Statistical analysis of individually matched case-control studies in epidemiology: factor under study a discrete variable taking multiple values

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Pike, M. C., Casagrande, J., and Smith, P. G. (1975). *British Journal of Preventive and Social Medicine*, **29**, 196-201. **Statistical analysis of individually matched case-control studies in epidemiology: factor under study a discrete variable taking multiple values.** It is now well established in case-control studies with individual matching that the statistical analysis must take the fact of individual matching into account. The problems of so doing have been thoroughly dealt with for the situation of the factor of interest being a two-level factor (all-or-none response) and with one or more matched controls per patient. These results are extended in this paper to the situation where the factor can assume multiple levels in studies where each patient is matched with a single control.

A method which is frequently used when selecting a control group in epidemiological studies is to choose a control subject for each case, the control being 'matched' with the case for factors which are not of direct interest in the investigation but which are known, or suspected, to be associated with the disease. In the absence of matching, these factors might confound comparisons between the case and control groups when examining the specific factor under investigation. Such individual matching is, for example, often undertaken for variables such as age, sex, social class, and area of residence.

The statistical evaluation of such investigations must take account of this matching procedure (see, for example, McNemar, 1947; Mantel and Haenszel, 1959; Billewicz, 1964; Miettinen, 1969; Pike and Morrow, 1970). As well as testing the statistical significance of observed differences in the factor of interest in case-control pairs, it is usually necessary to obtain an estimate of the relative risk (*r.r.*) associated with the factor under study.

In the most simple situation, in which *n* controls have been matched with *n* cases and the factor under study is either present or not (or can take only two values), the results of the investigation may be tabulated as in Table I. The maximum likelihood

TABLE I

Factor	Control		
	Absent	Present	
Case	Absent	n_{11} n_{12}	$n_{11} + n_{12}$
	Present	n_{21} n_{22}	$n_{21} + n_{22}$
	$n_{11} + n_{21}$	$n_{12} + n_{22}$	<i>n</i>

estimate, $\hat{f}$, of the true *r.r.*, *r*, associated with the factor is given by the ratio n_{21}/n_{12} (not $\{(n_{21} + n_{22}) / (n_{11} + n_{21})\} / \{(n_{11} + n_{12}) / (n_{12} + n_{22})\}$, which is the usual estimate of *r.r.* in studies in which there is no individual case-control matching); and the statistical significance level is calculated from the standard χ^2_1 test for equality of n_{12} and n_{21} , namely:

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$$\chi_1^2 = (|n_{21} - E(n_{21})| - \frac{1}{2})^2 / V(n_{21})$$

where

$$E(n_{21}) = \text{expected value of } n_{21} \\ = (n_{21} + n_{12})/2$$

and

$$V(n_{21}) = \text{variance of } n_{21} \\ = (n_{21} + n_{12})/4$$

(for details see Pike and Morrow, 1970).

In analysing a recent case-control study we were faced with a more general situation in which the factor under study could take more than two values. The problem may be illustrated by the fictitious data on the relationship between the ABO blood groups and a particular disease shown in Table II.

TABLE II

		Control				
Blood Group		A	B	AB	O	
Case	A	74	14	6	66	160
	B	2	4	2	4	12
	AB	10	12	2	12	36
	O	18	8	3	64	93
		104	38	13	146	301

The *r.r.* of disease for a particular blood group, say A, compared with another group, say AB, may 'crudely' be estimated as above, that is, $\hat{r}_{A,AB} = 6/10 = 0.60$. In general it will be found that these $\hat{r}$ estimates are not mutually consistent. From the above table, for example, we find

$$\hat{r}_{A,B} = 14/2 = 7.00$$

$$\hat{r}_{A,O} = 66/18 = 3.67$$

$$\hat{r}_{B,O} = 4/8 = 0.50$$

so that $\hat{r}_{A,B} \neq \hat{r}_{A,O}/\hat{r}_{B,O}$: whereas $r_{A,B}$ must equal $r_{A,O}/r_{B,O}$, that is the true *r.r.* of A compared with B must equal the true *r.r.* of A to O divided by the true *r.r.* of B to O.

This is clearly an undesirable property of these crude *r.r.* estimates and the problem of obtaining mutually consistent estimates in this situation of one to one matching and a multiple value factor is dealt with in this paper.

MAXIMUM LIKELIHOOD APPROACH

Suppose that there are *k* possible levels ($A_1, A_2, \dots, A_k$) of the factor (*A*) under study. The results of the case-control investigation may be represented as in Table III.

TABLE III

		Control			
Factor Level		A_1	A_i	A_j	A_k
Case	A_1	n_{11}	n_{1i}	n_{1j}	n_{1k}
	A_i	n_{i1}	n_{ii}	n_{ij}	n_{ik}
	A_j	n_{j1}	n_{ji}	n_{jj}	n_{jk}
	A_k	n_{k1}	n_{ki}	n_{kj}	n_{kk}

n_{ij} = number of case-control pairs in which the case was at level A_i and the control at level A_j

Let r_{ji} = *r.r.* of A_j compared with A_i . (If A_i and A_j were the only factor levels of interest, then the maximum likelihood estimate of r_{ji} would be simply n_{ji}/n_{ji} .) Define

$$r_j = r_{jk}$$

where

$$r_k = 1$$

then

$$r_{ji} = r_j / r_i \quad (1)$$

The likelihood of the n_{ij} 's conditional on the sums $(n_{ij} + n_{ji}) = N_{ij} = N_{ji}$ is proportional to

$$l = \prod_{i=1}^{k-1} \prod_{j=i+1}^k r_{ji}^{n_{ji}} / (1 + r_{ji})^{N_{ij}} \quad (2)$$

The log-likelihood function expressed in terms of the r_i 's is therefore, except for a constant, equal to

$$L_r = \sum_{i=1}^{k-1} \sum_{j=i+1}^k n_{ji} \log(r_j) - \sum \sum n_{ji} \log(r_i) \\ - \sum \sum N_{ij} \log(1 + r_j / r_i) \quad (3)$$

The first derivative of L_r with respect to r_h is

$$\delta L_r / \delta r_h = \sum_{i=1}^{h-1} \{ n_{hi} / r_h - N_{hi} / (r_i + r_h) \} \\ - \sum_{j=h+1}^k \{ n_{jh} / r_h - N_{jh} r_j / (r_h^2 + r_h r_j) \} \quad (4)$$

ESTIMATION

Maximum likelihood estimates $\hat{r}_i$'s of the r_i 's ($i=1, 2, \dots, k-1$) may be obtained by setting (4) to zero for $h=1, 2, \dots, k-1$ simultaneously.

TESTS OF SIGNIFICANCE

Approximate significance levels may be derived using likelihood ratio tests.

We may first do an overall test for evidence of the r_i 's departing from unity. If we assume that

$$r_1 = r_2 = \dots = r_{k-1} = 1 \quad (5)$$

then the log-likelihood, ignoring the constant term, is given by

$$L_1 = -\sum_{i=1}^{k-1} \sum_{j=i+1}^k N_{ij} \log(2) \quad (6)$$

Thus, if (5) holds,

$$C_1 = -2(L_r^* - L_1) \quad (7)$$

will be distributed approximately as χ^2 with $(k-1)$ degrees of freedom, where L_r^* is the value of (3) when r_i is set equal to $\hat{r}_i$ ($i=1, 2, \dots, k-1$).

CONFIDENCE INTERVALS

The log-likelihood function L_r may be far from symmetric in the r_i 's around its maximum and the derivation of approximate confidence intervals for the r_i 's is better accomplished working through the transformations

$$t_i = r_i/(1 + r_i) \quad (8)$$

(for $k=2$, t_1 is the binomial parameter for n_{12} and n_{21}).

Expressing (3) in terms of the t_i 's we have

$$\begin{aligned} L_t &= \sum \sum n_{ji} \log(t_j) - \sum \sum n_{ji} \log(1-t_j) \\ &\quad - \sum \sum n_{ji} \log(t_i) + \sum \sum n_{ji} \log(1-t_i) \\ &\quad - \sum \sum N_{ij} \log \{1 + t_j(1-t_i)/(t_i(1-t_j))\} \end{aligned} \quad (9)$$

and

$$\begin{aligned} \delta L_t / \delta t_h &= \sum_{i=1}^{h-1} \{ n_{hi}/t_h + n_{hi}/(1-t_h) \\ &\quad - N_{hi}(1-t_i)/(s_{ih}(1-t_h)) \} \\ &\quad - \sum_{j=h+1}^k \{ n_{jh}/t_h + n_{jh}/(1-t_h) \\ &\quad - N_{jh}t_j/(s_{jh}t_h) \} \end{aligned} \quad (10)$$

where $s_{ij} = t_i(1-t_j) + t_j(1-t_i)$.

$$\begin{aligned} \delta^2 L_t / \delta t_h^2 &= \sum_{i=1}^{h-1} \{ -n_{hi}/t_h^2 + n_{hi}/(1-t_h)^2 \\ &\quad - N_{ih}(1-t_i) \{ 1/(s_{ih}(1-t_h)^2) \\ &\quad - (1-2t_i)/(s_{ih}^2(1-t_h)) \} \} \\ &\quad - \sum_{j=h+1}^k \{ -n_{jh}/t_h^2 + n_{jh}/(1-t_h)^2 \\ &\quad + N_{jh}t_j \{ 1/(s_{jh}t_h^2) \\ &\quad + (1-2t_j)/(s_{jh}^2t_h) \} \} \end{aligned} \quad (11)$$

$$\delta^2 L_t / \delta t_h \delta t_g = N_{gh}/s_{gh}^2 \quad (12)$$

Now

$$E(n_{ij}) = N_{ij}t_i(1-t_j)/s_{ij} \quad (13)$$

Thus

$$E(\delta^2 L_t / \delta t_h^2) = -\sum_{i=1}^k N_{ih}t_i(1-t_i)/(s_{ih}^2(1-t_h)t_h) \quad (14)$$

$$E(\delta^2 L_t / \delta t_h \delta t_g) = N_{gh}/s_{gh}^2 \quad (15)$$

The variance-covariance matrix associated with the estimates $\hat{t}_i$ ($i=1, 2, \dots, k-1$) may be obtained by inverting the matrix of the expectations of the second partial differentials, which has diagonal elements (14) and off diagonal elements (15). Thus, by assuming approximate normality, confidence limits may be assigned to the $\hat{t}_i$'s and hence to the $\hat{r}_i$'s. In particular, in this way, the statistical significance of any one of the estimates $\hat{r}_i$ may be assessed.

We have thus assigned confidence intervals to the estimates $\hat{r}_i$ which are equal to $\hat{r}_{ik}$. To determine the confidence interval associated with $\hat{r}_{ji} = \hat{r}_j/\hat{r}_i$, it is simplest to redefine the rows and columns of Table III so that row i and row k are interchanged (and columns i and k are simultaneously reversed) and hence r_j will be redefined as r_{ji} . Confidence intervals may then be determined as above by inversion of the revised matrix of expectations of second differentials to give the variance-covariance matrix associated with the new r_j 's.

(For completeness the second derivatives of L_r with respect to the r_i 's are given in Appendix I.)

TESTING FOR CONSISTENCY

The r_i 's have been defined in such a way that mutually consistent estimates of $r.r.$ may be derived. However, it is generally desirable to test the reasonableness of this imposed restriction. In general there are $k(k-1)/2$ $r.r.$'s associated with the given problem. These are r_{ji} ($i = 1, 2, \dots, k-1$; $j = i+1, i+2, \dots, k$) and the 'unrestricted-inconsistent' maximum likelihood estimates are

$$\tilde{r}_{ji} = n_{ji}/n_{ij} \quad (16)$$

The log-likelihood, ignoring the constant term, is given by

$$L_s = \sum_{i=1}^{k-1} \sum_{j=i+1}^k n_{ji} \log(r_{ji}) - \sum \sum N_{ji} \log(1+r_{ji}) \quad (17)$$

and, if the assumption of consistent relative risks is correct, then

$$C_2 = -2(L_s^* - L_r^*) \quad (18)$$

will be distributed approximately as χ^2 with $(k-1)(k-2)/2$ degrees of freedom, where L_s^* is the value of (17) when r_{ji} is set equal to $\tilde{r}_{ji}$ ($i = 1, 2, \dots, k-1$; $j = i+1, i+2, \dots, k$) and L_r^* is the value of (3) when r_i is set equal to $\hat{r}_i$ ($i = 1, 2, \dots, k-1$).

AN EXAMPLE

For the data given in Table II let $A_1 =$ blood group A, $A_2 =$ B, $A_3 =$ AB, and $A_4 =$ O. Then

$$\tilde{r}_{1,4} = 66/18 = 3.667,$$

$$\tilde{r}_{2,4} = 4/8 = 0.500,$$

$$\tilde{r}_{3,4} = 12/3 = 4.000$$

The maximum likelihood consistent estimates are computed as (FORTRAN IV program available from authors on request):

$$\hat{r}_1 = 3.503, \hat{r}_2 = 0.559, \hat{r}_3 = 4.669$$

with

$$L_r^* = -81.40$$

$$L_s = -108.82$$

so that the overall test of significance is

$$C_1 = 54.84$$

distributed approximately as χ_3^2 ($P < 0.00001$).

$$L_2 = -81.14$$

so that the test for consistency assumption is

$$C_2 = 0.52 \sim \chi_3^2(P \div 0.90).$$

The $\hat{r}_i$'s are

$$\hat{r}_1 = 0.778, \hat{r}_2 = 0.358, \hat{r}_3 = 0.824$$

The approximate variance-covariance matrix of the $\hat{r}_i$'s is

0.001747	0.001052	0.000894
0.001052	0.009824	0.001582
0.000894	0.001582	0.003415

so that, for example, the approximate 95% confidence interval for t_2 is

$$\hat{r}_2 \pm 1.96 \sqrt{(0.009824)} \\ = 0.164, 0.552$$

Thus the approximate 95% confidence interval for r_2 is (0.196, 1.232).

An illustrative example for the case $k = 3$, which may be computed on a desk calculator, is shown in Appendix II.

DISCUSSION

The problem discussed in this paper is peculiar to studies in which there is individual matching of cases and controls, and where the matching is 'relevant', that is, affects the probabilities of the different answers.

This problem would arise, for example, in an investigation of whether there is any association between a specific disease and contraceptive practices. We might choose controls individually matched for factors such as age, parity, social class, etc. and record the type of contraceptive most used in the previous 12 months, the type being classified as, say, none, oral contraceptive, intrauterine device or other methods. The method of analysis we propose ensures that *all* of the relevant data are used in estimating the relative risks, and to do this we only have to impose the restriction that the estimates derived are mutually consistent. The method leads to a direct statistical test of this assumption, although, being based on multiple degrees of freedom, the test is not very powerful. The assumption of consistency is implicit in the commonly used, but incorrect, method of analysis which ignores the matching in deriving the relative risk estimates.

Finding that the relative risk estimates, using the paired data, are not consistent would suggest that the data should be examined for interactions between the matching variables and the relative risks. For example, if contraceptive practice was associated with the disease under study in one group but not another (say, parous or non-parous), then the relative risks might be consistent but *different* in the two

groups. If the data are tabulated ignoring parity, then the resulting relative risks based upon the pooled data would not be consistent.

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APPENDIX I

The second derivatives of L_r are

$$\delta^2 L_r / \delta r_h^2 = \sum_{i=1}^{h-1} \{ -n_{hi} / r_h^2 + N_{ih} / (r_i + r_h)^2 \} - \sum_{j=h+1}^k \{ -n_{jh} / r_h^2 + N_{hj} r_j (2r_h + r_j) / (r_h^2 + r_h r_j)^2 \} \quad (A1.1)$$

$$\delta^2 L_r / \delta r_h \delta r_g = N_{hg} / (r_g + r_h)^2 \quad (A1.2)$$

Now

$$E(n_{ij}) = N_{ij} r_i / (r_i + r_j) \quad (A1.3)$$

Thus

$$E(\delta^2 L_r / \delta r_h^2) = - \sum_{i=1}^k \sum_{i \neq h} N_{ih} r_i / \{ r_h (r_h + r_i)^2 \} \quad (A1.4)$$

$$E(\delta^2 L_r / \delta r_h \delta r_g) = N_{hg} / (r_g + r_h)^2 \quad (A1.5)$$

APPENDIX II

ILLUSTRATIVE COMPUTATION OF RELATIVE RISK ESTIMATES FOR RESPONSE VARIABLE TAKING THREE VALUES

Although the estimation procedures presented in this paper are most suitably performed on a computer, the simple case involving a response

variable taking three possible values, may be relatively easily handled on a desk calculator. These computations are illustrated below.

Suppose our study yields a table of the form:

		Control response		
		1	2	3
Case response	1	27	14	12
	2	10	34	12
	3	17	14	22

$$\begin{aligned} \text{Set: } a &= n_{13} - n_{21} = 2 & e &= n_{12} - n_{23} = 2 \\ b &= n_{21} + n_{31} = 27 & f &= n_{32} + n_{12} = 28 \\ c &= n_{31} - n_{12} = 3 & g &= n_{21} + n_{23} = 22 \\ d &= n_{12} + n_{13} = 26 & h &= n_{32} - n_{21} = 4 \end{aligned}$$

Then the equations (4) reduce to:

$$\hat{r}_1 = \hat{r}_2 (e + f \hat{r}_2) / (g - h \hat{r}_2) \quad (A2.1)$$

$$\hat{r}_2 = \hat{r}_1 (a - b \hat{r}_1) / (c \hat{r}_1 - d) \quad (A2.2)$$

Where $\hat{r}_1$ and $\hat{r}_2$ are the maximum likelihood estimates of relative risk.

The solution of (A2.1) and (A2.2) reduces to finding the real root of the cubic equation:

$$\hat{r}_2^3 + A \hat{r}_2^2 + B \hat{r}_2 + C = 0 \quad (A2.3)$$

where, if $D = f(bf - ch) = 20832$

$$\begin{aligned} \text{then } A &= [h(af - dh) + f(eb + gc) + e(fb - ch)] / D = 4656 / 20832 \\ B &= [e(ah + be) + g(ce + dh) + g(dh - af)] / D = 3600 / 20832 \\ C &= -g(dg + ae) / D = -12672 / 20832 \end{aligned}$$

(A2.3) may be simply solved using the Newton-Raphson iterative method. We first 'guess' a value for $\hat{r}_2$ - say x (in general $x = n_{23} / n_{32}$ would seem reasonable), then an improved estimate is given by

$$x - (x^3 + Ax^2 + Bx + C) / (3x^2 + 2Ax + B)$$

This procedure may be repeated until an estimate of the required accuracy is obtained. In the example, we thus obtain successive values of x of 0.857, 0.736, 0.718, 0.717, 0.717 and we may thus set $\hat{r}_2 = 0.717$ and, by substitution in (A2.1) $\hat{r}_1 = 0.827$

From equation (3)

$$\begin{aligned} L_r^* &= (n_{13} + n_{12}) \log(\hat{f}_1) + (n_{21} + n_{23}) \log(\hat{f}_2) \\ &\quad - N_{12} \log(\hat{f}_1 + \hat{f}_2) - N_{13} \log(1 + \hat{f}_1) \\ &\quad - N_{23} \log(1 + \hat{f}_2) = \underline{-54.2153} \\ &\quad \text{(note: } N_{ij} = n_{ij} + n_{ji}) \end{aligned}$$

From equation (6)

$$L_1 = -(N_{12} + N_{13} + N_{23}) \log(2) = \underline{-54.7586}$$

From equation (17)

$$\begin{aligned} L_s^* &= n_{21} \log(n_{21}/n_{12}) + n_{31} \log(n_{31}/n_{13}) \\ &\quad + n_{32} \log(n_{32}/n_{23}) - N_{21} \log(N_{21}/n_{12}) \\ &\quad - N_{31} \log(N_{31}/n_{13}) - N_{32} \log(N_{32}/n_{23}) \\ &= \underline{-53.9135} \end{aligned}$$

Thus, to test whether r_1 and r_2 differ from unity, from (7) we compute

$$C_1 = -2(L_r^* - L_1) = 1.09$$

which may be tested as χ^2 with 2 degrees of freedom. The test of consistency, from (18), is

$$C_2 = -2(L_s^* - L_r^*) = 0.60$$

which may be tested as χ^2 with 1 degree of freedom. To obtain the variances and covariance note from (8) that

$$\hat{f}_1 = \hat{f}_1 / (1 + \hat{f}_1) = 0.453$$

$$\hat{f}_2 = \hat{f}_2 / (1 + \hat{f}_2) = 0.418$$

$$\text{Let } s = \hat{f}_1(1 - \hat{f}_2) + \hat{f}_2(1 - \hat{f}_1) = 0.492$$

Then the 2×2 matrix, say M , defined by (14) and (15) is such that

$$M_{11} = (\hat{f}_2(1 - \hat{f}_2)N_{21} + s^2N_{31}) / (s^2\hat{f}_1(1 - \hat{f}_1)) = 214.375$$

$$M_{22} = (\hat{f}_1(1 - \hat{f}_1)N_{12} + s^2N_{23}) / (s^2\hat{f}_2(1 - \hat{f}_2)) = 207.862$$

$$M_{12} = M_{21} = -N_{12}/s^2 = -99.147$$

$$\text{Let } K = M_{11}M_{12} - M_{12}M_{21} = 34730.289$$

$$\text{Then } \text{Var}(\hat{f}_1) = M_{22}/K = 0.005985$$

$$\text{Var}(\hat{f}_2) = M_{11}/K = 0.006173$$

$$\text{Cov}(\hat{f}_1, \hat{f}_2) = -M_{12}/K = 0.002855$$

and approximate 95% confidence limits on $\hat{f}_1$ and $\hat{f}_2$ are:

$$t_1 = 0.453 \pm 1.96 \times 0.077 = (0.302, 0.604)$$

$$t_2 = 0.418 \pm 1.96 \times 0.079 = (0.263, 0.573)$$

and thus approximate 95% confidence limits on r_1 and r_2 are:

$$r_1 = (0.433, 1.525)$$

$$r_2 = (0.357, 1.342)$$

[noting that $r_1 = t_1/(1 - t_1)$; $r_2 = t_2/(1 - t_2)$]