Correspondence

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 are even more extreme than either RRtrue, the true risk ratio (with no random variation and no misclassification), or RRrand, 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 effect occurs 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 RRtrue, 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, respectively.1 Define RRtrue as the expected value of the risk ratio when exposure is misclassified and RRrand as an estimate of RRtrue called “apparent risk ratio” by Sorahan and Gilthorpe.1 Under these assumptions, as sample sizes increase, RRrand converges to the value RRtrue: 2

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\begin{align*}
(0.9 \times 0.0075) + (0.1 \times 0.005) & \quad (0.9 \times 0.005) + (0.1 \times 0.0075) \\
0.9 \times 5000 & \quad 0.1 \times 5000 \\
1.38 & \quad 1.38
\end{align*}
\]

The value RRrand is also very near the expected value of RRtrue for large samples, and, therefore, one should expect that the median of the distribution of RRrand from the simulation should be near RRtrue = 1.38. Indeed, 1.38 is exactly the median value reported in Sorahan and Gilthorpe’s table 2. Repeating this exercise for other sets, Sorahan and Gilthorpe simulate 1000 subjects and find that RRtrue is also below the RR of 1.5 and very close to the medians of RRrand reported in the table. 1 The fact that 1 < RRrand < RRtrue 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 and sometimes in opposition, in principle, make it so that fact that RRrand 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 realization 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 RRrand with RRtrue 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 RRtrue with RRrand, as in the intervention cases, raises a more extreme 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 realizations there is a stronger effect in the misclassified data than in the correctly classified data (RRrand > RRtrue)? In these instances, the misclassification actually was differential, not random. That is, even when the classification process yields effects 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 37.5 and 25, respectively, implying an RR of 1.5. But if 1% of the non-cases were misclassified as cases, we would observe a greater number of cases than the null in the classified data. In this example, to an estimate of 1.5 is more likely than a true value of 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 data were, in fact, generated by a process that covers the true value of the parameter with the specified probability. That is, sometimes RRtrue will be less than 1.37 and sometimes greater, and sometimes the confidence interval will not contain the parameter value. Thus, 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 1% for both cases and 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 to the left, 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. Our non-differential misclassification process, which is the converse of inferring that the true value must be above the value estimated with non-differential error in exposure assessment is unwarranted. 3 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 misclassifica-
tion 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" fea-
ture of the simulations. We concluded (to paraphrase) that for any particular epidemi-
ological study that investigates a cause-risk factor and in which each study subject had
the
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 reli-
able 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 simul-
ations that supported this conclusion to be "disturbing"; they seemed to us to be intuit-
ively obvious. What disturbed us was the fact that many researchers are convinced that the removal of non-differential misclassifi-
cation 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 con-
fusion about the definition of non-differential misclassification. We chose the definition that "all exposed and non-
exposed subjects have the same probability
of
misclassification (these two probabilities may be different, one must be not zero)". Wacholder et al describe this as mis-
classification "treated as a process". They note that non-differential misclassification may also be described in terms of "realisa-
tion" 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 set-
ting. Using our 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 misclassifica-
tion is invariably shown to operate on a pro-
portionate 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.

NOTICES

For a good working life. ICOH'96, the 25th International Congress of
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
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number of mini-symposia 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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National University Hospital, Singapore
- Participatory approaches in occupational
health. René Loewenson,
Zimbabwe
- What can health professionals do to pre-
vent musculoskeletal disorders? Philippe
Mairiaux, Université Catholique de
Louvain, Brussels, Belgium
- Working conditions and cardiovascular
diseases. Johannes Siegrist, Institut für
Medizinisches Soziologise, Düsseldorf,
Germany
- Dose concepts in occupational exposure
assessments. Thomas J Smith,
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USA
- Promoting safe behaviour. Carin
Sandström-Frisk, National Institute of
Occupational Health, Stockholm, Sweden
- Electromagnetic fields and cancer. Gilles
Thériault, McGill University, Montreal,
Canada

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SmithKline Beecham, Pasteur Mérix
MSD and the Swedish Power Association,
Svenska Kraftverksföreningen. Other spon-
sors are Samhall and SJ, the Swedish State
Railways. The official airline is SAS. There
will be an exhibition in conjunction with
the conference. Companies and organisations
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ICOH'96 secretariat.

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