Application of E-Value Analysis to Gauge Unmeasured Confounding in Real-World Data Studies

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Background

- Sensitivity analysis is an essential practice in assessing how robust results from real-world data (RWD) studies are to potential unmeasured confounding.
- The E-value was introduced in 2017 as a measure of the evidence for causality in observational studies that are subject to confounding.[1,2]
- The E-value is defined as "the minimum strength of association, on the risk ratio scale, that an unmeasured confounder would need to have with both the treatment and the outcome to fully explain away a specific treatment–outcome association, conditional on the measured covariates."[1]
- The E-value has been used relatively infrequently in research practice to date. Its performance and utility in supporting the interpretation of observational studies seeking to draw causal inferences is an area of active research.

Objective

- The objective of this study was to apply the E-value calculation to published RWD results from several therapeutic areas to assess robustness of results in terms of unmeasured confounding.

Methods

- A set of 10 statistically significant relative effect estimates with 95% confidence intervals (CIs) were abstracted from published RWD studies across an array of therapeutic areas.
- While not systematically selected, study searches focused on pharmacoepidemiologic studies based on large RWD sources and those published in high-impact biomedical journals.
- E-values for each point estimate and lower bound of the CI were calculated using software available at www.evalue-calculator.com.
- The proportion of E-values corresponding to "moderate" uncontrolled confounding effects (E-value ≥ 2) was calculated.

Results

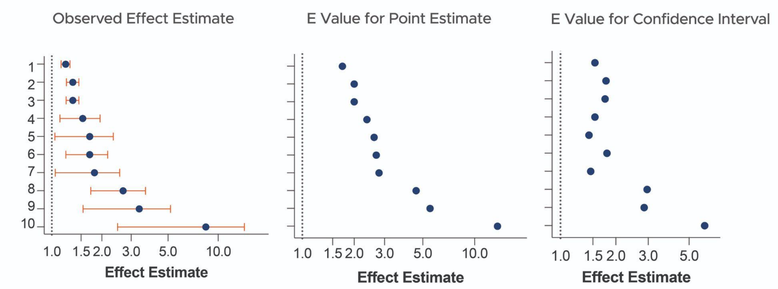
- A description of the included studies is provided in **Table 1**.
- The selected studies described treatment-outcome associations ranging from relative effect estimates of 1.61 to 7.04 and sample sizes from ~5,000 to 5,131,000 patients**.**
- E-values for these point estimates ranged from 1.71 to 13.56, with 90% indicating "moderate" uncontrolled confounding effects (E-value ≥ 2) that would be required to fully explain the observed association. The E-values for the CIs ranged from 1.43 to 6.08, with only 30% considered "moderate" confounding effects (**Figure 1**).

Table 1. Description of Included Studies

	Patient population	N	Exposure	Outcome	Confounding adjustment	Reference
1	Men with nonmetastatic prostate cancer	3,887	GnRH agonist treatment	Any clinical fracture	Matching	Smith MR et al., 2005
2	Patients with atrial fibrillation treated with ablation or medical therapy	183,760	Ablation (vs medical therapy alone)	All-cause mortality, stroke, major bleeding, and cardiac arrest	Propensity score weighting	Noseworthy PA, et al., 2019
3	Patients hospitalized with COVID-19	96,032	Hydroxychloroquine	In-hospital mortality	Modeling	Mehra MR, et al, 2020
4	Patients undergoing successful coronary artery stent implantation	5,018	Dual antiplatelet therapy (DAPT) disruption	Major adverse cardiac events (MACE)	Modeling	Mehran R et al., 2013
5	Patients with rheumatoid arthritis or psoriasis	13,905	TNF inhibitors (vs other non-biologic DMARDs)	Diabetes mellitus	Modeling	Solomon DH et al., 2011
6	General population	5,130,795	Use of antiepileptic drugs	Suicide-related events among patients with depression	Modeling	Arana A, et al, 2010
7	Patients with multiple sclerosis	6,421	Rituximab (vs interferon beta and glatiramer acetate)	Time until the first serious infection	Modeling	Luna G et al., 2020
8	General population	5,130,795	Use of antiepileptic drugs	Suicide-related events among patients without epilepsy or mental illness	Modeling	Arana A, et al, 2010
9	Patients who initiated antipsychotic therapy	43,287	Antipsychotics (vs other control drugs)	Type 2 diabetes	Propensity score matching	Bobo WV et al., 2013
10	Patients undergoing successful coronary artery stent implantation	5,018	First 7 days after DAPT disruption	MACE	Modeling	Mehran R et al., 2013

GnRH: Gonadotropin-releasing hormone; TNF: tumor necrosis factor; DMARD; disease modifying anti-rheumatic drugs

Figure 1. E-values calculated from RWD studies



Discussion

- E-values offer a computationally-simple approach to conducting sensitivity analyses for RWD studies seeking to draw inferences regarding causation.
- However, significant subject matter expertise and subjectivity is required to judiciously interpret E-values.
  - There is no standard or consensus threshold regarding E-values that are considered to be robust to the threat of unmeasured confounding.
- Relatively few assumptions are required to execute E-value analyses making them simple to conduct but of uncertain utility where specific parameters are available and germane to the assessment of unmeasured confounding.

Conclusion

- E-values are useful tools for assessment of the threat of unmeasured confounding, but more formal quantitative bias assessments may be indicated for evaluation of RWD-derived evidence used to support regulatory or clinical decision making.

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1. VanderWeele TJ, Ding P. Sensitivity Analysis in Observational Research: Introducing the E-Value. Ann Intern Med. 2017 Aug 15;167(4):268-274. doi: 10.7326/M16-2607. Epub 2017 Jul 11.
2. Haneuse S, VanderWeele TJ, Arterburn D. Using the E-Value to Assess the Potential Effect of Unmeasured Confounding in Observational Studies. JAMA. 2019 Feb 12;321(6):602-603.

Disclosures

All authors are employees of OM1 Inc. which is involved in matters related to this poster