residual-confounding risk? Well, several such formulas are (like E_{val}) suitable for pocket calculators and spreadsheets,[8,9] yet allow non-extreme and symmetric treatment of unknowns like confounder prevalences. Such formulas facilitate full portrayal of uncertainty about bias toward as well as away from the null—provided the user is acquainted enough with the topic, study design and data to specify plausible values for their inputs.

Acknowledgements

Conflict of interest

None declared.

References

1. VanderWeele TJ, Mathur MB, Ding P. Correcting misinterpretations of the E-value. *Ann Intern Med* 2019;**170**:131–32.
2. VanderWeele TJ, Ding P, Mathur M. Technical considerations in the use of the E-value. *J Causal Inference* 2019;**7**. https://biostats.bepress.com/harvardbiostat/paper215.
3. Haneuse S, VanderWeele TJ, Arterburn D. Using the E-value to assess the potential effect of unmeasured confounding in observational studies. *JAMA* 2019;**321**:602–03.
4. VanderWeele TJ, Mathur MB. Commentary: developing best-practice guidelines for the reporting of E-values. *Int J Epidemiol* 2020;**49**:1495–97.
5. Ioannidis JPA, Tan YT, Blum MR. Limitations and misinterpretations of E-values for sensitivity analyses of observational studies. *Ann Intern Med* 2019;**170**:108–11.
6. Hamra GB. Re: "Applying the E-value to assess the robustness of epidemiologic fields of inquiry to unmeasured confounding." *Am J Epidemiol* 2019;**188**:1578–580.
7. Blum MR, Tan YT, Ioannidis JPA. Use of E-values for addressing confounding in observational studies—An empirical assessment of the literature. *Int J Epidemiol* 2020;**49**:1482–94.
8. Greenland S, Lash TL. Bias analysis. In: Rothman KJ, Greenland S, Lash TL (eds). *Modern Epidemiology*. Chap. 19, 3rd edn. Philadelphia, PA: Lippincott Williams and Wilkins, 2008, pp. 345–80.
9. Lash TL, Fox MP, Fink AK. *Applying Quantitative Bias Analysis to Epidemiological Data*. New York: Springer, 2009.
10. Brown HK, Ray JG, Wilton AS, Lunsky Y, Gomes T, Vigod SN. Association between serotonergic antidepressant use during pregnancy and autism spectrum disorder in children. *JAMA* 2017;**317**:1544–552.
11. Greenland S, Mickey RM. Closed-form and dually consistent methods for $2 \times 2 \times K$ and $I \times J \times K$ tables. *Appl Stat* 1988;**37**:335–43.
12. Greenland S. Transparency and disclosure, neutrality and balance: shared values or just shared words? *J Epidemiol Community Health* 2012;**66**:967–70.
13. Greenland S. Invited commentary: the need for cognitive science in methodology. *Am J Epidemiol* 2017;**186**:639–45.
14. Amrhein V, Greenland S, McShane B. Scientists rise up against statistical significance. *Nature* 2019;**567**:305–07.
15. McShane BB, Gal D, Gelman A, Robert C, Tackett JL. Abandon statistical significance. *Am Stat* 2019;**73**:235–45.

Commentary: Quantifying the unknown unknowns

Rolf HH Groenwold [iD] [1,2]

[1]Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, The Netherlands and
[2]Department of Biomedical Data Sciences, Leiden University Medical Center, Leiden, The Netherlands

Corresponding author. Department of Clinical Epidemiology, Leiden University Medical Center, Albinusdreef 2, 2333 ZA Leiden, The Netherlands. E-mail: R.H.H.Groenwold@lumc.nl

Observational studies of the effects of exposures or medical treatments usually suffer from confounding. Whereas measured confounding variables can be adjusted for, it is often impossible to correct for unmeasured confounding. Unfortunately, the potential impact of unmeasured confounding, and whether an observed relation (or part of it) may be due to unmeasured confounding, is not often discussed.[1–3]

To guide the thinking about unmeasured confounding, a useful classification is in known, yet unmeasured, confounding variables (the 'known unknowns'), and unknown, and therefore unmeasured, confounding variables

(the 'unknown unknowns'). Given the former are known, their relation with exposure and outcome may be known too, and their potential confounding effect can often be quantified through bias analysis.[4–6]

A starting point for the discussion about unknown unknowns could be to ask what an unmeasured confounding variable should look like in order to explain the observed effect, if in fact there is no exposure–outcome relation.[6,7] This can be quantified by the E-value, which is the minimum strength of association, on a risk ratio scale, an unmeasured confounding variable would need to have with both exposure and outcome in order to explain the observed effect.[8] Although the E-value was proposed only recently, Blum *et al*. have already performed a systematic review of its use and interpretation, published in this issue.[9]

They found that studies that report similar E-values draw different conclusions about the potential for unmeasured confounding. Given that the E-value is merely a function of the effect estimate (e.g. estimated risk ratio), this basically shows that, despite similar effect estimates, the perceived potential for unmeasured confounding differs between studies. A simple reason is that one field of research may be more prone to unmeasured confounding than another.[10] Furthermore, the study design, rather than effect estimate, is informative about the potential for unmeasured confounding. Consider three almost identical studies of the same exposure–outcome relation. All three studies find that exposure increases the risk of the outcome by, say, 33% (relative risk = 1.33). For each study, the E-value is 2. But once you know that one study is a large randomized trial, one is an observational study with extensive adjustment for confounding variables, and one is an observational study with adjustment for age and sex only, the potential for unmeasured confounding clearly differs between the different studies, despite the E-value being the same.

Critics of the E-value might argue that it does not quantify other sources of bias. Indeed, E-values are intended to quantify the discussion about unmeasured confounding, but not about, e.g. measurement error or missing values. But since it was never the intention of E-values to do so, the E-value is not to be blamed. Also, E-values assume that the strength of the relations of the confounding variable with exposure and with the outcome are the same. Those who consider this unrealistic, can apply slightly more complicated formulae,[11] of which the E-value is just a particular case. Furthermore, the E-value considers the perhaps unrealistic situation that the exposure–outcome relation is null. It is, however, possible to calculate E-values for non-null hypotheses.[8] Finally, although E-values are often presented for a single unmeasured confounding variable, they can be thought of as a summary of multiple unmeasured variables.[11] Note that all these concerns are about the use of the E-value, not about the E-value itself.

A central issue in the debate about the E-value seems to be whether this tool is a useful first step when considering unmeasured confounding or whether it will do more harm than good by being too simplistic.[12–14] The latter concern is justified should the E-value prevent researchers from applying more advanced bias analysis methods. But current practice is that these methods are hardly ever used anyway.[1–3] Blum *et al*. argue that 'facile automation in calculating E-values may compound the already poor handling of confounding'.[9] However, that fear is not supported by the numbers found in their review. In 69 papers in which an E-value was reported, 18 made no comment about the potential impact of unmeasured confounding, whereas no such comment was made in 52 of the 69 matched control papers. These numbers suggest that, among researchers who reported an E-value, there appears to be more (not less!) attention to unmeasured confounding, which in any case is a starting point for further discussions about that topic.

Despite at least 60 years of literature about bias analysis for unmeasured confounding,[15] little progress has been made in practice: usually unmeasured confounding is addressed only vaguely, and often not at all.[1–3] We should move beyond unsubstantiated statements about unmeasured confounding being present or not. E-Values are not meant to reduce discussions about unmeasured confounding to the mindless reporting of a single value. Instead, they could provide a starting point for a substantive debate about what unknown unknowns might look like.

Funding

Conflict of interest

None declared.

References

1. Hemkens LG, Ewald H, Naudet F *et al*et al. Interpretation of epidemiologic studies very often lacked adequate consideration of confounding. *J Clin Epidemiol* 2018;**93**:94–102.
2. Pouwels KB, Widyakusuma NN, Groenwold RH, Hak E. Quality of reporting of confounding remained suboptimal after the STROBE guideline. *J Clin Epidemiol* 2016;**69**:217–24.
3. Groenwold RH, Van Deursen AM, Hoes AW, Hak E. Poor quality of reporting confounding bias in observational intervention studies: a systematic review. *Ann Epidemiol* 2008;**18**:746–51.

4. Lin DY, Psaty BM, Kronmal RA. Assessing the sensitivity of regression results to unmeasured confounders in observational studies. *Biometrics* 1998;**54**:948–63.

5. Lash TL, Fox MP, Fink AK. *Applying Quantitative Bias Analysis to Epidemiologic Data*. New York: Springer-Verlag, 2009.

6. Groenwold RH, Sterne JA, Lawlor DA, Moons KG, Hoes AW, Tilling K. Sensitivity analysis for the effects of multiple unmeasured confounders. *Ann Epidemiol* 2016;**26**:605–11.

7. Phillips CV. Quantifying and reporting uncertainty from systematic errors. *Epidemiology* 2003;**14**:459–66.

8. VanderWeele TJ, Ding P. Sensitivity analysis in observational research: introducing the E-value. *Ann Intern Med* 2017;**167**:268–74.

9. Blum MR, Tan YJ, Ioannidis JPA. Use of E-values for addressing confounding in observational studies—an empirical assessment of the literature. *Int J Epidemiol* 2020;**49**:1482–94.

10. Trinquart L, Erlinger AL, Petersen JM, Fox M, Galea S. Applying the E value to assess the robustness of epidemiologic fields of inquiry to unmeasured confounding. *Am J Epidemiol* 2019;**188**:1174–80.

11. Ding P, VanderWeele TJ. Sensitivity analysis without assumptions. *Epidemiology* 2016;**27**:368–77.

12. VanderWeele TJ, Mathur MB, Ding P. Correcting misinterpretations of the E-value. *Ann Intern Med* 2019;**170**:131–2.

13. Ioannidis JPA, Tan YJ, Blum MR. Limitations and misinterpretations of E-values for sensitivity analyses of observational studies. *Ann Intern Med* 2019;**170**:108–11.

14. Haneuse S, VanderWeele TJ, Arterburn D. Using the E-value to assess the potential effect of unmeasured confounding in observational studies. *JAMA* 2019;**321**:602–3.

15. Cornfield J, Haenszel W, Hammond EC, Lilienfeld AM, Shimkin MB, Wynder EL. Smoking and lung cancer: recent evidence and a discussion of some questions. *J Nat Canc Inst* 1959;**22**:173–203.

Commentary: The value of E-values and why they are not enough

Matthew P Fox,[1]* Onyebuchi A Arah[2] and Elizabeth A Stuart[3]

[1]Department of Epidemiology and Global Health, Boston University School of Public Health, Boston, MA, USA, [2]Department of Epidemiology, Fielding School of Public Health and Department of Statistics, College of Letters and Science, UCLA, Los Angeles, CA, USA and [3]Department of Mental Health, Biostatistics and Health Policy and Management, Johns Hopkins Bloomberg School of Public Health, Johns Hopkins, Baltimore, MD, USA

Corresponding author. Department of Epidemiology and Global Health, Boston University School of Public Health, Boston, MA, USA. E-mail: mfox@bu.edu

We appreciate Blum *et al.*'s E-value paper, published in this issue.[1] E-values[2] are an approach to exploring the sensitivity of non-experimental study results to unobserved confounding. We agree with many of the points made and disagree on others. We discuss each below and expand on additional points.

The strengths of E-values and related methods

To summarize the value of E-values: when measured associations are large, it may take a strong, highly imbalanced, unobserved confounder to 'explain away' an observed association (i.e. for the association to be due entirely to confounding). However, in an era of moderate to small effect sizes, less powerful unobserved confounders may explain our findings; approaches like E-values can help us be humbler in our conclusions. To the extent that E-values allow for more scepticism of our work and questioning of our assumptions, with some formal structure to it, we see this as a good thing.

Another positive aspect of simple approaches like E-values and simple quantitative bias analysis[3] is they do not require the primary data. A summary effect estimate[4] or 2×2 table suffices.[5,6] Thus, we do not have to rely on the authors' beliefs about confounding, but rather can generate analyses that represent assumptions and beliefs about the unmeasured confounder. In this sense, a simple-to-use sensitivity analysis method (like E-values) can turn vague concerns about unobserved confounding into some (even rough) quantitative statement regarding how much we might need to worry about it.