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

Editor—In a recent paper,SORAHAN andGilthorpe 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 are more extreme than either RR0, the true risk ratio (with no random variation and no misclassification), or RRemp, the risk ratio with random variation but no misclassification,called “actual risk ratio” 2 by Sorahan andGilthorpe.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 the bias occurs only when the measurement is so bad that the sum of specificity and sensitivity is below 1.0). 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 RR0, the expected value of the risk ratio estimator when there is no error. By calculation of the value of the 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 example, 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 groups respectively. If the RRemp as the expected value of the ratio when exposure is misclassified and RRemp as an estimate of RRemp called “apparent risk ratio” by Sorahan and Gilthorpe,1 Under these assumptions, as sample sizes increase, RRemp converges to the value RR0:2

\[
\begin{align*}
(0.9 \times 0.0075) + (0.1 \times 0.005) &= 0.0075 \\
(0.9 \times 0.0050) + (0.1 \times 0.0050) &= 0.0050 \\
&= 1.38.
\end{align*}
\]

The value RRemp is also very near the expected value of RRemp for large samples, and, therefore, one should expect that the median of the distribution of RRemp from the simulation should be near RR0 of 1.38. Indeed, 1.38 is exactly the median value reported in Sorahan and Gilthorpe’s table 2. Repeating this exercise for other scenarios considered by Sorahan and Gilthorpe yields RRemp that are also below the RR0 of 1.5 very close to the medians of RRemp reported in the table.3 The fact that 1 < RRemp < RR0 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.”4 The reason for this “assumption” is clear: these 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 and practice. The fact that RRemp was above 1.5 in some simulations shows the impact of random variation counteracting a systematic tendency. The combination of the two components also raise the 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 in exposed 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 RRemp with RR0 is in column 9 of table 1 of Sorahan and Gilthorpe,5 is the concern. By contrast, when differential misclassification refers to the data, comparison of RRemp with RR0, which is the issue, we have examined. 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 (RRemp > RR0)? In these instances, the misclassification actually operates in the opposite direction. 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 by chance.

A hypothetical example may help. Out of 5000 exposed and 5000 unexposed subjects, the expected numbers of cases are 375 and 25, respectively, implying an RR0 of 1.5. If we observe the 1.82, for example, in a particular study and would yield a value of 1.82 for the RRemp. How would the effects of non-differential and differential misclassification in the data affect these results? If the underlying subjects from the study were classified correctly and exactly 10% of exposed cases and non-cases were classified as unexposed, the apparent number of exposed and unexposed cases would be equal and the risk ratio estimate would be 1.69, less than 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 RR0 value of 1.5, as expected, because of 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 RRemp of 1.87, greater than the RRemp of 1.82 and greater than the RR0 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 RR0 or RRemp. It is also clear that a 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 misclassification process in the data.

(3) Although the simulations of Sorahan and Gilthorpe do not disprove the well established bias toward the null in the classic binary situations 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 books cited by Sorahan and Gilthorpe published during the 1980s, have identified circumstances where an overestimate is more likely than an underestimate. These include particular forms of non-differential misclassification that were not binary,1,6 when groupings have occurred,7 or when the errors in a continuous exposure are correlated with their true value.8

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 RR0 will be higher than 1-37 and sometimes lower, and sometimes the confidence interval will not cover the parameter. This is why 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 equal to 1-1. It could be observed in a particular study and would yield a value of 1-82 for the RRemp. How would the effects of non-differential and differential misclassification in the data affect these results? If the underlying subjects from the study were classified correctly and exactly 10% of exposed cases and non-cases were classified as unexposed, the apparent numbers of exposed and unexposed cases would be equal and the risk ratio estimate would be 1-69, less than 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 RR0 value of 1-5, as expected, because of 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 RRemp of 1-87, greater than the RRemp of 1-82 and greater than the RR0 of 1-5, even though the underlying process is non-differential.

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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 cause or 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 "obvious"; 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 setting. 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 nth 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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NOTICES

For a good working life. ICOH’96, the 25th International Congress of Occupational Health, Stockholm, Sweden. 15-29 October 1996.

The Congress will present the latest research discoveries in occupational health as well as provide a forum for exchange of ideas between practitioners and researchers. This ICOH Congress will be noted by the introduction of new subjects of great concern to the society of today and tomorrow, such as work organisation, psychosocial factors, and gender research. A large number of minisymposia will form a bridge between the more traditional occupational health research and the new challenges of promoting a good working life.

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- Working conditions and cardiovascular diseases. Johannes Siegrist, Institut für Medizinische Soziologie, Düsseldorf, Germany
- Dose concepts in occupational exposure assessments. Thomas J Smith, Harvard School of Public Health, Boston, USA
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For further information contact: Arne Wenneberg, secretary general ICOH’96, Lars Grönkvist, press officer ICOH’96, Elisabeth Lagerlöf, information ICOH’96, Maud Werner, secretariat ICOH’96, National Institute of Occupational Health S-171 84 SOLNA, Sweden. Tel (+46) 8 730 91 00; Fax (+46) 8 820 05 56.


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