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ORIGINAL ARTICLE

Effects of maternal smoking on offspring reproductive outcomes: an intergenerational study in the North East of Scotland

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STUDY QUESTION: How does exposure to cigarette smoke *in utero* influence women's reproductive outcomes?

SUMMARY ANSWER: Women exposed to cigarette smoke *in utero* were more likely to have a pregnancy and more likely to experience miscarriage.

WHAT IS ALREADY KNOWN: Existing epidemiological studies have been inconsistent, but generally suggest a small decrease in fertility of women exposed to cigarette smoke *in utero*.

STUDY DESIGN, SIZE, DURATION: This cohort study included all women born prior to 31st December 1972 as recorded in the Aberdeen Maternity and Neonatal Databank. Exposure to maternal cigarette smoking *in utero* was retrieved from their birth records within the database. The primary outcome was any pregnancy occurring in the offspring over the course of their reproductive life. The 12 321 eligible women were followed up for 40 years for any pregnancies and the outcome of those pregnancies recorded in the same database.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Within the cohort, 3836 women were exposed to cigarette smoke and 8485 women were not exposed to cigarette smoke *in utero*. Generalized estimating equations were used to generate odds ratios (OR) and 95% CIs for all outcomes with adjustment made for all differences between groups at baseline.

MAIN RESULTS AND THE ROLE OF CHANCE: The study did not find a link between exposure to cigarette smoke *in utero* and a decrease in fertility. Women exposed to cigarette smoke *in utero* were more likely to have a pregnancy than those whose mother did not smoke; adjusted OR = 1.25 (95% CIs: 1.13–1.38). Women exposed to cigarette smoke *in utero* were also likely to have a pregnancy earlier (adjusted OR for age at first delivery ≤19 years 1.31 [95% CIs: 1.12–1.54)] than those not exposed. Women exposed to cigarette smoke *in utero* were significantly more likely to have a miscarriage than those not exposed; adjusted OR = 1.16 (95% CIs: 1.01–1.32).

LIMITATIONS, REASONS FOR CAUTION: Although the cohort in this study was large, there were women for whom exposure data was unavailable. Data on the adult circumstances of women who did not record a pregnancy was unavailable, precluding adjustment for their own smoking status or social class. In addition, women who migrated from the area or chose childlessness voluntarily were not included in the study.

WIDER IMPLICATIONS OF THE FINDINGS: Despite the wide-ranging harmful effects of cigarette smoke on foetal reproductive development, the effect at a population level remains uncertain. An increased risk of miscarriage in women exposed to cigarette smoke is a potentially important novel finding, which should be investigated further. This study illustrates the lack of consensus on the reproductive effects of *in utero* cigarette exposure, compelling continuing study in this important area.

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TRIAL REGISTRATION NUMBER: N/A.

Key words: smoking / pregnancy / fertility / in utero / miscarriage

WHAT THIS MEANS FOR THE PATIENT

There is a growing interest in whether our fertility can be affected by what happens when we are in the womb, and this article looks at the impact of having a mother who smoked during pregnancy.

Previous research has suggested that there may be a small decrease in the fertility of women whose mothers smoked in pregnancy. This study used a databank in Aberdeen to look at the medical records of more than 12 000 women and followed them through for 40 years to see whether being born to a smoker had any impact on women's future fertility.

The study did not find a link with a decrease in fertility. Women whose mothers smoked were more likely to have a pregnancy, but the researchers suggest this could be linked to the fact that they were also more likely to get pregnant at an earlier age. The researchers did, however, find a significant increase in the chances of having a miscarriage among the women whose mothers had smoked in pregnancy. The database did not show whether the women born to smokers also smoked themselves when they were pregnant, which could have an impact, and so more research is needed to confirm the link found in this study.

Introduction

Infertility is a disease with profound social consequences affecting ~10–12% of women and men (Datta *et al.*, 2016). It is an area of growing scientific enquiry, as the use of ART in the population increases (Stephen *et al.*, 2016) and semen quality is widely considered to be deteriorating (Swan *et al.*, 2000). In addition, the societal trend of delaying childbearing means that many women have poor ovarian reserve when planning a pregnancy (Wallace and Kelsey, 2010), increasing the risk of infertility.

Consequently, there is considerable interest in determining potential factors that may predispose a couple to infertility. Exposure to environmental pollutants and chemicals has been suggested as an important influence on future fertility (Buck Louis, 2014). The timing of such exposures is also now acknowledged as important, with exposures *in utero* recognized as key influences on fertility as an adult. Building on the foetal origins of disease hypothesis (Barker, 1990), evidence is emerging that exposures that have an adverse effect on the uterine milieu can affect the long-term reproductive health of offspring (Håkonsen *et al.*, 2014). Cigarette smoking is still prevalent among women of reproductive age, with over 20% of women in Scotland smoking throughout pregnancy (Tappin *et al.*, 2010). Cigarette smoke contains more than 7000 harmful substances (Rodgman and Perfetti, 2013) many of which affect the developing foetus (Buck Louis, 2014).

There are few previous epidemiological studies examining the impact of exposure to cigarette smoke *in utero* on the fertility of women and none which used prospectively collected exposure data (Håkonsen *et al.*, 2014). Four epidemiological studies reported a decrease in fecundability of women exposed to cigarette smoke *in utero* (Weinberg *et al.*, 1989; Jensen *et al.*, 1998, 2006; Ye *et al.*, 2010) and two have reported no association between exposure to cigarette smoke *in utero* and fecundability (Baird and Wilcox, 1986; Joffe and Barnes, 2000).

The present study examined the fertility-related effects of maternal smoking on the offspring's entire reproductive life using routinely collected data from a large cohort of women in Aberdeen, Scotland.

Materials and Methods

Data source

The Aberdeen Maternity and Neonatal Databank (AMND) is an obstetric database with records of all pregnancies occurring in Aberdeen, North East Scotland from 1949 to the present day. The longitudinal nature of the database and the stability of the population in this region have meant that it is possible to link women's own birth records with their reproductive outcomes. This linkage has identified over 35 000 mother–daughter pairs (Ayorinde *et al.*, 2016) which were utilized in the present study. Linkage is made using the unique Community Health Index (CHI) number given to all individuals in Scotland at the time of their birth, which remains constant throughout their life. For the small number of records in the AMND without a CHI number, a probability matching process is adopted. This technique matches an individual's recorded date of birth and surname at the time of birth with cases with their maiden name recorded later in the database. Only linkages with a high degree of agreement were included in the study. This study included all women born on or before 31st December 1972 to allow at least 40 years of follow-up, as data were complete to 2012 at the time of analysis.

Definitions of exposure and outcomes

Information on exposure was collected directly from the mother at the time of the first antenatal visit and recorded in the individual's maternity records by a healthcare professional. Women whose mother was recorded in the self-reported category 'smoker' at the first antenatal visit were by definition the exposed group. Women whose mother was recorded in the self-reported category 'non-smoker' at the first antenatal visit were by definition the unexposed group. The primary outcome of this study was any pregnancy occurring in the offspring over the course of their reproductive life. A range of secondary outcomes was also examined, including the total number of pregnancies and the outcome of each pregnancy, including livebirth, miscarriage or stillbirth.

Statistical analyses

Exposed and unexposed women were compared at baseline and any characteristics for which there was a statistically significant ($P \leq 0.05$) difference

at baseline were adjusted for in the final model. These potential confounders included the mother's age at delivery as well as the woman's social class at birth, year of birth, gestational age and weight at delivery.

All women in the cohort could not be considered truly independent, as the cohort included a large number of sibling groups. To account for this clustering of data, a two-level multilevel modelling approach was adopted. Generalized estimating equations (GEE) were used to average results between women with the same mother and facilitate the generation of crude and adjusted odds ratios (OR) and 95% CIs for primary and secondary outcomes. The SPSS Statistics Version 22 software (IBM, Chicago, IL, USA) was used for all analyses in this study and a significance level of $P \leq 0.05$ was used throughout.

Ethical approval

Approval for the study was sought and granted by the AMND Steering Committee, who are the Caldicott guardian of the data. The North of Scotland Research Ethics Committee has granted ethical approval for such studies using anonymized data from the AMND.

Results

All women born on or before 31st December 1972 and recorded in the AMND with exposure data formed the cohort. Multiple pregnancies were excluded, resulting in a cohort of 12 321 women (Fig. 1). Population demographics were compared at baseline (Table I). Women exposed to cigarette smoke *in utero* were born to younger mothers, into a lower social class, born later in the cohort period, were more likely to be preterm or very preterm and had a lower birthweight than those not exposed.

GEEs generated crude and adjusted OR for all outcomes. Univariate analysis showed women whose mother smoked during pregnancy were significantly more likely to have at least one pregnancy recorded in the AMND than those whose mother did not smoke ($P < 0.001$). Multivariate analysis generated the OR of 1.25 (95% CIs: 1.13–1.38) for exposed women having a pregnancy after adjustment for differences between the groups at baseline (Table II).

Table III displays results for secondary outcomes. Women born to mothers who smoked during pregnancy had their own offspring at a younger age than those not exposed to cigarette smoke, adjusted OR = 1.31 (95% CIs: 1.12–1.54). Women exposed to cigarette smoke *in utero* had a greater number of pregnancies overall than those not exposed on univariate analysis, however, this result was not significant after adjustment for potential confounding factors, including mother's age and social class at delivery, the year, weight and gestational age of the women at birth, and smoking status as an adult. The number of live births recorded by women exposed to cigarette smoke *in utero* was also greater than for those not exposed on univariate analysis. After adjustment for differences in the groups at baseline, there was found to be no significant difference in the number of live births

Table I Characteristics of women exposed and not exposed to cigarette smoke *in utero*.

	Exposed, $n = 3836$	Unexposed, $n = 8485$	*P*-value[¶]
Mother's age at delivery			
Mean (SD)	24.7 years (5.3 years)	25.9 years (5.4 years)	**<0.001**
Mother's social class at delivery*			
Manual occupations	2377 (62.0%)	4953 (58.4%)	**<0.001**
Non-manual occupations	728 (19.0%)	2506 (29.5%)	
Missing	*762 (19.9%)*	*1026 (12.1%)*	
Year of birth			
1954 or before	2 (0.1%)	32 (0.4%)	**<0.001**
1955–1959	23 (0.6%)	39 (0.5%)	
1960–1964	69 (1.8%)	2666 (31.4%)	
1965–1969	1910 (49.8%)	3437 (40.5%)	
1970 or after	1832 (47.8%)	2311 (27.2%)	
Born prematurely**			
Yes	210 (5.5%)	331 (3.9%)	**<0.001**
No	3417 (89.1%)	7783 (91.7%)	
Missing	*209 (5.4%)*	*371 (4.4%)*	
Born very prematurely**			
Yes	51 (1.3%)	54 (0.6%)	**<0.001**
No	3576 (93.2%)	8060 (95.0%)	
Missing	*209 (5.4%)*	*371 (4.4%)*	
Birthweight			
Mean (SD)	3090 g (533 g)	3265 g (516 g)	**<0.001**

*Categorized by the primary wage earner in the household (not necessarily the mother's occupation).
**Born prematurely defined as births occurring before 37 weeks completed gestation. Born very prematurely defined as births occurring before 32 weeks completed gestation.
[¶]Independent samples *t*-test used to compare groups.
Bold values are Odds Ratios which are statistically significant. Italic values represent missing values.

between exposed and unexposed groups. There was also no significant difference between exposed and unexposed groups when proportions of women having one or more stillbirths were compared. The likelihood of having one or more miscarriages was found to be significantly higher in exposed women than those not exposed to cigarette smoke *in utero*, adjusted OR = 1.16 (95% CIs: 1.01–1.32).

Discussion

In this study of 12 321 women the programming effects of exposure to cigarette smoke *in utero* were examined over the complete course of their reproductive lives. Women exposed to cigarette smoke *in utero* were more likely to have a pregnancy than women who were not exposed, although there were no statistically significant differences in the total number of pregnancies in the two groups. Furthermore, women whose mother smoked during pregnancy were more likely to have a miscarriage than women whose mother was a non-smoker. There were no statistically significant differences found in the odds of livebirth or stillbirth, after adjusting for potential confounding factors.

It has been suggested that the small sample size of previous epidemiological studies in this field has contributed to imprecision in findings (Ye *et al.*, 2010), so the large number of cases included in this study represents a major strength. Data on exposure were collected directly from the women's mothers at the time of antenatal booking by a healthcare professional, eliminating potential recall bias associated with previous studies in this area (Baird and Wilcox, 1986; Joffe and Barnes, 2000; Jensen *et al.*, 2006; Ye *et al.*, 2010). Additionally, at the time of data collection there was less awareness of the harmful effects of smoking during pregnancy, thus women were less likely to misreport their smoking status or to change their smoking status during

Table II Likelihood of a pregnancy in women exposed and not exposed to maternal cigarette smoking *in utero*.

	Individuals whose mother smoked during pregnancy, *n* = 3836	Individuals whose mother did not smoke during pregnancy, *n* = 8485	Crude odds ratios (95% CIs)	Adjusted odds ratios * (95% CIs)
Pregnancy recorded in AMND				
No pregnancy	1588 (41.4%)	3843 (45.3%)	1.00	1.00
>=1 pregnancy	2248 (58.6%)	4642 (54.7%)	**1.16** (1.08–1.26)	**1.25** (1.13–1.38)

*Adjusted for mother's age at delivery, social class, offspring year of birth, offspring gestational period at delivery and offspring weight at delivery.
AMND: Aberdeen Maternity and Neonatal Databank.
Generalized estimating equations used to generate crude and adjusted odds ratios.

Table III Comparison of outcomes for women who had a pregnancy in exposed versus unexposed groups.

	Individuals whose mother smoked during pregnancy, *n* = 2248	Individuals whose mother did not smoke during pregnancy, *n* = 4642	Crude odds ratios (95% CIs)	Adjusted odds ratios * (95% CIs)
Offspring age at first delivery				
19 years or younger	747 (33.2%)	1094 (23.6%)	**1.58** (1.41–1.77)	**1.31** (1.12–1.54)
20 years or older	1498 (66.6%)	3545 (76.3%)	1.00	1.00
Missing	*3 (0.1%)*	*4 (0.1%)*		
Total number of pregnancies				
1 or two pregnancies	1148 (51.1%)	2609 (56.2%)	1.00	1.00
>= 3 pregnancies	1100 (48.9%)	2034 (43.8%)	**1.22** (1.11–1.35)	1.11 (0.97–1.27)
Number of live births				
1 or two live births	1575 (70.1%)	3456 (74.4%)	1.00	1.00
>=3 live births	530 (23.6%)	951 (20.5%)	**1.21** (1.07–1.37)	1.17 (0.99–1.37)
Missing	*143 (6.4%)*	*236 (5.1%)*		
Number of stillbirths				
No stillbirths	2219 (98.7%)	4591 (98.9%)	1.00	1.00
>= 1 stillbirths	29 (1.3%)	51 (1.1%)	1.18 (0.74–1.86)	1.11 (0.63–1.97)
Number of miscarriages				
No miscarriages	1101 (49.0%)	2628 (56.6%)	1.00	1.00
>=1 miscarriages	1147 (51.0%)	2014 (43.4%)	**1.36** (1.23–1.50)	**1.16** (1.01–1.32)

*Adjusted for mother's age at delivery, social class, offspring year of birth, offspring gestational period at delivery, offspring weight at delivery, offspring adult smoking status.
Generalized estimating equations used to generate crude and adjusted ORs.

pregnancy. Data were extracted from an existing dataset, requiring no additional input from study participants. This confers an advantage over previous studies measuring 'time to pregnancy', where a high level of commitment is required by participants, leading to selection bias (Baird and Wilcox, 1986; Jensen *et al.*, 1998).

A limitation of this study is that exposure to cigarette smoke *in utero* for women without data recorded on their mother's smoking status could not be assessed (n = 24 786) and included in the analysis. Furthermore, it was assumed women without a recorded pregnancy had not been pregnant, whereas these women may have chosen not to become pregnant or migrated from the area. Indeed, women born into higher social classes were less likely to be exposed *in utero* but may have had greater opportunities for migration and been more likely to delay or choose not to get pregnant. For women who did not have a pregnancy record, no data on their adult circumstances were available, precluding adjustment for characteristics such as their own smoking status on the likelihood of having a pregnancy. Women exposed to cigarette smoke *in utero* are also more likely to be exposed in childhood (Wilcox *et al.*, 1989) and it cannot be deduced from this study when exposure to tobacco smoke has the greatest effect on reproductive development.

Previous studies examining the relationship between maternal smoking and offspring fertility have given conflicting results. While four previous studies have demonstrated a negative impact of maternal smoking on fecundability of daughters (Weinberg *et al.*, 1989; Jensen *et al.*, 1998, 2006; Ye *et al.*, 2010) and two showed no effect (Baird and Wilcox, 1986; Joffe and Barnes, 2000), this is the first study to find increased fertility in offspring exposed to cigarette smoke *in utero*. One previous study has demonstrated increased fertility in individuals exposed to cigarette smoke in the early years of life (Wilcox *et al.*, 1989).

The results of this study suggest that despite potential detrimental effects of cigarette smoke on foetal reproductive development observed in laboratory studies (Fowler *et al.*, 2014), this may not result in fewer offspring born to women exposed to cigarette smoke *in utero* at an overall population level. This finding suggests that the reduction in fecundability is not large enough to reduce overall fertility, or that other factors may influence this effect, such as the use of ART or contraception.

In a potentially important observation, women exposed to cigarette smoke *in utero* had a higher likelihood of miscarriage than women whose

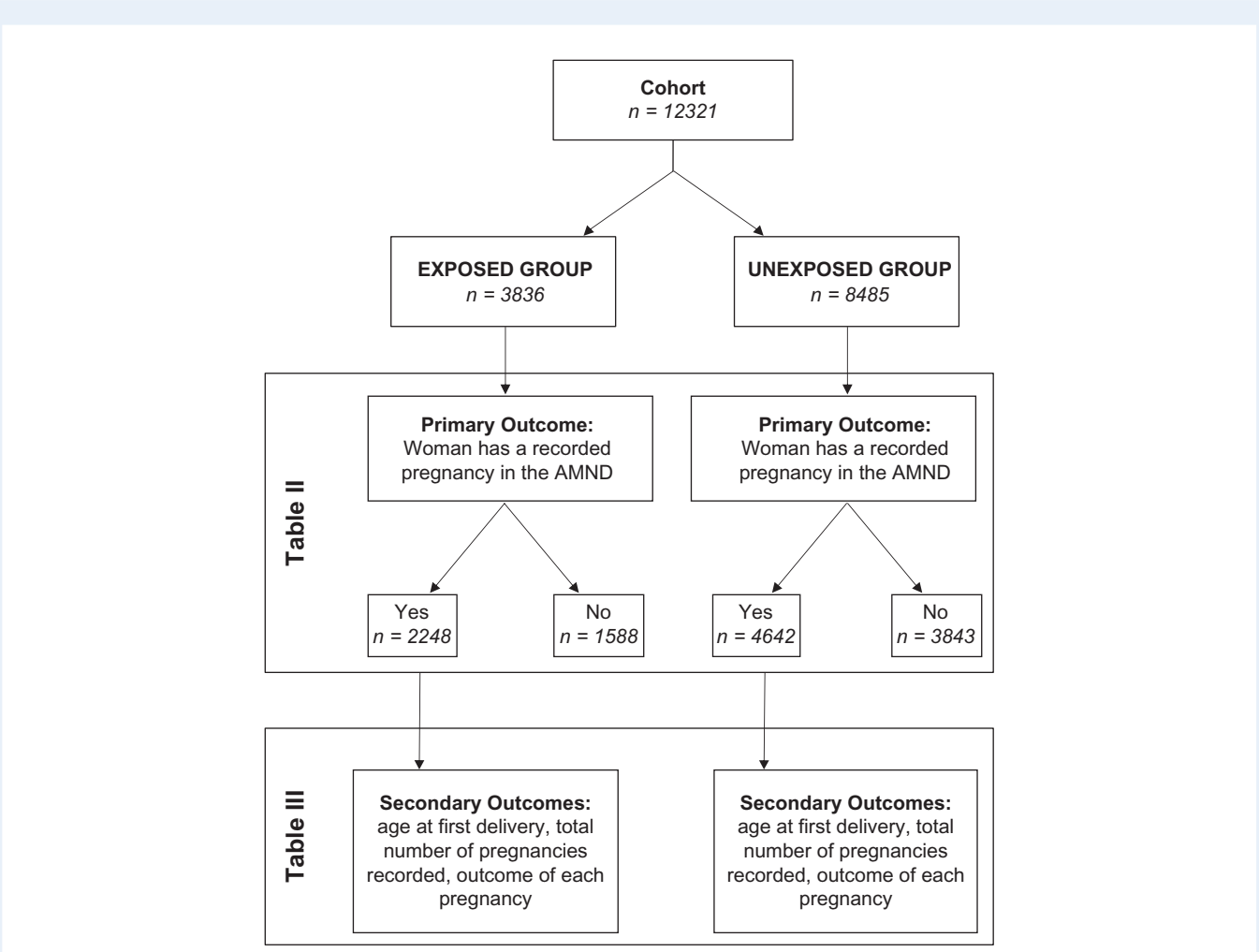

Figure 1 Flowchart of all cases and outcomes in an intergenerational study of the effects of maternal smoking (exposed) on offspring reproductive outcomes. AMND: Aberdeen Maternity and Neonatal Databank.

mother did not smoke. Only one previous study has examined the risk of foetal loss in 76 375 women who were exposed to cigarette smoke *in utero* (Cupul-Uicab *et al.*, 2011): this study generated an adjusted hazard ratio of late miscarriage for exposed women of 1.23 (95% CIs: 0.72–2.12) when compared with unexposed women. Although this effect did not reach statistical significance, a trend was observed towards increased risk of miscarriage in exposed women. A significant effect was seen in the current study, which showed an adjusted OR of 1.16 (95% CIs: 1.01–1.32) for the likelihood of having at least one miscarriage for exposed women compared to those unexposed. A major limitation of Cupul-Uicab *et al.* (2011) was that the study was underpowered and, because the data collection occurred at a later stage of pregnancy, they could only include late miscarriages. The present study has addressed this limitation since data was available on all miscarriages, consequently the effect reached significance and CIs were much narrower. A recent systematic review has demonstrated that the increased risk of miscarriage amongst women who smoke as adults is unequivocal (Pineles *et al.*, 2014). The finding of an increased likelihood of miscarriage in those exposed to cigarette smoke prenatally thus represents a promising line of further scientific enquiry.

Exposure to cigarette smoke *in utero* has many negative effects on the developing human reproductive system, including reducing the number of oogonia and somatic cells in the developing human foetal ovary (Lutterodt *et al.*, 2009). Cigarette smoke exposure *in utero* also causes a significant disruption in normal human foetal ovarian developmental signalling and primordial follicle formation (Fowler *et al.*, 2014). Hormone modulators, such as polycyclic aromatic hydrocarbons found in cigarette smoke, damage genes during cell proliferation and reduce proliferation rates in the human foetal ovary (Anderson *et al.*, 2014). Such effects during critical periods of foetal ovarian development will result in a reduction in the number of oocytes at birth (Lutterodt *et al.*, 2009). Further population level studies are warranted to determine how these biological effects impact overall fertility in women exposed to cigarette smoke prenatally.

Conclusion

Exposure to cigarette smoke *in utero* was associated with an overall increased likelihood of those women themselves having a pregnancy, although the effects of social class and younger age at first birth among women in the exposed group may have contributed to this finding. This contrasting result highlights the inconsistency of previous studies and suggests that the potential effects of cigarette smoking on foetal reproductive development are not yet clearly understood. Our findings also suggest an increased risk of miscarriage for women exposed to cigarette smoke *in utero*. Although this finding has biological plausibility, it should be interpreted with caution as it may have been influenced by the women's own smoking status. Future research into the links between *in utero* exposure to cigarette smoke and risk of miscarriage is needed to confirm this finding and should also account for the smoking status of participants.

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Authors' roles

S.T. was responsible for the design, analysis and interpretation of the research as well as drafting, revision and approval of the article. S.B. and P.A.F. contributed the conception and design of the project, guided interpretation of results, drafting, revision and approval of the final article.

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Conflict of interest

The authors declare no conflicts of interest regarding this study.

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