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THE EFFECT OF MISCLASSIFICATION IN THE PRESENCE OF COVARIATES

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The effects of misclassification on analyses involving a discrete covariate are examined. The following points are illustrated: 1) Analogous to the 2 × 2 table case, unbiased misclassification of the study exposure leads to reduction in the observed strength of the association of exposure with disease. 2) Both biased and unbiased misclassification will tend to distort the degree of heterogeneity in the measure of association being considered. 3) Misclassification of a confounder leads to a partial loss of ability to control confounding.

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A considerable volume of literature dealing with misclassification in 2-way contingency tables has appeared over the last 25 years. Copeland et al. (1) provide a good review of this work. Most of the discussion has focused on the effect of misclassifying only one of the two variables. A typical example of this occurs in a case-control study in which the test for the presence or past occurrence of the exposure under study has less than perfect sensitivity or specificity.

Previous work has concentrated on the effect of "unbiased" misclassification, in which the sensitivity and specificity of the test for exposure is independent of the other study variables. Bross (2) showed that unbiased misclassification in a 2 × 2 table could only diminish the apparent association between the two study variables (see Newell (3) for an important correction to the Bross article). Korn (4) derived several theorems regarding the effects of unbiased misclassification on the estimation of parameters for log-linear models of multidimensional contingency tables; these results thus have direct applications to studies in which the odds ratio is employed as a measure of association.

Of special interest in epidemiologic studies is the effect of misclassification in a 3-way table. The inclusion of a third variable in the classification may be dictated by the need to control confounding by that variable, or it may be of interest to study heterogeneity in the measure of effect of the primary study exposure across levels of the third variable, i.e., "effect modification" (5). The following discussion will examine the effects of misclassifying the primary study exposure (denoted F) or the third variable (denoted C) in a 3-way contingency table analysis of an epidemiologic study. For the sake of simplicity the study exposure F and the third variable C will be taken to be binary indicator variables for exposure history. Thus $F = 1$ if the subject was actually exposed to F, $F = 0$ if not, and similarly for C. The test for exposure to F will be denoted T_F, with $T_F = +$ if the test is positive for exposure to F, $T_F = -$ if not; simi-

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larly, T_C will denote the test for exposure to C, with $T_C = +$ if the test is positive for exposure to C, $T_C = -$ if not. The examples presented will illustrate the following points:

1) Analogous to the result for a 2 × 2 table, unbiased misclassification of F alone reduces the apparent strength of the association of F with the disease.

2) For the usual measures of effect, misclassification of either F or C will under very general conditions lead to either the spurious appearance or exaggeration of heterogeneity, or to the masking of actual heterogeneity.

3) If C is a confounder, misclassification of C will result in the final summary estimate of the effect of F on disease being confounded by C.

In the special case of several 2 × 2 tables these points are most easily seen as direct consequences of the findings of Bross (2) and Copeland et al. (1) for 2 × 2 tables. For unbiased misclassification, the points involving odds ratios turn out to be special cases of a general theorem due to Korn (4). General theorems regarding biased misclassification are unavailable, as the effects of the latter are highly dependent on the specific features of the test used and the joint distribution of the study variables. However, the comments regarding heterogeneity and confounding apply to both unbiased and biased misclassification, and to all commonly used measures of effect.

Misclassification of the study exposure in a 3-way table

The statements in points 1 and 2 with regard to the effect of misclassification of F on the odds ratio will be illustrated in the following example:

Example 1. Suppose table 1 represented the correctly classified structure in a case-control study, but that we could measure F only by means of a test T_F with sensitivity 0.8 and specificity 0.9, constant across the other variables. Our misclassified study data would be expected to appear as in table 2. (To construct each cell count in table 2, we take the corresponding cell in table 1, subtract the number of subjects misclassified out of that cell, and add on the number of subjects misclassified into that cell. For example, the first cell of the misclassified table, cases with $C = 1$ and $T_F = +$, will be composed of 80 per cent of the cases with $C = 1$ and $F = 1$ plus 10 per cent of the cases with $C = 1$ and $F = 0$. For a more detailed description of the construction see Copeland (1).) In table 2 we may note that misclassification has produced two major distortions of the odds-ratio structure seen in table 1:

(a) The strength of the summary association of F with the disease (as measured by the Mantel-Haenszel odds ratio (6)) has been reduced.

(b) There is a spurious appearance of odds-ratio heterogeneity, i.e., the odds ratio relating F to disease no longer appears constant across C.

TABLE 1

Correctly classified sample for example 1 (unobserved)

	$C = 1$		$C = 0$	
	$F = 1$	$F = 0$	$F = 1$	$F = 0$
Cases	120	100	45	200
Noncases	80	200	30	400
Stratum-specific odds ratios =	3.00		3.00	
Summary (Mantel-Haenszel) odds ratio = 3.00				

TABLE 2

Misclassified study data, example 1 (observed data)

	$C = 1$		$C = 0$	
	$T_F = +$	$T_F = -$	$T_F = +$	$T_F = -$
Cases	106	114	56	189
Noncases	84	196	64	366
Stratum-specific odds ratio =	2.17		1.69	
Summary odds ratio = 1.94				

Distortion (a) is unsurprising, since earlier results for 2 × 2 tables (1) imply that the stratum-specific odds ratios in table 1 would each be diminished by misclassification; hence we would expect that the summary odds ratio would also be diminished. In fact, we may observe that a direct generalization of the result for 2 × 2 tables holds: in a 3-way contingency table with homogeneous stratum-specific associations, unbiased misclassification of one of the variables will reduce the strength of the summary association of that variable with each of the remaining variables. It will become clear in the next section that this generalization does not hold if two or more variables are misclassified.

Distortion (b) is a result of the fact that the degree of reduction in each stratum-specific association is a function not only of the sensitivity and the specificity of the test, but also of the absolute stratum-specific frequency of the misclassified variable (1). Because C was strongly associated with exposure frequency in example 1, different reductions in the stratum-specific odds ratios occurred at the different levels of C, thus producing spurious heterogeneity. We may note from this that C would have to be associated with F in order for misclassification by F to produce spurious heterogeneity. (Note, however, that C is not an odds-ratio confounder in example 1; this can be seen by observing that C has no conditional association with the disease in table 1 (5).)

It is easy to demonstrate that misclassification of the study exposure could mask odds-ratio heterogeneity across C if such heterogeneity were present in the correctly classified sample. The reader may construct an example demonstrating this simply by replacing the 120 in the first cell in table 1 (cases with $C = 1$ and $F = 1$) with 85. The original table will then show an odds ratio of 2.13 in the "$C = 1$" stratum and 3.00 in the "$C = 0$" stratum,

TABLE 3
Correctly classified sample for example 2 (unobserved)

	$C = 1$		$C = 0$	
	$F = 1$	$F = 0$	$F = 1$	$F = 0$
Cases	90	20	40	40
Population at risk	900	300	400	600
Stratum-specific risk differences =	33/1000		33/1000	
Summary (regression) risk difference = 33/1000				

TABLE 4
Misclassified study data, example 2 (observed data)

	$C = 1$		$C = 0$	
	$T_F = +$	$T_F = -$	$T_F = +$	$T_F = -$
Cases	74	36	36	44
Population at risk	750	450	380	620
Stratum-specific risk differences =	19/1000		24/1000	
Summary (regression) risk difference = 21/1000				

while the misclassified table will show virtually equal odds ratios of 1.70 and 1.69 in the same respective strata.

The following example demonstrates an analogous situation regarding an additive measure of effect, the risk difference (or excess risk):

Example 2. Suppose table 3 represented the correctly classified (final) structure of a follow-up study population, but that we had measured F by means of the test T_F with sensitivity 0.8 and specificity 0.9, constant across other variables. Our misclassified data would be expected to appear as in table 4. Misclassification has produced two distortions of the additive structure of table 3:

(a) The strength of the summary association of F with the disease (as measured by the overall excess risk due to F derived from a weighted least squares regression of risk on F and C) has been reduced.

(b) There is a spurious appearance of heterogeneity in the risk difference, i.e., the excess risk due to F no longer appears constant across C.

As in the odds-ratio situation, distortion (a) would be expected from earlier results for the 2 × 2 case: the stratum-specific risk differences would each be diminished by unbiased misclassification, so that the overall excess risk due to F would also be reduced. Distortion (b) again follows from the fact that the degree of reduction in each stratum-specific association depends on the absolute frequency of F in the stratum; because of the strong association of C with F in example 2, different reductions in the stratum-specific risk differences occurred. And, similar to the odds ratio situation, it is easy to construct examples in which misclassification of F led to masking of risk-difference heterogeneity.

Misclassification of a confounder

We next examine the effect of misclassifying the third variable C under conditions in which a valid estimate of the causal association of the exposure F with the disease D can only be obtained by "controlling" for C in the analysis. In such a situation C is usually termed a confounder, and an estimate of the causal association of F with D from an analysis which fails to fully control for C is called confounded by C.

Example 3. Suppose now that table 5 represented the correct structure in a case-control study, but that we could measure C only by means of an unbiased test T_C with sensitivity 0.8 and specificity 0.9. The expected table of misclassified study data would then appear as in table 6. We see that misclassification has produced two distortions of the correct sample structure of table 3:

(a) The overall association of F with the disease is exaggerated.

(b) There is a spurious appearance of odds-ratio heterogeneity across C.

Table 5

Correctly classified sample for example 3 (unobserved)

	$C = 1$		$C = 0$	
	$F = 1$	$F = 0$	$F = 1$	$F = 0$
Cases	240	200	30	100
Noncases	80	200	40	400
Stratum-specific odds ratios =	3.00		3.00	

Summary odds ratio = 3.00
"Crude" odds ratio = 4.50

Table 6

Misclassified study data, example 3 (observed data)

	$T_C = +$		$T_C = -$	
	$F = 1$	$F = 0$	$F = 1$	$F = 0$
Cases	195	170	75	130
Noncases	68	200	52	400
Stratum-specific odds ratios =	3.37		4.44	

Summary odds ratios = 3.76

Distortion (a) runs counter to earlier examples, in which unbiased misclassification has only reduced associations. A detailed examination of the correct sample (table 5) explains this phenomenon: we see that in the correctly classified sample, C appears to be a "positive" confounder (in that the "crude" odds ratio—calculated by ignoring C in the analysis—is much higher than the summary odds ratio obtained after stratification by C). Both strata in table 6 are, in fact, mixtures of subjects with $C = 1$ and with $C = 0$, so that both the stratum-specific odds ratios in table 6 are positively confounded by C. As a consequence, the summary odds ratio from the misclassified data of table 6 is positively confounded. The spurious heterogeneity is a result of the fact that the degree of confounding by C is greater in the "$T_C = -$" stratum than in the "$T_C = +$" stratum.

It is easy to construct examples where C is a positive risk-difference confounder

and in which misclassification of C resulted in an exaggerated summary association of F with D and the spurious appearance of risk-difference heterogeneity. For the sake of brevity this will not be presented, but comments analogous to the odds-ratio case would apply.

If we had constructed the above example so that C was a negative confounder, we would observe that the summary measure of association obtained from data with C misclassified would be negatively confounded, though not confounded to the extent of the crude measure. This suggests that a confounder measured with some misclassification can still be useful as a control variable, as long as the misclassification of the confounder was unbiased.

The effects of misclassification of C on observations of heterogeneity of a measure are, in comparison, unpredictable. Misclassification of C can spuriously exaggerate or mask heterogeneity that was present in the true data structure. Examples of each such situation are easily constructed.

Misclassification of both factors

When both factors are misclassified, the details for a particular situation will be much easier to investigate if we are justified in assuming that the misclassifications are independent, i.e., that no matter what an individual's true values are, the probabilities of being misclassified on one variable do not change if the individual is misclassified on the other. But even given that the misclassification is independent and unbiased for both variables, any sort of distortion is possible if C is a confounder.

Example 4. Suppose that, in the situation described in example 3, we had additionally misclassified F using an unbiased test T_F of sensitivity 0.93 and specificity 0.97, and that the misclassifications of F and C are independent. Because of the independence assumption, we may construct the expected result by first misclassifying the correct structure (table 5) by C and then misclassifying the result of this (table 6) by F. The final result of this two-stage construction (rounded to whole numbers) is given in table 7. Note that in the first stratum the bias effects have cancelled out to produce the correct odds ratio, but the odds ratio in the second stratum and the summary odds ratio are still exaggerated. Had the misclassification of F been more severe (say, sensitivity and specificity of T_F both 0.9) there would have been a downward bias of the odds ratio in both strata.

TABLE 7
Misclassified study data, example 4 (observed data)

	$T_C = +$		$T_C = -$	
	$T_F = +$	$T_F = -$	$T_F = +$	$T_F = -$
Cases	186	179	74	131
Noncases	69	199	60	392
Stratum-specific odds ratios =	3.00		3.69	
Summary odds ratio = 3.26				

Discussion

Methods for dealing with bias due to misclassification are described (for the 2 × 2 case) by Copeland et al. (1) and Barron (7). Estimates of the sensitivity and specificity of the test used are employed to "calculate back" to the correctly classified sample. Such calculations can be extended to high dimensional tables in order to obtain an idea of the distortions produced by misclassification. Korn (4) provides a detailed method for correcting for unbiased, independent misclassification in contigency tables involving any number of variables with any number of categories, in the context of estimating parameters of hierarchical log-linear models for the tables; a crucial problem in applying many of these results, however, is the assumption of unbiasedness of all the tests involved. In case-control studies,

where the "tests" are often exposure-history recall items on a questionnaire, it has long been recognized that recall bias (a form of test bias) can produce biased misclassification in the case-control comparison (8). It will usually be a matter of judgement as to whether the unbiasedness assumption is satisfied and more powerful quantitative methods can be brought to bear on a problem of misclassification. Nevertheless, "back-calculation" to estimate the correctly classified sample structure can be performed whether or not the tests are unbiased (if a test is biased, then stratum-specific estimates of that test's sensitivity and specificity will be required). Such back-calculation, when possible, can provide the investigator with an idea of the extent of misclassification bias present in his results.

Misclassification of disease status will lead to the same sort of distortions as misclassification of exposure. However, the setting in which misclassification of disease occurs is usually different: in case-control studies, individuals will be misclassified with respect to the disease before the study subjects are drawn. In a rare disease situation, this will result in most of the misclassified cases being excluded from the study. Further, if all the cases in a source are selected for the study (as is often the situation), then most of the misclassified noncases will be included in the study as cases. The resulting differential distortion of the stratum-specific odds ratios will be quite profound unless the test for disease has a false-postive rate well below that of the actual disease rate. Back-calculation to obtain an estimate of the association corrected for misclassification will require some estimate of the proportion of members of the selected case series that are false positives. Improved case-detection plus careful screening of the case series to eliminate false positives will clearly yield a more valid study than any such back-calculation.

Finally, the comments about the effects of misclassification given in the above examples also apply to the classical risk ratio (i.e., relative risk (8)) used in follow-up studies. The arguments involved are analogous to those for the odds ratio and the risk difference.

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