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RE: "DOES NONDIFFERENTIAL MISCLASSIFICATION OF EXPOSURE ALWAYS BIAS A TRUE EFFECT TOWARD THE NULL VALUE?"

We read the contribution by Dosemeci et al. (1) with great interest mixed with some alarm.

For many epidemiologists, particularly those engaged in occupational and environmental epidemiology, the heuristic principle that when an effect exists, nondifferential misclassification causes bias only away from demonstrating this "true" effect is of great practical value. The idea that the effect can, therefore, not be manufactured by nondifferential misclassification is of great utility. The absence of an effect, in the presence of probable nondifferential misclassification, means that it is necessary to try harder by way of improved study design the next time around, provided further investigation is justified. Conversely, the demonstration of an effect in these circumstances may be relied upon with some considerable degree of confidence.

An incidental but useful spinoff is that management is often put at ease when it is explained to them that less than perfect exposure knowledge (if nondifferential) could not manufacture a false effect of exposure. This helps to diminish resistance to the performance of epidemiologic investigations in the workplace.

At first sight, the contribution by Dosemeci et al. (1) seems to undermine the utility of this principle. By their own admission, they use extreme numerical examples and misclassification scenarios. They are then able to demonstrate in their table 1 (1, p. 747) a loss of trend in the odds ratio from no through low to high exposure. However, the difference between high and no, or high and low exposure remains demonstrable. In their table 2 (1, p. 747) they either lose the dose-response relation together with a reversal in the odds ratio for both categories or they produce a "protective" dose-response relation with reversal of both odds ratios.

It is possible, however, to look at these scenarios as characterized by the failure to demonstrate as strong a positive relation, or as clear a trend, as the correctly classified data would have done in the case of their table 1. For their table 2, the manufactured negative dose-response relation is even further removed from the demonstration of a positive relation than the null value (odds ratios of 1.0 throughout). It is then clear that the utility of the heuristic principle remains. Nondifferential misclassification cannot manufacture a false positive association (given the larger picture of all three levels in their table 1) nor can it produce a false positive dose-response relation. The fact that it may bring about a weakened association, or even a negative trend, does not detract from the utility of what has always been understood as the effect of nondifferential misclassification—weaker positive associations and trends! In this sense then, their findings are another variation on this theme.

Dosemeci et al. also make several strange and artificial choices in their (nondifferential) misclassification scenarios. In an occupational setting (for which they provide an example), the typical situation would involve more or less equivalent misclassification in all directions between all categories rather than solely exchanges between extreme categories or unidirectional misclassification schemas which they have chosen.

If the reference data given in our table 1 represent re-misclassification of 40 percent of their original data in all directions from each category, the biases are universally toward the null with attenuation of trend. The same can be shown for their table 2 for 40 and 60 percent misclassification, respectively. This confirms the heuristic principle even with extreme numerical examples.

One could further refine these arithmetic calculations. However, the main point is that it remains difficult to manufacture positive associations or dose-response relations by nondifferen-

TABLE 1.

	Exposure status		
	No	Low	High
Reference distribution			
Case	100	200	600
Control	100	100	100
Odds ratio	1.0	2.0	6.0
Misclassified distribution 40%			
Case	220	260	420
Control	100	100	100
Odds ratio	1.0	1.18	1.91

TABLE 2.

	Exposure status	
	No	Yes
Reference distribution		
Case	25	75
Control	75	25
Odds ratio		9.00
Misclassified distribution 50%		
Case	50	50
Control	50	50
Odds ratio		1.00
Misclassified distribution 80%		
Case	35	65
Control	65	35
Odds ratio		0.30

tial misclassification. Counterintuitive "protective" effects for exposures of interest calculated from real data continue to require cautious treatment.

A further theoretical point arises in relation to the authors' opening paragraph where they state that for dichotomous exposures it is true that nondifferential misclassification of exposure can only bias an estimate of a true positive odds ratio downward and not away from or *beyond the null.* This is not necessarily a correct interpretation of Rothman (2) and other authors to whom they refer. Rothman, for instance, states: "When an effect exists, bias from nondifferential misclassification of exposure always is *in the direction of the null* value." Presumably, sufficiently severe bias could cause the estimate to extend beyond the null in this same direction without contradicting his statement.

We would argue further that there is no theoretical difference between 3 × 2 (or indeed M × N) tables and 2 × 2 tables in this regard as they claim. The authors' statement is only true for dichotomous exposures under the additional assumption that nondifferential bias is purely unidirectional. Our table 2 shows that it is possible to cause reversal of the odds ratio by means of nondifferential misclassification of exposure status. An odds ration of 9.0 for the reference data is reduced to an odds ratio of 1.0 given 50 percent misclassification in both directions for case and control groups. Beyond this, at say 80 percent, such misclassification causes reversal of the odds ratio (0.3)—a bias away from the null in the opposite direction to the true effect. It is only nondifferential misclassification in one direction that causes bias towards the null and not beyond! Otherwise the 2 × 2 table is subject to identical problems of bias direction.

We agree with the authors when they point out that caution is warranted when interpreting results, but we feel that it is also warranted when adopting critical approaches to well-established and useful heuristic principles.

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THE AUTHORS REPLY

Myers and Ehrlich are not pleased that we made several artificial choices in our nondifferential misclassification scenarios (1). The fact that their table 1 does not show a reversal of the direction of association does not detract from our point—we never claimed that reversal was the rule. Our intention was simply to show, by counterexamples, that a commonly believed "heuristic principle" does not always hold (2). We are currently investigating when the "heuristic principle" is violated.

Myers and Ehrlich (1) maintain that "nondifferential misclassification cannot manufacture a false positive association," and that the effects of nondifferential misclassification are "weaker positive associations and trends." We disagree. In example I of our table 2 (2, p. 747), we showed how low and high levels of exposures with elevated risks relative to the unexposed could appear to be at reduced risk due to nondifferential misclassification. Upon reversing the labels of "cases" and "controls" in the tables, the same numbers would show exposed categories changing from reduced risk (0.50 and 0.17 for low and high relative to none, respectively) to elevated risk (2.17 and 1.90 for low and high relative to none, respectively), and a positive trend changing to negative, as a consequence of nondifferential misclassification. It is true, as we stated in our article, that "a false inverse trend cannot be created under any nondifferential conditions when the true distribution has no dose-response trend" (2, p. 747, last paragraph before Discussion). Using the terminology of Myers and Ehrlich (1), we can rephrase this as "nondifferential exposure misclassification *cannot* manufacture positive (or negative) associations or dose-response relation if there is no true effect" but "it *can* manufacture positive (or negative) associations or dose-response relation if there is a true negative (or positive) effect."

We notice that the interpretation by Myers and Ehrlich of Rothman's statements (3) on the effects of nondifferential misclassification of exposure was different from ours. In his book, Rothman did not mention that the direction of the estimated effect may be reversed or that the strength may be exaggerated by nondifferential misclassification. In fact, the discussion (3, pp. 86–89) suggests to us that he believed it was impossible.

Myers and Ehrlich argue that "there is no theoretical difference" between 2 × 2 tables and K × 2 tables (1). In our clarification letter (4), we extended a rule originally proposed by Rogan and Gladen (5) for a reasonable exposure classification: that subjects be more likely to be classified into the correct category than into any other category. In a 2 × 2 table, this condition implies that the probabilities of misclassifying an exposed subject as unexposed and of misclassifying an unexposed subject as exposed are both less than 0.5 and, therefore, the sum of the two probabilities is less than 1. It can easily be shown that whenever the sum of these two probabilities is above 1 (as in the third panel of their table 2 (1)), a reversal of direction will occur; when the sum equals 1 (as in the second panel of their table 2 (1)), the estimate is null; and when the sum is below 1, the direction of the association does not change. Thus, with the extended Rogan and Gladen restriction, a reversal of direction cannot occur in a 2 × 2 table. We have proven by example (2, 4) that it can occur in a 3 × 2 table even with reasonable misclassification (40 percent of misclassification).

We also find these results, as well as results in our subsequent reports (6, 7), disturbing. We also believe, however, that investigators in this area need to rethink the "well established heuristic principle" on the effects of nondifferential misclassification and focus on subtle manifestations of differential misclassification in situations where, at first glance, misclassification appears to be nondifferential (6–8). These last three references (6–8) make us skeptical of claims of nondifferential misclassification and keen to learn about the impact of differential misclassification in these situations.

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