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 diseases. Risks of diseases including obesity and metabolic disorder, cardiovascular diseases. Risks of diseases including obesity and metabolic disorder, cardiovascular diseases. Risks of diseases including obesity and metabolic disorder, cardiovascular diseases. Risks of diseases including obesity and metabolic disorder, cardiovascular diseases. Risks of diseases including obesity and metabolic disorder, cardiovascular diseases. Risks of diseases including obesity and metabolic disorder, cardiovascular diseases. Risks of diseases including obesity and metabolic disorder, cardiovascular diseases. Risks of diseases including obesity and metabolic disorder, cardiovascular diseases. Risks of diseases including obesity and metabolic disorder, cardiovascular diseases. Risks of diseases including obesity and metabolic disorder, cardiovascular diseases. Risks of diseases including obesity and metabolic disorder, cardiovascular diseases. Risks of diseases including obesity and metabolic disorder, cardiovascular diseases. Risks of diseases including obesity and metabolic disorder, cardiovascular diseases. Risks of diseases including obesity and metabolic disorder, cardiovascular diseases. Risks of diseases including obesity and metabolic disorder, cardiovascular diseases. Mortality and morbidity from type 2 diabetes are increasing worldwide. Whether certain exposures before birth could alter disease risk in adulthood has drawn much interest (Table 1). Results from several longitudinal studies have shown an increased risk of type 2 diabetes in offspring to smoking during pregnancy. In addition, levels of fetal weight, body mass index (BMI) and central adiposity are increased with exposure to smoking during pregnancy, a finding that has been supported by several recent studies. These results suggest that smoking during pregnancy might cause increased fetal adiposity, which in turn may lead to an increased risk of type 2 diabetes.

In a recently published study, Jaddoe et al. analyzed data from the Nurses’ Health Study II to evaluate the associations of maternal and paternal smoking during pregnancy with the risk of type 2 diabetes in the offspring. 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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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. 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. 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. In a simulation study of a scenario without unmeasured confounding, 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.
depending 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, 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.

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.

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