interpreted without awareness of the bias, can have serious adverse consequences for counseling guidelines and health outcomes.

In theory, one can correct for index event bias by adjusting for all other risk factors for the outcome in question. Because some contributing factors are usually unknown, in practice the bias can only partially be removed. We invite Grantz et al. to compare their uncorrected relative risks with the corrected (published) ones in order to see whether adjustment generally led to a movement of relative risks away from the null among women with a previous preterm delivery. Unfortunately, absence of such a movement does not prove the absence of index event bias, but if the expected change is observed, this suggests that index event bias might be part of the explanation of the intriguing findings by Grantz et al.

ACKNOWLEDGMENTS
Conflict of interest: none declared.

REFERENCES

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DOI: 10.1093/aje/kwv275; Advance Access publication: November 14, 2015

FIVE AUTHORS REPLY
We appreciate the interest of Smits et al. (1) in our study (2). They raised an interesting point regarding possible “index event bias,” which is essentially a form of collider stratification bias that becomes possible when studying recurrent conditions. This can result in bias toward the null in crude associations between the risk factor of interest and disease outcome. One of the strengths of our study was our ability to adjust for multiple possible risk factors; however, the ability to adjust for unknown risk factors is a limitation in all epidemiologic studies and not only in this setting. Further, we agree with a point made by the authors in a prior publication (3); namely, the methods currently available to address index event bias in research related to the causal etiology of recurrent events are lacking, and additional methodological work is still needed to adequately address this issue.

Our main interest was not in answering a causal question but rather in prediction of preterm delivery risk in a second pregnancy given a prior history of either term or preterm delivery to assist in clinical attention. Nonetheless, in our example, the concern raised is that adjustment would lead to a movement of the relative risk away from the null among women who had had a previous preterm delivery. In fact, we observed the opposite. As calculated directly from Table 1 in our original article (1), the estimated unadjusted relative risk of a recurrent preterm birth was 1.34 (95% confidence interval: 0.98, 1.81) for smoking and 2.52 (95% confidence interval: 1.94, 3.28) for alcohol use. This is compared with the fully adjusted relative risks of 1.09 (95% confidence interval: 0.71, 1.19) and 2.38 (95% confidence interval: 1.53, 3.71) for smoking and alcohol use, respectively, published in our article (1). Thus, our estimates moved toward, not away from, the null. We believe this result to be reasonably strong evidence for a lack of index event bias in this case, although as Smits et al. rightly point out, it is not possible to completely rule out this type of bias. That said, we sincerely thank the authors for bringing to our attention the previous literature (including their own work) on this interesting area of bias and for giving us the opportunity to more thoroughly investigate the possible role of this bias in our new work.

ACKNOWLEDGMENTS
This work was supported by the Intramural Research Program of the Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health (contracts HHSN275200800002I and HHSN275000004).

Conflict of interest: none declared.

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DOI: 10.1093/aje/kwv277; Advance Access publication: November 14, 2015