JAMA Guide to Statistics and Methods

Using the E-Value to Assess the Potential Effect of Unmeasured Confounding in Observational Studies

Sebastien Haneuse, PhD; Tyler J. VanderWeele, PhD; David Arterburn, MD

Randomized trials serve as the standard for comparative studies of treatment effects. In many settings, it may not be feasible or ethical to conduct a randomized study,[1] and researchers may pursue observational studies to better understand clinical outcomes. A central limitation of observational studies is the potential for confounding bias that arises because treatment assignment is not random. Thus, the observed associations may be attributable to differences other than the treatment being investigated and causality cannot be assumed.

In the October 16, 2018, issue of *JAMA*, results from a large, multisite observational study of the association between bariatric surgery and long-term macrovascular disease outcomes among patients with severe obesity and type 2 diabetes was reported by Fisher et al.[2] Using data from 5301 patients aged 19 to 79 years who underwent bariatric surgery at 1 of 4 integrated health systems in the United States between 2005 and 2011 and 14 934 matched nonsurgical patients, they found that bariatric surgery was associated with a 40% lower incidence of macrovascular disease at 5 years (2.1% in the surgical group and 4.3% in the nonsurgical group; hazard ratio [HR], 0.60 [95% CI, 0.42-0.86]).

Two strategies were used to mitigate confounding bias. In the first, a matched cohort design was used where nonsurgical patients were matched to surgical patients on the basis of a priori–identified potential confounders (study site, age, sex, body mass index, hemoglobin A_{1c} level, insulin use, observed diabetes duration, and prior health care use). In the second strategy used to adjust for confounding bias, the primary results were based on the fit of a multivariable Cox model that adjusted for all of the factors used in the matching as well as a broader range of potential confounders (Table 1 in the article[2]). Thus, any imbalances in the observed potential confounders that remained after the matching process were controlled for by the statistical analysis. Despite these efforts, however, given the observational design, the potential for unmeasured confounding remained.

Why Is the E-Value Used?

While matching and regression-based analysis provide some control of confounding, it can only be with respect to factors that are measured. The potential for confounding from factors that were not measured in the study still exists. To assess how much of a problem unmeasured confounding factors may pose, researchers may conduct a sensitivity or bias analysis.[3] Common to most of these sensitivity analysis methods is the use of a formula for which 2 inputs are required: (1) the strength and direction of the association between the unmeasured confounder and treatment choice and (2) the strength and direction of association between the unmeasured confounder and outcome.[4]

Furthermore, additional inputs or information may be needed, such as the prevalence of the unmeasured confounder and how it is associated with measured confounders. When it is known what the unmeasured confounder is, these could potentially be obtained from published studies and/or through other data sources. For example, smoking is a known risk factor for developing cardiovascular disease but the smoking status for an individual patient may not be included in a database. In this case, an assumption about the prevalence of smoking could be made based on prior research where smoking status was considered in similar clinical conditions. However, the prevalence cannot be estimated for a true unknown confounder. Additionally, many approaches require making simplifying assumptions such as that the unmeasured confounder is binary. Thus, sensitivity analyses of this type can only proceed once additional information, typically in the form of a series of inputs for some formulas, has been specified by investigators. Because decisions about each of the assumptions can affect the analysis results, the most rigorous approach to these types of sensitivity analyses would involve investigators considering a broad range of values for each input and then examining how the results are influenced.

While achievable in principle, this approach has limitations. First, the approach has been criticized as being susceptible to misuse, in the sense that an investigator could choose to focus on assumptions that make the original result seem robust. Second, if many scenarios are considered, there is potential for conflicting results within the sensitivity analysis, which may make it difficult to draw firm conclusions.

The E-value is an alternative approach to sensitivity analyses for unmeasured confounding in observational studies that avoids making assumptions that, in turn, require subjective assignment of inputs for some formulas.[4] Specifically, an E-value analysis asks the question: how strong would the unmeasured confounding have to be to negate the observed results?[5] The E-value itself answers this question by quantifying the minimum strength of association on the risk ratio scale that an unmeasured confounder must have with both the treatment and outcome, while simultaneously considering the measured covariates, to negate the observed treatment–outcome association. If the strength of unmeasured confounding is weaker than indicated by the E-value, then the main study result could not be overturned to one of "no association" (ie, moving the estimated risk ratio to 1.0) by the unmeasured confounder. E-values can therefore help assess the robustness of the main study result by considering whether unmeasured confounding of this magnitude is plausible. The E-value provides a measure related to the *evidence* for causality, hence the name "E-value."

The E-value has many appealing features. First, in contrast to standard methods for sensitivity, it requires no assumptions from investigators. Second, it is intuitive because the lowest possible number is 1. The higher the E-value is, the stronger the unmeasured confounding must be to explain the observed association.

© 2019 American Medical Association. All rights reserved.

Downloaded from jamanetwork.com by guest on 01/24/2019

Third, the calculation is also readily applied to the bounds of a 95% CI. Thus, investigators can assess the extent of unmeasured confounding that would be required to shift the confidence interval so that it includes a risk ratio of 1.0 (ie, no association). Fourth, the E-value is simple to calculate for a range of effect measures, including relative risks, HRs, and risk differences, and study designs. The formulas for the E-value for different effect measures, including continuous outcomes, are available[4] and the E-value has been implemented in freely available software and an online calculator (https://evalue.hmdc.harvard.edu/app/).[6]

What Are the Limitations of the E-Value?

The E-value is a general tool for sensitivity analyses that does not require assumptions about the nature of the unmeasured confounder. In some settings, investigators may be amenable to making assumptions (eg, about the prevalence of an unmeasured confounder) so that their sensitivity analyses can be tailored to their specific study design and/or statistical analyses. Such analyses, however, should always be considered in the context of the plausibility of the assumptions made.

Why Did the Authors Use the E-Value in This Particular Study?

The data used by Fisher and colleagues[2] were abstracted retrospectively from the medical record databases of 4 integrated health care systems and, as such, are representative of clinical decisions and care at these institutions. Because the investigative team did not have control over whether patients underwent bariatric surgery (ie, treatment was not randomly assigned), the potential for unmeasured confounding bias needed to be acknowledged and thoroughly investigated.

How Should the E-Value Findings Be Interpreted in This Particular Study?

Fisher and colleagues[2] found that bariatric surgery was associated with a lower composite incidence of macrovascular events at 5 years (2.1% in the surgical group vs 4.3% in the nonsurgical group) that had an HR of 0.60 (95% CI, 0.42-0.86). The E-value for this was 2.72, meaning that residual confounding could explain the observed association if there exists an unmeasured covariate having a relative risk association at least as large as 2.72 with both macrovascular events and with bariatric surgery. The E-value for the upper limit of the confidence interval was 1.60. In the Fisher et al[2] study, the HRs for some of the known, powerful macrovascular disease risk factors were 1.09 (95% CI, 0.85-1.41) for hypertension, 1.88 (95% CI, 1.34-2.63) for dyslipidemia, and 1.48 (95% CI, 1.17-1.87) for being a current smoker. It is not likely that an unmeasured or unknown confounder would have a substantially greater effect on macrovascular disease development than these known risk factors by having a relative risk exceeding 2.72.

Caveats to Consider When Looking at Results Based on the E-Value

E-values must be interpreted, and indeed only have meaning, within the context of the study at hand. In particular, its magnitude may be large or small depending on the magnitude of the associations of other risk factors. For example, if most other risk factors have an HR of 1.1, then an E-value of 1.3 will be relatively large because unmeasured confounding would have to have much larger effects than most risk factors to explain away the reported association. In contrast, if many risk factors have an HR of 2.0, then an E-value of 1.3 will be relatively modest. The adjustments that have been performed (ie, for the observed confounders) should also be considered.

ARTICLE INFORMATION

Author Affiliations: Department of Biostatistics, Harvard T.H. Chan School of Public Health, Boston, Massachusetts (Haneuse, VanderWeele); Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, Massachusetts (VanderWeele); Kaiser Permanente Washington Health Research Institute, Seattle, Washington (Arterburn); Department of Medicine, University of Washington, Seattle (Arterburn).

Corresponding Author: Sebastien Haneuse, PhD, Department of Biostatistics, Department of Biostatistics, Harvard T.H. Chan School of Public Health, 655 Huntington Ave, Bldg II, Room 407, Boston, MA 02115 (shaneuse@hsph.harvard.edu).

Section Editors: Roger J. Lewis, MD, PhD, Department of Emergency Medicine, Harbor-UCLA Medical Center and David Geffen School of Medicine at UCLA; and Edward H. Livingston, MD, Deputy Editor, *JAMA*.

Published Online: January 24, 2019. doi:10.1001/jama.2018.21554

Conflict of Interest Disclosures: Drs Haneuse and VanderWeele reported receiving grants from the National Institutes of Health. Dr Arterburn reported receiving grants from the National Institutes of Health and Patient-Centered Outcomes Research Institute. No other disclosures were reported.

REFERENCES

1. Courcoulas AP, Yanovski SZ, Bonds D, et al. Long-term outcomes of bariatric surgery: a National Institutes of Health symposium. *JAMA Surg*. 2014; 149(12):1323-1329. doi:10.1001/jamasurg.2014.2440

2. Fisher DP, Johnson E, Haneuse S, et al. Association between bariatric surgery and macrovascular disease outcomes in patients with type 2 diabetes and severe obesity. *JAMA*. 2018; 320(15):1570-1582. doi:10.1001/jama.2018.14619

3. Lash TL, Fox MP, Fink AK. *Applying Quantitative Bias Analysis to Epidemiologic Data*. Berlin, Germany: Springer Science & Business Media; 2011.

4. Ding P, VanderWeele TJ. Sensitivity analysis without assumptions. *Epidemiology*. 2016;27(3): 368-377. doi:10.1097/EDE.0000000000000457

5. VanderWeele TJ, Ding P. Sensitivity analysis in observational research: introducing the E-value. *Ann Intern Med*. 2017;167(4):268-274. doi:10.7326/M16-2607

6. Mathur MB, Ding P, Riddell CA, VanderWeele TJ. Web site and R Package for computing E-values. *Epidemiology*. 2018;29(5):e45-e47. doi:10.1097/EDE.0000000000000864

© 2019 American Medical Association. All rights reserved.

Downloaded from jamanetwork.com by guest on 01/24/2019