

CONFOUNDING AND MISCLASSIFICATION

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Greenland, S. (UCLA School of Public Health, Los Angeles, CA 90024), and J. M. Robins. Confounding and misclassification. *Am J Epidemiol* 1985;122:495-506.

The authors examine some recently proposed criteria for determining when to adjust for covariates related to misclassification, and show these criteria to be incorrect. In particular, they show that when misclassification is present, covariate control can sometimes increase net bias, even when the covariate would have been a confounder under perfect classification, and even if the covariate is a determinant of classification. Thus, bias due to misclassification cannot be adequately dealt with by the methods used for control of confounding. The examples presented also show that the "change-in-estimate" criterion for deciding whether to control a covariate can be systematically misleading when misclassification is present. These results demonstrate that it is necessary to consider the degree of misclassification when deciding whether to control a covariate.

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Most epidemiologic studies are designed to estimate the effect of some exposure factor (or factors) on the risk of a particular disease. Despite considerable research, the issue of when adjustment for a covariate is necessary in this process remains controversial. Some recent works (1-3) have explicitly or implicitly put forth recommendations regarding adjustment when selection bias or misclassification is present in the study. Each of these works dealt with situations in which the covariates were treated as confounders, i.e., variables for which adjustment was necessary to remove bias in the estimator of effect. The purpose of this paper is to critically examine some recent recommendations regarding adjust-

ment for covariates related to classification, and to offer some alternative recommendations.

Current writings on confounding (1-4) suggest that if no other biases are present the following conditions are necessary for a covariate to be a confounder: 1) it must be a predictor of risk among the unexposed; 2) it must be a correlate of exposure in the population serving as the source of subjects; and 3) it should not be an intermediate variable in the causal pathway under study. Figure 1a illustrates these criteria in a path diagram.

In case-control studies, the preceding criteria can be broadened to allow adjustment for certain types of selection bias. Day et al. (1) note that if the covariate is a risk predictor but not a correlate of exposure in the source population (figure 1b), controlling it may still reduce bias if the covariate influences selection differentially with respect to exposure. And Miettinen and Cook (3) note that if the covariate is a correlate of exposure but not a risk predictor (figure 1c), controlling it may still reduce bias if

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Abbreviation: SMR, standardized morbidity ratio.

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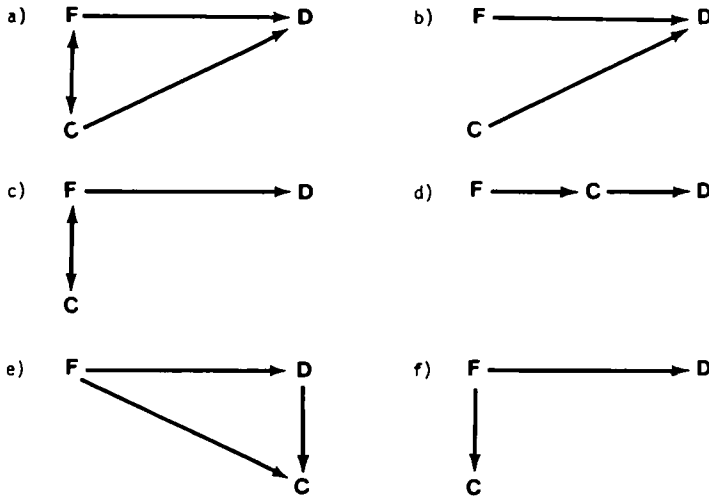


FIGURE 1. Path diagrams illustrating causal structures in source populations.

the covariate influences selection differentially with respect to disease status. Unfortunately, other authors have inappropriately extended these principles to situations in which the covariate is an intermediate variable (figure 1d) or a consequence of exposure and disease (figure 1e) (5). In such situations, there may indeed be selection bias due to the covariate, but adjustment for the covariate may produce a bias even more severe than the original selection bias (6). Thus, not all forms of selection bias can be regarded as confounding or be adequately dealt with by covariate control.

Some authors have suggested extensions of the above principles to situations involving misclassification of exposure or disease (2, 3). We will argue below that several of the extensions that have been proposed are incorrect. In particular, the counterexamples we will present will show that adjustment for a determinant of classification can aggravate bias.

The examples will concern epidemiologic studies of the effect of an exposure factor F ($F = 1$, present; $F = 0$, absent) on risk of a disease outcome D ($D = 1$, disease occurs; $D = 0$, disease does not occur) over a fixed risk period in a well-defined population. The covariate will be denoted C ($C = 1$, present; $C = 0$, absent). The effect of F will

be defined in terms of the rate ratio, estimated from case-control studies by the odds ratio. The disease will be assumed to be "rare" over the study period to avoid distinctions that arise in the general case. Nevertheless, all that follows applies to more general settings involving common diseases, multilevel factors, and measures of association other than the rate ratio and odds ratio.

"Expected values" will be taken to be large-sample expectations. Critical in what follows will be the idea of "net bias," defined for present purposes as the difference between the true effect parameter and the expected value of the chosen estimator.

(The definition of a confounder is not well agreed upon in settings in which the true effect parameter cannot be unbiasedly estimated from the observed data on F , C , and D . One might continue to define C to be a confounder only under the above conditions. Instead, in this paper, we will define C to be a confounder if the net bias of the crude estimator exceeds that of the adjusted estimator, regardless of conditions 1) and 2) above. As shown below, in the absence of information on misclassification rates, it is often impossible to determine from the data either the validity of conditions 1) and 2) or the relative bias of the crude and adjusted estimators.)

COVARIATES UNRELATED TO CLASSIFICATION

Consider a situation in which the covariate is associated with exposure but not a risk predictor (as in figures 1c or 1f). It has been suggested that the situation shown in figure 1f "may lead to genuine confounding when the variables are measured with error" (2, p. 106) and the following example was used to illustrate this assertion.

Example 1

Suppose that the underlying source population structure is as in table 1. A case-control study taking all cases and an equal number of controls, but nondifferentially misclassifying *F* 10 per cent of the time (i.e., sensitivity and specificity for measurement of *F* equals 0.9 across all levels of *C* and *D*) will have expected data as in table 2, where $F^* = 1$ for subjects classified as "*F* present" and $F^* = 0$ for subjects classified as "*F* absent." (To illustrate the construction of table 2, note that the upper left hand cell of table 2 is $0.9 (90) + 0.1 (1) =$

81 when rounded to the nearest whole number.) We can see from table 1 that, in the absence of other biases, the true effect corresponds to a rate ratio of 100. In contrast, the expected crude rate ratio estimate from the study (table 2) is 23, but the expected adjusted rate ratio estimate is 9, even more biased.

Contrary to the implication of the quote cited above, it is evident that adjustment for the covariate in example 1 dramatically increases the net bias, rather than reduces it. Thus, the covariate is *not* a genuine confounder in this situation. The example also demonstrates the pitfall of using the observed study data to judge whether confounding is present: misclassification can easily distort the apparent degree of confounding or effect modification by a third variable. This point has been made before by one of the present authors (7).

Example 1 turns out to be an illustration of a more general feature of nondifferential misclassification of exposure (proven in the Appendix): if the odds ratios are constant across strata, the covariate is associated with exposure but not classification or disease, and sensitivity and specificity sum to more than 1.0, then the misclassification bias in the standardized odds ratio will be greater than that in the crude (unless there is no association of exposure with disease, in which case neither estimate will be biased). As discussed in the Appendix, this theorem extends to cohort studies. The theorem also extends to case-control studies of populations in which the disease (rather than exposure) is nondifferentially misclassified and the covariate is associated with disease (instead of exposure). If, however, only one of exposure and disease are misclassified, the misclassification is nondifferential, and the covariate is associated only with the correctly classified variable, then both the standardized and crude odds ratios will be equally biased towards the null (this follows directly from a theorem of Korn (8)); furthermore, nondifferential misclassification of a nonconfounding co-

TABLE 1

Source population structure for examples 1 and 2

	C = 1		C = 0	
	F = 1	F = 0	F = 1	F = 0
Expected no. of incident cases	90	1	10	9
Population at risk	9,000	10,000	1,000	90,000
Rate ratio parameters	100		100	

Crude rate ratio parameter, 100.

TABLE 2

Expected data for example 1 (case-control study of population in table 1 with sensitivity and specificity of measurement of *F* having constant sensitivity = 0.90 and specificity = 0.90)

	C = 1		C = 0	
	F* = 1	F* = 0	F* = 1	F* = 0
Cases	81	10	10	9
Controls	9	10	10	81
Expected odd ratios	9		9	

Expected crude odds ratio, 23.

F*, measured value of *F*.

variate will produce no bias in either the standardized or crude odds ratio.

In example 1, nondifferential misclassification of the exposure generated the spurious appearance of confounding by a covariate (in the sense that the crude and adjusted values differ), and nondifferential misclassification of the disease can do so as well. As the following example shows, differential misclassification of a nonconfounding covariate can also generate the spurious appearance of confounding.

Example 2

Consider again the case-control study of the source population described in example 1 and table 1, but with *C* rather than *F* measured with error. Specifically, suppose the presence of *C* is detected with perfect specificity but with a sensitivity of 0.98 among cases and 0.90 among noncases (as might occur, for example, if the covariate represented an event for which the cases had better recall). The expected data would then be as in table 3. The expected crude odds ratio differs from the expected standardized morbidity ratio (SMR) estimate (9, 10) and the expected Mantel-Haenszel estimate (2, 4), yet it is the crude (rather than any adjusted value) that equals the correct population rate ratio. This occurs for two reasons: first, since *F* and *D* are not misclassified, the expected crude odds ratio equals the crude rate ratio parameters, and second, the crude parameter equals the

TABLE 3

Expected data for example 2 (case-control study of population in table 1 with differential misclassification of C: sensitivity = 0.98 among cases and 0.90 among controls, specificity = 1.00 in both groups)

	<i>C</i> * = 1		<i>C</i> * = 0	
	<i>F</i> = 1	<i>F</i> = 0	<i>F</i> = 1	<i>F</i> = 0
Cases	88	1	12	9
Controls	8	9	2	91
Expected odds ratios	99		61	

Expected crude odds ratio, 100.
 Expected SMR estimate (9, 10), 92.
 Expected Mantel-Haenszel odds ratio (2, 4, 18), 73.
*C**, measured value of *C*.

stratum-specific values. (The misclassification has also generated a spurious appearance of odds ratio heterogeneity.)

PREDICTORS OF EXPOSURE CLASSIFICATION

It has been suggested that in case-control studies "study procedures that bear on the accuracy of information on exposure . . . are confounders if they are distributed differently between the index (case) and reference [control] series" (3, p. 598). The following example shows that this claim is false as a general principle.

Example 3

Suppose the correctly classified expected data in a case-control study are as given in table 4, and that these numbers perfectly reflect the magnitude of the effect of the study factor on incidence. Let *C* = 1 indicate that the exposure information was obtained by direct interview with subject, and *C* = 0 that the subject had died before an interview could be performed (so information was obtained from next-of-kin). Note that a higher proportion of controls were directly interviewed. Suppose that interviews of next-of-kin of deceased subjects (*C* = 0) always had a sensitivity (for exposure) of 0.75 and a specificity of 0.85, while direct interviews of subjects (*C* = 1) always had a sensitivity of 0.90 and a specificity of 0.95. The expected misclassified data would then be as in table 5; we see that the crude odds ratio is 1.8, closer to the correct value of 2 than any of the adjusted or stratum-specific values. Thus, adjustment for the

TABLE 4

Expected correctly classified data for example 3. (C = 1 if subject directly interviewed, C = 0 otherwise.)

	<i>C</i> = 1		<i>C</i> = 0	
	<i>F</i> = 1	<i>F</i> = 0	<i>F</i> = 1	<i>F</i> = 0
Cases	20	80	120	480
Controls	100	800	40	320
Correct odds ratios	2.00		2.00	

Correct crude odds ratio, 2.00.

TABLE 5

Expected data under misclassification, example 3 (case-control study of subjects in table 4, with C a determinant of exposure classification: sensitivity = 0.90 and specificity = 0.95 when C = 1, sensitivity = 0.75 and specificity = 0.85 when C = 0)

	C = 1		C = 0	
	F* = 1	F* = 0	F* = 1	F* = 0
Cases	22	78	162	438
Controls	130	770	78	282
Expected odds ratios	1.67		1.34	
Expected crude odds ratio, 1.80.				
Expected SMR estimate, 1.37.				
Expected Mantel-Haenszel odds ratio, 1.39.				
F*, measured value of F.				
Expected crude odds ratio under matching on C, 1.37.				

source of information is unnecessary in this example, and in fact harmful in that it increases net bias.

Suppose in the above example one had matched the controls to cases on source of information (C), so the same proportion of controls as cases (14 per cent) had been directly interviewed. The expected adjusted odds ratios would then be about the same as before, but the expected crude odds ratio would now be only 1.4. Thus, matching on source of information would also be harmful in this example.

Note that the covariate in example 3 was not actually related to the exposure within either the case series or the control series (table 4). Thus, a covariate need *not* be related to the exposure in order to spuriously mimic a confounder through its effects on exposure classification. Example 1 illustrates that if a covariate is related to exposure, it need not be related to disease or classification in order to spuriously mimic a confounder.

Example 3 illustrates a failure of the oft-repeated validity criterion of *comparability of measurement* (11, 12): in the example, focusing the analysis within groupings based on measurement comparability led to less valid results than simple pooling of subjects without regard to measurement comparability. Even restriction of the analysis to the subjects with the most accurate

measurements (stratum C = 1) produced less valid results than a crude analysis of all subjects. Nevertheless, this comparability criterion may have its origin in examples such as the following, which parallels example 3 yet illustrates a general situation in which adjustment for a determinant of exposure classification reduces bias.

Example 4

Suppose the correctly classified expected data in a case-control study are as given in table 6, and that these numbers perfectly reflect the magnitude of the effect of the study factor on incidence (note in particular that there is no effect). Let C be defined as in example 3, and the sensitivities and specificities within levels of C be as in example 3. The expected misclassified data would then be as in table 7. We see that the crude odds ratio is biased away from the correct value of 1.00, whereas the stratified odds ratios are not. Thus, in this example, adjustment for the source of information (indicated by C) is essential for validity.

TABLE 6

Expected correctly classified data for example 4

	C = 1		C = 0	
	F = 1	F = 0	F = 1	F = 0
Expected no. of incident cases	10	80	60	480
Population at risk	100	800	40	320
Correct odds ratios	1.00		1.00	
Correct crude odds ratio, 1.00.				

TABLE 7

Expected data under misclassification, example 4 (case-control study of subjects in table 6, with C a determinant of exposure classification: same classification rates as example 3)

	C = 1		C = 0	
	F* = 1	F* = 0	F* = 1	F* = 0
Cases	13	77	117	423
Controls	130	770	78	282
Expected odds ratios	1.00		1.00	
Expected crude odds ratio, 1.32.				
F*, measured value of F.				

The effect of covariate adjustment on net bias in example 4 was opposite to that in example 3. Consequently, one cannot state that in general a predictor of exposure classification should or should not be treated as a confounder. Nevertheless, example 4 illustrates a general principle of hypothesis testing: suppose that no other biases are present, and within levels of the covariate misclassification of exposure is nondifferential and there is no true exposure-disease association; then the true large-sample alpha level (type I error rate) of any of the usual stratified tests of association (e.g., Mantel-Haenszel (4)) will not exceed their nominal alpha-level (8). And (except for some special cases of unusual structure) if the covariate is both a predictor of the (nondifferential) exposure classification errors and associated with disease, stratification on the covariate will be necessary to produce a test of size within the nominal alpha-level (this is because exposure will be differentially misclassified within the crude table). "Comparability of measurement" therefore remains a valid criterion for hypothesis testing. Although forcing "comparability of measurement" also guarantees that the measurement bias in point estimation will be towards the null, example 3 demonstrates that the net bias can sometimes be greatly increased by such action.

PREDICTORS OF DIAGNOSTIC ERROR

Misclassification of disease status is often referred to as misdiagnosis or diagnostic error. It has been stated that confounders "are predictors (determinants) of diagnosing the illness—by being either risk indicators or determinants of diagnostic errors—in the type of setting represented by the study" (3, p. 594). The following example shows that (contrary to the preceding quote) a determinant of diagnostic error may be associated with the study factor and yet not be a true confounder.

Example 5

Suppose our source population is actually as in table 8 (showing a true effect param-

eter of rate ratio = 2.00 and an association of C with F), and C is a determinant of diagnostic errors as shown in the table: in the population with C present, diagnosis of disease takes place with a 95 per cent sensitivity and a 0.08 per cent false positive rate over the study period, while in the population with C absent, diagnosis of disease takes place with 90 per cent sensitivity and 0.06 per cent false positive rate. If we do a follow-up study of the entire population and expend no additional case-finding or case-screening efforts, our expected data will be as in table 9: the expected crude rate ratio estimate is 1.67, while the expected adjusted estimates are around 1.56. Thus, adjustment for the determinant of diagnostic error is unnecessary in this example, and in fact harmful in that it increases net bias. As in the last two examples, the adjusted estimators are more biased than the crude, so that, despite its association with exposure and its influence on diagnostic errors, the covariate is not a true confounder. Note also that adjustment for the covariate would produce bias in a case-control study of this population.

The belief that pure determinants of diagnosis should be treated as confounders may have its origin in examples such as the following, which parallels example 5 yet illustrates a general situation in which adjustment for a determinant of diagnostic error reduces bias.

Example 6

Suppose the source population structure was as in table 10, with C a determinant of diagnostic errors as shown: F and C have the same association as in example 5, and the sensitivity and false positive rate of disease diagnosis is also the same as in example 5. The only difference is that, unlike in example 5, F has no effect. If we do a follow-up study of the entire population and take as cases all and only those diagnosed as such, our expected data will be as in table 11. We see that the crude rate ratio is biased away from the correct value of

TABLE 8
Source population structure for example 5

	C = 1		C = 0	
	F = 1	F = 0	F = 1	F = 0
Expected no. of				
Diagnosed cases	76	19	32	32
Undiagnosed cases	4	1	8	8
Expected no. of noncases diagnosed as cases	32	16	12	24
Population at risk	40,000	20,000	20,000	40,000
True rate ratio parameters (based on true cases only)	2.00		2.00	

Crude rate ratio parameter (based on true cases only), 2.00.

TABLE 9

Expected data for example 5 (follow-up study of population in table 8 using all diagnosed persons as cases, C a determinant of disease diagnosis)

	C = 1		C = 0	
	F = 1	F = 0	F = 1	F = 0
Apparent cases	108	35	44	56
Population at risk	40,000	20,000	20,000	40,000
Expected rate ratio estimates	1.54		1.57	

Expected crude rate ratio estimate, 1.67.

Expected SMR estimate, 1.55.

Expected Mantel-Haenzel rate ratio estimate, 1.56.

1.00 (albeit slightly), whereas the stratified rate ratios are not. Thus, in this example, adjustment for the diagnostic predictor was appropriate for validity.

The effect of covariate adjustment on net bias in example 6 was opposite to that in example 5. Therefore, one cannot state that in general a predictor of diagnostic errors should or should not be treated as a confounder. Nevertheless, example 6 illustrates a general principle parallel to the one given after example 4: suppose that no other biases are present, and within covariate levels there is no true exposure-disease association and diagnostic errors are non-differential; then the true large-sample alpha level of any of the usual stratified tests of association will not exceed their nominal alpha-level (8). And (except for some special cases of unusual structure) if the covariate is both a predictor of the (non-differential) diagnostic errors and associated

TABLE 10
Source population structure for example 6

	C = 1		C = 0	
	F = 1	F = 0	F = 1	F = 0
Expected no. of				
Diagnosed cases	38	19	18	36
Undiagnosed cases	2	1	2	4
Expected no. of noncases diagnosed as cases	32	16	12	24
Population at risk	40,000	20,000	20,000	40,000
True rate ratio parameters (based on true cases only)	1.00		1.00	

Crude rate ratio parameter (based on true cases only), 1.00.

TABLE 11

Expected data for example 6 (follow-up study for population in table 10 using all diagnosed persons as cases, *C* a determinant of disease diagnosis)

	<i>C</i> = 1		<i>C</i> = 0	
	<i>F</i> = 1	<i>F</i> = 0	<i>F</i> = 1	<i>F</i> = 0
Apparent cases	70	35	30	60
Population at risk	40,000	20,000	20,000	40,000
Expected rate ratio estimates	1.00		1.00	

Expected crude rate ratio estimate, 1.06.

with the exposure, stratification on the covariate will be necessary to produce a test of size within the nominal alpha-level (again, because the diagnostic errors will be differential within the crude table). Predictors of diagnostic accuracy may thus be treated as confounders in hypothesis testing. But example 5 demonstrates that control of such predictors can sometimes greatly increase net bias in point estimation.

IMPLICATIONS FOR THE CONTROL OF MISCLASSIFICATION BIAS

The above examples show that, despite conjectures to the contrary, predictors of classification or diagnosis cannot be adequately dealt with in the same framework as predictors of risk. In particular, a covariate can be a determinant of exposure classification or disease diagnosis but it may nevertheless be detrimental to adjust for the covariate. This appears to run counter to usual epidemiologic intuitions (cf., 11, 12), and yet the above examples ought to be sufficient to rule out a simple parallelism between confounder control and misclassification control. Furthermore, the misclassification rates employed above are not numerically extreme, making it doubtful that the hoped-for parallelism might hold approximately: for example, Copeland et al. (13, table 2) reviewed reported sensitivities and specificities of seven measurements and found four instances in which sensitivity was below 60 per cent or specificity was below 75 per cent. More recent studies have found under 80 per cent agreement between interview

responses and medical records for certain types of drug history items (14-16) (low agreement necessarily implies high error rates for one or both of the sources); differential recall was indicated in some instances (16). Even when the error rates appear "low," errors can produce sizeable distortions if the presence or absence of the exposure or disease is "rare" (as in example 4 or the real data reported by Schulz et al. (17)).

This leaves three strategies for the control of misclassification bias: 1) prevention of misclassification through improved measurement methods; 2) algebraic correction for misclassification (which requires a source of error-rate estimates, such as a validation substudy); and 3) control of those covariates for which control could be argued to reduce misclassification bias in the specific analysis being performed. The first two strategies have been extensively discussed in a number of recent publications (e.g., 13, 17-20), while the third appears to have been either ignored or misperceived. With regard to the third strategy, a general principle was illustrated by examples 3-6: if misclassification is non-differential *within* levels of a covariate but varies *across* levels of the covariate, then, in the absence of other sources of bias, control for the covariate will in general improve the validity of the *test* of association of factor and disease; nevertheless, control of the covariate may in some instances increase the net bias in *estimation* (cf., example 3, 5). In this case, the sole advantage of the adjusted point estimate is that the direction of its misclassification bias is known a priori (i.e., it is towards the null); if the misclassification is differential, however, this advantage is lost.

IMPLICATIONS FOR IDENTIFICATION OF CONFOUNDING

The above examples also show how study data can be systematically deceptive as to whether or not a covariate is a confounder (in the sense of requiring control). For ex-

ample, it may be known a priori that the covariate is associated with exposure while its status as a risk predictor may be unknown (or vice versa). In such situations the data are usually employed to decide whether or not the covariate is a confounder by comparing the crude and adjusted estimates; the latter is chosen if the two differ to an important extent. Even assuming no misclassification is present, this "change-in-estimate" criterion is problematic (3, 21); when misclassification is present (as it almost always is), the criterion may lead to unnecessary and even bias-producing control of the covariate (as in examples 1-3 and 5).

It follows that accuracy of confounder identification will benefit from application of the above three strategies for control of misclassification bias; the problems discussed here will not arise if misclassification is prevented; confounding should be evaluated after application of corrections for misclassification; and if control of a covariate can be argued to reduce misclassification bias, the rationale for controlling it no longer depends on whether it has both the associations depicted in figure 1a.

This still leaves situations in which both the degree of misclassification and the degree of covariate-exposure or covariate-disease association are unknown. Example 1 provides an extreme illustration of the problem: in actual practice, we would only observe the study data (table 2), which show a marked difference between the crude and adjusted estimates. If we attributed most of this difference to confounding by the covariate we should prefer the adjusted estimate, but if we attributed most of it to nondifferential misclassification of the study factor we should prefer the crude estimate. And if we were uncertain about the relative strength of each source of bias, we should be correspondingly uncertain about which estimate to prefer.

There are several informal ways of coping with this dilemma. The simplest is to present both the crude and adjusted results,

along with some arguments bearing on which is likely to be the more accurate of the two. A related approach is to compute confidence limits with and without controlling the covariate in question, and then base inference on an interval composed of the smallest lower limit and the largest upper limit. The interval so constructed should cover the true parameter at least at the nominal coverage rate if at least one of the crude and adjusted analyses is unbiased, or if the analyses are biased in opposite directions. If both analyses are biased in the same direction, the composite interval will still cover the true parameter no less than the better of the two original intervals.

The "composite interval" approach can be extended to deal with situations involving several sources of uncertainty in the analysis: one can compute limits controlling for various covariate subsets, or after applying corrections for misclassification based on various assumptions about the error rates; one then constructs the composite interval from the minimum of the set of lower limits and maximum of the set of upper limits so obtained. The obvious disadvantage of the resulting interval is its potentially extreme conservatism, as reflected by excessive width. Although a wide composite interval may in a rough sense properly reflect the degree of uncertainty in the results, we caution that we regard such intervals as an informal aid to study interpretation rather than a substitute for established statistical methods.

DISCUSSION

Most of the literature has not considered the combined effects of the various biases, for the good reason that the number of special situations to consider is enormous. There are, however, examples showing that misclassification can reduce one's ability to control confounding (7) and that (legitimate) strategies for confounder control can increase misclassification bias (22). More complex situations can be envisioned: con-

sider, for example, a matched-pair case-control study in which a confounder is used as a matching factor but is routinely misclassified during selection, resulting in the selection of mismatched controls. As a consequence, either the study results will remain confounded by the confounder or, if the confounder is correctly measured in the analysis, many of the subjects will be left unmatched; loss of validity or efficiency is thus inevitable in this situation.

In most epidemiologic studies, all sources of bias will variously cancel and interact in a manner too complex for accurate analysis. It is perhaps for this reason that some authors criticize overemphasis of formal statistical results in drawing and presenting conclusions from epidemiologic data. But granting that formal methods do not adequately address these problems, numerical reasoning can still be employed to evaluate the likely impact of various sources of biases on the study data at hand, and to check on the validity of any general recommendations that appear in the methodologic literature.

We have seen that misclassification bias (including biases arising from diagnostic errors) cannot in general be controlled by the same basic methods used to control confounding or some forms of selection bias. If we have accurate estimates of the classification probabilities, corrections for misclassification are possible (13, 18-20, 22). Nevertheless, the true classification rates are virtually never known, and estimates of them will usually be subject to considerable error so that the "corrected" estimates will not be fully corrected for misclassification bias. It is also known that relatively modest degrees of misclassification can produce large amounts of bias (7, 13, 22). These observations taken together indicate that, similarly to many other problems, prevention of misclassification bias is superior to any analytic cure.

The contingency-table results presented here and elsewhere (7, 8, 13, 18, 22) have immediate consequences for binary regres-

sion methods, such as logistic regression. Most importantly, we note that misclassification of a regressor can bias the coefficient estimates for other regressors, even if the misclassification is nondifferential (cf., example 1) or even if the true coefficient of the misclassified regressor is zero (cf., example 2); misclassification of a regressor can also bias interaction estimates (cf., examples 2 and 3, and reference 7). These observations point out the necessity of considering the measurement quality of all variables entered in a model, even when only certain effects within the model are the object of study. Similar conclusions have been reached by Kupper (23) in the case of ordinary regression. Examples 3 and 5 also imply that the addition of "data quality" indicators to models (such as a variable indicating whether data were obtained from the subject or from a surrogate (24)) can sometimes increase bias in some or all of the risk factor coefficients.

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APPENDIX

Proof of theorem corresponding to example 1

Suppose a covariate is associated with exposure but not associated with classification or the disease, the exposure is nondifferentially misclassified with sensitivity Q and specificity P (and $P + Q > 1$), and the true stratum-specific odds ratio R for the exposure-disease association is constant across the covariate levels. Then the misclassification bias in the standardized morbidity ratio (SMR) estimate ("internally" standardized odds ratio, weighting the odds ratios based on the covariate distribution in the exposed controls) (9, 10) will be greater than the misclassification bias in the crude odds ratio (unless $R = 1$, in which case neither are biased). In particular, if SMR and R_c represent the large-sample expectations of the standardized and crude estimators, we have that $R < 1$ implies $R < R_c < SMR < 1$ and $R > 1$ implies $R > R_c > SMR > 1$.

Proof: For stratum i of the covariate let

- X_i = expected true number of unexposed controls,
- T_i = expected exposure odds among controls ($T_i \neq T_j$ for some i, j)
- S = expected case-control ratio among the unexposed (S is constant across strata since the covariate is not a risk factor).

- Then $T_i X_i$ = expected number of exposed controls,
- SX_i = expected number of unexposed cases, and
- $RST_i X_i$ = expected number of exposed cases.

- Also, the apparent numbers expected after misclassification will be
- $A_i = SX_i(QRT_i + (1 - P))$ = apparent number of exposed cases,
- $B_i = SX_i(P + (1 - Q)RT_i)$ = apparent number of unexposed cases,
- $C_i = X_i(QT_i + (1 - P))$ = apparent number of exposed controls, and
- $D_i = X_i(P + (1 - Q)T_i)$ = apparent number of unexposed controls.

We will prove the theorem only for the case $R > 1$, $T_1 < T_0$, as proofs for the other three cases follow by symmetrical arguments.

For the binary case ($i = 0$ or 1 only), proof proceeds by the following lemmas:

Lemma 1. If $R > 1$ and $T_1 < T_0$, then $B_1 D_0 < B_0 D_1$.

Proof: By direct algebra, $B_1 D_0 - B_0 D_1 = P(1 - Q)(1 - R)S(T_0 - T_1)X_1 X_0$. $1 - R$ is the only negative term in the right hand product, hence both sides of the equation are negative.

Lemma 2. If $T_1 < T_0$ and $P + Q > 1$, then $C_1 D_0 < C_0 D_1$.

Proof: By direct algebra, $C_0 D_1 - C_1 D_0 = (P + Q - 1)(T_0 - T_1)X_1 X_0$. All the terms in the right hand product are positive, hence both sides of the equation are positive.

Lemma 3. If $R > 1$, $T_1 < T_0$, and $C_1 D_0 < C_0 D_1$, then $SMR < R_c$.

Proof: By Lemma 1 $B_1 D_0 - B_0 D_1 < 0$.

Hence

$$C_1D_0(B_1D_0 - B_0D_1) > C_0D_1(B_1D_0 - B_0D_1),$$

yielding

$$B_1C_1D_0^2 - B_0C_1D_1D_0 > B_1C_0D_1D_0 - B_0C_0D_1^2,$$

then

$$B_1C_1D_0^2 + B_0C_0D_1^2 > B_1C_0D_1D_0 + B_0C_1D_1D_0.$$

Adding $(B_1C_1 + B_0C_0)D_1D_0$ to both sides of the last inequality and factoring, we obtain

$$(B_1C_1D_0 + B_0C_0D_1)(D_1 + D_0) > (B_1 + B_0)(C_1 + C_0)D_1D_0,$$

then

$$B_1C_1/D_1 + B_0C_0/D_0 > (B_1 + B_0)(C_1 + C_0)/(D_1 + D_0).$$

Dividing both sides of the last inequality into $A_1 + A_0$ yields

$$SMR = \frac{A_1 + A_0}{(B_1C_1/D_1 + B_0C_0/D_0)} < \frac{(A_1 + A_0)(D_1 + D_0)}{(B_1 + B_0)(C_1 + C_0)} = R_c.$$

It is well known (e.g., see references 12, 13, and 18) that (within strata) nondifferential misclassification produces bias towards the null, hence $R > SMR > 1$; unrelatedness of the covariate to classification implies that the misclassification is also nondifferential in the crude table and hence $R > R_c$. The theorem now follows for binary covariates from Lemmas 1-3. Extension to the case of a covariate with K levels follows by mathematical induction: Suppose the theorem holds for $K - 1$ levels. Let SMR and R_c be the expected internally standardized and crude odds ratios obtained from all K covariate strata, SMR^* and R_c^* the corresponding expected values obtained from the first $K - 1$ strata only, and let SMR_c be the standardized odds ratio obtained by collapsing the first $K - 1$ levels of the covariate before adjustment (i.e., coding the covariate as "level K or not- K "). Finally, let A^* , B^* , C^* , and D^* be the sum of the corresponding cells in the first $K - 1$ strata, and

$$W^* = \sum_{i=1}^{K-1} B_iC_i/D_i.$$

Since $SMR^* = A^*/W^* < A^*D^*/B^*C^* = R_c^*$, we have $B^*C^*/D^* < W^*$, hence

$$SMR = \frac{A^* + A_K}{W^* + B_KC_K/D_K} < \frac{A^* + A_K}{B^*C^*/D^* + B_KC_K/D_K} = SMR_c.$$

The binary case yields $R_c > SMR_c$, hence $R_c > SMR$. As before, we have $R > R_c$ and $SMR > 1$ as well, proving the theorem.

Using arguments symmetrical to those given above, the theorem extends to the case in which the unexposed serve as the source of standardization weights (i.e., the "externally" standardized odds ratio), as well as any average of the exposed and unexposed weightings (such as weighting based on the combined distribution). The theorem also extends to cohort studies by letting R be the risk ratio, S the incidence in the unexposed, SMR the usual cohort standardized morbidity ratio, and X , T , C , and D refer to quantities in the total cohort (rather than the controls). Finally, the theorem extends to case-control studies of populations with nondifferential misclassification of disease by letting Q and P refer to the disease sensitivity and specificity, and assuming that the covariate is unassociated with exposure (instead of disease) and that no refinement of diagnosis is made for the study. We note, however, that the assumption of a constant odds ratio (in case-control studies) or risk ratio (in cohort studies) is necessary for the above results: examples show that under heterogeneity the misclassification bias in the crude ratio can sometimes exceed that in the standardized ratio. Such an example can be constructed by modifying example 1 (tables 1 and 2) so that the true number of cases at $F = C = 1$ is 1.