In Reply  We published a study on mode of delivery, more specifically birth by cesarean section (CS), and the development of autism spectrum disorder (ASD).1 In it, we found that CS was associated with ASD in the population. However, the association was attenuated when we used a sibling design, and we concluded that CS was likely not a cause of ASD and a more probable explanation of the association was confounding.

Schendel and Parner claim that results from sibling designs should be interpreted with caution in the case of ASD because ASD is not entirely heritable, and much of what determines diagnosis may not be shared between siblings. They cited a study by Sandin et al,2 which found the heritability of ASD to be lower than previously believed, and a study by Frisell et al3, which discussed some of the limitations of sibling designs. We thank Schendel and Parner for this opportunity to expand on sibling designs and their potential limitations. Although we agree that it is important to acknowledge the limitations of the analysis, we still believe sibling design to be appropriate in this case.

With regards to the study by Frisell et al,3 we disagree with Schendel and Parner’s interpretation of the effect of unshared factors relating to outcome. Frisell et al3 discussed unshared factors that are related to confounding or exposure and showed that, in instances where exposure is more shared within families than are confounders, sibling designs are inappropriate and can in fact lead to increased bias through the “backdoor” mentioned by Schendel and Parner. Conversely, when confounders are more strongly correlated than exposure, not conducting a sibling design can lead to similar bias through a different backdoor path. Thus, Frisell et al3 concluded that sibling designs are appropriate when it can be reasonably assumed that confounders are more correlated between siblings than are exposures.

As Frisell et al3 acknowledged, it is impossible to tell how correlated unmeasured confounders are between siblings and this must be assumed. As mentioned in our strengths and limitations section, the potential correlation of the mode of delivery between siblings is a limitation in our analysis. We did include subgroup analyses on primary CS births and first-born children, which showed no change in results.1 Although this may indicate that the potential clustering of exposure did not seem to impact our results, it is worth noting that this is still a possible limitation. However, we still believe that unmeasured confounding was likely more correlated. For example, if a mother had an unmeasured psychiatric disorder, she may be more likely to undergo a CS4 and more likely to have a child with ASD.5 Such a confounder would be shared among all sibling pairs. Therefore, we would still conclude that a sibling design was appropriate, and despite these limitations, our conclusion that the association between CS and ASD can be largely explained by familial confounding is still valid.

Eileen A. Curran, MPH
Louise C. Kenny, PhD, MRCOG
Ali S. Khashan, PhD

Author Affiliations: The Irish Centre for Fetal and Neonatal Translational Research (INFANT), Department of Obstetrics and Gynaecology, University College Cork, Cork, Ireland (Curran, Kenny, Khashan); Department of Epidemiology and Public Health, University College Cork, Cork, Ireland (Khashan).

Corresponding Author: Ali S. Khashan, PhD, Department of Epidemiology and Public Health, Western Gateway Building, Western Road, Cork, Ireland (a.khashan@ucc.ie).


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