- · Most previous studies on postpartum depression (PPD) risk factors are based on Western populations, which cannot be generalized to non-Western cultures.
- Based on a longitudinal population-based sample from Japan, we found that negative feelings about pregnancy, combined breast and bottle feeding, first-time motherhood, motherhood 24 years old, perceived maternal mental illness before pregnancy, and lack of social support were all significantly associated with PPD at three months after delivery.
- These risk factors should be identified and the mothers should be offered a suitable intervention, in order to prevent the development of PPD.

Abstract

Background: Postpartum depression (PPD) negatively impacts maternal health, parenting and development of children. Most previous studies on PPD risk factors are based on Western populations. Additionally, little is known about the association between psychosocial factors during early pregnancy period and PPD. We aimed to identify early risk factors for PPD until three months after delivery using a longitudinal population-based sample from Japan.

Methods: The data was collected from 1050 mothers at four time points: first trimester, after the birth, and one and three months post-delivery. Mothers who had a Japanese Edinburgh Postnatal Depression Scale (EPDS) cutoff score above 9 at 1 or 3 months after delivery were recognized as having PPD (n = 91/8.7%).

Results: Negative feelings about pregnancy, combined breast and bottle feeding, first-time motherhood, motherhood 24 years old, perceived maternal mental illness before pregnancy, and lack of social support were all significantly associated with PPD at 3 months after delivery.

Limitations: The data was collected from one city in Japan, which limits the generalization of the findings. Additionally, PPD was assessed by an EPDS questionnaire, and not by a clinical interview.

Conclusions: Even after controlling for the perceived mental illness before pregnancy, several risk factors as early as in the first trimester were associated with PPD. These risk factors should be identified and the mothers should be offered a suitable intervention, in order to prevent the development of PPD.

Key words

Postpartum depression; population based longitudinal study; risk factor

Early risk factors for postpartum depression: a longitudinal Japanese

population-based study

Mami Nakano¹, Andre Sourander², Terhi Luntamo², Chudal Roshan², Norbert Skokauskas³, Hitoshi

Kaneko4

1 Graduate School of Education and Human Development, Nagoya University, Furo-cho, Chikusa-

ku, Nagoya, Japan 464-8601, Japan

2 Research Center for Child Psychiatry, University of Turku, Lemminkäisenkatu 3/Teutori 3rd

Floor, Turku, 20014, Finland

3 Centre for Child and Adolescent Mental Health and Child Protection, Faculty of Medicine,

NTNU, NO-7491, Trondheim, Norway

4 Psychological Support and Research Center for Human Development, Nagoya University, Furo-

cho, Chikusa-ku, Nagoya, 464-8601, Japan

E-mail address:

Mami Nakano:nakano.mami@nagoya-u.jp

Terhi Luntamo: tetulu@utu.fi

Roshan Chudal: roshan.chudal@utu.fi

Norbert Skokauskas: norbert.skokauskas@ntnu.no

Andre Sourander: andsou@utu.fi

Hitoshi Kaneko: kaneko@cc.nagoya-u.ac.jp1

¹ Corresponding author:

Hitoshi Kaneko

Psychological Support and Research Center for Human Development,

Nagoya University, 464-8601, Japan

Phone: +81527892665, E-mail: kaneko@cc.nagoya-u.ac.jp

Introduction¹

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2 Postpartum depression (PPD) is defined as a major depressive episode that begins 3 within 4 weeks after delivery according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5; American Psychiatric Association 2013). However in 4 clinical practice, depression within one year after delivery has been recognized as PPD 5 (O'hara & McCabe, 2013). Mothers with PPD often exhibit sadness, loss of interest and 6 7 joy, difficulty in concentrating and remembering, feelings of guilt and helplessness, changes in appetite, and sleep disturbances (American Psychiatric Association 2013). 8 PPD may negatively impact maternal health, parenting and subsequently the 9 10 development of children. It can result in higher risk of maternal suicidal attempt and completed suicide (Weng et al., 2016), abusive parenting (Sagami et al., 2004), poor 11 mother-infant interaction (Righetti-Veltema et al., 2002; Væver et al., 2015) and 12 infanticide (Krischer et al., 2007). In addition, it can result in negative sequelae for the 13 offspring including delayed cognitive development (Brand & Brennan, 2009), 14 15 behavioral problems (Avan et al, 2010; Murray et al., 2011), and even suicidal ideation (Hammerton et al, 2016). PPD affects a significant number of mothers, children and 16 families, as the global prevalence of PPD has been reported to range from 3% in 17 18 Singapore to 38% in Chile (Hahn-Holbrook et al., 2018). PPD is a common phenomenon in Japan, with rates reported ranging from 10.3% to 27% (Kitamura et al., 19 2006; Miyake et al., 2006; Sagami et al., 2004; Ueda et al., 2006; Yamashita et al., 20 21 2000). Therefore, identifying risk factors for PPD is important for earlier detection and prevention of negative consequence of PPD in Japan. 22

¹ Abbreviations: Postpartum depression(PPD); Edinburgh Postnatal Depression Scale (EPDS)

Risk factors for PPD, reported in earlier studies, include unwanted pregnancy (Csatordai 1 et al., 2007), the history of depression (Silverman et al., 2018), poor marital relationship 2 3 (Azale et al., 2018), cesarean delivery (Silverman et al., 2017), preterm delivery, (Silverman et al., 2017), and poor social support (Baumgartner et al., 2016). However, 4 there are still some gaps in the literature on the psychosocial risk factors for PPD. First, 5 6 the majority of population-based studies have been conducted in Western countries and 7 cannot be generalized to non-Western cultures. Second, relatively little is known about 8 the psychosocial risk factors for PPD during the first trimester of pregnancy (Kirkan et al., 2015; Lee et al., 2007; Muchanga et al., 2017), as in most previous studies, 9 10 information on risk factors was collected only later, typically during the last trimester. 11 Studying early risk factors is essential as pregnancy is a valuable period for implementing successful psychological interventions to prevent adverse outcomes. 12 Third, most studies have used cross-sectional designs, and only a few studies have 13 14 assessed risk factors for PPD based on longitudinal design (Asano et al., 2014; Matsumoto et al., 2011; Watanabe et al., 2008). An important limitation in cross 15 sectional research is that mothers who do not have PPD at the time of assessment could 16 develop PPD later (Furumura et al., 2012; Hayakawa et al., 2012; Ishikawa et al., 2011). 17 Additionally, retrospective information about the mother's well-being may not be 18 19 reliable because of recall bias. The aim of this study was to investigate the prenatal and postnatal risk factors associated 20 with PPD up to three months after delivery in a Japanese urban population based study 21 22 using routinely collected data in maternal and child health care city services. In accordance with previous studies conducted mostly in Western countries (Davey et al., 23 2011; Dias & Figueiredo, 2015; Räisänen et al., 2013; Robertson et al., 2004; Sword et 24

- al., 2011; Vigod et al., 2010), we hypothesized that maternal negative feelings about
- 2 pregnancy, maternal mental illness before pregnancy, and social support would be
- 3 associated with PPD.

4 Method

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Procedure

- 6 The present study is a longitudinal, citywide population-based study, conducted as a
- 7 part of the routine work by the maternal and child health care services in Hekinan City,
- 8 Aichi prefecture, Japan from July 2013 to June 2015 during which the population of
- 9 Hekinan City was about 70,000. In Japan, public health centres in all municipalities
- provide continuous support to women and their families based on Maternal and Child
- Health Act since 1965. The present study followed the normal pattern of collecting
- information on depressive symptoms in public health centres. The Edinburgh Postnatal
- Depression Scale (EPDS) was provided to all mothers to be filled at the time of two
- 14 check-ups after delivery; one month and three months. The health care personnel
- provided the information sheet on the study and the EPDS to the mothers. With the
- mothers informed consent, their answers could be used in the study.
- 17 The data were collected at four time points: 1) from pregnancy notification forms
- submitted during the 11th week of gestation, 2) from birth registration forms submitted
- within 14 days after delivery, 3) during home visits one month after delivery, and 4) at
- 20 the infant's health check-up three months after delivery. EPDS were collected at two
- 21 instances after the delivery; one month and three months.
- 22 All procedures performed in this study have been approved by the ethical committee at
- 23 the Graduate School of Education and Human Development, Nagoya University, Japan

- 1 (Reference number: 490). Information on participation in the study was provided in the
- 2 questionnaire. Informed consent to participate in this study was obtained from all
- 3 individual participants before including them in the study. Details of data collection
- 4 have been reported previously (Nakano et al., 2019).

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Participants

- 7 The original cohort included 1163 mothers who came to the public health centre for
- 8 their infant's health check-up 3 months after delivery. Maternal inclusion criteria were
- 9 as follows: (1) Japanese, (2) carrying a single fetus and (3) Edinburgh Postnatal
- Depression Scale (EPDS) (Cox et al. 1987; Okano et al. 1996) was completed at least
- once, at one month or three months after delivery. A total of 1050 (90.28%) mothers
- were included in the analysis. One hundred and thirteen (9.71%) mothers were excluded
- because seven of them (0.60%) had twins, fifty-eight of them (4.99%) were not
- Japanese, and forty-eight of them (4.13%) did not complete the EPDS at either one
- month or three months after giving birth.
- 16 The mean age of the mothers was 29.95 years, with a standard deviation (SD) of 5.08
- 17 (range 16-44 years) and the mean gestational age was 38.96 weeks (SD 1.36, range 33-
- 41 weeks). Less than half of the participants (n = 424, 41.90%) were first-time mothers,
- and just over half of the babies were male (n = 543, 52.62%).

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Measurements

- 22 Edinburgh Postnatal Depression Scale (EPDS)
- 23 Edinburgh Postnatal Depression Scale (Cox et al., 1987; Okano, 1996) was used to
- 24 assess maternal PPD at one and three months after delivery. The EPDS is a self-rating

scale that includes 10 items scored from 0 (no, not at all) to 3 (yes, all the time). A 1 2 higher score of EPDS indicates greater depression possibility. A different cut-off score 3 has been recommended in different cultural groups (Gibson et al., 2009) for measuring PPD. In Japan, a cut-off score ≥9 has been adapted and generally used to identify PPD 4 (Miyake et al., 2006; Okano, 1996; Sagami et al., 2004; Ueda et al., 2006; Yamashita et 5 6 al., 2000), as Japanese women are reluctant to disclose their negative mood (Yoshida et al., 1997). The scale has a high internal consistency (Cronbach's alpha 0.87) and good 7 8 construct validity (Cox et al., 1987). The Japanese version of the EPDS has been 9 reported to have good validity, sensitivity (0.82) and specificity (0.95) (Okano, 1996; Yamashita et al., 2000). EPDS was collected at one month and three months after the 10 11 delivery by a public health nurse or other trained health care personnel. In this study, mothers who exceeded the EPDS cut-off score of ≥9 at least once (one month or three 12 months after delivery) were identified as having PPD. Public health nurses started 13 providing individual support to mothers who needed it based on the score of EPDS, 14 15 which are different from diagnostic interviews.

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Additional study variables

A pregnancy notification form was used to obtain sociodemographic and some other information including the mother's age (≤24, 25-34 or ≥35 years), parity (primipara or multipara), perceived mental illness before pregnancy (Have you suffered from a disease in the past or are currently getting treated for one (Disease name: mental illness (depression etc.)) (yes or no), feelings at the moment of discovering the pregnancy (delighted or negative feelings; i.e. unintended but happy, confused because unintended or worried), social support (yes or no). The type of birth (vaginal delivery; cesarean

section; assisted delivery, i.e. vacuum extraction or forceps delivery), and infant birth weight (≥ 2500g or < 2500g) were asked on the birth registration form. Childcare support (yes or no) was asked during the home visit one month after delivery. Gestational weeks (\geq 37 weeks or < 37 weeks), feeding style (only breastfeeding, only bottle-feeding or combined breast and bottle feeding), maternal health after delivery (problems or no problems) and maternal employment status during the antenatal period (employed or unemployed) were asked during the infant checkup three months after delivery. As only a few participants reported having no social support during the pregnancy (n = 11) or having no child-care support after delivery (n = 6), participants who answered either no social support in pregnancy or no childcare support after delivery were categorized as "no social support".

Statistical Analysis

Univariate and multivariate logistic regression analyses were conducted to examine the risk factors of PPD. The association between exposures and PPD was determined by odds ratios (ORs) with 95% confidence intervals (95% CIs). First, a univariate analysis was carried out to determine independent variables to be selected in the multivariate analysis. All variables with a significance level of p<0.10 in the univariate analysis was conducted in the multivariate analysis. Second, a multivariate analysis was conducted to identify the association between PPD and variables found to be significant in the univariate analysis. The level of statistical significance in the final analysis was p<0.05. All statistical analyses were carried out using SPSS 23.0.

Results

In our study, 8.9% (n = 93) of the 1.050 mothers had had PPD symptoms above the cut-1 off point (cut-off score ≥ 9) at least once (one month or three months after delivery). Out 2 of these 93 mothers, 29.0 % (n=27) had scored above the cut-off at both time points, i.e 3 at one month and 3 month after delivery. 42.0% (n=39) had scored above the cut-off 4 point only at 1 month follow-up while 29.0% (n=27) only at 3 month follow-up. The 5 prevalence of PPD at each instance was 6.3% (n = 66) of the 1,046 mothers at one 6 month after delivery, and 5.1% (n = 54) of the 1,049 mothers at three months after 7 delivery. Table 1 shows the frequencies of each variable investigated and the results of 8 9 the univariate and multivariate analyses. The risk factors associated with PPD in 10 multivariate analysis were negative feelings about pregnancy (OR=2.07, 95% CI=1.28-11 3.36), primipara mother (OR=2.01, 95% CI=1.21-3.35), maternal age under 24 years (OR=2.43, 95% CI=1.37-4.30), maternal mental illness before pregnancy (OR=4.84, 12 95% CI=2.09-11.19), combined breast and bottle feeding (OR=1.80, 95% CI=1.01-13 14 3.05) and lack of social support (OR=4.93, 95% CI=1.54-15.74). Low birth weight and only bottle-feeding were associated with PPD in the univariate analysis but did not 15 16 remain significant when adjusted with all other variables.

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Discussion

- 19 The main findings of the present longitudinal study were that maternal negative feelings
- 20 about pregnancy during the first trimester, combined bottle and breast feeding, being a
- 21 mother for the first time, mother's young age, mental problems before pregnancy, and
- 22 lack of social support were independently associated with PPD.
- 23 The finding that negative feelings about pregnancy when the mother discovered being

pregnant was associated with PPD is in line with previous studies (Kokubu et al., 2012; 1 2 Limlomwongse & Liabsuetrakul, 2006). Previous studies have suggested that mothers 3 who have negative feelings about their pregnancy are more likely to have subsequent issues during pregnancy, such as maternal antenatal depression (Kitamura et al., 2006) 4 and impaired maternal bonding toward their fetus (Hassan & Hassan, 2017). It is 5 important to note that in previous Japanese studies, negative feelings when discovering 6 being pregnant were assessed in last trimester while in the present study this 7 8 information was collected in the first trimester, thus minimizing the recall bias. A plausible explanation for the association between negative feelings about pregnancy and 9 10 PPD is that negative feelings and PPD may both be associated with other risk factors 11 such as low socioeconomic status (Dolbier et al., 2013; Goyal et al., 2010), family and relational problems, and partner's mental health problems, such as depression and 12 13 substance use (Nishimura & Ohashi, 2010; Tyrlik et al., 2013). 14 Combined bottle and breast feeding were independently associated with PPD, whereas bottle feeding alone did not independently associate with PPD in the final analysis. One 15 16 possible explanation for the results could be that breastfeeding was a protective factor against PPD. Previous studies have shown several positive effects of breastfeeding on 17 18 the mother's health. Breastfeeding reduced maternal perceived anxiety, stress, and 19 negative moods (Groër, 2005). Furthermore, breastfeeding promotes mother-infant interaction (Bigelow et al., 2014) including physical contact, gazing (Lavelli & Poli, 20 1998), and maternal responsiveness (Ventura, 2017). Another plausible explanation 21 22 might be that feeding style is the consequence of depression; that is, the depressive mothers have difficulty providing sufficient breast milk to their infants. Previous studies 23 reported that depressive mothers have a lower intensity or early cessation of 24

breastfeeding (Dennis & McQueen, 2007; Gaffney et al., 2014). Maternal stress and 1 2 depressive symptoms may negatively affect lactation and the mother's self-efficacy in 3 breastfeeding (Haku, 2007; Zubaran & Foresti, 2013). The other explanation is that there might be confounding factors regarding the association between combined bottle 4 5 and breastfeeding with PPD. A Japanese study (Maehara et al. 2017) reported higher child-related stress among mothers using combined feeding compared to mothers using 6 7 only breastfeeding. Additionally, combined feeding style was associated with shorter 8 hours of night-time sleep, possibly due to greater time spent and practical burden in 9 providing feedings, as well as higher levels of fatigue (Maehara et al. 2017). In any case, 10 our findings may be due to small number of mothers regarded as PPD using only bottle 11 feeding. In fact, 6.7% of the breastfeeding mothers were regarded as PPD (n=45); this rate was lower than both 12.5% of combined bottle and breastfeeding mothers (n=29) 12 13 and 13.3% of only bottle-feeding mothers (n=19). 14 Previous studies are inconsistent about the association between parity and risk of PPD. In the present study, PPD was associated with primipara motherhood. Accordingly, 15 16 previous Japanese studies reported that being a mother for the first time increased the 17 risk of PPD (Akman et al., 2007; Asano et al., 2014; Iwata et al., 2016; Satoh et al., 2009). However, some previous studies showed no significant association between 18 19 parity and PPD (Dietz et al., 2007; Wenzel et al., 2005) while some reported that primiparity is associated with lower odds of depressive symptoms (Dørheim et al., 20 2007; Figueiredo & Conde, 2011; Skari et al., 2002). The association between being a 21 mother for the first time and PPD might be explained by the challenging situation of 22 being first-time mothers, including more postpartum stress, concerns about maternal 23 role attainment and poor sleep quality when compared to second-time mothers 24

- 1 (Dørheim et al., 2009; Hung, 2007). Another explanation could be that mothers who
- 2 have had a depressive experience after the first delivery are less motivated to have more
- 3 children (Di Florio et al., 2014).
- 4 Younger maternal age was associated with the risk of developing PPD later. Both young
- 5 age (Milgrom et al., 2008; Mori et al., 2011; Sword et al., 2011; Zaidi et al., 2017) and
- 6 advanced age (Bell et al., 2016; Matsumoto et al., 2011; Mori et al., 2011; Muraca &
- 7 Joseph, 2014) have been associated with a higher risk of PPD in some studies, while
- 8 others have shown no association (Asano et al., 2014; Green et al., 2006; Kitamura et
- 9 al., 2006). One possibility is that young mothers are more likely to have psychosocial
- problems, such as financial instability, lower education, and unstable marital status,
- which also are possible risk factors for PPD (Muraca & Joseph, 2014; Seimyr et al.,
- 12 2004).
- 13 Consistent with previous research findings, both perceived maternal mental illness
- before pregnancy and lack of social support were associated with PPD. Both low social
- support and a history of mental illness are reported to be important risk factors for PPD
- 16 (Okubo et al., 2007; O'hara & McCabe, 2013; Sagami et al., 2004). In the present study,
- the definition of low social support was strict, indicating that according to the mother's
- 18 report, she did not have anyone supporting her. Mothers with no social support might
- 19 have a poor relationship with their partner, family, and friends and may not perceive
- 20 receiving support from the health or social services. Low social support may be
- 21 associated with the experience of loneliness, thereby increasing challenges in parenting
- 22 the infant (Hudson et al., 2000). PPD may adversely affect the perception of
- interpersonal relationships (Leskelä et al., 2008; Senturk et al., 2017) and mothers with

1 PPD may exaggerate the lack of social support.

Strengths and limitations

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3 The strengths of the study are that it includes a longitudinal population-based design in a non-Western country with low attrition rate, collection of information in early 4 pregnancy, and assessment of maternal depression at two time points. However, there 5 6 are several limitations to be considered when interpreting the results. First, the data was 7 collected from one city in Japan, which limits the generalization of the findings. About 4% of the mothers were not included in the analysis because they moved out of Hekinan 8 9 City or did not want to answer the EPDS questionnaire. Also, the overall prevalence of 10 EPDS > 9 of 8.9% in this study was much lower than that of the previous studies which ranged from 14.0 to 27.0% (Miyake et al., 2006; Sagami et al., 2004; Ueda et al., 2006; 11 Yamashita et al., 2000). The study design of this study differs from that of previous 12 studies. Data were collected by voluntary participation in previous studies, whereas this 13 study used data collected from the Maternal and Child Health Act, ensuring 14 participation of over 90% of mothers who live in Hekinan city. Therefore, possible 15 participation bias in previous studies could explain the variation of prevalence rate in 16 this study. We believe that our sampling method contributes to a more accurate 17 18 description of the issues and adds new knowledge to the current status. Second, PPD 19 was assessed by an EPDS questionnaire, and not by a clinical interview. However, 20 EPDS has been commonly used, especially in large population samples to measure pre-21 and postnatal depression. In an earlier Japanese study, the sensitivity of the EPDS for measuring PPD was 0.82 and specificity 0.95 (Yamashita et al. 2000). Third, 22 23 unfortunately, the study did not include some important factors known to be associated

- with postnatal depression. Although we inquired about maternal mental illnesses before
- 2 pregnancy, maternal depression during pregnancy, in addition to some other factors,
- 3 issues such as the family background with regard to mental health disorders and
- 4 personality and attachment characteristics of the mother were not assessed. Therefore,
- 5 the possible effects of these factors on PPD were not studied. It is also likely that the
- 6 association between some of the risk factors studied here and PPD are confounded or
- 7 mediated by additional risk factors mentioned above.

Conclusions

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- 9 Risk factors of PPD have been studied extensively, but mainly in Western societies, and
- the present study extends the earlier findings into Japanese society. Mothers who have
- 11 negative feelings about pregnancy should be identified at an early stage because they
- are at higher risk of later PPD. Mothers who exclusively breastfeed have lower odds of
- 13 PPD. The result is in line with the current practices to support mothers to breastfeed.
- 14 Mothers with primipara, low social support, young age, and history of mental health
- problems have an increased probability of having PPD. Assessing the risk factors by
- health care professionals may help identify mothers at a higher risk of developing PPD
- at an early stage of pregnancy when there is still enough time before delivery. Effective
- 18 interventions, such as counseling, should be considered for mothers at risk of
- developing PPD (US preventive Services Task Force, 2019).

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Table 1: Frequencies of each variable and the results of univariate and multivariate analyses

	N	(%)	Univariate analysis	Multivariate ¹ analysis
Variable	No PPD	PPD	OR (95%CI)	OR (95%CI)
Feelings about pregnancy (n = 992)				
Delighted	662 (93.11)	49 (6.89)	Reference	Reference
Negative feelings (unintended/worried)	243 (86.48)	38 (13.52)	2.11 (1.35-3.31)*	2.07 (1.28-3.36)*
Feeding style ($n = 1,046$)				
Only Breast feeding	626 (93.29)	45 (6.71)	Reference	Reference
Only Bottle feeding	124 (86.71)	19 (13.29)	2.13 (1.21-3.77)*	1.60 (0.82-3.00)
Breast and bottle feeding	203 (87.50)	29 (12.50)	1.99 (1.21-3.25)*	1.80 (1.01-3.05)*
Parity $(n = 1,012)$				
Multipara	550 (93.54)	38 (6.46)	Reference	Reference
Primipara	371 (87.50)	53 (12.50)	2.07 (1.34-3.20)*	2.01 (1.21-3.35)*
Mother's age (Years) $(n = 1,031)$				
≤24	133 (83.13)	27 (16.88)	2.64 (1.58-4.38)***	2.43 (1.37-4.30)*
25-34	610 (92.85)	47 (7.15)	Reference	Reference
≥ 35	197 (92.06)	17 (7.94)	1.12 (0.63-2.00)	1.00 (0.52-1.93)
Maternal mental illness before pregnand	ey (n = 1,030)			
No	914 (92.14)	78 (7.86)	Reference	Reference
Yes	25 (65.79)	13 (34.21)	6.09 (3.00-12.38)***	4.84 (2.09-11.19)*
Social support $(n = 1,007)$				
Yes	908 (91.7)	82 (8.3)	Reference	Reference
No	12 (70.6.7)	5 (29.4)	4.61 (1.59-13.42)*	4.93 (1.54-15.74)*
Birth weight $(n = 1,032)$				
≥ 2500g	880 (91.67)	80 (8.33)	Reference	Reference
< 2500g	61 (84.72)	11 (15.28)	1.98 (1.00-3.92)*	1.87 (0.90-3.87)

¹ The multivariate analysis comprises variables that were shown to be significantly associated with postpartum depression in the univariate analysis.

Infant's Sex $(n = 1,032)$				
Boy	500 (92.08)	43 (7.92)	Reference	Reference
Girl	441 (90.18)	48 (9.82)	1.23 (0.82-1.95)	1.49 (0.92-2.40)
Gestational weeks (n = 1,049)				
\geq 37 weeks	921 (91.28)	88 (8.72)	Reference	NA
< 37 weeks	35 (87.50)	5 (12.50)	1.50 (0.57-3.91)	NA
Employment status($n = 1,049$)				
Employed	503 (90.79)	51 (9.21)	Reference	NA
Unemployed	453 (91.52)	42 (8.48)	0.91 (0.60-1.40)	NA
Birth type $(n = 1,043)$				
Virginal delivery	686 (91.22)	66 (8.78)	Reference	NA
Caesarean section	196 (89.91)	22 (10.09)	0.60 (0.21-1.70)	NA
Assisted delivery	69 (94.52)	4 (5.48)	1.16 (0.70-1.94)	NA
Maternal health after delivery $(n = 1,046)$				
Reported no problem	906 (91.24)	87 (8.76)	Reference	NA
Reported problem	47 (88.68)	6 (11.32)	1.33 (0.55-3.20)	NA

^{***&}lt;0.0001, **<0.001, *<0.05, +<0.10 N.A = Not applicable

Conflict of interests

On behalf of all authors, the	corresponding author	states that there is no	conflict of interest.
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Author contributions

MN performed all the statistical analyses and wrote the first draft of the manuscript. HK supervised in designing and revised the paper critically. AS, TL, RC, NS, critically read and revised the manuscript. All authors participated in planning the statistical analyses and read and approved the final manuscript.

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