Letter to the Editor

RE: “EXPOSURE TO MATERNAL SMOKING DURING PREGNANCY AS A RISK FACTOR FOR TOBACCO USE IN ADULT OFFSPRING”

Rydell et al. (1) recently reported evidence that maternal smoking during pregnancy is associated with later offspring use of snus but not cigarettes. This adds to a substantial but conflicting body of literature on the relationship between maternal smoking during pregnancy and offspring tobacco use. What is notable in Rydell et al.’s study is that statistical adjustment for a range of potential confounders attenuated the association with cigarette smoking, but not the association with snus use (1). As Alberg and Korte noted in their commentary on the study (2), this is intriguing, but particular care is warranted when attempting to make causal inferences regarding the effects of maternal exposures in pregnancy, given the difficulty in disentangling these effects from those of the social environment during childhood and adolescence.

One possible solution to the problem of inferring causality in this situation is the use of a negative control group, where the relevant confounding structure can be expected to be similar but the relevant exposure is lacking. For example, in the case of maternal smoking during pregnancy, the strength of association with outcomes of interest can be compared with that observed for paternal smoking during pregnancy. This method is briefly mentioned by Rydell et al. in their response (3) to Alberg and Korte, but it has a long history in the American Journal of Epidemiology (4). Moreover, it has recently been used to show that the relationship between maternal smoking during pregnancy and later offspring smoking is unlikely to operate through intrauterine mechanisms (5) (although this was demonstrated in a population where snus use was negligible, so this particular outcome could not be tested). Similar methods have been used to show that the relationship between maternal smoking in pregnancy and later offspring conduct problems may be due to an intrauterine effect (6).

The use of negative controls is not without its limitations, of course. Critically, in the case of maternal smoking during pregnancy, it assumes that any biological effects of second-hand tobacco smoke exposure (i.e., passive smoking) via the father are much smaller than the effects of active smoking via the mother. However, we have recently shown that this assumption is likely to be valid (7). Other assumptions include that shared family factors are associated with maternal and paternal smoking to a similar degree, that genetic factors relate in the same way in men and women and do not demonstrate parent-of-origin effects, and that there are no unmeasured confounding factors that are specific to the relationship between either parent’s smoking and offspring outcomes (8).

It is notable that when Rydell et al. performed similar analyses in sibling pairs, which allows greater control for confounding by familial factors (both genetic and environmental), they found no clear evidence that maternal smoking during pregnancy was associated with either offspring smoking or offspring snus use (9). Ultimately, what is required is the triangulation of results arrived at using a range of different approaches (8). These approaches will all bring their own biases and limitations, but as long as they are not the same biases and limitations, we can be more confident in drawing causal inferences. The importance of this is well-recognized in epidemiology. Nevertheless, there is still perhaps a need to place more emphasis not only on alternative designs, including negative control methods, but also on other approaches such as Mendelian randomization (10) and between-sibling comparisons (9, 11), rather than relying too heavily on statistical adjustment.

ACKNOWLEDGMENTS

This work was supported by the Medical Research Council (grants MC_UU_12013/1 and MC_UU_12013/6). In addition, funding from British Heart Foundation, Cancer Research UK, the Economic and Social Research Council, the Medical Research Council, and the National Institute for Health Research, under the auspices of the United Kingdom Clinical Research Collaboration (UKCRC), is gratefully acknowledged.

A.E.T. and M.R.M. are members of the United Kingdom Centre for Tobacco and Alcohol Studies, a UKCRC Public Health Research Centre of Excellence.

Conflict of interest: none declared.

REFERENCES


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Editor’s note: In accordance with Journal policy, Rydell et al. were asked whether they wished to respond to this letter, but they chose not to do so.

DOI: 10.1093/aje/kwu269; Advance Access publication: October 7, 2014