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Regression Analysis of Maternal Smoking Effect on Birth Weight

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ABSTRACT

Risk factors for low birth weight (LBW) have been indicated in many studies, but in Japan few studies have examined the amount of reduction in birth weight (BW). The goal of this study was to examine the association between maternal smoking among pregnant women and subsequent reduction in BW, corrected by the effect of potential confounders. To assess the effect of background factors other than maternal smoking, we established a model to estimate the contribution of each explanatory variable using logarithmic multiple regression. We then used the adjusted BW model to evaluate the direct effect of maternal smoking. To obtain information on maternal characteristics, including smoking status and characteristics of their infants, including BW, we conducted a questionnaire survey. After statistical adjustment for background factors, the mean of BW among infants of participants who smoked during pregnancy was roundtable significantly lower than that of non-smoking participants, but there was no verification of a dose-response relationship. However, mean BWs were not significantly different when comparing participants who quit smoking during pregnancy to non-smoking participants, suggesting that stopping smoking during pregnancy is beneficial.

Key words: *Birth weight, Maternal smoking, Logarithmic multiple regression Questionnaire survey*

According to a report of the Japanese Ministry of Health, Labor and Welfare, the mean BW peaked in 1980 at 3230 g among boys and 3160 g among girls. However, it decreased to 3040 g among boys and 2960 g among girls in 2000[6]. Based on an analysis of the proportion of infants with LBW using national nutritional and smoking prevalence data, the recent increase in the occurrence of LBW related to an increase in smoking prevalence and a decrease in body mass index among young women[12]. The rate of smoking among pregnant woman increased from 5.6% in 1990 to 10.0% in 2000[11].

Numerous studies have demonstrated that smoking during pregnancy leads to a significantly undesirable effect on BW, a greater frequency of LBW, preterm births, and intrauterine growth restriction (IUGR)[2,5]. The term IUGR is sometimes referred to as small-for-gestational-age (SGA). There are two causes of reduced BW: IUGR and preterm birth[7,17].

Previous studies can be roughly divided into two types. One is based on a case-control study with multiple logistic regression, where a case is usually a single newborn with BW of 2500 g or less[8,16]. The other is based on ordinary multiple regression analysis of the relationship between actual BW and maternal cigarette consumption[1,3]. Such studies have demonstrated that maternal smoking during pregnancy is associated with LBW, IUGR, and preterm birth. In Japan, most studies have been performed using the case-control design[8,13]. Another report based on a large population-based survey, showed that the recent increase in LBW is due to an increase in preterm deliveries and multiple gestations rather than to an increased prevalence of maternal smoking[11]. A further report gives the impression that maternal smoking is not associated with the reduction in BW due to IUGR in Japan[16]. Such a conclusion is inconsistent with the results of studies in other countries. Furthermore, few studies in Japan have considered the association between level of maternal cigarette consumption and reduction in BW using the multiple regression approach.

In this study, we examined the relation between maternal cigarette consumption and reduction in BW using a logarithmic multiple regression analysis, which expresses interactions between covariates by a multiplicative covariate structure. We also examined how background factors, such as maternal age at delivery, birth order (parity), sex of the infant and length of gestational period affect BW, using a power transformation of BW as a response variable. In addition, the effects of environmental tobacco smoke (ETS) exposure to the adjusted BW were evaluated. ETS exposure often referred to as "passive smoking" has been noted to have an undesirable effect on fetal growth[17]. In this study, passive smoking was defined as the presence of smoking housemates during pregnancy.

MATERIALS AND METHODS

Materials data

To obtain maternal information and characteristics of their infants, we conducted a questionnaire survey during the period July-November 2006 among pregnant women living in the Kure region (population, about 280,000) of Hiroshima prefecture. The Japanese Ministry of Health, Labour and Welfare provides periodic checkups for infants at 3, 10, and 18 months of age. Questionnaires were distributed to mothers by postal mail along with notification of their checkup and they were collected at the checkup location. Non-respondents consisted both of mothers who did not participate in the checkup and mothers who did not return the questionnaire at the time of the checkup. Of 1,453 distributed questionnaires, 1,144 were returned. For statistical analyses, we excluded two pairs of twin infants and cases with incomplete or missing information. The effective number of samples for subsequent analysis was 939 single births. Maternal smoking status was originally classified into four categories: non-smoking group prior to and during pregnancy, smoked prior to but quit during pregnancy, smoked prior to and continued during pregnancy, and began to smoke during pregnancy. However, among the respondents there were no women who began to smoke during pregnancy. Thus, there were three groups of data, categorized in short as: NS for non-smoking, QS for quit-smoking and CS for continued-smoking. Among 939 participants, 733 were in the NS group, 136 were in the QS group and 70 were in the CS group. Detailed information on the data is shown in Table 1.

Analysis method for NS group data

The NS group data was used to estimate the degree of bias due to potential confounders. To find out the effect of background factors (other than maternal smoking) on BW, we analyzed data from the NS group using a multiple regression analysis. The response variable was transformed birthweight ($BW_{NS}^{(\lambda)}$) with λ=0, 1, 2 or 3, and the

Table 1. Maternal and infant characteristics by maternal smoking status and core variables

		Non-smoking	Quit-smoking	Continued-smoking	Variable
Infants					
Birth Weight (g)†)		3075.4(367.5)	3043.1 (420.5)	2897.8(348.4)	BW: Infants weight at birth
Gestational length (weeks) †)		38.9(1.7)	39(1.8)	38.6(2.2)	GL39: Gestational length minus its representative value (39)
Sex*)	Female	385(52.5%)	60(44.1%)	36(51.4%)	$SEX_{F\|M}$
	Male	348(47.5%)	76(55.9%)	34(48.6%)	
Mothers					
Age at delivery (years) †)		30.1(4.3)	27.6(4.6)	28.3(5.4)	AGE30: Age at delivery minus its representative value (30)
Height (cm) †)		157.5(5.2)	157.4(5.0)	157.8(5.4)	HEIGHT157: Height at delivery minus its representative value (157)
Body Mass Index (kg/m^2) †)		20.7(2.8)	20.8(3.1)	21.2(4.0)	BMI22: Body Mass Index minus its representative value (22)
Parity*)	First birth	328(44.7%)	86(63.2%)	29(41.4%)	$PARITY_{F\|S}$: Previous live births
	Subsequent birth	405(55.3%)	50(36.8%)	41(58.6%)	
ETS due to smoking housemate(s) during pregnancy*)	Present	320(43.7%)	100(73.5%)	62(88.6%)	ETS: Smoking status of housemate at presence of pregnant woman
	Absent	413(56.3%)	36(26.5%)	8(11.4%)	
Total number of samples		733	136	70	

†) mean (sd), *) number of samples (%)

explanatory variables were sex of infant ($SEX_{F/M}$), a parity indicator specifying whether it was the first birth ($PARITY_{F/S}$), age of the mother at delivery ($AGE30$), mother's height ($HEIGHT157$), pre-pregnancy body mass index ($BMI22$), infant's gestational length ($GL39$) and a parity indicator specifying whether there was exposure to smoking by housemates during pregnancy (ETS). Continuous variables were centered by subtracting their means (rounded to the nearest integer value), except for BMI which centered at the ideal value of 22 kg/m^2. Using such centered data, imply the estimated intercept of the multiple regression model represents the average of BW of NS group. The multiple regression model used herein, is specified explicitly as:

$$\begin{aligned} BW_{NS}^{(\lambda)} &= \mu^{(\lambda)} + \beta_{SEX}^{(\lambda)} SEX_{F/M} + \beta_{PARITY}^{(\lambda)} PARITY_{F/S} \\ &+ \beta_{AGE}^{(\lambda)} AGE30 + \beta_{HEIGHT}^{(\lambda)} HEIGHT157 \\ &+ \beta_{BMI}^{(\lambda)} BMI22 + \beta_{GL}^{(\lambda)} GL39 + \beta_{ETS}^{(\lambda)} ETS + \varepsilon^{(\lambda)} \end{aligned} \tag{1}$$

where $BW^{(1)}=BW$, $BW^{(2)}=\sqrt{BW}$, $BW^{(3)}=\sqrt[3]{BW}$ and $BW^{(10)}=\ln BW$, μ and the β's are unknown parameters to be estimated, and ε denotes a random error term assumed to be normally distributed with mean 0 and variance σ^2.

Bias estimation method for QS and CS groups data

Adjusted BW for the smoking groups QS and CS were obtained by subtracting the estimated bias from the original value. The fitted value of the best among those four transformed models in equation (1) is used to adjust the original value of BW in both smoking groups, i.e. QS and CS, using the following formula, respectively:

$$\begin{aligned} adj \ln BW_{QS} &= \ln BW_{QS} - \hat{\beta}_{SEX}^{(0)} SEX_{F/M} - \hat{\beta}_{PARITY}^{(0)} PARITY_{F/S} \\ &- \hat{\beta}_{HEIGHT}^{(0)} HEIGHT157 - \hat{\beta}_{BMI}^{(0)} BMI - \hat{\beta}_{GL}^{(0)} GL39 \end{aligned}$$

$$\begin{aligned} adj \ln BW_{CS} &= \ln BW_{CS} - \hat{\beta}_{SEX}^{(0)} SEX_{F/M} - \hat{\beta}_{PARITY}^{(0)} PARITY_{F/S} \\ &- \hat{\beta}_{HEIGHT}^{(0)} HEIGHT157 - \hat{\beta}_{BMI}^{(0)} BMI - \hat{\beta}_{GL}^{(0)} GL39 \end{aligned}$$

where the values of $\hat{\beta}_{SEX}^{(0)}$, $\hat{\beta}_{PARITY}^{(0)}$, $\hat{\beta}_{HEIGHT}^{(0)}$, $\hat{\beta}_{BMI}^{(0)}$ and $\hat{\beta}_{GL}^{(0)}$ are obtained after fitting the model in equation (1).

Analysis method for maternal smoking effect

To examine the effect of maternal smoking on BW, we then regressed the adjusted logarithmic transformed BW on maternal daily consumption of cigarettes (QSday for the QS group, CSday for the CS group) and ETS using the following models for QS and CS groups, respectively:

$$\begin{aligned} adj \ln BW_{QS} &= \mu_{QS} + \beta_{QS} QSday + \beta_{ETS\_QS} ETS + \varepsilon \\ adj \ln BW_{CS} &= \mu_{CS} + \beta_{CS} CSday + \beta_{ETS\_CS} ETS + \varepsilon \end{aligned} \tag{2}$$

To facilitate the comparison among adjusted BW of NS, QS and CS groups, we visualized the boxplots.

RESULTS

The multiple correlation coefficients of the four regression models specified by equation (1) with λ = 0, 1, 2, and 3 were 0.549, 0.543, 0.547 and 0.548. The largest one was obtained when λ = 0. In other words, the logarithmic transformation of BW provided the best fit of the regression model. It suggests that the regression has a multiplicative relationship rather than an additive structure. Explicitly, their relationship can be specified as follow:

$$\begin{aligned} \ln BW_{NS} &= 8.076 - 0.0459 SEX_{F/M} \\ &- 0.0293\, PARITY_{F/S} + 0.00446 HEIGHT157 \\ &+ 0.00787 BMI22 + 0.0443\, GL39. \end{aligned}$$

As described in the above fitted equation, multiple regression analysis with a logarithmic transformation of BW showed that sex of the infant, birth order, maternal height, pre-pregnancy BMI and length of gestational period had significant effects on BW in NS group participants. The effect of ETS was not significant and we did not use it in

Table 2. Estimated regression coefficients of background factors for the NS group

Variable	coef	s.e.	t value	p value	exp(coef)
Constant	8.076	0.00634			3215
Sex of baby (female)	-0.0459	0.00477	-6.14	0.00000	0.952
Parity (firstborn)	-0.0293	0.00754	-3.88	0.00011	0.971
Height of mother †	0.00446	0.00071	6.33	0.00000	1.046
BMI of mother	0.00787	0.00140	5.64	0.00000	1.008
Gestational length (weeks)	0.0443	0.00321	13.82	0.00000	1.045

† The regression coefficient for mother's height represents a difference of 10 cm.

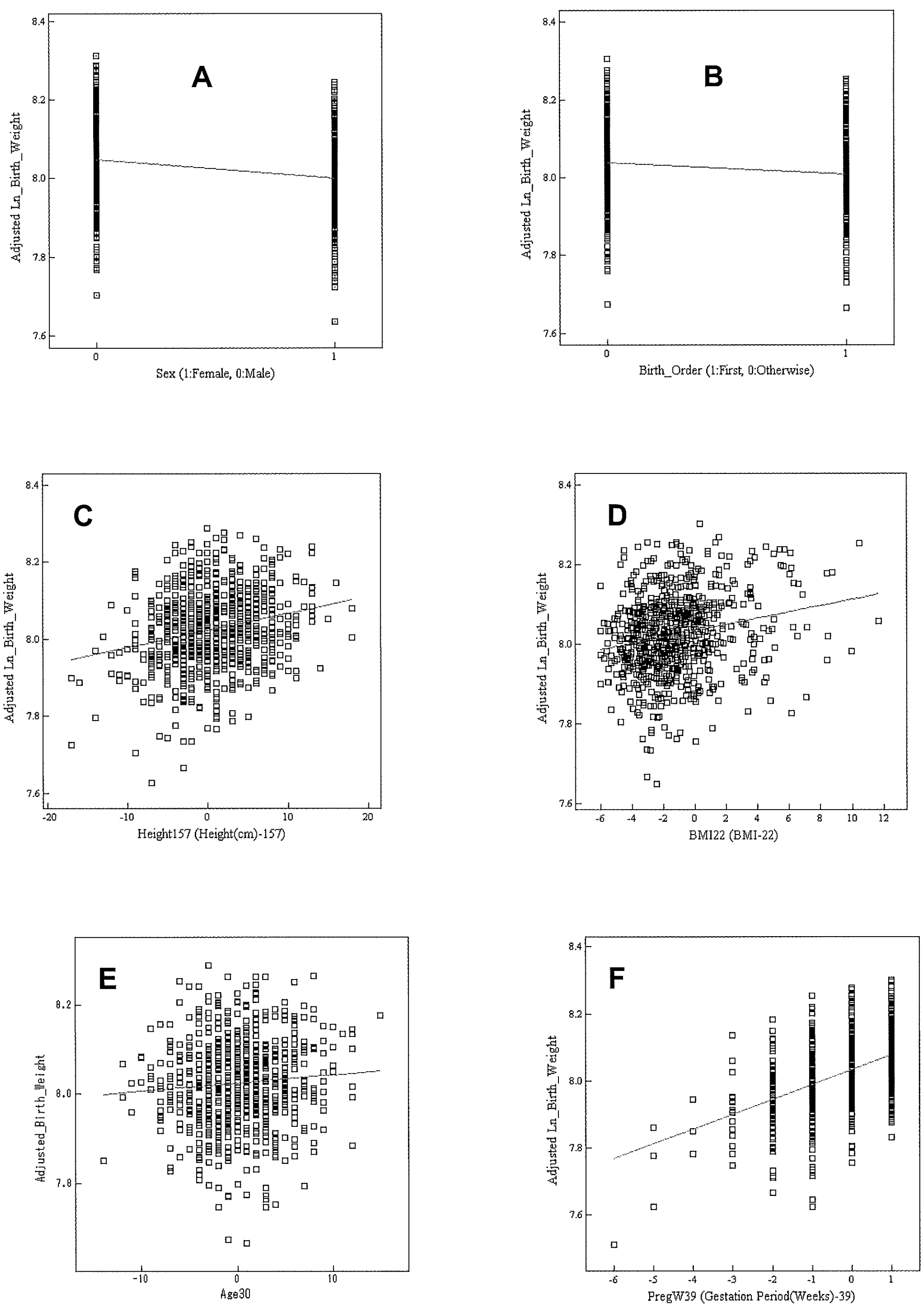

Fig. 1. Logarithmic transformed BW vs. explanatory variables in the NS group after adjustment by multiple regression analysis.
A: Sex of infant; B: Parity (first or subsequent birth); C: Height of mother (centered at 157 cm); D: Body mass index of mother (centered at 22 kg/m^2); E: Age of mother at time of birth (centered at 30 years); F: Gestational length (centered at 39 weeks).

the regression model. No interaction effects were found among these background factors. These tendencies are consistent with the results of previous studies[7,9]. According to the 'above relationship equation, the mean BW of female infants is 95.2% of male and the first born infants are 97.1% of subsequent births. Both differences are highly significant (Fig.1A~F). The effect of the other significant explanatory variables can be interpreted similarly from the above equation and Table 2.

The effect of mother's age at delivery was 0.0018 (95%CI, 0.00002 to 0.0036), showing that older mothers tended to have slightly heavier infants, but the slope of the linear trend was not

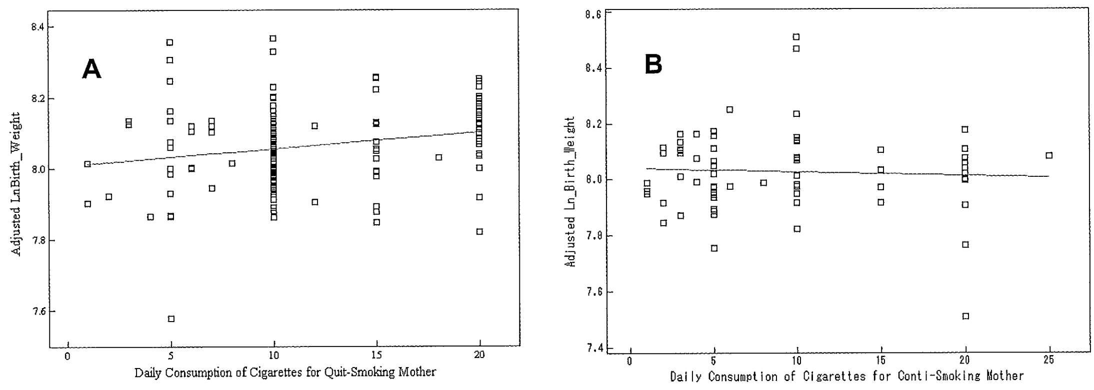

Fig. 2. Adjusted logarithmic transformed BW vs. daily consumption of cigarettes for mothers who quit smoking during pregnancy (A) and those who continued smoking during pregnancy (B). Neither slope was significant by a one-sided test (p>0.5).

Table 3. Effects of maternal smoking and environmental tobacco smoke (ETS) on BW

Quit-smoking group				Continued-smoking group			
Variable	coef	s.e.	p value	Variable	coef	s.e.	p value
QSday	0.00466	0.0020	0.978	CSday	-0.00126	0.0028	0.655
ETS	0.00875	0.0235	0.710	ETS	0.0121	0.0597	0.840

sharp. No reduction in BW due to ETS exposure was detected (estimated coefficient 0.0055 with 95%CI is 0.0097 to 0.0207). We therefore excluded mother's age at delivery and ETS from the factors used for background adjustment.

After eliminating the degree of bias by subtracting the fitted values of equation (1) from the original values of BW, the result of these logarithmic adjusted values then regressed on QSday and ETS for QS group and CSday and ETS for CS group respectively, using the model in equation (2). Here the means and standard deviations of QSday and CSday are 11.7 (5.2) and 9.2 (6.4), respectively. The results of fitted equations are as follow:

$$adj \ln BW_{QS} = 8.002 + 0.00466\, QSday + 0.00875\, ETS$$

$$adj \ln BW_{CS} = 8.029 - 0.00126\, CSday + 0.0121\, ETS.$$

According to the above equation, the estimated effects of maternal smoking were -0.00126 cig^{-1} (p>0.5) for the CS group and 0.00466 cig^{-1} (p>0.5) for the QS group. These effects were not statistically significant by a one-sided test (Fig. 2). There is also no significant reduction in BW due to ETS in either smoking group. The estimated regression coefficients were 0.0121 (p>0.5) for the CS group and 0.00875 (p>0.5) for the QS group (See Table 3).

Fig.3 shows the boxplot of the NS, QS and CS groups. The mean adjusted BW of the QS group was 4.41% (95%CI, 1.74% to 7.07%) lower than NS group and the mean adjusted BW of the QS group was only 1.38% (95%CI, -1.32% to 4.08%) lower than the NS group. By comparing adjusted BW among the NS, QS and CS groups, we showed that the CS group results were significantly lower relative to the NS group, but without verification

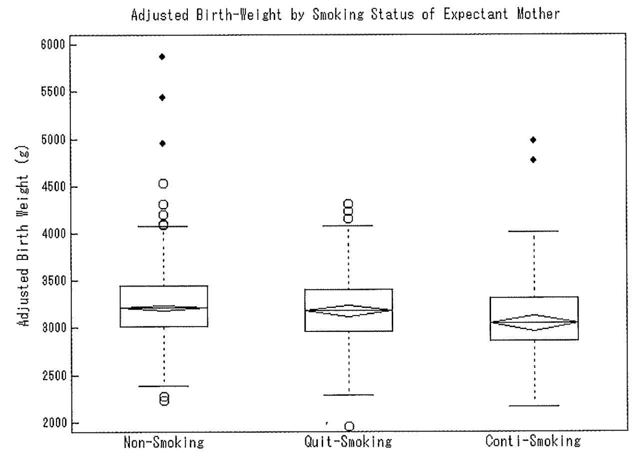

Fig. 3. Boxplots of BW by maternal smoking status after adjustment for background factors.
The means with standard deviations are 3241.9 (354.7) g, 3197.0 (376.8) g and 3099.0 (462.3) g for the NS, QS and CS group, respectively. Average infant BW was significantly lower for the group of mothers who continued to smoke during pregnancy compared to the NS group (p=0.0004), but no significant difference in BW was detected between the QS and NS groups (p=0.147).

on the dose-response relationship with maternal daily consumption of cigarettes.

DISCUSSION

Some studies conducted outside Japan showed that the amount smoked during pregnancy is significantly associated with BW[4,15,17]. Bernstein et al. reported a 27 g reduction in BW for each additional cigarette per day from a participant who smoked in the third trimester[1]. Secker-Walker et al showed that cigarette consumption and the exhaled carbon monoxide level at a prenatal clinic visit were significantly associated with BW, which is inconsistent with our result[15]. The reasons for this inconsistency might include: i) a true dose-response relationship may be undetectable due to the small sample size of the CS group, ii) confounding of the three smoking-status groups with educational level or degree of interest in health and iii) uncertainties (measurement error) in the self-reported consumption of cigarettes, which would lead to attenuation of the dose response. The insignificant difference of the mean BW between the QS and NS groups, suggests that cessation of smoking early in pregnancy may be beneficial to improving the BW of infants.

Although Horta et al reported that the effect of maternal smoking on BW is attributable to IUGR rather than preterm birth[5], a reduction in BW may be caused in part by preterm delivery as well. We examined the relationship between maternal smoking status, including ETS exposure and gestational length, defining a preterm delivery as one having a gestational length of 37 weeks or less. Table 4 shows frequencies of preterm versus normal-term (39 weeks or more) deliveries in two categories: smoking during pregnancy with ETS exposure and nonsmoking during pregnancy with non-ETS exposure. Based on χ^2-test, no significant association was detected between gestational length and those two categories. Therefore, we concluded that the reduction in BW may be due to IUGR. More information, such as whether or not an oxytocic agent was used is required to further examine the relationship between maternal smoking status and gestational length.

The undesirable effects of ETS on BW and IUGR have also been noted in other studies[10,17]. Some reports showed that the effects are smaller than maternal smoking[3,4]. We found no significant effect of ETS exposure on BW, but our sample size may have been too small to detect such an effect.

CONCLUSION

Based on a questionnaire survey, we conclude that continuing to smoke during pregnancy results in a significant reduction in BW, whereas smoking prior to pregnancy does not produce a significant effect if the pregnant woman stops smoking during pregnancy. Our inability to find a significant dose response for daily cigarette consumption, which is inconsistent with other studies, may be due to small sample size, unmeasured confounders, and/or measurement error in the self-reported data. We were also unable to establish a relationship between ETS and BW. However, for bias estimate, we establish a model to evaluate the contribution of each explanatory variable using a logarithmic multiple regression model. We then evaluated the direct effect of maternal cigarette consumption per day and ETS to the adjusted BW. In addition, our study confirms the potential hazard of smoking in terms of LBW and suggests that quitting smoking before pregnancy may be beneficial.

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Table 4. Number of participants by gestational length and smoking status

Gestational length	Continued-smoking with ETS exposure	Non-smoking without ETS exposure	Total
$\geq$39 weeks	36	269	305
$\leq$37 weeks	13	56	69
Total	49	325	374

(χ^2=2.53, df=1)

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