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On Sibling Designs

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To the Editor

Comparisons of siblings that are discordant for particular exposures or outcomes are increasingly used in epidemiology.¹ Frisell et al² have provided important insight into potential limitations of sibling comparisons. We would like to add three points to their thought provoking discussion.

First, given that uncontrolled, unshared environmental factors can bias the results of sibling-matched studies, Frisell et al² note that these aspects should be measured and controlled when possible. Usually discordant sibling studies do, however, control for systematic unshared aspects of the family environment that can be measured, for example, birth order, maternal and paternal age, and gestational age at birth. Furthermore, population estimates controlled for measured unshared aspects of the family environment often render similar estimates to the discordant sibling estimates. It is the nonsystematic aspects of the unshared environment that are most difficult to measure and that tend to be uncontrolled. But evidence suggests that these nonsystematic factors tend to be events that do not relate in any general way to confounding factors.³ Thus, after taking into account the way that discordant sibling studies are actually done, the extent to which their results will be biased by unshared factors remains unclear.

Second, Frisell et al² note that sibling-matched designs will yield causal estimates when all confounders are perfectly shared between siblings and there are no unshared confounders. Although subject to limitations, biometric models from genetically informative data suggest that some outcomes have a low shared environmental contribution to variance.³ Certainly, the lack of a shared environmental contribution to variation within a population, using these models, is not equivalent to no causal effect of shared environmental factors on health

Editors' note: Frisell et al declined an invitation to respond.

outcomes. Nevertheless, given that uncontrolled systematic factors of the nonshared environment will bias the results from discordant sibling designs, and that the purpose of using the discordant sibling design is to control for the shared environmental factors, one must question the appropriateness of a discordant sibling design when convergent evidence suggests that shared environmental factors contribute little to interindividual variation in the outcome of interest.

Third, Frisell et al² underscore the potential dilution of effects in the sibling design when a proportion of “discordant” pairs are actually concordant misclassified pairs—a point that they expand from previous findings in the economics literature.⁴ Frisell et al² discuss random misclassification, however. We suggest that misclassification may not be random. Consider the example of siblings from women discordant for smoking across pregnancies. Misclassification of smoking status may indeed vary systematically by nonshared familial factors such as birth order. For example, few women are likely to take up smoking in their second pregnancy if they did not smoke in the first. Thus, discordant women for whom data indicate smoking in a second but not first pregnancy would be more likely to be “concordant smokers” who were misclassified than women who smoked in a first but not subsequent pregnancies. The impact of this bias may be greater than the bias from random misclassification and may bias toward or away from the null.

Discordant sibling studies are increasingly used to help confirm results from population studies or to indicate the potential for bias in them. Also, genetically informative designs to understand developmental contributions to health increasingly inform these and other epidemiological studies. Discussions of potential biases that accompany evolving study designs will continue to improve our science. Frisell et al’s² thought provoking article should stimulate continued methodological work investigating the practical implications of the types of biases that sibling studies are prone to.

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