Poster #MSR130

Current Trends in Quantitative Bias Analysis for Unmeasured Confounders: A Targeted Literature Review

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Quantitative bias analysis (QBA) is being increasingly used in the analysis of real-world evidence (RWE), yet there remains a shortage of well-defined terminology and explicit methodologies for its application.

Background

- RWE and other non-randomised evidence are increasingly being used for healthcare decision-making.
- Due to their lack of randomisation, these data are at risk of bias from missing observations and unmeasured confounders which can introduce uncertainty in and bias the results.
- QBA can be used to test the strength of this non-randomised evidence and to understand how an unmeasured confounder might affect the observed relationship.
- Both England's National Institute for Health and Care Excellence (NICE) and the Canadian Agency for Drugs and Technologies in Health (CADTH) recommend the use of QBA in guidelines for using RWE as part of health technology assessment (HTA) submission packages.[1,2]
- Currently, there is no guidance available on which methods to use when performing QBA.

Objective

- This research aimed to summarise trends in the current use of QBA methods for unmeasured confounding and to describe various methods.

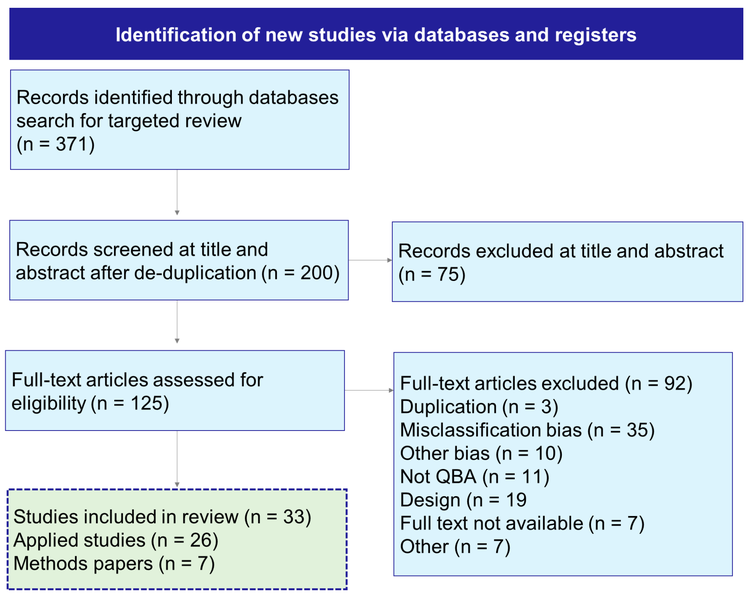
Methods

- A targeted literature review (TLR) was conducted in Embase, MEDLINE, and EconLit (on May 2, 2023) for studies applying QBA for unmeasured confounders or discussing QBA methods without application.
- Commentaries, letters, and systematic literature reviews were excluded, as well as studies that did not describe their approach to QBA, those focusing on probabilistic bias analysis, and those using QBA for misclassification or selection biases.
- Two reviewers screened and extracted results, with discrepancies resolved by a third reviewer.

Results

- Thirty-three studies published from 2013 to 2023 were included (Figure 1), with 95% of these published from 2018 onward (Figure 2).
- Twenty-six studies applied a QBA approach, while seven were methodology studies.

Figure 1. Identification of studies via TLR



Abbreviation: QBA, quantitative bias analysis

- Of the applied QBA studies, more than half (n = 14) used a derived bias method, followed by simulation-based methods (n = 9). (Figure 3)
- QBA was applied for a variety of acute and chronic disease indications, most frequently oncology (n = 6) and studies of epidemics/vaccines (n = 4).

Results (cont.)

- In methods where it was necessary to pre-determine potential sources of bias, 14 studies did not report how these confounding factors were identified and six relied on previously published literature. Other sources included administrative databases or using trial baseline data.
- Hazard ratio (n = 13) was the most common outcome of interest, followed by odds ratio (n = 8).

Figure 2. TLR summary of studies using QBA methods for unmeasured confounding by publication year

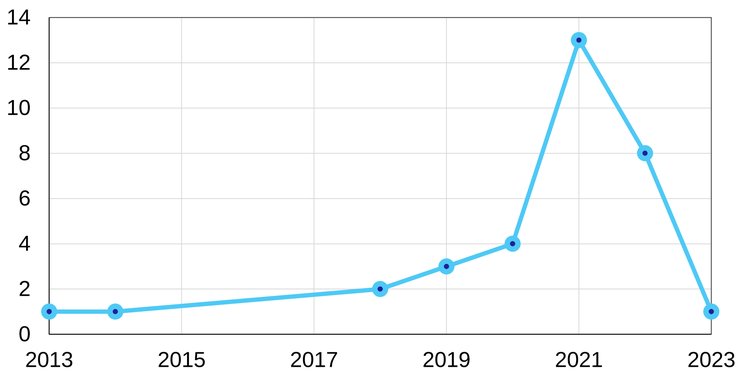
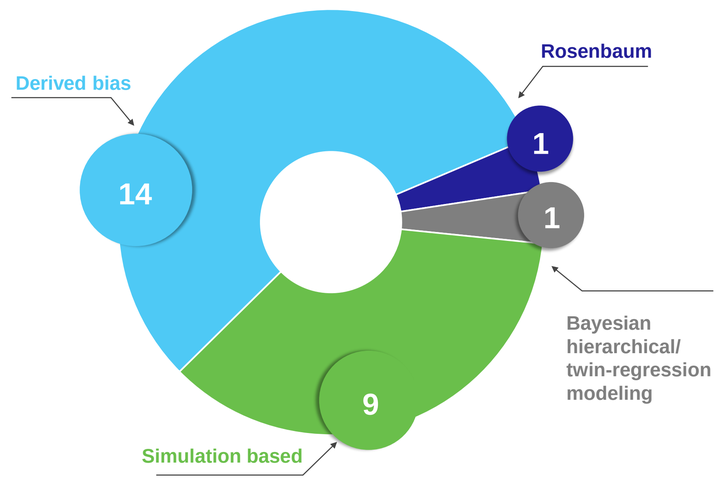


Figure 3. TLR summary of QBA methods for unmeasured confounding by type



- Derived bias methods included E-value, bias/bounding factor, contingency table, array/rule-out approach.
- Of derived bias methods, 11 employed the E-value formula, either on its own (n = 8) or in addition to another derived bias approach.
- Methodological studies varied and several papers outlined more than one method. The most common method described was the simulation-based method (n = 4), followed by bias/bounding factor (n = 2) and contingency table (n = 2).

Limitations

- Consistency was lacking across definitions for QBA terminology and methods. It is acknowledged that studies not defining a QBA method as described here may have been excluded in this review.
- Studies in this review included those that are not necessarily applicable to healthcare decision-making in the context of HTA, and there was an overlap with other fields, such as epidemiological papers on associative health outcomes.

Conclusions

- This TLR identified derived bias, particularly the E-value formula, as the most common QBA approach to evaluate unmeasured confounders.
- There is a shortage of information in reporting the precise methodology and practical implementation of QBA, particularly with respect to healthcare decision-making.

Overview of identified QBA methods

Rosenbaum's approach

- Involves estimating propensity scores to match treated and control groups, assessing the balance of covariates, and conducting sensitivity analysis to quantify the threshold of association between the unmeasured confounder on the estimated treatment effect, providing a more robust assessment of causal relationships.[3]

Bayesian hierarchical/twin-regression modelling

- Combines Bayesian techniques with hierarchical models to estimate the effects of both unobserved and observed factors on a study outcome, where the unmeasured confounder is modelled as missing data.[3]

Simulation method

- Involves generating hypothetical unmeasured confounders to mimic the real-world study which are simulated through assumptions and correlation with measured confounders. The treatment effect is then estimated under various bias scenarios.[4]

Derived bias methods

- Uses formulated equations derived from a statistical model, usually with some assumptions to adjust the initial point estimate and confidence interval for a range of sensitivity parameters.[3]

E-value

- Assesses the potential impact of unmeasured confounding on a study's results by quantifying the strength of association an unmeasured confounder would need to have with both the exposure and the outcome to fully explain away the observed effect. The E-value is a threshold for the minimum strength of unmeasured confounder that could undermine the study's findings.[5]

Array/rule out approach

- Involves creating an array of scenarios, each representing a different strength and direction of unmeasured confounding and analysing how these scenarios affect the study results. By comparing the observed effect with the range of effects within the array, researchers can assess the sensitivity of their conclusions to unmeasured confounding.

Contingency table method

- Involves creating a contingency table that cross-tabulates the exposure, outcome, and a potential unmeasured confounder. The table helps assess the association between the exposure and outcome while considering the impact of the confounder by comparing the distribution of outcomes.

Bias/bounding factor

- Modifies the group-level point estimate and corresponding confidence interval by incorporating sensitivity assumptions which require a connection between the unmeasured confounder and both the outcome and the treatment. In cases where the outcome is infrequent and the unmeasured confounder is binary, a bounding factor may be established and used to revise the treatment effect estimate.[4]

References

1.NICE. www.nice.org.uk/corporate/ecd9; 2. CADTH. 2023. Guidance for Reporting Real-World Evidence; 3. Leahy TP, Kent S, Sammon C, Groenwold RH, Grieve R, Ramagopalan S, Gomes M. Unmeasured confounding in nonrandomized studies: quantitative bias analysis in health technology assessment. J Comp Eff Res. 2022 Aug;11(12):851-859. doi: 10.2217/cer-2022-0029. Epub 2022 Jun 9. PMID: 35678151; 4. Leahy TP, Duffield S, Kent S, Sammon C, Tzelis D, Ray J, Groenwold RH, Gomes M, Ramagopalan S, Grieve R. Application of quantitative bias analysis for unmeasured confounding in cost-effectiveness modelling. J Comp Eff Res. 2022 Aug;11(12):861-870. doi: 10.2217/cer-2022-0030. Epub 2022 Jun 9. PMID: 35678168; 5. 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. PMID: 28693043

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