Understanding the potential threat of unmeasured confounding in RWE studies: what statistical methods can be used for robustness assessment?

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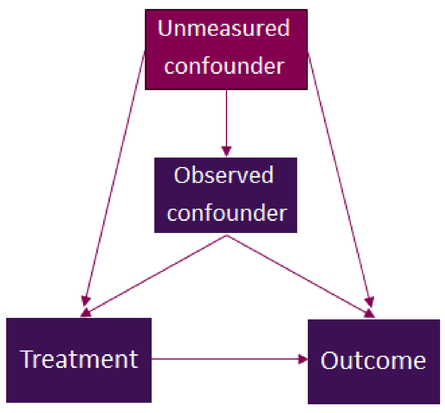
Why did we perform this research?

Unmeasured confounding is a primary concern about evidence generated from RWE studies.



Sources of concern:

- Confounder missing from data source
- Inaccuracies in confounder measurement
- Confounders unknown to study team
- Inappropriate adjustment of observed confounders

Quality of evidence will be a critical aspect of joint clinical assessment[1]. Sensitivity analyses may be required in response to criticism of RWE.

Aim: To provide practical considerations that will aid in selecting appropriate methods for addressing unmeasured confounding.

How did we perform this research?

Step-by step approach:

Search the literature for methodological reviews on the topic of addressing unmeasured confounding*

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Capture analytical methods

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Document key practical considerations on methods

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Identify the latest methods proposals$

PubMed search on 17 September 2024: (unmeasured confound[Title]) OR (uncontrolled confound*[Title]) OR (residual confound*[Title]) AND (method*[Text Word]) Filters: Review, in the last 10 years; $PubMed search on 17 September 2024 : (unmeasured confound*[Title]) OR (uncontrolled confound*[Title]) OR (residual confound*[Title]) AND ((adjust*[Title]) OR (assess*[Title])) Filters applied: in the last 1 year

RWE guidance (CADTH[2], EUnetHTA[3], IQWiG[4], NICE[5]) was reviewed for recommendations on use of sensitivity analysis.

What did we find?

Study planning

- NICE, CADTH: select appropriate confounders based on literature review and expert opinion.
- All guidance: assess robustness of findings to possible sources of uncertainty through sensitivity analyses. Pre-specify as far as possible.

Methods

- In total, 19 methods for addressing unmeasured confounding were identified from 8 methodological reviews[6-13].
- Sensitivity analyses ranged from simple threshold analyses to more complex bias modelling techniques.
- Use of the E-value was the most frequent sensitivity analysis in medical and epidemiological journals[13].
- NICE provide analytical suggestions including use of negative controls, propensity score calibration and quantitative bias analysis.
- New methods include a full data simulation approach[14] to inform study planning and use of negative control populations, for example, to identify placebo-effects[15].
- **Table 1** gives practical considerations on a selection of methods that meet different purposes (robustness assessment, bias quantification and bias detection).

Reporting

- All guidance: report studies in sufficient detail to enable independent reproducibility of results.
- This translates in our context to specifying sensitivity parameter inputs and assumptions in full and providing details of methods/tools used for implementation.

Table 1: High level practical considerations on methods to address unmeasured confounding

Type of method	Method	Design considerations			Analysis requirements			Output
		Nature of unmeasured confounder(s)	Sensitivity parameter inputs	Applicable effect measures	Internal data	External "out-of-sample" data	Implementation (availability of tools)	
Threshold analyses	**E-value**	None	None	RR, with approximations available for OR, HR, SMD	Treatment effect estimate	None	Simply plug in RR into formula. Calculator available: https://www.evalue-calculator.com/ [accessed 24 Sept. 2024]. Available in R package *Evalue*	Minimum strength of association that the confounder needs to have with treatment and the outcome to change the study conclusion
	Rosenbaum and Rubin 1983	One binary confounder	Confounder prevalence, association (OR) between confounder and outcome per group and association (OR) between confounder and treatment	OR, RR, RD (binary outcome measures)	Individual patient-level [for observed confounding control]	None	Based on ML estimation; mathematically straightforward. Calculations needed per strata of observed covariates or propensity scores. App available: *TippingSens*	Confounder-adjusted treatment effect estimate for varying sensitivity parameter inputs, aiding assessment of how strong confounding (associations with treatment and the outcome) need to be to change the study conclusion
	Array/rule-out approach	One binary confounder	Confounder prevalence per group and association between the confounder and outcome (RR)	RR, with approximations available for OR, HR, SMD	Treatment effect estimate	None	Straightforward formula to compute bias. Available in R package *episensr*	
Net bias assessment	**Negative control outcomes (exposures or populations)**	Assume there is an outcome that is not affected by treatment but has same confounding structure as study outcome	None	All applicable	Individual patient-level data	Internal data on negative control	Same as for the main study analysis but with the outcome replaced by negative control	Estimated treatment effect on negative control outcome, facilitating detection of unmeasured confounding and other sources of bias
Bias-adjustment methods	**Propensity score calibration**	Any form but need to know what the confounders are	None	All applicable	Individual patient-level data	Patient-level dataset comprising study treatment and all confounders	Uses propensity score estimation	Confounding-adjusted treatment effect estimate
	Probabilistic quantitative bias analysis	Any form but need to know what the confounders are	Plausible probability distributions representing uncertainty in bias	All applicable	Minimum requirement: Summary outcome data per treatment group	Evidence to inform construction of bias distributions	Uses Monte Carlo sampling. Available in software, such as the *b_probabilistic* R package	Confounding-adjusted treatment effect estimate incorporating uncertainty about extent of bias
	Multiple imputation	Any form but need to know what the confounders are	None	All applicable	Individual patient-level data	Subsample or out-of-sample dataset in which confounders are measured	Requires development of an imputation model. Key questions: which method, which variables?	Combined confounder-adjusted treatment effect across multiple imputed datasets
Study design: bias quantification	**Full data simulation approach**	Any form but need to know what the confounders are	Strength of confounder-treatment and confounder-outcome associations and correlations between confounder and proxy confounder	All applicable	None	Simulated data to mimic study data	Assumes data generating mechanism to simulate study-like dataset. R package available: *sim.BA*	Bias in planned study if confounder(s) is ignored; bias reduction through use of proxy confounder

Different methods may be complimentary:

- The E-value provides a convenient first step in assessing robustness of results to unmeasured confounding.
- Other methods allow robustness assessment based on what is understood about key confounders and associations with the study treatment and outcome.
- Net bias assessment methods such as those using negative controls may help to detect multiple sources of bias.
- More advanced methods can facilitate explicit adjustment of unmeasured confounders, incorporating uncertainty about the magnitude of bias.

How might this impact current practice?

- By providing practical considerations on methods to assess unmeasured confounding, we facilitate informed choices on which statistical method to use.
- Aiding pre-specification of methods for sensitivity analysis works towards building trust in RWE study findings.
- The practical considerations on methods highlight key components (assumptions, inputs, implementation) for reporting, enhancing transparency.
- Most methods require judgement on the plausible extent of confounding, thus highlighting a need for guidance on how to define plausibility.

Abbreviations

HR, hazard ratio; ML, maximum likelihood; OR, odds ratio; RD, risk difference; RR, risk ratio; RWE, real-world evidence; SMD, standardised mean difference.

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