

striction, the authors extrapolated the results to the entire pregnancy, which may not be justifiable. The clinical interpretation of the risk estimates in this study may not be applicable to shorter intervals between Tdap vaccinations or vaccines given during the first and second trimesters.

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1. Sukumaran L, McCarthy NL, Kharbanda EO, et al. Association of Tdap vaccination with acute events and adverse birth outcomes among pregnant women with prior tetanus-containing immunizations. *JAMA*. 2015;314(15):1581-1587.
2. Naleway AL, Gold R, Kurosky S, et al. Identifying pregnancy episodes, outcomes, and mother-infant pairs in the Vaccine Safety Datalink. *Vaccine*. 2013;31(27):2898-2903.
3. Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. *Lancet*. 2008;371(9606):75-84.
4. Shrank WH, Patrick AR, Brookhart MA. Healthy user and related biases in observational studies of preventive interventions: a primer for physicians. *J Gen Intern Med*. 2011;26(5):546-550.

In Reply Ms Zhu and colleagues express concerns regarding potential bias and confounding in the study evaluating the safety of repeated tetanus-containing vaccines in pregnancy.

First, they point to the accuracy of methods for identifying gestational age. The pregnancy episode algorithm was used to identify live births in our study but was not the method used for identifying gestational age. The validation data presented were specific to the pregnancy episode algorithm for identifying live births. We stated in the article that we limited the cohort for birth outcomes to “records that contained information on the neonate (ie, weight and gestational age).” In the Vaccine Safety Datalink, gestational age data come from electronic medical record and state birth registry data, which are based on clinician assessment. The clinician uses all available data to determine this estimate, including estimated due date based on ultrasound and last menstrual period data and can adjust this estimate based on the infant’s appearance at birth.

Zhu and colleagues also raise concerns about risk factors that were used in the analysis of birth outcomes. Despite the change in direction of the relative risk with adjustment, both the unadjusted and adjusted risk estimates were nonsignificant, and it is inappropriate to overinterpret nonsignificant point estimates on either side of the null. After adjustment for adequacy of prenatal care, comorbidities, and pregnancy complications (which were clinically similar between the groups compared), in addition to gestational age at vaccination, health care site, maternal age, and length of enrollment, we still did not find an association. These adjustments

strengthen the overall findings, especially because we had substantial statistical power to detect a difference in birth outcomes. A healthy user effect would not be expected, as all of the women in our study were vaccinated, and women during their prime childbearing years are generally healthy and seek preventive care during pregnancy.

Finally, Zhu and colleagues suggest that because most Tdap vaccinations in our study were given in the third trimester, our results might not apply to vaccinations given earlier in pregnancy. Although it is true that 67.4% of the pregnancies had Tdap in the third trimester, there were 9505 pregnancies in which vaccinations were given in the first or second trimester. The Advisory Committee on Immunization Practices currently recommends Tdap at any time during pregnancy with a preference for third trimester administration to “provide the highest concentration of maternal antibodies to be transferred closer to birth.”¹ This optimal timing for administration corresponds to the majority of vaccinations given in our study. Therefore, our findings are applicable to pregnant women whose clinicians are following recommendations. However, we agree that additional data for first trimester vaccination will further strengthen the evidence base regarding Tdap safety in early pregnancy.

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1. Centers for Disease Control and Prevention (CDC). Updated recommendations for use of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine (Tdap) in pregnant women—Advisory Committee on Immunization Practices (ACIP), 2012. *MMWR Morb Mortal Wkly Rep*. 2013;62(7):131-135.

Nonlinear Exposure-Outcome Associations and Public Health Policy

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 high-

lighted 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 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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1. Chokshi DA, El-Sayed AM, Stine NW. J-shaped curves and public health. *JAMA*. 2015;314(13):1339-1340.

2. Lawlor DA, Mortensen L, Andersen AM. Mechanisms underlying the associations of maternal age with adverse perinatal outcomes: a sibling study of 264 695 Danish women and their firstborn offspring. *Int J Epidemiol*. 2011;40(5):1205-1214.

3. Davey Smith G, Sterne JA, Fraser A, Tynelius P, Lawlor DA, Rasmussen F. The association between BMI and mortality using offspring BMI as an indicator of own BMI: large intergenerational mortality study. *BMJ*. 2009;339:b5043.

4. Silverwood RJ, Holmes MV, Dale CE, et al; Alcohol-ADH1B Consortium. Testing for nonlinear causal effects using a binary genotype in a mendelian randomization study: application to alcohol and cardiovascular traits. *Int J Epidemiol*. 2014;43(6):1781-1790.

5. Holmes MV, Dale CE, Zuccolo L, et al; InterAct Consortium. Association between alcohol and cardiovascular disease: mendelian randomisation analysis based on individual participant data. *BMJ*. 2014;349:g4164.

To the Editor The Viewpoint by Dr Chokshi and colleagues¹ discussed apparent nonlinear associations often reported in studies. However, the examples used to highlight the inherently paradoxical nature of J-shaped curves were misleading, especially in the context of a risk factor such as blood pressure.

Studies have shown an erosion of the J-shaped curve when a more informed analytical approach is taken and the risk of confounding is rigorously mitigated.² For example, in a large cohort of approximately 5000 men with a history of myocardial infarction,³ a J-shaped curve was observed between blood pressure and risk of all-cause and CHD mortality. But after accounting for reverse causality (2-year wash out), the same study reported linear associations.

In our opinion, the spurious associations described in the examples by Chokshi and colleagues could, in part, be attributable to flaws in the methods used,⁴ such as the lack of control of regression dilution bias, not accounting for reverse causality, confounding (time varying or unmeasured), conditioning models on colliders (that induce or exaggerate effects), or not adequately addressing mediators. A meta-analysis of large-scale interventional studies, which is not prone to such biases, has shown no differential effects of blood pressure lowering by the presence or absence of prior disease (eg, CHD, stroke) or by baseline blood pressure levels.⁵ If, however, a nonlinear relationship truly does exist, which may be the case for certain subpopulations, at certain risk factor ranges, or for selected outcomes, then the potential absolute effect of differential risk factor modification on individual and population health should be assessed before changing policies.

In the case of blood pressure, the more reliable evidence (by study design and methodology) suggests, in general, an absence of a J-shaped relationship with cardiovascular conditions. Until there is consensus on the shape of a relationship for specific cases, prudence should be exercised before recommending policy-level changes.

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1. Chokshi DA, El-Sayed AM, Stine NW. J-shaped curves and public health. *JAMA*. 2015;314(13):1339-1340.

2. Rahimi K, Emdin CA, MacMahon S. The epidemiology of blood pressure and its worldwide management. *Circ Res*. 2015;116(6):925-936.
3. Flack JM, Neaton J, Grimm R Jr, et al; Multiple Risk Factor Intervention Trial Research Group. Blood pressure and mortality among men with prior myocardial infarction. *Circulation*. 1995;92(9):2437-2445.
4. Marschner IC, Simes RJ, Keech A. Biases in the identification of risk factor thresholds and J-curves. *Am J Epidemiol*. 2007;166(7):824-831.
5. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. *BMJ*. 2009;338:b1665.

In Reply Dr Fraser and colleagues and Dr Kiran and colleagues underscore important methodologic issues surrounding J-shaped curves—particularly reverse causality and the need for rigorous research on the precise trajectories of exposure-outcome associations.

We agree with Fraser and colleagues that improvements in causal inference methods are crucial to understanding the public health implications of interventions. However, we caution that instrumental variables may have some limitations in cases in which nonlinear exposure-outcome relationships actually exist. At issue is the assumption that the instrument itself has a linear effect on the exposure variable at all levels of the distribution. Therefore, investigators must ensure that instruments behave similarly at the extremes of the exposure distribution for these tools to be helpful in the setting of J-shaped curves.

Kiran and colleagues take issue with the evidence for a J-shaped association between mortality and achieved blood pressure; we agree that the evidence remains disputed. Kiran and colleagues also appear to agree with our statement, “As illustrated by the case of blood pressure, the nature of interventions may matter as much as risk factor distributions.” That is, different methods to modify blood pressure may have differential effects on population-level mortality outcomes, and this must be measured.

Where we may diverge, however, is whether public health practitioners should await perfect evidentiary consensus prior to acting on major health issues such as hypertension. For example, the case of sodium consumption, a major risk factor for hypertension, lays bare an issue with public framing and communication. A recent Institute of Medicine report contested the evidence for limiting sodium intake in the general population to less than 2.3 g per day (and to less than 1.5 g per day in specific subpopulations).¹ In the wake of the report’s publication, controversy swirled around disagreement among governmental health agencies about targets for sodium intake. Yet lost in the public debate was the fact that the majority of Americans consume sodium in excess of virtually all recommended thresholds and remain at elevated risk for hypertensive heart disease. In this situation, empirical pursuit of the precise trajectory of the sodium-mortality curve is essential but should not preclude identification of clear excess as an opportunity to address

such a consequential risk factor. For instance, the New York City Department of Health and Mental Hygiene recently enacted a policy that requires chain restaurants to post warning labels next to individual items that contain more than 2.3 g of salt each.

Unintended consequences of population-based approaches to prevention are real; in fact, they are particularly salient for risk factors that follow a J-shaped curve. Public health leaders must therefore elucidate the causal mechanisms underlying major risk factors—but also pursue effective interventions to address them, even when precise mechanisms remain uncertain.

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1. Institute of Medicine. Sodium Intake in Populations: Assessment of Evidence. National Academies website. <http://iom.nationalacademies.org/Reports/2013/Sodium-Intake-in-Populations-Assessment-of-Evidence.aspx>. Accessed November 25, 2015.

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