

Association Between Antenatal Exposure to Selective Serotonin Reuptake Inhibitors and Autism: A Need for Further Analysis

To the Editor: The recent systematic review and meta-analysis by Brown et al¹ that aimed to assess risk of autism spectrum disorder (ASD) in children whose mothers were exposed to selective serotonin reuptake inhibitors (SSRIs) during pregnancy was interesting. The authors reported an unclear association between antenatal exposure to SSRI and risk of ASD in offspring that warranted future studies. We applaud Dr Brown and colleagues' meaningful work. However, several important methodological issues regarding study selection should be noted.

Of studies based on the same data sources and overlapping study periods and population, the authors retained the study with the highest rating score in quality assessment for meta-analysis. However, the authors failed to provide a clear theoretical background for that inclusion and exclusion. In the quality assessment section, a study by Hviid et al² was marked as moderate and was included for quantitative synthesis, but a study by Sørensen et al³ was marked as low and was excluded because Hviid et al controlled for other psychotropic drugs. This reason for excluding the study by Sørensen et al is not adequate. First, no other included studies controlled for other psychotropic drugs and met the criteria for adequate consideration of distorting influences. Second, those 2 studies^{2,3} were both rated as high quality using the Newcastle-Ottawa scale.⁴ More importantly, the cohort study by Sørensen et al had an extra data source, the Danish National Hospital Register, and thus had a larger sample size with more ASD cases (91 cases in the SSRI-exposed group) than the study by Hviid et al (52 cases in the SSRI-exposed group), so the study by Sørensen et al might be more capable of assessing the causal association considering that autism cases are relatively rare. In this case, sensitivity analyses should be performed by excluding the study by Hviid et al and including the study by Sørensen et al.

The rationale for excluding the case-control study by Gidaya et al⁵ is also unclear. The authors stated that of the 2 studies that had the same final quality rating, the retrospective study by Hviid et al² was retained because of better control for distorting influences. That reason is not convincing, as the case-control study by Gidaya et al had a better exposure measure. Besides, data extracted from

case-control studies and cohort studies were separately pooled in the quantitative analysis, so the interpretation of the results is based on the 2 pooled odds ratios. In consideration of the limited number of included studies, the results of a meta-analysis of case-control studies would be more robust with inclusion of the study by Gidaya et al.

Overall, even though several studies used the same data sources, those studies were inconsistent in some methodological respects such as study design, sample size, or statistical analysis, which may potentially influence the association of interest. For studies with the same design, sensitivity analyses could be performed to assess the robustness of the results by replacing studies from the same data sources, while for studies of different designs, separate quantitative analysis could also be performed.

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Dr Brown and Colleagues Reply

To the Editor: We thank Shi and Li¹ for their comments on our meta-analysis² regarding the association between antenatal selective serotonin reuptake inhibitor (SSRI) exposure and child autism. Methodological standards for meta-analyses note that, because the unit of observation is the study and not the article, care should be taken to include study subjects only once.³ Shi and Li comment on our decision to exclude, from the quantitative synthesis, 2 of 3 Danish studies with overlapping data sources and study periods.^{4–6} We address their comments below.

First, Shi and Li query why we included the retrospective cohort study by Hviid et al⁴ over that of Sørensen et al,⁵ which had a larger sample size. While we agree that statistical power is critical in the study of rare outcomes, our goal was to disentangle the effect of antenatal SSRI exposure from that of maternal mental illness. We therefore prioritized study quality—specifically, control for confounding by indication—as the criterion for inclusion in the quantitative synthesis. In addition to sociodemographic variables, Hviid et al controlled for maternal mental illness and other prescription drug use. Missing from Sørensen and colleagues' multivariable models were maternal affective disorders and other prescription drug use.

Second, Shi and Li note that a previous meta-analysis⁷ rated Hviid et al⁵ and Sørensen et al⁶ as having “high quality” using the Newcastle-Ottawa scale.⁸ However, this scale does not explicitly address confounding by indication. The Systematic Assessment of Quality in Observational Research (SAQOR) tool that we utilized specifically assesses whether mental illness, other prescription drugs, and all other confounders are controlled for.⁹ This most likely explains the difference in quality ratings between the scales.

Third, Shi and Li question our exclusion of Gidaya et al,⁶ since this study would have been included in pooled estimates for case-control studies, rather than cohort studies along with Hviid et al.⁴ We maintain that inclusion of both studies would have resulted in “duplication” of Danish study subjects³; any bias in these data would have unduly influenced conclusions in a given analysis. We prioritized Hviid et al because of their superior control for confounding by indication; their mental illness variables included not just depression, anxiety, and schizophrenia but other potential indications as well, such as personality disorders and eating disorders.^{10,11}

Fourth, Shi and Li propose that an alternative approach would be to conduct sensitivity analyses wherein the chosen study is replaced with an excluded study. However, given that both Sørensen et al⁵ and Gidaya et al⁶ had incomplete control for confounding by indication, the results would be less robust. In fact, Hviid et al⁴ was the only study, of 8 evaluated, that had adequate control for distorting influences.

In summary, we emphasize the importance of deliberate consideration of confounding by indication in studies of medication use in pregnancy and the use of appropriate quality assessment tools, such as SAQOR, which allow authors to do so in

meta-analyses. Such robust approaches are critical in the creation of appropriate clinical recommendations for women with mental illness in pregnancy.

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