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# Childhood secondhand smoke exposure and pregnancy loss in never smokers: the Guangzhou Biobank Cohort Study

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## ABSTRACT

**Objective** Studies of secondhand smoke (SHS) exposure especially childhood SHS exposure and pregnancy loss are limited. We used baseline data of the Guangzhou Biobank Cohort Study (GBCS) to examine the association of childhood SHS exposure with a history of pregnancy loss.

**Methods** Never smoking women aged 50 years or above in GBCS from 2003 to 2008 were included. Propensity score matching (PSM) was used to control for confounding. Negative binomial regression and logistic regression were used to examine the association of childhood SHS, assessed by number of smokers in childhood household and frequency of exposure, with past pregnancy loss.

**Results** Of 19 562 women, 56.7% (11 096) had SHS exposure during childhood. In negative binomial regression, after adjusting for age, education, past occupational dust exposure, past home fuel exposure, oral contraceptive, adulthood SHS exposure, age at first pregnancy and age at first menarche, compared to non-exposure, the incidence rate ratio of one more pregnancy loss was 1.20 (95% CI 1.05 to 1.37) in those who lived with  $\geq 2$  smokers in the same household, and 1.14 (95% CI 1.04 to 1.25) in those exposed  $\geq 5$  times/week. After similar adjustment, logistic regression showed that the OR of pregnancy loss  $\geq 2$  times (versus 0 to 1 time) was 1.25 (95% CI 1.00 to 1.57) and 1.20 (95% CI 1.03 to 1.40) for high density ( $\geq 2$  smokers in the same household) and frequency ( $\geq 5$  times/week) of childhood exposure, respectively.

**Conclusions** Childhood SHS exposure was associated with higher risks of pregnancy loss in middle-aged and older Chinese women.

## INTRODUCTION

The prevalence of pregnancy loss, defined as the death of an embryo or fetus before it is able to survive independently, was 17.3% in American women of childbearing age aged 24–44 years<sup>1</sup> in 1992–2009 and 4.36–12.2% in Chinese women of childbearing age (20–49 years) in 1988–1997.<sup>2</sup> There were several possible explanations for pregnancy loss, such as occupational and environmental exposure and unhealthy lifestyle factors.<sup>3</sup> Active smoking in pregnant women or their husbands was associated with a higher risk of pregnancy loss, and the risk was greater for smoking during pregnancy.<sup>4</sup>

Compared with directly inhaled tobacco smoke or mainstream smoke, the evidence indicates that undiluted sidestream smoke, the major contributor to secondhand smoke (SHS), contains higher levels

of chemical compounds considered to be carcinogenic or toxic—including benzene, formaldehyde, catechol and N-nitrosamines.<sup>5</sup> Concerns about the harmful effects of SHS have been increasing. Some previous studies showed that maternal<sup>6–8</sup> or prenatal<sup>9</sup> SHS exposure in adulthood was associated with a higher risk of pregnancy loss, but only a few examined the association between childhood SHS exposure and pregnancy loss.<sup>10–12</sup> Since childhood is a sensitive stage, such exposure to exogenous harmful substances, during this period may lead to adverse health outcomes in adulthood.<sup>13 14</sup> Animal and human studies found that exposure to tobacco smoke adversely affected embryo development,<sup>15</sup> suggesting that SHS exposure during childhood may increase the risk of pregnancy loss at reproductive age. However, evidence from population-based studies on childhood SHS exposure and pregnancy loss in adulthood is limited. We found only one community-based study from the USA showing a positive association of SHS exposure in childhood and adulthood with the risk of pregnancy loss.<sup>10</sup> To the best of our knowledge, there are no reports from Asian populations. In China, 98% women were never smokers<sup>15</sup> but 70.5% of them<sup>16</sup> were exposed to SHS in 2010. Thus, we examined the association of childhood SHS exposure with pregnancy loss in the Guangzhou Biobank Cohort Study (GBCS), the largest population-based cohort study of middle-aged and older Chinese people in southern China.

## METHODS

### Guangzhou Biobank Cohort Study

We used GBCS baseline data for the present analysis. Details of the methods have been reported elsewhere.<sup>17</sup> Briefly, GBCS is a collaborative project among the Guangzhou 12th Hospital and the Universities of Hong Kong and Birmingham. It is an ongoing prospective cohort study on permanent Guangzhou residents aged 50 years or above, and aims to examine environmental and genetic determinants of chronic diseases. Participants were recruited from a community social and welfare association, the Guangzhou Health and Happiness Association for the Respectable Elders, which is a large unofficial organisation aligned with the Guangzhou municipal government and has more than 150 branches and ~100 000 members. Those receiving treatment for life-threatening diseases such as cancer, or who did not provide informed consent, were excluded. Information on smoking, SHS exposure (adult and childhood), personal



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disease history and other factors were collected by face-to-face computer-assisted interview.

GBCS was approved by the Medical Ethics Committee of the Guangzhou Medical Association. All participants provided written informed consent before joining the study.

### Measurement

Information on socioeconomic position and lifestyle including age, sex, education, oral contraceptive use, smoking and alcohol use was collected by a computer-assisted standardised questionnaire administered by trained interviewers. Education was assessed and classified into three groups:  $\leq$ Primary school (0–6 years), Middle school (7–12 years),  $\geq$ College ( $\geq$ 13 years). Oral contraceptive use was self-reported, and the question was as follows: Have you ever used oral contraceptives before? Childhood was defined as the period between infancy and adulthood (28 days to 18 years). This is the usual definition of childhood in the Chinese population.

### Exposure

A never smoker was defined as one who had smoked  $<100$  cigarettes in her lifetime.<sup>18</sup> Childhood SHS exposure was defined as living with one or more smokers and being exposed to the smoker's tobacco smoke for at least 15 min/day on more than 1 day/week in the same household during childhood.<sup>4</sup> Two self-reported SHS measures were used. The first was density, defined by the presence of none, one or two or more smokers living in the same household when the participant was a child. The other was frequency, categorised into no exposure, low ( $<5$  times/week) and high ( $\geq 5$  times/week) levels of exposure (one time of exposure was defined as exposure  $\geq 5$  consecutive minutes). The density and frequency of childhood SHS exposure based on the questions were shown to be associated with young age at menarche in GBCS.<sup>19</sup>

### Study outcome

Pregnancy loss was defined as the death of an embryo or fetus before it is able to survive independently.<sup>20</sup> Information on times of pregnancy loss was obtained by self-report. Frequent pregnancy loss was defined as pregnancy loss of  $\geq 2$  times (versus 0 to 1). Sensitivity analysis was conducted using a cut-off of 3 times ( $<3$  vs  $\geq 3$  times).

### Statistical analysis

We compared the demographic characteristics between participants with and without childhood SHS exposure using t-test and  $\chi^2$  test. Logistic regression was used to examine associations of childhood SHS exposure with pregnancy loss.

Propensity score matching (PSM)<sup>21–22</sup> was performed to control for differences in baseline characteristics between those with and without childhood SHS exposure. Multivariable logistic regression including age, education, past occupational dust exposure, past home fuel exposure, oral contraceptive, adulthood SHS exposure, age at first pregnancy and age at first menarche was used to obtain propensity scores for each individual. These potential confounders were selected according to their association with pregnancy loss on the basis of clinical knowledge and previous studies.<sup>23–24</sup> We then performed nearest neighbour matching of the two groups at a 1:1 fixed ratio, using a caliper width of 0.2 of the SD of the logit of the propensity score. Balance achieved by matching was assessed by examining differences in baseline variables between the childhood exposure group and no childhood exposure group before and after PSM. Negative binomial regression analysis was used

to examine the association between childhood SHS exposure and the times of pregnancy loss (counts). Univariate analysis, logistic regression and propensity score matching were conducted by SPSS V.19.0 and negative binomial regression analysis was conducted by Stata V.12.0. A two tailed  $p < 0.05$  was considered statistically significant.

### Patient involvement

No patients were involved in setting the research question or the outcome measures, and nor were they involved in the design and implementation of the study. There are no plans to involve patients in dissemination.

### RESULTS

Of 30 518 participants of GBCS recruited from September 2003 to January 2008, 20 903 (68.5%) were female never smokers. After excluding 842 women with missing information on pregnancy loss and 499 women with infertility, 19 562 were included in the present analysis (figure 1). A total of 866 (4.4%) had pregnancy loss  $\geq 2$  times and 267 (1.4%)  $\geq 3$  times. The mean age at first pregnancy was 24.7 (SD 3.6) years, and at first menarche was 15.1 (SD2.1) years (Table not shown).

Table 1 shows that 56.7% (11 096/19 562) women were exposed to SHS during childhood. Those with childhood SHS exposure were younger, had a lower level of education and prevalence of past home fuel exposure and adulthood SHS exposure, but had a higher prevalence of past occupational dust exposure and use of oral contraceptive than those without exposure (table 1). They also had a younger age at first menarche (14.9 vs 15.3 years,  $p < 0.001$ ) and an older age at first pregnancy (25.0 vs 24.5 years,  $p < 0.001$ ). After matching on the propensity score ( $n = 7782$  for each group, total included: 15 564), the SD of the logit of the propensity score width was  $< 0.2$ , suggesting a successful matching.<sup>25</sup>

Table 2 model 2 shows that, after adjusting for age, education, past occupational dust exposure, past home fuel exposure, oral contraceptive, adulthood SHS exposure, age at first pregnancy and age at first menarche, compared to non-exposure, the incidence rate ratio (IRR) for one more pregnancy loss in those with childhood SHS exposure was 1.20 (95% CI 1.05 to 1.37) for those who lived with  $\geq 2$  smokers in the same household and 1.14 (95% CI 1.04 to 1.25) for those with an exposure frequency of  $\geq 5$  times/week.

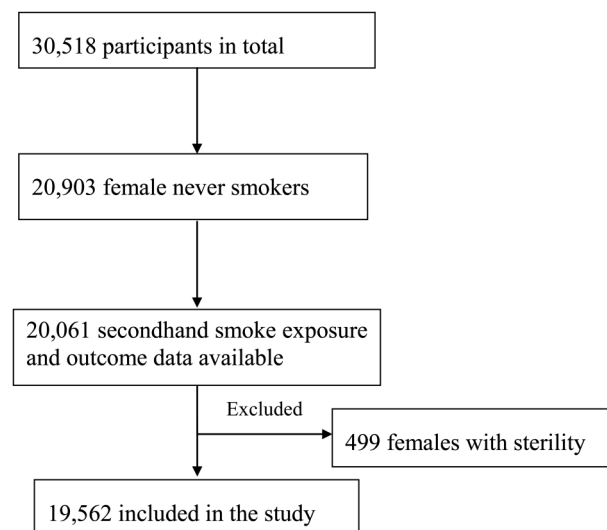


Figure 1 Flow diagram of the study population.

**Table 1 Demographic** characteristics of the participants by childhood secondhand smoke exposure at home before and after PSM

	Number (%) Total N=19 562	Childhood home exposure (before PSM)		p	Childhood home exposure (after PSM)		p Value
		Yes (n=11 096)	None (n=8466)		Yes (n=7782)	None (n=7782)	
Age (years)				<0.001			0.50
50–59	10 025 (51.3)	6502 (58.6)	3523 (41.6)		3555 (45.7)	3522 (45.3)	
60–69	7184 (36.7)	3618 (32.6)	3566 (42.1)		3267 (42.0)	3333 (42.8)	
≥70	2353 (12.0)	976 (8.8)	1377 (16.3)		960 (12.3)	927 (11.9)	
Education				<0.001			0.68
≤Primary school	9157 (46.8)	4981 (44.9)	4176 (49.3)		3711 (47.7)	3691 (47.4)	
Middle school	9232 (47.2)	5510 (49.7)	3722 (44.0)		3566 (45.8)	3559 (45.7)	
≥College	1173 (6.0)	605 (5.5)	568 (6.7)		505 (6.5)	532 (6.8)	
Past occupational dust exposure				<0.001			0.20
Yes	936 (4.8)	613 (5.5)	323 (3.8)		346 (4.4)	314 (4.0)	
None	18 626 (95.2)	10 483 (94.5)	8143 (96.2)		7436 (95.6)	7468 (96.0)	
Past home fuel exposure				0.49			<0.001
Yes	9405 (48.1)	5311 (47.9)	4094 (48.4)		4056 (52.1)	3720 (47.8)	
None	10 157 (51.9)	5785 (52.1)	4372 (51.6)		3726 (47.9)	4062 (52.2)	
Oral contraceptive				<0.001			0.001
Yes	3539 (18.1)	2152 (19.4)	1387 (16.4)		1490 (19.1)	1334 (17.1)	
None	16 023 (81.9)	8944 (80.6)	7079 (83.6)		6292 (80.9)	6448 (82.9)	
Adulthood home exposure				<0.001			0.70
Yes	4182 (21.4)	2026 (18.3)	2156 (25.5)		1750 (22.5)	1730 (22.2)	
None	15 380 (78.6)	9070 (81.7)	6310 (74.5)		6032 (77.5)	6052 (77.8)	
Childhood home exposure							
None	8466 (43.3)				7782 (100.0)	7782 (100.0)	
Yes	11 096 (56.7)						
Number of home smokers							
One	8504 (43.5)	8504 (76.6)			5938 (76.3)		
Two or more	2592 (13.3)	2592 (23.4)			1844 (23.7)		
Frequency of exposure							
<5 times/week	2790 (14.3)	2790 (25.1)			1925 (24.7)		
≥5 times/week	8306 (42.5)	8306 (74.9)			5857 (75.3)		

PSM, propensity score matching.

Table 3 model 2 shows that, after similar adjustment, compared to non-exposure, both high density (childhood SHS exposure  $\geq 2$  smokers in the same household) and high frequency of exposure ( $\geq 5$  times/week) were associated with a higher risk of frequent pregnancy loss ( $\geq 2$  times vs 0–1 time) (OR 1.25, 95% CI 1.00 to 1.57, and 1.20, 95% CI 1.03 to 1.40, respectively).

Sensitivity analysis using pregnancy loss  $\geq 3$  times as the definition of frequent pregnancy loss showed similar results for frequency  $\geq 5$  times/week (adjusted OR 1.30, 95% CI 1.00 to 1.71; table 3).

## DISCUSSION

Based on GBCS baseline data, we have shown that never smoking women exposed to SHS during childhood, particularly with higher density (greater number of smokers) and frequency, were associated with higher risks of pregnancy loss in adulthood. To the best of our knowledge, this is the first study showing the association in Asians. The major strength of our study was the comprehensive control and adjustment of a wide range of potential confounders using different statistical models. The similar results demonstrated the robustness of the results. Moreover, since childhood SHS exposure undoubtedly occurred before pregnancy loss, the problem of reverse causality, one of the major limitations in cross-sectional studies, should not be a major concern in our study.

Several previous studies showed that maternal SHS exposure in adulthood was associated with pregnancy loss,<sup>6–8</sup> but only a few examined the association between childhood SHS exposure and pregnancy loss.<sup>10–12</sup> Meeker *et al*<sup>12</sup> recruited 2162 non-smoking women from couples undergoing in vitro fertilisation or intra cytoplasmic sperm injection in three Boston, Massachusetts area clinics from August 1994 to June 2003 and found that women who reported having two parents who smoked during their childhood were associated with an increased risk of spontaneous abortion compared to those without such exposure (OR 1.8, 95% CI 1.0 to 3.0). However, information of SHS exposure frequency was not reported. Peppone *et al* showed that in women who visited a cancer hospital, SHS exposure both at home during childhood and at the time of the survey was associated with fetal loss (OR 1.39, 95% CI 1.17 to 1.66). However, the association of childhood SHS exposure with fetal loss was not statistically significant, probably because of the relatively small sample size (n=4794).<sup>11</sup> Hyland *et al*<sup>10</sup> analysed historical reproductive data of 80 762 women from the Women's Health Initiative Observational Study in the USA and showed that in never-smoking women, compared to those without SHS exposure, those with the highest levels of lifetime SHS exposure, defined as childhood exposure >10 years, adulthood home exposure >20 years and/or adulthood work exposure >10 years, had a higher risk of spontaneous abortion (OR 1.17, 95% CI 1.05 to 1.30). However, the

**Table 2** IRR of pregnancy loss times (counts) from childhood secondhand smoke exposure in female never smokers by negative binominal regression (after PSM)

	N	IRR (95% CI)		
		Crude model	Model 1	Model 2
Number of smokers				
None (reference)	7782	1	1	1
1 smoker	5938	1.02 (0.93 to 1.12)	1.03 (0.94 to 1.14)	1.03 (0.94 to 1.13)
≥2 smokers	1844	1.18 (1.03 to 1.35)*	1.21 (1.06 to 1.38)*	1.20 (1.05 to 1.37)*
P for trend		0.03	0.01	0.02
Frequency of exposure				
None (reference)	7782	1	1	1
<5 times/week	1925	0.82 (0.71 to 0.95)	0.84 (0.72 to 0.97)	0.84 (0.73 to 0.97)
≥5 times/week	5857	1.14 (1.04 to 1.25)*	1.15 (1.05 to 1.26)*	1.14 (1.04 to 1.25)*
P for trend		0.007	0.004	0.006

\*p<0.05.

Model 1: Adjusted for age.

Model 2: Adjusted for age, education, past occupational dust exposure, past home fuel exposure, oral contraceptive, adulthood passive smoke exposure, age at first pregnancy and age at first menarche.

IRR, incidence rate ratio; PSM, propensity score matching.

**Table 3** OR of frequent pregnancy loss (≥2 or ≥3 times) from childhood secondhand smoke exposure in female never smokers by logistic regression (after PSM)

	Number (%)	OR (95% CI)		
		Crude model	Model 1	Model 2
Pregnancy loss ≥2				
Number of smokers				
None (reference)	360 (4.6)	1	1	1
1 smoker	293 (4.9)	1.07 (0.91 to 1.25)	1.09 (0.93 to 1.27)	1.07 (0.91 to 1.26)
≥2 smokers	104 (5.6)	1.23 (0.99 to 1.54)	1.27 (1.01 to 1.59)*	1.25 (1.00 to 1.57)*
P for trend		0.08	0.04	0.06
Frequency of exposure				
None (reference)	360 (4.6)	1	1	1
<5 times/week	72 (3.7)	0.80 (0.62 to 1.04)	0.84 (0.65 to 1.08)	0.84 (0.65 to 1.09)
≥5 times/week	325 (5.5)	1.21 (1.04 to 1.41)*	1.22 (1.05 to 1.43)*	1.20 (1.03 to 1.40)*
P for trend		0.02	0.01	0.03
Pregnancy loss ≥3				
Number of smokers				
None (reference)	108 (1.4)	1	1	1
1 smoker	97 (1.6)	1.18 (0.90 to 1.56)	1.19 (0.91 to 1.57)	1.18 (0.89 to 1.55)
≥2 smokers	28 (1.5)	1.10 (0.72 to 1.67)	1.12 (0.74 to 1.71)	1.09 (0.72 to 1.67)
P for trend		0.39	0.33	0.46
Frequency of exposure				
None (reference)	108 (1.4)	1	1	1
<5 times/week	18 (0.9)	0.67 (0.41 to 1.11)	0.70 (0.42 to 1.15)	0.70 (0.42 to 1.15)
≥5 times/week	107 (1.8)	1.32 (1.01 to 1.73)*	1.33 (1.02 to 1.74)*	1.30 (1.00 to 1.71)*
P for trend		0.05	0.04	0.06

\*p<0.05.

Model 1: Adjusted for age.

Model 2: Adjusted for age, education, past occupational dust exposure, past home fuel exposure, oral contraceptive, total pregnancy times, adulthood passive smoke exposure, age at first pregnancy and age at first menarche.

authors did not distinguish childhood SHS exposure from adulthood SHS exposure. Thus, our results are consistent with the studies above and have provided new evidence supporting a positive association between childhood SHS exposure and the risk of pregnancy loss.

The mechanistic pathway of how childhood SHS exposure may lead to pregnancy loss is still unclear. However, earlier

evidence has shown the toxic effects of active smoking on pregnancy and fertility.<sup>26 27</sup> In vitro studies have reviewed the mechanistic pathways including the effects of active smoke exposure on uterine micro vasculature, cytotrophoblast invasion, mitotic activity, differentiation and attachment during placental development and on embryonic development.<sup>28</sup> In vivo studies also suggested that tobacco compounds exert a deleterious effect on the

process of ovarian follicle maturation.<sup>29</sup> Furthermore, some previous studies showed that SHS might alter endocrine and menstrual function in women.<sup>30–31</sup> Maternal smoking exposure was associated with retarded embryo growth in the uterus.<sup>32</sup> Since childhood is the critical development stage of all tissues, organs and systems, and children's lungs and immune system are immature, they are vulnerable to the adverse effects of SHS exposure and may subsequently suffer from adverse health outcomes in adulthood including pregnancy loss.

This study had several limitations. Since the information on exposure and pregnancy loss was based on recall, random error could not be fully ruled out, which may lead to a bias towards null. Although differential reporting of exposure was possible, the reliability of the questionnaire was tested in 200 participants with  $\kappa$  values of 0.88 and 0.96 for the two questions about smoking status, respectively.<sup>17–33</sup> Second, our sample may not be completely representative of the general older populations in southern China. However, within sex and age group, the participants had a fairly similar prevalence of chronic diseases such as diabetes and hypertension to nationally representative samples of urban Chinese.<sup>17</sup> The representativeness of our sample should not affect the internal validity substantially in the present study. The third limitation is the lack of information on the sources of childhood SHS exposure. However, since very few women smoke (<2%) in China,<sup>16</sup> most of the childhood SHS exposure was from paternal smoking. Fourth, we did not have information to assess the association of genetic abnormality with pregnancy loss. However, since chromosomal abnormality was unlikely to influence childhood SHS exposure, it could not be a confounder of the association between childhood SHS exposure and times of pregnancy loss. Fifth, we did not collect any information on ventilation system of the respondents' houses. However, since all participants in our study were aged 50 years or above and were born before 1953, the ventilation systems of the houses where they lived in childhood (ie, before 1971) were almost the same at that time in China. Thus, it is unlikely to confound the results. Sixth, since information on age of (first) pregnancy loss was not available in this study, the association of childhood SHS exposure in childhood with age of (first) pregnancy loss could not be examined. We can add questions about the age of pregnancy loss in further follow-up interviews. Finally, we cannot examine the association of SHS exposure at different periods of the life course and stages of pregnancy with pregnancy loss of our participants because of the lack of detailed information on participants' SHS exposure during each of their pregnancies.

In conclusion, our study showed that childhood SHS exposure was associated with higher risks of pregnancy loss. Given that the participants' SHS exposure reflects the societal smoking prevalence from ~50 years ago, when cigarette smoking was much less popular than today (note that annual sales of cigarettes in China increased from 80 billion in 1952 to 2375.2 billion in 2010),<sup>34</sup> a high level of exposure in China in recent years is expected, which would lead to a substantially higher healthcare burden related to pregnancy loss, if a causal relationship can be established. Our findings support the enactment of stringent national smoke-free laws and strict enforcement in China, and promotion of smoke-free homes to protect children, as well as the need for campaigns to change social norms of smoking and passive smoking.

## What this paper adds

Evidence from population-based studies on childhood secondhand smoke (SHS) exposure and pregnancy loss in adulthood is limited. We examined and found the association of childhood SHS exposure with pregnancy loss in the Guangzhou Biobank Cohort Study (GBCS), the largest population-based cohort study of middle-aged and older Chinese people in southern China.

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**Contributors** SY, LX and YH contributed to data analysis and manuscript writing. CJ, KKC, YJ and WZ contributed to study design and data collection. THL contributed to study design, manuscript revision and approval of the final submission. All authors contributed to the drafting and editing of this manuscript and approved the final version submitted for publication.

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**Competing interests** None declared.

**Patient consent** Obtained.

**Ethics approval** The study has ethics approval from the Guangzhou Medical Ethics Committee of the Chinese Medical Association, Guangzhou, China.

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