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Maternal Passive Smoking And Risk Of Small For Gestational Age Among Non-Smoking Chinese Women

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Abstract

Maternal active smoking is an established risk factor for small for gestational age (SGA). The role of maternal passive smoking in SGA, however, is unclear. The present study analyzed data from a birth cohort study conducted in Lanzhou, China between 2010 and 2012 including 8,638 non-smoking women who delivered singleton live births. Among those, 775 were SGA and 7,863 were appropriate for gestational age (AGA). Multivariate logistic regression models were used to calculate odds ratios (ORs) and 95% confidence intervals (95% CIs). Potential confounding variables included in the final models were maternal age, education, employment status during pregnancy, parity, maternal pre-pregnancy body mass index (BMI), gestational hypertension, prior delivery of a low birth weight (LBW) infant, and total energy intake during pregnancy. Exposure to passive smoking during pregnancy was associated with an increased risk of SGA (OR=1.29, 95% CI: 1.08, 1.54). Risk of SGA increased with increasing duration of exposure (P_{trend}=0.003). Passive smoking exposure at home was associated with greater risk compared to exposure at other locations (OR=1.35, 95% CI: 1.11, 1.64 and OR=1.13, 95% CI: 0.78, 1.65, respectively). The results suggested a positive association between maternal passive smoking and risk of SGA.

Keywords: birth cohort, passive smoking, small for gestational age, SGA, China

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1 Introduction

Small for gestational age (SGA), which is usually defined as a birth weight below the 10th percentile of the gestational age- and gender-specific population standard, is often used as a proxy for intrauterine growth retardation (IUGR) [1, 2, 6]. IUGR, a term describing a failure of the fetus to achieve its growth potential, is a major public health issue [1]. IUGR is an important cause of perinatal mortality and morbidity and is related to various adult-onset chronic diseases, such as diabetes, obesity, hypertension, dyslipidemia, and metabolic syndrome [2, 3]. The prevalence of IUGR is estimated to be 4-8% among pregnancies in developed countries and up to 27% in developing countries, whereas the expenditures pertaining to IUGR account for more than half of the costs incurred for all neonates [1, 4, 5].

Maternal active smoking is an established risk factor for SGA [7-12]. The role of maternal passive smoking in SGA, however, is less clear. Some studies have shown that maternal passive smoking is associated with an increased risk of SGA [13-24], while others saw no association [25-31]. Ahluwalia et al. found that maternal passive smoking increased the risk of SGA birth among women aged 30 years or older, but no significant association was seen among younger mothers [32]. Three meta-analyses have suggested a non-significant positive association between maternal passive smoking and SGA [19, 33, 51]. However, the heterogeneity among the studies was significant. Varying definitions of maternal passive smoking, multiple measurements and levels of exposure, incomplete information on confounders, and variations in genetic

susceptibility in study populations may contribute to the inconsistent results. Additionally, most early studies included both active and non-active smokers as their study population. As a strong risk factor for SGA, maternal active smoking may create or mask an association between maternal passive smoking and SGA. It is ideal to study the association between passive smoking and SGA among never smokers.

The Chinese population contains a high proportion of non-smoking women. Though China is the largest tobacco consuming country in the world, the distribution of active smokers varies widely by gender. According to the Global Adult Tobacco Survey in 2010, more than half (52.9%) of men but only 2.4% of women in China were active smokers [34]. This provides a unique opportunity to study maternal passive smoking and SGA among non-active smoking women. In light of the inconclusive findings linking maternal passive smoking and SGA, we analyzed data from a birth cohort study in Lanzhou, China to test the hypothesis that maternal exposure to passive smoking is associated with an increased risk of SGA among non-smoking women. Additionally, we investigated whether the association varied by timing, duration and location of exposure.

2 Literature review

While maternal active smoking has been well established as a risk factor of SGA, the effects of maternal passive smoking on risk of SGA have been less well studied and are less consistent in

the previous literatures.

A total of 20 studies investigated the association between maternal passive smoking exposure during pregnancy and risk of SGA were reviewed [13-32]. The majority of these studies reported either significantly [15, 16, 20, 21] or non-significantly [13, 14, 17-19, 22-24, 32] elevated risk of SGA associated with maternal passive smoking, while several others found no association [25-31].

Among the 20 reviewed studies, maternal passive smoking was collected by self-report questionnaire in 18 studies [13, 15-20, 22-32], or biologically in two studies using nicotine and/or cotinine levels in hair [14, 21]. Maternal passive smoking was assessed either as domestic exposure (exposure at home) in 7 studies [13, 15-17, 24, 26, 32], or as domestic and occupational exposure (exposure at work) in 8 studies [18-20, 22, 23, 25, 28, 31]. The remaining 5 studies assessed maternal passive smoking exposure at any location (at home, at work, and/or at other locations) [14, 21, 27, 29, 30].

In 7 out of the 20 studies, maternal passive smoking exposure were assessed using prospective cohorts [20, 25-29, 32]. Ten studies used retrospective ascertainment of exposure [13, 14, 16-19, 22-24, 31], and recorded exposure data usually within one month after delivery. The remaining three studies used a case-control design in which cases were SGA [15, 21, 30]. Four studies

included only term infants with gestational age ≥37 weeks [22, 24, 30, 31], and the remaining studies recruited both term and preterm neonates.

There were 4 studies conducted in East Asian populations [13, 24, 25, 27]. All of them reported either a non-significantly positive association between maternal passive smoking exposure and risk of SGA [13, 24] or no association [25, 27].

3 Methods and Materials

The present study was based on data from a birth cohort study which was conducted at the Gansu Provincial Maternity and Child Care Hospital (GPMCCH), the largest maternity and child care hospital in Lanzhou, China.

3.1 Study population

The birth cohort study design has been described previously [35]. Briefly, a total of 14,535 pregnant women came to the hospital for delivery between 2010-2012. After exclusion of ineligible women, 14,359 women who aged 18 years or older, had no mental illness, and were with gestational age ≥20 completed weeks were eligible to participant in the study. Of those, 3,712 refused to participate and 105 did not complete in-person interviews, which yielded 10,542 (73.4%) women participated in the study.

All study procedures were approved by the Human Investigation Committees at GPMCCH and Yale University. Each participant was informed of the study procedure upon their arrival at the hospital for delivery. After obtaining written consent, participants were interviewed by trained study interviewers using a standardized and structured questionnaire either before or after delivery in the maternity wards. The majority of women (84%) were interviewed within 1 to 3 days after delivery. Information on maternal passive smoking exposure and potential confounders (demographic factors, reproductive and medical history, alcohol and tea consumption, physical activity, occupational and residential history, and dietary intake) were collected via questionnaire. Information on birth weight and pregnancy complications was abstracted from medical records.

3.2 Exposure assessment

Active smokers were defined as ever smokers who had ever smoked one or more cigarettes per day for at least one month. 85 active smokers were excluded from the study population.

Passive smokers were defined as women who were exposed to someone else's cigarette smoke during pregnancy. For passive smokers, information on exposure included whether or not they were exposed to passive smoking at home (yes/no), at work (yes/no), and/or in any other places (yes/no) during pregnancy, how many hours per day had the family members smoked in front of the pregnant women, and how many hours per day had the pregnant women exposed to someone

else's cigarette smoke at work and/or other locations. Exposure to passive smoking at home was defined as exposed to any family member's cigarette smoke at home. Information on duration (hours per day) and location (at home or other location) of passive smoking were asked separately for each trimester.

3.3 Outcome definition

SGA birth was defined as an infant born with a birth weight below the 10th percentile of the gestational age- and gender-specific birth weight standards for Chinese newborns [6]. Gestational age at delivery was calculated in completed weeks from the first day of the last menstrual period. Large for gestational age (LGA) birth was defined as an infant born with a birth weight above the 90th percentile using the same standards. Neonates who weighed between the 10th and 90th percentiles were defined as appropriate for gestational age (AGA) births. The range of gestational age in the Chinese national standard was from 28 to 44 weeks. For the neonates with gestational age 22 to 27 weeks, the US national reference based on 2009-2010 US live births was used as a surrogate standard [36]. Since no gestational age- and gender-specific birth weight standards were available for gestational age less than 22 weeks, 4 participants with gestational age less than 22 weeks were excluded. After further exclusion of individuals with missing birth weight (n=39), and those who were LGA (n=1,413), the final sample size was 8,638 (775 SGA and 7,863 AGA).

3.4 Statistical analysis

Chi-square test and Fisher's exact test were performed to compare the frequency distribution of selected characteristics between SGA and AGA and between passive smoking exposed and non-exposed. Means and standard deviations (SDs) of exposure duration by exposure timing and locations were assessed by student's t-test. Logistic regression models were used to estimate odds ratios (ORs) and 95% confidence intervals (95% CIs) for the association between maternal passive smoking during pregnancy and SGA. We also examined the associations by exposure timing (first, second, and/or third trimesters), duration (<1 hour/day or ≥1 hour/day for estimating ORs and 95% CIs, and continuous for estimating P_{trend}s) and location (at home or at other locations). Definition of exposure duration and location was consistent with previous study [35]. Cut-off of exposure duration was based on the distribution of duration values (Mean ± SD = 0.92 ± 1.81 hours per day) and previous study [35].

The regression models were adjusted for maternal age (continuous), education (≤12 or ≥13 years), employment status during pregnancy (yes or no), parity (primiparity or pluriparity), maternal pre-pregnancy body mass index (BMI) (≤18.5, 18.6-23.9, ≥24 kg/m^2, cut-off for Chinese [54]), gestational hypertension (yes or no), prior delivery of a low birth weight (LBW, <2,500 g) infant (yes or no), and total energy intake during pregnancy (≤1425.9, 1426.0-1683.4, 1683.5-1984.6, ≥1984.7 kcal/day, quartiles). Additional adjustment for family income, maternal weight gain during pregnancy, maternal exercise during pregnancy, gestational diabetes,

maternal anemia, and alcohol consumption during pregnancy did not result in material changes in the observed associations and thus were not included in the final models.

We performed linear regression analysis to estimate the decrease in mean birth weight attributed to passive smoking exposure before and after controlling for the potential confounders, respectively. We also performed stratified analyses by gestational age, maternal age, pre-pregnancy BMI, parity, gestational hypertension, and maternal anemia to assess potential effect modification. Sensitivity analyses were also performed by using the US national reference as the only standard to re-define SGA.

All tests were two-sided with α=0.05. Analyses were conducted using SAS software, version 9.3 (SAS Institute, Inc., Cary, North Carolina).

4 Results

4.1 Description of study population

There were 1660 (19.2%) women who reported that they had ever been exposed to passive smoking during pregnancy.

Table 1 presents the distributions of demographic and pregnancy-related characteristics in non-smoking women with SGA and AGA births. Women who gave birth to SGA infants were

more likely to be younger, less educated, unemployed during pregnancy, and had lower family income. Women who gave birth to SGA infants were also more likely to have low or high pre-pregnancy BMI, have less total energy intake, have gained less weight during pregnancy, have preterm delivery, be multiparous, and have previously delivered a LBW infant. Women who were diagnosed with gestational hypertension were also more likely to deliver SGA infants. Distributions of maternal physical activity, alcohol consumption during pregnancy, gestational diabetes, and maternal anemia were similar between SGA and AGA neonates.

The distributions of selected maternal characteristics between passive smokers and non-passive smokers are presented in Table 2. Passive smokers were younger and less educated, and had lower family income. Passive smokers were also more likely to have preterm delivery, be multiparous, diagnosed with anemia, physically active, report higher alcohol consumption, and report lower total energy intake during pregnancy. Distributions of employment status during pregnancy, maternal pre-pregnancy BMI and weight gain during pregnancy, gestational hypertension and diabetes, and history of delivery LBW infant were similar among passive smokers and non-passive smokers.

The average duration of exposure to maternal passive smoking was 0.92 hours per day with SD 1.81 hours per day. Compared to exposure at home, exposure at other locations had a greater duration (0.87 ± 1.79 hours per day and 1.15 ± 1.86 hours per day, respectively). The average

intensities of exposure were similar with respect to different trimesters (Table 3).

4.2 Primary analysis

As shown in Table 4, exposure to passive smoking during pregnancy was associated with an increased risk of SGA (OR=1.29, 95% CI: 1.08, 1.54). The observed associations were slightly stronger for the exposure during the second or third trimesters (OR=1.33, 95% CI: 1.10, 1.60 and OR=1.35, 95% CI: 1.11, 1.64, respectively) as compared to the first trimester (OR=1.24, 95% CI: 1.03, 1.49). The risk of SGA increased with increasing duration of exposure (P_{trend}=0.003 for the entire pregnancy, P_{trend}=0.009 for the first trimester, P_{trend}<0.001 for the second and third trimesters) (Table 5).

When the association was assessed by exposure locations (Table 6), exposure to passive smoking at home showed a greater risk as compared to exposure at other locations (OR=1.35, 95% CI: 1.11, 1.64 and OR=1.13, 95% CI: 0.78, 1.65, respectively). Similar associations were found with respect to exposure during different trimesters.

4.3 Stratified analysis

Stratified analyses were performed among preterm and term births. When the analyses were restricted to term births, the results were consistent with primary results (Table 7). Among term births, exposure to passive smoking during pregnancy was associated with an increased risk of

SGA (OR=1.22, 95% CI: 1.00, 1.49). Among preterm births, maternal exposure to passive smoking was associated with greater risk of SGA (OR=1.71, 95% CI: 1.11, 2.65) (table 8). However, the risk difference between term and preterm births was non-significant ($P_{interaction}$=0.373, data not shown).

Stratified analyses were further conducted by maternal age, pre-pregnancy BMI, parity, gestational hypertension, and maternal anemia. The observed associations between passive smoking and SGA were significantly stronger among women diagnosed with gestational hypertension as compared to women without gestational hypertension (OR=2.32, 95% CI: 1.39, 3.87 and OR=1.18, 95% CI: 0.97, 1.43, respectively; $P_{interaction}$=0.012) (Table 9). Maternal age, pre-pregnancy BMI, parity, and maternal anemia did not significantly modify the association between maternal passive smoking and risk of SGA ($P_{interaction}$=0.816, 0.518, 0.804, and 0.125, respectively). Similar patterns were observed for different trimesters (data not shown).

4.4 Sensitivity analysis

Sensitivity analyses showed that the association between maternal passive smoking exposure and risk of SGA did not materially changed when the US national reference were used as the only standard to define SGA (OR=1.33, 95% CI: 1.14, 1.57) (Table 10). Therefore, application of different population standards to define SGA might not affect the observed association.

5 Discussion

This study found that maternal passive smoking was associated with elevated risk of SGA, and risk increased with increasing duration of exposure. The study also suggested that risk was greater for those exposed to passive smoking at home compared to other locations. The risk was similar among term and preterm births. Furthermore, gestational hypertension might modify the association between passive smoking and SGA.

Passive smoke, also called environmental tobacco smoke (ETS), is a complex and dynamic system. It consists of more than 7,000 toxic chemicals, including nicotine, tar, carbon monoxide, nitrogen oxide, and polycyclic aromatic hydrocarbons (PAHs) [38]. The concentrations of chemicals and sizes of particles in passive smoke differ slightly from active smoke. For example, the fraction of nicotine in the gas phase is higher in passive smoke as compared to active smoke [39]. Passive smokers could be exposed to higher concentration of nicotine and suffer more from nicotine-induced uterine vasoconstriction [9, 40]. Passive smoke also contains smaller particles than active smoke, which can get deeper into the lung, be uptaken more from the lung to the circulation, and cause more severe adverse reproductive effects [38]. Dejmek et al. found a significant association between SGA and exposure to particles and PAHs [41], and also observed significantly increased levels of bulky DNA adducts in the placentas of mothers who were exposed to passive smoking and mothers who delivered SGA babies [42]. Therefore, it is biologically plausible that passive smoking increases the risk of SGA.

It has been reported that exposure to passive smoking during later period in the pregnancy had a stronger effect on reduction of birth weight as compared to exposure during early pregnancy [52]. We also observed slightly greater risk of SGA associated with passive smoking during the second and third trimesters as compared to the first trimester. The crude mean difference in birth weight between non-exposed and exposed women was 46 g in our study. After adjustment for potential confounders, the mean difference was 25 g. Our reported decreases in birth weight were comparable to the 33 g reduction reported in a recent meta-analysis [33].

This study also found that exposure to passive smoking at home showed a greater risk of SGA as compared to exposure at other locations. This finding was consistent with a previous study which reported a positive association between SGA and maternal passive smoking exposure at home compared to other locations [29]. Although the average duration of exposure was smaller at home (0.87 hours per day, SD: 1.81 hours per day) compared to other locations (1.15 hours per day, SD: 1.86 hours per day), it is possible that the concentrations of ETS were higher in the home due to confined space and poor ventilation. Because the number of women who exposed to passive smoking at other locations were relatively small as compared to those exposed at home, the non-significant results from other locations could be due to small sample size.

A number of studies have investigated the association between maternal passive smoking

exposure during pregnancy and risk of SGA [13-32]. While the majority of these studies reported either significantly [15, 16, 20, 21] or non-significantly [13, 14, 17-19, 22-24, 32] elevated risk of SGA associated with passive smoking, several studies found no association [25-31]. Comparison of results across studies is a major challenge. Passive smoking was defined as paternal smoking [13, 24], self-reported exposure to passive smoke during pregnancy [20, 32], number of smokers in the home during pregnancy [15], number of cigarettes smoked in the presence of the mother [17], and concentrations of biomarkers (such as cotinine and nicotine) measured in maternal hair samples [14, 21]. Most studies defined SGA as birth weight below the 10th percentile of the gestational age- and gender-specific population standards [13, 17, 21-26]. However, one study used 5th percentile [15], and several others defined SGA as a birth weight being 1.5 or 2 standard deviations below the gestational age-specific mean birth weight of the general population [20, 27, 29, 30, 32].

Zhang and Ratcliffe reported a non-significant decrease in birth weight and increased proportion of SGA among infants exposed to prenatal ETS in a Chinese case-control study conducted in Shanghai, China [24]. However, in this study prenatal ETS exposure was defined as paternal smoking, and included no measure of duration or mention of other household smokers or other sources of ETS exposure outside of the home. This method of assessment could potentially misclassify true ETS exposed women as unexposed and bias results toward the null. Additionally, authors did not account for certain potential confounders such as maternal BMI, pregnancy

complications, and total energy intake during pregnancy.

Pogodina et al. reported that maternal active smoking during pregnancy was a potential effect modifier of the association between passive smoking and SGA. They found a positive association between passive smoking and SGA among non-smoking women but no association among smoking women [5]. A small number of studies have restricted to non-smoking women [23, 24, 29] and two suggested a positive association, consistent with our study findings.

We found significantly higher risk of SGA associated with passive smoking among women who were diagnosed with gestational hypertension as compared to women without gestational hypertension. The mechanism of this effect modification is still unclear. A potential explanation could be placental dysfunction, which is closely associated with gestational hypertension [53]. Toxic chemicals in tobacco smoke can cause placental vasoconstriction and increase carboxyhemoglobin levels of the placental arteries, resulting in fetal hypoxia [9, 40]. Mothers with gestational hypertension may have impaired placental microcirculation, and are thus more susceptible to adverse effects of passive smoking on placental microcirculation compared to healthy women. Ahluwalia et al. reported that the association between passive smoking and SGA was stronger among mothers aged 30 years or older [32]. However, age did not modify the results in our study.

In our study, similar to many prior epidemiologic studies examining the association between passive smoking and SGA, maternal exposure to active and passive smoking were collected retrospectively by self-report. Therefore, potential recall bias cannot be ruled out. Additionally, women might underreport exposure to passive smoking due to social desirability tendency, or potentially because they are unaware of their exposure [47, 48], resulting in non-differential misclassification of exposure and underestimation of the true association. However, several studies indicated that self-reported active and passive smoking exposure during pregnancy was as reliable as appropriate biomarkers [14, 49, 50].

This study excluded both current and former smokers, eliminating potential differences in health outcomes for active versus passive smokers. All study participants were Chinese, minimizing differences in genetic susceptibility to passive smoking by ethnic group. Detailed information on potential confounding factors were collected and controlled for in the analysis. Birth outcomes and maternal complications during pregnancy were obtained from medical records, which minimized misclassification. SGA was defined by the most recent reference of gestational age- and gender-specific birth weight percentiles for Chinese newborns (2006-2010) [6]. Thus, the misclassification of outcome variable should also be minimal.

6 Conclusion

In conclusion, this study supports the hypothesis that maternal passive smoking is associated

with an increased risk of SGA. Future studies should be conducted to examine gestational hypertension as an effect modifier of the relationship between passive smoking and SGA. Our findings indicated a strong need for public health campaigns to increase awareness of the negative health effects of passive smoking, especially during pregnancy, in order to protect the health of women and infants.

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Appendix

A.1 List of abbreviations

- AGA: Appropriate for gestational age
- BMI: Body mass index
- CI: Confidence interval
- ETS: Environmental tobacco smoke
- GPMCCH: Gansu Provincial Maternity and Child Care Hospital
- IUGR: Intrauterine growth retardation
- LBW: Low birth weight
- LGA: Large for gestational age
- OR: Odds ratio
- PAH: Polycyclic aromatic hydrocarbon
- SD: Standard deviation
- SGA: Small for gestational age

A.2 List of previous studies on maternal passive smoking and small for gestational age (SGA)

Author (by year)	Setting	Design	Sample size	Exposure assessment	Exposure measurement	Result OR (95% CI)	Conclusion
Ko (2014)[13]	Taiwan 2005-2006	Birth cohort study	21,248	Retrospectively self-report	Paternal smoking	Preconception: 1.12 (0.90-1.40) First trimester: 1.10 (0.88-1.38) Second and third trimester: 1.09 (0.87-1.36)	Non-significantly positive association
Miyake (2013)[25]	Japan 2007-2008	Prospective cohort study	1,565	Self-report	Domestic & occupational	Exposure at home: 0.80 (0.51-1.24) Exposure at work: 0.96 (0.48-1.78)	No association
Almeida (2011)[14]	Montreal, Canada 1999-2004	Nested case-control study	431	Hair biomarkers	Hair nicotine & cotinine	1.66 (0.81-3.42)	Non-significantly positive association
Fantuzzi (2008)[15]	Italy 1999-2000	Case-control study	84 cases 858 controls	Retrospectively self-report	Number of smokers at home	2.51 (1.59-3.95)	Significantly positive association
Steyn (2006)[26]	South Africa 1990	Prospective cohort study	1,593 (7.3% SGA)	Self-report	Number of smokers at home	*Chi-square test, no OR and 95% CI were reported	No association
Goel (2004)[16]	India	Cross-sectional study	576	Retrospectively self-report	Domestic	2.10 (1.27-3.48)	Significantly positive association

A.2 List of previous studies on maternal passive smoking and small for gestational age (SGA) (continued)

Author (by year)	Setting	Design	Sample size	Exposure assessment	Exposure measurement	Result OR (95% CI)	Conclusion
Dejmek (2002)[17]	Czech Republic 1994-1999	Retrospective study	6,866	Self-report	Domestic	1.08 (0.82-1.43)	Non-significantly positive association
Matsubara (2000)[27]	Japan 1989-1991	Prospective cohort study	7,411	Self-report	Any exposure	Paternal smoking: 0.95 (0.72-1.26) Any other exposure: 0.95 (0.71-1.26)	No association
Windham (2000)[28]	California, USA 1990-1991	Prospective cohort study	4,454	Self-report	Domestic & occupational	0.62 (0.25-1.50)	No association
Hanke (1999)[18]	Poland 1996-1997	Birth cohort study	1,757 (111 SGA)	Retrospectively self-report	Domestic & occupational	1.26 (0.68-2.35)	Non-significantly positive association
Sadler (1999)[29]	Connecticut, USA 1988-1992	Nested case-control study	2,283	Prospectively self-report	Any exposure	0.82 (0.51-1.33)	No association
Windham (1999)[19]	USA 1986-1987	Retrospective study	992	Self-report	Paternal smoking & occupational	1.4 (0.8-2.5)	Non-significantly positive association
Dejin-Karlsson (1998)[20]	Malmo, Sweden 1991-1992	Prospective cohort study	826 (6.7% SGA)	Self-report	Domestic & occupational	3.9 (1.4-10.7)	Significantly positive association

A.2 List of previous studies on maternal passive smoking and small for gestational age (SGA) (continued)

Author (by year)	Setting	Design	Sample size	Exposure assessment	Exposure measurement	Result OR (95% CI)	Conclusion
Nafstad (1998)[21]	Norway 1995	Case-control study	58 cases 105 controls	Hair biomarkers	Hair nicotine	4.2 (1.5-11.5)	Significantly positive association
Ahluwalia (1997)[32]	USA 1989-1994	Prospective cohort study	17,412	Self-report	Domestic	Maternal age <30 years: 0.97 (0.75-1.26) Maternal age ≥30 years: 1.28 (0.76-2.15)	No association among younger women; Non-significantly positive among older women
Chen (1995)[30]	California, USA 1991	Case-control study	111 cases 124 controls	Retrospectively self-report	Any exposure	0.47 (0.13-1.69)	No association
Roquer (1995)[22]	Spain	Retrospective study	129	Self-report	Domestic & occupational	*Chi-square test, no OR and 95% CI were reported	Non-significantly positive association
Fortier (1994)[23]	Quebec, Canada 1989	Birth cohort study	4,644	Retrospectively self-report	Domestic & occupational	1.09 (0.85-1.39)	Non-significantly positive association
Zhang (1993)[24]	Shanghai, China 1986-1987	Birth cohort study	1,785	Retrospectively self-report	Paternal smoking at home	*Chi-square test, no OR and 95% CI were reported	Non-significantly positive association
Lazzaroni (1990)[31]	Italy	Birth cohort study	1,004	Retrospectively self-report	Domestic & occupational	*Chi-square test, no OR and 95% CI were reported	No association

Table 1. Distribution of demographic and pregnancy-related characteristics among non-smokers (n=8,638) by gestational age weight.

	Small for gestational age (n=775)		Appropriate for gestational age (n=7,863)		P
	Number	%	Number	%	
Maternal age (years)					<0.001
<25	169	21.8	1,274	16.2	
25-29	331	42.7	3,799	48.3	
≥30	275	35.5	2,790	35.5	
Education (years)					<0.001
≤12	414	53.4	3,015	38.3	
≥13	345	44.5	4,701	59.8	
Missing	16	2.1	147	1.9	
Employment					<0.001
Yes	344	44.4	4,109	52.3	
No	431	55.6	3,754	47.7	
Family income (￥/person)					<0.001
<2000	255	32.9	1,834	23.3	
2000-4000	320	41.3	3,684	46.9	
>4000	116	15.0	1,605	20.4	
Missing	84	10.8	740	9.4	
Parity					0.003
1	528	68.1	5,750	73.1	
2+	247	31.9	2,113	26.9	
Maternal prepregnancy BMI (kg/m²)					<0.001
≤18.5	195	25.2	1,687	21.5	
18.6-23.9	462	59.6	5,181	65.9	
≥24	77	9.9	742	9.4	
Missing	41	5.3	253	3.2	
Maternal weight gain during pregnancy (kg)					<0.001
1st tertile (≤14.5)	329	42.5	2,458	31.3	
2nd tertile (14.6-19)	248	32.0	2,833	36.0	
3rd tertile (≥19.1)	145	18.7	2,263	28.8	
Missing	53	6.8	309	3.9	

Table 1. Distribution of demographic and pregnancy-related characteristics among non-smokers (n=8,638) by gestational age weight (continued).

	Small for gestational age (n=775)		Appropriate for gestational age (n=7,863)		P
	Number	%	Number	%	
Maternal exercise during pregnancy					0.171
Yes	636	82.1	6,639	84.4	
No	122	15.7	1,098	14.0	
Missing	17	2.2	126	1.6	
Gestational hypertension					<0.001
Yes	114	14.7	304	3.9	
No	661	85.3	7,559	96.1	
Gestational diabetes					0.229
Yes	3	0.4	61	0.8	
No	772	99.6	7,802	99.2	
Maternal anemia					0.273
Yes	98	12.7	891	11.3	
No	677	87.4	6,972	88.7	
Prior delivery of a low birth weight infant					<0.001*
Yes	13	1.7	20	0.3	
No	762	98.3	7,843	99.8	
Alcohol consumption during pregnancy					0.639*
Yes	2	0.3	13	0.2	
No	773	99.7	7,850	99.8	
Total energy intake during pregnancy					<0.001
1st quartile (≤1425.9 kcal/day)	268	34.6	1,900	24.2	
2nd quartile (1426.0-1683.4 kcal/day)	192	24.8	1,909	24.3	
3rd quartile (1683.5-1984.6 kcal/day)	143	18.5	1,948	24.8	
4th quartile (≥1984.7 kcal/day)	154	19.9	1,935	24.6	
Missing	18	2.3	171	2.2	
Gestational age (weeks)					<0.001
<37	151	19.5	733	9.3	
≥37	624	80.5	7,130	90.7	

* The frequency distribution was compared by Fisher's exact test.

Table 2. Distribution of demographic and pregnancy-related characteristics among non-smokers (n=8,638) by passive smoking exposure.

	Passive smoking (n=1,660)		Non-passive smoking (n=6,978)		P
	Number	%	Number	%	
Maternal age (years)					<0.001
<25	338	20.4	1,105	15.8	
25-29	749	45.1	3,381	48.5	
≥30	573	34.5	2,492	35.7	
Education (years)					<0.001
≤12	806	48.6	2,623	37.6	
≥13	833	50.2	4,213	60.4	
Missing	21	1.3	142	2.0	
Employment					0.152
Yes	882	53.1	3,571	51.2	
No	778	46.9	3,407	48.8	
Family income (￥/person)					<0.001
<2000	499	30.1	1,590	22.8	
2000-4000	758	45.7	3,246	46.5	
>4000	288	17.4	1,433	20.5	
Missing	115	6.9	709	10.2	
Parity					<0.001
1	1,115	67.2	5,163	74.0	
2+	545	32.8	1,815	26.0	
Maternal prepregnancy BMI (kg/m²)					0.390
≤18.5	357	21.5	1,525	21.9	
18.6-23.9	1,092	65.8	4,551	65.2	
≥24	165	9.9	654	9.4	
Missing	46	2.8	248	3.6	
Maternal weight gain during pregnancy (kg)					0.432
1st tertile (≤14.5)	555	33.4	2,232	32.0	
2nd tertile (14.6-19)	599	36.1	2,482	35.6	
3rd tertile (≥19.1)	437	26.3	1,971	28.3	
Missing	69	4.2	293	4.2	

Table 2. Distribution of demographic and pregnancy-related characteristics among non-smokers (n=8,638) by passive smoking exposure (continued).

	Passive smoking (n=1,660)		Non-passive smoking (n=6,978)		P
	Number	%	Number	%	
Maternal exercise during pregnancy					0.002
Yes	1,444	87.0	5,831	83.6	
No	198	11.9	1,022	14.7	
Missing	18	1.1	125	1.8	
Gestational hypertension					0.270
Yes	89	5.4	329	4.7	
No	1,571	94.6	6,649	95.3	
Gestational diabetes					0.171
Yes	8	0.5	56	0.8	
No	1,652	99.5	6,922	99.2	
Maternal anemia					<0.001
Yes	233	14.0	756	10.8	
No	1,427	86.0	6,222	89.2	
Prior delivery of a low birth weight infant					0.463
Yes	8	0.5	25	0.4	
No	1,652	99.5	6,953	99.6	
Alcohol consumption during pregnancy					0.015*
Yes	7	0.4	8	0.1	
No	1,653	99.6	6,970	99.9	
Total energy intake during pregnancy					<0.001
1st quartile (≤1425.9 kcal/day)	517	31.1	1,651	23.7	
2nd quartile (1426.0-1683.4 kcal/day)	412	24.8	1,689	24.2	
3rd quartile (1683.5-1984.6 kcal/day)	359	21.6	1,732	24.8	
4th quartile (≥1984.7 kcal/day)	350	21.1	1,739	24.9	
Missing	22	1.3	167	2.4	
Gestational age (weeks)					0.037
<37	193	11.6	691	9.9	
≥37	1,467	88.4	6,287	90.1	

* The frequency distribution was compared by Fisher's exact test.

Table 3. Means and standard deviations of duration of maternal passive smoking among exposed women by exposure locations and trimesters.

Timing of exposure	Exposure at any location	Exposure at home	Exposure at other locations
	Means±SD (hours/day)		
During whole pregnancy	0.92 ± 1.81	0.87 ± 1.79	1.15 ± 1.86
During the first trimester	1.07 ± 1.97	0.99 ± 1.95	1.39 ± 2.06
During the second trimester	1.10 ± 2.10	1.01 ± 2.10	1.45 ± 2.09
During the third trimester	1.10 ± 2.12	0.94 ± 1.93	1.66 ± 2.61

Table 4. Associations between passive smoking and small for gestational age.

Passive smoking	Appropriate for gestational age	Small for gestational age	
		N	OR* (95% CI)
No	6,392	586	1.00
Yes	1,471	189	1.29(1.08-1.54)
During the first trimester	1,380	171	1.24(1.03-1.49)
During the second trimester	1,254	167	1.33(1.10-1.60)
During the third trimester	1,107	151	1.35(1.11-1.64)

*Adjusted for maternal age (continuous), education, employment, parity, maternal prepregnancy BMI, gestational hypertension, history of delivery low birth weight infant, and total energy intake during pregnancy.

Table 5. Associations between passive smoking and small for gestational age by duration of exposure.

Duration of passive smoking (hours/day)	Appropriate for gestational age	Small for gestational age	
		N	OR* (95% CI)
No passive smoking	6,392	586	1.00
During the entire pregnancy			
<1	1,075	132	1.23(1.00-1.51)
≥1	396	57	1.47(1.09-1.98)
P for trend			0.003
During the first trimester			
<1	920	107	1.13(0.91-1.42)
≥1	460	64	1.45(1.09-1.91)
P for trend			0.009
During the second trimester			
<1	834	102	1.20(0.96-1.51)
≥1	420	65	1.58(1.19-2.09)
P for trend			<0.001
During the third trimester			
<1	740	94	1.24(0.97-1.57)
≥1	367	57	1.58(1.17-2.13)
P for trend			<0.001

*Adjusted for maternal age (continuous), education, employment, parity, maternal prepregnancy BMI, gestational hypertension, history of delivery low birth weight infant, and total energy intake during pregnancy.

Table 6. Associations between passive smoking and small for gestational age by location of exposure.

Location of passive smoking	Appropriate for gestational age	Small for gestational age	
		N	OR* (95% CI)
No passive smoking	6,392	586	1.00
During the entire pregnancy			
Home	1,098	156	1.35(1.11-1.64)
Other locations	354	32	1.13(0.78-1.65)
During the first trimester			
Home	1,022	139	1.28(1.04-1.56)
Other locations	336	32	1.19(0.82-1.74)
During the second trimester			
Home	925	138	1.40(1.14-1.72)
Other locations	309	28	1.13(0.75-1.68)
During the third trimester			
Home	841	124	1.37(1.10-1.70)
Other locations	256	26	1.27(0.83-1.93)

*Adjusted for maternal age (continuous), education, employment, parity, maternal prepregnancy BMI, gestational hypertension, history of delivery low birth weight infant, and total energy intake during pregnancy.

Table 7. Associations between passive smoking and small for gestational age among term births.

	Appropriate for gestational age	Small for gestational age	
		N	OR* (95% CI)
Passive smoking			
No	5,806	481	1.00
Yes	1,324	143	1.22(1.00-1.49)
During the first trimester	1,240	131	1.19(0.97-1.46)
During the second trimester	1,132	126	1.26(1.01-1.54)
During the third trimester	994	113	1.27(1.02-1.58)
Duration of passive smoking (hours/day)			
During the entire pregnancy			
<1	968	101	1.17(0.93-1.48)
≥1	356	42	1.35(0.96-1.89)
P for trend			0.037
During the first trimester			
<1	828	81	1.08(0.84-1.39)
≥1	412	50	1.40(1.03-1.92)
P for trend			0.011
During the second trimester			
<1	753	78	1.15(0.89-1.48)
≥1	379	48	1.45(1.05-1.99)
P for trend			0.064
During the third trimester			
<1	667	71	1.17(0.90-1.53)
≥1	327	42	1.47(1.05-2.06)
P for trend			0.094

*Adjusted for maternal age (continuous), education, employment, parity, maternal prepregnancy BMI, gestational hypertension, history of delivery low birth weight infant, and total energy intake during pregnancy.

Table 7. Associations between passive smoking and small for gestational age among term births (continued).

	Appropriate for gestational age	Small for gestational age	
		N	OR* (95% CI)
Location of passive smoking			
During the entire pregnancy			
Home	978	117	1.29(1.04-1.60)
Other locations	329	26	1.05(0.69-1.59)
During the first trimester			
Home	909	104	1.22(0.98-1.54)
Other locations	312	27	1.15(0.76-1.73)
During the second trimester			
Home	823	102	1.32(1.05-1.66)
Other locations	289	24	1.10(0.71-1.69)
During the third trimester			
Home	745	91	1.29(1.01-1.65)
Other locations	239	22	1.24(0.79-1.94)

*Adjusted for maternal age (continuous), education, employment, parity, maternal prepregnancy BMI, gestational hypertension, history of delivery low birth weight infant, and total energy intake during pregnancy.

Table 8. Associations between passive smoking and small for gestational age among preterm births.

	Appropriate for gestational age	Small for gestational age	
		N	OR* (95% CI)
Passive smoking			
No	586	105	1.00
Yes	147	46	1.71(1.11-2.65)
During the first trimester	140	40	1.49(0.94-2.35)
During the second trimester	122	41	1.87(1.18-2.97)
During the third trimester	113	38	1.91(1.18-3.09)
Duration of passive smoking (hours/day)			
During the entire pregnancy			
<1	107	31	1.56(0.94-2.59)
≥1	40	15	2.12(1.05-4.25)
P for trend			0.011
During the first trimester			
<1	92	26	1.46(0.84-2.53)
≥1	48	14	1.53(0.76-3.05)
P for trend			0.002
During the second trimester			
<1	81	24	1.63(0.93-2.88)
≥1	41	17	2.32(1.18-4.54)
P for trend			0.048
During the third trimester			
<1	73	23	1.79(1.00-3.21)
≥1	40	15	2.12(1.05-4.27)
P for trend			0.070

*Adjusted for maternal age (continuous), education, employment, parity, maternal prepregnancy BMI, gestational hypertension, history of delivery low birth weight infant, and total energy intake during pregnancy.

Table 8. Associations between passive smoking and small for gestational age among preterm births (continued).

	Appropriate for gestational age	Small for gestational age	
		N	OR* (95% CI)
Location of passive smoking			
During the entire pregnancy			
Home	120	39	1.61(1.00-2.57)
Other locations	25	6	2.02(0.76-5.35)
During the first trimester			
Home	113	35	1.46(0.90-2.38)
Other locations	24	5	1.71(0.60-4.89)
During the second trimester			
Home	102	36	1.78(1.08-2.91)
Other locations	20	4	1.56(0.49-5.04)
During the third trimester			
Home	96	33	1.75(1.05-2.92)
Other locations	17	4	1.84(0.56-6.08)

*Adjusted for maternal age (continuous), education, employment, parity, maternal prepregnancy BMI, gestational hypertension, history of delivery low birth weight infant, and total energy intake during pregnancy.

Table 9. Stratified associations between passive smoking and small for gestational age.

	Appropriate for gestational age	Small for gestational age	
		N	OR* (95% CI)
Maternal age (years)			
< 30			
Non-passive smoking	4,107	379	1.00
Passive smoking	966	121	1.26(1.01-1.57)
≥ 30			
Non-passive smoking	2,285	207	1.00
Passive smoking	505	68	1.34(0.99-1.82)
P for interaction			0.816
Maternal prepregnancy BMI (kg/m²)			
≤ 18.5			
Non-passive smoking	1,383	142	1.00
Passive smoking	304	53	1.53(1.08-2.17)
18.6-23.9			
Non-passive smoking	4,195	356	1.00
Passive smoking	986	106	1.14(0.90-1.45)
≥ 24			
Non-passive smoking	596	58	1.00
Passive smoking	146	19	1.42(0.80-2.49)
Missing			
Non-passive smoking	218	30	1.00
Passive smoking	35	11	2.11(0.87-5.11)
P for interaction			0.518

*Adjusted for maternal age (continuous), education, employment, parity, maternal prepregnancy BMI, history of delivery low birth weight infant, and total energy intake during pregnancy.

Table 9. Stratified associations between passive smoking and small for gestational age (continued).

	Appropriate for gestational age	Small for gestational age	
		N	OR* (95% CI)
Parity			
1			
Non-passive smoking	4,752	411	1.00
Passive smoking	998	117	1.26(1.01-1.57)
≥ 2			
Non-passive smoking	1,640	175	1.00
Passive smoking	473	72	1.34(0.99-1.82)
P for interaction			0.804
Gestational hypertension			
Yes			
Non-passive smoking	253	76	1.00
Passive smoking	51	38	2.32(1.39-3.87)
No			
Non-passive smoking	6,139	510	1.00
Passive smoking	1,420	151	1.18(0.97-1.43)
P for interaction			0.012
Maternal anemia			
Yes			
Non-passive smoking	694	62	1.00
Passive smoking	197	36	1.64(1.04-2.61)
No			
Non-passive smoking	5,698	524	1.00
Passive smoking	1,274	153	1.23(1.01-1.49)
P for interaction			0.125

*Adjusted for maternal age (continuous), education, employment, parity, maternal prepregnancy BMI, history of delivery low birth weight infant, and total energy intake during pregnancy.

Table 10. Associations between passive smoking and small for gestational age based on the US national reference.

	Appropriate for gestational age	Small for gestational age	
		N	OR* (95% CI)
Passive smoking			
No	6,794	725	1.00
Yes	1,535	234	1.33(1.14-1.57)
During the first trimester	1,442	212	1.28(1.08-1.51)
During the second trimester	1,311	203	1.35(1.14-1.60)
During the third trimester	1,155	184	1.37(1.15-1.64)
Duration of passive smoking (hours/day)			
During the entire pregnancy			
<1	1,127	160	1.24(1.03-1.49)
≥1	408	74	1.61(1.24-2.09)
P for trend			<0.001
During the first trimester			
<1	968	127	1.12(0.91-1.38)
≥1	474	85	1.61(1.26-2.07)
P for trend			<0.001
During the second trimester			
<1	876	119	1.17(0.95-1.44)
≥1	435	84	1.71(1.33-2.20)
P for trend			<0.001
During the third trimester			
<1	782	111	1.21(0.97-1.50)
≥1	373	73	1.72(1.32-2.25)
P for trend			<0.001

*Adjusted for maternal age (continuous), education, employment, parity, maternal prepregnancy BMI, gestational hypertension, history of delivery low birth weight infant, and total energy intake during pregnancy.

Table 10. Associations between passive smoking and small for gestational age based on the US national reference (continued).

	Appropriate for gestational age	Small for gestational age	
		N	OR* (95% CI)
Location of passive smoking			
During the entire pregnancy			
Home	1,134	194	1.43(1.20-1.71)
Other locations	382	39	1.06(0.75-1.49)
During the first trimester			
Home	1,060	172	1.35(1.12-1.62)
Other locations	361	39	1.12(0.79-1.57)
During the second trimester			
Home	960	168	1.45(1.21-1.75)
Other locations	331	34	1.05(0.73-1.52)
During the third trimester			
Home	867	151	1.43(1.18-1.74)
Other locations	278	32	1.19(0.81-1.73)

*Adjusted for maternal age (continuous), education, employment, parity, maternal prepregnancy BMI, gestational hypertension, history of delivery low birth weight infant, and total energy intake during pregnancy.