

Risk Ratio Estimation in Case-Cohort Studies

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In traditional (cumulative-incidence) case-control studies, the exposure odds ratio can be used as an estimator of the risk ratio only when the disease under study is rare. The case-cohort study is a recently developed useful modification of the case-control study. This design allows direct estimation of the risk ratio from a fixed cohort, but does not require any rare-disease assumption. This article reviews recent developments in risk ratio estimation procedures for the analysis of case-cohort data. In the crude analysis, it is shown that the empirical risk ratio estimator is not fully efficient, and the maximum likelihood estimation of the crude risk ratio is discussed. In the stratified analysis, several common risk ratio estimation procedures and standardization methods have been proposed for large strata. However, the Mantel-Haenszel risk ratio and its variance estimator are the only available methods for sparse data. — *Environ Health Perspect* 102(Suppl 8):53–56 (1994)

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Introduction

Cohort and case-control studies are well established epidemiologic designs for studying individual level exposure-disease relationship. Suppose we are interested in estimating a risk ratio that is a ratio of incidence proportions between the exposed and unexposed populations. In fixed cohort studies, the exposed and unexposed subjects, initially disease-free, are followed over a given risk period. We then ascertain disease-specific incidence proportions between these two groups and have an estimate of the risk ratio. In traditional case-control studies, cases of a study disease are sampled from all incident cases in a fixed cohort and controls are sampled from noncases, the population at risk at the end of the risk period. Exposure histories among cases and controls are identified retrospectively and compared. In such a cumulative-incidence sampling of controls (1), we cannot estimate incidence proportions without external information. However, we may use the exposure odds ratio as a good approximation of the risk ratio when the disease under study is "rare" (2).

In 1975, Kupper et al. (3) proposed a useful modification of traditional case-control studies. In their design, cases are sampled from all incidence cases, which is the same as traditional case-control studies; but controls are sampled from the initial cohort

members (the population at risk at the start of the risk period) regardless of their future disease status. This design allows estimation of the risk ratio without the need for the rare-disease assumption. Since it is a compromise between fixed cohort and case-control studies, Kupper et al. called it the hybrid epidemiologic design. It is also called the case-base (4) or case-cohort (5) study, because the control group is a sample from the study "base" or the full cohort. (Some use the term case-base for risk ratio estimation and case-cohort for incidence rate ratio estimation (6), but I use the term case-cohort throughout the article.)

In this article, I will review recent developments in risk ratio estimation procedures in case-cohort studies, and discuss the maximum likelihood method and sparse risk ratio estimation.

Crude Analysis

Suppose that a fixed cohort of N initially disease-free subjects are followed for a given risk period and that M out of N subjects develop a disease under study by the end of the risk period. In case-cohort studies, m cases are randomly selected from the total of M incident cases with a sampling proportion r_1 ; and n controls (subcohort) are randomly selected from the N initial cohort members with a sampling proportion r_0 (3,4). We assume that (N, M) and (r_1, r_0) are unobservable.

The subcohort may contain cases (7); some are included in the case sample and some are not. The observed and expected counts in the case-cohort sample are shown in Table 1. Here p_1 and p_0 are incidence proportions in the exposed and the unexposed, and p_e is the exposure prevalence in the initial cohort. Let $a_+ = a_0 + a_1 + a_2$ and $b_+ = b_0 + b_1 + b_2$, which are all the exposed and the unexposed cases, $e = a_1 + a_2$ and $f = b_1 + b_2$,

the exposed and the unexposed cases in the subcohort, and $n_1 = a_1 + a_2 + c$ and $n_0 = b_1 + b_2 + d$, the exposed and the unexposed in the subcohort.

We assume that the appropriate effect measure is the risk ratio which is defined by

$$\phi = \frac{p_1}{p_0} = \frac{P(E|D)/[1-P(E|D)]}{p_e/(1-p_e)},$$

where $P(E|D)$ is the exposure prevalence in diseased cases. Since a_+/b_+ and n_1/n_0 consistently estimate $P(E|D)/[1-P(E|D)]$ and $p_e/(1-p_e)$, respectively, the empirical estimator of the crude risk ratio (3,4) is given by

$$\hat{\phi}_E = \frac{n_0 a_+}{n_1 b_+} \quad [1]$$

Kupper et al. (3) considered the situation that the sampled cohort was the target population. As criticized by Mantel (8), they failed to take account of random incidence variation, and hence their confidence interval method is not valid for inference beyond that cohort. The correct variance estimate of $\log \hat{\phi}_E$ is given by

$$V_E = \frac{1}{a_+} + \frac{1}{b_+} + \left(1 - 2 \frac{e+f}{a_+ + b_+}\right) \left(\frac{1}{n_1} + \frac{1}{n_0}\right),$$

which is independently derived by Greenland and Nurminen (S. Greenland, personal communication, 1992), reported in Miettinen (4). When the full cohort is observed ($r_1 = r_0 = 1$), $\hat{\phi}_E$ turns to the full cohort risk ratio, and V_E becomes identical to the variance estimator of its logarithm. When the subcohort has no cases, $\hat{\phi}_E$ turns to the odds ratio and V_E becomes identical to the variance estimator of log odds ratio (9).

For risk ratio estimation in Equation 1, we do not exclude the cases from the sub-

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cohort. Miettinen (4), however, noted that we should make a usual case and noncase comparison, as in traditional case-control studies, when testing zero exposure effect. He gave the simple Pearson chi-square statistic given by

$$X_0^2 = \frac{t(a_+d - b_+c)}{(a_+ + b_+)(a_+ + c)(b_+ + d)(c + d)}, [2]$$

where $t = a_+ + b_+ + c + d$, the total number of distinct subjects in the case-cohort sample. Given that the exposure has no effect, X_0^2 has an approximately chi-square distribution with one degree of freedom (d.f.).

Example 1. Miettinen (4) considered a case-cohort data which are $a_0 = 5$, $e = 5$, $c = 5$, $b_0 = 35$, $f = 15$, and $d = 75$. The test of zero exposure effect gives $X_0^2 = 3.89$ with P value = 0.049. The empirical risk ratio estimate and the variance estimate of its logarithm are $\hat{\phi}_E = 1.80$ and $V_E = 0.157$, yielding the logarithm based 95% limits for the crude risk ratio of $1.80 \exp(\pm 1.96 \sqrt{0.157}) = (0.83, 3.91)$.

Since the test and the confidence interval method in the above example are inconsistent, Nurminen (9) proposed the alternative test for zero exposure effect. Noting that $\hat{\phi}_E$ is the solution to the following estimating equation

$$n_0 a_+ - \phi n_1 b_+ = 0,$$

he used the null asymptotic distribution of the contrast $n_0 a_+ - n_1 b_+$ for testing $\phi = 1$. The test statistic is given by

$$X_1^2 = \frac{(n_0 a_+ - n_1 b_+)^2}{n_1 n_0 (a_+ + b_+)}, [3]$$

which has an approximately chi-square distribution with one d.f.

Nurminen's test gives that $X_1^2 = 2.96$ and P value = 0.085. The result is consistent with the previous 95% limits of 0.83 and 3.91.

The empirical contrast used in the test statistic (Equation 3) is decomposed by

$$n_0 a_+ - n_1 b_+ = (a_+ d - b_+ c) + (a_0 f - b_0 e),$$

where the first term in the right hand side is the case and noncase contrast used in Equation 2. From the expected counts given in Table 1, it is clear that $E(a_0 f) = E(b_0 e)$. This means the expectation of the second term is zero regardless of the value of ϕ . Consequently, Nurminen's test is conservative because it takes random varia-

Table 1. Observed and expected counts in the case-cohort sample.

	Exposed		Unexposed	
Cases				
Case sample only	a_0	$Nr_1(1-r_0)p_1 p_e$	b_0	$Nr_1(1-r_0)p_0(1-p_e)$
Case and subcohort	a_1	$Nr_1 r_0 p_1 p_e$	b_1	$Nr_1 r_0 p_0(1-p_e)$
Subcohort only	a_2	$M(1-r_1)r_0 p_1 p_e$	b_2	$M(1-r_1)r_0 p_0(1-p_e)$
Noncases	c	$Nr_0(1-p_1)p_e$	d	$Nr_0(1-p_0)(1-p_e)$

tion of $a_0 f - b_0 e$. Since the empirical risk ratio estimator $\hat{\phi}_E$ has the same problem, we may have a more efficient estimator when we substitute a common estimate between $E(a_0 f)$ and $E(b_0 e)$ into $\hat{\phi}_E$. The simplest choice is $(a_0 f + b_0 e)/2$ as an estimate of $E(a_0 f) = E(b_0 e)$. The resulting risk ratio estimator is given by

$$\hat{\phi}'_E = \frac{a_+ d + [a_+ f + b_+ e]/2}{b_+ c + [a_+ f + b_+ e]/2},$$

and the large-sample variance of its logarithm is

$$\text{Var}^A(\log \hat{\phi}'_E) = \text{var}^A(\log \hat{\phi}_E) +$$

$$\frac{r_1(1-r_0)(p_1 + p_0)}{4r_0 R} \left[\frac{p_0 - 3p_1}{p_1 p_e} + \frac{p_1 - 3p_0}{p_0(1-p_e)} \right],$$

where var^A is the asymptotic variance and $R = r_1 - r_1 r_0 + r_0$. When $1/3 \leq \phi \leq 3$, it holds that $\text{var}^A(\log \hat{\phi}'_E) \leq \text{var}^A(\log \hat{\phi}_E)$; however the large-sample variance of $\log \hat{\phi}'_E$ is not always smaller than that of $\log \hat{\phi}_E$.

What does $E(a_0 f) = E(b_0 e)$ mean? Consider a 2x2 table of all cases in the case-cohort data in which entries are the exposed and the unexposed cases only in the case sample (a_0, b_0) and in the subcohort (e, f). The equation $E(a_0 f) = E(b_0 e)$ means this 2x2 table of all cases is structurally independent. Then the null expectations for the cases in the subcohort become

$$\bar{e} = a_+ \frac{e+f}{a_+ + b_+} \text{ and } \bar{f} = b_+ \frac{e+f}{a_+ + b_+}.$$

Using these expectations we have a new risk ratio estimator

$$\hat{\phi}_{ML} = \frac{\bar{n}_0 a_+}{\bar{n}_1 b_+} [4]$$

where $\bar{n}_1 = \bar{e} + c$ and $\bar{n}_0 = \bar{f} + d$. Under the multinomial model with the expectations given in Table 1, this estimator is the maximum likelihood estimator (10). The large-sample variance estimator of $\log \hat{\phi}_{ML}$ is given by

$$V_{ML} = \frac{1}{a_+} + \frac{1}{b_+} + \left(1 - 2 \frac{e+f}{a_+ + b_+} \right) \left(\frac{1}{\bar{n}_1} + \frac{1}{\bar{n}_0} \right) - \frac{n^2 a_+ b_+ (a_0 + b_0)(e+f)}{(a_+ + b_+)^3 \bar{n}_1^2 \bar{n}_0^2}$$

Since the last term in the right hand side is negative, V_{ML} is always smaller than V_E . Surprisingly, the efficient score test for $\phi = 1$ is identical to the chi-square test, Equation 2, proposed by Miettinen (4).

The maximum likelihood approach gives that $\hat{\phi}_{ML} = 2.20$ and $V_{ML} = 0.132$, yielding the 95% limits of $2.20 \exp(\pm 1.96 \sqrt{0.132}) = (1.08, 4.48)$. This confidence interval is consistent with P value = 0.049 from Equation 2.

Stratified Analysis

Since any real study will require adjustment for confounding factors, we next consider the stratified analysis. Suppose the subjects are stratified into K strata by several confounders. With obvious notation, Kupper et al. (3) proposed the summary risk ratio which was given by

$$\hat{\phi}_K = \frac{n_0 \sum_k n_k a_{+k} / (a_{+k} + b_{+k})}{n_1 \sum_k n_k b_{+k} / (a_{+k} + b_{+k})},$$

where summations are over all strata. Greenland (11) showed that this summary risk ratio is asymptotically biased. The large-strata expectation becomes

$$E^A(\hat{\phi}_K) = \frac{1-p_e}{p_e} \frac{\sum_k \frac{N_k p_{ek} p_{1k}}{p_{ek} p_{1k} + (1-p_{ek}) p_{0k}}}{\sum_k \frac{N_k (1-p_{ek}) p_{0k}}{p_{ek} p_{1k} + (1-p_{ek}) p_{0k}}}$$

with simple random sampling of the cases and the subcohort. Kupper et al.'s sum-

mary risk ratio is neither consistent for the standardized morbidity ratio (SMR)

$$\phi_{SMR} = \frac{\sum_k N_k p_{ek} p_{1k}}{\sum_k N_k p_{ek} p_{0k}}$$

nor any other epidemiologically meaningful standardized risk ratio. Even when the risk ratios are constant across strata that $\phi_k = \phi$, the large-strata expectation of $\hat{\phi}_K$ becomes

$$E^A(\hat{\phi}_K) \equiv \frac{1-p_c}{p_c} \frac{\sum_k \frac{N_k p_{ek}}{\phi p_{ek} + (1-p_{ek})}}{\sum_k \frac{N_k (1-p_{ek})}{\phi p_{ek} + (1-p_{ek})}}$$

It does not reduce to the common value ϕ except when $\phi=1$.

The unbiased adjustment methods have been given by Greenland (11). Applying Miettinen's arguments (12), he derived the SMR estimator by

$$\hat{\phi}_{SMR} = \frac{a_+}{\sum_k n_{1k} b_{+k} / n_{0k}}$$

and the large-strata variance estimator of its logarithm

$$V_{SMR} = \sum_k a_{+k}^2 V_{Ek} / a_+^2$$

We may use the stratum-specific maximum likelihood estimators in the SMR estimator (10).

Modifications are quite simple: change the number of the exposed and the unexposed in the subcohort (n_{1k}, n_{0k}) to their maximum likelihood estimators ($\tilde{n}_{1k}, \tilde{n}_{0k}$). We then have the efficient SMR estimator and the variance of its logarithm

$$\hat{\phi}_{SMR}^* = \frac{a_+}{\sum_k \tilde{n}_{1k} b_{+k} / \tilde{n}_{0k}} \text{ and } V_{SMR}^* = \sum_k a_{+k}^2 V_{MLk} / a_{+k}^2$$

Other standardization methods (13) that have reasonable interpretation are available (10).

Although the SMR does not require risk ratio homogeneity, we will have a more efficient estimator for the common risk ratio when the stratum-specific risk ratios are common across strata. By analogy with the Mantel-Haenszel odds ratio (14), Miettinen (15) gave a Mantel-Haenszel like risk ratio, which is expressed by

$$\hat{\phi}_M = \frac{\sum_k n_{0k} a_{+k} / (a_{+k} + b_{+k} + n_k)}{\sum_k n_{1k} b_{+k} / (a_{+k} + b_{+k} + n_k)}$$

Since Miettinen failed to account for the overlap between $a_{+k}t + b_{+k}$ and n_k , i.e., $e_k + f_k$, $\hat{\phi}_M$ have to be modified (9). Greenland (11) gave two closed-form Mantel-Haenszel type estimators for the common risk ratio. One is the Tarone estimator:

$$\hat{\phi}_T = \frac{\sum_k n_{0k} a_{+k} / s_k}{\sum_k n_{1k} b_{+k} / s_k}$$

where $s_k = a_{0k} + b_{0k} + c_k + d_k$. It is the inverse null variance weighting of the stratum-specific risk ratios, and asymptotically fully efficient under zero exposure effect. When we study the full cohort, $\hat{\phi}_T$ becomes identical to the Tarone estimator for the common risk ratio (16). The other is the Mantel-Haenszel estimator:

$$\hat{\phi}_{MH} = \frac{\sum_k n_{0k} a_{+k} / t_k}{\sum_k n_{1k} b_{+k} / t_k}$$

where $t_k = a_{+k} + b_{+k} + c_k + d_k$, the total number of distinct subjects in the k th stratum. The Mantel-Haenszel estimator is dually consistent for ϕ , that is, consistent in both the large-strata and the sparse-data (the number of strata K becomes large, as in the matched sample), while the Tarone estimator is consistent only in the large-strata.

Greenland (11) gave the large-strata variance estimator of $\log \hat{\phi}_T$ (and implicitly of $\log \hat{\phi}_{MH}$). The dually consistent variance estimator of $\log \hat{\phi}_{MH}$ is given by

$$V_{MH} = \frac{\sum_k W_k / t_k^2}{(\sum_k n_{0k} a_{+k} / t_k)(\sum_k n_{1k} b_{+k} / t_k)}$$

where $W_k = (b_{0k} + d_k) n_{1k} a_{+k} + (a_{0k} + c_k) n_{1k} b_{+k} + a_{0k} d_k + b_{0k} c_k$ (17). With the full cohort observed, V_{MH} becomes identical to the Mantel-Haenszel variance derived by Greenland and Robins (18). By changing t_k 's in V_{MH} to s_k , we have the variance estimator of $\log \hat{\phi}_T$, but it is consistent only in the large strata. The confidence interval method based on the estimating function is also proposed (17).

Three other large-strata common risk ratio estimators, more efficient than the Tarone or the Mantel-Haenszel estimator, are available. Greenland (11) gave the Woolf (the weighted least squares) estima-

tor based on the stratum-specific empirical risk ratios. Using the corresponding maximum likelihood estimators, we have the modified Woolf estimator

$$\log \hat{\phi}_W^* = \frac{\sum_k \log \hat{\phi}_{MLk} / V_{MLk}}{\sum_k 1 / V_{MLk}}$$

and the large-strata variance estimator of $\log \hat{\phi}_W^*$

$$V_W^* = (\sum_k 1 / V_{MLk})^{-1}$$

The following two estimators do not have a closed form. Nurminen (9) proposed an estimator as an extension of the cohort chi-square function approach (19). Nurminen's estimator is the solution to the estimating equation

$$\sum_k \frac{n_{0k} a_{+k} / n_{1k} b_{+k}}{\phi n_{1k} + n_{0k}} = 0$$

He gave a score-like interval for ϕ based on the asymptotic distribution of the above estimating function. Sato (10) proposed the maximum likelihood estimator for the common risk ratio. It requires the iterative solution of a set of $3K+1$ score equation for $(\phi, \{r_{1k}, r_{0k}, p_{ek}\})$, or $K+3$ for $(\phi, r_1, r_0, \{p_{ek}\})$ under a certain design situation, for example, simple random sampling of the cases and the subcohort.

For the test of zero exposure effect, extending the case and noncase comparison in the crude analysis, the Mantel-Haenszel test statistic is given by

$$X_{MH}^2 = \frac{[a_+ - \sum_k (a_{+k} + c_k)(a_{+k} + b_{+k}) / t_k]^2}{\sum_k \frac{(a_{+k} + b_{+k})(c_k + d_k)(a_{+k} + c_k)(b_{+k} + d_k)}{t_k^2 (t_k - 1)}}$$

which has an asymptotically chi-square distribution with one degree of freedom under zero exposure effect (11,15). This test is applicable to both large-strata and the sparse-data cases.

Example 2. Consider a stratified case-cohort data with $K=2$: $a_{01}=74, a_{11}=4, a_{21}=5, c_1=75, b_{01}=2, b_{11}=0, b_{21}=0$, and $d_{11}=19$ for stratum 1; and $a_{02}=8, a_{12}=0, a_{22}=1, c_2=41, b_{02}=6, b_{12}=1, b_{22}=0$, and $d_{22}=190$ for stratum 2 (10,17). The Mantel-Haenszel test gives $X_{MH}^2=26.7$ with P value=0.0, highly significant. Several summary risk ratios and 95% confidence intervals are shown in Table 2.

Table 2. Summary risk ratios.

	ϕ	95% CI
Common risk ratio		
Tarone	7.45	(3.00, 18.5)
Mantel-Haenszel	7.41	(3.01, 8.13)
Woolf	6.85	(2.95, 15.9)
Nurminen	6.96	(3.23, 14.9)
Maximum likelihood	6.96	(3.08, 15.7)
Indirect standardization		
SMR	8.86	(2.34, 33.5)
Modified SMR	8.96	(2.37, 33.8)

The upper half of Table 2 gives the common risk ratio estimates and the lower half the indirect standardization. The Tarone and the Mantel-Haenszel risk ratios give the virtually the same results. The Woolf, Nurminen, and maximum likelihood also

give close point estimates, but the Nurminen method gives the narrower 95% interval. The two SMR estimates are also close.

Concluding Remarks

In the crude analysis of the case-cohort data, the maximum likelihood estimator for the risk ratio should be used. It is more efficient than the empirical risk ratio estimator and easy to compute. The chi-square test given by Miettinen (4) is still valid, because it is identical to the efficient score test. In the stratified analysis, there are several options for summary risk ratio estimation in large strata. Greenland (11) gives tentative recommendations on choosing between large-strata estimators. When the data are sparse, the Mantel-Haenszel estimator is the only available common risk ratio estimator. We may improve its

efficiency simply using the contrasts $\bar{n}_{0k}a_{+k} - \phi\bar{n}_{1k}b_{+k}$ rather than $n_{0k}a_{+k} - \phi n_{1k}b_{+k}$. The modified Mantel-Haenszel estimator becomes

$$\hat{\phi}_{MH}^* = \frac{\sum_k \bar{n}_{0k} a_{+k} / t_k}{\sum_k \bar{n}_{1k} b_{+k} / t_k},$$

and $\hat{\phi}_{MH}^* = 7.45$ for Example 2. However, it is difficult to derive a variance estimator for it.

This article has reviewed recent developments in risk ratio estimation procedures in case-cohort studies when censoring is unimportant. If censoring is important, the risk ratio estimate not adjusted for it is misleading (20) and the correct risk ratio estimation procedure is proposed by Flanders et al. (21). When time to response is of primary concern, incidence rate ratio (hazard ratio) estimation is available (5).

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