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.

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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 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.

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