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Letter

Need to Account for Familial Confounding in Systematic Review and Meta-analysis of Prenatal Tobacco Smoke Exposure and Schizophrenia

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In the context of continued uncertainty regarding the long-term mental health effects of prenatal exposure to maternal smoking during pregnancy, we read with great interest the recently published meta-analysis of smoking and schizophrenia by Hunter and colleagues.[1] Although the meta-analysis found that "exposure to prenatal smoke increased the risk of schizophrenia by 29%" (p. 3), the authors noted that "familial confounding may explain some of the observed association" (p. 8). We agree with the importance of this alternative hypothesis. In fact, we were surprised that the review did not consider the results of sibling comparison studies that have directly addressed it, particularly given that the review had the opportunity to do so using data from articles included in the meta-analysis. As we illustrate below—and as has been discussed previously[2]—we are concerned that limiting the focus of the review to only findings potentially subject to familial confounding rather than incorporating these sibling comparison results may lead to inaccurate inferences from the reviewed literature.

Schizophrenia and smoking are both genetically influenced phenotypes and may share genetic influences.[3] Thus, observed associations between maternal smoking during pregnancy and offspring schizophrenia may actually represent passive gene-environment correlation (or the influence of other familial factors) rather than a true teratogenic effect.[4,5] Sibling comparison designs, which have been described in detail elsewhere, can help disentangle familial confounding from causal environmental effects.[6] They capitalize on differential exposure to maternal smoking within families (ie, across pregnancies) to rule out the possibility of confounding by all measured or unmeasured sources of sibling similarity (eg, genes, family environment) *by design*. Consequently, they can provide stronger tests of prenatal exposure hypotheses than may be possible in traditional observational designs that rely solely on statistically adjusting for measured covariates. Indeed, research employing family-based designs has revealed that shared genetic influences or other familial confounding may explain much of the associations between maternal smoking during pregnancy and a range of offspring cognitive, behavioral, and social outcomes.[7]

We, therefore, believe that the sibling comparison results from the two largest studies in the review should have contributed to its conclusions.[8,9] Unfortunately, these available sibling comparison data were not included in the meta-analysis, which instead extracted the methodologically weaker covariate-adjusted estimates from those studies. The two studies of interest represented over 60% of the weighted sample. They yielded covariate-adjusted hazard ratios of 1.33 (95% confidence interval [CI], 1.23–1.45) and 1.13 (95% CI, 1.05–1.23). However, their sibling comparison results, which were excluded from the review, were weaker and not statistically significant (hazard ratios, 1.21 [95% CI, 0.96–1.52] and 1.09 [0.84–1.42], respectively). These results suggest that familial confounding, rather than a true casual effect, explains much of the observed associations. The weaker associations from the sibling comparisons may thus dampen enthusiasm regarding a potentially meaningful role of exposure to maternal smoking during pregnancy in offspring schizophrenia. An approximately 10%–20% relative difference in rates of what is a rare outcome would suggest that modifying maternal smoking would have only a limited impact on the incidence of offspring schizophrenia.

Like all designs, sibling comparisons are imperfect and have known limitations. The two sibling comparison studies tested a number of the limitations of the design by, for example, also comparing cousins and employing multiple statistical models. Across tests, results supported the familial confounding explanation. This approach is consistent with recommendations for systematically examining assumptions and alternative explanations in family-based studies.[10]

None of the above is intended to suggest that exposure to smoking during pregnancy is harmless. Rather, we believe that the

application of multiple family-based or other quasi-experimental designs—and their inclusion in research syntheses—is vitally important to accurately assess its adverse effects. Further research using these designs could generate a clearer understanding of the public health impact of smoking on future generations and might offer needed insight into the possible environmental causes of schizophrenia.

Supplementary Material

A Contributorship Form detailing each author's specific involvement with this content, as well as any supplementary data, are available online at https://academic.oup.com/ntr.

Funding

Declaration of Interests

None declared.

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