

## BIAS DUE TO MISCLASSIFICATION IN THE ESTIMATION OF RELATIVE RISK

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Lack of bias in the estimation of relative effect in epidemiologic studies depends on the internal validity of the study. This paper conveys in graphic and tabular form the direction and magnitude of bias due to misclassification of study subjects. A series of computer-generated graphs shows that the departure of the estimate of effect (relative risk or odds ratio) from its true value is a function of sensitivity and specificity (measures of classification validity), disease frequency, and exposure frequency. The discussion of bias emphasizes misclassification of the "outcome" variable; i.e., disease occurrence in a cohort study and exposure rate in a case-control study. Examples are used to illustrate that the magnitude of the bias can be large under circumstances which occur readily in epidemiologic research. When misclassification is equal for the two compared groups, the estimate is biased toward the null value, and in some instances beyond; when differential misclassification occurs (as in selective recall in case-control studies) the bias can be in either direction, and may be great. Formulas are derived to estimate the underlying true value of the relative risk or odds ratio using the investigator's observations together with the estimated sensitivity and specificity of the classification procedure.

### biometry; epidemiologic methods

Lack of bias in the estimation of relative risk in epidemiologic studies depends on the internal validity of the study. Two of the three major impediments to internal validity—confounding effects and bias in selection of study subjects—have been ex-

amined often in the epidemiologic literature (1-6). The purpose of this paper is to describe, empirically, the bias which can occur due to misclassification of study subjects. This bias will be shown to be a function of the sensitivity and specificity of the classification procedure, the disease frequency, and the exposure frequency. Equally important, the bias depends on whether the misclassification is the same or different, that is, nondifferential or differential, in the two compared groups.

Some of the consequences of misclassification of study subjects, in biasing the estimates of effect, have been described elsewhere (7-13). The most frequently discussed situation relates to data sets reducible to a  $2 \times 2$  (or fourfold) table. In this scheme, both the exposure and the disease

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Abbreviations: *RR*, relative risk; *RR'*, apparent relative risk.

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are categorized as binary "yes-no" variables.

Bross (7) has shown that misclassification of the same magnitude and in the same direction in two compared populations (i.e., nondifferential misclassification) tends to understate differences in proportions.

Diamond and Lilienfeld (8,9) have dealt with the effect of nondifferential misclassification on relative risk estimates from case-control studies and have concluded that this type of bias, under certain circumstances, can produce an overestimate of relative risk. However, their method of applying misclassification rates derived from one study to data from another has been challenged by Newell (10), who supported Bross (7) in asserting an attenuation of the estimated effect relative to the true value. Newell (10) further illustrated that, in the case of nondifferential misclassification, the expected value of the observed difference in exposure rates is a function of the sensitivity and specificity of the classification scheme. More recently, Goldberg (11) has shown that the odds ratio is biased to a greater extent by the false positive rate (a function of specificity) than by the false negative rate.

Keys and Kihlberg (12) qualified the concept that misclassification produces an underestimation of the true effect, by stipulating that this holds only when the misclassification errors are independent of any relationship between the variables (disease and exposure) under investigation. The case of nondifferential misclassification with respect to both exposure and disease, in which the two types of misclassification are independent, has been considered by Gullen et al. (13). The authors conclude that, again, misclassification biases the effect measures toward the null value. Most of the previous discussion of the effects of misclassification on effect measures has been presented in detailed algebraic fashion. This paper does not derive general formulas for bias due to misclassification; rather, it presents an empir-

ical description of the extent and direction of the bias under various representative circumstances.

Three simplifying assumptions are made here, in generating these empirical results. The first is that the misclassification affects only the comparison criterion—that is, disease occurrence in cohort or follow-up studies, and exposure history in case-control studies. The second assumption is that the misclassified variable is dichotomous. A third assumption is that there is no bias due to selection or confounding in the data from which the estimates are calculated, thereby allowing the use of simple, unadjusted ratio measures of effect.

#### STUDY SUBJECT CLASSIFICATION

Table 1 shows the classification of study subjects in a format which is familiar in the context of screening. Notice that the actual status is found in the columns (yielding  $(A + C)$  positives and  $(B + D)$  negatives), but that the subjects are categorized in a study according to the imperfect classification criteria represented by the rows, giving an apparent dichotomy of  $(A + B)$  positives and  $(C + D)$  negatives. By definition, the sensitivity of the classification scheme (the proportion of correctly classified positives) equals  $A/(A + C)$ , and the specificity (the proportion of correctly classified negatives) equals  $D/(B + D)$ . Whenever either the sensitivity or specificity of the classification procedure is less than 100 per cent, the point estimate of effect will be biased to some extent. In the

TABLE 1  
*Distribution of study subjects according to both actual and classified status\**

Classified status	Actual status		
	+	-	Total
"+"	A	B	(A + B)
"-"	C	D	(C + D)
Total	(A + C)	(B + D)	(A + B + C + D)

\* Sensitivity =  $A/(A + C)$ ; specificity =  $D/(B + D)$ .

TABLE 2

*Examples of reported sensitivities and specificities of tests used in epidemiologic studies*

Test	Validation	Sensitivity (%)	Specificity (%)
<i>Cohort</i>			
Glucose tolerance by UGDP criteria (14)	By WHO criteria	91	94
Pap smear (15)	Biopsy	86	91
Peptic ulcer by questionnaire (16)	Radiologic diagnosis	50	98
Protoporphyrin assay-microhematocrit (17)	Blood lead concentration	95	73
Rose questionnaire (18)	Clinical interview	44	93
<i>Case-control</i>			
Circumcision status by questionnaire (19)	Physician's examination	83	44
Smoking history by next-of-kin (20)	Personal questionnaire	94	88

examples to follow, the positives and negatives are replaced by diseased ( $D$ ) and disease-free ( $\bar{D}$ ) categories in the cohort studies, and by exposed ( $E$ ) and unexposed ( $\bar{E}$ ) categories in the case-control studies.

Table 2 lists some tests which have been used in cohort and case-control studies (references 14-20). Their reported sensitivities and specificities, as validated by the criteria indicated, are also given. The range of values listed lies within the range that will be considered in the following examples.

#### NONDIFFERENTIAL MISCLASSIFICATION

##### *Cohort studies*

Table 3 shows bias due to nondifferential misclassification in a cohort study. That is, for both populations,  $A$  and  $B$ , the sensitivity and specificity equal .8 and .9, respectively. Here the true cumulative incidence of the disease in population  $A$  is .40, which can be read from the lower marginal as the number of subjects with disease  $D$ , 40, over the total number of subjects in population  $A$ , 100. Similarly, for population  $B$  the incidence is 20 over 100, or .20. Therefore, the true relative risk of disease in the two populations is .40/.20, or 2.0. However, looking at the columns labeled "Total", one sees that the diagnostic criteria used have yielded apparent incidence rates of 38/100 in population  $A$  and

TABLE 3

*Bias due to misclassification in a cohort study with sensitivity = .8 and specificity = .9 for both populations*

Classified status†	Actual status*					
	Population A			Population B		
	$D$	$\bar{D}$	Total	$D$	$\bar{D}$	Total
$D$	32	6	38	16	8	24
$\bar{D}$	8	54	62	4	72	76
Total	40	60	100	20	80	100

\* The true relative risk of  $A$  to  $B$  is  $(40/100)/(20/100) = 2.0$ .

† The apparent relative risk is  $(38/100)/(24/100) = 1.6$ .

24/100 in population  $B$ . The ratio of these detected incidence rates gives an apparent relative risk of 1.6. Notice that the biased estimate is less than the true estimate. Some statisticians have concluded that misclassification produces a bias in the effect toward the null value (7,10-13), but one should be aware that this is strictly true only in the case of nondifferential misclassification.

Figure 1 gives a graphic representation of how the apparent relative risk varies as a function of sensitivity and specificity in a cohort study. Here, the populations  $A$  and  $B$  have a true relative risk of 2.0, and cumulative disease incidences of .1 in  $A$  and .05 in  $B$ . Specificity is plotted along the  $x$ -axis and the apparent relative risk is

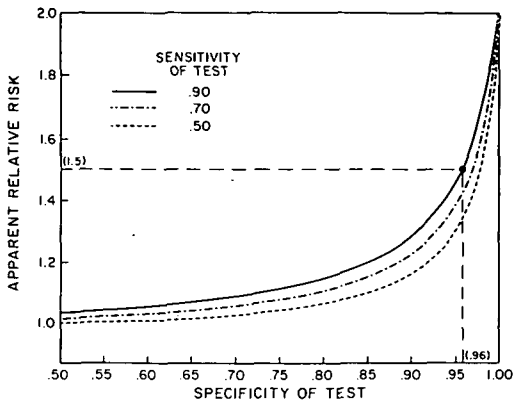


FIGURE 1. Cohort study: Bias as a function of sensitivity and specificity. Disease incidence (cumulative) in populations A and B, .10 and .05, respectively. True relative risk (of A to B) equals 2.0.

given on the y-axis. The three curves represent three levels of sensitivity, the solid line being .90, the dash-dotted line being .70, and the dashed line, .50. As an example, let us pick a specificity of .96 and a sensitivity of .90. Even with these seemingly reassuring levels of sensitivity and specificity it can be seen that the bias is marked; the apparent relative risk observed is approximately 1.5.

More generally, it can be seen that the specificity is more important than the sensitivity in determining the bias in the estimate, and most of the bias occurs even before the specificity drops below 85 per cent. As the specificity drops below about 80 per cent the curves level off uninterruptedly. It is also of interest to note that the apparent relative risk is exactly unity when both the sensitivity and the specificity equal .50. This is an example of the more general property that, if the sensitivity and specificity add to 1.0, the estimate of effect will be unity for both cohort and case-control studies. Notice that the two populations, A and B, are of equal size in this example. Given that we are here discussing bias as it affects the point estimate of relative risk, and are not considering the variance of this estimate, population size is irrelevant.

The solid line in figure 1, where sensi-

tivity equals .90, is duplicated as the solid line in figure 2, which shows the bias as a function of the specificity and the disease incidence while the sensitivity is held constant. Now, the upper dashed line represents cumulative incidences of .2 in A and .1 in B, and the lower dotted line shows incidences of .05 and .025 in A and B, respectively. Thus, all three situations yield a true relative risk of 2.0, the value along the top of the graph. Figure 2 clearly shows that the rarer the disease (the bottom curve), the greater the bias. With a rare disease, the true positives become rapidly swamped with the false positives, producing a dilution of the effect measure.

#### Case-control studies

The next two figures show, in analogous fashion, the bias in the odds ratio in a case-control study, due to misclassification of the exposure variable. These calculations employ the cross-product odds ratio for unmatched, unstratified data. In figure 3, the true exposure rates are .4 in the cases and .2 in the controls, yielding a true odds ratio of 2.67, which is marked with an "X" in the upper-right corner of the graph. As in the cohort example, the three lines represent three different levels of sensitivity, and specificity is plotted along the x-axis. Again, all the estimates are biased below the true value. The curves are not as steep

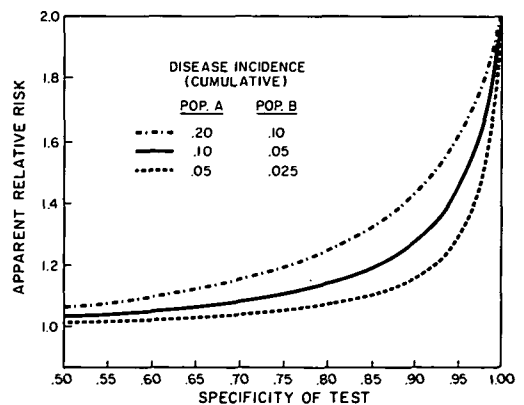


FIGURE 2. Cohort study: Bias as a function of specificity and disease incidence. Sensitivity equals .90 and true relative risk, 2.0.

in the upper range of specificity as in the cohort example, and there is greater separation between the sensitivity curves, implying that sensitivity plays a larger role in the bias of the estimate in a case-control study.

Since the sensitivity of the exposure classification in a case-control study is likely to be below 90 per cent, the middle curve from figure 3 is duplicated as the solid curve in figure 4, which holds the sensitivity constant at 70 per cent. Figure 4 thus shows the apparent odds ratio in a case-control study as a function of the specificity and the exposure rate. The solid line

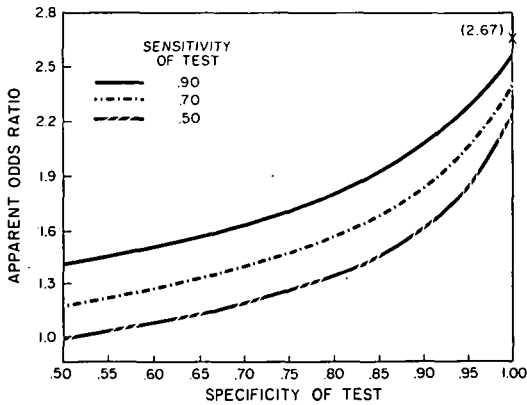


FIGURE 3. Case-control study: Bias as a function of sensitivity and specificity. Exposure rate in cases and controls, .4 and .2, respectively. True odds ratio equals 2.67.

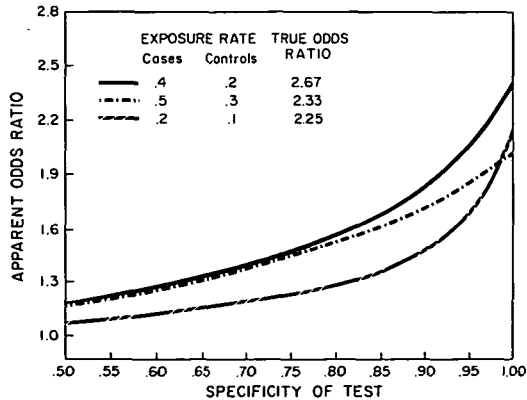


FIGURE 4. Case-control study: Bias as a function of specificity and exposure rate. Sensitivity equals .70.

represents exposure rates of .4 and .2 for cases and controls, respectively, and the other two are, respectively, .5 and .3, and .2 and .1, as indicated. These curves are less easy to compare because each pair of exposure rates yields a slightly different true odds ratio. However, the curves indicate that the less prevalent the exposure in the cases and controls the greater is the bias.

DIFFERENTIAL MISCLASSIFICATION

Tables 4 and 5 show that differential misclassification can produce an estimate that is biased away from the null value, in contrast to the biases shown in all previous figures. In a case-control study, selective recall among cases and controls is likely to produce differential misclassification of the exposure variable.

Table 4 shows the true status: 60 per cent of the cases were exposed to the agent under investigation, and 30 per cent of the controls were exposed. This yields a true

TABLE 4  
Bias due to differential misclassification in a case-control study: True exposure rates\*

Exposure status	Disease status		
	Cases	Controls	Total
Exposed	60	30	90
Unexposed	40	70	110
Total	100	100	200

\* Exposure rates: cases = .60, controls = .30. True odds ratio =  $(60)(70)/(30)(40) = 3.5$ .

TABLE 5  
Bias due to differential misclassification in a case-control study: Observed exposure rates

Classified status	Actual status					
	Cases*			Controls†		
	E	$\bar{E}$	Total‡	E	$\bar{E}$	Total‡
E	54	12	66	18	7	25
$\bar{E}$	6	28	34	12	63	75
Total	60	40	100	30	70	100

\* Sensitivity = .9, specificity = .7.

† Sensitivity = .7, specificity = .9.

‡ Apparent odds ratio =  $(66)(75)/(25)(34) = 5.8$ .

odds ratio of 3.5. Table 5 shows the reported exposure rates. The values for sensitivity and specificity are different for the cases and controls, but none is unrealistically low. The "Total" columns of the tables give the reported exposed and unexposed rates: 66 per cent exposed in the cases and 25 per cent exposed in the controls, producing an apparent odds ratio of 5.8, which is considerably higher than the true underlying value of 3.5.

#### RECALCULATION OF RELATIVE RISK

If the investigator has some idea of the sensitivity and specificity of his classification procedure, then it is possible to use the observed data to estimate the underlying true value of the relative risk. An example is given in table 6.

Suppose one is confirming, in cohort study fashion, the incidence of cervical cancer in 5000 women, classified by some exposure variable, such as marital status, or parity. The diagnostic criterion used is the Pap smear, which is known to be imperfect, but is more practical than a biopsy on such a large sample. Imagine observing the cell frequencies given in table 6, leading to an apparent relative risk of 1.1. Nesbitt et al. (15) have studied the validity of the Pap smear test using biopsy as the validation criterion. One pair of estimates obtained was 88.5 per cent and 91.2 per cent for sensitivity and specificity, respectively.

Now, by applying these levels of sensitivity and specificity to the data in table 6

TABLE 6

*Cohort study\* of incidence of cervical cancer in two exposure categories, using the Pap smear† as the diagnostic criterion*

Observed exposure status	Observed disease status		
	<i>D</i>	$\hat{D}$	Total
<i>E</i>	406	2394	2800
$\hat{E}$	289	1911	2200
Total	695	4305	5000

\* Hypothetical data;  $RR' = (406/2800)/(289/2200) = 1.1$ .

† Sensitivity = 88.5%; specificity = 91.2%.

one can calculate better estimates of the true cell frequencies,  $a$  and  $c$ , where  $a$  is the actual number of diseased subjects in the exposed group and  $c$  is the actual number of diseased subjects in the unexposed group. (Note that the observed values,  $a'$  and  $c'$ , from table 6, are 406 and 289, respectively.) Using the formulas presented in the appendix, one can calculate the frequencies as follows:

$$a = \frac{406 - 2800(1 - .912)}{.885 + .912 - 1} = \frac{159.6}{.797} \approx 200$$

$$c = \frac{289 - 2200(1 - .912)}{.885 + .912 - 1} = \frac{95.4}{.797} \approx 120$$

The ratio of the derived incidence rates,  $(200/2800)/(120/2200)$ , yields an estimate of relative risk of 1.3. Although the new ratio of 1.3 is not very different from the apparent relative risk ( $RR'$ ) of 1.1, it should be remembered that this example involves relatively high levels of sensitivity and specificity.

#### SUMMARY

These hypothetical data show that bias due to misclassification is a function of the sensitivity and specificity of the classification procedure, the exposure frequency, and the disease frequency. In general, nondifferential misclassification produces an underestimate of the effect measure. In cohort studies, the bias is primarily dependent on the specificity, and increases with disease rarity. In case-control studies, the sensitivity of the exposure classification plays a significant role in the bias of the estimate, and the less prevalent the exposure in the cases and controls, the greater is the bias. Differential misclassification, which is likely to arise from selective recall in case-control studies, can bias the estimate greatly, either toward or away from the null value.

Despite the empirical nature of this paper, the findings related to nondifferential misclassification do agree with those of most previous statistical papers. It would be of value to go beyond the simplifying

assumptions of the models in this paper and explore the nature of bias due to misclassification under other circumstances, such as in matched data sets, and in instances in which the outcome variable is classified into more than two categories.

Classification errors cannot be ignored, and the investigator should have some idea of their magnitude in order to appreciate—and perhaps even make adjustments for—the bias that the errors induce in the estimate of effect.

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#### APPENDIX

##### *Calculation of better estimate of relative risk, making adjustments for bias due to misclassification*

Consider the symbolic data layout shown in Appendix table A1, which represents the observed findings from a cohort study. From the observed cell frequencies in this table the apparent relative risk ( $RR'$ ) can be calculated as follows:  $RR' = (a'/N_1)/(c'/N_0)$ .

Given some knowledge of the sensitivity and specificity of the disease status classification, one can generate a fourfold table in which better estimates of the true cell frequencies are made. Such a data layout

is depicted in table A2, with  $N_1$  and  $N_0$  equal to  $N_1$  and  $N_0$ , respectively, from table A1.

From table A2, the better estimate of relative risk ( $RR$ ) is calculated as:  $RR = (a/N_1)/(c/N_0)$ .

The problem, then, is to derive the cell frequencies in table A2, given the observed findings of table A1. This can be done by expressing the cell frequencies in table A1 in terms of the presumed true cell frequencies ( $a, b, c, d$ ) and the sensitivity and

TABLE A1  
Observed cell frequencies in a cohort study

Exposure status	Disease status		
	<i>D</i>	$\bar{D}$	Total
<i>E</i>	<i>a'</i>	<i>b'</i>	<i>N</i> <sub>1</sub>
$\bar{E}$	<i>c'</i>	<i>d'</i>	<i>N</i> <sub>0</sub>
Total	<i>a' + c'</i>	<i>b' + d'</i>	<i>N</i> <sub>1</sub> + <i>N</i> <sub>0</sub>

TABLE A2  
Estimated cell frequencies in a cohort study

Exposure status	Disease status		
	<i>D</i>	$\bar{D}$	Total
<i>E</i>	<i>a</i>	<i>b</i>	<i>N</i> <sub>1</sub>
$\bar{E}$	<i>c</i>	<i>d</i>	<i>N</i> <sub>0</sub>
Total	<i>a + c</i>	<i>b + d</i>	<i>N</i> <sub>1</sub> + <i>N</i> <sub>0</sub>

specificity (estimated from previous research) of the classification procedure used.

The exposed (*E*) and unexposed ( $\bar{E}$ ) subjects from table A1 can be theoretically classified into diseased (*D*) and disease-free ( $\bar{D}$ ) subjects as shown in table A3. In this table, *e*<sub>1</sub> = number of exposed subjects correctly classified as *D*; *f*<sub>1</sub> = number of exposed subjects incorrectly classified as *D*; *g*<sub>1</sub> = number of exposed subjects incorrectly classified as  $\bar{D}$ ; *h*<sub>1</sub> = number of exposed subjects correctly classified as  $\bar{D}$ ; *e*<sub>0</sub> = number of unexposed subjects correctly classified as *D*; *f*<sub>0</sub> = number of unexposed subjects incorrectly classified as *D*; *g*<sub>0</sub> = number of unexposed subjects incorrectly classified as  $\bar{D}$ ; and *h*<sub>0</sub> = number of unexposed subjects correctly classified as  $\bar{D}$ .

If we now let *S* = sensitivity and *Sp* = specificity, and assume that neither the sensitivity nor the specificity differs between the two exposure groups, *E* and  $\bar{E}$ , it is easily shown that:

$$S = e_1/a = e_0/c, \text{ and} \tag{1}$$

$$Sp = h_1/b = h_0/d. \tag{2}$$

It then follows that

$$a' = e_1 + f_1 = (S)(a) + (1 - Sp)(b), \tag{3}$$

$$b' = g_1 + h_1 = (1 - S)(a) + (Sp)(b), \tag{4}$$

$$c' = e_0 + f_0 = (S)(c) + (1 - Sp)(d), \tag{5}$$

$$d' = g_0 + h_0 = (1 - S)(c) + (Sp)(d). \tag{6}$$

TABLE A3  
Results of misclassification: Interrelation between observed and true cell frequencies

Classified disease status	Actual disease status					
	Exposed ( <i>E</i> )			Unexposed ( $\bar{E}$ )		
	<i>D</i>	$\bar{D}$	Total	<i>D</i>	$\bar{D}$	Total
<i>D</i>	<i>e</i> <sub>1</sub>	<i>f</i> <sub>1</sub>	<i>a'</i>	<i>e</i> <sub>0</sub>	<i>f</i> <sub>0</sub>	<i>c'</i>
$\bar{D}$	<i>g</i> <sub>1</sub>	<i>h</i> <sub>1</sub>	<i>b'</i>	<i>g</i> <sub>0</sub>	<i>h</i> <sub>0</sub>	<i>d'</i>
Total	<i>a</i>	<i>b</i>	<i>N</i> <sub>1</sub>	<i>c</i>	<i>d</i>	<i>N</i> <sub>0</sub>

To find the true relative risk, we need only solve for *a* and *c*. (For calculation of the true odds ratio in a case-control study, all four parameters—*a*, *b*, *c*, *d*—must be found.)

It is simple to solve for *a* from equation 3:

$$a' = (S)(a) + (1 - Sp)(b). \tag{3}$$

First we can substitute (*N*<sub>1</sub> - *a*) for *b*:

$$(S)(a) = a' - [(1 - Sp)(N_1 - a)]$$

$$(S)(a) = a' - N_1 + (Sp)(N_1) + a - (Sp)(a)$$

$$(S)(a) + (Sp)(a) - a = a' - N_1 + (Sp)(N_1)$$

$$a(S + Sp - 1) = a' - N_1 + (Sp)(N_1)$$

$$a = \frac{a' - N_1 + (Sp)(N_1)}{S + Sp - 1}$$

$$a = \frac{a' - N_1(1 - Sp)}{S + Sp - 1} \tag{7}$$

One can solve for *c* in a similar fashion from equation 5, yielding

$$c = \frac{c' - N_0(1 - Sp)}{S + Sp - 1}. \tag{8}$$

Now the true relative risk can be found by substituting the values of *a* and *c* in the formula

$$RR = \frac{a/N_1}{c/N_0}.$$

Notice that the denominators of *a* and *c* are identical so that the formula for *RR* reduces to:

$$RR = \frac{[a' - N_1(1 - Sp)]/N_1}{[c' - N_0(1 - Sp)]/N_0},$$

such that the sensitivity, *S*, is not needed to compute the estimated true relative risk.