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Reconciling Sex-Related Bias: An Alternative Method for Data Analysis

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During development, hormones guide the processes that underlie the normal formation and function of tissues.[1,2] Boys' and girls' different hormonal backdrops mean they may differ in their vulnerabilities to endocrine-disrupting chemicals (EDCs).[2,3] However, as highlighted in a new study in *Environmental Health Perspectives*,[3] the relationships between confounding factors and outcomes may themselves differ by sex, and failure to account for this may result in false estimates of effect. The authors of the study propose a new method to address this issue.

"If you think your exposure might act differently on the outcome by sex, you should think about confounders that might *also* act differently by sex, and account for that," says Jessie Buckley, an assistant professor at the Johns Hopkins Bloomberg School of Public Health, who coauthored the new study.

Researchers typically use one of two approaches to determine whether associations between exposures and outcomes differ by sex. The first is stratification, where sex-specific associations are estimated using separate models for males and for females. The second uses a single model with an exposure-by-sex "product term" that allows the estimated associations to differ between males and females.

Both approaches are often assumed to yield estimates that are essentially equivalent. However, this is not always the case given that the product term model does not accommodate sex-related confounding.[3]

In the new study, the authors proposed an augmented product term approach. The alternative model allows exposure–outcome associations to vary between girls and boys. What is unusual is that it also allows confounders—that is, factors that are associated with the exposure of interest, and are also a separate cause or predictor of the outcome—to differ by sex.

To test whether the alternative model produced more accurate estimates than traditional methods, the researchers simulated data from a simple hypothetical EDC study and created a variety of scenarios in which confounding factors, as well as effects of the EDC exposure, differed for girls versus boys. Then they used each of the three models to estimate sex-specific associations between the hypothetical exposure and health outcome.

Because the authors used simulated data for this analysis, they could compare the sex-specific estimates from each model with the "true" exposure–outcome associations that they had determined when they generated the data for the different

Boys and girls can respond in different, sex-specific ways to certain environmental exposures. A new method for analyzing study data may help researchers identify these sex-specific responses more accurately. Image: © monkeybusinessimages/iStockphoto.

scenarios. These comparisons showed that the stratified and augmented product term models produced accurate estimates of sex-specific effects in almost all cases, whereas the traditional product term model performed worse in five of the eight scenarios.[3]

Next, the researchers applied the models to data from an earlier study they had conducted on prenatal phthalate exposure in boys and girls.[4] They found that estimates from the traditional product term model (which—remember—does not allow sex-specific confounding) differed from those generated using the stratified and augmented product term models.[3]

"The different methods do produce slightly different answers, both in the simulated data and in the real-world data, but they are subtle differences," says Joseph Braun, an assistant professor of epidemiology at Brown University who was not involved with the study. However, he also indicates that such differences are important to note. "When taken in concert with all of the other things that you are not accounting for, like selection bias, you may be missing things or getting the wrong answer," he says.

The study authors recommend that future EDC studies consider whether a confounder might have a sex-specific impact on the outcome of interest and incorporate the augmented product term approach in statistical analysis to reduce the risk of inaccurate conclusions. "We just wanted to make sure that people knew the assumption of the models that they are running," says Buckley. "The two approaches that people use are not equivalent when the confounders have different effects on the outcome based on sex."

Drawing attention to this lack of equivalency is a particular strength of the study, in Braun's opinion. "This is the first study that I am aware of that has taken the steps to actually compare the two standard methods that everyone uses to examine effect measure modification," he says. "I think it is a real advancement in the state of science in that it gives us information about whether or not some of the methods we might be using are biased."

Julia R. Barrett, MS, ELS, a Madison, Wisconsin–based science writer and editor, is a member of the National Association of Science Writers and the Board of Editors in the Life Sciences.

References

1. Braun JM. 2017. Early-life exposure to EDCs: role in childhood obesity and neurodevelopment. Nat Rev Endocrinol 13(3):161–173, PMID: 27857130, https://doi.org/10.1038/nrendo.2016.186.
2. Weiss B. 2012. The intersection of neurotoxicology and endocrine disruption. Neurotoxicology 33(6):1410–1419, PMID: 22659293, https://doi.org/10.1016/j.neuro.2012.05.014.
3. Buckley JP, Doherty BT, Keil AP, Engel SM. 2017. Statistical approaches for estimating sex-specific effects in endocrine disruptors research. Environ Health Perspect 125(6):067013, PMID: 28665274, https://doi.org/10.1289/EHP334.
4. Doherty BT, Engel SM, Buckley JP, Silva MJ, Calafat A, Wolff MS. 2017. Prenatal phthalate biomarker concentrations and performance on the Bayley Scales of Infant Development-II in a population of young urban children. Environ Res 152:51–58, PMID: 27741448, https://doi.org/10.1016/j.envres.2016.09.021.