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Nonlinear Exposure-Outcome Associations and Public Health Policy

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To the Editor

Dr Chokshi and colleagues¹ highlighted the challenges of nonlinear associations for effective public health interventions, including the potential harms caused by adopting the approach of shifting an entire exposure distribution.

These concerns are valid if the exposure-outcome relationship is causal and the J-shape of the association is a true representation of the causal relationship. If the association is not causal, then intervening on the exposure will have no effect, although it may divert resources from effective interventions. Furthermore, if the lower end of the apparent J-shape is biased and there is in fact a causal linear association, then their concerns are unwarranted. Key is the need to understand what types of bias could produce an association in one end of the distribution that is in the direction opposite to that in the rest of the distribution. Chokshi and colleagues highlighted the importance of reverse causality, in which existing (but unknown) disease at the time of exposure assessment influences its level and the outcome. For example, the observational J-shaped association of alcohol with coronary heart disease (CHD) has been attributed to patients with disease being more likely to quit drinking.

Recent studies highlight ways of assessing potential biases, including matched study designs and instrumental variable analyses. A large, matched sibling study suggested that the U-shape of the association of maternal age with adverse perinatal outcomes was linear or J-shaped, highlighting the greater risk of older maternal age.² Another large study used offspring body mass index (BMI) as an instrumental variable for an individual's own BMI, because offspring BMI will not be influenced by any existing disease, and showed that the J-shape of the BMI-respiratory disease association is likely to be biased at the lower end, with the causal relationship probably positively linear.³ Using genetic variants as instrumental variables (mendelian randomization) has become increasingly popular, because genetic variants are unaffected by disease and not likely to be related to confounding factors that explain nongenetic associations. Applications of mendelian randomization have assumed

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linear associations between exposure and outcome and between genes and exposure, but new developments allow use of genetic variants to test nonlinear assumptions⁴ and suggest that the causal association between alcohol and CHD is positive and linear.⁵

Improving public health requires interventions that target causes of disease and so depends on improving causal inference, including understanding the veracity of J-shaped associations. Using a range of different methods can help improve causal inference and may suggest linear effects that challenge some of the concerns of Chokshi and colleagues.

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