Non-differential misclassification and bias towards the null: a clarification

Editor—In a recent paper, Sorahan and Gilthorpe use simulation studies to produce estimates of risk ratios (RRs) with data that are misclassified randomly and independently of disease state.[1] They show that these estimates can be more extreme than either RR_T, the true risk ratio (with no random variation and no misclassification), or RR_{NM}, the risk ratio with random variation but no misclassification, called "actual risk ratio" by Sorahan and Gilthorpe.[1] This is an important point for readers to appreciate. Their report prompts several observations on the general topic of non-differential misclassification in either cohort (their example) or case-control studies.

(1) The most important and the simplest point is that non-differential misclassification of a binary exposure (exposed or not) and a perfectly classified binary outcome (diseased or not) does indeed produce a *bias* toward the null. Always. (In one special case, the effect of misclassification is bias *beyond* the null. This reversal of the direction of association can occur only when the measurement is so bad that the sum of specificity and sensitivity is below 1.) *Bias* refers to a *systematic tendency* and not to a particular result. Here, the bias is the difference between the expected value (average over infinitely many hypothetical replications) of an estimator of the risk ratio calculated with misclassified exposure and the RR_T, the expected value of the risk ratio estimator when there is no error.

By calculation of the value of the risk ratio with the specified rates of misclassification and of disease in the exposed and unexposed populations, one can establish the existence and magnitude of bias. For set 1 of Sorahan and Gilthorpe's simulation, the classification had 90% sensitivity and specificity of exposure and probabilities of disease of 0·0075 and 0·0050 for exposed and unexposed people, respectively.[1] Define RR_{EM} as the expected value of the risk ratio when exposure is misclassified and $\widehat{RR}_{EM}$ as an estimate of RR_{EM} called "apparent risk ratio" by Sorahan and Gilthorpe.[1] Under these assumptions, as sample sizes increase, $\widehat{RR}_{EM}$ converges to the value RR_{EM}.[2]

$$\frac{\dfrac{(0{\cdot}9 \times 0{\cdot}0075) + (0{\cdot}1 \times 0{\cdot}005)}{(0{\cdot}9 \times 5000) + (0{\cdot}1 \times 5000)}}{\dfrac{(0{\cdot}9 \times 0{\cdot}005) + (0{\cdot}1 \times 0{\cdot}0075)}{(0{\cdot}9 \times 5000) + (0{\cdot}1 \times 5000)}} = 1{\cdot}38.$$

The value $\widehat{RR}_{EM}$ is also very near the expected value of $\widehat{RR}_{EM}$ for large samples, and, therefore, one should expect that the median of the distribution of $\widehat{RR}_{EM}$ from the simulation should be near RR_{EM} = 1·38. Indeed, 1·38 is exactly the median value reported in Sorahan and Gilthorpe's table 2.[1] Repeating this exercise for the other situations considered by Sorahan and Gilthorpe yields $\widehat{RR}_{EM}$s that are also below the RR_T of 1·5 and very close to the medians of $\widehat{RR}_{EM}$ reported in the table.[1] The fact that $1 < RR_{EM} < RR_T$ in each case proves that the bias in these situations is towards the null.

Sorahan and Gilthorpe note that, in previous work, "both disease outcome and exposure misclassification were assumed to operate on a proportionate rather than a random basis".[1] The reason for this "assumption" is clear: these simple calculations can show, *without simulations*, the magnitude of the bias from random misclassification.

(2) The study of Sorahan and Gilthorpe shows well how the systematic and the random components, which are quite distinct in principle, may interact in practice. The fact that $\widehat{RR}_{EM}$ was above 1·5 in some simulations shows the impact of random variation counteracting a systematic tendency. The combination of the two components also raises an interesting point about the theoretical treatment of misclassification in the epidemiological literature. Sometimes non-differential misclassification is treated as a process—that is, misclassification is not more likely on average in cases or controls—and sometimes as the realisation in the data—that is, the same fraction of cases and controls were misclassified in the study at hand. When the misclassification is treated as a process, bias, estimated by comparison of RR_{EM} with RR_T as in column 9 of table 1 of Sorahan and Gilthorpe,[1] is the concern. By contrast, when differential misclassification refers to the data, comparison of $\widehat{RR}_{EM}$ with $\widehat{RR}_{NM}$ (column 10) is the issue. When the investigator cannot calculate empirical misclassification percentages, one must judge whether the process is non-differential.

The distinction between a misclassification process and the empirical misclassification in a study provides another way to understand the simulation results that Sorahan and Gilthorpe find disturbing. How do we explain the fact that for many of the realisations there is a stronger effect in the misclassified data than in the correctly classified data ($\widehat{RR}_{EM} > \widehat{RR}_{NM}$)? In these instances, the misclassification actually was differential *in the data*. That is, even when the classification *process* yields errors for cases and non-cases equally often in the long run, the *empirical* misclassification in any given study can easily be differential simply due to chance.

A hypothetical example may help. Out of 5000 exposed and 5000 unexposed subjects, the expected numbers of cases are 37·5 and 25, respectively, implying an RR_T of 1·50. By chance, 40 and 22 could be observed in a particular study and would yield a value of 1·82 for the $\widehat{RR}_{NM}$. How would the effects of non-differential and differential misclassification *in the data* affect these results? If the unexposed subjects from the study were classified correctly and exactly 10% of exposed cases and non-cases were misclassified as unexposed, the apparent numbers of exposed and unexposed cases would be 36 and 26, and the risk ratio estimate would be 1·69, less than the 1·82 already calculated from the data correctly classified but subject to random variation. Thus, misclassification that is non-differential in the data results in a reduction in the rate ratio that would be obtained in the study. Still, the estimate from the misclassified data is greater than the RR_T value of 1·5, as a consequence of random variability. Actual misclassification among exposed subjects of 15% for non-cases and 10% for cases are empirically differential but realistic for an underlying misclassification process that is random and non-differential; these would yield an $\widehat{RR}_{EM}$ 1·87, greater than the $\widehat{RR}_{NM}$ of 1·82 and greater than the RR_T of 1·5, even though the underlying process is non-differential.

Our example shows that random variation in a non-differential classification process can lead to an effect that is greater than either the true RR_T value or the value that would result from the study with perfect classification. This occurs because, by chance, the non-differential process may result in differential misclassification in the data. Of course, statistical theory and the simulation results show that exaggeration of the risk ratio is less likely than attenuation.

(3) Although the simulations of Sorahan and Gilthorpe[1] do not disprove the well established bias towards the null in the classic binary situation they studied, there are special circumstances in which the bias towards the null ought not be invoked without further examination of the statistical model and the likely error structure. Several papers published since 1990 have shown that there are special circumstances where there is a bias towards exaggeration of effects. Dosemeci *et al* identified a scenario where non-differential misclassification of exposure more often than not leads to an overestimate of the odds ratio in an *intermediate* exposure category when there are more than two exposure levels. Other papers that have appeared since the textbooks cited by Sorahan and Gilthorpe[1] were published during the 1980s, have identified circumstances where an overestimate is more likely than an underestimate. These include particular forms of non-differential misclassification when an exposure is not binary,[3,4] when grouping has occurred,[5,6] or when the errors in a continuous exposure are correlated with their true value.[7]

Ultimately, investigators must interpret a specific estimate, such as 1·37, without the information to help us distinguish between the effects of sampling variation and of misclassification. If we then posit neither misclassification nor other biases, we can infer that the confidence interval covers the true value of the parameter with the specified probability. That is, sometimes RR_T will be higher than 1·37 and sometimes lower, and sometimes the confidence interval will not cover the parameter value. The procedure we used to obtain our estimate and confidence interval will perform as expected. On the other hand, if we posit an exposure classification process that has a probability of error that is equal for cases and for non-cases, then we ought to infer that the estimate of 1·37 is *more likely* to fall below the true value than to exceed it. Further, the confidence interval is shifted too low, may have incorrect width, and will cover the true parameter less often than the specified probability.

Many epidemiological studies contend with non-differential measurement error. Sorahan and Gilthorpe show why the practice of inferring that the true value *must* be above the value estimated with non-differential error in exposure assessment is unwarranted.[1] They correctly state that the estimate *may* exceed the true value even when the misclassification process for a binary exposure is non-differential. Still, the estimate is more likely to fall below the true value.

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Author's reply—Our short report on the properties of non-differential misclassification of exposure, as judged by computer simulations, has prompted Wacholder *et al* to make several useful observations.[1] These observations include a restatement of what we judged to be the "more important" feature of the simulations. We concluded (to paraphrase) that for any particular epidemiological study that investigates a causal risk factor and in which each study subject had the *same probability* of being misclassified (with respect to a single binary exposure variable), it would be *incorrect* to infer that the measure of effect obtained from the study—for example, relative risk or rate ratio—could *only* be increased if more reliable information were to be obtained such that all misclassification could be removed. We are pleased to learn that Wacholder *et al* are of the opinion "that this is an important point for readers to appreciate". We did not find those results of the computer simulations that supported this conclusion to be "disturbing"; they seemed to us to be intuitively obvious. What disturbed us was the fact that many researchers are convinced that the removal of non-differential misclassification of exposure from their studies can only increase the point estimate of relative risk (or rate ratio).

Why is our conclusion so little known? We have three possible explanations; all could be prompted by the comments of Wacholder *et al*. It may be because of confusion about the definition of non-differential misclassification. We chose the definition that "all exposed and non-exposed subjects have the same *probability* of being misclassified (these two probabilities may be different, one must be not zero)". Wacholder *et al* describe this as misclassification "treated as a process". They note that non-differential misclassification may also be defined in terms of "realisation" in a given data set—that is, the same fraction of diseased and non-diseased subjects were, in fact, misclassified. The first definition seems more relevant to study settings. Under the second definition, non-differential misclassification would rarely occur and a researcher would not be aware when it had occurred. (It would never occur when there was an even number of diseased subjects and an odd number of non-diseased subjects!)

A second explanation is the influence of textbook examples in which misclassification is invariably shown to operate on a proportionate rather than a random basis. We choose not to believe that errors are made every *n*th record and prefer to believe that random misclassification is more relevant to study settings.

A third possible explanation is the way in which the word *bias* is interpreted. Sometimes the word is used to indicate a tendency toward a given distortion, and sometimes (perhaps incorrectly) to indicate a distortion that will occur on each and every occasion—for example, in the game of bowls, the oblique course of a bowl due to its lopsided form is said to be due to bias. If the first definition were in universal use, our conclusion would be well known.

Our short report may be viewed as a call for more appropriate interpretation of study findings.[1] The observations of Wacholder *et al* may be viewed in the same light.

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1 Sorahan T, Gilthorpe MS. Non-differential misclassification of exposure always leads to an underestimate of risk: an incorrect conclusion. *Occup Environ Med* 1994;**51**: 839–40.

NOTICES

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