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Association between maternal passive smoking and increased risk of delivering small-for-gestational-age infants at full-term using plasma cotinine levels from The Hokkaido Study: a prospective birth cohort

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ABSTRACT

Objectives To investigate the association between plasma cotinine level measured at the 8th gestational month and the delivery of small-for-gestational-age (SGA) infants, using a highly sensitive ELISA method.

Design Prospective birth cohort study from The Hokkaido Study on Environment and Children's Health.

Setting Hokkaido, Japan.

Participants Our sample included 15 198 mother-infant pairs enrolled in 2003–2012.

Main outcome measures SGA, defined as a gestational age-specific weight Z-score below −2.

Results The number of SGA infants was 192 (1.3%). The cotinine cut-off level that differentiated SGA infants from other infants was 3.03 ng/mL for both the total population and the full-term births subgroup (sensitivity 0.307; positive predictive value 2.3%). Compared with infants of mothers with a plasma cotinine level of <3.03 ng/mL, infants of mothers with a plasma cotinine level of ≥3.03 ng/mL showed an increased OR for SGA in the total population and the full-term infant group (2.02(95% CI 1.45 to 2.83) and 2.44(95% CI 1.73 to 3.44), respectively).

Conclusion A plasma cotinine level of ≥3.03 ng/mL, which included both passive and active smokers, was associated with an increased risk of SGA. This finding is of important relevance when educating pregnant women about avoiding prenatal passive and active smoking due to the adverse effects on their infants, even those born at full-term.

Strengths and limitations of this study

- This study examined the association between plasma cotinine level and small-for-gestational-age (SGA) birth at full-term and preterm.
- Receiver operating characteristic analysis showed that plasma cotinine ≥3.03 ng/mL, which can be observed in both passive and active smokers, is associated with an increased risk of delivering an SGA infant at full-term.
- Although the sensitivity of the cut-off values was low, a significant association between plasma cotinine ≥3.03 ng/mL and twice the risk of SGA at full-term was observed in logistic regression models.
- The limitation of this study was that preterm births (22–36 weeks) were very few in numbers.
- The findings are relevant and important for educating pregnant women on the adverse health effects that prenatal passive and active smoking have on infants, even those born at full-term.

INTRODUCTION

Small-for-gestational-age (SGA) has been associated with a higher susceptibility to delayed growth and neurodevelopment in infancy as well as an increased risk of obesity and metabolic syndrome in childhood.[1–4] Infants born in late preterm (34–36 weeks) and full-term SGA (37–41 weeks) infants are more predisposed to mortality compared with infants with normal birth weight for gestational age.[5] Compared with infants born with normal weight for gestational age, very SGA (<3rd percentile) infants carry a twofold risk of infant mortality.[6] Although the Hokkaido prefecture had a similar rate of low birth weight (<2500 g) compared with all of Japan in 2015 (9.3% vs 9.5%),[7] this prefecture had the highest female smoking rate in Japan in 2016 (16.1% vs 9.5%).[8] Therefore, it is particularly important to examine the risk factors associated with preterm and full-term SGA birth in Hokkaido.

Maternal active smoking during pregnancy is known to be a risk factor for SGA.[9–11] Studies of non-smoking pregnant women

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have reported that maternal passive smoking is not associated with SGA.[10 12 13] However, other studies have found a onefold to fivefold increased risk of SGA among infants of mothers who were exposed to passive tobacco smoke during pregnancy.[14–18] Hence, the association between maternal passive smoking during pregnancy and SGA is not concordant. One reason for this may be the fact that most studies have relied on self-reported maternal smoking status. The problem with self-reported smoking status is under-reporting of active smoking and heavy exposure to passive smoking.[19–21] To overcome this problem, measuring the biomarkers of smoking status, such as nicotine, is more accurate than self-reporting.[20] A recent study in Korea, which used nicotine in the hair as a biomarker, found that infants of mothers in the highest nicotine group (0.63–5.99 ng/mg) were 1.59 times more likely to be SGA compared with the lowest nicotine group (0.0–0.28 ng/mg).[17]

Cotinine, a major metabolite of nicotine, is an objective biomarker for validating both active and passive exposure to tobacco smoke. Levels of cotinine in the hair, urine or blood of pregnant women have been used in determining relationships with pregnancy outcomes.[17 22–31] The associations between nicotine or cotinine levels and birth weight or SGA have been reported.[10 12–18 26 32] However, reports of the association between cotinine levels and SGA are limited, compared with reports of the association between self-reported smoking during pregnancy and SGA. One Spanish study used urine samples of pregnant women to establish an optimal cut-off point for differentiating occasional smokers from passive smokers.[33] Although the passive tobacco smoke exposure level can be measured objectively by cotinine, a threshold cotinine level to identify an increased risk of SGA has not yet been clarified.

Our previous prospective birth cohort study, 'Hokkaido Study on Environment and Children's Health' in Japan established a plasma cotinine cut-off point of 0.21 ng/mL to differentiate non-passive from passive smokers.[34] Passive smokers had plasma cotinine levels of between 0.21 and 11.48 ng/mL and active smokers had plasma cotinine levels greater than 11.48 ng/mL.[34] We elucidated the gene-environment interaction of child growth at and after birth for maternal active and passive smoking during pregnancy in the previous studies,[27 28 35] and the dose-dependent association between birth weight and plasma cotinine levels during pregnancy.[28] However, there is limited information in the previous studies comparing the association between SGA and for the mothers of the passive and active smoking during pregnancy. Therefore, objective clarification is necessary.

Hence, the aim of this study was to examine the association between maternal plasma cotinine level during pregnancy and SGA with stratification by gestational age (full-term and preterm) using a receiver operating characteristic (ROC) curve analysis. With the plasma cotinine cut-off point established by this study, we also aimed to investigate the association between the cotinine level and SGA.

METHODS

Study participants

The study participants included Japanese mother-infant pairs recruited from an ongoing prospective birth cohort of 'The Hokkaido Study on Environment and Children's Health'. Enrolment was from February 2003 to March 2012. The study protocol has been described in a previous study.[36–38] Figure 1 shows the characteristics of the study participants. Of the 20 788 mother-infant pairs, 15 506 had complete questionnaire data for the first trimester, recorded plasma cotinine levels and birth records. After excluding 308 mother-infant pairs who met the exclusion criteria (stillbirth (n=21), artificial abortion (n=1),

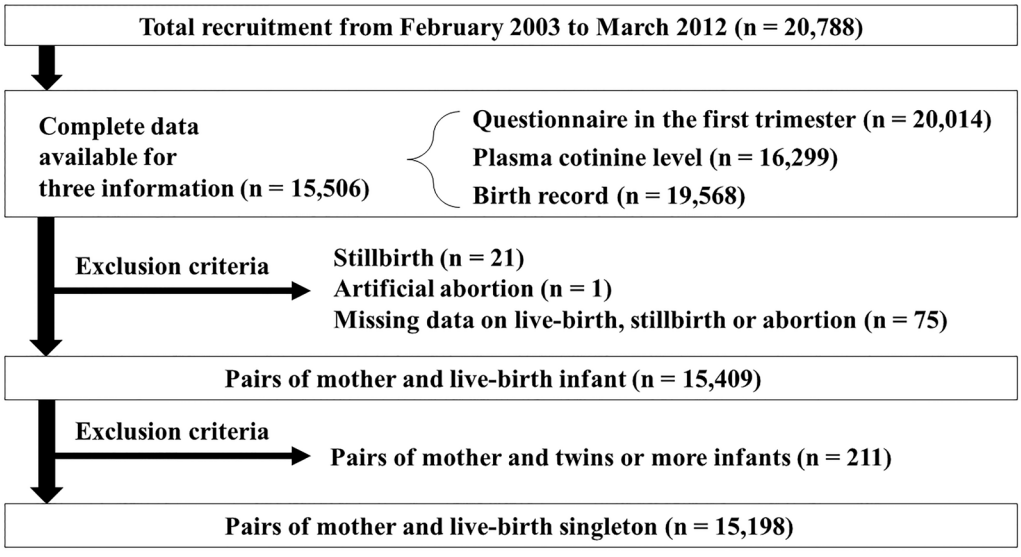


Figure 1 Flowchart of the participants.

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missing data on live-birth, stillbirth or abortion (n=75) and twins or multiple birth (n=211)), a total of 15 198 mother-infant pairs were finally included.

Questionnaires and medical records

Participants completed a baseline questionnaire during the first trimester of pregnancy. The questionnaire included basic maternal information regarding age, height, weight before pregnancy, parity, drinking during the first trimester and annual household income. We obtained the gestational age, medical history of mothers during pregnancy (pregnancy-induced hypertension and gestational diabetes mellitus based on the information declared from medical doctors), infant sex and single or multiple births and live-birth, stillbirth or abortion from the medical records.

Measurement of plasma cotinine levels during the third trimester

During the 8th gestational month, plasma cotinine levels were measured using the highly sensitive ELISA developed by Cosmic Corporation, Tokyo, Japan. Details of the protocol have been described in our previous study.[34] The limit of detection (LOD) was 0.12 ng/mL, while the detection rate was 75.3%. For samples with cotinine levels below the detection limit, we used a value of half the LOD. In differentiation between passive and active smokers, we used the cotinine cut-off amounts used in our previous study.[34] Using this cut-off value,[34] non-passive smokers, passive smokers and active smokers were defined by cotinine levels of ≤0.21 ng/mL, 0.21<to ≤11.48 ng/mL and >11.48 ng/mL, respectively.

Definition of birth outcome

In the Japan Pediatric Society guidelines, standardised birth weight values are expressed in relation to gestational age in terms of SD from the growth curve, according to parity, infant sex and gestational age.[39] The parity-specific, infant sex-specific and gestational age-specific birth weight Z (SD) score, which is based on the definition of the Japan Pediatric Society, was calculated using software prepared by the Japanese Society for Pediatric Endocrinology.[40] Accordingly, we defined SGA as a weight Z-score below −2 SD and non-SGA as a weight Z-score equal to or above −2 SD.

Statistical methods

First, non-detectable cotinine levels were assigned a half value of LOD before the statistical analyses. The sensitivity and specificity of plasma cotinine levels were calculated using ROC curve analyses. Subgroup analyses of ROC curves were also calculated for full-term and preterm births. The optimal cut-off values to separate a group of SGA infants from a group of non-SGA infants were obtained by locating the points with maximum sensitivity and specificity on the curve using the Youden index method.[41] Agreement between SGA-classified groups and cotinine-classified groups were assessed using three measured values: the positive predictive value, the negative predictive value and the likelihood ratio. The positive predictive value (calculated as true positives/(true positives+false positives)) was the proportion of correctly identified SGA or non-SGA infants with positive test results. The negative predictive value (calculated as true negatives/(true negatives+false negatives)) was the proportion of correctly identified SGA or non-SGA infants with negative test results. The likelihood ratio was a predictor of whether cotinine analysis considerably altered the chance of an infant being correctly classified as SGA or non-SGA. Second, logistic regression analyses were used to evaluate the association between plasma cotinine levels and SGA with adjustment for the following covariates: maternal age, height, weight before pregnancy, alcohol drinking during the first trimester, education level, annual household income, pregnancy-induced hypertension and gestational diabetes mellitus. There were no multicollinearity issues due to the high correlation (r_s>0.7) of the Spearman's rank moment correlation coefficient between variables of the above-mentioned covariates. We performed multiple imputation for the missing data using Bayesian methods in SPSS (SPSS, Chicago, Illinois, USA). The minimum and maximum values were set for each variable. To create and analyse the 25 datasets, we imputed the missing confounders on, maternal age ($n_{missing}$=1 (0.0%)), maternal height ($n_{missing}$=157 (1.0%)), maternal weight before pregnancy ($n_{missing}$=332 (2.2%)), alcohol drinking during pregnancy ($n_{missing}$=336 (2.2%)), education level ($n_{missing}$=138 (0.9%)), annual household income ($n_{missing}$=2,293 (15.1%)), pregnancy-induced hypertension ($n_{missing}$=0 (0.0%)) and gestational diabetes mellitus ($n_{missing}$=0 (0.0%)) using the multiple imputation package for SPSS (SPSS). All statistical analyses were performed using SPSS Ver.24.0 software (SPSS). The percentage of missing data was high only for annual household income. The results were similar in multivariate regression models with or without imputations for missing data.

Patient and public involvement

Patients were not involved in this study.

RESULTS

The characteristics of infants and mothers are shown in table 1. The numbers of infants who were SGA and preterm at birth were 192 (1.3%) and 533 (3.5%), respectively. The mean maternal age was 30.3±4.8 years. The numbers of mothers who were primiparous, drank alcohol during pregnancy, had pregnancy-induced hypertension and had gestational diabetes mellitus were 6040 (39.7%), 1923 (12.7%), 249 (1.6%) and 129 (0.8%), respectively. The numbers of SGA infants born to non-passive smokers, passive smokers and active smokers were 67 (1.1%), 76 (1.1%) and 49 (2.2%), respectively.

The frequency distribution of plasma cotinine levels in the participants was bimodal (figure 2A and online supplementary table 1). The line graph showed that the rate of SGA, according to birth weight, increased with increasing

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Table 1 Characteristics of infants and mothers

Characteristics	All (n=15 198)	Plasma cotinine level during the third trimester (ng/mL)		
		Non-passive smokers (≤0.21) (n=6045)	Passive smokers (>0.21 to ≤11.48) (n=6878)	Active smokers (>11.48) (n=2275)
Infants				
Sex				
Male	7622 (50.2)	3025 (50.0)	3423 (49.8)	1174 (51.6)
Female	7576 (49.8)	3020 (50.0)	3455 (50.2)	1101 (48.4)
Birth weight (g)	3054.6±393.5	3073.0±387.2	3065.7±397.6	2972.2±387.6
Small-for-gestational-age	192 (1.3)	67 (1.1)	76 (1.1)	49 (2.2)
Gestational age (weeks)	38.9±1.3	38.9±1.3	39.0±1.4	38.8±1.4
Preterm (<37 weeks)	533 (3.5)	225 (3.7)	225 (3.3)	83 (3.6)
Full-term (≥37 weeks)	14 664 (96.5)	5820 (96.3)	6653 (96.7)	2191 (96.3)
Missing data	1 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Mothers				
Age (years)	30.3±4.8	31.4±4.5	29.5±4.8	29.6±4.9
Height (cm)	158.2±5.4	158.2±5.2	158.1±5.3	158.1±6.2
Weight before pregnancy (kg)	53.0±8.8	53.1±8.6	52.6±8.5	53.5±10.4
Parity				
Primiparous	6040 (39.7)	2090 (34.6)	3221 (46.8)	729 (32.0)
Multiparous	8270 (54.4)	3544 (58.6)	3302 (48.0)	1424 (62.6)
Missing data	888 (5.8)	411 (6.8)	335 (5.2)	122 (5.4)
Alcohol drinking during pregnancy				
No	12 939 (85.1)	5283 (87.4)	5819 (84.6)	1837 (80.7)
Yes	1923 (12.7)	646 (10.7)	892 (13.0)	385 (16.9)
Missing data	336 (2.2)	116 (1.9)	167 (2.4)	53 (2.3)
Education level				
Junior high school	799 (5.3)	117 (1.9)	332 (4.8)	350 (15.4)
Senior high school	6666 (43.9)	2209 (36.5)	3150 (45.8)	1307 (57.5)
Junior college	6017 (39.6)	2695 (44.6)	2770 (40.3)	552 (24.3)
University	1578 (10.4)	969 (16.0)	562 (8.2)	47 (2.1)
Missing data	138 (0.9)	55 (0.9)	64 (0.9)	19 (0.8)
Annual household income (million Japanese yen)				
<3	2985 (19.6)	881 (14.6)	1489 (21.6)	615 (27.0)
3 to <5	5782 (38.0)	2348 (38.8)	2553 (37.1)	881 (38.7)
5 to <8	3230 (21.3)	1540 (25.5)	1354 (19.7)	336 (14.8)
≥8	908 (6.0)	435 (7.2)	382 (5.6)	91 (4.0)
Missing data	2293 (15.1)	841 (13.9)	1100 (16.0)	352 (15.5)
Pregnancy-induced hypertension	249 (1.6)	86 (1.4)	120 (1.7)	43 (1.9)
Gestational diabetes mellitus	129 (0.8)	56 (0.9)	52 (0.8)	21 (0.9)

Data are presented as n (%) or mean±SD.
The parity-specific, infant sex-specific and gestational age-specific birth weight Z (SD) score, which was based on definition from the Japan Pediatric Society,[26 39] was calculated using software prepared by Japanese Society for Pediatric Endocrinology.[40] Accordingly, we defined SGA) as weight Z-score below −2 SD and non-SGA as weight Z-score equal or above −2 SD.
Cut-off, 0.21 ng/mL (value differentiating non-passive smokers from passive smokers among non-active smokers), 11.48 ng/mL (value differentiating non-active smokers from active smokers).[34]
SGA, small-for-gestational-age; weight Z-score, gestational age-specific Z-score.

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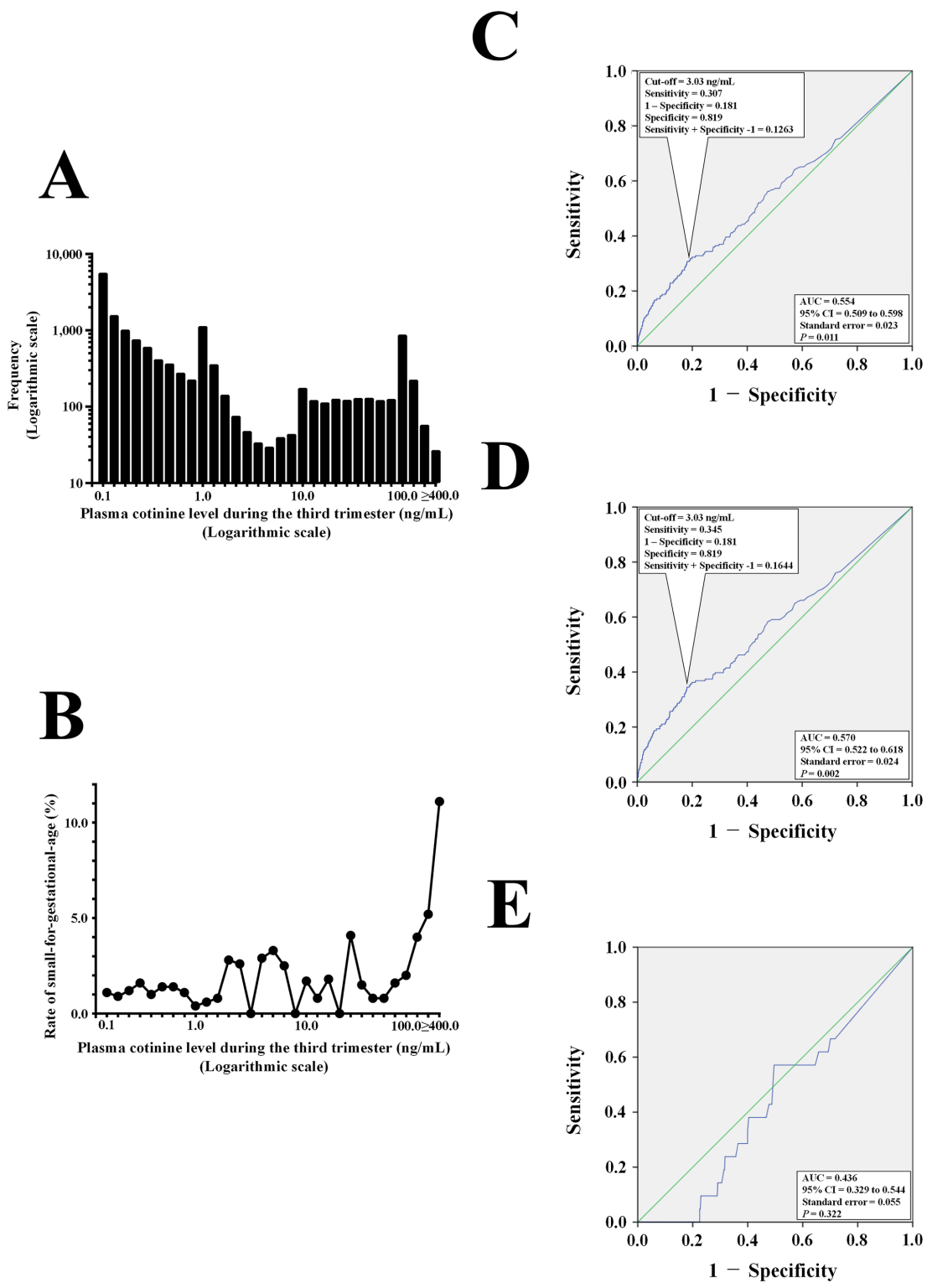


Figure 2 (A) Frequency distribution of plasma cotinine level during the third trimester, (B) line graph of rate of SGA according to plasma cotinine level during the third trimester and ROC curve analysis of plasma cotinine levels for differentiating SGA infants from non-SGA infants among (C) the total population, (D) the full-term subgroup and (E) the preterm subgroup Plasma cotinine levels during the third trimester: rate of detection=73.6%, mean=18.5 ng/mL, minimum=0.12 ng/mL, 10 percentiles=0.12 ng/mL, 25 percentiles=0.12 ng/mL, median =0.32 ng/mL, 75 percentiles=1.25 ng/mL, 90 percentiles=74.1 ng/mL, maximum=1088.3 ng/mL. Cut-off: 0.21 ng/mL (value differentiating non-passive smokers from passive smokers among non-active smokers), 11.48 ng/mL (value differentiating non-active smokers from active smokers).[34] The parity, infant sex and gestational age-specific birth weight Z (SD) score, which was based on definition from the Japan Pediatric Society,[39] was calculated using software prepared by Japanese Society for Pediatric Endocrinology.[40] Accordingly, we defined SGA as weight Z-score below –2 SD and non-SGA as weight Z-score equal or above –2 SD. AUC, area under the curve; ROC, receiver operating characteristics; SGA, small-for-gestational-age.

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Table 2 Comparison of the frequency of small-for-gestational-age with plasma cotinine levels of ≥3.03 ng/mL (excluded from missing values)

Plasma cotinine level (ng/mL)	Small-for-gestational-age								
	All (n_{all}=15 198; $n_{missing}$=918)			Full-term (n_{all}=14 664; $n_{missing}$=893)			Preterm (n_{all}=533; $n_{missing}$=24)		
	Yes (% out of total)	No	Total	Yes (% out of total)	No	Total	Yes (% out of total)	No	Total
≥3.03	59 (2.3)	2550	2609	59 (2.3)	2457	2516	0 (0.0)	93	93
<3.03	133 (1.1)	11 538	11 671	112 (1.0)	11 143	11 255	21 (5.0)	395	416
Total	192 (1.3)	14 088	14 280	171 (1.2)	13 600	13 771	21 (4.1)	488	508

The parity-specific, infant sex-specific and gestational age-specific birth weight Z (SD) score, which was based on definition from the Japan Pediatric Society,[39] was calculated using software prepared by Japanese Society for Pediatric Endocrinology.[40] Accordingly, we defined SGA as weight Z-score below −2 SD and non-SGA as weight Z-score equal or above −2 SD.
All, likelihood ratio=19.4, sensitivity=0.307, specificity=0.819, positive predictive value=2.3%, negative predictive value=98.9%.
Full-term, likelihood ratio=29.5, sensitivity=0.345, specificity=0.819, positive predictive value=2.3%, negative predictive value=99.0%.
Preterm, likelihood ratio=8.6, sensitivity (-), specificity=0.809, positive predictive value (-), negative predictive value=94.6%.

cotinine levels (figure 2B and online supplementary table 1).

Figure 2C–E shows the ROC curve analyses performed to determine the plasma cotinine cut-off level that differentiated SGA infants from non-SGA infants. The cotinine cut-off level for differentiating between the two groups was 3.03 ng/mL (all: sensitivity=0.307, specificity=0.819, and area under the curve (AUC)=0.554; full-term: sensitivity=0.345, specificity=0.819 and AUC=0.570) in both the total population and the full-term birth subgroup; however, the level could not be determined in the preterm birth subgroup.

The SGA rate in pregnant women with plasma cotinine levels of ≥3.03 ng/mL is shown in table 2. Of all births, 30.7% (n=59) of 192 mothers of SGA infants had plasma cotinine levels of ≥3.03 ng/mL. The positive predictive value was 2.3% and the negative predictive value was 98.9%. For the preterm births, none of the 21 mothers of SGA infants had plasma cotinine levels of ≥3.03 ng/mL.

For all, compared with infants of mothers with plasma cotinine level of <3.03 ng/mL, infants of mothers with plasma cotinine level of ≥3.03 ng/mL were associated with an increased OR of 2.02 (95% CI 1.45 to 2.83) for SGA among all births (online supplementary file 2).

For full-term births, infants of both passive and active smokers showed an increased OR for SGA compared with infants of mothers with plasma cotinine levels of <3.03 ng/mL (2.44 (95% CI 1.73 to 3.44)) (figure 3A and online supplementary table 2). Infants of passive smokers and active smokers showed an increased OR for SGA (2.42 (95% CI 1.24 to 4.72) and 2.44 (95% CI 1.69 to 3.52], respectively) (figure 3B and online supplementary table 2). Compared with infants of non-passive smokers, infants of passive smokers with plasma cotinine levels of <3.03 ng/mL did not have an increased risk of SGA (OR: 0.89 (95% CI 0.61 to 1.31)); however, infants of passive smokers and active smokers did show an increased OR for SGA (2.28 (95% CI 1.13 to 4.59) and 2.30 (95% CI 1.52 to 3.49), respectively) (figure 3C and online supplementary table 2).

DISCUSSION

Main findings in relation to the literature

In this study, the cut-off plasma cotinine level established for identifying an increased risk of SGA (3.03 ng/mL) was equivalent to the passive smoking level found in our previous study.[34] When compared with infants of mothers with plasma cotinine levels of <3.03 ng/mL, infants of mothers with plasma cotinine levels of ≥3.03 ng/mL showed an increased risks of delivering a SGA infant with ORs of 2.02 and 2.44 for all births and full-term births, respectively. Pregnant passive smokers with cotinine levels of ≥3.03 ng/mL had almost the same risk of giving birth to a SGA infant as active smokers with cotinine levels of >11.48 ng/mL. It is, therefore, noteworthy that even full-term infants of passive smoking mothers are at a higher risk of SGA compared with infants of non-passive smokers.

Until now, there has been no evidence of an association between plasma cotinine levels and SGA. While some previous studies have reported a relationship between hair nicotine levels of non-smokers during pregnancy and SGA,[17 30] two other studies found no such relationship.[12 25] The results of these two previous studies[17 30] are consistent with our findings.

Given the AUC 0.554–0.557 result in the present study, we considered the ability of plasma cotinine levels to accurately predict SGA to be low. Moreover, low sensitivity (0.307–0.345 in the present study) meant that most women delivering term-SGA infants would not test positive for plasma cotinine. In previous studies, term-SGA was associated with sociodemographic status, smoking and various medical conditions.[42 43] In our previous study, compared with maternal non-smokers, as defined by plasma cotinine levels in the third trimester, maternal smokers were associated with a lower household income, lower education levels and smoking partners and cohabitants.[22 23] As smoking status and prevalence of SGA are affected by factors such as lifestyle and socioeconomics in a population group, cotinine level as smoking biomarker may also be affected by these factors, and the cotinine

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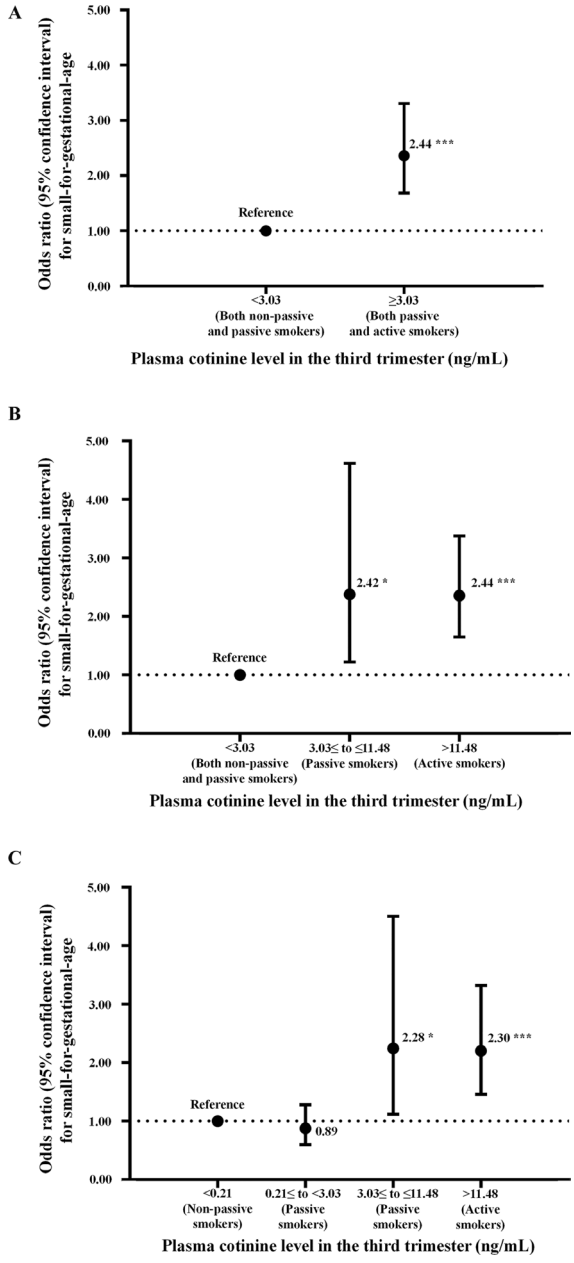


Figure 3 OR of full-term SGA infants of passive and active smokers compared with (A and B) mothers with plasma cotinine levels of <3.03 ng/mL (both non-passive and passive smokers) and (C) mothers with plasma cotinine levels of ≤0.21 ng/mL (non-passive smokers). Cut-off: 0.21 ng/mL (value differentiating non-passive smokers from passive smokers among non-active smokers), 11.48 ng/mL (value differentiating non-active smokers from active smokers).[34] The parity-specific, infant sex-specific and gestational age-specific birth weight Z (SD) score, which was based on definition from the Japan Pediatric Society,[39] was calculated using software prepared by Japanese Society for Pediatric Endocrinology.[40] Accordingly, we defined SGA as weight Z-score below −2 SD and non-SGA as weight Z-score equal or above −2 SD. Logistic regression models are adjusted for maternal age, height, weight before pregnancy, alcohol drinking during the first trimester, education level, annual household income, pregnancy-induced hypertension and gestational diabetes mellitus. Bar represents OR (±95% CI) for SGA compared with infants of reference group. *P<0.05; **P<0.01; ***P<0.001. SGA, small-for-gestational-age.

cut-off values for SGA might be different in each population group.

As a Z-score of −2 (−2 SD) is the same as 2.3 percentiles in the standard normal distribution, the prevalence of SGA (1.3%) in this study was low. As a positive predictive value (2.3%) is dependent on a low prevalence of SGA (1.3%), this value might be low due to the results analysed in the population with the low prevalence of SGA in the present study. Moreover, as the risk factors for term-SGA are broader than just smoking status, the multiple risk factors might be linked to both the low accuracy and low sensitivity of individual cotinine levels for SGA.

The prevalence of pregnancy-induced hypertension has been reported as 3.1%–4.7%,[44–46] and the prevalence of gestational diabetes mellitus as 1.0%–2.2%[44 46 47] in the previous Japanese studies. These percentages are slightly higher compared with this study. The participants in the present study were relatively healthier pregnant women. We consider that possible misclassifications of these complications are low.

The major points in the present study are that cotinine levels cannot be used as a biomarker of term-SGA. The cotinine threshold level of 3.03 ng/mL for term-SGA is considered low. However, the accuracy of a dose-dependent association between cotinine levels and increased risk of term-SGA appeared high because of the above-mentioned knowledge and the results of our previous study.[23] These findings suggest that active smokers and strong passive smokers in the third trimester have a higher risk of term-SGA compared with non-passive smokers.

Limitations and strengths of the study

The main strength of this study was the large cohort comprising 15 198 mother-infant pairs. Therefore, the accuracy of the causal relationship between plasma cotinine levels and SGA risk was high. The second strength was that we measured cotinine levels at the 8th month of pregnancy because we know that birth size reduction is related to maternal smoking during the third trimester.[48] The 4–8th month of pregnancy represents the critical window of maternal exposure to chemicals leading to low birth weight,[49] fetal growth is the most rapid from the 9–10th month of gestation with an average increase of 240 g per week[50] and head circumference below the 10th percentile during the 7.5–9th month of gestation is associated with an increased risk of low birth weight.[51] Therefore, we considered that cotinine measurement of the 8th month of gestation, before the period of most rapid infant growth, provides high validity. However, there were also limitations. First, we did not measure the cotinine level from dietary sources. However, these dietary sources of nicotine, such as *Solanaceae*, tomato and potato, contain very little (only 0.7% of a typical passive smoker's cotinine dose).[52 53] Second, the short biological half-life of cotinine (17.9 hours)[54] means that a single measurement does not reflect the amount of exposure over the entire pregnancy. Third, although the sensitivity

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of the cut-off values was low (0.307–0.345), the significant association between cotinine levels of >3.03 ng/mL and an increased risk of SGA, as determined by the logistic regression models remained. Fourth, preterm births (22–36 weeks) were very few in numbers (3.5% of total sample) and there was a limited duration of intrauterine growth from the cotinine measurements (28–31 weeks equivalent to the 8th month of pregnancy). As a result, we did not investigate the association between plasma cotinine levels and preterm births. Fifth, the low sensitivity and positive predictive values mean that the cut-off levels of individual cotinine levels for SGA represent low accuracy. Hence, caution is warranted in data interpretation. Sixth, although a reduced birth weight was associated with both maternal smoking and dioxin levels and genetic factors in our previous studies,[27 28 55] these results were not considered in relation to other environmental factors, except for smoking and genetic factors of mothers.

Public health implications for practice

This study shows that if efforts are made to encourage pregnant women to avoid both active and passive smoking especially during the third trimester, the risk of SGA may be reduced. The association observed between passive smokers with plasma cotinine levels of 3.03–11.48 ng/mL and an increased risk of SGA observed in this study was close to the risk associated with active smokers with plasma cotinine levels of >11.48 ng/mL and an increased risk of SGA.

Cotinine measurement is fast and easy to perform.[56] Furthermore, although cotinine cut-off levels for distinguishing SGA from non-SGA involve low accuracy, knowing a pregnant woman's cotinine levels can be helpful so as to avoid or reduce passive and active smoking exposure during pregnancy and therefore prevent subsequent SGA. Hence, it is necessary to inform pregnant women on the risk of giving birth to SGA infants due to prenatal exposure to active and passive smoking.

In conclusion, passive and active smoking are important risk factors for SGA. Hence, our findings are relevant and important when educating pregnant women about the adverse health effects on their infants due to prenatal passive and active smoking, even in infants born at full-term.

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Competing interests None declared.

Patient consent Not required.

Ethics approval This study was conducted with the written, informed consent of all participants. The Institutional Ethical Board for Epidemiological Studies of Hokkaido University Center for Environmental and Health Sciences approved the study protocol. The guidelines of the Declaration of Helsinki were followed.

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Data sharing statement Researchers interested in collaborations or further information are invited to contact Reiko Kishi, MD. PhD, MPH. Email: rkishi@med.hokudai.ac.jp.

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