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Left Truncation Bias as a Potential Explanation for the Protective Effect of Smoking on Preeclampsia

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Background: We carried out a study to examine whether left truncation bias could explain the negative association between smoking and preeclampsia.

Methods: Monte Carlo and other simulation models were used to determine the effect of differential rates of early pregnancy loss among smokers on the relation between smoking and preeclampsia at ≥20 weeks' gestation. Assumptions included no association between smoking and the abnormal placentation that characterizes preeclampsia, and higher rates of early pregnancy loss among smokers, pregnancies with abnormal placentation, and smokers with abnormal placentation.

Results: Monte Carlo simulation yielded a rate ratio for preeclampsia, given smoking of 0.85 (95% confidence interval = 0.73, 0.98). The protective effect of smoking was also evident in simulations that did not require assumptions about early pregnancy loss rates.

Conclusion: Left truncation bias due to differential rates of early pregnancy loss among smokers is a plausible explanation for the inverse association between maternal smoking and preeclampsia.

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Preeclampsia is typically characterized by elevated blood pressure and systemic inflammation (eg, proteinuria) occurring after 20 weeks' gestation.[1–3] While the cause of preeclampsia is unknown, current hypotheses postulate a placental pathogenesis.[1,4,5] Abnormal placentation leading to preeclampsia is marked by the failure of the trophoblast to induce physiologic dilatation and remodeling of spiral arteries, resulting in reduced placental blood flow.[1,4,5]

Smoking during pregnancy is inversely associated with preeclampsia.[6–11] This negative relation between smoking and preeclampsia is puzzling because smoking is associated with several adverse perinatal outcomes, including early pregnancy loss, fetal death, preterm birth, and small-for-gestational age live birth.[8,9,12] However, the apparent protective effect of smoking on preeclampsia is remarkably consistent across studies (10%–40% reduction in the risk of preeclampsia),[6–10,13] including studies that used biomarkers to ascertain smoking behavior[14] and others examining dose-response relationships.[7]

Whereas the mechanism of the protective effect of smoking on preeclampsia has not been adequately explained, current hypotheses suggest that nicotine, carbon monoxide, or other compounds within cigarette smoke inhibit placental cytokine production, oxidative stress, or vascular constriction,[15,16] all of which are implicated in the development of preeclampsia.[17] However, an alternative explanation for this phenomenon is left truncation bias due to differential rates of early pregnancy loss among smokers before preeclampsia diagnosis. We carried out a simulation study to examine whether such a bias could explain the observed protective effect of maternal smoking on preeclampsia.

METHODS

We first performed a Monte Carlo simulation with estimates of the probability of abnormal placentation and early pregnancy loss (by smoking status and abnormal placentation) obtained from the literature[18–20] and plausible distributions constructed to express the uncertainty in these estimates. In a second simulation, we avoided modeling early pregnancy loss rates associated with smoking and abnormal placentation. Instead, we assumed a baseline rate of early pregnancy loss among non-smokers without abnormal placentation and modeled the relative effects of abnormal placentation and smoking on early pregnancy loss. This latter approach was intended to highlight the importance (or lack thereof) of uncertainty in early pregnancy loss rates in the Monte Carlo simulation.

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The underlying assumptions used in both simulations were as follows: (1) abnormal placentation marked by failure to induce remodeling of spiral arteries leads to preeclampsia; (2) similar rates of abnormal placentation occur in smokers and non-smokers; (3) higher rates of early pregnancy loss occur among smokers versus non-smokers; (4) higher rates of early pregnancy loss occur among women with versus without abnormal placentation; and (5) the highest rates of early pregnancy loss occur among smokers with abnormal placentation.

For the Monte Carlo simulation, we constructed a hypothetical cohort of women with singleton pregnancies. We assumed the rate of abnormal placentation to be between 5% and 10% for both smokers and non-smokers using a uniform distribution across this range. The estimated rates of early pregnancy loss were based on the literature[18–20]; 10% among non-smokers without abnormal placentation; 20% among smokers without abnormal placentation; 20% among non-smokers with abnormal placentation; and 40% among smokers with abnormal placentation. The combined effect of smoking and abnormal placentation assumed effect modification on an additive scale but not on a multiplicative scale. Uncertainty in estimates of rates of early pregnancy loss was incorporated by assuming a normal distribution with a standard deviation (SD) of 3%.

The size of the hypothetical cohorts of smokers and non-smokers was set to 1,000,000 women each. The Monte Carlo simulation included 100,000 iterations based on the specified probabilities and probability distributions and yielded estimates of the rate ratio for preeclampsia at ≥20 weeks' gestation given smoking. The mean rate ratio and 95% confidence interval (CI) were calculated from the simulated rate ratio distribution. Sensitivity analyses were carried out varying rates of early pregnancy loss (eg, among non-smokers without abnormal placentation, rates were assumed to be 5%, 15%, and 20% instead of 10%). Similarly, the rate of abnormal placentation was allowed to range between 5% and 55% instead of 5% and 10%.

In model 2, we simulated the association between smoking and preeclampsia after varying the rate ratios for early pregnancy loss due to smoking (RR_{SMK}) and due to abnormal placentation (RR_{AP}) from 1 to 3. Rate ratios for the combined effect of smoking and abnormal placentation were calculated

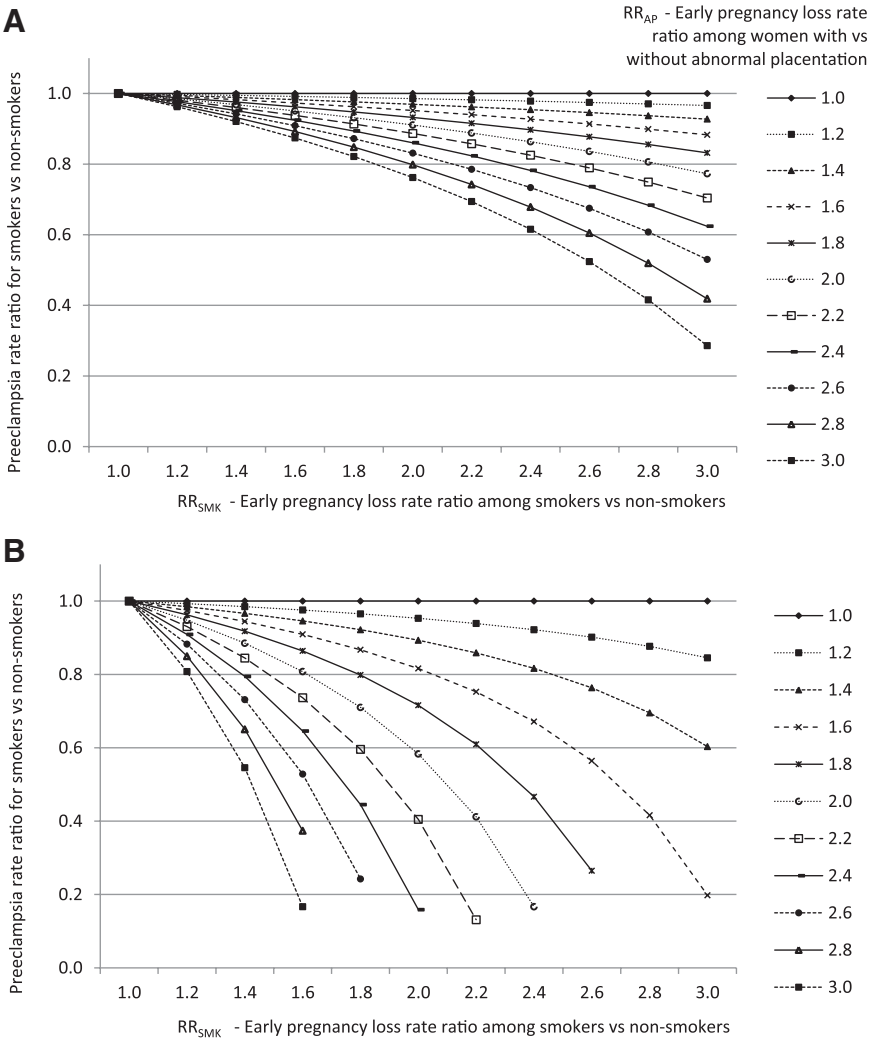

FIGURE 1. Rate ratios expressing the association between smoking and preeclampsia at ≥20 weeks' gestation as a function of the association between smoking and early pregnancy loss. The rate of early pregnancy loss among non-smokers without abnormal placentation was assumed to be 10% (A) and 20% (B). The model assumed a multiplicative effect (without effect modification) for the combined influence of smoking and abnormal placentation on early pregnancy loss.

on a multiplicative scale ($RR_{SMK\_AP} = RR_{SMK} \times RR_{AP}$) and on an additive scale ($RR_{SMK\_AP} = RR_{SMK} + RR_{AP} - 1$). We estimated the early pregnancy loss rate among non-smokers without abnormal placentation to be 10%. Sensitivity analyses were carried out assuming a baseline early pregnancy loss rate of 20% instead of 10%.

All analyses were carried out using SAS software, version 9.3 (SAS Institute Inc., Cary, NC). Appendices show the SAS program used to generate model 1 and model 2, respectively (available as Supplemental Digital Content at http://links.lww.com/EDE/A887).

RESULTS

The rate of early pregnancy loss in 100,000 iterations of the Monte Carlo simulation varied widely: a range from 0.0% to 23.0% (mean, 10.0%; SD = 3.0%) among non-smokers without abnormal placentation; from 7.5% to 33.8% (mean, 20.0%; SD = 3.0%) among non-smokers with abnormal placentation; from 6.8% to 32.1% (mean, 20.0%; SD = 3.0%) among smokers without abnormal placentation; and from 27.4% to 57.5% (mean, 40.0%; SD = 3.0%) among smokers with abnormal placentation. The simulation yielded a RR for preeclampsia among smokers of 0.85 (95% CI 0.73, 0.98). Sensitivity analyses varying the probability of early pregnancy loss rates and the probability of abnormal placentation had little effect (all RRs and 95% CIs were below 1).

Figure 1 shows the results of the model 2 with the combined effect of smoking and abnormal placentation modeled on a multiplicative scale. Early pregnancy loss was assumed to be 10% among non-smoking women without abnormal placentation in Figure 1A and 20% among such women in Figure 1B. A 2-fold higher early pregnancy loss rate among smokers versus non-smokers (RR_{SMK} = 2.0, x-axis) and a 2-fold higher rate of early pregnancy loss among women with abnormal placentation (RR_{AP} = 2.0, legend in Figure 1) resulted in a 10% lower rate of preeclampsia among smokers (RR_{PE} = 0.90, y-axis, Figure 1A). Larger assumed effects of

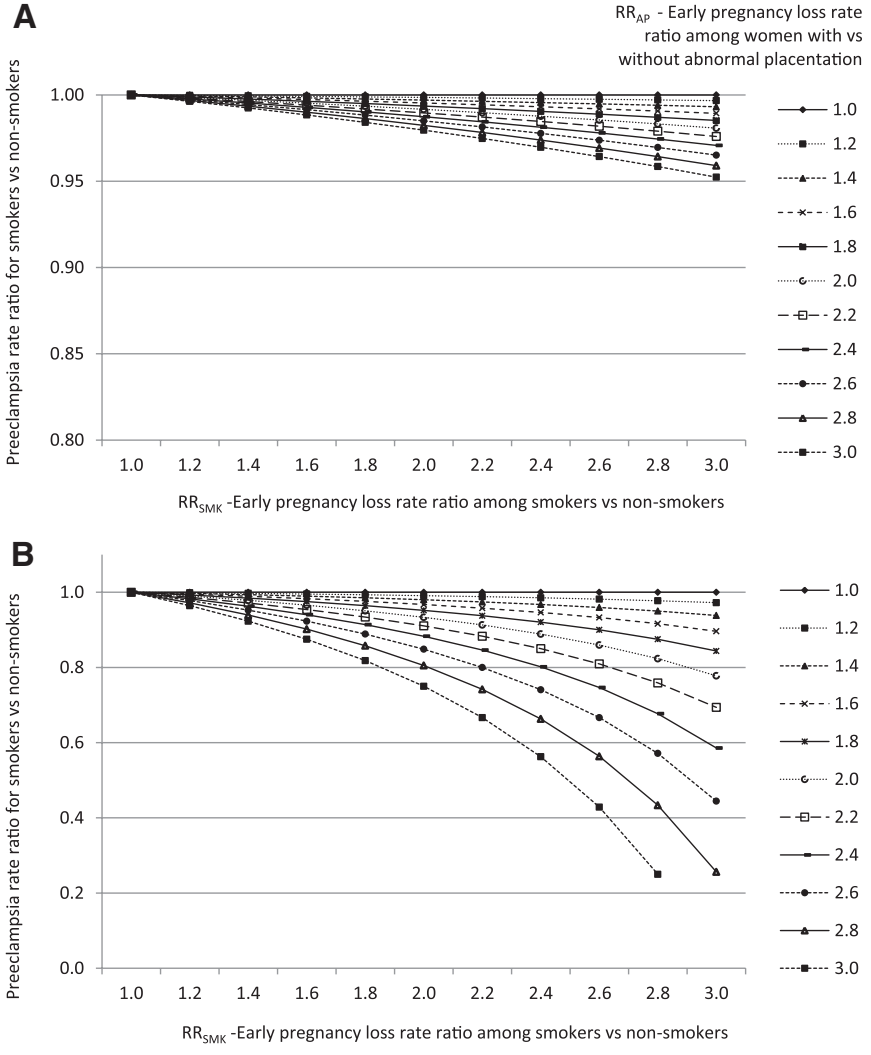

FIGURE 2. Rate ratio expressing the association between smoking during pregnancy and preeclampsia at ≥20 weeks' gestation as a function of the association between smoking and early pregnancy loss. The rate of early pregnancy loss among non-smokers without abnormal placentation was assumed to be 10% (A) and 20% (B). The model assumed an additive effect (without effect modification) for the combined influence of smoking and abnormal placentation on early pregnancy loss.

smoking and abnormal placentation on early pregnancy loss led to a stronger inverse association between smoking and preeclampsia. Similar results were obtained when the combined effect of smoking and abnormal placentation on early pregnancy loss was modeled on an additive scale (Figure 2).

DISCUSSION

Our study showed that the paradoxical inverse association between smoking during pregnancy and preeclampsia can be explained as a left truncation phenomenon resulting from differential early pregnancy losses that occur before diagnostic recognition of preeclampsia. All probabilities used in our simulations were based on the literature and incorporated plausible ranges for the uncertainty in estimates. Nevertheless, the results showed a protective effect for maternal smoking on preeclampsia over a wide range of scenarios.

Survival bias[21,22] can distort associations, and such a selection bias can be viewed as a result of stratification on a collider. A collider is characterized as a common "effect" associated with both the exposure and the outcome under the study.[23,24] In our study, both abnormal placentation and smoking were associated with survival to 20 weeks' gestation although only abnormal placentation was associated with preeclampsia. Restricting the study population to ongoing pregnancies at 20 weeks thus represented stratification on a collider (survival).

The inverse association between maternal smoking and preeclampsia may also be viewed as a bias arising from competing risks. A pregnancy may end in an early pregnancy loss, stillbirth, or preterm birth before preeclampsia onset. If any of these events occurs at a higher rate among smokers who are also at high risk of preeclampsia, then preeclampsia rates will be lower at late gestation among smokers. A similar hypothesis involving competing risks has been proposed to explain the apparent protective effect of smoking on malignant melanoma occurrence.[25]

This explanation for the negative association between smoking and preeclampsia is consistent with the results of most studies. Studies show that the protective effect of smoking on preeclampsia increases with the intensity of smoking.[8,9] Higher smoking intensity is associated with increased rates of early pregnancy loss, stillbirth, preterm birth, and small-for-gestational-age live births,[26] and thereby lowers the probability of preeclampsia later in pregnancy.

Limitations of our study include the assumptions underlying our simulations, even though we used the best estimates from the literature and incorporated the uncertainty in estimates in our models. Also, the origins of preeclampsia are largely unknown, and abnormal placentation may not be the only mechanism leading to preeclampsia syndrome.

Our findings highlight a phenomenon similar to effects observed in studies on reproductive toxins. For example, toxic exposure results in pregnancy losses and lower rates of congenital anomalies, whereas lower exposure is associated with higher rates of congenital anomalies at birth.[27,28] Left truncation may potentially explain other unexpected relationships such as the lower rate of adverse outcomes among older mothers with multifetal pregnancies.[29–31] The inherent causal bias notwithstanding the observed effects on pregnancy outcomes are valid from a prognostic standpoint. For women at 20 weeks' gestation, the chance of developing preeclampsia is lower among smokers than non-smokers.

In summary, we have shown that left truncation and selective survival can explain the paradoxical inverse association between smoking and preeclampsia. Our findings have implications for preeclampsia research directed at discovering smoking-related preventive agents and, more generally, for etiologic research related to the combined effects of 2 or more adverse influences.

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