Biostatistics (2003), **4**, 3, *pp.* 423–431
Printed in Great Britain

Generalized least squares for the synthesis of correlated information

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SUMMARY

This paper deals with the synthesis of information from different studies when there is lack of independence in some of the contrasts to be combined. This problem can arise in several different situations in both case-control studies and clinical trials. For efficient estimation we appeal to the method of generalized least squares to estimate the summary effect and its standard error. This method requires estimates of the covariances between those contrasts that are not independent. Although it is not possible to estimate the covariance between effects that have been adjusted for confounding factors we present a method for finding upper and lower bounds for this covariance. In the simplest discussion homogeneity of the relative risks is assumed but the method is then extended to allow for heterogeneity in an overall estimate. We then illustrate the method with several examples from an analysis in which case-control studies of cervical cancer and oral contraceptive use are synthesized.

Keywords: Case-control studies; Correlation; Meta-analysis; Overview; Overdispersion.

1. INTRODUCTION

This paper deals with some issues arising in the synthesis of information from different studies when there is lack of independence in some of the contrasts to be combined. One simple illustration arises from a series of case-control studies in which two or more distinct contrasts with a common control are to be combined. If the full data are available there would be no special problem in that a full analysis assuming the contrasts are identical could be done and, where appropriate, mutual consistency of the separate contrasts studied. Very often, however, all that is available for analysis are the relevant contrasts, log relative risks, and their estimated standard errors, typically obtained after adjusting for potential confounding variables by logistic regression.

For example, in an analysis where a series of published case-control studies of cervical cancer and oral contraceptive use were synthesized (Smith *et al.*, 2003), in most of the publications authors had presented relative risks for all types of cervical cancer combined. However, a few authors published the relative risk

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Table 1. *Two case-control studies of cervical cancer and oral contraceptive (OC) use that share the same group of controls*

	Cancer type			
	Invasive[a]		In situ[b]	
Duration of OC use	⩾10 yrs	Never	⩾10 yrs	Never
Cases	38	269	31	87
Controls	60	386	60	386
Adjusted relative risk	1.82		1.40	
Adjusted SE	0.277		0.335	
Unadjusted SE	0.222		0.251	

[a]Brinton *et al.*, 1986. [b]Jones *et al.*, 1990. Relative risks (and their standard errors) were adjusted for number of sexual partners and number of cervical smears.

associated with oral contraceptive use separately for two sub-types of cervical cancer (invasive and in situ cancers, see Table 1). Because the same control group was used to calculate the relative risk for each sub-group the two risks are not independent. As the relative risks were also adjusted for other potential confounding factors the standard errors (SEs) are inevitably somewhat greater than they would have been had there been no such adjustment (the unadjusted SE). If the risks had not been adjusted, estimation of the relative risk for both sub-types of cancer combined could easily have been obtained by the pooling of the relevant frequencies. However, due to the adjustments this would not be appropriate in the present instance.

Such issues can arise in several ways. The first is the situation just described where the risks are published for two sub-groups (such as type of cancer) relative to the same group of controls. The second situation is when some authors have published relative risks for a finer stratification of exposure than others have used. For the example of the synthesis of cervical cancer studies, most authors published relative risks for cervical cancer associated with $\leqslant 5$ years of oral contraceptive use compared with never-users. However, some authors used a finer degree of stratification of $\leqslant 2$ and 3–5 years of oral contraceptive use compared with never-users. These two relative risks are not independent as they share the same baseline comparison group of never-users of oral contraceptives.

As well as for case-control studies somewhat similar problems can arise in connection with clinical trials. Yet another possibility is the construction of a regression analysis of log risk regressed on a measure of exposure bringing together information from a number of sources each with a common control group. Greenland and Longnecker (1992) discuss this by methods similar to those used here; see Section 2.3 for further comment.

In all the above situations if the correlation between the sub-groups is ignored, i.e. a method such as standard weighted least-squares analysis is used, then the amount of information that is available will be overestimated, the summary estimate will not be quite optimal and its variance will be underestimated. Therefore, in this paper we describe a method that can be used to address this problem taking the correlation into account. In the simplest discussion homogeneity of the series is assumed. However, it is also important to check for appreciable heterogeneity. The method is, therefore, extended to allow for heterogeneity between the series that are being synthesized, revising the estimate and its uncertainty. We then illustrate the method with several examples from an analysis in which case-control studies of cervical cancer and oral contraceptive use are synthesized.

2. METHOD

2.1 *Generalized least-squares*

We start with a series of log relative risks, where appropriate adjusted for potential confounders, and denoted by $\hat{\theta}_k$ for $k = 1, \ldots, n$. Now if the separate $\hat{\theta}_k$ are independent, the covariance matrix V of the $n \times 1$ vector $\hat{\theta}$ is diagonal and is known; quite often in applications it is determined from published normal-theory-based confidence limits. If, however, two or more of the $\hat{\theta}_k$ are not independent then V is not diagonal. In fact, V will typically be block diagonal with each block corresponding to values of $\hat{\theta}_k$ with the same control.

We assume temporarily that these covariances also have been estimated and that the matrix V is therefore known. For efficient estimation we appeal to the method of generalized least-squares to estimate the summary log relative risk ($\hat{\beta}$) and its variance (var($\hat{\beta}$)) under the model $\hat{\theta} = X\beta + \epsilon$ where X is a matrix of explanatory variables. Then, in matrix notation,

$$\hat{\beta} = (X^{\mathrm{T}} V^{-1} X)^{-1} X^{\mathrm{T}} V^{-1} \hat{\theta} \tag{1}$$

and

$$\mathrm{var}(\hat{\beta}) = (X^{\mathrm{T}} V^{-1} X)^{-1}, \tag{2}$$

where

$$X = \begin{bmatrix} 1 \\ \vdots \\ 1 \end{bmatrix}, \; V = \begin{bmatrix} v_{11} & \ldots & v_{1n} \\ \vdots & & \vdots \\ v_{n1} & \ldots & v_{nn} \end{bmatrix}, \; \hat{\theta} = \begin{bmatrix} Y_1 \\ \vdots \\ Y_n \end{bmatrix}. \tag{3}$$

The off-diagonal terms v_{jk} represent the covariances between the sub-groups or studies. If all these terms are zero, because the series are all independent, then the procedure simplifies to the method of weighted least-squares. These formulae apply also when a more general linear model is fitted, specified by an appropriate X.

2.2 *Estimating the covariances*

From each publication it should be possible to extract estimates of the log relative risks ($\hat{\theta}_1, \ldots, \hat{\theta}_n$), their variances ($v_{11}, \ldots, v_{nn}$) and the numbers of exposed and unexposed cases and controls. The terms (v_{jk}), the covariances between the log relative risks for the non-independent series, will not generally be known and it is therefore necessary to estimate them from whatever data are available. If the relative risks have been adjusted for confounding variables then ideally we require an estimate of the covariance between these adjusted risks. However, the information necessary to estimate these will almost certainly not be available in the publications although it would be recoverable from the original detailed analysis, should this be available.

One possible solution is to assume that the covariance between the adjusted log relative risks is approximately equal to the covariance between the unadjusted log relative risks. Under the first situation described in the introduction, in which there are two risks estimated from two sub-types of cervical cancer relative to the same group of controls, then using the notation given in Table 2, $c_j = c_k$ and $d_j = d_k$ and the covariance (v_{jk}) between the log relative risks is approximately

$$v_{jk} = \frac{1}{c_j} + \frac{1}{d_j}. \tag{4}$$

Table 2. *Cell frequencies for the numbers of exposed and unexposed cases and controls from the two sub-groups*

	Sub-group j		Sub-group k	
	Exposed	Unexposed	Exposed	Unexposed
Cases	a_j	b_j	a_k	b_k
Controls	c_j	d_j	c_k	d_k

In the second and third situations where the two sub-groups are two categories of exposure that both share the same baseline comparison group then, using the notation in Table 2, $b_j = b_k$ and $d_j = d_k$. In this situation the covariance between the two log relative risks is approximately

$$v_{jk} = \frac{1}{b_j} + \frac{1}{d_j}. \tag{5}$$

Equations (4) and (5) follow, for example, by treating the observed counts as independent Poisson variables, and the log relative risks as contrasts among the log counts (Breslow and Day, 1980). A further possibility is that the controls in the two sub-groups are not exactly the same but rather that one group of controls is a sub-set of the other group of controls. For the cervical cancer investigation, there were two studies conducted by the World Health Organization where this situation arose. The first was a case-control study of invasive cervical cancer with 13 868 controls (WHO, 1993) and the second was a study of in situ cervical cancers for which a sub-set of 3488 of the original 13 868 controls were used (Ye *et al.*, 1995). To include both these studies in the calculation of a summary relative risk requires that this lack of independence is taken into account. In this instance the covariance between the log relative risks in these two studies is also approximately

$$v_{jk} = \frac{1}{b_j} + \frac{1}{d_j}, \tag{6}$$

where b_j and d_j are the number of exposed and un-exposed controls in the first (i.e. the larger) study.

2.3 *Upper and lower bounds for the covariance estimates*

Although it is not possible to estimate the covariance between the adjusted relative risks it is possible to find upper and lower bounds for it. These bounds can then be entered into the calculations to assess the sensitivity of $\hat{\beta}$, var($\hat{\beta}$) and the heterogeneity test (Q) (see Section 2.4) to a range of possible covariances.

It can be shown that for any logistic regression in which the regression effects are relatively small, the sampling errors in the resulting estimates are of the same general form as in ordinary least-squares theory. Thus if $\hat{\theta}_A$, $\hat{\theta}_U$ are the adjusted and unadjusted log relative risks then

$$\hat{\theta}_A = \hat{\theta}_U + \hat{\gamma}, \tag{7}$$

where $\hat{\gamma}$ is an estimated adjustment. We can therefore arrange that $\hat{\gamma}$ is essentially like a regression correction in analysis of covariance, so that cov($\hat{\gamma}$, $\hat{\theta}_U$) ≈ 0. Further, $\hat{\gamma}$ has essentially the form

$$\hat{\gamma} = -\hat{\lambda}^T z, \tag{8}$$

where $\hat{\lambda}$ is an estimated vector of regression coefficients and the elements of the vector z specify the mean differences between cases and controls in the variables used for adjustment. Then

$$\text{var}(\hat{\theta}_A) = \text{var}(\hat{\theta}_U) + \text{var}(\hat{\gamma}), \tag{9}$$

where $\mathrm{var}(\hat{\gamma}) = z^T \mathrm{cov}(\hat{\lambda}) z$. In the context considered here the major complication arises because $\hat{\lambda}$ and z are typically not available; were they available a more detailed analysis would, of course, be feasible. We can, however, use the value of $\mathrm{var}(\hat{\theta}_{\mathrm{A}})$ obtained from the published data combined with $\mathrm{var}(\hat{\theta}_{\mathrm{U}})$ derived directly from the observed frequencies to obtain $\mathrm{var}(\hat{\gamma})$ by subtraction.

However, it is more difficult to calculate the covariance between two estimates $\hat{\theta}_{\mathrm{A}j}, \hat{\theta}_{\mathrm{A}k}$, say with a common control. Then

$$\mathrm{cov}(\hat{\theta}_{\mathrm{A}j}, \hat{\theta}_{\mathrm{A}k}) = \mathrm{cov}(\hat{\theta}_{\mathrm{U}j}, \hat{\theta}_{\mathrm{U}k}) + \mathrm{cov}(\hat{\gamma}_j, \hat{\gamma}_k) \tag{10}$$

and again $\mathrm{cov}(\hat{\theta}_{\mathrm{U}j}, \hat{\theta}_{\mathrm{U}k})$ can be calculated from the frequencies (as described in Section 2.2). It is conceivable that the two adjustments are derived from different explanatory variables. In that case it is impossible to make a detailed calculation of $\mathrm{cov}(\hat{\gamma}_j, \hat{\gamma}_k)$. If, however, a common set of explanatory variables and a single regression coefficient are used then we have that

$$\mathrm{cov}(\hat{\gamma}_j, \hat{\gamma}_k) = z_j^T \mathrm{cov}(\hat{\lambda}) z_k \tag{11}$$

so that by the Cauchy–Schwarz inequality

$$-\sqrt{\{\mathrm{var}(\hat{\gamma}_j)\mathrm{var}(\hat{\gamma}_k)\}} \leqslant \mathrm{cov}(\hat{\gamma}_j, \hat{\gamma}_k) \leqslant \sqrt{\{\mathrm{var}(\hat{\gamma}_j)\mathrm{var}(\hat{\gamma}_k)\}}. \tag{12}$$

In the Examples that follow we have used this to bound the variances of interest, namely the variance of the optimal linear combination of $\hat{\theta}_{\mathrm{A}j}$ and $\hat{\theta}_{\mathrm{A}k}$.

Because the adjustments to the crude estimates depend on the discrepancies between cases and controls in the explanatory variables, the directions of these discrepancies in the two or more groups of cases may tend to be in the same direction. This makes a positive covariance in (12) more likely than a negative covariance, although there is no necessity for this. This is one reason for preferring the upper bound on the variance of the estimated contrast to the lower bound. While we have not proved this formally it is likely that the worst case for the variance of the overall estimate arises when the individual covariance estimates are all taken at their upper limits. Greenland and Longnecker (1992), in their treatment of this issue uses a correlation approximately equivalent to

$$\frac{\mathrm{cov}(\hat{\theta}_{\mathrm{A}j}, \hat{\theta}_{\mathrm{A}k})}{\sqrt{\{\mathrm{var}(\hat{\theta}_{\mathrm{A}j})\mathrm{var}(\hat{\theta}_{\mathrm{A}k})\}}} = \frac{\mathrm{cov}(\hat{\theta}_{\mathrm{U}j}, \hat{\theta}_{\mathrm{U}k})}{\sqrt{\{\mathrm{var}(\hat{\theta}_{\mathrm{U}j})\mathrm{var}(\hat{\theta}_{\mathrm{U}k})\}}}. \tag{13}$$

As noted above, the covariance depends on the relations between the explanatory variables in the groups under comparison and we have preferred the cautious route of taking this as unknown.

2.4 *Heterogeneity*

With the same assumptions regarding the elements of the covariance matrix V, then under the method of generalized least-squares the test statistic Q for heterogeneity between the series of estimates is

$$Q = (\hat{\theta} - X^{\mathrm{T}}\hat{\beta})V^{-1}(\hat{\theta} - X^{\mathrm{T}}\hat{\beta}), \tag{14}$$

where Q is, under the null hypothesis, distributed approximately as chi-squared with $n - 1$ degrees of freedom. If significant heterogeneity is detected then it may be appropriate to use a random effects model to re-estimate the summary effect and its variance taking into account this between-series component of variance. This heterogeneity may be due to true differences between the risks or to differences in study design, type of controls, data collection methods or data quality. For a critical review of some of the issues involved in the present context, see Cox and Solomon (2002, Section 4.5).

Such over-dispersion can be taken into account by recalculating $\hat{\beta}$ and var($\hat{\beta}$) under the model $\hat{\theta} = X\beta^* + \eta + \epsilon$ where $E(\eta\eta^{\mathrm{T}}) = \sigma_\eta^2 I$ and $E(\epsilon\epsilon^{\mathrm{T}}) = V$. It can then be shown that

$$E(Q) = (n-1) + \sigma_\eta^2[\mathrm{tr}(V^{-1}) - \mathrm{tr}(V^{-1}X(X^{\mathrm{T}}V^{-1}X)^{-1}X^{\mathrm{T}}V^{-1})] \tag{15}$$

therefore

$$\hat{\sigma_\eta^2} = \frac{Q-(n-1)}{\mathrm{tr}(V^{-1}) - \mathrm{tr}(V^{-1}X(X^{\mathrm{T}}V^{-1}X)^{-1}X^{\mathrm{T}}V^{-1})}. \tag{16}$$

where tr denotes the trace of a matrix. We then replace V in equations (1) and (2) with $V^* = V + \sigma_\eta^2 I$ so that under the new model

$$\hat{\beta^*} = [X^{\mathrm{T}}(V^*)^{-1}X]^{-1}X^{\mathrm{T}}(V^*)^{-1}\hat{\theta} \tag{17}$$

$$\mathrm{var}(\hat{\beta^*}) = [X^{\mathrm{T}}(V^*)^{-1}X]^{-1}, \tag{18}$$

and Q is redefined with the covariance matrix V^* and corresponding estimate $\hat{\beta^*}$. These estimates are not fully efficient statistically although, provided that any overdispersion is relatively small, the estimates are unlikely to be capable of appreciable improvement. One route to an efficient estimate is to iterate to convergence using a new form of Q with a revised covariance matrix.

3. EXAMPLES

Individual patient data from the UK cervical cancer study (Berrington *et al.*, 2002) were used to investigate the performance of our method in practice. From these data log relative risks were estimated for four risk factors using the individual patient data with adjustment for various confounding factors. These are referred to as the 'actual values'. Then each of these risk factors were divided into two strata and the log relative risks calculated for each. For example, for oral contraceptive use, <5 years of use was divided into $\leqslant 2$ and 3–4 years of use. These two strata are not independent as they both share the same baseline group of never-users of oral contraceptives. The two strata were then recombined using the method described in this paper, first using the unadjusted covariance estimates (see Section 2.2) then using the lower and upper bounds for the covariance (see Section 2.3). These values are referred to as the 'estimated values'. The 'actual value' and the three 'estimated values' for each risk factor are shown in Table 3.

For oral contraceptive use, the log relative risks (and SE) associated with $\leqslant 2$ and 3–4 years of oral contraceptive use compared with never-users were 0.121 (0.408) and 0.232 (0.431) respectively. The 'actual' log relative risk associated with <5 years of oral contraceptive was 0.165 with a SE of 0.387 (Table 3). The method of generalized least-squares with the unadjusted covariance gives an 'estimated' log relative risk associated with <5 years of oral contraceptive of 0.169, which is slightly higher than the 'actual value' of 0.165, with a SE of 0.373, slightly lower than the 'actual value' of 0.387. For three of the four risk factors in this example the estimated SE based on the upper bound for the covariance were the closest to the 'actual values'. For all four risk factors the upper covariance bound gave the highest, and hence most conservative, error estimate.

The method was then applied to the synthesis of cervical cancer case-control studies mentioned in the introduction, the results of which have been published elsewhere (Smith *et al.*, 2003). Briefly, the aim of the study was to synthesise the risks of cervical cancer associated with short (<5 years), medium (5–9 years) and long (10+ years) duration of oral contraceptive use. First, relative risks of cervical cancer and

Table 3. *Actual and estimated adjusted relative risks for cervical cancer associated with various risk factors*

	Unadjusted values		Actual values	Estimated values		
Risk factor[a]	SE(logRR)	cov(logRR)	logRR (SE)	Unadjusted cov. logRR (SE)	Lower bound cov. logRR (SE)	Upper bound cov. logRR (SE)
OC use (<5[b] years/never)	0.352	0.104	0.165 (0.387)	0.169 (0.373)	0.171 (0.352)	0.163 (0.392)
Smoking (ever[c]/never)	0.173	0.018	-0.210 (0.200)	-0.223 (0.193)	-0.225 (0.176)	-0.177 (0.206)
AFI (⩽16[d] yrs/⩾20 yrs)	0.251	0.049	1.055 (0.289)	1.015 (0.276)	0.989 (0.253)	1.079 (0.294)
Negative smears (1+[e]/0)	0.171	0.014	-0.842 (0.191)	-0.841 (0.186)	-0.839 (0.173)	-0.843 (0.198)

[a] Data are from the UK national case-control study of cervical cancer (Berrington *et al.*, 2002) all risks are adjusted for age, number of sexual partners, and each of the risk factors above. The two strata that were combined for each risk factor were [b] ⩽2 and 3–4 years of oral contraceptive use, [c] 1–9 yrs and 10+ yrs of smoking, [d] age at first intercourse (AFI) ⩽16 and 16–17 years, and [e] number of previous negative smears 1 and ⩾2.

their 95% confidence intervals associated with short duration of oral contraceptive use (<5 years) were extracted from publications. However, 25 of the 31 risks associated with short duration of use were found not to be independent for one or other of the reasons discussed in the introduction. Also, as there are many important confounding factors that may affect the association between oral contraceptive use and cervical cancer risk, all the risks had been adjusted for factors such as smoking and number of cervical smears.

Table 4 shows the comparison of the estimates of the summary log relative risks for short duration of oral contraceptive use (<5 years) from these 31 studies estimated first using the method of weighted least-squares (WLS) which incorrectly assumed that all the studies were independent and then using the method of generalized least-squares (GLS) taking into account the fact that many of the *n* studies were not independent. Three estimates for the method of GLS are shown, first using the unadjusted covariance estimates for all the non-independent studies, second using lower bounds for the covariances and third using upper bounds for the covariances. The values of Q for the fixed-effects model are considerably larger than the expected value, 31, and provide very strong evidence of additional variability. Therefore, the analysis was repeated using a random-effects model. The same method was then applied to estimate the summary relative risk for the 14 studies that published risks associated with long duration of oral contraceptive use (10+ years), six of which were not independent (Table 5). Note that while Q for the fixed-effects model exceeds its expectation, the evidence for over-dispersion from Table 5 on its own is less strong. Nevertheless, for comparability the random effects analysis is reported here also.

In the fixed-effects analysis of short duration of use, in which 25 of 31 risks were not independent, the SE of the log relative risk obtained using the upper covariance bounds was just slightly larger than that from the unadjusted covariances. In the random-effects analysis this difference was somewhat greater. In the analysis of long duration of use, in which only six of the 14 studies were not independent, the pattern was similar but the differences between the estimated SEs were smaller. The relatively small but systematic differences between the point estimates obtained in fixed- and random-effects analysis reflect the somewhat reduced relative weight given to the large studies in the second form.

Table 4. *Log relative risk (*logRR*) of cervical cancer associated with <5 years oral contraceptive use*

Model	Method	n	logRR (SE)	Q
Fixed effects	WLS[a]	31	0.1164 (0.0312)	58.9
	GLS (unadjusted cov)[b]	31	0.1016 (0.0346)	56.9
	GLS (upper bound cov)[c]	31	0.1070 (0.0359)	104.8
	GLS (lower bound cov)[d]	31	0.0930 (0.0316)	73.4
Random effects	WLS	31	0.0989 (0.0564)	39.1
	GLS (unadjusted cov)	31	0.0873 (0.0571)	39.8
	GLS (upper bound cov)	31	0.0893 (0.0708)	39.0
	GLS (lower bound cov)	31	0.1001 (0.0577)	39.3

[a]Weighted least-squares. [b]Generalized least-squares using the unadjusted covariance estimates, [c]using the upper bound for each of the covariance estimates and [d]using the lower bound for each of the covariance estimates. Measure of dispersion Q: approximately chi-squared with $n-1$ degrees of freedom.

Table 5. *Log relative risk (*logRR*) of cervical cancer associated with ⩾10 years oral contraceptive use*

Model	Method	n	logRR (SE)	Q
Fixed effects	WLS[a]	14	0.6844 (0.0681)	20.5
	GLS (unadjusted cov)[b]	14	0.6866 (0.0698)	19.6
	GLS (upper bound cov)[c]	14	0.6813 (0.0717)	20.2
	GLS (lower bound cov)[d]	14	0.6902 (0.0668)	20.1
Random effects	WLS	14	0.6269 (0.0986)	15.6
	GLS (unadjusted cov)	14	0.6374 (0.0969)	15.5
	GLS (upper bound cov)	14	0.6341 (0.0991)	15.7
	GLS (lower bound cov)	14	0.6354 (0.0960)	15.5

[a]Weighted least-squares. [b]Generalized least-squares using the unadjusted covariance estimates, [c]using the upper bound for each of the covariance estimates and [d]using the lower bound for each of the covariance estimates. Measure of dispersion Q: approximately chi-squared with $n-1$ degrees of freedom.

4. DISCUSSION

There is an extensive literature on the many different problems that are encountered during the synthesis of published data, see for example Brumback *et al.* (2000). In this paper we have presented a method for dealing with one such problem, that is the synthesis of information from different studies when there is lack of independence in some of the contrasts to be combined. We have given three answers, all based on generalized least-squares but using three different estimates of the covariances involved. For general use we recommend the approach using the upper bound on the covariances. There are several reasons for this. Firstly, it is likely to give the most cautious assessment of error and this is sensible on general grounds. Secondly, we have already noted below (12) that positive covariances are more likely than negative ones. Finally, in our empirical comparison based on Table 3 it gives results closest to the estimates and SEs based on the full information, thus confirming in that situation the general theoretical point just alluded to. Note that these considerations concern the SE of the estimated log RR; the estimates

themselves differ by amounts that are small compared with the relevant SEs and we can see no simple basis for choosing between them.

A further point to note with respect to the random-effects model is that using all the upper or all the lowest covariance bounds does not necessarily provide the most extreme estimates of the possible error of the log relative risk. Some combinations of covariance estimates could give more extreme results. Estimates under every possible permutation of covariance estimates (unadjusted, upper and lower bound) would be needed to find the most extreme results. However, as discussed above, we recommend the approach using the upper bound for the covariances along with a sensitivity analysis to assess the magnitude of the effect that the use of the lower bounds or the unadjusted covariance estimates has on the summary log relative risk and its SE. In most applications it is likely that the conclusions will not be sensitive to these choices.

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[*Received July 8, 2002; revised October 31, 2002; accepted for publication November 14, 2002*]