Association between antibiotic exposure during pregnancy and postpartum depressive symptoms: The Japan Environment and Children's Study

（妊娠中の抗菌薬使用と産後うつ症状の関係について：エコチル調査）

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ABSTRACT

Postpartum depressive symptoms (PDS) are a common mental health condition among women after delivery. Although various causative factors have been reported, PDS remains a challenging condition to predict and prevent. The disruption of the gut microbiota due to antibiotic exposure has been reported to affect psychiatric conditions. Similarly, previous research suggests that antibiotic exposure during pregnancy could be related to PDS. Therefore, this prospective study examines the association between antibiotic exposure during pregnancy and PDS for 6 months after delivery. Data were obtained from 65,272 mothers from the Japan Environment and Children's Study, a prospective birth cohort study. The ratios of maternal PDS at 1 and 6 months after delivery were 12.3% and 10.1%, respectively. During pregnancy, 10.7% of women took antibiotics orally. Antibiotic exposure during pregnancy was associated with an increased risk of PDS only at 6 months after delivery (OR = 1.13, 95% CI [1.00, 1.26]), adjusted for potential confounding factors. An increase in Edinburgh Postnatal Depression Scale scores in relation to antibiotic exposure during pregnancy was primarily observed via psychological distress during pregnancy. Although a causal link was not established, antibiotic exposure during pregnancy may be a contributing risk factor for PDS. Therefore, when antibiotic administration is required, clinical practitioners and perinatal care providers should consider the potential risk for PDS.

No Patient or Public Contribution

There was no patient or public contribution in this study, as the authors used secondary data originally collected for the Japan Environment and Children's Study.

1 INTRODUCTION

Anxiety disorder and depression during pregnancy and the postpartum period affect approximately 7–25% of the women who have given births. Mental disorders are a serious perinatal public health concern (Adynski et al., 2019; Beck, 2006; Ghaedrahmati et al., 2017; Halbreich & Karkun, 2006; Kettunen et al., 2014; Klainin & Arthur, 2009; World Health Organization (WHO), 2019). Globally, suicide is the second leading cause of mortality in the first year after delivery, accounting for 20% of the deaths among postpartum women (Payne & Maguire, 2019; Wisner et al., 2019). In Japan, suicide was the leading cause of maternal death during pregnancy until 1 year after delivery between 2015 and 2016 (Ministry of Health, Labour and Welfare, 2019). Current studies indicate that postpartum depressive symptoms (PDS) affect mothers and their family members in different ways, lowering their quality of life and influencing the long-term emotional, intellectual, and cognitive development of the offspring including newborns; these factors can negatively affect them in the early stages (Kikuchi et al., 2021; Norhayati et al., 2015; WHO, 2019). Furthermore, the children of mothers with anxiety were twice at risk of attention-deficit/hyperactivity disorder at 4 and 7 years of age (Fawcett et al., 2019). The impact of PDS on mothers and their family members can be detrimental; thus, identifying at-risk women and implementing preventive measures are necessary (Klainin & Arthur, 2009; O'Hara & McCabe, 2013; Righetti-Veltema et al., 2003).

Although many studies have tried to identify the causes of PDS, the pathogenesis and associated risk factors are not fully understood (Gelaye et al., 2016; Milgrom et al., 2008). Various risk factors for PDS have been identified, including physical and biological (e.g., poor physical health, premenstrual symptoms), psychological (e.g., antenatal depression and anxiety, previous psychiatric illness, depression during pregnancy, poor marital relationship, stressful life events),

obstetric and pediatric (e.g., unplanned pregnancy, mode of delivery, parity), socioeconomic (e.g., maternal age, education, income), and cultural factors (Adynski et al., 2019; Kettunen et al., 2014; Klainin & Arthur, 2009; Norhayati et al., 2015). Despite the increasing evidence on the risk factors affecting the pathogenesis of PDS, effective PDS prediction and intervention remain challenging.

Recently, the association between the gut microbiota and the host's health has become more relevant due to increased research efforts. The gut microbiota forms a network with various parts of the nervous system, called gut–brain communication (covariant; Cryan & Dinan, 2012; Mayer et al., 2015; Rhee et al., 2009). Several research reports suggest that changes in the gut microbiome increase the risk of neuropsychiatric disorders, such as depression, anxiety, and even schizophrenia (Evrensel & Ceylan, 2015; Foster & McVey Neufeld, 2013; Klein-Petersen et al., 2021; Rieder et al., 2017). The gut microbiota plays an important role in stabilizing a host's mental status. According to animal experiments, when the gut microbiota is disrupted, the hosts experience anxiety and depression (Crumeyrolle-Arias et al., 2014; Jang et al., 2018). Disruption of the microbiota in humans can be caused by exposure to various external factors, such as toxins, drugs, food, and pathogens (Carding et al., 2015). It has been also reported that antibiotic treatment affects the microbiome (Ferrer et al., 2017; Schwartz et al., 2020). The research results suggesting that antibiotic treatment affects the microbiome are of serious concern because antibiotics are the most common drugs prescribed over the perinatal period (Blaser, 2016). Approximately 62% of pregnant women take medications and as many as one quarter take antibiotics (Santos et al., 2012; Smolina et al., 2015). The most frequent indication for antibiotic prescription during pregnancy is urinary tract infection, which affects approximately 8% of all pregnant women (Ailes et al., 2018). A U.S. study found a possible connection between maternal antibiotic exposure intrapartum through 14 days postpartum and the risk of PDS within the first 6 months after delivery (Murphy

et al., 2018). Another prospective cohort study of antibiotic exposure and PDS was recently conducted in Australia and the researchers' initial analysis of antenatal depression (but not PDS) was published (Pouranayatihosseinabad et al., 2023, 2024).

PDS is, thus, a growing concern and antibiotic prescriptions during pregnancy have increased since 2000 (Murphy et al., 2018). However, no study has investigated the relationship between antibiotic exposure during pregnancy and PDS other than Murphy et al. (2018). Hence this study examines whether antibiotic exposure during pregnancy is associated with PDS, using data from the Japan Environment and Children's Study (JECS), a large-scale nationwide cohort study. Additionally, it is common for mothers with PDS to experience depression during pregnancy (Beck, 2006; Dubber et al., 2015; Kettunen et al., 2014). Psychological distress during pregnancy has been associated with developing PDS (Khanlari et al., 2019; Milgrom et al., 2008). Antibiotic exposure has been associated with changes in the gut microbiome, which itself is associated with anxiety and depression (Evrensel & Ceylan, 2015; Foster & McVey Neufeld, 2013; Klein-Petersen et al., 2021; Rieder et al., 2017). Hence, the mediation of psychological distress during pregnancy and antibiotic exposure along with PDS is also examined. This study provides new insights regarding antibiotic exposure and maternal mental health, highlighting the need for further research in this area.

2 METHODS

2.1 Study design and participants

The JECS is a nationwide government-funded birth cohort study led by the Ministry of the Environment of Japan. Its goal is "to identify environmental factors that affect children's health and development in order to help decision makers design better chemical risk management

strategies" (Kawamoto et al., page 2, 2014). The study focuses on the effect of exposure to chemical substances during the fetal period and/or early childhood. Expectant mothers from 15 regions throughout Japan were recruited to participate in the JECS between January 2011 and March 2014. In total, 103,062 pregnant women were enrolled. Please refer to Kawamoto et al. (2014) for the study design details.

This study used the JECS-an-20180131 dataset (JECS's fixed data up to 1 year after birth, released in March 2018), which includes data during pregnancy and at 1 and 6 months after delivery (Figure 1). Health and medical information were collected from medical record transcriptions. In this study, antibiotic use, PDS, and psychological distress were considered as exposure, outcome, and potential contributing factors, respectively.

The JECS protocol was approved by the Institutional Review Board of Epidemiological Studies of the Ministry of the Environment and the ethics committees of all participating institutions. The JECS was conducted in accordance with the Declaration of Helsinki and its future amendments and other relevant national regulations and guidelines. Written informed consent was obtained from all participating mothers.

2.2 Assessment of postpartum depressive symptoms

The Edinburgh Postnatal Depression Scale (EPDS; Cox et al., 1987), validated for the Japanese population (Okano et al., 1996), was used to assess PDS at 1 and 6 months postpartum. The EPDS is a 10-item screening instrument that measures depressive symptoms experienced within the previous 7 days. Responses were rated on a four-point scale, and the cumulative scores ranged from 0 to 30. Higher scores indicated more severe symptoms. Okano et al. (1996) reported that the Cronbach's alphas of the Japanese version of the EPDS at 1 and 3 months

postpartum were 0.668 and 0.742, respectively, which indicates moderate reliability. In this study, the Cronbach's alphas were 0.805 and 0.802 at 1 and 6 months postpartum, respectively. Although Cox et al. (1987) suggested that an EPDS score of 12/13 is the cut-off value for depressive illness, Okano et al. (1996) reported that a score of 8/9 is an appropriate cut-off for PDS in the Japanese population, with 75% sensitivity and 93% specificity. Therefore, in this study, an EPDS score of ≥ 9 indicated PDS.

2.3 Antibiotic exposure

Prenatal antibiotic exposure was defined as the intake of antimicrobial agents during pregnancy. Information was collected via first interview questionnaires administered to mothers after enrollment (T1 = Term 1) and during mid-late pregnancy (T2 = Term 2) (Figure 1). In this study, antibiotic exposure was defined as a record of "antibiotic use since the confirmation of pregnancy until the enrollment" in the questionnaires. Answers about medication use were recorded by research coordinators based on a medication list.

2.4 Covariates and mediating variables

Based on previous studies on PDS, biological plausibility, and directed acyclic graphs, the following covariates were selected and included in the multivariate analysis: age, education, household income, marital status, parity, smoking habits, alcohol consumption habits, energy intake, complications during pregnancy or delivery, multiple pregnancies, low birth weight, and physical anomalies in newborns. In addition, to eliminate the effects of other medications used in combination with antibiotics, antipyretic/analgesic drug use during pregnancy was selected as a covariate. Considering PDS's association with the gut microbiota, a history of gastrointestinal

diseases (e.g., gastritis, gastric ulcer, duodenal ulcer, irritable bowel syndrome, Crohn's disease, or ulcerative colitis) was also selected as a covariate. Energy intake was calculated using data obtained from food frequency questionnaires validated in the Japan Public Health Center-based Prospective Study for the Next Generation (Yokoyama et al., 2016). Psychological distress was assessed using the six-item Kessler Psychological Distress Scale (K6) validated for the Japanese population (Furukawa et al., 2008; Kessler et al., 2002). Responses were rated on a five-point scale, with the total score ranging from 0 to 24 points. Mothers completed the K6 questionnaire during mid-late pregnancy regarding their psychological status in the past one month (Figure 1). A priori, we planned to evaluate whether the association between antibiotic exposure during pregnancy and postpartum depressive tendencies was mediated by psychological distress during pregnancy; for this, we conducted a path analysis with the K6 scores as an intermediate variable. Table 1 shows the categorical distributions of the covariates.

2.5 Statistical analysis

Binomial logistic regression analysis was performed to estimate the odds ratios (ORs) for PDS observed at 1 and 6 months after delivery in relation to antibiotic exposure. Multinomial logistic regression analysis was performed on PDS at 1 month only, at 6 months only, and at both 1 and 6 months. The associations between antibiotic exposure and PDS were analyzed using three models. The crude model was not adjusted for any covariates. Adjusted model 1 was adjusted for age, education, household income, marital status, parity, smoking habits, alcohol consumption habits, energy intake, antipyretic/analgesic drug use during pregnancy, history of gastrointestinal diseases, complications during pregnancy or delivery, multiple pregnancies, low birth weight, and physical anomalies in newborns. To examine the effect of psychological distress on the

association between antibiotic exposure and PDS, we additionally included the K6 scores as continuous variables in Adjusted model 2 and observed the changes in the effect of antibiotic exposure on PDS. We further included an interaction term (K6 score * antibiotic exposure) in Adjusted model 2 to examine whether there is an interaction effect between the K6 scores and antibiotic exposure. Interactions were considered to be significant at $p < 0.1$. The forced-entry method was used to include all covariates. There was no collinearity among the exploratory variables (the correlation coefficients of the exploratory variables < 0.26). Missing values for the covariates were complemented via multiple imputations by chained equations. Specifically, each missing value was replaced with a series of substituted plausible values by creating 10 filled-in complete datasets and integrating the values according to Rubin's (1987) rule.

Furthermore, two sensitivity analyses were performed to assess the robustness of the results of the logistic regression analyses. First, to eliminate the effect of antibiotic use on different gastrointestinal conditions, we performed analyses that excluded cases with history of colorectal disease (Crohn's disease or ulcerative colitis). Second, complete case analyses were performed after the missing data for the covariates were excluded.

Subsequently, path analysis was performed to assess the mediation of psychological distress (K6 scores) during pregnancy in the relationship between antibiotic exposure and PDS (EPDS scores) at 1 and 6 months. The EPDS and K6 scores were included as continuous variables. Figure 2 shows the path diagram. The association between antibiotic exposure and PDS at 1 month had direct and indirect effects via the K6 scores. The association between antibiotic exposure and the EPDS scores at 6 months had direct and indirect effects via the K6 scores, and the indirect effect included paths with and without the EPDS scores at 1 month. For each association, the sum of the direct and indirect effects was considered as the total effect.

Covariates on mothers (i.e., age, education, household income, marital status, parity, smoking habits, alcohol consumption habits, energy intake, antipyretic/analgesic drug use during pregnancy, history of gastrointestinal diseases, complications during pregnancy or delivery, and multiple pregnancies) were set to be associated with antibiotic exposure, the K6 scores, and the EPDS scores at 1 and 6 months. Covariates on children (i.e., low birth weight and physical anomalies in newborns) were set to be associated with the EPDS scores at 1 and 6 months. To address the missing values, the direct, indirect, and total effects were estimated via Bayesian estimation. The model's goodness-of-fit was evaluated via the maximum likelihood method. We considered the model to fit well if the comparative fit index (CFI) was ≥ 0.95 and the root mean square error of approximation (RMSEA) was ≤ 0.05. All analyses were conducted using SPSS Statistics Base, SPSS Regression, and SPSS Amos v. 27 (IBM Corp., Armonk, NY, USA).

3 RESULTS

3.1 Participants' background characteristics

A total of 103,062 mothers were registered. We excluded 37,790 of them from our analysis owing to incomplete data on the key variables, cesarean section for which the use of antibiotics is essential, or a history of psychiatric illness. Hence, 65,272 mothers were included (Figure 3). Only a few differences in the prevalence of PDS, antibiotic exposure, and the main characteristics of the mother and child were observed between the included and excluded cases. Of the included mothers, 10.7% took antibiotics orally during pregnancy (see Supporting Information Table S1).

At 1 and 6 months postpartum, 8,042 (12.3%) and 6,604 (10.1%) women were classified as having experienced PDS, respectively. Table 1 presents the participants' main characteristics

according to having PDS at 6 months postpartum. Mothers with PDS were younger (< 25 years, 16.8%), less educated (< 10 years, 6.7%; 10–12 years, 36.4%), lower income earners (< 4 million Japanese yen, 45.2%), unmarried (7.1%), and more likely to be smokers during pregnancy (6.3%). Severe mental disorders were reported by 11.8% of the women with PDS and 1.3% of those without during mid-late pregnancy. Meanwhile, psychological distress was reported by 53.3% and 20.5% of the women with and without PDS, respectively. By contrast, 33.5% and 77.3% of the women with and without PDS, respectively, were mentally stable (reported no disorders or stress).

3.2 Association between antibiotic exposure and postpartum depressive symptoms based on the logistic regression models

The results of the logistic regression analysis are shown in Table 2. Antibiotic exposure was associated with a significantly increased OR for PDS at 1 and 6 months after delivery, not adjusted for the covariates. In Adjusted model 1, the inclusion of the covariates decreased the ORs marginally, indicating that these covariates had a small confounding effect, and antibiotic exposure became nonsignificant: PDS at 1 month after delivery (OR = 1.05, 95% CI [0.97, 1.13]) and 6 months after delivery (OR = 1.07, 95% CI [0.99, 1.16]). When the timing of the PDS assessment was classified as 1 month only, 6 months only, or 1 month and 6 months, antibiotic exposure was solely associated with PDS at 6 months after delivery (OR = 1.07, 95% CI [0.97, 1.19], OR = 1.13, 95% CI [1.00, 1.26], and OR = 1.07, 95% CI [0.93, 1.16], respectively). The two sensitivity analyses for cases with no colorectal disease and complete cases for the covariates showed a similar association between PDS and antibiotic exposure (see Supporting Information Table S2).

In Adjusted model 2, which included the K6 scores (psychological distress) as an additional covariate, the association between antibiotic exposure and PDS at 6 months disappeared. No interaction between antibiotic exposure and the K6 scores was observed in these associations.

3.3 Association between antibiotic exposure and postpartum depressive symptoms and mediation of psychological distress during pregnancy based on the path analysis

Path analysis was conducted to examine the effects of antibiotic exposure on the EPDS scores at 1 and 6 months after delivery, including the direct effects, indirect effects via the K6 scores during pregnancy, and total effects (Figure 2). The model fit the data well according to all the goodness-of-fit measures (CFI = 0.964, RMSEA [90% CI] = 0.036 [0.035, 0.037]). An insignificant direct effect of antibiotic exposure on the EPDS scores at 1 month after delivery (β = 0.003, 95% Bayesian credible interval (BCI) [-0.004, 0.009]) and a positive, significant, indirect effect via the K6 scores during pregnancy were observed (β = 0.011, 95% BCI [0.008, 0.014]), as shown in Table 3. The results were very similar for the effect on the EPDS scores at 6 months. Regarding the total effects, the EPDS scores at 1 and 6 months were both increased significantly by antibiotic exposure (β = 0.014, 95% BCI [0.006, 0.021] for 1 month and β = 0.012, 95% BCI [0.005, 0.019] for 6 months).

4 DISCUSSION AND CONCLUSIONS

Our results showed a weak association between antibiotic exposure during pregnancy and an increased risk of PDS at 6 months after delivery. Nevertheless, this association disappeared when adjusted for the K6 scores (psychological distress) during pregnancy in the logistic regression

models. However, because K6 was measured at only one time point in the second questionnaire, we were unable to determine if psychological distress preceded antibiotic exposure, which would indicate that K6 was a confounding variable, or if antibiotic exposure preceded psychological distress, which would indicate that K6 was an intermediate variable. Therefore, we explored the role of psychological distress (K6) through the path analysis, with the results suggesting that increased PDS at 1 and 6 months after delivery was fully mediated by psychological distress during pregnancy, not by a direct association with antibiotic exposure. However, this finding in itself is not conclusive without further evidence of a causal relationship between antibiotic exposure and psychological distress. This finding could be an interesting focus for future studies to consider when studying the link between antibiotic exposure and PDS.

We found that antibiotic exposure during pregnancy was associated with PDS at 6 months, defined as above the cut-off value, but not at 1 month or at both 1 and 6 months. PDS commonly occurs within 4 to 6 weeks after delivery and could last up to 1 or even 2 years after delivery (Beck, 2006; Kettunen et al., 2014; Kikuchi et al., 2021; Norhayati et al., 2015). Some PDS at 1 month after delivery can be attributed to postpartum blues, which 50–75% of new mothers experience a few days after delivery and often disappear within 10 days (Beck, 2006; Kettunen et al., 2014; Norhayati et al., 2015). Our findings suggest that antibiotic exposure increased PDS onset, which could appear a few months after delivery, rather than early PDS, which includes the temporary postpartum blues.

Our path analysis results indicated that antibiotic exposure during pregnancy was not associated with postpartum depressive tendencies directly, but affected these tendencies through psychological distress during pregnancy. It seems that antibiotic exposure during pregnancy was associated with increased psychological distress during pregnancy, which was strongly

associated with postpartum depressive tendencies at 1 and 6 months. Several prospective studies have reported that prenatal anxiety and depression are strong risk factors for PDS (Milgrom et al., 2008; Sutter-Dallay et al., 2004; Underwood et al., 2017). Our analysis showed that the K6 scores during pregnancy were directly related to the EPDS scores at 6 months as well as at 1 month. This result indicates that psychological distress during pregnancy may be related to late-onset postpartum depression, which is different from the temporary postpartum blues. Although antibiotic exposure during pregnancy was not significantly associated with the risk of PDS at 1 month according to the logistic regression analysis, the results of the path analysis indicated that antibiotic exposure during pregnancy contributed to an increase of postpartum depressive tendencies at 1 month via increased psychological distress during pregnancy.

A possible explanation for the association between antibiotic exposure and psychological distress during pregnancy is that the disruption of the microbiota in pregnant women caused by antibiotic exposure leads to increased psychological distress during pregnancy. Abundant evidence has suggested that changes in the gut microbiota increase the risk of neuropsychiatric disorders (e.g., depression and anxiety), which are mediated through the gut–brain axis (Evrensel & Ceylan, 2015; Liang et al., 2018; Rieder et al., 2017). The gut–brain axis has been recognized to function through neural, hormonal, and immunological routes (Cryan & Dinan, 2012; Foster & McVey Neufeld, 2013). Further, the GABA receptor expression plays an important role in the pathogenesis of developing depression and anxiety, and could be caused by the disruption of the microbiota (Carding et al., 2015). Therefore, the disruption of the microbiota due to antibiotic exposure could lead to depressive symptoms.

Another explanation could be that a pathogenic infection that requires antibiotic treatment may affect maternal mental health. It is also possible that anxiety or the guilt about the

299 effects of medication on the fetus could affect the mother's mental condition. However, since the
300 analysis model was adjusted for antipyretic/analgesic drug use during pregnancy, the effects of
301 an infection and the anxiety due to the use of medication may have been excluded. Some studies
302 have revealed the association between antibiotic treatment and higher risk of depression or other
303 mental disorders (Köhler-Forsberg et al., 2019; Liang et al., 2018; Lurie et al., 2015). Therefore,
304 antibiotic treatment during pregnancy may contribute to the risk for PDS.
305 Our results were partially consistent with those of Murphy et al. (2018), in that both
306 studies showed a relationship between antibiotic exposure during pregnancy and postpartum
307 depressive tendencies. Our data indicated a relationship between antibiotic exposure during
308 pregnancy and PDS at 6 months after delivery, whereas Murphy et al. (2018) reported an
309 association between maternal peripartum antibiotic exposure and PDS at 1 and 2 months but not
310 at 3 or 6 months. These discrepancies may be attributed to the differences in sample size, the
311 target period of antibiotic exposure, and data analysis method. We only considered antibiotic
312 exposure during pregnancy. Conversely, Murphy et al. (2018) considered antibiotic exposure
313 during pregnancy and the first 14 days postpartum. Nevertheless, our results support the
314 hypothesis that antibiotic exposure during pregnancy is a risk factor for PDS.
315 There are approximately 800,000 births in Japan each year and the period prevalence of
316 postpartum depression 6–12 months after birth was 11.5% between 1994 and 2017 (Tokumitsu et
317 al., 2020). Although the effect size was small, our data indicated an association between
318 antibiotic intake and the onset of PDS within the 6 months after delivery not adjusting for
319 prenatal psychological distress. This small increase translates into an increase by approximately
320 0.6– 0.7 % of risk for PDS at 1 month after delivery and, at 6 months after delivery.

Since PDS is related to a high suicide rate, difficulties in bonding with infants, harming newborns, and interrupting children's development, and is a serious public health concern (Dubber et al., 2015; Grace et al., 2003; WHO, 2019; Wisner et al., 2019). Various advocacy programs have been implemented in many countries. These include home visits by nurses or local community health staff, interviews with clinicians, and social support (Centers for Disease Control and Prevention, 2020; Kendig et al., 2017; Milgrom et al., 2008; Segre et al., 2010; WHO, 2019; Wisner et al., 2019). However, the effects of antibiotic treatment on PDS are not clearly understood as a risk factor in perinatal healthcare. If perinatal healthcare staff are aware of the risks, they could pay more attention to providing support after antibiotic use, which may eventually reduce the risk of PDS.

Furthermore, probiotics may help prevent and treat PDS. Although they are not same as the gut microbiota, probiotics and/or prebiotics could replace the lost microbiota and improve depressive symptoms (Blaser, 2016; Jang et al., 2019; Mörkl et al., 2020; Slykerman et al., 2017).

This study has some limitations. First, the data on antibiotic exposure were drawn from a self-reported questionnaire. Therefore, there may have been a non-differential misclassification bias in the reporting and coding of medications. Second, we were unable to accurately determine the specific type, timing, and duration of antibiotic use during pregnancy. Therefore, differences in effects according to the timing or spectrum of the antibiotics could not be evaluated. Third, while the reasons for antibiotic use during pregnancy and the acquisition of infection itself may have also affected the mental status of the mothers, no related data were obtained. Fourth, we measured K6 at only one point of time, which was in the second questionnaire; therefore, we were unable to describe the causal relationship between antibiotic exposure and psychological

distress. Fifth, the hypothetical role of the gut microbiota in postpartum mood disorders was not examined because no information on microbiota was available. Although limited evidence suggests that the microbiome may contribute to PDS via a potential relationship with antibiotics, this is an important area for future research. To confirm our results, future studies should use more detailed data on antibiotic exposure and participants' gut microbiota. Finally, important information, such as the participants previous history of stress, depression, and/or family history of depression, was not obtained. This may have resulted in a shortfall in the PDS evaluation.

Overall, we observed a small increase in the risk of PDS at 6 months after delivery among women who received antibiotics during pregnancy, which may be explained by psychological distress during the antenatal period. Our study highlights a compelling focus for future research that antibiotic exposure can cause psychological distress, which mediates the pathway to PDS. Prospective epidemiological studies are needed to establish a causal link between antibiotic exposure and antenatal psychological distress and confirm the hypothesized causal pathway. Although the use of antibiotics when medically necessary does not need to be changed, additional postnatal follow-ups should be considered in the future when antibiotics are prescribed to pregnant women who show signs of depression. Observation after antibiotics use by healthcare providers is recommended to monitor the mental health of pregnant and postpartum women. Increased monitoring may reduce the development of PDS or hasten its early recognition and treatment.

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TABLES

TABLE 1. Participants' main characteristics according to their postpartum depressive symptoms at 6 months postpartum (N = 65,272)

	Postpartum depressive symptoms at 6 months postpartum			
	Yes (EPDS[a] ≥ 9)		No (EPDS[a] < 9)	
	n	(%)	n	(%)
Number	6,604	(10.1)	58,668	(89.9)
Maternal characteristics				
Age at delivery (years)				
< 25	1,108	(16.8)	5,234	(8.9)
25–29	2,086	(31.6)	16,824	(28.7)
30–34	2,056	(31.1)	21,608	(36.8)
≥ 35	1,353	(20.5)	15,000	(25.6)
Missing	1	(0.0)	2	(0.0)
Education (years)				
< 10	442	(6.7)	2,104	(3.6)
10–12	2,406	(36.4)	17,447	(29.7)
≥ 13	3,695	(56.0)	38,808	(66.1)
Missing	61	(0.9)	309	(0.5)
Annual household income (million Japanese yen)				
< 4	2,986	(45.2)	20,744	(35.4)

4 to < 6	1,831	(27.7)	18,658	(31.8)
6 to < 8	770	(11.7)	9,124	(15.6)
≥ 8	444	(6.7)	6,250	(10.7)
Missing	573	(8.7)	3,892	(6.6)
Marital status at study enrollment				
Married	6,097	(92.3)	56,348	(96.0)
Neither married, divorced, nor widowed	471	(7.1)	2,108	(3.6)
Missing	36	(0.5)	212	(0.4)
Parity				
0	2,661	(40.3)	23,074	(39.3)
1	2,547	(38.6)	22,430	(38.2)
≥ 2	1,229	(18.6)	11,818	(20.1)
Missing	167	(2.5)	1,346	(2.3)
Smoking				
Never	3,484	(52.8)	35,379	(60.3)
Former	2,632	(39.9)	20,792	(35.4)
Smoking at mid-late pregnancy	414	(6.3)	2,018	(3.4)
Missing	74	(1.1)	479	(0.8)
Alcohol consumption				
Never	2,139	(32.4)	19,733	(33.6)
Former	4,183	(63.3)	36,869	(62.8)
Drinking at mid-late pregnancy	215	(3.3)	1,581	(2.7)

Missing	67	(1.0)	485	(0.8)
Energy intake (kcal, in tertile)				
Low (< 1,475)	2,021	(30.6)	19,761	(33.7)
Medium (1,475–1,943)	1,967	(29.8)	20,053	(34.2)
High (≥ 1,944)	2,615	(39.6)	18,851	(32.1)
Missing	1	(0.0)	3	(0.0)
Antipyretic/analgesic drug use during pregnancy				
Yes	1,496	(22.7)	11,188	(19.1)
History of gastrointestinal diseases				
Yes	841	(12.7)	5,639	(9.6)
Complications during pregnancy or delivery				
Yes	2,987	(45.2)	25,366	(43.2)
Missing	91	(1.4)	954	(1.6)
Multiple pregnancy				
Yes	12	(0.2)	100	(0.2)
Low birth weight (< 2,500 g)				
Yes	420	(6.4)	3,492	(6.0)
Missing	0	(0.0)	11	(0.0)
Physical anomalies in newborns				
Yes	400	(6.1)	3,213	(5.5)
Missing	121	(1.8)	1,098	(1.9)
Maternal psychological distress at mid-late pregnancy (K6 score[b])				
Mentally stable (< 5)	2,215	(33.5)	45,358	(77.3)

Psychological distress (5–12)	3,521	(53.3)	12,021	(20.5)
Severe mental disorder (> 12)	782	(11.8)	787	(1.3)
Missing	86	(1.3)	502	(0.9)

569 *Note*: [a] EPDS, Edinburgh Postnatal Depression Scale; [b] K6, Kessler Psychological Distress Scale.

TABLE 2. The association between antibiotic exposure and postpartum depressive symptoms at 1 and 6 months postpartum based on the binomial and multinomial logistic regression models (N = 65,272)

Postpartum depressive symptoms	Cases		Crude model		Adjusted model 1		Adjusted model 2		*p* value for interaction
(EPDS[a] score ≥ 9)	n	(%)	OR[b]	95% CI[c]	OR	95% CI	OR	95% CI	(K6 scores[d]×antibiotics)
At 1 month[e]	8,042	(12.3)	**1.09**	**[1.01, 1.17]**	1.05	[0.97, 1.13]	0.96	[0.89, 1.05]	0.938
At 6 months[e]	6,604	(10.1)	**1.17**	**[1.08, 1.26]**	1.07	[0.99, 1.16]	0.98	[0.90, 1.07]	0.178
At 1 month only[f]	4,543	(7.0)	1.06	[0.96, 1.16]	1.07	[0.97, 1.19]	1.01	[0.91, 1.11]	0.691
At 6 months only[f]	3,105	(4.8)	**1.20**	**[1.07, 1.34]**	**1.13**	**[1.00, 1.26]**	1.05	[0.93, 1.18]	0.322
At both 1 and 6 months[f]	3,499	(5.4)	**1.15**	**[1.03, 1.28]**	1.07	[0.93, 1.16]	0.92	[0.81, 1.04]	0.689

Note: Adjusted model 1 includes age, education, household income, marital status, parity, smoking, alcohol consumption, energy intake, antipyretic/analgesic drug use during pregnancy, history of gastrointestinal diseases, complications during pregnancy or delivery, multiple pregnancies, low birth weight, and physical anomalies in newborns as covariates. Adjusted model 2 includes the K6 score in addition to the variables in Adjusted model 1.

[a] EPDS, Edinburgh Postnatal Depression Scale; [b] OR, odds ratio; [c] CI, confidence interval; [d] K6, Kessler Psychological Distress Scale; [e] Analysis using binomial logistic regression; [f] Analysis using multinomial logistic regression.

578 Bold letters indicate that the estimates in which the 95% CI does not include 0.

TABLE 3. Relationship between antibiotic exposure (by mid-late pregnancy) and PDS at 1 and 6 months via psychological distress (at mid-late pregnancy) estimated by mediation analysis (N = 65,272)

limita	Path		Standardized estimate	
			β	[95% BCI[c]]
At 1 month	Direct effect	Exposure → EPDS scores at 1 month	0.003	[-0.004, 0.009]
	Indirect effect	Exposure → K6[b] scores → EPDS scores at 1 month	**0.011**	**[0.008, 0.014]**
	Total effect		**0.014**	**[0.006, 0.021]**
At 6 months	Direct effect	Exposure → EPDS scores at 6 months	0.000	[-0.006, 0.005]
	Indirect effect (1 + 2)	1. Exposure → K6 scores → EPDS scores at 6 months 2. Exposure → K6 scores → EPDS scores at 1 month → EPDS scores at 6 months	**0.013**	**[0.008, 0.018]**
	Total effect		**0.012**	**[0.005, 0.019]**

Note: [a] EPDS, Edinburgh Postnatal Depression Scale; [b]K6, Kessler Psychological Distress Scale; [c] BCI, Bayesian credible interval. Bold letters indicate that the estimates in which the 95% BCI does not include 0.

585 **SUPPORTING INFORMATION**

586 TABLE S1. Comparison of the major characteristics of the included and excluded participants

Maternal characteristics	Included (n = 65,272)			Excluded (n = 37,790)		
	Valid N	n	(%)	Valid N	n	(%)
Postpartum depressive symptoms (EPDS[a] score)						
At 1 month	65,272			30,261		
< 9		57,230	(87.7)		24,723	(81.7)
≥ 9		8,042	(12.3)		5,538	(18.3)
At 6 months	65,272			25,874		
< 9		58,668	(89.9)		21,842	(84.4)
≥ 9		6,604	(10.1)		4,032	(15.6)
Psychological distress at mid-late pregnancy (K6[b] score)	64,684			32,475		
Mentally stable (< 5)		47,573	(73.5)		21,454	(66.1)
Psychological distress (5–12)		15,542	(24.0)		9,384	(28.9)
Severe mental disorder (> 12)		1,569	(2.4)		1,637	(5.0)
Antibiotic use during pregnancy	65,272			32,191		
No		58,290	(89.3)		28,405	(88.2)
Yes		6,982	(10.7)		3,786	(11.8)
Age at delivery (years)	65,269			35,814		
< 25		6,342	(9.7)		3,811	(10.6)
25–29		18,910	(29.0)		8,881	(24.8)

30–34	23,664	(36.3)	12,028	(33.6)	
≥ 35	16,353	(25.1)	11,094	(31.0)	
Education (years)	64,902		32,576		
< 10	2,546	(3.9)	2,180	(6.7)	
10–12	19,853	(30.6)	10,831	(33.2)	
≥ 13	42,503	(65.5)	19,565	(60.1)	

587

588 *Note*: [a] EPDS, Edinburgh Postnatal Depression Scale; [b] K6, Kessler Psychological Distress Scale.

TABLE S2. Sensitivity analyses for the association between antibiotic exposure and postpartum depressive symptoms at 1 and 6 months after delivery

Postpartum depressive symptoms (EPDS[a] score ≥ 9)	Number of cases	Crude model OR[b]	Crude model 95% CI[c]	Adjusted model 1 OR	Adjusted model 1 95% CI
No colorectal disease (imputed, n = 65,105)					
At 1 month[d]	8,019	**1.09**	**[1.01, 1.17]**	1.05	[0.97, 1.13]
At 6 months[d]	6,590	**1.17**	**[1.08, 1.26]**	1.07	[0.99, 1.16]
At 1 month only[e]	4,530	1.06	[0.96, 1.17]	1.07	[0.97, 1.19]
At 6 months only[e]	3,101	**1.20**	**[1.08, 1.34]**	**1.13**	**[1.00, 1.26]**
At both 1 and 6 months[e]	3,489	**1.15**	**[1.03, 1.28]**	1.04	[0.93, 1.16]
Complete case (n = 57,020)					
At 1 month[d]	6,822	1.08	[1.00, 1.17]	1.05	[0.94, 1.17]
At 6 months[d]	5,642	**1.19**	**[1.10, 1.30]**	**1.14**	**[1.01, 1.29]**
At 1 month only[e]	3,862	1.03	[0.93, 1.15]	0.99	[0.92, 1.06]
At 6 months only[e]	2,682	**1.22**	**[1.09, 1.37]**	**1.14**	**[1.04, 1.24]**
At both 1 and 6 months[e]	2,960	**1.18**	**[1.05, 1.32]**	1.06	[0.94, 1.19]

Note: Adjusted model 1 includes age, education, household income, marital status, parity, smoking habits, alcohol consumption habits, energy intake, antipyretic/analgesic drug use during pregnancy, history of gastrointestinal diseases, complications during pregnancy or delivery, multiple pregnancies, low birth weight, and physical anomalies in newborns as covariates.

[a] EPDS, Edinburgh Postnatal Depression Scale; [b] OR, odds ratio; [c] CI, confidence interval; [d] Analysis using binomial logistic regression; [e] Analysis using multinomial logistic regression. The models were adjusted for all the covariates.

598 Bold letters indicate that the estimates in which the 95% CI does not include 0.

FIGURE CAPTIONS

Figure 1. Flowchart of the data collection for antibiotic exposure, postpartum depressive symptoms, and psychological distress

Note: T1 = Term 1; T2 = Term 2; K6 = Kessler Psychological Distress Scale; EPDS = Edinburgh Postnatal Depression Scale

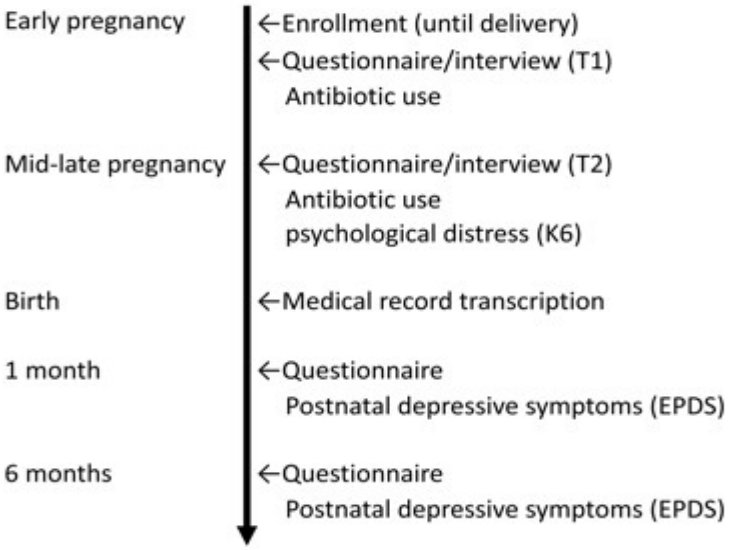
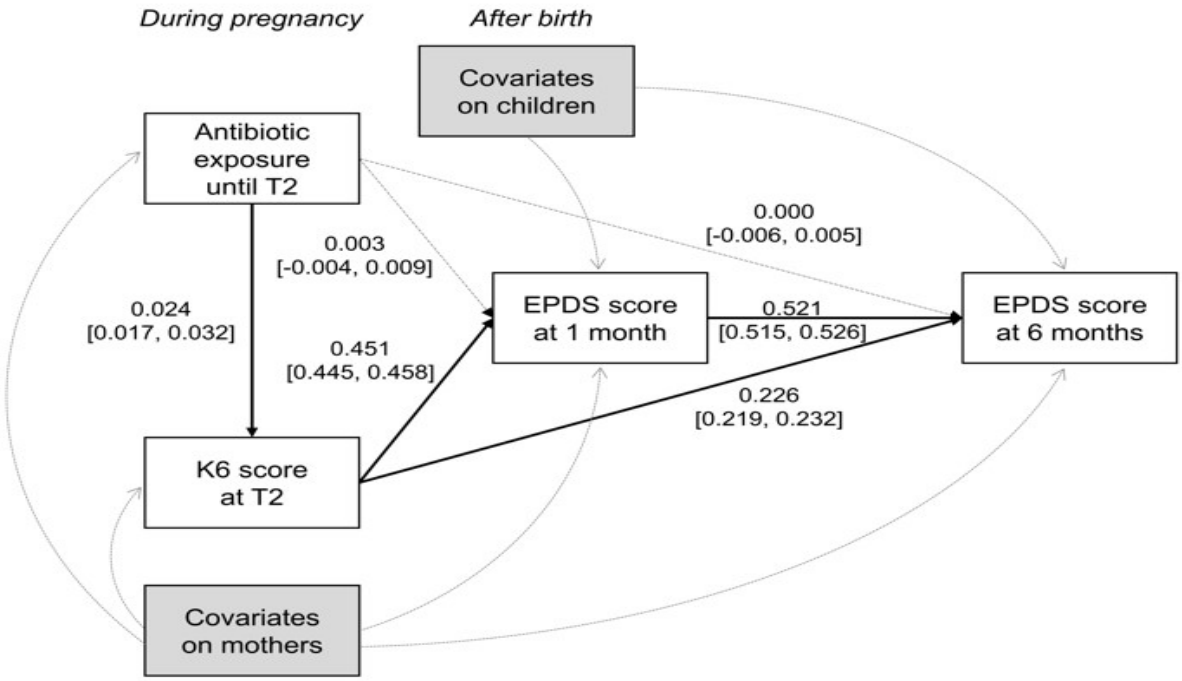


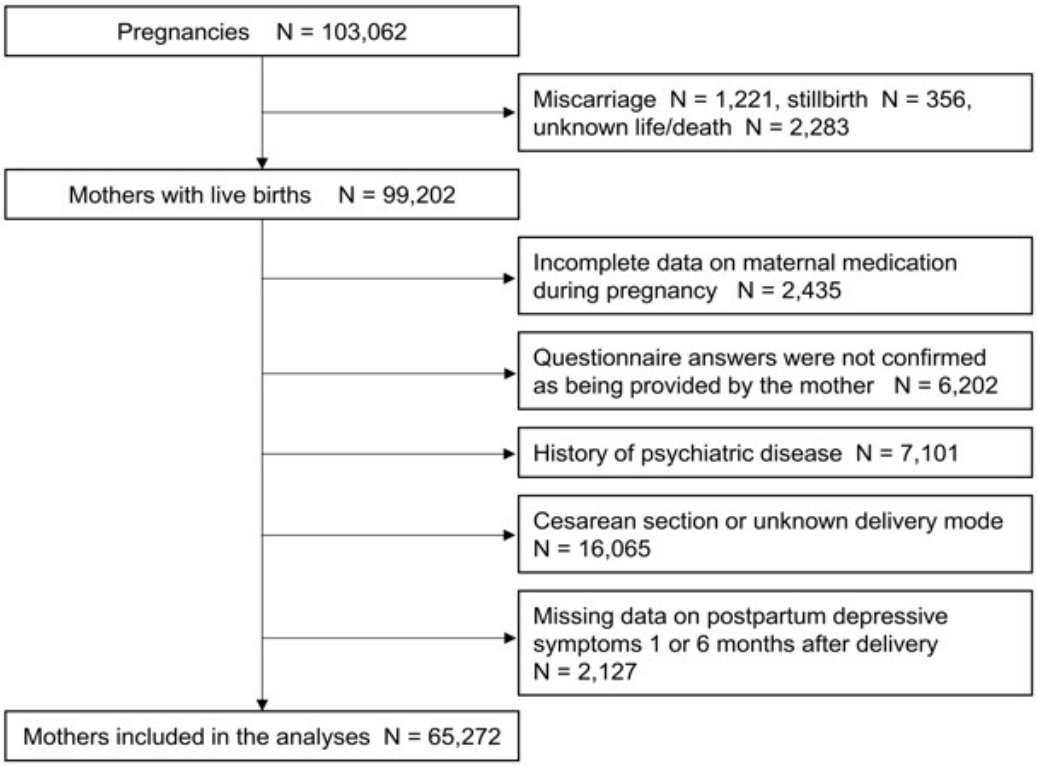
Figure 2. Path model for the relationship between antibiotic exposure and psychological distress (K6 scores) during pregnancy and PDS (EPDS scores)

Note: "Covariates on mothers" included age, education, household income, marital status, parity, smoking habits, alcohol consumption habits, energy intake, antipyretic/analgesic drug use during pregnancy, history of gastrointestinal diseases, complications during pregnancy or delivery, and multiple pregnancies. "Covariates on children" included low birth weight and physical anomalies in newborns. Values indicate standardized β and Bayesian credible intervals.



612

613 Figure 3. Selection of the participants



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