EBM Learning

Catalogue of bias: Verification bias

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Abstract

This article is part of the Catalogue of Bias series. We present a description of verification bias, outline its potential impact on research studies, and the preventive steps to minimise its risk. We also have teaching slides in the supplementary files. Verification bias (sometimes referred to as "work-up bias") concerns the test(s) used to confirm a diagnosis within a diagnostic accuracy study. Verification bias occurs when only a proportion of the study participants receives confirmation of the diagnosis by the reference standard test, or if some participants receive a different reference standard test [1].

Background

Diagnostic accuracy studies determine the ability of a new test to rule in (confirm) or rule out (exclude) a disease. To achieve this, investigators subject all study participants to both an index test (the new test) and a reference standard test (usually the test that is considered to be best at diagnosing the target condition and is often referred as the 'gold standard'). The results of the index test and the reference standard test are then compared and the number of patients that tested true positive (TP), true negative (TN), false positive (FP) and false negative (FN) is determined. The sensitivity and specificity of the index test can then be calculated (sensitivity = TP/(TP+FN), specificity = TN/(TN+FP)).

Verification bias occurs when only some of the participants who received the index test go on to have the reference standard test, or when some participants receive one reference standard test and others have a different reference standard test. Accurate and consistent confirmation of disease is crucial in diagnostic accuracy studies; if two different reference standard tests are used, varying accuracy of disease confirmation is introduced.

There are two types of verification bias: p*artial* verification bias: where only some patients receive the reference standard test, with the other patients not receiving any reference standard test, and *differential* verification bias: where two different reference standard tests are used, typically alternating depending on whether the index test was positive or negative.

Many reference tests are invasive, expensive, or carry a procedural risk (e.g. angiography, biopsy, and surgery), and therefore, in many studies verification bias is unavoidable. This paper details examples, impact and preventive steps for verification bias.

EXAMPLE:

A study assessed the accuracy of D-dimer testing for diagnosing deep vein thrombosis (DVT) [2]. Patients that had a positive D-dimer result were further assessed with ultrasonography (reference standard test 1), whereas patients that had negative D-dimer

results were assessed with routine 3-month clinical follow up (reference standard test 2). Therefore, patients who had a DVT, but a negative d-dimer may not have been diagnosed by routine follow-up (symptoms may have resolved in the interim). This study design thus risks underestimating the number of false negatives, and thus may overestimate the sensitivity of a new test.

Impact

Verification bias affects the accuracy of an index test in a diagnostic accuracy study. Partial verification bias will frequently underestimate the number of false negative patients, and as such, will often overestimate the sensitivity. The impact of differential verification bias is less clear cut. The effect of differential verification bias on the sensitivity and specificity of the index test depends on the diagnostic accuracy of the two reference standard tests, relative to each other.

Further research is required to adequately quantify the effect of verification bias on diagnostic accuracy. A 2006 analysis of 31 meta-analyses of diagnostic accuracy studies stated that 'studies that relied on 2 or more reference standards to verify the results of the index test reported (diagnostic) odds ratios (DOR) that were on average 60% higher than the (diagnostic) odds ratios in studies that used a single reference standard'[3]. The result, however, was not statistically significant. The same study reported that studies that were subject to partial verification bias overestimated diagnostic odds ratios by 10%, although this was also non-significant [3] (DOR is a single estimate of a test's accuracy taking into account both sensitivity and sensitivity [4]).

Studies where the reference standard test is an expensive or invasive test are particularly prone to verification bias. For instance, studies assessing the diagnostic accuracy of faecal occult blood test (FOBT) often only use a confirmatory colonoscopy on patients that test positive with FOBT. A meta-analysis comparing the diagnostic accuracy of FOBT for colorectal cancer found that 'the pooled sensitivity of FOBT without verification bias was significantly lower (0.36 vs. 0.70) than those studies with this bias. The pooled specificity of the studies without verification bias was also higher (0.96 vs.0.88) [5]. The authors concluded that 'The sensitivity of guaiac-based FOBT for colorectal cancer has been overestimated as a result of verification bias. This test may not be sensitive enough to serve as an effective screening option for colorectal cancer' [5].

Preventive steps

Ideally, in a diagnostic accuracy study all patients should receive the same reference test. However, obtaining a reference test in every patient may not be ethical, practical, or cost effective. When this is not achievable, there are a collection of statistical methods that can be employed to try and account for this bias. Like all statistical adjustment [6], correction for verification bias attempts to reclassify patients into a group that reflects their actual outcome. For correction of verification bias, statistical approaches attempt to reclassified patients that tested negative into the false negative category (to account for the number of false negatives missed due to verification bias). Begg and Greenes [7,8] proposed a widely used method to correct for verification bias [9]. Their method utilises Bayesian techniques; an empirical probability of verification (receiving the reference standard test) is calculated and then applied to the observed TP, FP, TN, FNs to generate the adjusted estimates (this paper [9] and its appendix files explain this in more detail).

Nevertheless, statistical adjustment in diagnostic accuracy studies subject to verification bias should be approached with caution. Diagnostic accuracy studies subject to verification bias often have low numbers of false negative patients. In these cases, the application of

statistical adjustment can substantially and most likely, inappropriately, affect the results [9]. When the total number of false negatives is low, reclassification can have dramatic effects on the sensitivity and specificity of a test. For instance, in a study that aimed to determine the accuracy of an HPV DNA test to diagnose cervical cancer [10], the reported sensitivity was 100%, but the reclassification of one patient into the false negative category would have reduced the sensitivity to 70% [9].

The obvious solution to avoid verification bias is to use one reference standard test in all patients. When this is not possible, the above statistical adjustment techniques are appropriate in situations were there are an adequate number of false negative patients. When the number of false negatives is low, randomly sampling a number of true negative patients and then confirming diseases status with the reference standard test is recommended, although this may unnecessarily risk adverse effects to healthy patients or be expensive.

Discussion

Verification bias is common and can have dramatic effects on the sensitivity and specificity of diagnostic tests [9]. We have detailed what verification bias is, how it can impact real clinical practice and steps to avoid its effect on results. Researchers should be familiar with this common bias and its consequences. When reporting diagnostic accuracy studies where verification bias is unavoidable, researchers should always clearly discuss the potential impact of this bias on their results, as well as the potential clinical consequences.

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