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Impact of maternal smoking and secondhand smoke exposure during singleton pregnancy on placental abruption: analysis of a prospective cohort study (the Japan Environment and Children's Study)

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ABSTRACT

Objectives This study aimed to investigate the association and population-attributable fraction (PAF) of maternal smoking and secondhand smoke (SHS) exposure during pregnancy with placental abruption.

Design Prospective cohort study.

Setting 15 regional centres in Japan.

Participants Pregnant women registered between January 2011 and March 2014 from the Japan Environment and Children's Study.

Outcome measures Data were transcribed from medical records and two self-administered questionnaires. The outcome measure was the incidence of placental abruption. Maternal smoking exposure during pregnancy was categorised based on the number of cigarettes smoked (≤10 or ≥11 cigarettes per day). SHS exposure during pregnancy was evaluated by frequency and duration (almost never or never, 1–3 days/week and/or <1 hour/day and 4–7 days/week and ≥1 hour/day). A modified Poisson regression model, adjusted for known placental abruption risk factors, calculated the risk ratio (RR) and PAF for placental abruption with a 95% CI.

Results Of the 81 974 eligible pregnant women, pregnant women smoking ≥11 cigarettes/day during pregnancy had a significantly higher risk of placental abruption. The adjusted RR (aRR) was 2.21 (95% CI 1.21 to 4.06), and the adjusted PAF (aPAF) was 1.90% (95% CI 0.09 to 3.71%). Pregnant women among never-smokers with SHS exposure of 4–7 days/week and ≥1 hour/day had a significantly higher risk (aRR: 2.34, 95% CI 1.29 to 4.28), and the aPAF was 1.89% (95% CI −0.05 to 3.83). Additionally, pregnant women among those who smoked during pregnancy with similar SHS exposure had a significantly higher risk (aRR: 2.21, 95% CI 1.30 to 3.76), with the aPAF of 2.29% (95% CI 0.11 to 4.48).

Conclusions Maternal smoking and SHS exposure during pregnancy significantly contribute to the risk of placental abruption in Japan. Therefore, preventive interventions and measures to reduce exposure are required to prevent placental abruption.

STRENGTHS AND LIMITATION OF THIS STUDY

⇒ This was a large birth cohort study in Japan to investigate the risk and population attributable fraction of placental abruption associated with maternal smoking and secondhand smoke (SHS) exposure during pregnancy.
⇒ This study quantified maternal smoking by the number of cigarettes smoked and SHS exposure during pregnancy by its current frequency and duration, allowing for a detailed analysis of their association with placental abruption.
⇒ A variety of potential confounding factors, such as socioeconomic status, maternal characteristics and geographic location, were accounted for in the analysis.
⇒ Data on maternal smoking and SHS exposure during pregnancy were obtained using self-administered questionnaires, which may be susceptible to recall bias and under-reporting.

INTRODUCTION

Placental abruption is defined as the premature separation of a normally implanted placenta before delivery.[1] It occurs in approximately 0.4%–1% of births.[2 3] Placental abruption is a serious pregnancy complication that can lead to maternal and perinatal mortality

and morbidity. Maternal consequences include hypovolemic shock, disseminated intravascular coagulation and, rarely, death.[1] Neonatal consequences include preterm birth, acidosis, encephalopathy and severe respiratory disorder.[4 5] Several risk factors for placental abruption have been reported including maternal age of 35 or older, multiparity, in vitro fertilisation embryo transfer pregnancy, hypertensive disorders of pregnancy (HDP) and maternal smoking exposure.[1 6 7]

Ananth *et al* reported in a meta-analysis that maternal smoking was associated with a 90% increase in the risk of placental abruption (OR 1.9; 95% CI 1.8 to 2.0).[8] In a meta-analysis by Shobeiri, there was a significant association between smoking and placental abruption (OR 1.80; 95% CI 1.75 to 1.85).[9] Several studies have reported an increased risk of placental abruption with an increase in the average number of cigarettes smoked;[10–12] however, studies in East Asia are limited. Therefore, we aimed to evaluate the association between maternal smoking exposure during pregnancy and the risk of placental abruption in a Japanese population, including the average number of cigarettes smoked.

Correspondingly, secondhand smoke (SHS) comprises two types of smoke from burning tobacco: mainstream and sidestream smoke. Sidestream smoke contains higher concentrations of nicotine and cancer-causing agents than mainstream smoke.[13] Some effects of SHS on pregnant women have been reported. However, there have been no studies on the association between SHS exposure during pregnancy and the risk of placental abruption.

In Japan, the number of female smokers has decreased significantly over the past decade, with the 2014 National Health and Nutrition Survey reporting a female smoking rate of 8.5%. However, women in the reproductive ages of 20s and 30s have high smoking rates, with the proportions being 11.7% and 14.3%, respectively.[14] However, research on SHS exposure in Japan is limited, with a 2018 survey reporting high passive smoking rates of 49% in the workplace, 55% in restaurants and 83% in bars.[15]

As smoking is a modifiable risk factor, clarifying the effects of maternal smoking and SHS exposure during pregnancy could help decrease the risk of placental abruption. Therefore, we sought to evaluate the association among maternal smoking, SHS exposure during pregnancy and placental abruption. Additionally, to provide a quantitative target for the effective implementation of public health policies, we examined the population attributable fraction (PAF) of maternal smoking and SHS exposure during pregnancy to placental abruption prevalence.

METHODS

Study design

This study was part of the Japan Environment and Children's Study (JECS), a nationwide birth cohort study conducted in Japan.[16] The JECS was initiated in January 2011 to evaluate the effects of environmental factors on children's health and development. Participants were registered between January 2011 and March 2014 and recruited from 15 regional centres. These regional centres are located in Hokkaido, Miyagi, Fukushima, Chiba, Kanagawa, Koshin, Toyama, Aichi, Kyoto, Osaka, Hyogo, Tottori, Kochi, Fukuoka and south Kyusyu/Okinawa. Cooperating healthcare providers associated with each regional centre include hospitals and clinics within or in the vicinity of the study areas. Details of the JECS study design have been described in previous studies.[16 17] From the JECS dataset, we specifically accessed the maternal self-administered questionnaires obtained during the first trimester and second/third trimesters, referred to as MT1 and MT2, respectively.[18–20] Medical doctors, nurses/midwives and/or research coordinators transcribed information on maternal medical backgrounds and obstetric outcomes from the medical records transcriptions.[17]

Maternal smoking during pregnancy

Maternal smoking was defined as active smoking by the mother. Information on maternal smoking was obtained from both MT1 and MT2, which asked the following questions: Never, previously did but quit before realising current pregnancy, previously did but quit after realising current pregnancy and currently smoking. Furthermore, the current smoker group was asked about the average number of cigarettes they smoked per day. Maternal smoking during pregnancy was categorised into five categories as follows: never-smokers, previously did but quit before realising the current pregnancy, previously did but quit after realising the current pregnancy, smoking at MT1 and MT2 (≤10 cigarettes/day) and smoking at MT1 and/or MT2 (≥11 cigarettes/day).[8]

SHS exposure during pregnancy

SHS was defined as exposure to cigarettes smoked by others at home, at work or in other indoor locations. Information on SHS exposure during pregnancy was obtained using MT2. Data was collected on both the current frequency of exposure to SHS at any indoor location per week and the number of hours of exposure to SHS per day. With respect to the current frequency of SHS exposure at any indoor location, the data were classified into the following categories: almost never, once a week, 2–3 times a week, 4–6 times a week and every day. As for the number of hours exposed to SHS per day, the data were classified within the subsequent categories: <1 hour, 1–2 hours and ≥2 hours. By combining the frequency and number of hours exposed to SHS, SHS exposure during pregnancy was divided into three categories as follows: almost never or never, 1–3 days/week and/or <1 hour/day, 4–7 days/week and ≥1 hour/day.

Placental abruption

Information on placental abruption was obtained from the dataset Dr0M, transcribed by physicians or research coordinators immediately after delivery. The clinical diagnosis of placental abruption was transcribed from the

medical records by physicians, midwives, nurses and/or research coordinators after delivery. Placental abruption was clinically diagnosed according to the International Classification of Diseases, 10th revision code (O45).[21]

Statistical analysis

Statistical Analysis System (SAS) software (V.9.4; SAS Institute, Cary, North Carolina, USA) and R V.4.3.0 (The R Foundation for Statistical Computing, Vienna, Austria) were used for statistical analysis. Continuous variables were presented as medians and IQRs. Categorical variables were expressed as numbers and percentages. Differences in the baseline characteristics between participants who were eligible for analysis and those who were excluded due to missing data were evaluated using Student's t-test or χ^2 test, as appropriate.

A modified Poisson regression model was used to calculate the risk ratio (RR) and the 95% CI. These were used to assess the associations between maternal smoking exposure and placental abruption, as well as SHS exposure during pregnancy and placental abruption.[22] Furthermore, we estimated the PAF to quantify the proportion of placental abruption cases that could have been prevented in the absence of maternal smoking and SHS exposure during pregnancy. Based on the formula, as described below, we calculated the PAF and 95% CI using the SAS nonlinear estimate (NLEST) macro.[23]

$$\textit{Estimated excess placental abruption case} = Pe(RRe - 1)/RRe$$

$$PAF = \textit{estimated excess placental abruption case}/\textit{all placental abruption cases} \times 100$$

Pe represents the proportion of placental abruption cases within each category and RRe denotes the RR of placental abruption associated with exposure to maternal smoking and SHS during pregnancy.[24 25] Additionally, we defined the composite PAF as the sum of the estimated excess placental abruption cases in each category divided by the total number of placental abruption cases, as described below.

$$\textit{Composite PAF} = \textit{sum of estimated excess placental abruption case of each category}/\textit{all placental abruption cases} \times 100$$

For the analysis of RR in the association between maternal smoking exposure during pregnancy and placental abruption, pregnant women who had never smoked were used as references. In the analysis of PAF for the risk of placental abruption from maternal smoking exposure during pregnancy, pregnant women who had never smoked and those who previously did but quit before or after realising the current pregnancy were set as reference categories.

To analyse the RR and PAF for the risk of placental abruption due to SHS exposure during pregnancy, pregnant women with almost never or never exposure to SHS were used as references.

Three models were constructed to calculate RRs and PAFs. Model 1 was defined as the crude model. Models 2 and 3 were defined as adjusted models. In Model 2, the following variables were included as covariates; maternal age in MT1, prepregnancy body mass index (BMI), parity, conception method, Kessler Psychological Distress Scale score, marital status, alcohol consumption, history of kidney disorder, adenomyosis uteri, uterine malformation, history of placental abruption in the previous pregnancy, the highest level of maternal education, annual household income, folic acid supplement intake), regions where regional centres exist.[1 26–29] In Model 3, maternal smoking exposure or SHS exposure during pregnancy was adjusted in addition to Model 2. Prepregnancy BMI was included in the model as continuous variables. The other covariates were included as categorical variables in the model. The collection method, definition and classification of covariates used in the study are shown in the online supplemental material. Maternal blood pressure level, new-onset HDP, pregestational diabetes, glycosylated haemoglobin level and anaemia have been reported as risk factors for placental abruption.[1 30–32] However, these variables were not adjusted for in the current study because they may be intermediate variables.[33–38] Additionally, a history of hypertension was not also adjusted in the main analysis because it was unclear whether it acted as an intermediate or confounding variable in the JECS dataset. Furthermore, intimate partner violence was adjusted as a potential confounding factor in a sensitivity analysis.[39 40] (Online supplemental figure 1) presents a directed acyclic graph (DAG) of the association between maternal smoking during pregnancy, SHS exposure and placental abruption. A DAG was created using the R package, DAGitty.[41] About the RRs and PAFs, linear graded associations of maternal smoking and SHS exposure during pregnancy with placental abruption were also investigated. The p values for the trend in RR of placental abruption for maternal smoking exposure during pregnancy were calculated across the following three categories of maternal smoking; 'never-smokers and those who did not continue smoking during pregnancy,' 'smoking at MT1 and MT2 (≤10 cigarettes/day)' and 'smoking at MT1 and/or MT2 (≥11 cigarettes/day).'

Missing covariate values were completed by the single-imputation method using the k-nearest neighbours in the R simputation package.[42] A general linear model was used to assess multicollinearity among the covariates, and all variance inflation factors were <10.

A cross-classification analysis by maternal smoking and SHS exposure during pregnancy and placental abruption was also performed to evaluate the association of SHS exposure during pregnancy with placental abruption. After maternal smoking exposure during pregnancy were categorised into the following three categories; 'never-smokers,' 'those who did not continue smoking during pregnancy and 'those who smoked at MT1 and/or MT2,' pregnant women were classified into nine categories based on maternal smoking and SHS exposure during pregnancy. Never-smokers with almost never or never

SHS exposure during pregnancy comprised the reference group.

Furthermore, the risk of placental abruption due to maternal smoking was additionally analysed in seven categories of maternal smoking during pregnancy as follows: never-smokers, previously did but quit before realising the current pregnancy, previously did but quit after realising the current pregnancy, quit before or after realising the current pregnancy but smoking at MT2, smoking at MT1 but quit at MT2, smoking at MT1 and MT2 (≤10 cigarettes/day) and smoking at MT1 and/or MT2 (≥11 cigarettes/day).

In addition, as a sensitivity analysis, multiple imputations using Markov Chain Monte Carlo simulation for missing covariates were used to calculate adjusted RRs.[43 44] Maternal smoking, SHS exposure during pregnancy, placental abruption and the covariates in Model 3 were used to create the imputation model. After 10 datasets were generated, each dataset was analysed. Subsequently, 10 results were combined using Rubin's rule.[45]

Patient and public involvement

None.

RESULTS

Participant selection and baseline character

The participant selection flowchart is shown in figure 1. Among the 103 060 pregnancies in the 'jecs-ta-20190930' dataset, the initial participation data was only used for 5647 pregnant women who entered the JECS twice or more. Since placental abruption is a possible cause of miscarriage and stillbirth, pregnant women who miscarried and had stillbirths were included in this study. Participants with multiple pregnancies, consent withdrawal or censoring were excluded from the study. Missing data

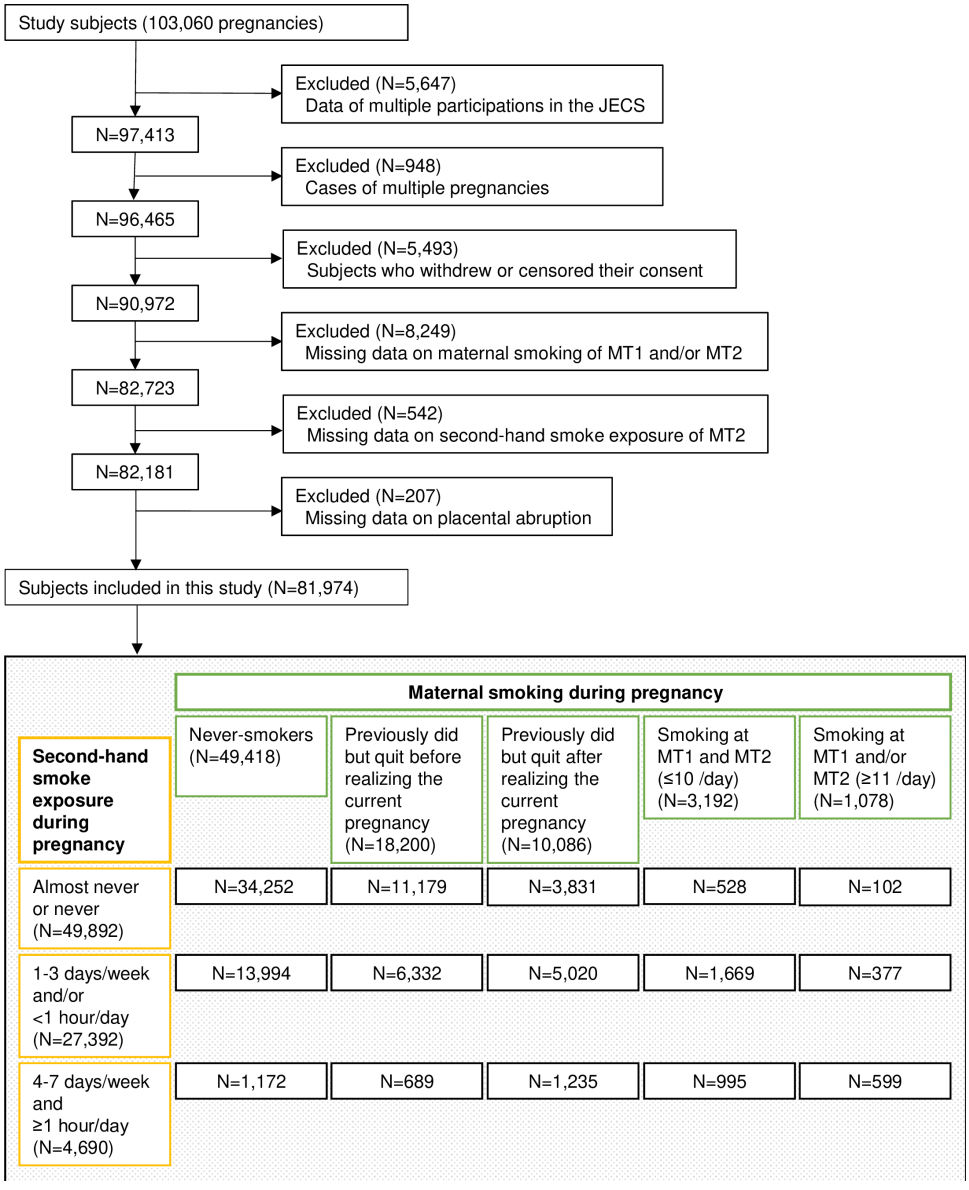


Figure 1 Study flowchart. JECS, Japan Environment and Children's Study.

on maternal smoking in MT1 and MT2 and missing data on SHS exposure during pregnancy in MT2 were also excluded. Patients with missing data on the diagnosis of placental abruption were excluded. Finally, 81 974 women were eligible for analysis.

Table 1 shows maternal and neonatal characteristics according to the categories of maternal smoking during pregnancy. The numbers of pregnant women in never-smokers, previously did but quit before realising the current pregnancy, previously did but quit after realising the current pregnancy, smoking at MT1 and MT2 (≤10 cigarettes/day) and smoking at MT1 and/or MT2 (≥11 cigarettes/day) were 49 418 (60.3%), 18 200 (22.2%), 10 086 (12.3%), 3192 (3.9%) and 1078 (1.3%), respectively. Women who continued smoking during pregnancy had higher rates of SHS exposure, lower levels of education and lower income. The prevalence of placental abruption in each category was as follows: never-smokers, 0.4%; previously did but quit before realising the current pregnancy, 0.4%; previously did but quit after realising the current pregnancy, 0.4%; smoking at MT1 and MT2 (≤10 cigarettes/day), 0.6%; and smoking at MT1 and/or MT2 (≥11 cigarettes/ day), 1.3%. (Online supplemental table 1) shows the other maternal and neonatal characteristics. (Online supplemental table 2) shows the differences in baseline characteristics between the participants who were eligible for analysis and those who were excluded because of missing data on maternal smoking, SHS exposure during pregnancy and placental abruption. There were statistically significant differences in the following variables: maternal age at MT1, prepregnancy BMI, parity, conception method, marital status, maternal educational background and annual household income.

Table 2 shows maternal and neonatal characteristics according to categories of SHS exposure during pregnancy. The numbers of pregnant women in almost never and never, 1–3 days/week and/or <1 hour/day and 4–7 days/week and ≥1 hour/day were 49 892 (60.9%), 27 392 (33.4%) and 4690 (5.7%), respectively. Pregnant women with SHS exposure during pregnancy were less educated and had a lesser income. The prevalence of placental abruption according to SHS exposure during pregnancy was as follows: almost never and never, 0.4%; 1–3 days/week and/or <1 hour/day, 0.4% and 4–7 days/week and≥1 hour/day, 0.7%. (Online supplemental table 3) shows other maternal and neonatal characteristics.

Main results

Figure 2A shows the results of the associations between maternal smoking and SHS exposure during pregnancy and placental abruption when maternal smoking and SHS exposure during pregnancy were included in the model separately. In Model 2, the adjusted model, pregnant women who previously smoked but quit before or after realising their current pregnancy did not show a significant increase in the risk of placental abruption. Compared with never-smokers, pregnant women who smoked ≤10 cigarettes/day at MT1 and MT2 tended to have a higher risk of placental abruption; however, this was not statistically significant (adjusted RR (aRR): 1.21; 95% CI 0.74 to 1.97). Pregnant women who smoked ≥11 cigarettes/day at MT1 and/or MT2 had a significantly high risk of placental abruption, of which aRR was 2.54 (95% CI 1.47 to 4.40). There was a significant linear graded association between maternal smoking exposure during pregnancy and risk of placental abruption (p value for trend=0.0005).

For SHS exposure during pregnancy, pregnant women with SHS exposure of 4–7 days/week and ≥1 hour/day had a significantly higher risk of placental abruption compared with those who had almost never or never exposure to SHS. The aRR was 1.56 (95% CI 1.06 to 2.29) in Model 2.

Figure 2B illustrates the PAFs for the risk of placental abruption owing to maternal smoking and SHS exposure during pregnancy. As a result of the adjusted PAFs (aPAFs) from maternal smoking in Model 2, the aPAFs of smoked ≤10 cigarettes/day at MT1 and MT2 and ≥11 cigarettes/day at MT1 and/or MT2 were 1.20% (95% CI -1.18 to 3.58%) and 2.30% (95% CI 0.42 to 4.17%), respectively. Therefore, the composite PAF for the risk of placental abruption from maternal smoking was 3.50 % in Model 2.

The PAF for the risk of placental abruption from SHS exposure during pregnancy of 4–7 days/week and ≥1 hour/day was 3.47% (95% CI 0.25% to 6.69%) in Model 1. In Model 2, when pregnant women with SHS exposure of almost never or never were set as a reference category, the aPAFs were 0.91% (95% CI −6.81% to 8.63%) in those with SHS exposure of 1–3 days/week and/or <1 hour/day and 3.09% (95% CI −0.16% to 6.33%) in those with SHS exposure of 4–7 days/week and ≥1 hour/day, respectively, which slightly failed to reach significance. The aPAFs from maternal smoking exposure and SHS exposure during pregnancy did not show a significant linear graded association in the risk of placental abruption (p values for trend: 0.25 and 0.83, respectively).

We then sought the associations of maternal smoking and SHS exposure during pregnancy with placental abruption when maternal smoking and SHS exposure during pregnancy were simultaneously included in Model 3, as delineated in figure 3A. Pregnant women who smoked ≥11 cigarettes/day at MT1 and/or MT2 had a significantly higher risk of placental abruption, compared with never-smokers (aRR: 2.21; 95% CI 1.21 to 4.06). While other categories of maternal smoking and SHS exposure during pregnancy were not statistically significantly associated with placental abruption, there was a significant linear graded association between maternal smoking exposure during pregnancy and the risk of placental abruption (p value for trend=0.005).

Figure 3B shows the aPAFs for the risk of placental abruption from maternal smoking and SHS exposure during pregnancy in Model 3. The aPAFs for smoking ≤10 cigarettes/day at MT1 and MT2 and ≥11 cigarettes/day at MT1 and/or MT2 were 0.89% (95% CI −1.39% to 3.17%)

Table 1 Maternal and neonatal characteristics according to categories of maternal smoking during pregnancy

Maternal smoking exposure during pregnancy					
Variables	**Never-smokers (n=49 418)**	**Previously did but quit before realising the current pregnancy (n=18 200)**	**Previously did but quit after realising the current pregnancy (n=10 086)**	**Smoking at MT1 and MT2 (≤10/day) (n=3192)**	**Smoking at MT1 and/or MT2 (≥11/day) (n=1078)**
Age categories in MT1, N (%)					
<20 years	432 (0.9)	48 (0.3)	227 (2.3)	77 (2.4)	20 (1.9)
20–24.9 years	4012 (8.1)	1218 (6.7)	1925 (19.1)	598 (18.7)	174 (16.1)
25–29.9 years	14 505 (29.4)	4720 (25.9)	3363 (33.3)	962 (30.1)	323 (30.0)
30–34.9 years	17 781 (36.0)	6982 (38.4)	2903 (28.8)	912 (28.6)	318 (29.5)
≥35 years	12 687 (25.7)	5232 (28.7)	1668 (16.5)	643 (20.1)	242 (22.4)
Missing	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Prepregnancy BMI categories, N (%)					
Underweight (<18.5 kg/m^2)	8145 (16.5)	2555 (14.0)	1790 (17.7)	599 (18.8)	190 (17.6)
Normal range (18.5–24.9 kg/m^2)	36 696 (74.3)	13 529 (74.3)	7009 (69.5)	2152 (67.4)	692 (64.2)
Overweight (≥25.0 kg/m^2)	4562 (9.2)	2106 (11.6)	1282 (12.7)	438 (13.7)	196 (18.2)
Missing	15 (0.0)	10 (0.1)	5 (0.0)	3 (0.1)	0 (0.0)
Parity, N (%)					
0 (Primipara)	21 710 (43.9)	5974 (32.8)	5149 (51.1)	1141 (35.7)	311 (28.8)
1	17 962 (36.3)	7748 (42.6)	2850 (28.3)	1045 (32.7)	349 (32.4)
2	6977 (14.1)	3284 (18.0)	1387 (13.8)	652 (20.4)	233 (21.6)
≥3	1494 (3.0)	842 (4.6)	420 (4.2)	296 (9.3)	174 (16.1)
Missing	1275 (2.6)	352 (1.9)	280 (2.8)	58 (1.8)	11 (1.0)
Conception method, N (%)					
Spontaneous pregnancy	45 424 (91.9)	16 716 (91.8)	9750 (96.7)	3129 (98.0)	1065 (98.8)
Non-ART	2104 (4.3)	685 (3.8)	199 (2.0)	33 (1.0)	6 (0.6)
ART	1706 (3.5)	708 (3.9)	85 (0.8)	22 (0.7)	4 (0.4)
Missing	184 (0.4)	91 (0.5)	52 (0.5)	8 (0.3)	3 (0.3)
SHS exposure during pregnancy, N (%)					
Almost never or never	34 252 (69.3)	11 179 (61.4)	3831 (38.0)	528 (16.5)	102 (9.5)
1–3 days/week and/or <1 hour/day	13 994 (28.3)	6332 (34.8)	5020 (49.8)	1669 (52.3)	377 (35.0)
4–7 days/week and ≥1 hour/day	1172 (2.4)	689 (3.8)	1235 (12.2)	995 (31.2)	599 (55.6)
Marital status, N (%)					
Unmarried or divorced or widowed	1463 (3.0)	486 (2.7)	995 (9.9)	400 (12.5)	183 (17.0)

Continued

Table 1 Continued

Maternal smoking exposure during pregnancy					
Variables	Never-smokers (n=49 418)	Previously did but quit before realising the current pregnancy (n=18 200)	Previously did but quit after realising the current pregnancy (n=10 086)	Smoking at MT1 and MT2 (≤10/day) (n=3192)	Smoking at MT1 and/or MT2 (≥11/day) (n=1078)
Married	47 816 (96.8)	17 661 (97.0)	9019 (89.4)	2749 (86.1)	875 (81.2)
Missing	139 (0.3)	53 (0.3)	72 (0.7)	43 (1.3)	20 (1.9)
Highest level of maternal education, N (%)					
<13 years	12 586 (25.5)	7106 (39.0)	5771 (57.2)	2187 (68.5)	858 (79.6)
≥13 years	36 624 (74.1)	11 000 (60.4)	4257 (42.2)	976 (30.6)	208 (19.3)
Missing	208 (0.4)	94 (0.5)	58 (0.6)	29 (0.9)	12 (1.1)
Annual household income (million, Japanese Yen), N (%)					
<4	15 795 (32.0)	6989 (38.4)	4990 (49.5)	1735 (54.4)	629 (58.3)
4–5.99	24 442 (49.5)	8483 (46.6)	3610 (35.8)	1023 (32.0)	300 (27.8)
≥6	6095 (12.3)	1634 (9.0)	559 (5.5)	138 (4.3)	49 (4.5)
Missing	3086 (6.2)	1094 (6.0)	927 (9.2)	296 (9.3)	100 (9.3)
Placental abruption, N (%)	222 (0.4)	65 (0.4)	41 (0.4)	18 (0.6)	14 (1.3)

ART, assisted reproductive technology; BMI, body mass index; SHS, secondhand smoke.

and 1.90% (95% CI 0.09% to 3.71%), respectively. Therefore, the composite PAF for the risk of placental abruption from maternal smoking was 2.79% in Model 3. The aPAFs for the risk of placental abruption due to SHS exposure during pregnancy were not statistically significant.

(Online supplemental table 4) shows the association between maternal smoking exposure during pregnancy and placental abruption, which was classified into seven groups based on maternal smoking status. Pregnant women who smoked ≥11 cigarettes/day at MT1 and/or MT2 had a significantly higher risk of placental abruption compared with never-smokers (aRR: 2.47; 95% CI 1.33 to 4.57).

Association between SHS exposure during pregnancy and placental abruption (cross-classification by maternal smoking and SHS exposure during pregnancy and placental abruption)

To directly compare all groups stratified by maternal smoking and SHS exposure during pregnancy, a cross-classification analysis of maternal smoking and SHS exposure during pregnancy and placental abruption was conducted, as shown in online supplemental figure 2. Online supplemental figure 2A shows the RRs of the risk of placental abruption due to SHS exposure during pregnancy in each category. Among never-smokers and pregnant women who smoked at MT1 and/or MT2, pregnant women with SHS exposure of 4–7 days/week and ≥1 hour/day had a significantly higher risk of placental abruption compared with those who had almost never or never exposure to SHS during pregnancy. The aRR was 2.34 (95% CI 1.29 to 4.28) and 2.21 (95% CI 1.30 to 3.76).

Online supplemental figure 2B illustrates the PAFs for the risk of placental abruption due to SHS exposure during pregnancy for each category. The aPAF for pregnant women with SHS exposure of 4–7 days/week and ≥1 hour/day among never-smokers slightly did not reach statistical significance but tended to have a high risk of placental abruption, which aPAF was 1.89% (95% CI −0.05% to 3.83%). The composite PAF for the risk of placental abruption from SHS exposure during pregnancy among never-smokers was 2.96%. The aPAF for pregnant women with SHS exposure of 4–7 days/week and ≥1 hour/day among pregnant women who smoked at MT1 and/or MT2 was statistically significant. The aPAF was 2.29% (95% CI 0.11% to 4.48%). The composite PAF for the risk of placental abruption from SHS exposure during pregnancy among pregnant women who smoked at MT1 and/or MT2 was 3.54%.

Online supplemental table 5 shows the associations between maternal smoking and SHS exposure during pregnancy and placental abruption after adjusting for intimate partner violence. The results of this sensitivity analysis were consistent with those of the present analysis.

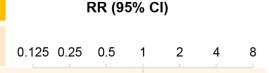
Table 2 Maternal and neonatal characteristics according to categories of SHS exposure during pregnancy

SHS exposure during pregnancy			
Variables	**Almost never or never (n=49 892)**	**1–3 days/week and/or <1 hour/day (n=27 392)**	**4–7 days/week and ≥1 hour/day (n=4690)**
Age categories in MT1, N (%)			
<20 years	213 (0.4)	393 (1.4)	198 (4.2)
20–24.9 years	3400 (6.8)	3488 (12.7)	1039 (22.2)
25–29.9 years	13 754 (27.6)	8682 (31.7)	1437 (30.6)
30–34.9 years	18 776 (37.6)	8874 (32.4)	1246 (26.6)
≥35 years	13 748 (27.6)	5955 (21.7)	769 (16.4)
Missing	1 (0.0)	0 (0.0)	1 (0.0)
Prepregnancy BMI categories, N (%)			
Underweight (<18.5 kg/m^2)	8188 (16.4)	4246 (15.5)	845 (18.0)
Normal range (18.5–24.9 kg/m^2)	37 158 (74.5)	19 783 (72.2)	3137 (66.9)
Overweight (≥25.0 kg/m^2)	4527 (9.1)	3352 (12.2)	705 (15.0)
Missing	19 (0.0)	11 (0.0)	3 (0.1)
Parity, N (%)			
0 (Primipara)	20 538 (41.2)	11 804 (43.1)	1943 (41.4)
1	19 068 (38.2)	9433 (34.4)	1453 (31.0)
2	7480 (15.0)	4257 (15.5)	796 (17.0)
≥3	1590 (3.2)	1241 (4.5)	395 (8.4)
Missing	1216 (2.4)	657 (2.4)	103 (2.2)
Conception method, N (%)			
Spontaneous pregnancy	45 751 (91.7)	25 792 (94.2)	4541 (96.8)
Non-ART	2079 (4.2)	866 (3.2)	82 (1.7)
ART	1865 (3.7)	611 (2.2)	49 (1.0)
Missing	197 (0.4)	123 (0.4)	18 (0.4)
Maternal smoking during pregnancy, N (%)			
Never-smokers	34 252 (68.7)	13 994 (51.1)	1172 (25.0)
Previously did but quit before or after realising the current pregnancy	15 010 (30.1)	11 352 (41.4)	1924 (41.0)
Smoking at MT1 and/or MT2	630 (1.2)	2046 (7.5)	1594 (34.0)
Marital status, N (%)			
Unmarried or divorced or widowed	1295 (2.6)	1591 (5.8)	641 (13.7)
Married	48 479 (97.2)	25 661 (93.7)	3980 (84.9)
Missing	118 (0.2)	140 (0.5)	69 (1.5)
Highest level of maternal education, N (%)			
<13 years	13 414 (26.9)	11 807 (43.1)	3287 (70.1)
≥13 years	36 256 (72.7)	15 439 (56.4)	1370 (29.2)
Missing	222 (0.4)	146 (0.5)	33 (0.7)
Annual household income (million, Japanese Yen), N (%)			
<4	16 021 (32.1)	11 538 (42.1)	2579 (55.0)
4–5.99	24 968 (50.0)	11 555 (42.2)	1335 (28.5)
≥6	5928 (11.9)	2301 (8.4)	246 (5.2)
Missing	2975 (6.0)	1998 (7.3)	530 (11.3)
Placental abruption, N (%)	209 (0.4)	119 (0.4)	32 (0.7)

ART, assisted reproductive technology; BMI, body mass index; SHS, secondhand smoke.

A

	n	PA (%)	Model 1* RR [95% CI]	P-value for trend	Model 2† aRR [95% CI]	P-value for trend
Maternal smoking during pregnancy						
Never-smokers	49,418	222 (0.45)	Ref		Ref	
Previously did but quit before realizing the current pregnancy	18,200	65 (0.36)	0.80 [0.60−1.05]	<0.0001	0.77 [0.59−1.02]	0.0005
Previously did but quit after realizing the current pregnancy	10,086	41 (0.41)	0.90 [0.65−1.26]		0.89 [0.62−1.27]	
Smoking at MT1 and MT2 (≤10 cigarettes/day)	3,192	18 (0.56)	1.26 [0.78−2.03]		1.21 [0.74−1.97]	
Smoking at MT1 and/or MT2 (≥11 cigarettes/day)	1,078	14 (1.30)	2.89 [1.69−4.94]		2.54 [1.47−4.40]	
SHS exposure during pregnancy						
Almost never or never	49,892	209 (0.42)	Ref		Ref	
1-3 days/week and/or <1 hour/day	27,392	119 (0.43)	1.03 [0.83−1.30]	0.07	1.03 [0.82−1.29]	0.12
4-7 days/week and ≥1 hour/day	4,690	32 (0.68)	1.63 [1.12−2.36]		1.56 [1.06−2.29]	



B

	n	PA (%)	Model 1* PAF [95% CI]	P-value for trend	Model 2† aPAF [95% CI]	P-value for trend
Maternal smoking during pregnancy						
Never-smokers and quit realizing the current pregnancy	77,704	328 (0.42)	Ref		Ref	
Smoking at MT1 and MT2 (≤10 cigarettes/day)	3,192	18 (0.56)	1.29 [-1.11−3.69]	0.15	1.20 [-1.18−3.58]	0.25
Smoking at MT1 and/or MT2 (≥11 cigarettes/day)	1,078	14 (1.30)	2.66 [0.62−4.70]		2.30 [0.42−4.17]	
SHS exposure during pregnancy						
Almost never or never	49,892	209 (0.42)	Ref		Ref	
1-3 days/week and/or <1 hour/day	27,392	119 (0.43)	1.22 [-6.37−8.82]	1.00	0.91 [-6.81−8.63]	0.83
4-7 days/week and ≥1 hour/day	4,690	32 (0.68)	3.47 [0.25−6.69]		3.09 [-0.16−6.33]	

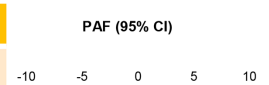


Figure 2 Association between maternal smoking and SHS exposure during pregnancy and placental abruption when maternal smoking exposure during pregnancy and SHS exposure during pregnancy were included in the model separately. (A) RRs of placental abruption due to maternal smoking and SHS exposure during pregnancy. (B) PAFs of placental abruption from maternal smoking and SHS exposure during pregnancy. aPAF, adjusted population attributable fraction; aRR, adjusted risk ratio; BMI, body mass index; K6, Kessler Psychological Distress Scale; PA, placental abruption; PAF, population attributable fraction; RR, risk ratio; SHS, secondhand smoke. *Crude model. †Adjusted for maternal age in MT1, prepregnancy BMI, parity, conception method, K6 score, marital status, alcohol consumption, history of kidney disorder, adenomyosis uteri, uterine malformation, history of placental abruption in the previous pregnancy, the highest level of maternal education, annual household income, intake of the folic acid supplement and regions where regional centres exist.

Online supplemental table 6 presents the results of the sensitivity analysis using multiple imputations. These aRRs were similar to those used in the main analysis.

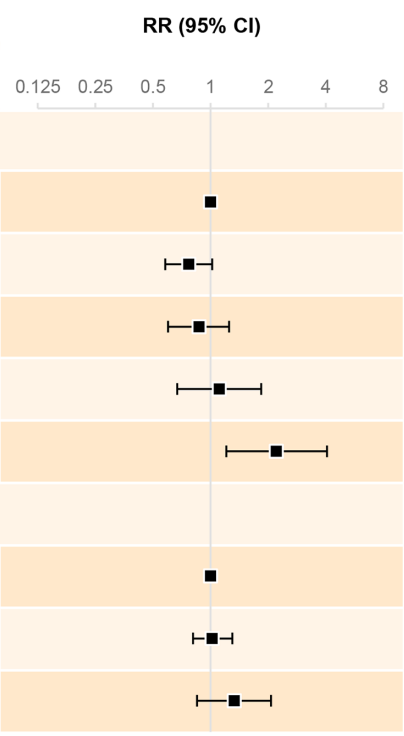
DISCUSSION

This is the first nationwide birth cohort study in Japan to investigate the risk and PAF of placental abruption associated with maternal smoking and SHS exposure during pregnancy. A significantly higher risk of placental abruption was observed in pregnant women who smoked ≥11 cigarettes/day during the first and/or second trimester and pregnant women with SHS exposure of 4–7 days/week and ≥1 hour/day among never-smokers and those who smoked during pregnancy. After adjusting for potential confounding factors, including socioeconomic status, maternal characteristics and geographic location, 2.8% of placental abruption was attributable to maternal smoking exposure during pregnancy when SHS exposure during pregnancy was included in the model simultaneously. Among never-smokers, 3.0% of placental abruptions were attributable to SHS exposure during pregnancy. Furthermore, among pregnant women who smoked during pregnancy, 3.5% had placental abruption attributable to SHS exposure during pregnancy.

Matsuda *et al* reported a 1.0% incidence of placental abruption in Japan, which is higher than our findings.[6] Many hospitals in the previous study were perinatal medical centres, which tend to have more severe cases

A

	n	PA (%)	Model 3* aRR [95% CI]	P-value for trend
Maternal smoking during pregnancy				
Never-smokers	49,418	222 (0.45)	Ref	
Previously did, but quit before realizing the current pregnancy	18,200	65 (0.36)	0.77 [0.58−1.02]	0.005
Previously did, but quit after realizing the current pregnancy	10,086	41 (0.41)	0.87 [0.60−1.25]	
Smoking at MT1 and MT2 (≤10 cigarettes/day)	3,192	18 (0.56)	1.11 [0.67−1.84]	
Smoking at MT1 and/or MT2 (≥11 cigarettes/day)	1,078	14 (1.30)	2.21 [1.21−4.06]	
SHS exposure during pregnancy				
Almost never or never	49,892	209 (0.42)	Ref	
1-3 days/week and/or <1 hour/day	27,392	119 (0.43)	1.02 [0.81−1.30]	0.38
4-7 days/week and ≥1 hour/day	4,690	32 (0.68)	1.33 [0.85−2.07]	



B

	n	PA (%)	Model 3* aPAF [95% CI]	P-value for trend
Maternal smoking during pregnancy				
Never-smokers and quit before or after realizing the current pregnancy	77,704	328 (0.42)	Ref	
Smoking at MT1 and MT2 (≤10 cigarettes/day)	3,192	18 (0.56)	0.89 [-1.39−3.17]	0.49
Smoking at MT1 and/or MT2 (≥11 cigarettes/day)	1,078	14 (1.30)	1.90 [0.09−3.71]	
SHS exposure during pregnancy				
Almost never or never	49,892	209 (0.42)	Ref	
1-3 days/week and/or <1 hour/day	27,392	119 (0.43)	0.17 [-7.58−7.91]	0.35
4-7 days/week and ≥1 hour/day	4,690	32 (0.68)	1.64 [-1.40−4.69]	

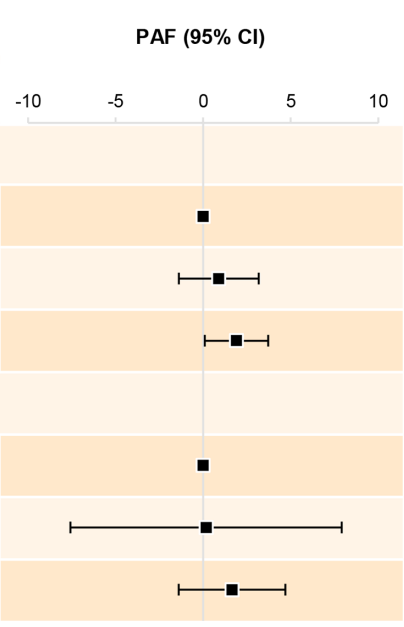


Figure 3 Association between maternal smoking and SHS exposure during pregnancy and placental abruption when maternal smoking exposure during pregnancy and SHS exposure during pregnancy were included in the model simultaneously. (A) aRR of placental abruption due to maternal smoking and SHS exposure during pregnancy. (B) aPAF of placental abruption from maternal smoking and SHS exposure during pregnancy. aPAF, adjusted population attributable fraction; aRR, adjusted risk ratio; BMI, body mass index; K6, Kessler Psychological Distress Scale; PA, placental abruption; PAF, population attributable fraction; RR, risk ratio; SHS, secondhand smoke. *Adjusted for maternal age in MT1, prepregnancy BMI, parity, conception method, K6 score, marital status, alcohol consumption, history of kidney disorder, adenomyosis uteri, uterine malformation, history of placental abruption in the previous pregnancy, the highest level of maternal education, annual household income, intake of the folic acid supplement, regions where regional centres exist, maternal smoking exposure during pregnancy and SHS exposure during pregnancy.

than the general pregnant population in Japan. In contrast, our study included a broader range of healthcare institutions, such as clinics, general hospitals and perinatal care centres, which may explain the lower incidence of placental abruption observed in the current study. Furthermore, as shown in online supplemental table 2, several variables show statistically significant differences between the analysed and excluded groups. However, the characteristics of pregnant women in our study were generally consistent with those in the other birth cohort studies in Japan.[17 46–48] Therefore, the external validity of the current study would not be low. Consistent with our results, previous meta-analyses have shown that maternal smoking is associated with an increased risk of placental abruption.[8 9] The current study supports the existing literature by showing a dose-response association between the number of cigarettes smoked by pregnant women and the risk of placental abruption. Furthermore, our results suggest that, even in the absence of maternal smoking, SHS exposure during pregnancy is a significant risk factor for placental abruption.

The pathophysiology of placental abruption includes defective placentation with abnormal development of the spiral arteries, placental infarction[49 50] and inflammation-related pathology.[51] Maternal smoking and SHS exposure during pregnancy can lead to placental abruption; however, the underlying mechanisms remain unclear. Maternal smoking exposure during pregnancy has been associated with several adverse perinatal outcomes, including placenta previa, premature rupture of membranes, preterm birth, intrauterine growth restriction and sudden infant death syndrome.[52] Additionally, perinatal outcomes, such as preterm birth,[53 54] HDP,[35] fetal congenital heart defects[55] and hyperactivity/inattention among boys,[56] have been associated with SHS exposure during pregnancy. Cigarette smoke contains toxicants that activate p53-dependent cell death pathways and induce oxidative stress in trophoblast cells,[57] and nicotine directly affects the proliferation and differentiation of cytotrophoblasts (CTB),[58] which can adversely affect pregnancy outcomes. Maternal smoking reduces uterine blood flow to the placenta, causing chronic placental hypoxia due to vasoconstriction.[59–61] It may also lead to villus hypoxia in early pregnancy[62] and contribute to chorioallantoic haemorrhage and intervillous thrombus formation during pregnancies with placental abruption.[63]

Placental hypoxia and ischaemia resulting from smoking can increase antiangiogenic factors, decrease angiogenic factors and elevate inflammatory cytokines owing to increased oxidative stress, causing vascular endothelial dysfunction. These factors have also been implicated in HDP and can contribute to placental abruption.[64] Altogether, maternal smoking and SHS exposure during pregnancy could potentially contribute to placental abruption through various mechanisms, including placental hypoxia, increased levels of inflammatory cytokines and direct effects on CTB cells. Given that HDP and placental abruption share common pathophysiological mechanisms related to smoking exposure, HDP may serve as an intermediate variable. However, after adjusting for HDP, including both new-onset HDP and a history of hypertension in our analysis, the results remained consistent with those of the current analysis (data not shown). The associations between maternal smoking, SHS exposure during pregnancy and placental abruption persisted, indicating that these associations cannot be fully attributed to HDP alone. These findings suggest that targeted identification of at-risk pregnant women and the provision of specialised guidance to prevent maternal smoking and SHS exposure during pregnancy could be instrumental in reducing the risk of placental abruption. According to the American College of Obstetricians and Gynaecologists committee opinion, pregnancy is often a strong motivator to quit smoking. Approximately 54% of women who smoked before pregnancy successfully quit either before or during pregnancy.[65] The benefits of smoking cessation apply to both the pregnant woman and fetus at any stage of pregnancy, with the greatest benefits observed when smoking is discontinued by the 15th week of gestation.[65 66]

Despite the well-established risks associated with cigarette smoking, several barriers prevent pregnant women from quitting smoking. Factors such as low educational attainment, low economic status and absence of pregnancy counsellors have been identified as significant barriers to smoking cessation during pregnancy.[67] Moreover, pregnant women whose partners are current smokers have difficulty quitting cigarette smoking and are more likely to relapse post partum.[68 69] Consistent with these findings, pregnant women who smoke or with SHS exposure during pregnancy were more likely to be less educated and have lower annual household incomes. Additionally, the study revealed that pregnant women who smoked during pregnancy tended to have SHS exposure during pregnancy compared with never-smokers and those who did not continue smoking during pregnancy. Smoking rates among young people remain high, and measures to combat SHS are lagging in Japan;[14 15] therefore, comprehensive public health policies are required to reduce maternal smoking and SHS exposure during pregnancy.

Our findings suggest that SHS exposure significantly increases the risk of placental abruption, even in pregnant women who smoke during pregnancy. This indicates the importance of not only discouraging maternal smoking but also avoiding SHS exposure during pregnancy, including those who smoked during pregnancy. In addition, this study suggests that SHS exposure during pregnancy may be a risk factor for placental abruption, even in the absence of maternal smoking. However, in this study, the risk of placental abruption associated with SHS exposure during pregnancy did not increase in pregnant women who did not continue to smoke during pregnancy. Reverse causality and selection bias may have

occurred in observational studies.[70] Our study was unable to identify the specific factors that influenced pregnant women to continue smoking or exposure to SHS. Further research is necessary to understand the various factors that contribute to the risk of placental abruption associated with both maternal smoking and SHS exposure during pregnancy.

This study had a few limitations. First, the data on maternal smoking and SHS exposure during pregnancy were obtained using self-administered questionnaires. This approach is susceptible to underestimation and recall bias as participants may not accurately remember or report their smoking habits and SHS exposure. Second, the definition of placental abruption in our study adhered to the international criteria. However, placental abruption is also diagnosed based on clinical evaluation and ultrasound findings, which may lead to misclassification. Third, although we adjusted for known confounders available in the datasets, significant factors causing placental abruption, such as cocaine use, thrombophilia, a history of abdominal trauma and uterine surgery, or other residual confounding were not included in the dataset and thus could not be adjusted for in our analysis.[1 71]

In conclusion, pregnant women with a higher maternal smoking exposure have a significantly higher risk of placental abruption. Our study also provides compelling evidence for the risk of placental abruption associated with SHS exposure during pregnancy. Relevant public health interventions are required to reduce maternal smoking and SHS exposure during pregnancy and reduce the risk of placental abruption.

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Contributors HK-M, HH, NI, HT, KT, RK, NK, HW, SI, ZW, NT, MI, TO, HM, CO, SK, TA, NY and MS. HK-M performed the statistical analysis, interpreted the data and wrote the manuscript. HH designed the study, helped interpret the data and drafted the manuscript. NI designed this study, performed the statistical analysis with the first author, interpreted the data and revised the manuscript. HT, KT, RK, NK, HW, SI, ZW, NT, MI, TO, MS and CO helped interpret the data and critically revised the manuscript. MI, HM, SK, TA and NY collected and interpreted the data and revised the manuscript. HH was responsible for the overall content as guarantor. All authors have approved the final manuscript.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants. The JECS protocol was reviewed and approved by the Ministry of the Environment Government of Japan's Institutional Review Board on Epidemiological Studies and the Ethics Committees of all participating institutions (ethical number: No.100910001). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available. Data are unsuitable for public deposition because of ethical restrictions and the legal framework of Japan. The Act on the Protection of Personal Information (Act No. 57 of 30 May 2003 amended on 9 September 2015) prohibits the public deposition of data containing personal information. The Ethical Guidelines for Medical and Health Research Involving Human Subjects enforced by the Japan Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labour and Welfare also restrict the open sharing of epidemiological data. All inquiries regarding data access can be sent to Dr Shoji F Nakayama (jecs-en@nies.go.jp), JECS Program Office, National Institute for Environmental Studies.' https://www.env.go.jp/chemi/ceh/en/index.html.

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