Response by Boyd et al to Letter Regarding Article, "Association Between Fetal Congenital Heart Defects and Maternal Risk of Hypertensive Disorders of Pregnancy in the Same Pregnancy and Across Pregnancies"

Heather A. Boyd, PhD
Saima Basit, MSc
Jan Wohlfahrt, MSc, DrMed
Nina Øyen, MD, MPH, DrMed

In Response:

We thank Ziliang Ye and colleagues for their comments on our article, in which we reported associations between offspring congenital heart defects and maternal hypertensive disorders of pregnancy.[1] They suggest 3 possible limitations that may have weakened our study. We contend that, although our study undoubtedly had limitations, those mentioned by Ye et al are not among them.

First, Ye et al argue that our results may have been confounded by medication use, specifically the use of folic acid and vitamin B_{12} to prevent neural tube defects, and the use of medications to treat hypertensive disorders of pregnancy (HDPs). To be a confounder, use of a particular medication would have to be associated with the risks of both HDP and congenital heart defects. Available evidence suggests that periconceptional and first-trimester folic acid use by pregnant women is not associated with increased risk of offspring heart defects.[2] Cardiovascular medications such as nifedipine, labetalol, and magnesium sulfate may (or may not) be teratogenic and are indeed used to treat HDP, but because the signs and symptoms of HDP typically appear at the end of the second trimester, use of these medications to treat HDP is initiated well after heart development is complete (in week 11). Consequently, medication use of the type suggested by Ye et al is unlikely to have confounded associations observed in the same pregnancy; such confounding across pregnancies is even less likely.

Second, Ye et al state that our results might have been more reliable and novel had we considered interactions, presumably between medications. We cannot deny that such interactions might exist and are a possible explanation for the observed association between offspring heart defects and maternal HDP, but a maternal environment hostile to fetal heart development is just as likely. We had no a priori reason to believe that use of specific medications deserved closer study (and Ye et al do not offer any specific candidates), and with a rare exposure and a rare outcome, we did not have the power to evaluate the effect of all possible combinations of medications used by the women in our study cohort on the observed associations.

Finally, Ye et al suggest that we could have used interpolation methods in sensitivity analyses that included pregnancies ending in stillbirth. However, we were not just missing some data on heart defects in stillbirths—we had no data on heart defect status for any stillborn child. Instead, therefore, we based our analysis on assumptions about heart defect prevalence in stillbirths by using the results from other studies. This approach is similar to imputation, with additional external imputation of the essential component that was unknown. The

method also allowed us to investigate the sensitivity of our results to varying heart defect prevalences among stillborn babies.

DISCLOSURES

None.

AFFILIATIONS

Department of Epidemiology Research, Statens Serum Institut, Copenhagen, Denmark (H.A.B., S.B., J.W., N.Ø.). Department of Global Public Health and Primary Care, University of Bergen, Norway (N.Ø.). Center for Medical Genetics and Molecular Medicine, Haukeland University Hospital, Bergen, Norway (N.Ø.).

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