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LETTER TO THE EDITOR

Association between prenatal exposure to Crohn's disease and offspring psychiatric regulatory disturbances

Sir,

We thank Khawar et al. for their Letter "Reconsidering the association between maternal Crohn's disease and offspring psychiatric outcomes" published in *Acta Obstetricia et Gynecologica Scandinavica*,[1] raising concerns regarding our study "Offspring exposure to Crohn's disease during pregnancy and association with psychiatric regulatory disturbances in childhood."[2]

Khawar et al. propose that corticosteroid exposure may explain the associations we detected between Crohn's disease (CD) and offspring sleeping disorder, incontinence, and feeding disorders. Corticosteroids, commonly prescribed during CD flares, cross the placenta and have been associated with adverse neurodevelopmental risks. Although our original models adjusted for grouped anti-inflammatory-medication use in maternal CD (ATC codes A07E (intestinal anti-inflammatory agents), H02A (corticosteroids for systemic use), L04A (immunosuppressants) [yes/no]) dispensed either within (i) 3 months before pregnancy (B3)/trimester one (T1) or (ii) T2–T3, we acknowledge that corticosteroids might constitute distinct pharmacological exposures. To address this, we conducted post-hoc sensitivity analyses adjusting for corticosteroid medication (H02A) during these periods. Corticosteroids were dispensed to 11.7% of mothers with CD and were associated with mildly increased risks of sleeping disorders (HR_{B3-T1} = 1.67 (1.30–2.15), HR_{T2-T3} = 2.02 (1.55–2.63)), incontinence (HR_{B3-T1} = 1.20 (1.00–1.44), HR_{T2-T3} = 1.29 (1.05–1.59)), and other feeding disorders (HR_{B3-T1} = 1.46 (1.12–1.90), HR_{T2-T3} = 1.68 (1.23–2.29)). However, the adjustment for corticosteroid medication did not attenuate the effect sizes of the reported associations[2] between maternal CD and offspring sleeping disorders, incontinence, or other feeding disorders. We refer to Gastroenterology Rep review,[3] supporting continued use of most IBD therapies during pregnancy, citing low-risk profile for fetal neurodevelopment and emphasizing the importance of maternal disease control.

Khawar et al. suggest that the associations we observed between CD exposure and childhood sleeping, incontinence, and feeding disorders may reflect genetic predisposition. They cite GWAS findings,[4,5] indicating that polygenic-risk scores for CD are associated with neurobiological pathways regulating sleep, appetite, and hypothalamic signaling. We agree that shared genetic mechanisms warrant further investigation. However, our population-based epidemiological study was without access to genetic data and was designed to explore associations between maternal CD and specific, often understudied, childhood psychiatric outcomes. We clearly stated that the study did not allow causal claims. We also adjusted for maternal psychiatric diagnoses before delivery, which partially accounts for familial psychiatric vulnerability. Therefore, we are concerned that Khawar et al. may have misunderstood the scope and conclusions of our study.

Khawar et al. further cite a Danish registry study by Jølving et al.,[6] that found no increased risk of certain long-term morbidities, including certain psychiatric disorders, in offspring of mothers with IBD. We appreciate this reference, but the outcomes assessed, such as schizophrenia, anxiety, and personality disorders, differ meaningfully from early-onset regulatory disorders (sleeping, incontinence and feeding disturbances) associated with CD in our study. Thus, the outcomes in Jølving et al.,[6] are not directly comparable with ours, raising concerns about the appropriateness of using that study to challenge the generalizability of ours.

Further research is needed to disentangle the roles of in-utero environmental exposure and genetic predisposition in neurodevelopment. Still, our population-based findings, supported by sensitivity analyses, provide valuable insights into associations between maternal CD and early psychiatric regulatory outcomes.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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