Opioid use during pregnancy is common. In the US, approximately 7% of women are prescribed opioids during pregnancy. In Scandinavian countries, approximately 1% of women use opioids during pregnancy. While the causes of opioid use and the consequences of their use for the mother have been well studied, the long-term influence of intrauterine exposure to opioid on offspring neurodevelopment is much less clear. Ideally, a randomized clinical trial would provide this evidence, but trials in pregnant women are mostly ethically unfeasible. To evaluate the potential outcomes of fetal exposure to opioids during pregnancy associated with long-term cognitive performance, we rely on observational data, which provides major challenges.

The study by Trønnes et al gives insight into the scholastic skills of children prenatally exposed to opioid analgesics, using data from a large, nationwide, Norwegian birth cohort. The authors compared 1483 children exposed to opioid analgesics during pregnancy with a reference group of 731 children born to mothers with only prepregnancy exposure. The choice of a control group is a sensitive one. Although it might appear straightforward to choose children who were never exposed as controls, the authors argue against this strategy. The never-exposed population is considered an improper counterfactual because such comparison does not correspond to the relevant question and would never have been addressed in a randomized clinical trial. The findings of Trønnes et al suggest that children with intrauterine exposure to opioids and those born to mothers who only used opioids prepregnancy have similar scholastic skills.

Trønnes et al provide an elegant demonstration of how to incorporate the use of inverse probability of treatment weighting (IPTW) in an attempt to control for confounding in large-scale observational data. Confounding occurs when allocation to exposure is related to certain conditions, such as the preference or decision of a medical practitioner (ie, confounding by indication). To illustrate, pregnant women with risk factors, such as young maternal age, that in turn are associated with poor cognitive development in offspring, might be more likely to be prescribed opioids. In this context, IPTW calculates the probability of being exposed to opioid analgesics during pregnancy given an individual’s baseline characteristics. The inverse of this probability is used to obtain weights for each exposed individual. The same applies for individuals in the reference group; each pregnant woman is given a weight corresponding to the inverse of their probability of not being exposed. Hence, higher weights are given to individuals who have a low probability of membership in their group. By applying these weights (zooming in on those that appear out of place in their particular group) a pseudopopulation emerges in which measurable confounders are more balanced within and across groups.

The ability of IPTW to control for confounding depends on how many and how well confounders are measured. Trønnes et al were able to include many important covariates and imputed any missing covariate data. In addition, the authors attempted to address further confounding by indication in their study design, restricting the study sample to women who reported an indication for opioid analgesia during pregnancy.

The restricted study sample, however, has consequences for the generalizability of their results to the general population of Norway, and certainly the US. The findings should be generalized very cautiously in light of the specific Norwegian study base. First, as the authors point out, generalizability to the population of Norway might be affected by self-selection bias owing to a 41%
initial participation rate. Second, data on scholastic performance were not available for children with special educational needs or special language training needs. Although this was the case for less than 5% of the children in the study, it leaves out a very important group possibly affected by opioid exposure. However, the population base of this study allows for a nonresponse analysis, which most US cohorts cannot do given the lack of population registers, and the use of inverse probability with attrition weighting can provide insight in the extent of possible selection bias.5

The generalizability of these results to the US is questionable. In addition to considerable differences in population characteristics, there are substantial differences when it comes to the perception and treatment of pain, as well as the prevalence of opioid prescriptions, between Western Europe and the US.6 The prevalence of prescribed opioid use among women in Norway is in general higher than that of the surrounding Scandinavian countries. However, this higher prevalence is mainly due to Norwegian patients who received small doses of weak opioids, such as codeine and tramadol.7 Furthermore, although the prevalence of prescription of the strong opioid oxycodone seems to be increasing in the Nordic countries and the rest of Western Europe, this increase is nowhere near the alarming increase observed in the US. Prescription incentive for opioids is largely absent in Europe, and if anything, several medicine agencies in the European Union discourage prescriptions of strong opioids. The substantial population differences and the fact that this study lacks information on the exact type of opioid use and dosage precludes a comparison with the current practice in the US. However, this study does convincingly suggest that careful prescription of largely weak opioids in pregnancy need not affect the scholastic performance of the offspring.

Trønnes et al3 were unable to provide insight into the type of opioids, doses, and duration of use because the study relied completely on self-reported data. From 2004 onwards, Norway has a centralized registry with information on drugs dispensed by prescription from pharmacies across the country.8 Registry data provide a rich source of information when it comes to type, doses, and duration of drugs prescribed. In addition, using pharmacy registry data enables the emulation of an intention-to-treat analysis, with the results based on initial treatment assignment. This epidemiologic approach has the advantage of mitigating certain biases owing to nonrandom attrition or crossover. Future studies into the association of opioid use with child cognitive outcomes should make use of the pharmacy registry database.

To conclude, by using an excellent study design and IPTW to address confounding, the authors contribute important evidence on the neurodevelopmental safety of prenatal analgesic opioid exposure in pregnant Norwegian women. The study provides the medical community with potentially useful news. Although opioid use is associated with numerous poor outcomes in the mothers, the neurodevelopmental consequences of carefully prescribed and monitored opioid use on offspring neurodevelopment may not be as problematic.

ARTICLE INFORMATION
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