Ch.11.04 A. Prenatal Antidepressants and autism

To address the question of whether use of serotonergic antidepressants (Prozac®, Zoloft® and others) during pregnancy might cause autism spectrum disorder (ASD) in offspring, Brown et al[1] did a retrospective cohort study of women who were receiving public prescription drug coverage during pregnancy in Ontario, Canada, 2002-2010. To adjust for possible confounding variables, they used a computerized algorithm to create a high-dimensional propensity score (HDPS), for which they controlled using inverse-probability weighting. They also generated a multivariate model not using the HDPS.

a. The methods section states: "We weighted serotonergic antidepressant users by the inverse of the HDPS and nonusers by 1 minus the inverse of the HDPS." Is this exactly correct? If not, what would be the correct weighting scheme? (Hint: see Chapter 9.)

No, the correct weighting scheme for nonusers would be the inverse of 1 minus the HDPS.

b. The authors present their results using hazard ratios (HR), which are like risk ratios but more suitable for time-to-event data. From the results of the study: "Risk of autism spectrum disorder was significantly higher with serotonergic antidepressant exposure (4.51 exposed vs 2.03 unexposed per 1000 person- years; between-group difference, 2.48 [95% CI, 2.33-2.62] per 1000 person-years) in crude (HR, 2.16 [95% CI, 1.64- 2.86]) and multivariable-adjusted analyses (HR, 1.59 [95% CI, 1.17-2.17]) (Table 2). After inverse probability of treatment weighting based on the HDPS, the association was not significant (HR, 1.61 [95% CI, 0.997-2.59]) (Table 2)."

The authors' conclusion was: "In children born to mothers receiving public drug coverage in Ontario, Canada, in utero serotonergic antidepressant exposure compared with no exposure was not associated with autism spectrum disorder in the child." Considering the results quoted above, do you agree with the conclusion? Why or why not?

We disagree. The point estimates for the statistically significant multivariable-adjusted analyses (HR 1.59) and for the inverse probability-weighted HDPS analysis (HR 1.61) are almost identical. The only difference is that the 95% CI for the inverse probability-weighted analyses is wider and just barely crosses 1.

The authors' conclusion absurdly dichotomizes statistical significance at 0.05 and selects the less precise estimate so they can fail to reject the null hypothesis. The results of this paper suggest that exposure is associated with about a 60% increased hazard. Of course, the association still may not be causal, but to say exposure "was not associated with autism spectrum disorder in the child" does not accurately represent the results.

REFERENCES

1. Brown HK, Ray JG, Wilton AS, Lunsky Y, Gomes T, Vigod SN. Association Between Serotonergic Antidepressant Use During Pregnancy and Autism Spectrum Disorder in Children. JAMA. 2017;317(15):1544-52.