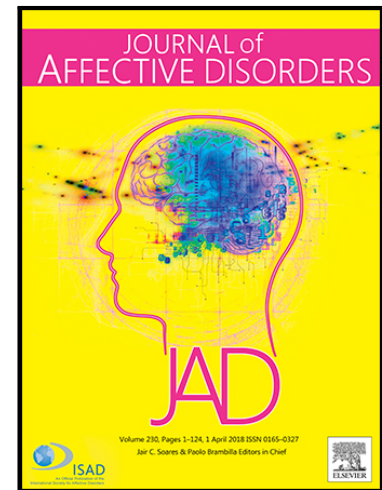


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Prenatal Tobacco Smoking is associated with Postpartum Depression in Japanese Pregnant Women: The Japan Environment and Children's Study

Meishan Cui , Takashi Kimura , Satoyo Ikehara , Jia-Yi Dong , Kimiko Ueda , Yoko Kawanishi , Tadashi Kimura , Hiroyasu Iso , the Japan Environment and Children's Study Group

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Highlights:

- This is a nationwide study which was representative of Japanese pregnant women.
- Nine percent of participants screened positive for PPD one month after childbirth.
- Current study suggest that prenatal tobacco smoking is associated with PPD.
- Smoking 5 years before childbirth may be associated with an increased risk of PPD.

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Abstract

Introduction: Previous studies in Western countries have examined the association between prenatal smoking and risk for Postpartum depression (PPD). However, evidence from Japan is lacking, despite the high prevalence of smoking among pregnant women. Therefore, we examined the association between prenatal smoking and PPD among pregnant Japanese women.

Methods: We analyzed data for up to 1 month after childbirth from the Japan Environment and Children's Study (JECS), a nationwide birth cohort study. Among the 103,070 pregnant women recruited, 80,872 eligible participants were included in the analysis. PPD was defined as a score of ≥ 9 on the Edinburgh Postnatal Depression Scale (EPDS). Prenatal smoking and length of smoking cessation among ex-smokers were obtained using self-administered questionnaires at second/third trimester.

Results: Among 80,872 pregnant women, 9.0% reported PPD. Multivariable-adjusted odds ratios (OR) (95% confidence intervals) for PPD (reference: never smoked) were 1.24 (1.12–1.37) for women who quit smoking after becoming pregnant, and 1.38 (1.21–1.56) for those who smoked during pregnancy. Compared with women who had never smoked, those who quit smoking ≤ 5 years before childbirth had a higher occurrence of PPD, with a multivariable-adjusted OR of 1.10 (1.00–1.22).

Limitations: Questionnaire data was self-reported by participants, thus smoking status might be under-reported.

Conclusions: Women who smoked during pregnancy, quit smoking after becoming pregnant, and quit smoking ≤ 5 years before childbirth are more likely to experience PPD than those who had never smoked.

Keywords: postpartum depression, EPDS, smoking

Prenatal Tobacco Smoking is associated with Postpartum Depression in Japanese Pregnant Women: The Japan Environment and Children's Study

Meishan Cui, PhD¹; Takashi Kimura, PhD²; Satoyo Ikehara, PhD¹; Jia-Yi Dong, PhD¹; Kimiko Ueda, MD, PhD³; Yoko Kawanishi, MD⁴; Tadashi Kimura, MD, PhD⁴; Hiroyasu Iso, MD, PhD^{1,5*}; and the Japan Environment and Children's Study Group

¹ Public Health, Department of Social Medicine, Osaka University Graduate School of Medicine, Osaka, Japan

² Department of Public Health, Hokkaido University School of Medicine, Sapporo, Japan.

³ Osaka Maternal and Child Health Information Center, Osaka Women's and Children's Hospital, Osaka, Japan

⁴ Department of Obstetrics and Gynecology, Osaka University Graduate School of Medicine, Osaka, Japan

⁵ Department of Public Health Medicine, Faculty of Medicine, University of Tsukuba, 1-1-1 Tennodai, Tsukuba, Ibaraki 305-8577, Japan

*Correspondence author. Public Health, Department of Social Medicine, Osaka University Graduated School of Medicine, 2-2 Yamadaoka Suita, Osaka 562-0871, Japan. E-mail address: iso@pbhel.med.osaka-u.ac.jp Telephone: +81-6-6879-3912

Introduction

Postpartum depression (PPD) is a common disorder, which have been reported to affects 12% to 20% of pregnant women (Fisher et al., 2012; Shorey et al., 2018). It is a complex combination of physical, emotional, and behavioral changes linked to chemical, social, and psychological changes following childbirth (Pearlstein et al., 2009). Extensive evidence suggests that PPD disrupts a woman's life and has negative effects on the mother-child relationship and the mother's relationship with her partner (Field, 2010; Gress-Smith et al., 2012; Pearlstein et al., 2009; Reck et al., 2004). Women who suffer from PPD have higher rates of marital separation and divorce, child abuse and neglect, chronic depression, suicide, and infanticide (Reck et al., 2004). Numerous studies have linked maternal depression to poor cognitive function and increased behavioral problems among infants and children (Cornelius and Day, 2000; Gunlicks and Weissman, 2008; Pawlby et al., 2008; Verbeek et al., 2012).

Maternal smoking during pregnancy is causally related to risks for premature birth, stillbirth, low birth weight infants, and placental abruption (Andres and Day, 2000; Cnattingius, 2004; Goldenberg et al., 2008). The rate of smoking among Japanese women is 7.9%, which is relatively low among Organization for Economic

Co-operation and Development (OECD) countries (OECD iLibrary, 2017), but is in the top five among Asian countries (WHO, 2018). The prevalence of prenatal smokers in Japan was reported as 7.8% which was much higher than the globally estimated prevalence of prenatal smokers (1.7%) (Lange et al., 2018). According to a Japanese national report (Ministry of Health, Labour and Welfare, 2014), 9.8% of Japanese women is suffered from PPD at 1 month after childbirth which is similar with the United States and Canada (Dagher and Shenassa, 2012; Lanes et al., 2011). However, associations between prenatal smoking and risk of PPD in Japan have not been investigated systematically. Furthermore, to our knowledge, no study has investigated the association between the duration of quitting smoking before or after pregnancy and PPD. We hypothesized that prenatal smoking elevates odds of PPD, and the shorter duration of quitting smoking had the higher odds of PPD. To test our hypothesis, we examined the data of the Japanese Environment and Children's Study (JECS), a birth cohort study of approximately 100,000 mother-child pairs.

Methods

Study population

The JECS is a nationwide, government-funded prospective birth cohort study. The study

protocol has been described in detail elsewhere (Kawamoto et al., 2014; Michikawa et al., 2018). Briefly, after written informed consent was obtained from all participants, 103,070 pregnancies were recruited from 15 areas in Japan between January 2011 and March 2014. After excluding women with multiple births, multiple participate, stillbirths, and miscarriages, JECS participants were 92,796 pregnant women. To investigate the association between smoking and PPD, the eligibility criteria for participants in this study were: 1) completed questionnaire covering the smoking status during pregnancy at second/third trimester and Edinburgh Postnatal Depression Scale (EPDS) at 1 month after childbirth; 2) no history of mental illness and did not use antidepressants during pregnancy or within 1 year before pregnancy; and 3) did not experience depressive symptoms (Kessler Psychological Distress Scale [K6] score ≥ 13) (Furukawa et al., 2008) in the second/third trimester of pregnancy. In total, 80,872 eligible participants were drawn from the JECS sample.

The JECS protocol was reviewed and approved by the Ministry of the Environment's Institutional Review Board on Epidemiological Studies and the ethics committees of all participating institutions.

Data collection

Self-administered questionnaires were collected from pregnant women at three time points: prenatal period including the first trimester (T1); second/third trimester (T2); and postpartum period, defined as 1 month after childbirth (1M). Information was collected on participants' socioeconomic status, lifestyle, physical environment, medical history, medication history, and mental health (measured with the K6) at T1 and T2. Information on the baby's care, mother-child relationship, mother's lifestyle, health condition, family support, and mental health (measured with the EPDS) was collected at 1M. Maternal anthropometric data before and during pregnancy, complications before and during pregnancy, history of previous pregnancy, perinatal outcomes (e.g., birth weight and gestational duration), and congenital anomalies were transferred from medical records that were provided by participants' obstetricians.

The EPDS is a self-administered, 10-item scale that is used for early detection of PPD (Cox et al., 1987; Kubota et al., 2014). Each item has four possible responses (from 0–3), with a minimum score of 0 and a maximum of 30. The scale captures the intensity of depressive symptoms experienced within the previous 7 days. We defined PPD as an EPDS score ≥ 9 , which was consistent with previous reports (Okano, 1996; Yamashita et al., 2000).

Statistical analyses

The present study was based on the dataset jecs-ag-20160424. We presented participants' characteristics according to prenatal smoking status as means or proportions. To compare the mean EPDS scores and proportions of potential confounding factors according to PPD, we used analysis of variance and chi-square tests. We calculated unadjusted and multivariable-adjusted odds ratios (OR) and 95% confidence intervals (CI) for PPD according to prenatal smoking status and quit duration using logistic regression analysis. Interaction analyses were conducted to examine whether the association between prenatal smoking and risk for PPD differed by age and education. We used dummy variables for cross products of age (0: <30 years, 1: ≥ 30 years) or education (0: high school or less, 1: more than high school) with smoking status (0: never smokers, 1: quit before pregnancy, 2: quit after becoming pregnant, 3: smoked during pregnancy). Variables considered as possible confounding factors are listed in Supplemental Table.

We performed all statistical analyses using SAS version 9.4 (SAS Institute Inc. Cary, NC, USA). All probability values for statistical tests were two-tailed, and $p < 0.05$ was regarded as statistically significant.

Results

As shown in Table 1, mean EPDS scores were progressively higher with the longer exposure to smoking during pregnancy; 5.6 in women that had never smoked, 5.7 in those who quit smoking before becoming pregnant, 5.8 in those who quit smoking after becoming pregnant, and 5.9 in women who continued smoking during pregnancy. Compared with never smokers, women with the longer exposure to smoking during pregnancy were less educated, more likely to be drinkers, exposed to secondhand smoke, and to suffer from domestic violence during pregnancy. Women who quit smoking before pregnancy were older and more likely to live with partner, to be unemployed, to have caesarean section, low birth weight and gestational diabetes compared with never smokers. Women who quit smoking after becoming pregnant were younger and more likely to be unmarried, to be unemployed, to live with partner, to intake less fish and to have pregnancy-induced hypertension compared with never smokers. Women who smoked during pregnancy were younger and more likely to be unmarried, unemployed, to intake less fish, to have caesarean section, preterm delivery, low birth weight and infant abnormality compared with never smokers.

Table 2 presents crude and multivariable-adjusted ORs (95% CI) for PPD according to smoking status during pregnancy. In total, 9.0% women had PPD. Women

who quit smoking before pregnancy, quit smoking after becoming pregnant, and continued smoking during pregnancy showed a higher occurrence of PPD compared with women who had never smoked. After adjustment for potential confounding factors, the multivariable-adjusted ORs (95% CI) for PPD (reference: women who had never smoked) were 1.04 (0.96–1.13) for women who quit smoking before pregnancy, 1.24 (1.12–1.37) for women who quit smoking after becoming pregnant, and 1.38 (1.12–1.56) for women who smoked during pregnancy.

Table 3 shows that compared with women who had never smoked, former smokers who quit ≤ 5 years before childbirth had a higher occurrence of PPD, whereas former smokers who quit > 5 years before childbirth had no increased odds of PPD. These associations did not change substantially after adjustment for potential confounding factors: the multivariable ORs (95% CI) for PPD were 1.03 (0.88–1.21) for women who had quit smoking for more than 10 years, 0.96 (0.86–1.08) for women who had quit smoking for > 5 –10 years, and 1.10 (1.00–1.22) for women who quit less than 5 years before childbirth.

The age- and education-stratified ORs (95% CI) for PPD according to smoking status during pregnancy were shown in Table 4. Participants who were aged 30 years or older showed a stronger association between smoking status and risk for PPD, with an

increased odds of women who quit smoking after pregnancy or continued smoking during pregnancy (p for interaction=0.003). The associations between prenatal smoking and the risk of PPD did not differ between higher and lower educated groups (p for interaction=0.25).

Discussion

In this large-scale nationwide study, we found a significant association between prenatal smoking and risk for PPD in Japanese women. Compared with women who had never smoked, women who quit smoking after pregnancy or who continued smoking during pregnancy had a 24% and 38% higher odds of PPD, respectively. In contrast, women who quit smoking before pregnancy showed no increased odds of PPD compared with those who had never smoked. Women who quit smoking ≤ 5 years before childbirth and those who were aged 30 years or older at childbirth also had an increased odds of PPD.

The findings on smoking and PPD are consistent with the previous studies. The Pregnancy Risk Assessment Monitoring System survey involving a representative sample of 75,234 American women reported that prenatal smoking was associated with a 1.6-fold higher risk for PPD (Pooler et al., 2013). A prospective cohort study involving 622 pregnant women reported that prenatal smoking increased 1.7-time risk

of PPD in American Women (Dagher and Shenassa, 2012).

Women are vulnerable to depression and prone to mood fluctuations during periods of hormonal change such as pregnancy, the postpartum period, and menopause, because of changes in sex steroid hormones (e.g., estrogen and progesterone) (Fernandez et al., 2013; Mehta et al., 2014; Schiller et al., 2015). Smoking has an anti-estrogenic effect of lowering endogenous estrogen biosynthesis (Baron, 1984; Ruan and Mueck, 2015) and bioavailability, which results in an increased risk for PPD (Michnovicz et al., 1986).

Smoking causes diverse changes in immunity, i.e., elevated blood levels of pro-inflammatory cytokines, such as interleukin-1, interleukin-6 and tumor necrosis factor- α (Lee et al., 2012; McEvoy et al., 2015), and the smoking also increased oxidative stress due to free radicals from cigarette smoke which peroxides the polyunsaturated fatty acids of cell membranes (Yanbaeva et al., 2007). Changes in immune system, increased oxidative stress, and nicotine acetylcholine receptors stimulate hypothalamic-pituitary-adrenal (HPA) axis (Black et al., 2015; Pace and Miller, 2009; Philip et al., 2010; Silverman and Sternberg, 2012), and the elevated HPA axis activity increases the release of cortisol (Pariante and Lightman, 2008). Although a minute pathway between increased cortisol and depression has not yet to be fully

understood, depressed patients had increased levels of cortisol than non-depressed persons (Okano and Nomura, 1992; Stetler and Miller, 2011), and antidepressant treatment led to the normalization of plasma cortisol levels (Linkowski et al., 1987; Ventura-Juncá et al., 2014).

A previous study showed similar results to our study regarding smoking cessation during pregnancy (Munafo et al., 2008), in that the risk for PPD among women who quit smoking during pregnancy was 1.3-fold higher than among those who had never smoked. Abrupt cessation of smoking induces nicotine withdrawal syndromes (Breslau et al., 1992; Hesami et al., 2010), including depression. Many studies reported that 7% to 41% of smoking quitters suffered from depression (Breslau et al., 1992; Covey et al., 1997; Madden et al., 1997; Tsoh et al., 2000).

We found a stronger association between smoking status and odds of PPD among women aged ≥ 30 years compared with those aged < 30 years at childbirth. This may be because women of advanced maternal age are at higher risk for depression in the postpartum period (Aasheim et al., 2012).

The strengths of the present study were the large sample size and prospective data collection, which allowed us to measure changes in smoking behavior before and after pregnancy, and PPD. To our knowledge, this study is the first to investigate the

association between duration of smoking cessation and PPD. We found that women who quit smoking ≤ 5 years before childbirth had an increased odds of PPD compared with those who had never smoked, while women with >5 years smoking cessation had no increased risk for PPD compared with those that had never smoked.

A limitation that should be considered when interpreting our results was that the questionnaire data were self-reported by participants. Several studies (Dietz et al., 2011; Klesges et al., 1995) have observed that self-reported questionnaire data tend to be under-reported, especially smoking status during pregnancy (Dietz et al., 2011). However, other studies (Steffen et al., 2014) indicated that self-report of smoking status is sufficiently accurate to be a valid method to assess tobacco use.

In conclusion, we found an increased odds of PPD associated with quitting smoking after becoming pregnant as well as for continuing to smoke during pregnancy. Our findings suggest the importance of quitting smoking before pregnancy to help prevent PPD.

Authorship Statement

Manuscript title: Prenatal Tobacco Smoking is associated with Postpartum Depression in Japanese Pregnant Women: The Japan Environment and Children's Study

All persons who meet authorship criteria are listed as authors, and all authors certify that they have participated sufficiently in the work to take public responsibility for the content, including participation in the concept, design, analysis, writing, or revision of the manuscript. Furthermore, each author certifies that this material or similar material has not been and will not be submitted to or published in any other publication before its appearance in the *Journal of Affective Disorders*.

Authorship contributions

Conception and design of study: Meishan Cui, Hiroyasu Iso

Acquisition of data: Satoyo Ikehara, Kimiko Ueda, Tadashi Kimura, Hiroyasu Iso

Analysis and/or interpretation of data: Meishan Cui, Takeshi Kimura, Jia-Yi Dong,
Youko Kawanishi, Hiroyasu Iso

Drafting the manuscript: Meishan Cui, Hiroyasu Iso

Revising the manuscript: Meishan Cui, Takeshi Kimura, Satoyo Ikehara, Jia-Yi Dong,
Kimiko Ueda, Youko Kawanishi, Tadashi Kimura, Hiroyasu Iso

Approval of the version of the manuscript to be published:

Meishan Cui, Takeshi Kimura, Satoyo Ikehara, Jia-Yi Dong,
Kimiko Ueda, Youko Kawanishi, Tadashi Kimura, Hiroyasu Iso

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Members of the JECS (principal investigator, Michihiro Kamijima) as of 2019: Shin

Yamazaki (National Institute for Environmental Studies, Tsukuba, Japan), Yukihiro Ohya (National Center for Child Health and Development, Tokyo, Japan), Reiko Kishi (Hokkaido University, Sapporo, Japan), Nobuo Yaegashi (Tohoku University, Sendai, Japan), Koichi Hashimoto (Fukushima Medical University, Fukushima, Japan), Chisato Mori (Chiba University, Chiba, Japan), Shuichi Ito (Yokohama City University, Yokohama, Japan), Zentaro Yamagata (University of Yamanashi, Chuo, Japan), Hidekuni Inadera (University of Toyama, Toyama, Japan), Michihiro Kamijima (Nagoya City University, Nagoya, Japan), Takeo Nakayama (Kyoto University, Kyoto, Japan), Hiroyasu Iso (Osaka University, Suita, Japan), Masayuki Shima (Hyogo College of Medicine, Nishinomiya, Japan), Youichi Kurozawa (Tottori University, Yonago, Japan), Narufumi Suganuma (Kochi University, Nankoku, Japan), Koichi Kusuhara (University of Occupational and Environmental Health, Kitakyushu, Japan), and Takahiko Katoh (Kumamoto University, Kumamoto, Japan). We thank Audrey Holmes, MA, from Edanz Group for editing a draft of this manuscript.

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Conflict of interest

All authors declare there are no conflicts of interest to report.

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Table 1. Participants' characteristics according to smoking status during pregnancy

	Total n=80,872	Never smoker n=47,864	Quit before pregnancy n=18,961	Quit after becoming pregnant n=10,807	Smoked during pregnancy n=3,240
Mean EPDS (SE)	5.7 (0.01)	5.6 (0.01)	5.7 (0.02)**	5.8 (0.02)***	5.9 (0.04)***
Age, year (SE)	31.3 (0.02)	31.5 (0.02)	32.0 (0.03)**	29.5 (0.05)***	30.1 (0.10)***
Married, %	95.1	96.4	96.4	89.6***	85.8***
Living with partner, %	92.6	93.7	94.3**	86.8***	84.0***
High school or less, %	34.7	25.5	39.4***	56.8***	71.5***
Unemployed, %	46.3	44.7	49.5***	47.2***	49.0***
Drank during pregnancy, %	2.7	1.8	3.7***	3.2***	9.1***
Secondhand smoke, %	36.9	28.6	36.8***	59.7***	85.1***
Fish intake, g/day (SE)	33.6 (0.1)	34.0 (0.1)	34.5 (0.3)	30.7 (0.3)***	32.4 (0.9)*
Domestic violence, %	12.7	10.8	13.1***	17.8***	21.7***
Primiparity, %	32.6	36.7	23.8***	34.1**	18.6***
Caesarean section, %	18.5	18.0	19.4***	18.8	19.1*
Preterm delivery, %	4.2	4.2	4.3	4.1	5.4***
Low birth weight, %	7.7	7.7	7.1**	7.7	12.7***
Infant abnormality, %	9.5	9.5	9.3	9.4	11.2***
Pregnancy-induced hypertension, %	3.1	2.9	3.1	3.5**	3.3
Gestational diabetes, %	2.7	2.5	2.9*	2.8	2.8

* p<0.05, ** p<0.01, *** p<0.001 compared with never smoker.

EPDS, Edinburgh Postnatal Depression Scale.

Table 2. Odds ratios and 95% confidence intervals for postpartum depression according to smoking status during pregnancy

	Never smokers	Quit before pregnancy	Quit after becoming pregnant	Smoked during pregnancy
Total	47,864	18,961	10,807	3,240
No. of events	3,965	1,652	1,243	418
Crude OR (95% CI)	1.00	1.06 (1.00-1.12)	1.44 (1.35-1.54)	1.64 (1.47-1.83)
Multivariable OR (95% CI) ^a	1.00	1.04 (0.96-1.13)	1.24 (1.12-1.37)	1.38 (1.21-1.56)

CI, confidence interval; OR, odds ratio.

^a Adjusted for age, marital status, living with partner, education, employment status, domestic violence, parity, preterm birth, low birth weight, infant abnormality, gestational diabetes, caesarean section, pregnancy-induced hypertension, drinking habit, fish intake, secondhand smoke, the number of cigarettes smoked per day, unit

Table 3. Odds ratios and 95% confidence intervals for postpartum depression according to quit duration before childbirth

	Never smokers	Quit before pregnant		
		>10 years	>5~10 years	≤5 years
Total	47,864	2,476	6,146	9,909
No. of events	3,965	209	473	924
Crude OR (95% CI)	1.00	1.02 (0.88-1.18)	0.92 (0.84-1.02)	1.14 (1.06-1.23)
Multivariable OR (95% CI) ^a	1.00	1.03 (0.88-1.21)	0.96 (0.86-1.08)	1.10 (1.00-1.22)

CI, confidence interval; OR, odds ratio.

^a Adjusted for age, marital status, living with partner, education, employment status, domestic violence, parity, preterm birth, low birth weight, infant abnormality, gestational diabetes, caesarean section, pregnancy-induced hypertension, drinking habit, fish intake, secondhand smoke, the number of cigarettes smoked per day, unit

Table 4. Odds ratios and 95% confidence intervals for postpartum depression according to smoking status during pregnancy, stratified by age and education

	Never smokers	Quit before pregnancy	Quit after becoming pregnant	Smoked during pregnancy
Age				
<30 yrs				
No. of PPD	1,478	590	664	191
Crude OR (95% CI)	1.00	1.18 (1.06-1.30)	1.40 (1.27-1.55)	1.47 (1.26-1.73)
Multivariable OR (95% CI) ^a	1.00	1.12 (0.97-1.27)	1.17 (1.01-1.35)	1.17 (0.97-1.41)

≥30 yrs

No. of PPD	2,487	1,062	579	227
Crude OR (95% CI)	1.00	1.01 (0.94-1.09)	1.43 (1.30-1.57)	1.76 (1.53-2.04)
Multivariable OR (95% CI) ^a	1.00	1.01 (0.91-1.13)	1.29 (1.13-1.47)	1.56 (1.32-1.86)
Education				
High school or less				
No. of PPD	1,231	718	758	313
Crude ORs (95% CI)	1.00	0.95 (0.86-1.04)	1.25 (1.14-1.38)	1.39 (1.22-1.59)
Multivariable OR (95% CI) ^a	1.00	1.00 (0.88-1.14)	1.19 (1.04-1.37)	1.29 (1.10-1.51)
More than high school				
No. of PPD	2,734	934	485	105
Crude OR (95% CI)	1.00	1.07 (0.99-1.15)	1.40 (1.26-1.55)	1.55 (1.26-1.90)
Multivariable OR (95% CI) ^a	1.00	1.03 (0.92-1.16)	1.24 (1.07-1.43)	1.44 (1.15-1.82)

CI, confidence interval; OR, odds ratio, PPD, postpartum depression.

^a Adjusted for age, marital status, living with partner, education, employment status, domestic violence, parity, preterm birth, low birth weight, infant abnormality, gestational diabetes, caesarean section, pregnancy-induced hypertension, drinking habit, fish intake, secondhand smoke, the number of cigarettes smoked per day, unit