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Bias—Is it a problem, and what should we do?

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ABSTRACT

Observational studies are prone to two types of errors: random and systematic. Random error arises as a result of variation between samples that might be drawn in a study and can be reduced by increasing the sample size. Systematic error arises from problems with the study design or the methods used to obtain the study data and is not influenced by sample size. Over the last 20 years, veterinary epidemiologists have made great progress in dealing more effectively with random error (particularly through the use of multilevel models) but paid relatively little attention to systematic error. Systematic errors can arise from unmeasured confounders, selection bias and information bias. Unmeasured confounders include both factors which are known to be confounders but which were not measured in a study and factors which are not known to be confounders. Confounders can bias results toward or away from the null. The impact of selection bias can also be difficult to predict and can be negligible or large. Although the direction of information bias is generally toward the null, this cannot be guaranteed and its impact might be very large. Methods of dealing with systematic errors include: qualitative assessment, quantitative bias analysis and incorporation of bias parameters into the statistical analyses.

1. Introduction

Observational studies can be compromised by both random error and systematic error. The latter is also referred to as bias. Over the past 30 years, veterinary epidemiologists have made great progress in improving their handling of random error. Specifically, the advent and widespread adoption of multilevel modelling techniques (also known as random effects models) has enabled researchers to assess the statistical significance of factors operating at multiple levels of the data hierarchy. Although the addition of random effects for "groups" does have a role to play in removing confounding due to unmeasured group-level confounders (Dohoo and Stryhn, 2006), the main contribution of multilevel modelling has been to improve our ability to obtain valid confidence intervals for estimates of effects at various levels of the hierarchy (i.e. to quantify the random error correctly).

Unfortunately, very little attention has been paid to systematic error. Improving study designs to minimize or eliminate systematic errors is the crucial first step in addressing this problem (and I believe we have made considerable progress in this area), but we cannot eliminate all errors. We should be doing more to address the impact of systematic errors in our research.

The objectives of my paper are to:

1. briefly review random and systematic errors,
2. present some thoughts as to the nature, origin and impact of selection bias,
3. present some thoughts as to the magnitude of misclassification bias,
4. provide an overview of approaches for dealing with bias,
5. introduce quantitative bias analysis (QBA), and
6. show how bias parameters can be incorporated into the analysis of observational study data.

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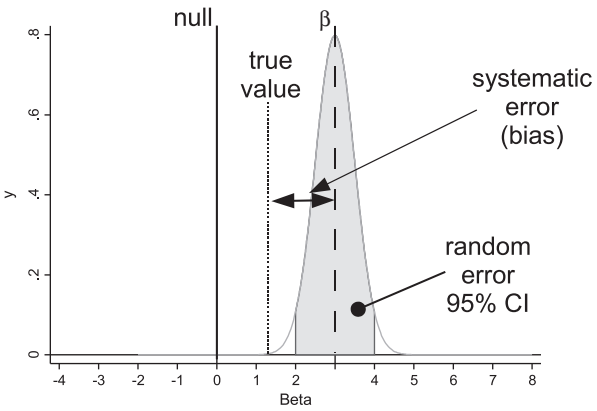

Fig. 1. Graphic representation of random and systematic errors. β is an estimate of the parameter of interest and the shaded area of the graph shows the 95% confidence interval around this estimate. This reflects the fact that random error exists and the width of the confidence interval reflects the precision of the estimate. The dotted vertical line shows the true value of the parameter of interest. Assuming that the estimate (β) represents the estimate which would be obtained from an infinitely large sample, the discrepancy between the true value and β is attributable to systematic error.

2. Random and systematic errors

Observational studies inevitably collect data on a subset of animals in the population of interest. Even if this subset is a true random sample, the estimate(s) (e.g. risk ratio, odds ratio) will vary somewhat from the true population value as a result of random variation inherent in the sampling process. We usually express our uncertainty in the estimate by computing a confidence interval which provides the reader with some idea as to the range of values within which the true population value might lie. The key features of random error are: we can always reduce the error by increasing the sample size (i.e. increasing the precision of the estimate), and the point estimate is asymptotically unbiased (i.e. in the long run – either with lots of data or with multiple repetitions of the study, the estimate will be correct).

Systematic error arises when some feature of the study leads us to obtain an estimate which is not equal to the true population value. Increasing the sample size does nothing to reduce the magnitude of the systematic error. Fig. 1 portrays random and systematic errors graphically.

There are three main types of bias which generate systematic errors: confounding, selection bias and information bias. The latter two will be discussed in subsequent sections of this paper.

Confounding arises when an unmeasured (or measured but ignored) factor is related to both the exposure and outcome of interest and is not intermediate (in the causal pathway) between the exposure and outcome. Unmeasured confounders can either be "known but not measured" or "unknown (and hence not measured)". Confounders that are known but not measured might include factors such as a livestock producer's managerial ability (which is a very difficult factor to measure) which we suspect is related to both risk factors being investigated and also to an outcome (e.g. disease) of interest. Unknown confounders are ones which we have not even considered as possible sources of confounding.

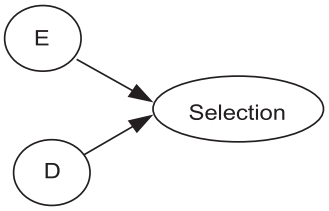

Fig. 2. General framework for selection bias. Adapted from Hernan et al. (2004).

For known (and measured) confounders, confounding can be controlled through the use of: (i) restriction, (ii) matching, or (iii) analytical control (e.g. by inclusion in a statistical model).

Analytical control is the most widely used form of control. Given the substantial advances in methods for multilevel modelling over the last 15 years, we can now appropriately control for known confounders at all levels of the hierarchy. For unmeasured confounders at the group level, controlling confounding is facilitated by the use of statistical models which take the hierarchical structure of the data into account. If a confounder is a true group-level confounder (i.e. no variation within groups), simulations have shown that the confounding effects of the group-level confounder are completely removed by including a random effect for group in the model (Dohoo and Stryhn, 2006; Dohoo et al., 2009 – Section 20.4.2).

3. Selection bias

There is no consistency in the literature as to how various study populations are named, but for the purpose of this manuscript I will use definitions presented in Dohoo et al. (2009) – Section 2.1.3, which are broadly consistent with the terminology used by Rothman et al. (2008).

Target population – the population to which it might be possible to extrapolate results. (The target population is often not clearly defined).

Source population – the population from which the study subjects are drawn.

Study group (or sample) – the actual subjects (animals or groups of animals) which end up in the study and whose data are used in the analysis.

Selection bias arises whenever the study group is not representative of the source population. Selection bias can arise in many ways such as non-response, loss to follow-up, selective survival, and admission risk bias. The possible causes are numerous and the reader is referred to general textbooks (Dohoo et al., 2009 – Chapter 12; Rothman et al., 2008 – Chapter 12) for a more complete discussion. Throughout this paper, I will generally consider selection bias arising from non-response.

Hernan et al. (2004) published a general framework for understanding selection bias. Any factor which is related to – and consequent to – both the exposure and disease can be a source of selection bias. Fig. 2 shows the simplest representation of this situation in that both the exposure (E)