Response to Invited Commentary

Mumford et al. Respond to “Dietary Fiber, Estradiol, and Cholesterol”

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We appreciate the comments made by Dr. Levitan (1). We agree that the issues related to effect decomposition are indeed of interest in many areas of epidemiologic and clinical research. Methods for addressing effect decomposition require assumptions which must be carefully evaluated in practice (2–5). With advancements in methodology related to effect decomposition, the term direct effect is no longer sufficient to describe the estimated parameter. In the accompanying paper (6), we estimated the “controlled direct effect” of high fiber intake on lipoprotein cholesterol levels. Because estradiol levels are known to vary with age and according to menarcheal and menopausal status (7), we were specifically interested in the direct effects at different controlled estradiol levels, that is, controlled direct effects. In other words, the controlled direct effect corresponds to the effect of fiber intake on lipoprotein cholesterol levels when estradiol is set to a specific level that might be achieved through an intervention. In our case, we considered that estradiol levels could be set by either the onset of menopause, the use of oral contraceptives, or any other intervention that would set estradiol at a certain value.

However, in certain settings researchers may be interested in answering questions related to estimation of “natural direct effects,” in which the intermediate variable is fixed for each individual to the level it would have been under the presence or absence of treatment. In our case, the natural direct effect would correspond to the effect of fiber intake on cholesterol levels, independent of estradiol levels, assuming that estradiol was set to the level it would have been for each subject had she consumed a low (or high) amount of fiber. Essentially, natural direct effects correspond to direct effects where the level of estradiol is allowed to vary across individuals for a fixed level of fiber consumption. This natural direct effect corresponds to a slightly different question, and the distinction is important in the interpretation of results. An advantage of natural direct and indirect effects is that they allow for effect decomposition of a total effect into a natural direct and indirect effect even in the presence of interactions.

In the estimation of direct effects (whether controlled or natural), several assumptions of no unmeasured confounding are required. To estimate controlled direct effects, we must assume that there is no unmeasured confounding of the fiber-cholesterol and estradiol-cholesterol relations. In addition to these assumptions, natural direct effects also require no unmeasured confounding of the fiber-estradiol relation and no estradiol-cholesterol confounders that are effects of fiber intake. In this setting, while we could adjust for confounders of the fiber-estradiol relation, the last assumption was not met. Because of the complex feedback mechanisms that regulate hormone levels throughout the menstrual cycle, levels of other reproductive hormones (such as luteinizing hormone and follicle-stimulating hormone) represent time-varying confounders of the fiber-estradiol relation that are themselves affected by fiber intake (8). However, in settings where these assumptions hold, one can estimate natural direct effects in a manner similar to our analysis, but by constructing 2 marginal structural models which are conditional on baseline covariates, as outlined by VanderWeele (2). If we could have assumed that there was no interaction between fiber intake and estradiol on the individual level, then the controlled and natural direct effects would have been equivalent. In any case, if one is interested in controlled or natural direct effects, sensitivity analyses for unmeasured confounders are always relevant and important in assessing the conclusiveness of one’s findings (9).

Inherent in any analysis are assumptions that affect our interpretation of the results. When estimating controlled or natural direct effects, special attention needs to be paid to the assumptions required for effect decomposition and for identification (i.e., the no-unmeasured-confounding assumptions above). Furthermore, one should be clear about the questions being answered by each effect and the specific interpretation of these effect estimates.
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REFERENCES
