Quantifying possible bias in clinical and epidemiological studies with quantitative bias analysis: common approaches and limitations

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Abstract

Bias in epidemiological studies can adversely affect the validity of study findings. Sensitivity analyses, termed quantitative bias analyses, are available to quantify potential residual bias arising from measurement error, confounding, and selection into the study. Effective application of these methods benefits from the input of multiple parties including clinicians, epidemiologists, and statisticians. In this article, we provide an overview of a few common methods to facilitate both the use of these methods and critical interpretation of applications in the published literature. Quantitative bias analysis methods are described and illustrated using examples. Considerations to be made when choosing between methods are outlined and limitations of quantitative bias analysis are discussed.

Key points

- Quantitative bias analysis methods allow investigators to quantify potential residual bias and to objectively assess the sensitivity of study findings to this potential bias.
- Bias formulas, bounding methods, and probabilistic bias analysis can be used to assess sensitivity of results to potential residual bias. Each of these approaches has strengths and limitations.
- Quantitative bias analysis relies on assumptions about bias parameters (e.g. the strength of association between unmeasured confounder and outcome) which can be informed by sub-studies, secondary studies, the literature, or expert opinion.
- When applying, interpreting, and reporting quantitative bias analysis it is important to transparently report assumptions, to consider multiple biases if relevant, and to account for random error.

Bias in epidemiological studies is a major concern. Biased studies have the potential to mislead, and as a result to negatively impact on clinical practice and public health. The potential for residual systematic error due to measurement bias, confounding, or selection bias is often acknowledged in publications but is seldom quantified. [1] Therefore, for many studies it is difficult to judge the extent to which residual bias could impact study findings, and how confident we should be about their conclusions. Increasingly large datasets with millions of patients are available for research, such as insurance claims data and electronic health records. With increasing dataset size, random error decreases but bias remains, potentially leading to incorrect conclusions.

Sensitivity analyses to quantify potential residual bias are available. [2-7] However, usage of these methods is limited. Effective use typically requires input from multiple parties including clinicians, epidemiologists, and statisticians, to bring together clinical and domain-area knowledge, epidemiological expertise, and a statistical understanding of the methods. Improved awareness of these methods and their pitfalls will enable more frequent and effective implementation, as well as critical interpretation of their application in the medical literature.

In this article our aim is to provide an accessible introduction, description, and demonstration of three common approaches of quantitative bias analysis, and to describe their potential limitations. We briefly review bias in epidemiological studies due to measurement error, confounding, and selection. We then introduce quantitative bias analyses, methods to quantify the potential impact of residual bias (i.e. bias that has not been accounted for through study design or statistical analysis). Finally, we discuss limitations and pitfalls in the application and interpretation of these methods.

Types of bias

All clinical studies, both interventional and non-interventional, are potentially vulnerable to bias. Bias is ideally prevented or minimised through careful study design and the choice of appropriate statistical methods. In non-interventional studies three major biases that can impact findings are measurement bias (also known as information bias) due to measurement

error (referred to as misclassification for categorical variables), confounding and selection bias.

Misclassification occurs when one or more categorical variables (such as the exposure, outcome, and/or covariates) are mismeasured or misreported. [8] Continuous variables may also be mismeasured leading to measurement error. As one example, misclassification occurs in some studies of alcohol consumption due to misreporting by study participants of their alcohol intake. [9, 10] As another example, in studies using electronic health records or insurance claims data there may be outcome misclassification if the outcome is not always reported to, or recorded by, the individual's health care professional. [11] Measurement error is said to be differential when the probability of error depends on another variable (e.g., differential participant recall of exposure status depending on the outcome). Errors in measurement of multiple variables may be dependent (i.e. associated with each other) particularly when data is collected from a single source (e.g., electronic health records). Measurement error can lead to biased study findings in both descriptive and aetiological (i.e. cause-effect) non-interventional studies. [12]

Confounding arises in aetiological studies when the association between exposure and outcome is not solely due to the causal effect of the exposure, but rather is partly or wholly due to one or more other causes of the outcome associated with the exposure. For example, it has been found that greater adherence to statins is associated with a reduction in motor vehicle accidents and an increase in the use of screening services. [13] However, this is almost certainly not due to a causal effect of statins on these outcomes, but more probably because attitudes to precaution and risk that are associated with these outcomes are also associated with adherence to statins.

Selection bias occurs when non-random selection of people or person-time into the study results in systematic differences between results obtained in the study population and results that would have been obtained in the population of interest. [14, 15] This bias can arise due to selection at study entry or due to differential loss to follow-up. For example, in a cohort study where the patients selected are those admitted to hospital in respiratory distress, COVID-19 and COPD may be negatively associated, even if there was no association in the overall population, because if you do not have one condition it is more likely you have the other in order to be admitted. [16] Selection bias can affect both descriptive and etiological non-interventional studies.

Handling bias in practice

All three biases should ideally be minimised through study design and analysis. For example, misclassification can be reduced by the use of a more accurate measure, confounding through measurement of all relevant potential confounders and their subsequent adjustment, and selection bias through appropriate sampling from the population of interest and accounting for loss to follow-up. Other biases should also be addressed, for example immortal time bias through the appropriate choice of time zero, and sparse data bias through collection of a sample of sufficient size or by the use of penalised estimation. [17, 18]

Even with the best available study design and most appropriate statistical analysis, we typically cannot guarantee that residual bias will be absent. For instance, it is often not possible to perfectly measure all required variables, or it may be either impossible or impractical to collect or obtain data on every possible potential confounder. For instance, studies conducted using data collected for non-research purposes, such as insurance claims and electronic health records, are often limited to the variables previously recorded. It may also not be practically feasible to sample randomly from the population of interest, especially if individuals are not willing to participate.

To ignore potential residual biases can lead to misleading results and erroneous conclusions. Often the potential for residual bias is acknowledged qualitatively in the discussion, but these qualitative arguments are typically subjective and often downplay the impact of any bias. Heuristics are frequently relied on, but these can lead to an misestimation of the potential for residual bias. [19] Quantitative bias analysis allows both authors and readers to assess robustness of study findings to potential residual bias rigorously and quantitatively.

Quantitative bias analysis

When designing or appraising a study there are a number of key questions related to bias that need to be considered (box 1). [20] If, on the basis of the answers to these questions, there is potential for residual bias(es), then quantitative bias analysis methods can be considered to estimate the robustness of findings.

Box 1: Key bias-related questions when designing and appraising a non-interventional study

- Misclassification and measurement error: Are the exposure, outcome, and covariates likely to be measured and recorded accurately?
- Confounding: Are there potential causes of the outcome, or proxies for these causes, which may differ in prevalence between exposure groups? Are these potential confounders measured and controlled through study design or analysis?
- Selection bias: What is the target population? Are individuals in the study representative of this target population?

There are a large number of quantitative bias analysis methods, though only a few of these are regularly applied in practice. In this article we will introduce three straightforward, commonly applied, and general approaches[1]: bias formulas, bounding methods, and probabilistic bias analysis. Alternative methods, including methods for bias-adjustment of linear regression with a continuous outcome, are also available. [7, 21, 22] Methods for dealing with misclassification of categorical variables are outlined in this article. Corresponding methods for sensitivity analysis to address mismeasurement of continuous variables are available and are described in depth in the literature. [23, 24]

Bias formulas

We can use simple mathematical formulas to estimate the bias in a study and to estimate what the results would be in the absence of that bias. [4, 25-28] Commonly applied formulas, along with details of available software to implement methods listed, are provided in the appendices. Some of these methods can be applied to the summary results (e.g. risk ratio), whereas other methods require access to 2x2 tables or participant-level data.

These formulas require us to specify additional information, typically not obtainable from the study data itself, in the form of bias parameters. Values for these parameters quantify the extent of bias present due to confounding, misclassification, or selection.

Bias formulas for unmeasured confounding generally require us to specify the following bias parameters:1) the prevalence of the unmeasured confounder in the unexposed individuals, 2) the prevalence of the unmeasured confounder in the exposed individuals (or alternatively the association between exposure and unmeasured confounder), 3) the association between unmeasured confounder and outcome. [4, 28, 29]

These bias formulas can be applied to the summary results (e.g. risk ratios, odds ratios, risk differences, hazard ratios etc.) and to 2x2 tables, and they produce "corrected" results assuming the specified bias parameters are correct. Generally, the exact bias parameters are unknown so a range of parameters can be entered into the formula, producing a range of possible bias-adjusted results under more or less extreme confounding scenarios.

Bias formulas for misclassification work in a similar way, but typically require us to specify positive predictive value and negative predictive value, or sensitivity and specificity, of classification, stratified by exposure and/or outcome. These formulas typically require study data in the form of 2x2 tables. [7, 30]

Bias formulas for selection bias are applicable to the summary results (e.g. risk ratios, odds ratios) or to 2x2 tables, and normally require us to specify probabilities of selection into the study for different levels of exposure and outcome. [25] An example of the application of bias formulas for selection bias is given in Box 2. When participant-level data is available, a very general method of bias analysis is to weight each individual by the inverse of their probability of selection. [31]

Box 2: An application of bias formulas for selection bias

In a cohort study of pregnant women investigating the association between lithium use, relative to non-use, and cardiac malformations in live-born infants, the observed covariate-adjusted risk ratio was 1.65 (95% CI, 1.02-2.68). [32] Only live-born infants were selected into the study, and therefore there was potential for selection bias if there were differences in the termination probabilities of foetuses with cardiac malformations between exposure groups.

Because the outcome is rare, the odds ratio approximates the risk ratio, and we can apply a bias formula for the odds ratio to the risk ratio. The bias parameters are selection probabilities for the unexposed with outcome S_{01}, exposed with outcome S_{11}, unexposed without outcome S_{00}, and exposed without outcome S_{10}.

$$OR_{BiasAdj} = OR_{Obs}\frac{S_{01}S_{10}}{S_{00}S_{11}}$$

For example, if we assume that probability of terminations is 30% among unexposed with malformations, 35% among exposed with malformations, 20% among unexposed without malformations, and 25% among exposed without malformations, then the bias-adjusted odds ratio is 1.67.

$$OR_{BiasAdj} = 1.65 \times \frac{0.7 \times 0.75}{0.65 \times 0.8} = 1.67$$

In the study, a range of selection probabilities, stratified by exposure and outcome status, were specified, informed by the literature. Depending on assumed selection probabilities, the bias-adjusted estimates of the risk ratio ranged from 1.65 to 1.80 (Figure 1), indicating that the estimate was robust to this selection bias under given assumptions.

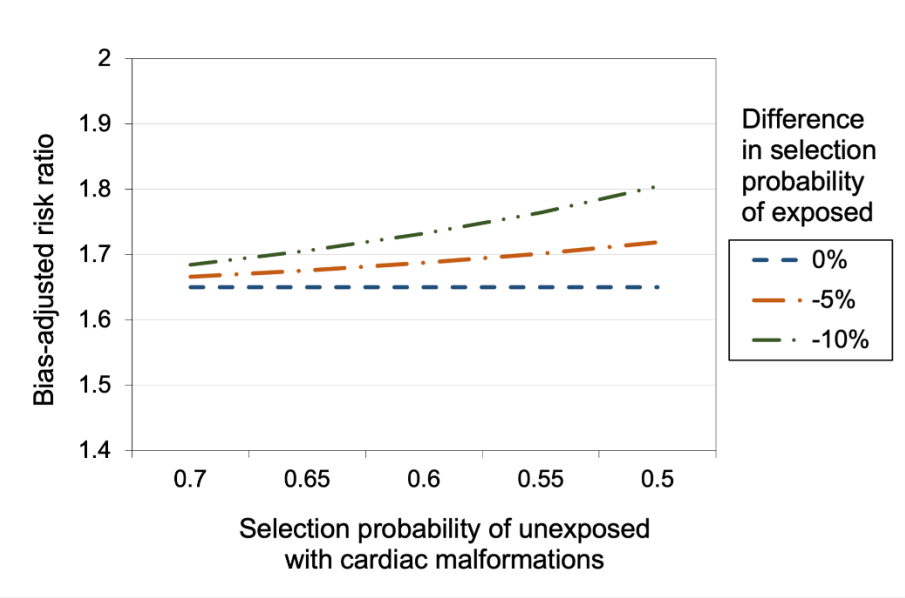

Figure 1: Bias-adjusted risk ratio for different assumed selection probabilities

***** Selection probability of unexposed without cardiac malformations was assumed to be 0.8 (i.e. 20% probability of termination). Selection probabilities in exposed were defined relative to unexposed by outcome status (i.e. -0%, -5%, and -10%).

It is possible to incorporate measured covariates in these formulas, but specification then generally becomes more difficult as we typically have to specify bias parameters, such as the prevalence of the unmeasured confounder, within strata of measured covariates.

Although we may not be able to estimate these unknowns from the main study itself, we can specify plausible ranges based on the published literature, clinical knowledge, or a secondary study or sub-study. Secondary studies or sub-studies, in which additional information from a subset of study participants or from a representative external group are collected, are particularly valuable as they are more likely to accurately capture unknown values. [33] However, depending on the particular situation, they may be infeasible for a given study due to data access limitations and resource constraints. The published literature can be informative if there are relevant publications and the study populations in the published studies are sufficiently similar to the population under investigation. Subjective judgements of plausible values for unknowns are vulnerable to the viewpoint of the investigator, and as a result may not accurately reflect the true unknown values. The validity of quantitative bias

analysis depends critically on the validity of the assumed values. When implementing quantitative bias analysis, or appraising quantitative bias analysis in a published study, it is important to question the choices made for these unknowns, and for study investigators to report these choices with transparency.

Bounding methods

Bounding methods are mathematical formulas, similar to bias formulas, that we can apply to study results for confounding, selection bias, and misclassification. [5, 34-36] However, unlike bias formulas, they require only a subset of the unknown values to be specified. While this seems advantageous, one important disadvantage is that bounding methods generate a bound on the maximum possible bias, rather than an estimate of the association adjusted for bias. When values for all unknown parameters (e.g., prevalence of an unmeasured confounder) can be specified, and there is reasonable confidence in their validity, bias formulas or probabilistic bias analysis can generally be applied, and provide more information than bounding methods. [37]

One very popular bounding method for unmeasured confounding is the E-value. [5, 35] Using E-value formulas it is possible to calculate a bound on the bias-adjusted estimate by specifying the association (e.g. risk ratio) between exposure and unmeasured confounder and between unmeasured confounder and outcome, while leaving the prevalence of the unmeasured confounder unspecified. The E-value itself is the minimum value on the risk ratio scale that either the association between exposure and unmeasured confounder or between unmeasured confounder and outcome must exceed to potentially reduce the bias-adjusted findings to the null (or alternatively to some specified value e.g., a protective risk ratio of 0.8). If the plausible strength of association between the unmeasured confounder and both exposure and outcome is smaller than the E-value then that one confounder could not fully explain the observed association, providing support to the study findings. If the strength of association between the unmeasured confounder and either exposure or outcome is plausibly larger than the E-value, then we can only conclude that residual confounding *might* explain the observed association, but it is not possible to say whether such confounding is in truth sufficient, as we have not specified the prevalence of the unmeasured confounder. The use of bounding methods for unmeasured confounding is illustrated in Box 3. Although popular, the application of E-values has been criticised as they have been commonly misinterpreted, and have been used frequently without careful consideration of a specific unmeasured confounder, or the possibility of multiple unmeasured confounders or other biases. [38]

Box 3: An application of bounding-methods

In a cohort study investigating the association between proton pump inhibitors, relative to H2 receptor antagonists, and all-cause mortality, investigators found evidence that individuals prescribed proton pump inhibitors were at higher risk of death after adjusting for several measured covariates including age, sex, and comorbidities (covariate-adjusted hazard ratio [HR] 1.38, 95% CI 1.33-1.44). [39] However, unmeasured differences in frailty between users of H2 receptor antagonists and users of proton pump inhibitors may bias findings. Because the prevalence of the unmeasured confounder in the different exposure groups was unclear, the E-value was calculated. Because the outcome was rare at the end of follow-up, and therefore the risk ratio approximates the hazard ratio given proportional hazards[40], the E-value formula, which applies to the risk ratio, was applied to the hazard ratio.

$$\text{E-value} = RR_{Obs} + \sqrt{RR_{Obs}(RR_{Obs} - 1)}$$

$$= 1.38 + \sqrt{1.38 \times (1.38 - 1)} = 2.10$$

The E-value for the point estimate of the adjusted HR, 1.38, was 2.10. Hence either the adjusted risk ratio between exposure and unmeasured confounder, or that between unmeasured confounder and outcome, must be greater than 2.10 to potentially explain the observed association of 1.38. The E-value can be applied to the bounds of the confidence interval to account for random error. The calculated E-value for the lower bound of the 95% confidence interval (i.e. covariate-adjusted HR = 1.33) was 1.99. We can plot a curve to show the values of risk ratios necessary to potentially reduce to the null the observed association as estimated by a) the point estimate and b) the lower bound of the confidence interval (Figure 2). An unmeasured confounder with strengths of associations below the green line could not fully explain the point estimate, and below the orange line could not fully explain the lower bound of the confidence interval.

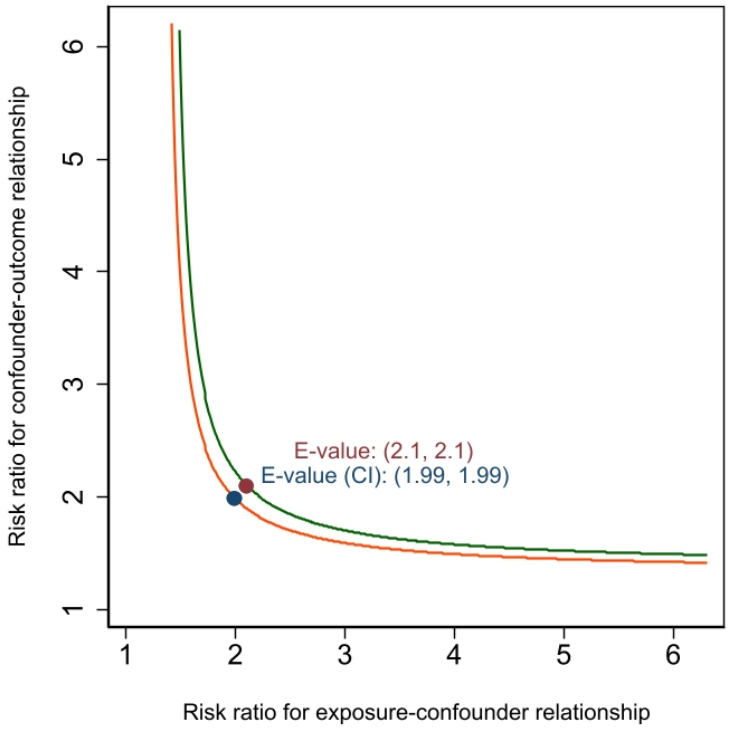

Figure 2: E-value plot for unmeasured confounding of association between proton pump inhibitors and mortality

Given risk ratios >2 observed in the literature between frailty and mortality, unmeasured confounding could not be ruled out as a possible explanation for observed findings. However, given that we used a bounding method, and did not specify unmeasured confounder prevalence, we could not say with certainty whether such confounding was likely to explain the observed result. Additional unmeasured or partially measured confounders may have also contributed to the observed association.

Probabilistic bias analysis

Probabilistic bias analysis takes a different approach to handling uncertainty around the unknown values. Rather than specifying a single value or a range of values for an unknown, a probability distribution (e.g. a normal distribution) is specified for each of the unknown quantities. This represents the uncertainty about the unknown values, and values are sampled repeatedly from this distribution before applying bias formulas using the sampled values. This approach can be applied to either summary or participant-level data. The result is a distribution of bias-adjusted estimates. Resampling should be performed a sufficient number of times (e.g. 10,000 times), though this can become computationally burdensome when performing corrections at the patient record-level.[41] An example of probabilistic bias analysis for misclassification is given in Box 4.

Probabilistic bias analysis can readily handle a large number of unknowns, which makes it particularly useful for handling multiple biases simultaneously. [42] However, it can be difficult to specify a realistic distribution if there is little information on the unknowns from published studies or from additional data collection. Commonly chosen distributions include uniform, trapezoidal, triangular, beta, and normal distributions. [7] Sensitivity analyses can be conducted varying the distribution and assessing the sensitivity of findings to distribution chosen. . When performing corrections at the patient record-level, analytical methods such as regression can be applied after correction to adjust associations for measured covariates. [43]

Box 4: An application of probabilistic bias analysis

In a cohort study of pregnant women conducted in insurance claims data, the observed covariate-adjusted risk ratio for the association between antidepressant use and congenital cardiac defects, among women with depression, was 1.02 (95% CI, 0.90-1.15). [44]

Some misclassification of the outcome, congenital cardiac defects, was expected, and therefore probabilistic bias analysis was conducted. A validation study was conducted to assess the accuracy of classification. In this validation study, full medical records were obtained and used to verify diagnoses for a subset of pregnancies with congenital cardiac defects recorded in the insurance claims data. Based on positive predictive values estimated in this validation study, triangular distributions of plausible values for sensitivity (Figure 3) and of specificity of outcome classification were specified and were used for probabilistic bias analysis.

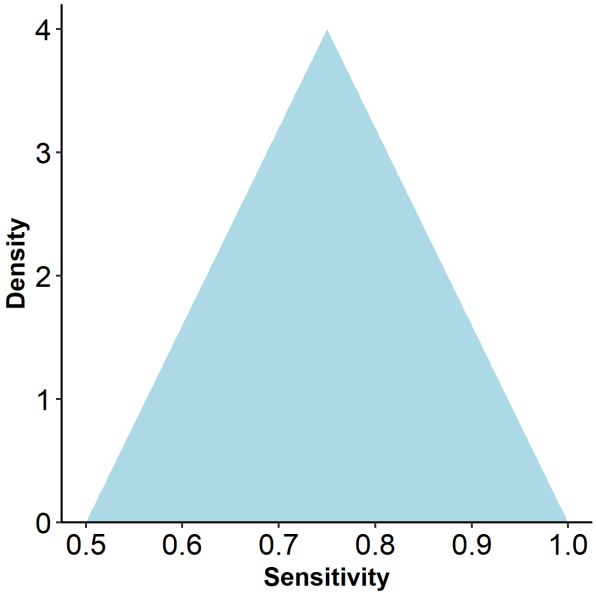

Figure 3: Specified distribution of values for sensitivity of outcome ascertainment

Values were sampled at random 1,000 times from these distributions and were used to calculate a distribution of bias-adjusted estimates incorporating random error. The median bias-adjusted estimate was 1.06, and the 95% simulation interval was 0.92-1.22. This finding indicates that under the given assumptions the results were robust to outcome misclassification, as the bias-adjusted results were similar to the initial estimates. Both sets of estimates suggested no evidence of association between antidepressant use and congenital cardiac defects.

Pitfalls of methods

Incorrect assumptions

Study investigators and readers of published research should be aware that the outputs of quantitative bias analyses are only as good as the assumptions made. These include both

assumptions about the values chosen for the bias parameters (see Table 1), and assumptions inherent to the methods. For example, applying the E-value formula directly to a hazard ratio rather than a risk ratio is an approximation, and only a good approximation when the outcome is rare. [45]

Simplifying assumptions are required by many quantitative bias analysis methods. For example, it is often assumed that the exposure does not modify the unmeasured confounder-outcome association. [4] If these assumptions are not met then the findings of quantitative bias analysis may be inaccurate.

Ideally, assumptions would be based on supplemental data collected in a subset of the study population (e.g. internal validation studies to estimate predictive values of misclassification) or, in the case of selection bias, in the source population from which the sample was selected, but this is not always feasible. [7] Validation studies can be an important source of evidence on misclassification, though proper design is important to obtain valid estimates. [33]

Multiple biases

It is a mistake to assume that if the results are robust to one source of bias, they must necessarily reflect the causal effect. Depending on the particular study there may be multiple residual biases, and jointly quantifying the impact of all of these is necessary to properly assess robustness of results. [34] Bias formulas and probabilistic bias analyses can be applied for multiple biases, but specification is more complicated, and the biases should typically be accounted for in the reverse order from which they arise (see Appendix 2 for an applied example). [7, 46, 47] Bounding methods are available for multiple biases. [34]

Prespecification

Prespecification of quantitative bias analysis in the study protocol is valuable so that choice of unknown values and choice to report bias analysis is not influenced by whether the results of bias analysis are in line with the investigators expectations. Clearly a very large range of analyses is possible, though we would encourage judicious application of these methods to address biases judged to be of specific importance given the limitations of the specific study being conducted.

Accounting for random and systematic error

Both systematic errors, such as bias due to misclassification, and random error due to sampling, impact study results. To accurately reflect this issue, quantitative bias analysis should jointly account for random error as well as systematic bias. [48] Bias formulas, bounding methods, and probabilistic bias analysis approaches can be adapted to account for random error (Appendix 1).

Reporting

Deficiencies in the reporting of quantitative bias analysis have been previously noted. [1, 48-50] When reporting quantitative bias analysis, it is important to state:

(1) The method used and how it has been implemented

(2) Details of the residual bias anticipated (such as which specific potential confounder was unmeasured)
(3) Any estimates for unknown values that have been used, with justification for the chosen values or distribution for these unknowns
(4) Which simplifying assumptions (if any) have been made

Quantitative bias analysis is a valuable addition to a study, but as with any aspect of a study, should be interpreted critically and reported in sufficient detail to allow for critical interpretation.

Alternative methods

Commonly applied and broadly applicable methods have been described in this article. Other methods are available, and include modified likelihood and predictive value weighting with regression analyses[51-53], propensity score calibration using validation data[54, 55], multiple imputation using validation data[56], methods for matched studies[3], and Bayesian bias analysis if a fully Bayesian approach is desired. [57, 58]

Conclusions

Quantitative bias methods provide a means to quantitatively and rigorously assess the potential for residual bias in non-interventional studies. Increasing the appropriate use, understanding, and reporting of these methods has potential to improve the robustness of clinical epidemiological research and reduce the likelihood of erroneous conclusions.

Table 1: Common bias parameters for bias formulas and probabilistic bias analysis

Confounding	Selection Bias	Misclassification
• Prevalence of unmeasured confounder in unexposed • Prevalence in exposed (or association between exposure and confounder) • Association between confounder and outcome	• Probabilities of selection into the study for different levels of exposure and outcome	• Positive predictive value and negative predictive value Or: • Sensitivity and specificity

Contributors and Sources

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Competing interests

All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/disclosure-of-interest/ and declare: AC, NG, and JH were paid employees of GSK at the time of the submitted work; AC, IJD, NG, and JH own shares in GSK; AC is currently a paid employee of McKesson Corporation in a role unrelated to the submitted work; DN is UK Kidney Association Director of Informatics Research; JPB was funded by a GSK studentship received by IJD and reports unrelated consultancy work for WHO Europe and CorEvitas; SL has received unrelated grants with industry collaborators from IMI Horizon, but no direct industry funding; all authors report no other relationships or activities that could appear to have influenced the submitted work.

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Appendix 1: Commonly applied bias formulas and bounding methods

Quantitative bias analysis for unmeasured confounding

Bias formulas

Risk ratios

The simplest setting is when there is a binary exposure *Z*, binary outcome *Y*, binary unmeasured confounder *U*, and no interaction between the effects of the exposure and unmeasured confounder on the outcome on the risk ratio scale. Formulas are available that take account of interaction. [1]

In this situation a bias formula can be applied to the observed risk ratio, $RR_{ZY(Obs)}$, to calculate a bias-adjusted risk ratio $RR_{ZY(BiasAdj)}$. The bias formula (1) is based on the risk ratio between unmeasured confounder and outcome $RR_{UY|Z}$ adjusted for exposure, the prevalence of the unmeasured confounder amongst exposed, $\mathrm{P(U = 1|Z = 1)}$, and unexposed, $\mathrm{P(U = 1|Z = 0)}$, and the observed risk ratio $RR_{ZY(Obs)}$. [2]

$$RR_{ZY(BiasAdj)} = RR_{ZY(Obs)} \frac{1 + \mathrm{P(U = 1|Z = 0)}\left(RR_{UY|Z} - 1\right)}{1 + \mathrm{P(U = 1|Z = 1)}\left(RR_{UY|Z} - 1\right)} \quad (1)$$

Categorical and multiple unmeasured confounders

We can instead specify that *U* is categorical, with reference level *u'*. In this setting we must specify stratum-specific prevalence of the unmeasured confounder and associations between each level of unmeasured confounder *u* and outcome, relative to the reference level *u'*. Again, we assume no interaction between the effects of the exposure and unmeasured confounder on the outcome on the risk ratio scale, leading to the bias formula (2). [1]

$$RR_{ZY(BiasAdj)} = RR_{ZY(Obs)} \frac{\mathrm{P(U = u'|Z = 0)} + \sum_u RR_{uu'Y|Z}\,\mathrm{P(U = u|Z = 0)}}{\mathrm{P(U = u'|Z = 1)} + \sum_u RR_{uu'Y|Z}\,\mathrm{P(U = u|Z = 1)}} \quad (2)$$

To incorporate multiple unmeasured confounders, we can specify multiple variables as one categorical variable (e.g. for alcohol and tobacco consumption: non-smoker non-drinker, smoker non-drinker, non-smoker drinker, smoker drinker).

Risk difference

We can calculate a bias-adjusted risk difference, $RD_{ZY(BiasAdj)}$, with a simple formula assuming a binary unmeasured confounder and no interaction between the effects of the exposure and unmeasured confounder on the outcome on the risk difference scale. We need only specify the observed risk difference, $RD_{ZY(Obs)}$, the risk difference for the unmeasured confounder-outcome association adjusted for exposure, $RD_{UY|Z}$, and the difference in prevalence of the unmeasured confounder between exposure groups, as follows[1]:

$$RD_{ZY(BiasAdj)} = RD_{ZY(Obs)} - RD_{UY|Z}(\mathrm{P(U = 1|Z = 1)} - P(U = 1|Z = 0)) \quad (3)$$

Formulas for more general cases relaxing these assumptions are available, such as for categorical unmeasured confounders, though these formulas become more complicated to specify. [1]

Other effect estimates

We can use formulas (1) and (2) for rate ratios, replacing all risk ratios in the equation with rate ratios.

If the outcome is rare, and hence the odds ratio is a good approximation to the risk ratio, we can substitute the odds ratio for the risk ratio in formulas (1) and (2). [1] Exact formulas for the bias of the odds ratio are available, but are more difficult to specify practically. [1] If the outcome is rare at the end of follow-up and hazards are proportional, the hazard ratio approximates the risk ratio[3], and can be substituted for the risk ratio in formulas (1) and (2). [4]

Random error

Formulas (1-3) can be applied to the bounds of the 95% CI to account for random error. [1] Alternatively, when participant-level data is available, bootstrapping can be used to calculate confidence intervals by repeatedly resampling participants with replacement, calculating the effect estimate, and applying the bias formula. [1] Random error can also be incorporated as part of a probabilistic bias analysis. [5]

Incorporating measured covariates

We can apply formulas (1-3) to effect measures conditioned on measured covariates. However, we then need to use ratios or differences between unmeasured confounder and outcome within strata of measured covariates, and the prevalence of the unmeasured confounder within each stratum of the measured covariates. [1]

If we assume no effect measure modification of the exposure-outcome association by the measured covariates, then we can use prevalence of unmeasured confounder within any one stratum of measured covariates to calculate a bias-adjusted association (e.g. if adjusting for binary [yes/no] diabetes status, then prevalence of unmeasured confounder amongst exposed and unexposed diabetics). Bias formulas are also available for marginal treatment effects such as the average effect of treatment in the overall study population, the average effect of treatment among the treated group, and the average effect of treatment amongst the untreated group. [1]

Bounding methods

Cornfield conditions

We can specify bounds on the bias-adjusted estimate. In order for an unmeasured confounder positively associated with the outcome to potentially reduce the positive bias-adjusted risk ratio between exposure and outcome to a specific value (e.g. a risk ratio of one, a typical null-hypothesis value), the association between unmeasured confounder and outcome $RR_{UY|Z}$, and between exposure and unmeasured confounder RR_{ZU}, must be greater than the ratio of the

observed risk ratio $RR_{ZY(Obs)}$ to the bias-adjusted risk ratio (4, 5). [2, 6, 7] These bounds are known as Cornfield conditions.

$$RR_{UY|Z} \geq \frac{RR_{ZY(Obs)}}{RR_{ZY(BiasAdj)}} \quad (4)$$

$$RR_{ZU} \geq \frac{RR_{ZY(Obs)}}{RR_{ZY(BiasAdj)}} \quad (5)$$

These bounds also apply exactly to rate ratios (replacing risk ratios with the outcome with rate ratios), and approximately to odds ratio or hazard ratios when the outcome is rare. [8]

These bounds, while true, are very conservative. We can only rule out unmeasured confounding as an explanation if either of these inequalities is not true. We cannot say that unmeasured confounding is likely if these inequalities are satisfied.

E-values

A less conservative bound, known as the E-Value, can also be specified if we consider jointly the association between unmeasured confounder and outcome $RR_{UY|Z}$ and between exposure and unmeasured confounder RR_{ZU}. [6] One of the exposure-unmeasured confounder and unmeasured confounder-outcome associations must be as large as or larger than the threshold (6) to potentially reduce the observed estimate to the specified (usually null) bias-adjusted estimate. The calculated E-Value will be larger in value than the Cornfield conditions,

$$\max\left(RR_{ZU}, RR_{UY|Z}\right) \geq \left\{RR_{ZY(Obs)} + \sqrt{RR_{ZY(Obs)}\left(RR_{ZY(Obs)} - RR_{ZY(BiasAdj)}\right)}\right\} / RR_{ZY(BiasAdj)} \quad (6)$$

If both of these risk ratios are below this threshold, then the unmeasured confounder cannot reduce the observed association to the specified bias-adjusted value.

This formula can also be applied to the rate ratio, and assuming the outcome is rare, to the odds ratio or hazard ratio.

Random error

Formulas (4) to (6) can be applied to the limits of the 95% confidence interval to account for random error. [6]

Positive associations

These formulas assume positive associations between unmeasured confounder and outcome and between exposure and outcome. Analogous formulas are available for an apparent preventive association. [6]

Incorporating measured covariates

A major advantage of bounding methods for unmeasured confounding is the ease of application to adjust for bias with covariate-adjusted estimates. We can apply the bounding formulas to covariate-adjusted estimates without the need to specify strata-specific prevalence of the unmeasured confounder.

Quantitative bias analysis for misclassification

Bias formulas

We can apply bias formulas for exposure or outcome misclassification with a binary exposure and binary outcome to 2x2 tables. [5]

Exposure misclassification

Consider a 2x2 table with true binary exposure Z, misclassified binary exposure Z', and binary outcome Y.

	Z' = 1	**Z' = 0**
Y = 1	a	b
Y = 0	c	d

We can calculate a corrected table using the sensitivity [Se] (i.e. proportion of those who truly are exposed who are categorised as exposed) and specificity [Sp] (i.e. proportion of those who truly are unexposed who are categorised as unexposed). If misclassification is differential (i.e. it depends on the outcome value) then we have to specify sensitivity and specificity separately amongst those with and without the outcome (as indicated by Se_{Y1}, etc.).

	Z = 1	**Z = 0**
Y = 1	$A = \frac{a-(a+b)(1-Sp_{Y1})}{Se_{Y1}+Sp_{Y1}-1}$	$B = a + b - A$
Y = 0	$C = \frac{c-(c+d)(1-Sp_{Y0})}{Se_{Y0}+Sp_{Y0}-1}$	$D = c + d - C$

Outcome misclassification

Consider a 2x2 table with misclassified binary outcome Y' and binary exposure Z.

	Z= 1	**Z = 0**
Y' = 1	a	b
Y' = 0	c	d

We can calculate a corrected table using the sensitivity [Se] (i.e. proportion of those who truly have the outcome who are categorised as having the outcome) and specificity [Sp] (i.e. proportion of those who truly do not have outcome who are categorised as not having the outcome). If misclassification is differential (i.e. it depends on the exposure value) then we

have to specify sensitivity and specificity separately for exposed and unexposed groups (as indicated by SE_{Z1}, etc.).

	Z= 1	**Z = 0**
Y = 1	$A = \frac{a-(a+c)(1-Sp_{Z1})}{Se_{Z1}+Sp_{Z1}-1}$	$B = \frac{b-(b+d)(1-Sp_{Z0})}{Se_{Z0}+Sp_{Z0}-1}$
Y = 0	$C = a + c - A$	$D = b + d - B$

Sensitivity and specificity

Quantitative bias analysis formulas applied to 2x2 tables are also available which use the positive predictive value (PPV) and negative predictive value (NPV). [5] Choice of formula will depend on which parameters are easier for the investigator to specify based on information available. Sensitivity and specificity may be preferred if using information from an external population rather than information from an internal validation, study given that PPV and NPV can vary considerably between populations depending on variable prevalence. [9]

Incorporating measured covariates

We can stratify the 2x2 tables by measured covariates and average the bias-adjusted results. This is, however, challenging if there are a large number of measured covariates, or if there are continuous covariates.

Measured covariates can alternatively be accounted for by patient record-level correction. [10] Alternatively, modification of the regression likelihood can be used with logistic regression to adjust for bias due to outcome misclassification while adjusting for measured covariates. [11]

Random error

Random error can be incorporated through bootstrapping, through formulas for misclassification-adjusted variance estimates, or as part of a probabilistic bias analysis. [12]

Categorical variables with more than two levels

Quantitative bias analysis for misclassification of categorical variables with more than two levels can be conducted using matrix methods. [10]

Quantitative bias analysis for selection bias

Bias formulas

2x2 tables

We can apply simple bias formulas to 2x2 tables or to an odds ratio.

Consider a 2x2 table with exposure Z and outcome Y.

	Z = 1	**Z = 0**
Y = 1	a	b
Y = 0	c	d

We can create a bias adjusted table by dividing each table cell by the selection probability for that combination of exposure and outcome (S_{00} etc.).

	Z = 1	**Z = 0**
Y = 1	a/S_{11}	b/S_{01}
Y = 0	c/S_{10}	d/S_{00}

Odds ratios

To adjust an odds ratio for bias, we can multiply the observed odds ratio by a function of the selection probabilities, as follows:

$$OR_{ZY(BiasAdj)} = OR_{ZY(Obs)} \frac{S_{01}S_{10}}{S_{00}S_{11}}$$

Risk or hazard ratios

When the outcome is rare among the selected sample, the odds ratio will approximate the risk ratio, and this, in turn, when the outcome is rare at the end of follow-up and hazards are proportional, will approximate the hazard ratio. [3] Hence the formula above can be applied to the risk ratio or hazard ratio with a rare outcome, with the proviso that it is an approximation rather than exact.

Incorporating measured covariates

We can apply these bias formulas within strata of measured covariates, though this is challenging when there are many covariates.

If we assume that the probability of selection is independent of measured covariates given exposure and outcome, we can apply the formula for the bias-adjusted odds ratio to the odds ratio adjusted for measured covariates.

Incorporating random error

We can apply the formula for odds ratios not only to the point estimate of association, but also to the limits of the 95% confidence interval. More generally, random error can be incorporated by bootstrapping or as part of a probabilistic bias analysis.

Inverse probability of selection weighting

It can be cumbersome to stratify data by measured covariates, C, if there are many covariates. An alternative is to weight each data point by the inverse of the probability of selection. [13] As

regards loss to follow-up, if censoring is independent of the outcome given specified covariates that are measured amongst those lost to follow-up, then we can estimate inverse probability of censoring weights from the sample data rather specifying the weights based on external information.

$$w_i = \frac{1}{P(S = 1|Z = z,\ Y = y,\ C = c)}$$

Appendix 2: Tools and packages

Spreadsheets for conducting quantitative bias analysis, which accompany the book *Applying Quantitative Bias Analysis* by Fox et al. 2021, are available online: https://sites.google.com/site/biasanalysis/.

There are a number of software options for quantitative bias analysis, which have been reviewed in depth elsewhere. [14] Software packages for application of bias formulas include a STATA packages "*episens"*, R package "*episensr"* and SAS macro "*sensmac"* . SAS and R code is available for probabilistic bias analysis for misclassification. [15] Code to generate the applied examples in this manuscript, alongside further examples including for multiple biases, is provided online (https://jeremy-p-b.github.io/qba-applied) or is alternatively available in a supplementary .Rmd file.

For E-values, an E-value calculator is available online: https://www.evalue-calculator.com/. Furthermore, there is an R package "*EValue"* and a Stata package "*EVALUE"*.

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