ADHD at 8–9 years: pathways via parenting behavior. *Eur Child Adolesc Psychiatry*. 2019;28(7):923–932.
17. Say GN, Karabekiroğlu K, Babadağı Z, et al. Maternal stress and perinatal features in autism and attention deficit/hyperactivity disorder. *Pediatr Int (Roma)*. 2016;58(4):265–269.
18. Chen MH, Lan WH, Hsu JW, et al. Risk of developing type 2 diabetes in adolescents and young adults with autism spectrum disorder: a nationwide longitudinal study. *Diabetes Care*. 2016;39(5):788–793.
19. Chen MH, Pan TL, Li CT, et al. Risk of stroke among patients with post-traumatic stress disorder: nationwide longitudinal study. *Br J Psychiatry*. 2015;206(4):302–307.
20. Chen MH, Su TP, Chen YS, et al. Attention deficit hyperactivity disorder, tic disorder, and allergy: is there a link? a nationwide population-based study. *J Child Psychol Psychiatry*. 2013;54(5):545–551.
21. Andrews-Fike C. A review of postpartum depression. *Prim Care Companion J Clin Psychiatry*. 1999;1(1):9–14.
22. Vigo D, Thornicroft G, Atun R. Estimating the true global burden of mental illness. *Lancet Psychiatry*. 2016;3(2):171–178.
23. Liu CY, Hung YT, Chuang YL, et al. Incorporating development stratification of Taiwan townships into sampling design of large scale health interview survey. *J Health Management (Chin)*. 2006;4:1–22.
24. Kivimäki M, Batty GD, Pentti J, et al. Association between socioeconomic status and the development of mental and physical health conditions in adulthood: a multi-cohort study. *Lancet Public Health*. 2020;5(3):e140–e149.
25. Lee SC, DelPozo-Banos M, Lloyd K, et al. Area deprivation, urbanicity, severe mental illness and social drift—a population-based linkage study using routinely collected primary and secondary care data. *Schizophr Res*. 2020;220:130–140.
26. Chen H, Cohen P, Chen S. How big is a big odds ratio? interpreting the magnitudes of odds ratios in epidemiological studies. *Commun Stat Simul Comput*. 2010;39(4):860–864.
27. Sham PC, MacLean CJ, Kendler KS. A typological model of schizophrenia based on age at onset, sex and familial morbidity. *Acta Psychiatr Scand*. 1994;89(2):135–141.
28. Jones PB. Adult mental health disorders and their age at onset. *Br J Psychiatry suppl*. 2013;54:s5–s10.
29. Rogers A, Obst S, Teague SJ, et al. Association between maternal perinatal depression and anxiety and child and adolescent development: a meta-analysis. *JAMA Pediatr*. 2020;174(11):1082–1092.
30. Cummings EM, Davies PT. Maternal depression and child development. *J Child Psychol Psychiatry*. 1994;35(1):73–112.
31. Birmaher B, Axelson D, Goldstein B, et al. Psychiatric disorders in preschool offspring of parents with bipolar disorder: the Pittsburgh Bipolar Offspring Study (BIOS). *Am J Psychiatry*. 2010;167(3):321–330.
32. Sohr-Preston SL, Scaramella LV. Implications of timing of maternal depressive symptoms for early cognitive and language development. *Clin Child Fam Psychol Rev*. 2006;9(1):65–83.
33. Bloch M, Schmidt PJ, Danaceau M, et al. Effects of gonadal steroids in women with a history of postpartum depression. *Am J Psychiatry*. 2000;157(6):924–930.
34. Schiller CE, Meltzer-Brody S, Rubinow DR. The role of reproductive hormones in postpartum depression. *CNS Spectr*. 2015;20(1):48–59.
35. El-Ibiary SY, Hamilton SP, Abel R, et al. A pilot study evaluating genetic and environmental factors for postpartum depression. *Innov Clin Neurosci*. 2013;10(9-10):15–22.
36. Mitchell C, Notterman D, Brooks-Gunn J, et al. Role of mother's genes and environment in postpartum depression. *Proc Natl Acad Sci U S A*. 2011;108(20):8189–8193.
37. Comasco E, Sylvén SM, Papadopoulos FC, et al. Postpartum depression symptoms: a case-control study on monoaminergic functional polymorphisms and environmental stressors. *Psychiatr Genet*. 2011;21(1):19–28.
38. Engineer N, Darwin L, Nishigandh D, et al. Association of glucocorticoid and type 1 corticotropin-releasing hormone receptors gene variants and risk for depression during pregnancy and post-partum. *J Psychiatr Res*. 2013;47(9):1166–1173.
39. Corwin EJ, Pajer K. The psychoneuroimmunology of postpartum depression. *J Womens Health (Larchmt)*. 2008;17(9):1529–1534.
40. Hendrick V, Altshuler LL, Suri R. Hormonal changes in the postpartum and implications for postpartum depression. *Psychosomatics*. 1998;39(2):93–101.
41. Gadow KD, DeVincent CJ, Siegal VI, et al. Allele-specific associations of 5-HTTLPR/rs25531 with ADHD and autism spectrum disorder. *Prog Neuropsychopharmacol Biol Psychiatry*. 2013;40:292–297.
42. Gadow KD, Roohi J, DeVincent CJ, et al. Association of COMT (Val158Met) and BDNF (Val66Met) gene polymorphisms with anxiety, ADHD and tics in children with autism spectrum disorder. *J Autism Dev Disord*. 2009;39(11):1542–1551.
43. Flouri E, Midouhas E, Joshi H, et al. Emotional and behavioural resilience to multiple risk exposure in early life: the role of parenting. *Eur Child Adolesc Psychiatry*. 2015;24(7):745–755.
44. Shimao M, Matsumura K, Tsuchida A, et al; The Japan Environment And Children's Study Group. Influence of infants' feeding patterns and duration on mothers' postpartum depression: a nationwide birth cohort—The Japan Environment and Children's Study (JECS). *J Affect Disord*. 2021;285:152–159.
45. Macdonald JA, Greenwood C, Letcher P, et al. From adolescence to parenthood: a multi-decade study of preconception mental health problems and postpartum parent-infant bonds [published online ahead of print October 1, 2020]. *Soc Psychiatry Psychiatr Epidemiol*.

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POSTTEST

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1. **You are consulted by an obstetrician colleague about a 34-year-old woman with a newborn baby. She has developed an irritable and depressed mood within two weeks after delivery and discloses having thoughts of self-harm. Which of the following statements to your colleague would NOT be correct?**
   a. The World Health Organization reported that postpartum depression has a lifetime prevalence of at least 10% in developed countries.
   b. Postpartum depression cannot be diagnosed yet because criteria require at least 4 weeks after delivery to have passed.
   c. Studies have suggested postpartum depression as a clinical marker of subsequent bipolar disorder and postpartum psychosis as a presentation of bipolar disorder.
   d. Women with postpartum depression, especially those with thoughts of self-harm, are more likely to develop long-term affective disorders.

2. **You have an outpatient who is a 25-year-old pregnant woman with a history of 3 episodes of major depressive disorder (MDD) since age 17 years. Her MDD is in remission. Which of the following statements related to the need for short-term and/or long-term monitoring is NOT correct?**
   a. She should be closely monitored for the development of depression or psychosis during and after pregnancy.
   b. Postpartum depression and psychosis may be related to subsequent schizophrenia or bipolar disorder in mothers.
   c. Postpartum depression has been linked to a risk for subsequent attention-deficit disorder and autism spectrum disorder in offspring.
   d. Postpartum psychosis has been linked to a risk for subsequent attention-deficit disorder and autism spectrum disorder in offspring.

3. **Regarding the pathophysiology of postpartum depression and psychosis, which of the following descriptions is NOT correct, according to current literature?**
   a. A subgroup of women who were differentially sensitive to mood-destabilizing effects of gonadal steroids were more likely to develop postpartum depression or psychosis after delivery.
   b. Shared genetic liability, such as the Val66Met polymorphism of the *BDNF* gene and the BcII polymorphism of the glucocorticoid receptor, was observed between postpartum depression and psychosis and other severe mental disorders, eg, bipolar disorder.
   c. Delivery may abruptly shift the immune system into an anti-inflammatory state, which may last for several weeks or even months.
   d. The interaction between changes in reproductive hormones concentrations after delivery, the dysregulated immune system, psychosocial adversities, and genetic vulnerability may contribute to the development of postpartum depression and psychosis.