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COMPARATIVE ANALYSIS OF TWO RATES*

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SUMMARY

In this paper, we examine comparative analysis of rates with a view to each of the usual comparative parameters—rate difference (RD), rate ratio (RR) and odds ratio (OR)—and with particular reference to first principles. For RD and RR we show the prevailing statistical practices to be rather poor. We stress the need for restricted estimation of variance in the chi-square function underlying interval estimation (and also point estimation and hypothesis testing). For RR analysis we propose a chi-square formulation analogous to that for RD and, thus, one which obviates the present practice of log transformation and its associated use of Taylor series approximation of the variance. As for OR analysis, we emphasize that the chi-square function, introduced by Cornfield for unstratified data, and extended by Gart to the case of stratified analysis, is based on the efficient score and thus embodies its optimality properties. We provide simulation results to evince the better performance of the proposed (parameter-constrained) procedures over the traditional ones.

KEY WORDS Asymptotic confidence intervals Biometry Constrained maximum likelihood estimation Epidemiologic methods

INTRODUCTION

Comparative analysis of two rates is a characteristic problem in the study of the occurrence of illness (epidemiology) and in many other investigative contexts.

The compared rates take one of two forms, proportions or incidence densities. A proportion-type empirical rate (r) expresses the number of 'cases' (c) as a proportion of the number of subjects (S): $r = c/S$. When the cases occur as events in the follow-up of a dynamic population, then the rate (incidence density) expresses the number of cases in relation to the amount of population-time (T) of follow-up: $r = c/T$.

Either way, comparative analysis concerns the relative magnitudes of the theoretical (expected) rates, R_1 and R_0, corresponding to the compared categories of a determinant (potential or known) of the magnitude of the rate. The relative magnitudes are commonly thought of in terms of either

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rate difference (RD), rate ratio (RR), or odds ratio (OR):

$$\mathrm{RD} = R_1 - R_0$$
$$\mathrm{RR} = R_1/R_0$$
$$\mathrm{OR} = [R_1/(1-R_1)]/[R_0/(1-R_0)]$$

The usual aspects of data analysis with respect to each of these comparative parameters are three: (a) testing of the 'null hypothesis' of $R_1 = R_0$ (i.e. RD = 0, RR = 1, OR = 1), (b) point estimation of the comparative parameter of interest and (c) computation of a confidence interval for it.

Practices in these analyses have remained theoretically unattractive, in part for reasons of computational ease. But now that computational complexity is no longer a tenable reason for theoretically deficient analyses, it is time to examine the nature of theoretically more appropriate procedures and to update analytic practices accordingly.

The presentation that follows is an attempt to delineate theoretically proper procedures for comparative analysis of rates, and to show numerically that such procedures do, indeed, have better performance characteristics than some of those currently in use. The outlook here is predominantly didactic, but some novelties do also arise.

SINGLE PROPORTION

As a preliminary to comparative analysis of two rates, consider the analysis (asymptotic) of a *single* proportion-type rate. With c cases among S subjects, the number c is viewed as a realization for a binomial sampling distribution with parameters R (the theoretical rate) and S. Asymptotically, then, c is taken as a realization for a Gaussian sampling distribution with expectation and variance equal to those of the binomial, that is SR and SR$(1-R)$, respectively. Equivalently, the empirical rate $r = c/S$ is viewed as a realization for a Gaussian sampling distribution with parameters R and $R(1-R)/S$.

For any null value $R = R_0$ the test statistic is commonly taken as

$$X_0^2 = (r - R_0)^2/[R_0(1-R_0)/S] \quad (1)$$

which is a direct corollary of the asymptotic model, and its value is referred to the chi-square distribution with one degree of freedom.

The point estimate is generally taken as the empirical value: $\hat{R} = r$.

Confidence limits (two-sided) are commonly derived as

$$r \pm \chi_\alpha[r(1-r)/S]^{1/2} \quad (2)$$

where χ_α is the square root of the $100(1-\alpha)$ centile of the chi-square distribution, one degree of freedom.

A theoretically preferable approach to interval estimation is based, as Wilson[1] has noted, on consideration of the generalization of the null chi-square, that is, on chi-square as a function of R:

$$X_R^2 = (r-R)^2/[R(1-R)/S] \quad (3)$$

$100(1-\alpha)$ per cent confidence limits are the values of R such that

$$X_R^2 = \chi_\alpha^2 \quad (4)$$

—for 95% limits equal to $3{\cdot}84 = (1{\cdot}96)^2$. In a way, this idea traces back to Laplace, as Wilks[2] has pointed out.

Example 1

With $r = 0/10$, the 95 per cent interval based on (2) is 0·00 to 0·00, whereas (3) and (4) give 0·00 to 0·28. The 'exact' upper bound (based on mid-P) is 0·26.

The latter approach is not only preferable to that commonly used, but, indeed, theoretically ideal since it derives from the 'efficient score' approach described by Cox and Hinkley,[3] among others.

A worthy alternative results from the principle that the logarithm of the likelihood ratio, multiplied by two, has asymptotically the chi-square distribution with one degree of freedom. This implies the chi-square function

$$X_R^2 = 2 \log \frac{r^c (1-r)^{S-c}}{R^c (1-R)^{S-c}} \tag{5}$$

Its performance, although excellent for R in the vicinity of r, can be inferior to that of the function in (3) in the context of large discrepancies between the empirical (r) and the theoretical (R). (In applying likelihood ratio statistics it is necessary to instruct the computer to take $0^0 = 1$.)

Example 2

Recall Example 1 above. With the chi-square function in (5), the relation in (4) gives the upper bound of 0·17—somewhat inferior to that based on (3).

The chi-square function does not serve interval estimation alone; it is a summary of all of the statistical evidence in the data. Point estimate ($\hat{R} = r$) corresponds to $X_R^2 = 0$, and the null chi-square is the function's value at $R = R_0$. Moreover, the likelihood ratio function—the Bayesian summary of evidence—is implicit in the chi-square function.

TWO PROPORTIONS WITHOUT STRATIFICATION: RATE DIFFERENCE

Now consider *two* rates, an index rate $r_1 = c_1/S_1$ and a reference rate $r_0 = c_0/S_0$, corresponding to an overall (marginal) rate of $r = c/S$ (where $c = c_1 + c_0$, and $S = S_1 + S_0$). These are data whose usual array is the 2×2 table.

For the null hypothesis of RD $= 0$ ($R_1 = R_0$) the proper chi-square statistic is, as is well known,

$$X_0^2 = (r_1 - r_0)^2 / \{r(1-r)[S/(S-1)](1/S_1 + 1/S_0)\} \tag{6}$$

It derives from two types of argument—one unconditional and the other conditional on the marginal rate.[4,5] Note the use of the unbiased estimator of the Bernoulli variance in the unconditional approach.

The point estimate is, of course, taken as $\widehat{\text{RD}} = r_1 - r_0$.

Analogously with the common practice for a single rate, confidence limits are usually derived as

$$r_1 - r_0 \pm \chi_\alpha [r_1(1-r_1)/S_1 + r_0(1-r_0)/S_0]^{1/2} \tag{7}$$

This means incoherence between the null test statistic and confidence limits.[6] It can also mean quite poor results.

Example 3

Consider the data $r_1 = 0/10$, $r_0 = 0/20$. The 95 per cent confidence interval based on (7) is 0·00 to 0·00—even though, clearly, both negative and positive values of RD are consistent with the data.

For proper interval estimation, then, one needs a generalization of the null chi-square in (6) to a chi-square function of RD, with (6) a special case of it, analogously with the generalization of (1) to (3).

Following, as a paradigm, Wilson's approach to the analysis of a single rate, we take the numerator of the function as the square of $r_1 - r_0 - \text{RD}$. But the pivotal matter is the denominator (variance of $r_1 - r_0$). The usual interval in (7) corresponds to the use of r_1 and r_0 in place of R_1 and R_0, respectively. By contrast, the paradigm in (3) calls for estimation of R_1 and R_0 in a restricted way, with the theoretical value of RD taken into account. The null chi-square in (6) does involve the restriction of RD = 0 in the estimation of R_1 and R_0 (as $\tilde{R}_1 = \tilde{R}_0 = r$). More generally, the denominator of the chi-square function, based on $r_1 - r_0 - \text{RD}$ in the numerator, is to be taken as

$$\tilde{V}_{r_1 - r_0} = [\tilde{R}_1(1 - \tilde{R}_1)/S_1 + \tilde{R}_0(1 - \tilde{R}_0)/S_0]S/(S-1) \quad (8)$$

with the tilde denoting an estimator restricted by $\tilde{R}_1 - \tilde{R}_0 = \text{RD}$. Thus we may take $\tilde{R}_1 = \tilde{R}_0 + \text{RD}$, and solve $\tilde{R}_0$ from the likelihood equation based on two independent binomials involving the estimated probabilities $\tilde{R}_0 + \text{RD}$ and $\tilde{R}_0$, corresponding to S_1 and S_0, respectively. Even though the likelihood equation is of the third degree, a unique closed solution for $\tilde{R}_0$ is given in Appendix I. The chi-square function thus derives from computing

$$X^2_{\text{RD}} = (r_1 - r_0 - \text{RD})^2/\tilde{V}_{r_1 - r_0} \quad (9)$$

for a succession of values of RD.

Example 4

Recall Example 3 above (with $r_1 = 0/10$ and $r_0 = 0/20$). With this chi-square function, the 95 per cent limits for RD, corresponding to $X^2_{\text{RD}} = 3{\cdot}84$, are $-0{\cdot}17$ and $0{\cdot}28$. The value RD $= -0{\cdot}17$ corresponds to $\tilde{R}_1 = 0{\cdot}00$ and $\tilde{R}_0 = 0{\cdot}17$ for the variance in (8) and (9), and RD $= 0{\cdot}28$ implies $\tilde{R}_1 = 0{\cdot}28$ and $\tilde{R}_0 = 0{\cdot}00$ for it. By extension, were the data to be $r_1 = 10/10$ and $r_0 = 20/20$, the 95 per cent interval would be $-0{\cdot}28$ to $0{\cdot}17$.

In this formulation of the chi-square function the accent was on proper formulation of the variance, the denominator—with the contrast $(r_1 - r_0 - \text{RD})$ in the numerator adopted simply by analogy with $r - R$ in the context of a single rate. Theoretically that contrast is inferior to the 'efficient score'. This latter approach, somewhat more complicated, is examined in Appendix II, and the likelihood ratio approach in Appendix III.

TWO PROPORTIONS WITHOUT STRATIFICATION: RATE RATIO

When the analysis is directed to the value of rate ratio, the chi-square for the null value of RR = 1 is the one given in (6) for RD = 0 ($R_1 = R_0$).

Just as naturally, the point estimate ($\widehat{\text{RR}}$)—the zero point of the chi-square function—is the empirical value r_1/r_0.

Values of RR corresponding to $X^2_{\text{RR}} = \chi^2_\alpha$, or $100(1-\alpha)$ per cent confidence limits, are usually solved from an approach involving log transformation of r_1/r_0 and first-order Taylor series approximation of the variance of $\log(r_1/r_0)$—with evaluation at (r_1, r_0).[7]

Example 5

With $r_1 = 10/10$ and $r_0 = 20/20$, the 95 per cent interval for RR according to the approach described by Katz *et al.*[7]

$$\exp\{\log(r_1/r_0) \pm 1{\cdot}96[(1-r_1)/c_1 + (1-r_0)/c_0]\}$$

is 1·00 to 1·00—even though values on either side of unity are, obviously, consistent with the data.

To the extent that this approach merits use at all, it needs to be mended by the use of $(\tilde{R}_1, \tilde{R}_0)$ in place of (r_1, r_0) in the variance—with $\tilde{R}_1$ and $\tilde{R}_0$ the ML estimates restricted by $\tilde{R}_1 = \tilde{R}_0(\text{RR})$.

A chi-square function for RR more closely analogous to that in (9) for RD is apparent by viewing the numerator contrast in the latter not as $(r_1 - r_0) - \text{RD}$ but as $r_1 - (r_0 + \text{RD})$. This suggests[8]

$$X^2_{\text{RR}} = [r_1 - r_0(\text{RR})]^2/\tilde{V}_{r_1 - r_0(\text{RR})} \tag{10}$$

with

$$\tilde{V}_{r_1 - r_0(\text{RR})} = [\tilde{R}_1(1-\tilde{R}_1)/S_1 + (\text{RR})^2 \tilde{R}_0(1-\tilde{R}_0)/S_0]S/(S-1) \tag{11}$$

In this variance, $\tilde{R}_1 = \tilde{R}_0(\text{RR})$, while for $\tilde{R}_0$ the likelihood equation (quadratic) gives

$$\tilde{R}_0 = [-B - (B^2 - 4AC)^{1/2}]/(2A) \tag{12}$$

with

$$A = S(\text{RR})$$

$$B = -[S_1(\text{RR}) + c_1 + S_0 + c_0(\text{RR})]$$

$$C = c$$

(see Appendix I). This formulation obviates not only the use of the log transformation but asymptotic (Taylor series) approximation of the variance as well. Also, at RR = 1 this function reduces to the null chi-square in (6), so that in these terms interval estimation and 'hypothesis testing' become mutually coherent, as with RD, in contrast to the prevailing procedures.

Example 6

Recall Example 5 (with $r_1 = 10/10$, $r_0 = 20/20$). With the chi-square function in (10), the 95 per cent limits for RR, corresponding to $X^2 = 3{\cdot}84$, are 0·72 and 1·20. With RR = 0·72, we have $\tilde{R}_1 = 0{\cdot}72$ and $\tilde{R}_0 = 1{\cdot}00$, whereas with RR = 1·20, the values are $\tilde{R}_1 = 1{\cdot}00$ and $\tilde{R}_0 = 0{\cdot}83$. It is worth noting that the corresponding limits for RD are −0·28 and 0·17 (cf. Example 4).

The chi-square function for RR based on the score statistic, somewhat complicated, is examined in Appendix II, and that based on the likelihood ratio statistic in Appendix III.

TWO PROPORTIONS WITHOUT STRATIFICATION: ODDS RATIO

For odds ratio analysis, the null chi-square in routine use is again that in (6), and the point estimate is commonly taken as the empirical value, $[r_1/(1-r_1)]/[r_0/(1-r_0)]$.

Values of OR corresponding to $X^2_{\text{OR}} = \chi^2_\alpha$ (asymptotic confidence limits) are being computed in various ways, including those of Woolf[9] and Cornfield.[10] One can also compute exact limits, for OR, in contrast to RD or RR.[11]

The type of chi-square function proposed above for RD and RR is easy to derive for OR as well, the numerator contrast being $r_1 - r_0(\text{OR})/[1 + r_0(\text{OR} - 1)]$. This approach involves a problem, however, as this contrast is no longer a linear combination of r_1 and r_0: an asymptotic variance (Taylor series approximation) needs to be used.

On the other hand, the score statistic approach is readily applicable to OR, as the marginal rate can be viewed as an ancillary statistic so that no nuisance parameter needs estimation. The chi-square function takes the form of

$$X^2_{\text{OR}} = \frac{\left[\dfrac{r_1 - \tilde{R}_1}{\tilde{R}_1(1-\tilde{R}_1)} - \dfrac{r_0 - \tilde{R}_0}{\tilde{R}_0(1-\tilde{R}_0)}\right]^2}{\left[\dfrac{1}{S_1\tilde{R}_1(1-\tilde{R}_1)} + \dfrac{1}{S_0\tilde{R}_0(1-\tilde{R}_0)}\right]\dfrac{S}{S-1}} = \frac{[S_1(r_1 - \tilde{R}_1)]^2}{\left[\dfrac{1}{S_1\tilde{R}_1(1-\tilde{R}_1)} + \dfrac{1}{S_0\tilde{R}_0(1-\tilde{R}_0)}\right]^{-1}\dfrac{S}{S-1}} \tag{13}$$

where

$$\tilde{R}_1 = \tilde{R}_0(\text{OR})/[1+\tilde{R}_0(\text{OR}-1)]$$
$$\tilde{R}_0 = [-B+(B^2-4AC)^{1/2}]/(2A)$$

with

$$A = S_0(\text{OR}-1)$$
$$B = S_1(\text{OR})+S_0-c(\text{OR}-1)$$
$$C = -c$$

(see Appendix II). This statistic can be recognized as that underlying the limits Cornfield[10] gave—with the exceptions that we have omitted the 'continuity correction'[12] and have used the unbiased estimator of the variance. It may be of interest to note that the derivation here (Appendix II) is not conditional on the marginal rate, in contrast to Cornfield's, this duality being the general form of that underlying the null chi-square in (6).

For the likelihood ratio approach, see Appendix III.

STRATIFIED PAIRS OF PROPORTIONS

If, in the interest of comparability, the data require stratification by a covariate, then we need generalizations of the chi-square functions presented above.

For the statistic for RD in (9) the stratified counterpart may be taken as

$$X^2_{\text{RD}} = [\Sigma_j W_j(r_{1j}-r_{0j}-\text{RD})]^2/(\Sigma_j W_j^2\,\tilde{V}_{r_{1j}-r_{0j}}) \tag{14}$$

with W_j—the weight for the jth stratum—suitably proportional to the amount of comparative information in it. This function may be recast as

$$X^2_{\text{RD}} = (r_1^*-r_0^*-\text{RD})^2/[\Sigma_j(W_j/\Sigma_j W_j)^2\,\tilde{V}_{r_{1j}-r_{0j}}] \tag{15}$$

where r_1^* and r_0^* are mutually standardized rates with the weights of standardization taken as W_j:

$$r_i^* = \Sigma_j W_j r_{ij}/\Sigma_j W_j$$

For the null chi-square Cochran[13] took the weights as $(1/S_{1j}+1/S_{0j})^{-1}$ assuming that $R_j(1-R_j)$ is constant over j. In the general case we may assume, analogously, that $R_{ij}(1-R_{ij})$ is constant over j and, thus, take

$$W_j = \left[\frac{\tilde{R}_1^*(1-\tilde{R}_1^*)}{\tilde{R}_0^*(1-\tilde{R}_0^*)}/S_{1j}+1/S_{0j}\right]^{-1} \tag{16}$$

with $\tilde{R}_i^* = \Sigma_j W_j\tilde{R}_{ij}/\Sigma_j W_j$. Naturally, $\tilde{R}_1^* = \tilde{R}_0^*+\text{RD}$, and $\tilde{R}_{0j}$ is computed as is shown in Appendix I. With these definitions, admittedly somewhat circular, one may proceed by first taking W_j as $(1/S_{ij}+1/S_{0j})^{-1}$ and computing the corresponding values of $\tilde{R}_1^*$ and $\tilde{R}_0^*$, then applying these to (16) thus obtaining the second approximations to the weights, etc.

For RR the corresponding function is, naturally,

$$X^2_{\text{RR}} = [r_1^*-r_0^*(\text{RR})]^2/[\Sigma_j(\text{W}_j/\Sigma_j\text{W}_j)^2\,\tilde{V}_{r_{1j}-r_{0j}(\text{RR})} \tag{17}$$

with r_1^* and r_0^* the mutually standardized rates involving the weights

$$W_j = \left[\frac{1-\tilde{R}_1^*}{1-\tilde{R}_0^*}\;/\;S_{1j}+(\text{RR})/S_{0j}\right]^{-1} \tag{18}$$

Here $\tilde{R}_1^* = \tilde{R}_0^*(\text{RR})$, and $\tilde{R}_0^* = \Sigma_j W_j \tilde{R}_{0j}/\Sigma_j W_j$, with $\tilde{R}_{0j}$ computed according to (12). As with RD, first approximations to the W_j may be obtained by assuming $\tilde{R}_1^* = \tilde{R}_0^*$, second approximations by using the first approximation weights in $\tilde{R}_1^*$ and $\tilde{R}_0^*$ incorporated in (18), etc.

For OR the stratified score statistic, a generalization of (13), is

$$X^2_{\text{OR}} = \frac{\left\{\Sigma_j W_j \left[\dfrac{r_{1j}-\tilde{R}_{1j}}{\tilde{R}_{1j}(1-\tilde{R}_{1j})} - \dfrac{r_{0j}-\tilde{R}_{0j}}{\tilde{R}_{0j}(1-\tilde{R}_{0j})}\right]\right\}^2}{\Sigma_j W_j^2 \left[\dfrac{1}{S_{1j}\tilde{R}_{1j}(1-\tilde{R}_{1j})} + \dfrac{1}{S_{0j}\tilde{R}_{0j}(1-\tilde{R}_{0j})}\right] \dfrac{S_j}{S_j - 1}} \tag{19}$$

with

$$W_j = \frac{S_{1j}S_{0j}[(1-\tilde{R}_{1j})\tilde{R}_{0j}]^2}{S_{1j}\tilde{R}_{1j}(1-\tilde{R}_{1j}) + S_{0j}\tilde{R}_{0j}(1-\tilde{R}_{0j})}$$

(see Appendix II). An alternative formulation of this statistic is (cf. (13))

$$X^2_{\text{OR}} = \frac{[\Sigma_j S_{1j}(r_{1j}-\tilde{R}_{1j})]^2}{\Sigma_j \left[\dfrac{1}{S_{1j}\tilde{R}_{1j}(1-\tilde{R}_{1j})} + \dfrac{1}{S_{0j}\tilde{R}_{0j}(1-\tilde{R}_{0j})}\right]^{-1} \dfrac{S_j}{S_j - 1}} \tag{20}$$

which can be recognized as that underlying the limits Gart[14] gave as the stratified generalization of the Cornfield limits for unstratified data—here again without the 'continuity correction' and with an unbiased estimator of variance.

Each of the chi-square functions above implies a point estimator for the comparative parameter at issue—the value for which the corresponding chi-square function takes on the value zero.

It is worthy of note that in the null case of $R_1 = R_0$ (RD = 0, RR = 1, OR = 1) all three of the chi-square functions above—X^2_{RD} in (15), X^2_{RR} in (17), and X^2_{OR} in (19) and (20)—reduce to the same null chi-square,

$$X_0^2 = \frac{\left[\Sigma_j \dfrac{S_{1j}S_{0j}}{S_j}(r_{1j}-r_{0j})\right]^2}{\Sigma_j \dfrac{S_{1j}S_{0j}}{S_j - 1} r_j(1-r_j)} \tag{21}$$

$$= (r_1^* - r_0^*)^2/[\Sigma_j (W_j/\Sigma_j W_j)^2 r_j(1-r_j)(1/S_{1j} + 1/S_{0j})S_j/(S_j - 1)]$$

with

$$W_j = S_{1j}S_{0j}/S_j$$
$$= (1/S_{1j} + 1/S_{0j})^{-1}$$

This null statistic is recognizable as that given by Cochran[13] (with the ML estimator of variance) and again by Mantel and Haenszel,[15] based on derivations without and with conditioning by the stratum-specific marginal rates, respectively. As it derives from the score statistic for OR (cf. References 16 and 17, and Appendix II), it is natural that it is uniformly most powerful for the detection of non-null situations with constant OR over the strata—a property proven expressly by Birch[18] and Radhakrishna.[19]

INCIDENCE DENSITY DATA

When the rate denominators represent population-time of observation (for incidence of events), the comparative parameters of direct interest can be only RD and RR, exclusive of OR.

For RD the chi-square function still has the form given in (15), but now

$$\tilde{V}_{r_{1j}-r_{0j}} = \tilde{R}_{1j}/T_{1j} + \tilde{R}_0/T_{0j} \quad (22)$$

with $\tilde{R}_{1j} = \tilde{R}_{0j} + \mathrm{RD}$ and $\tilde{R}_{0j}$ solved from a quadratic likelihood equation as is shown in Appendix I. Also, the weights in (16) are replaced by

$$W_j = \left[\frac{\tilde{R}_1^*}{\tilde{R}_0^*} \; /T_{1j} + 1/T_{0j}\right]^{-1} \quad (23)$$

computed as delineated in the context of (16).

For RR, similarly, the chi-square function is still of the form in (17). In it,

$$\tilde{V}_{r_{1j}-r_{0j}(\mathrm{RR})} = \tilde{R}_{1j}/T_{1j} + (\mathrm{RR})^2\, \tilde{R}_{0j}/T_{0j} \quad (24)$$

with $\tilde{R}_{1j} = \tilde{R}_{0j\,(\mathrm{RR})}$ and $\tilde{R}_{0j}$ derived as is shown in Appendix I. The weights in this context of incidence densities are

$$W_j = [1/T_{1j} + (\mathrm{RR})/T_{0j}]^{-1} \quad (25)$$

NUMERICAL EVALUATION

The presentation above includes proposed new methods for the analysis of RD and RR, which were argued, on theoretical grounds, as superior to the corresponding methods now in common use. It was also suggested that the proposed methods should compare favourably with ones based on the likelihood ratio approach.

To supplement theory, we carried out computer simulations for a variety of situations involving two independent binomials with particular values for the theoretical rates. For each situation, we generated 10,000 two-by-two tables, computed the 95 per cent intervals for the comparative parameter for each table, and classified each interval as to whether it failed to cover the theoretical value of the comparative parameter and, if so, whether the error derived from the lower or the upper bound.

The results appear in Tables I and II, for RD and RR, respectively. Evidently, the simulations confirm the theoretical contentions.

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APPENDIX I. RESTRICTED ESTIMATION OF COMPARED RATES

The chi-square functions for all three comparative parameters (RD, RR and OR) involve the need to estimate the compared rates on the constraint that the comparative parameter at issue has a particular value. These are the estimates $\tilde{R}_1$ and $\tilde{R}_0$ as distinct from the empirical values r_1 and r_0.

For analyses directed to RD, the constraint is that $R_1 - R_0$ equals a particular value RD. Thus,

$$\tilde{R}_1 = \tilde{R}_0 + RD \quad (26)$$

The value of $\tilde{R}_0$ is the one that, subject to this restriction, maximizes the likelihood corresponding

Table I. Error rates (per cent) for 95 per cent confidence intervals for rate difference, separately for lower bound (ER_L), upper bound (ER_U) and overall ($ER = ER_L + ER_U$)

Model				Method								
				Usual*			Proposed†			Likelihood ratio‡		
R_1	R_0	S_1	S_0	ER_L	ER_U	ER	ER_L	ER_U	ER	ER_L	ER_U	ER
0·5	0·5	10	10	4·3	4·0	8·3	2·0	2·0	4·0	2·5	2·5	5·0
		10	50	4·2	4·1	8·3	2·5	2·5	5·0	3·0	3·2	6·2
0·2	0·2	25	25	2·9	3·1	6·0	2·7	2·8	5·5	2·7	2·9	5·6
		25	125	1·5	6·7	8·2	2·8	2·1	4·9	2·5	3·3	5·8
0·1	0·1	50	50	2·9	3·1	6·0	2·4	2·6	5·0	2·1	3·2	5·3
		50	250	1·0	6·3	7·3	2·8	1·5	4·3	2·1	3·2	5·3
		250	50	6·2	0·9	7·1	1·2	3·1	4·3	3·1	2·3	5·4
0·65	0·35	10	10	4·2	2·3	6·5	1·6	2·3	3·9	4·2	2·3	6·5
		10	50	6·4	3·0	9·4	2·0	2·9	4·9	3·5	2·9	6·4
0·35	0·05	50	50	2·7	3·0	5·7	2·5	2·4	4·9	2·6	2·7	5·3
		50	250	2·1	3·3	5·4	2·6	2·0	4·6	2·4	2·3	4·7
		250	50	5·2	1·3	6·5	2·2	2·9	5·1	3·8	2·5	6·3
0·15	0·05	50	50	2·0	4·0	6·0	3·3	2·0	5·3	3·3	2·7	6·0
		50	250	1·2	5·5	6·7	2·7	1·6	4·3	2·2	3·0	5·2
		250	50	6·3	0·9	7·2	1·2	2·9	4·1	4·0	2·4	6·4

* Expression (7).
† Based on expressions (8) and (9).
‡ Based on expression (38).

Table II. Error rates (per cent) for 95 per cent confidence intervals for rate ratio, separately for lower bound (ER_L), upper bound (ER_U), and overall ($ER = ER_L + ER_U$)

Model				Method								
				Usual*			Proposed†			Likelihood ratio‡		
R_1	R_0	S_1	S_0	ER_L	ER_U	ER	ER_L	ER_U	ER	ER_L	ER_U	ER
0·5	0·5	10	10	0·8	0·9	1·7	2·0	2·0	4·0	2·5	2·5	5·0
		10	50	5·3	0·2	5·5	2·5	2·5	5·0	3·0	2·9	5·9
0·2	0·2	25	25	1·2	1·2	2·4	2·7	2·8	5·5	2·7	2·9	5·6
		25	125	3·3	0·5	3·8	2·8	2·1	4·9	2·6	3·2	5·8
0·1	0·1	50	50	1·5	1·7	3·2	2·4	2·6	5·0	3·0	3·1	6·1
		50	250	3·0	0·5	3·5	2·8	1·6	4·4	2·1	3·2	5·3
		250	50	0·5	3·3	3·8	1·2	3·1	4·3	3·1	2·3	5·4
0·65	0·35	10	10	1·2	4·1	5·3	1·8	3·2	5·0	3·3	2·8	6·1
		10	50	4·3	0·6	4·9	2·3	2·7	5·0	3·1	2·6	5·7
0·35	0·05	50	50	7·5	3·9	11·4	0·1	3·9	4·0	6·4	2·5	8·9
		50	250	2·0	2·0	4·0	2·1	2·2	4·3	3·0	2·0	5·0
		250	50	7·8	4·1	11·9	0·0	4·0	4·0	7·8	2·3	10·1
0·15	0·05	50	50	7·7	2·7	10·4	1·1	3·1	4·2	5·1	2·5	7·6
		50	250	2·4	1·1	3·5	2·4	1·9	4·3	2·4	2·5	4·9
		250	50	7·6	3·4	11·0	0·1	3·4	3·5	6·9	2·1	9·0

* Katz *et al.*[7], method C.
† Based on expressions (10) and (11).
‡ Based on expression (38).

to c_1 and c_0. In the context of proportion-type rates the likelihood is the product of two binomial probabilities—that of c_1 on the parameters $R_0 + \text{RD}$ and S_1, and that of c_0 on R_0 and S_0. The derivative of log-likelihood, equated to zero, yields a third-degree likelihood equation:

$$\sum_{k=0}^{3} L_k \tilde{R}_0^k = 0 \tag{27}$$

with

$$L_3 = S$$
$$L_2 = (S_1 + 2S_0)(\text{RD}) - S - c$$
$$L_1 = [S_0(\text{RD}) - S - 2c_0](\text{RD}) + c$$
$$L_0 = c_0(\text{RD})(1 - \text{RD})$$

where $c = c_1 + c_0$. This equation can be found to have a unique closed-form solution—following the guidelines set forth by Bronshtein and Samendyayev,[20] among others. This solution is

$$\tilde{R}_0 = 2p \cos(a) - L_2/(3L_3) \tag{28}$$

where

$$a = (1/3)[\pi + \cos^{-1}(q/p^3)]$$
$$p = \pm[L_2^2/(3L_3)^2 - L_1/(3L_3)]^{1/2}$$
$$q = L_2^3/(3L_3)^3 - L_1 L_2/(6L_3^2) + L_0/(2L_3)$$

with the sign of p chosen so as to have it coincide with that of q. For this closed solution the alternative is to use an iterative procedure with the constraint that $0 \leqslant \tilde{R}_0 + \text{RD} \leqslant 1$. For any given value of RD, the corresponding values of $\tilde{R}_1$ and $\tilde{R}_0$ are used to derive the variance estimate for the chi-square at that value of RD (cf. (8) and (9)).

If RR is the object of the analysis, then, naturally,

$$\tilde{R}_1 = \tilde{R}_0(\text{RR}) \tag{29}$$

The likelihood involves $R_0(\text{RR})$ in place of R_1, and the likelihood equation is of the second degree, with the solution given in (12).

In analyses for OR, the definition $\text{OR} = [R_1/(1 - R_1)]/[R_0/(1 - R_0)]$ implies the constraint between $\tilde{R}_1$ and $\tilde{R}_0$. Specifically,

$$\tilde{R}_1 = \frac{\tilde{R}_0(\text{OR})}{1 + \tilde{R}_0(\text{OR} - 1)} \tag{30}$$

In the likelihood, R_1 is replaced by $R_0(\text{OR})/[1 + R_0(\text{OR} - 1)]$, and the likelihood equation, of the second degree, has the solution given in the context of (13).

It is instructive to note that in the context of RD and RR the relation $(S_1\tilde{R}_1 + S_0\tilde{R}_0)/S = r$ obtains only on the null condition ($\text{RD} = 0$, $\text{RR} = 1$) and at the point estimate ($\text{RD} = r_1 - r_0$, $\text{RR} = r_1/r_0$), whereas in analyses directed to OR it holds for all values of this comparative parameter. It may be considered to be for this reason that confidence limits for RD and RR cannot be set conditionally on the marginal rate, in contrast to limits for OR.[11] On the other hand, even if analyses conditional on the marginal rate are admissible for OR, this viewpoint is not necessary, as was shown above.

When the data represent incidence densities, the likelihood involves Poisson probabilities (for c_1. and c_0) with parameters R_iT_i. Naturally we still take $\tilde{R}_1 = \tilde{R}_0 + \text{RD}$ and $\tilde{R}_1 = \tilde{R}_0(\text{RR})$ in analyses of RD and RR, respectively. The estimate of R_0 for any given value of RD derives from a quadratic likelihood equation. Thus it is of the form of (12), but the entries are $A = T$, $B = T(\text{RD}) - c$, and

$C = -c_0$ (RD), with $T = T_1 + T_0$. In the context of RR the likelihood equation is of the first degree, and $\tilde{R}_0 = c/[T_1(\text{RR}) + T_0]$.

APPENDIX II. CHI-SQUARE FUNCTION BASED ON THE EFFICIENT SCORE

The chi-square functions proposed in this paper for RD and RR focus on $r_1 - (r_0 + \text{RD})$ and $r_1 - r_0(\text{RR})$, respectively—contrasts or 'scores' with expectations equal to zero and variance estimates that depend on $\tilde{R}_1$ and $\tilde{R}_0$ (Appendix I) as is shown in (8) and (11), respectively. These scores have the virtue of simplicity, but they are not based on any principle suggesting optimality in terms of total capture of the comparative information in the data.

Theory, as outlined by Cox and Hinkley[3] among others, suggests as 'the efficient score' the derivative of the log-likelihood with respect to the comparative parameter at issue, with R_1 and R_0 replaced by $\tilde{R}_1$ and $\tilde{R}_0$, respectively. In comparative analysis of two rates this score takes the form

$$\sum_{i=0}^{1} (r_i - \tilde{R}_i)\tilde{I}_i \tilde{R}'_i \tag{31}$$

where the information element ($\tilde{I}_i$) and partial derivative ($\tilde{R}'_i$) are

$$\tilde{I}_i = S_i/[\tilde{R}_i(1 - \tilde{R}_i)]$$
$$\tilde{R}'_i = \partial\tilde{R}_i/\partial P$$

with P the comparative parameter. It is seen that the efficient score involves the deviation of each of the two empirical rates from their respective expected values estimated conditionally on P, and that this deviation is weighted not only by the amount of information in (precision of) the empirical rate but also by the extent to which the corresponding theoretical rate reflects (changes with) the comparative parameter. All of this is very appealing. The expectation of this score is zero, evidently. Its variance estimator, the negative of the expectation of its derivative (or of the second derivative of the log-likelihood) evaluated with $\tilde{R}_i$ in place of r_i is

$$\sum_{i=0}^{1} \tilde{I}_i (\tilde{R}'_i|_{r_i = \tilde{R}_i})^2$$

Thus the chi-square function for comparative analysis of two proportion-type rates based on the efficient score has the general form of

$$X_P^2 = \frac{[(r_1 - \tilde{R}_1)\tilde{I}_1 \tilde{R}'_1 + (r_0 - \tilde{R}_0)\tilde{I}_0 \tilde{R}'_0]^2}{[\tilde{I}_1(\tilde{R}'_1|_{r_1 = \tilde{R}_1})^2 + \tilde{I}_0(\tilde{R}'_0|_{r_0 = \tilde{R}_0})^2]S/(S-1)} \tag{32}$$

the particulars of the function depending on what the comparative parameter (P) is. For stratified data the corresponding function is, as a simple extension,

$$X_P^2 = \frac{\{\Sigma_j(r_{1j} - \tilde{R}_{1j})\tilde{I}_{1j}\tilde{R}_{1j} + (r_{0j} - \tilde{R}_{0j})\tilde{I}_{0j}\tilde{R}'_{0j}]\}^2}{\Sigma_j[\tilde{I}_{1j}(\tilde{R}'_{1j}|_{r_{1j} = \tilde{R}_{1j}})^2 + \tilde{I}_{0j}(\tilde{R}'_{0j}|_{r_{0j} = \tilde{R}_{0j}})^2]S_j/(S_j - 1)} \tag{33}$$

In the context of $P = \text{OR}$ we have as $\tilde{R}'_{ij}$

$$\frac{\partial\tilde{R}_{1j}}{\partial(\text{OR})} = \frac{S_{0j}[(1 - \tilde{R}_{1j})\tilde{R}_{0j}]^2}{S_{1j}\tilde{R}_{1j}(1 - \tilde{R}_{1j}) + S_{0j}\tilde{R}_{0j}(1 - \tilde{R}_{0j})}$$
$$= \left.\frac{\partial\tilde{R}_{1j}}{\partial(\text{OR})}\right|_{r_{1j} = \tilde{R}_{1j}},$$

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$$\frac{\partial \tilde{R}_{0i}}{\partial(\mathrm{OR})} = \frac{-S_{1j}[(1-\tilde{R}_{1j})\tilde{R}_{0j}]^2}{S_1\tilde{R}_{1j}(1-\tilde{R}_{1j})+S_{0j}\tilde{R}_{0j}(1-\tilde{R}_{0j})} \tag{34}$$

$$= \left.\frac{\partial \tilde{R}_{0j}}{\partial(\mathrm{OR})}\right|_{r_{0j}=\tilde{R}_{0j}}$$

These may be derived as $(\partial P/\partial \tilde{R}_{ij})^{-1}$ with $P = \mathrm{OR} = [\tilde{R}_{1j}/(1-\tilde{R}_{ij})]/[\tilde{R}_{0j}/(1-\tilde{R}_{0j})]$ and the relation of $S_{1j}\tilde{R}_{1j}+S_{0j}\tilde{R}_{0j} = S_j r_j$ (which holds for OR but not for RR or RD). $\tilde{R}_{1j}$ and $\tilde{R}_{0j}$ are based on the data from the ith stratum according to the specifications in (13). Similarly, the stratum-specific information elements ($\tilde{I}_{1j}$ and $\tilde{I}_{0j}$) in the statistic in (33) are based on the stratum-specific data, using the definition in the context of (31). In these terms, the chi-square function for OR based on the efficient score becomes the one given in (19) and (20).

If the comparative parameter is RR, then the derivatives of the restricted estimators of rate take the forms

$$\frac{\partial R_{1j}}{\partial(\mathrm{RR})} = \frac{[S_{1j}(r_{1j}-\tilde{R}_{1j})+S_{0j}r_{0j}(1-\tilde{R}_{1j})]^2}{S_j[S_{1j}(r_{1j}-\tilde{R}_{1j})(r_j-\tilde{R}_{1j})+S_{0j}(1-\tilde{R}_{1j})(r_j-r_{0j}\tilde{R}_{1j})]}$$

$$\frac{\partial R_{0j}}{\partial(\mathrm{RR})} = \frac{-\tilde{R}_{0j}^2[S_{1j}(1-\tilde{R}_{0j})+S_{0j}(r_j-\tilde{R}_{0j})]^2}{S_j[S_{1j}(1-\tilde{R}_{0j})(r_j-r_{1j}\tilde{R}_{0j})+S_{0j}(r_{0j}-\tilde{R}_{0j})(r_j-\tilde{R}_{0j})]} \tag{35}$$

These may again be derived as $(\partial P/\partial \tilde{R}_{ij})^{-1}$, but here $P = \mathrm{RR} = \tilde{R}_{1j}[S_{1j}(r_{1j}-\tilde{R}_{1j})+S_{0j}(1-\tilde{R}_{1j})]/[S_{1j}(r_{1j}(r_{1j}-\tilde{R}_{1j})+S_{0j}r_{0j}(1-\tilde{R}_{1j})]$ for $\partial\tilde{R}_{1j}/\partial(\mathrm{RR})$ and $P = \mathrm{RR} = [S_{1j}r_{1j}(1-\tilde{R}_{0j})+S_{0j}(r_{0j}-\tilde{R}_{0j})]/\{\tilde{R}_{0j}[S_{1j}(1-\tilde{R}_{0j})+S_{0j}(r_{0j}-\tilde{R}_{0j})]\}$ for $\partial R_{0j}/\partial(\mathrm{RR})$, these relations being the solutions for RR of $\partial \log L(\tilde{R}_{ij}, \mathrm{RR})/\partial(\tilde{R}_{ij}) = 0$. As obvious corollaries, for the variance in the chi-square function,

$$\left.\frac{\partial \tilde{R}_{1i}}{\partial(\mathrm{RR})}\right|_{r_{ij}=\tilde{R}_{ij}} = \frac{S_{0j}[(1-\tilde{R}_{1j})\tilde{R}_{0j}]^2}{S_j(1-\tilde{R}_{1j})(r_j-\tilde{R}_{1j}\tilde{R}_{0j})}$$

$$\left.\frac{\partial \tilde{R}_{0j}}{\partial(\mathrm{RR})}\right|_{r_{ij}=\tilde{R}_{ij}} = \frac{-\tilde{R}_{0j}^2[S_{1j}(1-\tilde{R}_{0j})+S_{0j}(r_j-\tilde{R}_{0j})]^2}{S_jS_{1j}(1-\tilde{R}_{0j})(r_j-\tilde{R}_{1j}\tilde{R}_{0j})} \tag{36}$$

The null chi-square can be found upon substitution of $\tilde{R}_{ij} = r_j$, to be

$$X^2_{\mathrm{RR}=1} = \frac{\left[\Sigma_j \dfrac{S_{1j}S_{0j}}{S_j(1-r_j)}(r_{1j}-r_{0j})\right]^2}{\Sigma_j \dfrac{S_{1j}S_{0j}r_j}{(S_j-1)(1-r_j)}} \tag{37}$$

In contrast to the score statistic for OR = 1 in (21), this statistic for RR = 1 is seen to be problematic: any stratum with $r_j = 1$ makes an infinite contribution to both the numerator and the denominator. (Perhaps a reasonable statistic could be based on empirical Bayes approach to the nuisance parameters, especially by the use of a Beta distribution model for them.)

With RD the comparative parameter, the values of $\partial R_{ij}/\partial(\mathrm{RD})$ for any given RD need to be derived numerically—as the change in $\tilde{R}_{ij}$ from RD to RD + ε divided by ε, with $\varepsilon = 0{\cdot}01$, say. For the denominator of the chi-square function, the corresponding values conditional on $r_{1j} = \tilde{R}_{ij}$ are derived with $\tilde{R}_{ij}$ based on (27) with $S_{1j}\tilde{R}_{ij}+S_{0j}\tilde{R}_{0j}$ substituted for c_j and $S_{0j}\tilde{R}_{0j}$ for c_{0j}. But again, strata with $r_j = 1$ or $r_j = 0$, while informative about RD to a finite degree, make I_{ij} in (33) equal to infinity for either $i = 1$ or $i = 0$ (or both)—indicating that this approach is questionable in general, at least without resorting to Bayesian techniques.

APPENDIX III. CHI-SQUARE FUNCTION BASED ON LIKELIHOOD RATIO

When based on the likelihood ratio, the chi-square function for the comparison of two proportions is of the following general form:

$$X_P^2 = 2 \log \frac{L(r_1, r_0)}{L(\tilde{R}_1, \tilde{R}_0)}$$

$$= 2 \log \left[\left(\frac{r_1}{\tilde{R}_1}\right)^{c_1} \left(\frac{1-r_1}{1-\tilde{R}_1}\right)^{S_1 - c_1} \left(\frac{r_0}{\tilde{R}_0}\right)^{c_0} \left(\frac{1-r_0}{1-\tilde{R}_0}\right)^{S_0 - c_0} \right] \quad (38)$$

When $P = \text{RD}$, the values of $\tilde{R}_1$ and $\tilde{R}_0$ (for any given value of RD) are derived according to (26) and (28). For $P = \text{RR}$ the corresponding specifications are (29) and (12), whereas for OR they are given in (30) and (13).

The extension to stratified data is straightforward:

$$X_P^2 = 2 \log \left\{ \Pi_j \left[\left(\frac{r_{1j}}{\tilde{R}_{1j}}\right)^{c_{1j}} \left(\frac{1-r_{1j}}{1-\tilde{R}_{1j}}\right)^{S_{1j} - c_{1j}} \left(\frac{r_{0j}}{\tilde{R}_{0j}}\right)^{c_{0j}} \left(\frac{1-r_{0j}}{1-\tilde{R}_{0j}}\right)^{S_{0j} - c_{0j}} \right] \right\}$$

$$= 2\, \Sigma_j \Sigma_i \left[c_{ij} \log \frac{r_{ij}}{\tilde{R}_{ij}} + (S_{ij} - c_{ij}) \log \frac{1 - r_{ij}}{1 - \tilde{R}_{ij}} \right] \quad (39)$$

The performance of results from this approach is theoretically, and also empirically (Tables I and II), somewhat inferior to those based on the approaches advocated in the main presentation above, especially in the context of appreciable discrepancies between the empirical and theoretical rates.

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