Response to Invited Commentary

The Authors Respond to “Issues With the Consecutive-Pregnancies Approach”

Ya-Hui Yu, Lisa M. Bodnar, Maria M. Brooks, Katherine P. Himes, and Ashley I. Naimi*

* Correspondence to Dr. Ashley I. Naimi, Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, 5131 Parran Hall, 130 DeSoto Street, Pittsburgh, PA 15261 (e-mail: ashley.naimi@pitt.edu).

Initially submitted March 14, 2019; accepted for publication March 18, 2019.

We thank Drs. Snowden and Leonard (1) for elaborating on the generalizability of our results on the relationship between incident obesity and stillbirth (2). To quantify the association between *incident* obesity and stillbirth, we restricted our analyses to women who were not obese at the time of their first pregnancy. Women who became obese prior to a subsequent pregnancy were then classified as exposed.

We agree with the general points made by Snowden and Leonard, which imply that internal and external validity are important considerations. However, they cast the relationship between internal validity and external validity in terms of a trade-off between “estimating causal effects and estimating associations that apply broadly at the population level” (1, p. 1337). This is a common approach to considering the trade-offs between internal and external validity. However, it is important to recognize that notions of generalizability (i.e., whether an association will “apply,” narrowly or broadly, to a population) are also difficult to define when the causal effect of the exposure is ill-defined.

There is renewed interest in the relationship between and relative importance of internal and external validity in the epidemiologic literature (3, 4). Recently, target validity has been proposed as an overall measure that formalizes notions of bias resulting from both internal and external validity (5). However, underlying all characterizations of validity is the critical assumption that the causal effect of interest can be clearly defined. Indeed, bias (whether from threats to internal validity or threats to external validity) is itself defined as a function of the causal effect of interest (5). Therefore, ambiguity in the causal effect translates directly into ambiguous notions of bias—that is, whether an effect is internally or externally valid.

Snowden and Leonard assert that not restricting the analyses to multiparous women leads to associations that are more “broadly applicable” (1). However, they do not clarify what they mean by “applicable.” Reaching clarity on this matter is no easy task, given the many difficulties involved in defining what is meant by the “effect” of prepregnancy obesity on infant and pregnancy outcomes (6). Among these difficulties is the fact that most registry data include women who were obese long before

they became pregnant, as well as women who became obese closer to their conception date. The intended purpose of our analysis was to gauge whether this distinction mattered. We evaluated this by restricting the analyses to women who were not obese at the time of their first pregnancy, and our results suggest that, indeed, the association between prepregnancy obesity and stillbirth remains. In our view, restricting the analyses to this group of women was well worth it, particularly since 1) there is already a large body of evidence in more general populations demonstrating a consistently strong association between prepregnancy obesity and stillbirth (7) and 2) it is not possible to evaluate the notion of whether such associations are externally valid, given the complications in defining the causal effect of obesity.

Many of these concerns also apply to our analysis restricted to women who were not obese in their first pregnancy. The effect of *becoming obese* is just as difficult to define as the effect of obesity in more representative samples of pregnancies. However, without information on precisely when and why women became obese, we felt that restricting our data to focus on incident obesity would provide important information on the robustness of the association between obesity and stillbirth when assessed in different ways. It would be better to study the effect of interventions aimed at modifying or maintaining body mass over a well-defined time period (6). In this case, it would be much easier to both define the effect of interest and to articulate what is meant by external validity.

ACKNOWLEDGMENTS

Author affiliations: Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, Pennsylvania (Ya-Hui Yu, Lisa M. Bodnar, Maria M. Brooks, Ashley I. Naimi); Department of Obstetrics, Gynecology, and Reproductive Sciences, School of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania (Lisa M. Bodnar, Katherine

P. Himes); and Magee-Womens Research Institute, Pittsburgh, Pennsylvania (Lisa M. Bodnar, Katherine P. Himes).

This study was supported by grant HD065807 from the Eunice Kennedy Shriver National Institute of Child Health and Human Development.

Conflict of interest: none declared.

REFERENCES

1. Snowden JM, Leonard SA. Invited commentary: the causal association between obesity and stillbirth—strengths and limitations of the consecutive-pregnancies approach. *Am J Epidemiol.* 2019;188(7):1337–1342.
2. Yu Y-H, Bodnar LM, Brooks MM, et al. Comparison of parametric and nonparametric estimators for the association between incident prepregnancy obesity and stillbirth in a population-based cohort study. *Am J Epidemiol.* 2019;188(7):1328–1336.
3. Lesko CR, Buchanan AL, Westreich D, et al. Generalizing study results: a potential outcomes perspective. *Epidemiology.* 2017;28(4):553–561.
4. Hernán MA, VanderWeele TJ. Compound treatments and transportability of causal inference. *Epidemiology.* 2011;22(3):368–377.
5. Westreich D, Edwards JK, Lesko CR, et al. Target validity and the hierarchy of study designs. *Am J Epidemiol.* 2019;188(2):438–443.
6. Naimi AI. Obtaining actionable inferences from epidemiologic actions. *Epidemiology.* 2019;30(2):243–245.
7. Aune D, Saugstad OD, Henriksen T, et al. Maternal body mass index and the risk of fetal death, stillbirth, and infant death: a systematic review and meta-analysis. *JAMA.* 2014;311(15):1536–1546.