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Confidence Intervals for Effect Parameters Common in Cancer Epidemiology

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This paper reviews approximate confidence intervals for some effect parameters common in cancer epidemiology. These methods have computational feasibility and give nearly nominal coverage rates. In the analysis of crude data, the simplest type of epidemiologic analysis, parameters of interest are the odds ratio in case-control studies and the rate ratio and difference in cohort studies. These parameters can estimate the instantaneous-incidence-rate ratio and difference that are the most meaningful effect measures in cancer epidemiology. Approximate confidence intervals for these parameters including the classical Cornfield's method are mainly based on efficient scores.

When some confounding factors exist, stratified analysis and summary measures for effect parameters are needed. Since the Mantel-Haenszel estimators have been widely used by epidemiologists as summary measures, confidence intervals based on the Mantel-Haenszel estimators are described. The paper also discusses recent developments in these methods.

Introduction

In the study of cancer or other chronic disease epidemiology, the most frequently used measure of disease occurrence is the instantaneous incidence rate, which is the number of new cases per unit of person-time at risk (also called the incidence density or hazard rate). As for measures of exposure-disease association, attention is centered to the rate ratio and difference between the instantaneous-incidence-rates in the exposed and the unexposed groups.

Both of these two parameters of interest are directly estimated in cohort studies, while only the rate ratio can be estimated by the odds ratio in case-control studies. For a long period statisticians considered that the odds ratio could estimate the risk ratio for the ratio of two cumulative incidence rates, given that the disease under study is rare (*1*). However, it is explained that the odds ratio estimates the rate ratio, and the rate ratio can approximate the risk ratio if the disease is rare (*2*).

Many procedures have been proposed for calculating approximate confidence intervals for the parameters of interest in cancer epidemiology. The best-known approximation procedure is Cornfield's (*3*) method for the odds ratio. In the analysis of crude (i.e., unstratified) data, the approximate large-sample confidence intervals, based on unconditional efficient scores including Cornfield's method, may perform well.

Although a crude analysis possesses a cogency, stratified or matched analysis is often needed to remove confounding. The approximate methods based on efficient scores can extend in a straightforward manner to common effect parameters when the number of strata remains fixed but sample sizes become large (large strata). However, the unconditional score methods will fail when fine stratification or matching has been made (sparse data). Since the famous Mantel-Haenszel estimators for the common odds ratio (*4*), and the common rate ratio (*5*) and difference (*6*) are consistent in both large-strata and sparse-data large-sample theories (*7,8*), the approximate confidence intervals based on the Mantel-Haenszel estimators have been developed in the past 10 years. Both of the first-order Taylor series intervals and Fieller-like intervals based on the Mantel-Haenszel approach perform well, and the latter possesses relations to tests of null association.

Approximate Methods for Crude Data

Odds Ratio from Case-Control Studies

Consider a pair of independent binomial observations (X,Y) with denominators (n,m) and success probabilities (p_1, p_0). In case-control studies, X and Y denote the number of exposed persons out of n cancer cases and m controls. We wish to find approximate confidence intervals for the odds ratio $\psi = p_1(1 - p_0)/[p_0(1 - p_1)]$ based on efficient scores.

The unconditional log-likelihood may be the sum of the logarithms of two binomials with parameters (p_1, p_0). When one reparametrizes by letting $p_1 = \psi p_0/(\psi p_0 + 1 - p_0)$, then the score statistics are

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$$S_\psi(\psi,p_0) = \partial L(\psi,p_0)/\partial\psi = (X - np_1)/\psi$$

and

$$S_{p_0}(\psi,p_0) = \partial L(\psi, p_0)/\partial p_0 = [t - (np_1 + mp_0)] / [p_0(1 - p_0)]$$

where $t = X + Y$. The maximum likelihood estimator (MLE) of the nuisance parameter p_0, $\tilde{p}_0$, is the solution to the equation $S_{p_0}(\psi, \tilde{p}_0) = 0$. Using the conventional notation that $E^A = E^A(X;\psi) = n\tilde{p}_1$ and $\tilde{p}_1 = \psi\tilde{p}_0/[\psi\tilde{p}_0 + (1 - \tilde{p}_0)]$, E^A could be determined as the appropriate root of the quadratic equation

$$E^A(m - t + E^A) = \psi(n - E^A)(t - E^A).$$

The score method is based on $S_\psi(\psi\ \tilde{p}_0) = (X - E^A)/\psi$. Its asymptotic variance is estimated by

$$\widehat{\text{var}}^A[S_\psi(\psi, \tilde{p}_0)] = (\psi^2\tilde{v})^{-1}$$

where

$$\tilde{v} = \left[\frac{1}{n\tilde{p}_1(1 - \tilde{p}_1)} + \frac{1}{m\tilde{p}_0(1 - \tilde{p}_0)}\right]^{-1}$$

The approximate $1 - \alpha$ confidence interval (ψ_L, ψ_U) is thus the two solutions to the equation

$$T_c(\psi) = (|X - E^A| - c')^2/\tilde{v} = z^2_{\alpha/2}, \qquad (1)$$

where $z_{\alpha/2}$ is the $100(1 - \alpha/2)$ percentile of the normal distribution and $c' = 1/2$, when a correction for continuity is needed, or $c' = 0$, otherwise. This equation is identical with that proposed by Cornfield (*3*), and some algorithms to solve it iteratively are given by Gart (*9*) and Fleiss (*10*). Gart and Thomas (*11,12*) showed that Cornfield's method with and without the continuity correction perform well in the conditional and unconditional sample spaces, respectively.

As an alternative to Cornfield's method based on unconditional scores, we may use more accurate approximate mean and variance of X conditional on t in Eq. (1). The conditional distribution of the data is the noncentral hypergeometric distribution with noncentral parameter ψ. Harkness (*13*) showed an exact relation between the mean and variance that $E[X(m - t + X)|t] = \psi E[(n - X)(t - X)|t]$, i.e., $E(X|t)[m - t + E(X|t) + \widehat{\text{var}}(X/t) = \psi[\{n - E(X|t)\}\{t - E(X|t)\} + \widehat{\text{var}}(X|t)]$. McCullagh (*14*) proposed approximate mean E^A_M and variance $\tilde{v}'$ determined to satisfy simultaneously the two equations

$$E^A_M(m - t + E^A_M) + \tilde{v}' = \psi[(n - E^A_M)(t - E^A_M) + \tilde{v}'] \qquad (2)$$

and

$$\tilde{v}' = \frac{N}{N - 1}\left[\frac{1}{E^A_M} + \frac{1}{n - E^A_M} + \frac{1}{t - E^A_M} + \frac{1}{m - t + E^A_M}\right]^{-1} \qquad (3)$$

where $N = n + m$ is the total sample size. For $\psi = 1$, the exact mean and variance satisfy Eqs. (2) and (3). Substituting $E^{\hat{A}}_M$ and $\tilde{v}'$ instead of E^A and $\tilde{v}$ in Eq. (1), an alternative approximate confidence interval is obtained as the two solutions to

$$T_M(\psi) = (|X - E^A_M| - c')^2/\tilde{v}' = z^2_{\alpha/2}. \qquad (4)$$

This equation may also be solved iteratively, but it is easily calculated with the same manner to solve Eq. (1).

For a numerical comparison between Cornfield's method [Eq.(1)] and McCullagh's methods [Eq. (4)], we consider a crude case-control data from the Ille-et-Vilaine study of esophageal cancer that have been used by Breslow and Day (*15*). Among 200 male cases diagnosed with esophageal cancer, 96 were exposed to high daily alcohol consumption, while 109 among 775 controls were exposed to high daily alcohol consumption. The (unconditional) maximum likelihood estimate of the odds ratio is $\psi = 5.640$. The approximate 95% confidence intervals (ψ_L, ψ_U) are:

Cornfield's method	(4.033, 7.947)
with the continuity correction	(3.943, 8.071)
McCullagh's method	(3.995, 7.924)
with the continuity correction	(3.935, 8.048)

For these data McCullagh's intervals show close agreement with Cornfield's intervals, both with and without the correction for continuity. Since Breslow and Cologne (*16*) showed that McCullagh's approximation would be accurate whenever ψ is near unity or N is large, calculations of the actual coverage rates of McCullagh's method for large ψ and moderate N will be informative.

Rate Ratio and Difference from Cohort Studies

In follow-up studies of dynamic populations, X and Y denote the number of persons contracting the disease out of n exposed and m unexposed fixed person-time denominators. Thus X and Y are modeled as a pair of independent Poisson observations with means (nr_1, mr_0), where r_1 and r_0 are the instantaneous incidence rates of the exposed and the unexposed. The parameters of interest are the rate ratio $\omega = r_1/r_0$ and the rate difference $\xi = r_1 - r_0$.

First we consider the approximate confidence interval for the rate ratio based on efficient scores. Similar to the odds ratio situation, by letting $r_1 = \omega r_0$, the scores are

$$S_\omega(\omega, r_0) = \partial L(\omega, r_0)/\partial\omega = (X - nr_1)/\omega$$

and

$$S_{r_0}(\omega, r_0) = \partial L(\omega, r_0)/\partial r_0 = [t - (nr_1 + mr_0)] / r_0$$

where $t = X + Y$. The MLE of r_0 is $\tilde{r_0} = t/(n\omega + m)$, which is the solution to the equation $S_{r_0}(\omega, \tilde{r}_0) = 0$. The asymptotic variance of $S\omega(\omega, \tilde{r}_0)$ is estimated by

$$\widehat{\text{var}}^A[S_\omega(\omega, \tilde{r}_0)] = \left[\frac{\omega(n\omega + m)}{nm\tilde{r}_0}\right]^{-1} = \frac{nmt}{\omega(n\omega + m)^2}$$

Hence the approximate $1 - \alpha$ confidence interval (ω_L, ω_U) is the two roots of the quadratic equation

$$T(\omega) = \frac{(mX - n\omega Y)^2}{\omega nmt} = z^2_{\alpha/2} \tag{5}$$

This equation is identical with that derived from the asymptotic normal approximation of $mX - n\omega Y$ or X conditional on t, or the conditional score method (*17*).

For the rate ratio, it is well known that the conditional distribution of X given t is the binomial with success probability $n\omega/(n\omega + m)$ and size t. The exact confidence interval may be obtained using the mathematical link between the binomial and the F distributions (*18*). That is,

$$(\omega_L, \omega_U) = \left(\frac{mX}{n(Y + 1)F_{\alpha/2}(2Y + 2, 2X)}, \frac{m(X + 1)F_{\alpha/2}(2X + 2, 2Y)}{nY}\right) \tag{6}$$

where $F_{\alpha/2}(\upsilon_1, \upsilon_2)$ is the $100(1 - \alpha/2)$ percentile of the F distribution with υ_1 and υ_2 degrees of freedom. Paulson (*19*) proposed an approximation to $F_{\alpha/2}(\upsilon_1, \upsilon_2)$, namely $f(2/(9\upsilon_1), 2/(9\upsilon_2))$, which is

$$f(a, b) = \left[\left((1 - a)(1 - b) + z_{\alpha/2}\sqrt{a(1 - b)^2 + b(1 - a)^2 - abz_{\alpha/2}}\right) \Big/ (1 - b)^2 - bz^2_{\alpha/2}\right]^3 \tag{7}$$

We can thus obtain more accurate approximate interval for ω using Eq. (6) with Paulson's approximation [Eq. (7)].

In making inferences about the rate difference it is necessary to employ the unconditional distribution of (X, Y). By letting $r_1 = r_0 + \xi$ we have

$$S_\xi(\xi, \tilde{r}_0) = (X - n\tilde{r}_1)/\tilde{r}_1$$

where $\tilde{r}_1 = \tilde{r}_0 + \xi$ and

$$\tilde{r}_0 = [t - N\xi + \sqrt{(t - N\xi)^2 + 4NY\xi}] / (2N)$$

where $N = n + m$. From Sato (*17*), we have

$$\widehat{\text{var}}^A[S_\xi(\xi, \tilde{r}_0)] = \left(\frac{\tilde{r}_1}{n} + \frac{\tilde{r}_0}{m}\right)^{-1}$$

The asymmetric confidence interval (ξ_L, ξ_U) is the two solutions to

$$T(\xi) = \left(\frac{X - n\tilde{r}_1}{\tilde{r}_1}\right)^2 \left(\frac{\tilde{r}_1}{n} + \frac{\tilde{r}_0}{m}\right) = z^2_{\alpha/2}\,. \tag{8}$$

Sato (*17*) gave the Newton-Raphson procedure to solve Eq. (8) iteratively. Alternatively, the usual first-order Taylor series interval is given by

$$\left(\frac{X}{n} - \frac{Y}{m}\right) \pm z_{\alpha/2}\sqrt{\frac{X}{n^2} \pm \frac{Y}{m^2}} \tag{9}$$

To illustrate these confidence interval methods for the rate ratio and difference, we use follow-up data on the breast cancer for women with tuberculosis repeatedly exposed to multiple X-ray fluoroscopies and women with tuberculosis not so exposed (*20*). Among the exposed group, 41 women suffered from breast cancer out of 28,010 person-years, while 15 women suffered from breast cancer out of 19,017 person-years among the unexposed group. The estimated rate ratio is $\hat{\omega} = 1.856$. The approximate 95% confidence interval based on the score method [Eq. (5)] is (1.036, 3.325), while that obtained by Eq. (6) with Eq. (7) is (1.006, 3.611). The lower limits are very close, but the upper limit by the score method is smaller than that by the approximate conditional method. It is because the normal approximation in the use of the score method will be inadequate unless t is large. When the rate difference is of interest, its estimate is $\xi = 67.50$ per 100,000 person-years. The approximate 95% interval based on the score method Eq. (8) is (4.320, 129.0) per 100,000 person-years, while that given by the usual method Eq. (9) is (7.493, 127.5) per 100,000 person-years. Sato (*17*) showed that the score method δ gave nominal coverage rates under several values for the parameters ξ, r_0, n, and m except for $\xi = 0$, $r_0 = 0.2$ per 1000 person-years and $n = m = 5000$ person-years.

Stratified Analysis Based on the Mantel-Haenszel Estimator

Stratified and Matched Case-Control Analysis

Consider a series of K strata formed by pairs of independent binomial observations (X_k, Y_k) with denominators (n_k, m_k), success probabilities (p_{1k}, p_{0k}) for $k = 1, \ldots, K$, and common odds ratio ψ. Let $\hat{p}_{1k} = X_k/n_k$, $\hat{p}_{0k} = Y_k/m_k$, and $N_k = n_k + m_k$. Noting that $E[\hat{p}_{1k}(1 - \hat{p}_{0k}) - \psi\hat{p}_{0k}(1 - \hat{p}_{1k})] = 0$ either conditional on $t_k = X_k + Y_k$ or not, an unbiased estimating function for ψ is arrived at by assigning weights a_k to $\hat{p}_{1k}(1 - \hat{p}_{0k}) - \psi\hat{p}_{0k}(1 - \hat{p}_{1k})$ such that

$$W(\psi) = \sum_{k=1}^{K} a_k[\hat{p}_{1k}(1 - \hat{p}_{0k}) - \psi\hat{p}_{0k}(1 - \hat{p}_{1k})]. \tag{10}$$

Mantel and Haenszel (*4*) chose standard weights $(1/n_k + 1/m_k)^{-1} = n_k m_k/N_k$ as a_k and proposed an estimator that is the solution of $W(\psi) = 0$. The Mantel-Haenszel odds ratio is explicitly defined by $\psi_{MH} = \sum_{k=1}^{K} R_k / \sum_{K=1}^{K} S_k$, where $R_k = a_k\hat{p}_{1k}(1 - \hat{p}_{0k}) = X_k(m_k - Y_k)/N_k$ and $S_k = a_k\hat{p}_{0k}(1 - \hat{p}_{1k}) = Y_k(n_k - X_k)/N_k$. All the

other Mantel-Haenszel estimators are derived by the estimating function similar to Eq. (10) with the standard weights.

The first formula for an asymptotic variance of $\hat{\psi}_{MH}$ was given by Hauck (*21*) on the basis of large-strata limiting model where the number of strata K remained fixed but each N_k tended to infinity. Breslow (*7*) proposed the conditional variance, based on the noncentral hypergeometric distribution, using a sparse-data limiting model in which K tended to infinity but a finite number of different configurations of (n_k, m_k) occurred. A well-known example of this limiting model is (1, M) matched case-control design. In both limiting models $\hat{\psi}_{MH}$ is consistent for ψ and asymptotically normal. Although $\hat{\psi}_{MH}$ is not asymptotically fully efficient (*22*) unless ψ is unity, it maintains high efficiency relative to the efficient estimators for ψ under both large-strata and sparse-data cases (*23,24*).

Because of the skewness of the distribution of $\hat{\psi}_{MH}$, the natural log transformation is usually used to construct the confidence intervals for ψ (*25*). Robins et al. (*26*) and Phillips and Holland (*27*) showed that the asymptotic variance of $\ln\hat{\psi}_{MH}$ under both limiting models is given by

$$\mathrm{var}^{A}(\ln\hat{\psi}_{MH}) = \frac{\sum_{k=1}^{K} \mathrm{var}(R_k - \psi S_k)}{\left[\sum_{k=1}^{K} \mathrm{E}(R_k)\right]^2}$$

and proposed an easily computed consistent estimator of $\mathrm{var}^{A}(\ln\hat{\psi}_{MH})$ defined by

$$V_{RBG} = \frac{1}{2}\left[\frac{\sum_{k=1}^{K} P_k R_k}{(\sum_{k=1}^{K} R_k)^2} + \frac{\sum_{k=1}^{K} (Q_k R_k + P_k S_k)}{(\sum_{k=1}^{K} R_k)(\sum_{k=1}^{K} S_k)} + \frac{\sum_{k=1}^{K} Q_k S_k}{(\sum_{k=1}^{K} S_k)^2}\right] \quad (11)$$

where $P_k = (X_k + m_k - Y_k)/N_k$ and $Q_k = (Y_k + n_k - X_k)/N_k$, from a first-order Taylor's series expansion. Flanders (*28*) proposed a consistent estimator similar to V_{RBG}. Unfortunately, his estimator is not invariant under interchange of the labels, i.e., the cases and the controls, or the exposed and the unexposed. Under such interchange, only the sign of $\ln\hat{\psi}_{MH}$ changes, and the true variance cannot change. Obviously V_{RBG} has this invariance property. An invariant version of Flanders' variance is given by

$$V_{FS} = V_{RBG} - \left[\frac{\hat{\psi}_{MH} - 1}{2\left(\sum_{k=1}^{K} R_k\right)\left(\sum_{k=1}^{K} S_k\right)} \sum_{k=1}^{K} \frac{1}{N_k} \left(\frac{R_k}{\hat{\psi}_{MH}} - S_k\right)\right]$$

which is the arithmetic average of an original estimator and a recomputed one after interchange. The second term of the right-hand side of the above equation is equal to zero when N_k are constant across strata, and tends to zero when N_k are increased as in large-strata case. As a result, Flanders' estimator may essentially be the same as V_{RBG}. The resulting $1 - \alpha$ Taylor series confidence interval for ψ (ln-method) is obtained by

$$\hat{\psi}_{MH} \exp[\pm z_{\alpha/2}\sqrt{V_{RBG}}] . \quad (12)$$

A Fieller-like interval proposed by Sato (*29*) is based on the statistic $W(\psi) = \sum_{k=1}^{K} (R_k - \psi S_k)$. Using the results given by Robins et al. (*26*), we find $W(\psi)$ will be asymptotically normal with asymptotic mean zero and variance $\sum_{k=1}^{K} \mathrm{var}(R_k - \psi S_k)$ under both sparse data and large strata. An unbiased and invariant estimator of $\mathrm{var}(R_k - \psi S_k)$ is given by

$$\widehat{\mathrm{var}}(R_k - \psi S_k) = \psi\left[(Q_k + \frac{1}{N_k})R_k + (P_k + \frac{1}{N_k})S_k\right] . \quad (13)$$

If ψ is known, $\sum_{k=1}^{K} \widehat{\mathrm{var}}(R_k - \psi S_k)$ will be consistent for $\sum_{k=1}^{K} \mathrm{var}(R_k - \psi S_k)$. Hence the Fieller-like interval (ψ_L, ψ_U) is the two roots to the quadratic equation

$$T(\psi) = \frac{\left[\left|\sum_{k=1}^{K} (R_k - \psi S_k)\right| - c\right]^2}{\psi \sum_{k=1}^{K} \left[\left(Q_k + \frac{1}{N_k}\right)R_k + \left(P_k + \frac{1}{N_k}\right)S_k\right]} = z_{\alpha/2}^2 \quad (14)$$

where $c = (1 + \psi)/4$, when the continuity correction is needed, or $c = 0$, otherwise. The correction value $(1 + \psi)/4$ is chosen in order to hold the invariance under interchange of the labels. In the matched-pairs case, Eq. (14) with the continuity correction reduces to the equation based on the normal approximation to the conditional distribution given by Breslow and Day (*15*).

The Fieller-like interval [Eq. (14)] is closely related to the Cochran-Mantel-Haenszel (*4,30*) test of null association (*29*). Consider the problem of testing that $\psi = 1$. For this null value, the following simplifications

occur:

$$R_k - S_k = X_k - t_k \frac{n_k}{N_k} = X_k - \mathrm{E}(X_k|t_k, \psi = 1),$$

and noting that $\mathrm{E}[\widehat{\mathrm{var}}(R_k - \psi S_k)|t_k] = \mathrm{var}(R_k - \psi S_k|t_k)$ even if t_k is fixed,

$$\mathrm{E}[\widehat{\mathrm{var}}(R_k - \psi S_k)|t_k, \psi = 1] = \mathrm{var}(R_k - \psi S_k|t_k, \psi = 1) = \mathrm{var}(X_k|t_k, \psi = 1)$$

where $\mathrm{E}(X_k|t_k, \psi = 1)$ and $\mathrm{var}(X_k|t_k, \psi = 1)$ are the mean and variance of the (central) hypergeometric distribution. Consequently $T(\psi)$ under $\psi = 1$ is asymptotically equivalent to the Cochran-Mantel-Haenszel test both in sparse-data and large-strata models. In the special case of (1, M)-matching $T(\psi)$ with the continuity correction reduces exactly to the test statistic derived by Miettinen (*31*) and Pike and Morrows (*32*), and so it reduces to McNemar's test in the matched-pairs case.

For a numerical comparison of the ln- and Fieller-like methods, we use two data sets that are examples of sparse-data and large-strata cases. Table 1 gives the (1, 4)-matched case-control data that is the study of the effect of exogeneous estrogens on the risk of endometrial cancer at Los Angeles (*15*). The Mantel-Haenszel odds ratio is $\hat{\psi}_{\mathrm{MH}} = 8.462$. We found the approximate 95% intervals $(\psi_L, \psi_U) = (3.412, 20.99)$, (3.535, 20.25), 3.294, 23.53) for the ln-method [Eq. (12)], the Fieller interval [Eq. (14)] without and with the continuity correction, respectively. These methods give very close intervals. Table 2 gives stratified data of the Ille-et-Vilaine study (*15*) referred to previously. The Mantel-Haenszel odds ratio is $\hat{\psi}_{\mathrm{MH}} = 5.158$. The approximate 95% interval based on the ln-method is (3.562, 7.468), while those obtained by the Fieller-like method without and with the continuity correction are (3.580, 7.431) and (3.498, 7.656). Again these intervals are reasonably close.

Stratified Cohort Analysis

Consider now a series of K pairs of independent Poisson observations (X_k, Y_k) with fixed person-time denominators (n_k, m_k) and means $(n_k r_{1k}, m_k r_{0k})$, where r_{1k} and r_{0k} are the instantaneous incidence rates of the exposed and the unexposed. First suppose that the rate ratio $\omega = r_{1k}/r_{0k}$ remains constant across strata. Let $\hat{r}_{1k} = X_k/n_k$, $\hat{r}_{0k} = Y_k/m_k$, $N_k = n_k + m_k$, and $t_k = X_k + Y_k$. Similar to the odds ratio case, the Mantel-Haenszel estimating function for ω is arrived at

$$W(\omega) = \sum_{k=1}^{K} \frac{n_k m_k}{N_k} [\hat{r}_{1k} - \omega \hat{r}_{0k}]$$

Hence the Mantel-Haenszel rate ratio (*5*) is the solution of $W(\omega) = 0$ that $\hat{\omega}_{\mathrm{MH}} = \sum_{k=1}^{K} R_k / \sum_{k=1}^{K} S_k$, where $R_k = m_k X_k / N_k$ and $S_k = n_k Y_k / N_k$. In both sparse data and large strata $\hat{\omega}_{\mathrm{MH}}$ is also consistent but inefficient; however, it maintains relatively high efficiency (*8,33*). Because of the skewness of the distribution of $\hat{\omega}_{\mathrm{MH}}$, the log scale may be used to set the confidence intervals for ω. The asymptotic variance formula of $\ln\hat{\omega}_{\mathrm{MH}}$ is similar to that of $\ln\hat{\psi}_{\mathrm{MH}}$. Noting that $\widehat{\mathrm{var}}(R_k - \omega S_k) = \omega n_k m_k t_k / N_k^2$, we have

$$\mathrm{var}^{\mathrm{A}}(\ln\hat{\omega}_{\mathrm{MH}}) = \frac{\sum_{k=1}^{K} n_k m_k t_k / N_k^2}{\left[\sum_{k=1}^{K} \mathrm{E}(R_k)\right]\left[\sum_{k=1}^{K} \mathrm{E}(S_k)\right]}$$

Since $\widehat{\mathrm{var}}(R_k - \omega S_k) = \mathrm{var}(R_k - \omega S_k|t_k)$, and $\mathrm{E}(R_k|t_k)$, $\mathrm{E}(S_k|t_k)$ are unbiased for $\mathrm{E}(R_k)$ and $\mathrm{E}(S_k)$, Breslow (*33*) proposed a conditional variance estimator defined by

$$V_{\mathrm{B}} = \frac{\sum_{k=1}^{K} n_k m_k t_k / N_k^2}{\hat{\omega}_{\mathrm{MH}}\left[\sum_{k=1}^{K} \frac{n_k m_k t_k}{N_k(n_k\hat{\omega}_{\mathrm{MH}} + m_k)}\right]^2} \qquad (15)$$

Since R_k and S_k are also unbiased for $\mathrm{E}(R_k)$ and $\mathrm{E}(S_k)$, respectively, Greenland and Robins (*8*) proposed a simple unconditional variance estimator given by

$$V_{\mathrm{GR}} = \frac{\sum_{k=1}^{K} n_k m_k t_k / N_k^2}{\left(\sum_{k=1}^{K} R_k\right)\left(\sum_{k=1}^{K} S_k\right)}. \qquad (16)$$

Eqs. (15) and (16) are invariant under interchange of the exposed and the unexposed. Thus $1 - \alpha$ confidence intervals for ω based on the ln-method are

$$\hat{\omega}_{\mathrm{MH}} \exp[\pm z_{\alpha/2}\sqrt{V_i}], \; i \in \{\mathrm{B}, \mathrm{GR}\}. \qquad (17)$$

Table 1. The Los Angeles endometrial cancer data.

	Number of controls exposed				
Case status	0	1	2	3	4
Exposed	3	17	16	15	5
Unexposed	0	4	1	1	1

Table 2. The stratified Ille-et-Vilaine data.

Age class	25–34		35–44		45–54		55–64		65–74		75 +	
Daily alcohol consumption	High	Low	High	Low	High	Low	High	Low	High	Low	High	Low
Case	1	0	4	5	25	21	42	34	19	36	5	8
Control	9	106	26	164	29	138	27	139	18	88	0	31

The Fieller-like method also extends in a straightforward manner to the common rate ratio (*29*). Using arguments that parallel those given in the odds ratio case, the approximate interval (ω_L, ω_U) is obtained as the two solutions to the quadratic equation

$$T(\omega) = \frac{\left[\left|\sum_{k=1}^{K}(R_k - \omega S_k)\right| - c\right]^2}{\omega\left[\sum_{k=1}^{K} n_k m_k t_k / N_k^2\right]} = z_{\alpha/2}^2, \quad (18)$$

where $c = (1 + \omega)/4$ with the continuity correction, or otherwise zero.

Next we consider the situation in which the rate difference $\xi = r_{1k} - r_{0k}$ remains constant across strata. Let $\hat{\xi}_k = \hat{r}_{1k} - \hat{r}_{0k}$. The Mantel-Haenszel rate difference (*6*) is defined as the solution to the estimating equation

$$W(\xi) = \sum_{k=1}^{K} \frac{n_k m_k}{N_k}(\hat{\xi}_k - \xi) = 0,$$

leading to $\hat{\xi}_{MH} = [\sum_{k=1}^{K}(m_k X_k - n_k Y_k)/N_k]/(\sum_{k=1}^{K} n_k m_k / N_k)$. Using that $E[m_k^2 X_k + n_k^2 Y_k] = \text{var}(m_k X_k - n_k Y_k)$, Greenland and Robins (*8*) proposed a variance estimator of $\hat{\xi}_{MH}$ analogous to Eq. (16) that is defined by

$$\widehat{\text{var}}^{A}(\xi_{MH}) = \frac{\left[\sum_{k=1}^{K}(m_k^2 X_k + n_k^2 Y_k)/N_k^2\right]}{\left(\sum_{k=1}^{K} n_k m_k / N_k\right)^2}.$$

The $1 - \alpha$ Taylor series interval for ξ is thus obtained by

$$\hat{\xi}_{MH} \pm z_{\alpha/2}\sqrt{\text{var}^{A}(\hat{\xi}_{MH})} \quad (19)$$

As an alternative to the Taylor series interval, we propose a Fieller-like method similar to Eqs. (14) and (18). We may easily give

$$\widehat{\text{var}}(m_k X_k - n_k Y_k) = E[n_k m_k(m_k - n_k)\xi + n_k m_k t_k]$$

If ξ is known, $\xi[\sum_{k=1}^{K} n_k m_k(m_k - n_k)/N_k^2 + \sum_{k=1}^{K} n_k m_k t/N_k^2$ is consistent for $(\sum_{k=1}^{K} n_k m_k / N_k)^2 \text{var}^{A}(\hat{\xi}_{MH})$. Hence the Fieller-like interval for ξ is the two solutions to the quadratic equation

$$T(\xi) = \frac{\left[\left|\sum_{k=1}^{K}(m_k X_k - n_k Y_k)/N_k - \xi\left(\sum_{k=1}^{K} n_k m_k / N_k\right)\right| - c'\right]^2}{\xi\left[\sum_{k=1}^{K} n_k m_k(m_k - n_k)/N_k^2\right] + \sum_{k=1}^{K} n_k m_k t_k / N_k^2} = z_{\alpha/2}^2 \quad (20)$$

where $c' = 1/2$ with the continuity correction, or otherwise zero.

It is noteworthy that the Fieller-like methods Eqs. (18) and (20) have close relation to test of null exposure-disease association. When testing null association that $\omega = 1$ and $\xi = 0$, both $T(\omega)$ and $T(\xi)$ can reduce to

$$T(\omega|\omega = 1) = T(\xi|\xi = 0) = \frac{\left[\left|\sum_{k=1}^{K}(X_k - n_k t_k/N_k)\right| - c'\right]^2}{\sum_{k=1}^{K} n_k m_k t_k / N_k^2}$$

which is identical with the efficient score test of null association given by Shore et al. (*34*).

To illustrate the confidence intervals methods for the rate ratio, we consider the Montana study of arsenic exposure and respiratory cancer (*35*). Table 3 gives observed deaths and person-years of the Montana study stratified by age, class and calendar period. We find a summary rate ratio estimate of $\hat{\omega}_{MH} = 3.138$. The conditional and unconditional variance estimates of $\ln\hat{\omega}_{MH}$ are calculated according to Eq. (15) of $V_B = 0.0501$ and Eq. (16) of $V_{GR} = 0.0520$. The approximate 95% confidence intervals based on the ln-method [Eq. (17)] are (2.023, 4.867) with the conditional variance and (2.007, 4.907) with the unconditional one, while those obtained by solving Eq. (18) are (2.014, 4.889) without the correction and (1.948, 5.102) with it. Similar to the odds ratio situation, these intervals are quite close.

Although both the rate ratio and difference cannot remain constant in a data set, in order to illustrate the

Table 3. Deaths from respiratory cancer among Montana smelter workers.

		Period							
		1938–1949		1950–1959		1960–1969		1970–1977	
Age	Arsenic exposure	Deaths	Person-years	Deaths	Person-years	Deaths	Person-years	Deaths	Person-years
40–49	High	0	337.29	0	121.00				
	Low	2	3075.27	0	936.75				
50–59	High	4	626.72	3	349.53	1	142.33		
	Low	2	2849.76	3	2195.59	3	747.77		
60–69	High	9	672.09	7	441.10	3	244.82	1	100.64
	Low	2	2085.43	7	1675.91	10	1501.73	1	440.21
70–79	High	1	277.25	2	268.27	1	197.20	2	92.75
	Low	3	833.61	6	973.32	6	1027.12	6	674.44

methods for the rate difference we use the same Montana data. A summary rate difference is $\hat{\xi}_{MH} = 589.8$ per 100,000 person-years. The approximate 95% interval based in Eq. (19) is (288.1, 891.4) per 100,000 person-years, while the Fieller-like intervals are (320.3, 936.9) per 100,000 person-years without the correction and (306.5, 954.7) per 100,000 person-years with it. The intervals for the Fieller-like method are shifted to the right of that for the first-order Taylor series interval.

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