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COMMENTARY

Fetal exposure to parental smoking and the risk of type 2 diabetes: Are lifestyle-related factors more important?

Whether certain exposures before birth can affect disease risk in adulthood has drawn much attention in the scientific community for many years. Maternal exposures during pregnancy that have been extensively examined include diet, smoking, alcohol consumption, environmental toxins, drugs and infectious diseases. Risks of diseases including obesity and metabolic disorder, cardiovascular disease, cancers, respiratory disease, psychiatric disorders, and cognitive function, have been reported to be associated with maternal exposure to these factors[1]. However, whether the observed maternal association truly reflects a biological intrauterine effect still remains controversial. Because it takes many decades to have the outcome of interest occurring in later life, it is more practical to use a retrospective study design to obtain exposure information during pregnancy. What makes things more complicated is that many factors, including lifestyle, socioeconomic status, genetic and adverse events that occur during pregnancy, are closely correlated with the exposure of interest, and might also influence pregnancy and later life outcome (Figure 1). These potential confounding factors are very difficult to ascertain accurately in a retrospective way. To address the issue of potential residual confounding, Smith[2] proposed to contrast maternal and paternal exposure association in the analyses. This maternal–paternal approach compares the magnitude of the association of the maternal exposure with child outcome to that of the equivalent association for paternal exposure with child outcome. A biological intrauterine effect would be expected if there is a stronger maternal association, relative to the paternal association, assuming paternal exposure would not be expected to substantially affect the intrauterine environment. Furthermore, when including both maternal and paternal exposures into the model, there will be a persistent association with maternal exposure, but that for paternal exposure will be markedly attenuated. In contrast, if a similar or a stronger strength of association is found for paternal exposure than that of maternal exposure, and including both maternal and paternal exposures in the model leaves residual effects of similar magnitude, residual confounding rather than a direct intrauterine mechanism might be responsible for the observed association[3]. This approach has been used in several studies sought to delineate the true intrauterine effect of maternal pre-pregnancy overweight on child cognition and neuropsychological development[4,5].

In a recently published study, Jaddoe *et al.*[6] analyzed data from the Nurses' Health Study II to evaluate the associations of both maternal and paternal smoking during pregnancy with the risk of type 2 diabetes in daughters. They observed that after adjusting for perinatal and adult life variables, maternal continuing smoking <15 cigarettes per day, but not ≥15 cigarettes per day, was significantly associated with the risk of type 2 diabetes in their daughters. Meanwhile, the association of paternal continuing smoking of ≥15 cigarettes per day during pregnancy was even stronger than that for maternal smoking of the same number of cigarettes. These findings, which lack a dose–response relationship and a larger effect estimate for paternal smoking, might suggest that the association could be due to family-based or lifestyle-related factors rather than a true intrauterine effect.

Did their findings that maternal smoking during the first trimester only was persistently associated with the risk of type 2 diabetes in the offspring, even after adjusting for confounders, birthweight, body mass index (BMI) at age 18 years and current BMI, imply a true causation? There are several concerns about potential biases. First, the authors excluded study participants who reported to have diabetes at baseline (1989). Because the information about maternal smoking during pregnancy was collected in 2001, it is possible that nurses' mothers would respond differentially to the questions that asked them whether they ever smoked or stopped smoking during pregnancy with the nurse daughter, depending on whether their nurse daughters had been diagnosed with type 2 diabetes in 1989–2001. A further analysis stratified by different study period (1989–2000 and 2001–2009) will be helpful to determine whether recall bias could partially explain the association. Second, in the supplementary data provided by the authors, mothers who quit smoking during the first trimester had a lower proportion of mother's weight gain <9.1 kg (i.e. higher weight gain) during pregnancy and a higher education level (attending college), as compared with those who continued smoking during pregnancy, but without any clues about why those mothers stopped smoking after the first trimester. More importantly, it might be the reasons that led to the

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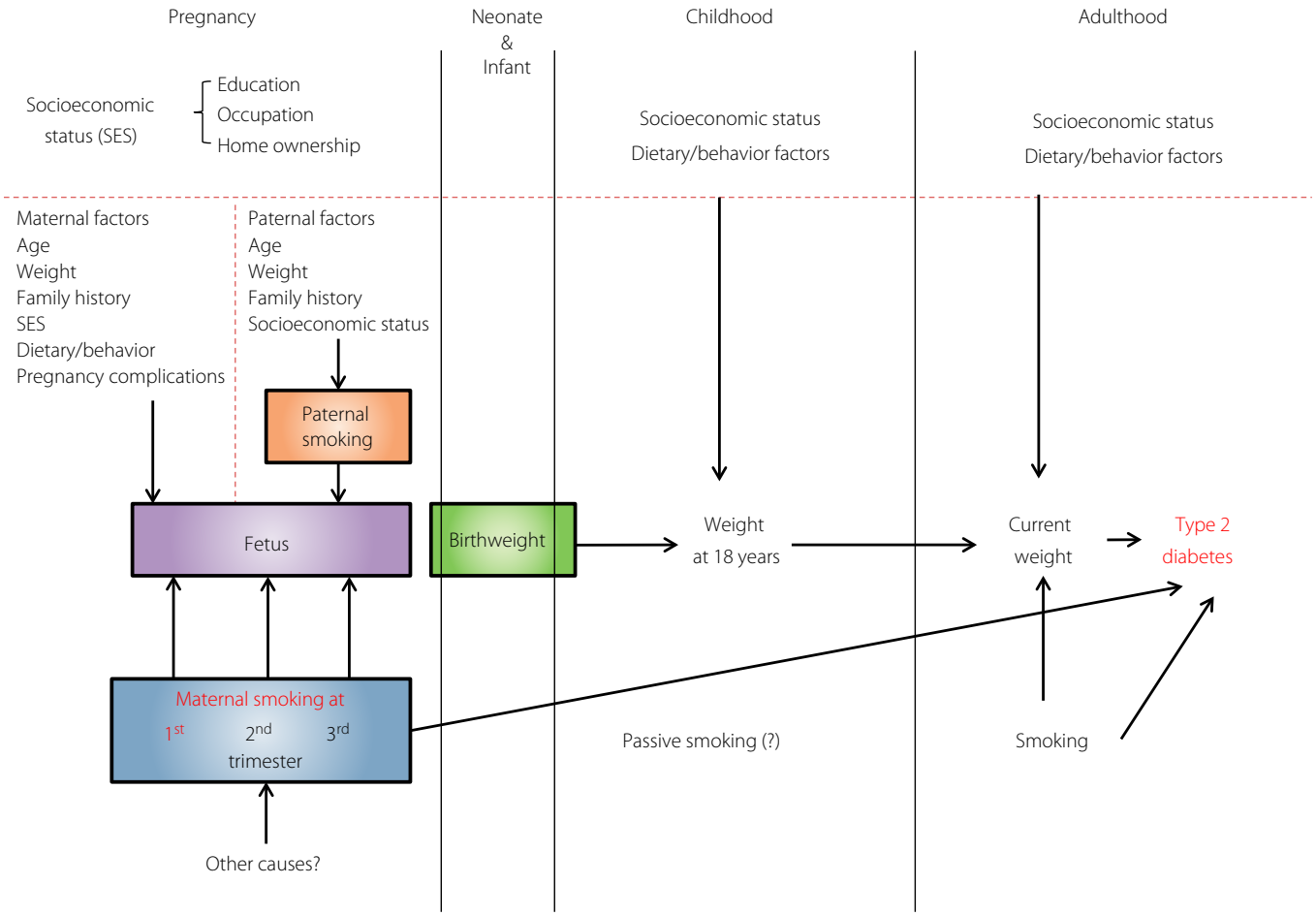

Figure 1 | The complex relationship among maternal smoking, maternal and paternal factors, birthweight, weight at 18 years-of-age, current weight, and risk of type 2 diabetes. There are many factors, including lifestyle, socioeconomic status, genetic and adverse events that occur during pregnancy, which are closely correlated with exposure to smoking *in utero*, that could also influence the risk of type 2 diabetes in later life. SES, socioeconomic status.

mother's smoking cessation during the first trimester that are causally linked to a higher risk of type 2 diabetes in adulthood. Future research that explores the reasons for first-trimester-only maternal smoking might shed new light on the association between fetal exposure to smoking and risk of type 2 diabetes in adulthood.

The next question is about whether an attenuated effect estimate after statistical adjustment for current BMI can be causally interpreted as "the risk was largely explained by current BMI." There has been a continuing debate about whether intermediate variables (variables in the causal pathway) and variables that were affected by exposure should be adjusted in the epidemiological literature[7]. The most famous example is the "birthweight paradox" or "reversal paradox"; that is, the magnitude or even the direction of the association between prenatal exposure and health outcome in later life is changed after birthweight or current weight is considered[8]. For instance, after adjustment for current weight, low birthweight is associated with higher blood pressure in adulthood, which suggests that an unfavorable environment *in utero* could induce lifetime effects on the subsequent body systems development, and hence give rise to a range of chronic disease in later life (fetal origins of adult disease hypothesis). This theory has been questioned, as the observed association might be due to selection bias caused by inappropriately restricting (or adjusting for) the analysis to those with low birthweight, a common effect of maternal smoking, and unmeasured residual confounding, such as socioeconomic status, which is also a risk factor for type 2 diabetes[9]. In a simulation study of a scenario without unmeasured confounding[10], it was found that even if there was null association between birthweight and adult blood pressure, control for current weight (intermediate variable) created an inverse association. When there was a genuine positive relationship between birthweight and adult blood pressure, adjustment for current weight could reverse the association, and the effect size

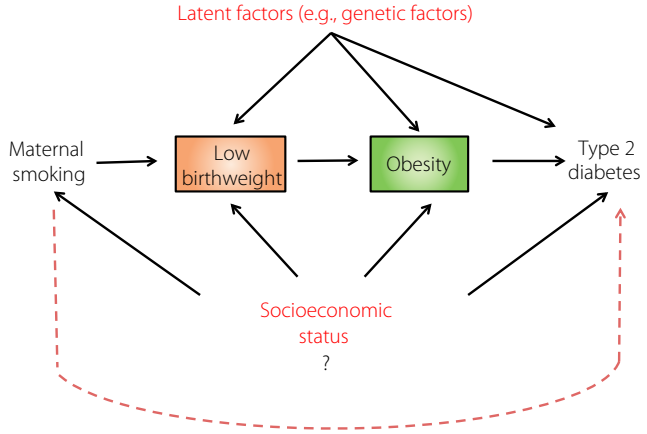

Figure 2 | Causal diagram for the association between maternal smoking and type 2 diabetes in adulthood, with the concern that adjusting for birthweight, weight at 18 years-of-age and current weight might introduce bias. Because birthweight, weight at age 18 years and current weight are probably in the causal pathway that leads to type 2 diabetes, and are both affected by unmeasured common causes (such as genetic factors), which are also risk factors for type 2 diabetes, analyses that controls for these variables might introduce bias.

depended on the ratio of blood pressure standard deviation to that of the birthweight standard deviation. These findings show that results from the analysis that "controls for intermediate variable" probably cannot be reliably interpreted as "direct effect" estimates, because of the statistical artifact with no valid causal interpretation. Because birthweight is likely to be affected by prenatal exposure (such as smoking), weight at age 18 years and current weight are probably in the causal pathway that leads to type 2 diabetes (Figure 2), and are both affected by unmeasured common causes (such as genetic factors), which are also risk factors for type 2 diabetes. The results from analyses that control for these variables to calculate the proportion of effects that can be explained by intermediate variables might introduce overadjustment bias and require very careful interpretation.

What should we do if we really want to evaluate the relationship among maternal smoking, birthweight and type 2 diabetes, while taking genetic, maternal lifestyle and socioeconomic factors during pregnancy into account? It is suggested that by a natural experiment we can observe mothers with multiple singleton pregnancies, collecting information on maternal age, dietary, lifestyle and socioeconomic factors, perinatal and adult lifestyle variables, and then compare birthweight and outcomes of siblings from one family with discordant exposure status of maternal smoking during pregnancy. As sisters and brothers from one family share similar genetic and socioeconomic status during their fetal development, confounding from these factors might be reduced. A proper statistical method that takes into account the dependency between siblings is required. The effect from lifestyle-related or family-based factors can also be explored by comparing children from different families. If the study aim is to examine the relationship between maternal smoking and the risk of type 2 diabetes in adulthood, controlling for birthweight or current weight might not be required, as both are in the causal network between the exposure and the outcome.

In conclusion, current evidence suggests that although fetal exposure to smoking might increase the risk of type 2 diabetes in later life, lifestyle factors either during pregnancy or in adulthood might play a more important role. A "family-based association study" design might be helpful to detangle the relationship among intrauterine exposure, lifestyle factors and the risk of diabetes in later life.

DISCLOSURE

The authors declare no conflict of interest.

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