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Assessing the combined effect of asbestos exposure and smoking on lung cancer: A Bayesian approach

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SUMMARY

We review the literature on the combined association between lung cancer and two environmental exposures, asbestos exposure and smoking, and explore a Bayesian approach to assess evidence of interaction between the exposures. The meta-analysis combines separate indices of additive and multiplicative relationships and multivariate relative risk estimates. By making inferences on posterior probabilities we can explore both the form and strength of interaction. This analysis may be more informative than providing evidence to support one relation over another on the basis of statistical significance. Overall, we find evidence for a more than additive and less than multiplicative relation. Copyright © 2006 John Wiley & Sons, Ltd.

KEY WORDS: Bayesian; interaction; meta-analysis; asbestos; smoking; lung cancer

1. INTRODUCTION

There is well-documented evidence indicating that both long-term exposure to asbestos and active smoking are independent risk factors for lung cancer. The statistical form of their combined effect is less clear. The question of interest here is whether the risk from exposure to both asbestos and smoking is an additive, multiplicative or other relation of the risk from exposure to each factor alone.

Methodologies for assessing the relationship between risk factors have been the subject of much research [1–3]. As well as interpreting interaction in the context of classical relative risk models [4] recent studies have explored the viability of non-parametric models [5].

Evidence for a multiplicative association between exposure to asbestos and active smoking and the outcome of lung cancer was indicated by an early study of U.S. workers [6]. Subsequent

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studies and reviews of the literature with an objective to assess the form of the relationship further have indicated mixed results, ranging from mixed evidence for either an additive or multiplicative relation to strong evidence for a supramultiplicative relation [1, 7–9].

The importance of understanding the combined effect of asbestos exposure and smoking can be placed in both a public health and legal context. From a public health perspective, evidence for a multiplicative relation between asbestos exposure and smoking has lead to recommendations for asbestos-exposed smokers to quit smoking, since cases of lung cancer induced by both exposures would be prevented, along with those induced by smoking alone [10]. In a legal context, a greater understanding of the combined effect has been required in the attribution of damages in cases where there is a history of exposure to both asbestos and smoking [11].

The objective of this paper is to review the evidence for the combined effect of smoking and asbestos, the relationship of which is frequently debated in epidemiology, and to propose a Bayesian approach for combining this information. The strength of the Bayesian approach, in this context, is twofold. First, through the hierarchical structure of likelihoods and priors, informed opinion about variance structures and relationships between studies and outcomes can be integrated with the observed data. The second is the ability to make useful probability statements on the basis of all information, rather than simple significance statements based on specific hypothesis tests.

2. ASSESSING INTERACTION BETWEEN ASBESTOS AND SMOKING

While a conceptual basis for assessing interaction between two risk factors is well known [12], in general, tests for interaction and the interpretation of results are less well understood [13]. Incorrect approaches to assess interaction appear frequently in the literature [14]. Further, as many studies are underpowered to assess interaction, assessments of strength of interaction, rather than statistical significance may be important [1].

A conceptual basis for understanding interaction between risk factors is found in Rothman's [15] component sufficient-cause paradigm of disease causation. Under this paradigm, synergistic or positive interaction occurs if two exposures are component causes in the same sufficient cause. In the context of this study, a case for synergistic interaction can be made if some persons develop lung cancer only under exposure to both asbestos and smoking.

A synergistic interaction effect, in the biological sense, is tested by departure from additivity of absolute effects. That is, the relative excess risk among those with combined exposure should exceed the sum of the relative excess risks for each of the component causes, referenced to those not exposed to both causes. This description is analogous to the basis for the synergy index (S) introduced by Rothman [16] and outlined in the next section.

Hallqvist *et al.* [14] describe some of the problems with approaches which have been used in the literature. For example, an inappropriate approach is to compare a higher cumulative incidence of a joint exposure to that observed for either risk factor separately and infer that one risk factor is exacerbating the effect of the other, since the relationship of each risk factor to a joint exposure may be less than additive. Another common approach to assessing interaction is to include a product term in a logistic or log-linear regression. As both types of regressions assume a multiplicative form, including an interaction term assesses departure from a simple multiplicative model but provides no information in support of an additive relation.

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2.1. Synergy index (S)

A common test for an additive relation used in the epidemiological literature is the synergy index (S). The theoretical basis for S has been well described [15, 16]. Here we present the methodology as outlined by Rothman [15].

Suppose that there are two independently acting causal agents, in this case say A for asbestos and S for smoking, and underlying (background) causes denoted collectively as C, also independent of A and S. Then,

$$P_T = P_A + P_S + P_C - P_A P_S - P_A P_C - P_S P_C + P_A P_S P_C \tag{1}$$

where P denotes the probability that a disease develops alone (with appropriate subscripts), and the subscript T denotes the total probability (where A, S and C are present). The combined or joint effect of A and S on the probability of disease (risk) is given by $P_T - P_C$, i.e. $P_A + P_S - P_A P_S - P_A P_C - P_S P_C + P_A P_S P_C$ (under independence).

Using risk notation, define $R_{AS} = P_T$, $R_{00} = P_C$, $R_A = P_A + P_C - P_A P_C$ and $R_S = P_S + P_C - P_S P_C$. Assuming that P_A and P_S are small (the implications of this are discussed by Wildner and Markuzzi [17]), this can be simplified to

$$P_T - P_C \cong P_A + P_S \tag{2}$$

which in risk notation becomes

$$R_{AS} - R_{00} \cong R_A + R_S - 2R_{00} \tag{3}$$

Equation (3) can be expressed in relative risk terms (by dividing each term by R_{00}), which can then be defined as a synergy index (S),

$$S = \frac{\mathrm{RR}_{AS} - 1}{\mathrm{RR}_S + \mathrm{RR}_A - 2} = \frac{\mathrm{ERR}_{AS}}{\mathrm{ERR}_A + \mathrm{ERR}_S} \tag{4}$$

where ERR is the excess relative risk. Thus, positive interaction or synergy is observed if the relative risk attributable to combined exposure exceeds the sum of the risks attributable to each exposure separately. Alternatively, S can be interpreted as the excess risk from exposure (to both exposures) when there is interaction relative to the excess risk from exposure (to both exposures) without interaction. Under the additive hypothesis $S = 1$, whereas for a more than additive model $S > 1$ and a less than additive model is reflected by $S < 1$. On the basis of S, estimates can be obtained of the attributable proportion of risk due to interaction, $\mathrm{API} = S/(S-1)$ [18]. The API expresses the proportion of lung cancer risk for those exposed to both factors (including background risk) that can be attributed to the combined (as distinct from the separate) effects of the two factors. The calculation for the standard error of S is described in the Appendix.

2.2. Multiplicativity index (V)

A common test for a multiplicative relation is to include an interaction term in a logistic or log-linear model [19]. Alternatively, in a recent review of the literature, Lee [3] defines and uses a 'test of multiplicativity'. Since this is not strictly a test we use this here in the equivalent sense of a multiplicativity index.

Following Lee [3], for a multiplicative relation to hold, the product of risks for R_{00} and R_{AS} should equal that for R_A and R_S:

$$R_{AS} R_{00} = R_A R_S \tag{5}$$

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or in relative risk terms (by dividing by R_{00})

$$\mathrm{RR_{AS}} = \mathrm{RR_S RR_A} \tag{6}$$

The multiplicativity index (V) is simply then,

$$V = \frac{\mathrm{RR_{AS}}}{\mathrm{RR_S RR_A}} \tag{7}$$

Under the multiplicative hypothesis $V = 1$, whereas for a more than multiplicative model (e.g. an exponential relation) $V > 1$, and for a less than multiplicative model $V < 1$. The calculation for the standard error of V is described in the Appendix.

Note that there is no specific value of S that corresponds to a multiplicative model. Similarly, there is no specific value of V that corresponds to an additive model. Therefore, neither index confirms one model and rejects the other, but an investigation of both indices together provides an assessment of the degree of support for additive or multiplicative relationships.

2.3. The relationship between exposure to asbestos and smoking

In the earliest reported assessment of the interaction between exposure to asbestos and smoking on lung cancer, Doll found some evidence for a multiplicative hypothesis, although it was 'far from convincing' [20]. Subsequent reviews by Saracci [1, 21, 22] and Erren *et al.* [7] indicated evidence in support of the multiplicative hypothesis, while evidence from Berry *et al.* [23] was inconclusive. Consistent with the evidence from a number of studies, two recent reviews of the literature by Lee [3] and Liddell [2] arrived at slightly different conclusions as to the form of the combined effect. Lee [24] found little evidence to reject a multiplicative relation: 'The asbestos relative risk may be somewhat lower in smokers than non-smokers, but the available data do not clearly reject the simple multiplicative relation. More complex models of joint action might indeed fit the data better, but in view of the general problems with the data, it seems doubtful whether more detailed statistical analysis would shed any greater insight.' (p. 496). However, Liddell [25] highlighted differences in the results of the case–control *versus* cohort studies, finding evidence against a simple multiplicative hypothesis. 'Therefore, the multiplicative hypothesis is not generally satisfactory. Nor, of course, is the additive hypothesis, although it does fit some data sets very well. Evidently, interaction takes several forms.' (p. 495).

Both authors agreed that the form of the combined effect is more than a simple additive relation, but the strength and nature of the more complex association was not unanimously determined.

3. METHODS

3.1. Studies

In our assessment of the interaction between exposure to asbestos and smoking we restrict our attention to the set of studies included in two recent reviews of the literature by Lee [3] and Liddell [2], as it is here that the debate over the relationship between asbestos exposure and smoking crystallized. The inclusion of these studies also allows a comparison of results from the approaches explored in this paper. A full search of the MEDLINE reference database (1966–May 2004) was performed to confirm the information on the studies included in the two reviews and to assess the influence of results from studies published since then. Details and results of studies

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published after 1998 are provided in the discussion section. Details of studies up to and including the reviews by Lee and Liddell (1966–1998) are shown in Table I.

A summary of the relevant results from studies which provided enough information to estimate relative risk of lung cancer for each exposure category is given in Table II. Differences in results between studies can be partly explained by variability in exposure levels for both asbestos and smoking. For example, some of the studies included ex-smokers and light smokers in the non-smoking group. The variability in exposure levels is discussed further in Section 5, and addressed in the sensitivity analysis (Section 4.1). Our review found much variability both in the use of formal statistical methods to assess the combined effect, and the conclusions reached. The statistical methods to assess interaction ranged from visually comparing relative risk estimates for exposure groups to more formal significance testing. There was no consistent conclusion in favour of either an additive or multiplicative relation.

Lee [3, 24] and Liddell [2, 25] described their criteria for excluding studies, with many studies excluded for insufficient reporting of exposure levels, and absences of lung cancer cases in the non-smoking group. The set of studies for which there was some agreement on their inclusion (see Reference [24, p. 495, Table I, Studies 1–12, 14–19]) are identified and numbered in the right-hand column of Table I.

3.2. Methods to assess interaction

3.2.1. Bayesian meta-analysis of V and S. We are interested in an overall estimate of the combined effect of asbestos and smoking using estimates from each study. The main advantage of which is to 'borrow strength' across studies, in order to gain greater precision for the estimate of the variable of interest, in this case S and V. For each study we estimate the value of S and V using equations (4) and (7), respectively, and their associated variances as outlined above. The information given by Study 11 was insufficient to calculate an appropriate estimate for the variance of S, and hence we excluded the estimate from this study in estimating the overall measure. The influence of this exclusion on the overall results is presented separately in Section 4.

Consider first a hierarchical model for S. We suppose that we have k studies, and that

$$Y_i = \text{observed } \log(s_i)$$

$$\theta_i = \text{true } \log(s_i) \text{ for study } i,\ i = 1, \ldots, k$$

where s_i denotes the synergy index for the ith study. Following Dumouchel [26] for the univariate analysis, we make the following distributional assumptions:

$$Y|\theta, \sigma \sim \mathrm{N}(\theta, \sigma^2 C)$$

$$\sigma^{-2} \sim \chi^2(\mathrm{d}f_\sigma)/\mathrm{d}f_\sigma$$

and

$$\theta|\mu, \tau \sim \mathrm{N}(X\mu, \tau^2 V)$$

$$\mu|\tau \sim \mathrm{N}(0, D \to \infty)$$

$$\tau^{-2} \sim \chi^2(\mathrm{d}f_\tau)/\mathrm{d}f_\tau$$

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Table I. Details of studies used for statistical analysis.

Author	Location	Study type and population	Period followed	Study ref.*
Selikoff and Hammond (1975)	Cohort 1: New York and Newark NJ, Cohort 2: U.S.A. and Canada	Cohort. Asbestos insulation workers	Cohort 1: 1963–1973, Cohort 2: 1967–1972	13
Martischnig *et al.* (1977)	Gateshead, England	Hospital CC in shipbuilding area	1972–1973	2
Blot *et al.* (1978)	Georgia, U.S.A.	Hospital CC in shipbuilding area	1970–1976	7
Hammond *et al.* (1979)	U.S.A. and Canada	Cohort. Asbestos insulation workers	1967–1976	15
Blot *et al.* (1980)	Virginia, U.S.A.	Hospital CC in shipbuilding area	1972–1976	8
Selikoff *et al.* (1980)	New Jersey, U.S.A.	Cohort. Amosite asbestos factory workers	1961–1977	14
Blot *et al.* (1982)	Florida, U.S.A.	Hospital-based CC in shipbuilding area	1970–1975	9
Liddell *et al.* (1984)	Quebec, Canada	Cohort. Chrysotile miners and millersa	1967–1975	17
Pastorino *et al.* (1984)	Lombardy, Italy	CC in industrial areas	1976–1979	3, 4
Berry *et al.* (1985)	East London, England	Cohort. Asbestos factory workers	1960–1970, 1971–1980	16, 18
Kjuus *et al.* (1986)	Telemark and Vestfold, Norway	Hospital CC in industrial and shipbuilding areas	1979–1983	6
de Klerk *et al.* (1991)	Wittenoom, Australia	Nested CC in crocidolite miners and millers	1979–1986	1
Bovenzi *et al.* (1993)	Trieste, Italy	Decedent CC in industrial and shipbuilding area	1979–1981, 1985–1986	5
McDonald *et al.* (1993)	Quebec, Canada	Cohort. Chrysotile miners and millers	1950–1992	10
Zhu and Wang (1993)	8 factories, China	Cohort. Chrysotile asbestos products workers	1972–1986	11
Meurman *et al.* (1994)	North Savo, Finland	Anthophyllite miners	1953–1991	12

Note: *Study numbering for the purposes of this statistical review (as used by Lee [24], except Studies 14–19 are referenced here as Studies 13–18), and in Table II. For study references, see Reference [3].

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Table II. Reported results of studies.

Study	Author	Observed relative risk estimates (95% CI)			Covariance of relative risk estimates
		RR_S	RR_A	RR_{AS}	
1	deKlerk	3.44 (0.74, 16.01)	2.24 (0.41, 12.28)	9.57 (2.25, 40.65)	1.65
2	Martischnig	1.78 (0.75, 4.20)	1.08 (0.19, 6.05)	5.57 (2.04, 15.18)	1.17
3	Pastorino, no PAH	5.47 (0.40, 74.20)	2.82 (0.04, 188.22)	9.86 (0.69, 140.09)	5.50
4	Pastorino, PAH	6.93 (0.30, 159.08)	2.21 (0.02, 206.42)	15.50 (0.63, 380.37)	11.72
5	Bovenzi	10.13 (1.13, 91.06)	1.83 (0.10, 33.82)	15.89 (1.77, 142.80)	3.45
6	Kjuus	5.41 (2.09, 13.99)	2.41 (0.46, 12.50)	19.86 (5.57, 70.78)	1.21
7	Blot, Georgia	4.71 (2.27, 9.77)	1.28 (0.27, 6.01)	7.58 (3.31, 17.35)	1.13
8	Blot, Virginia	3.09 (1.43, 6.70)	1.88 (0.64, 5.50)	4.87 (2.04, 11.58)	1.14
9	Blot, Florida	6.01 (1.45, 24.92)	1.80 (0.14, 22.85)	7.79 (1.77, 34.18)	1.66
10	McDonald	4.46 (2.34, 8.48)	1.65 (0.70, 3.88)	4.51 (2.38, 8.57)	1.11
11	Zhu	1.83 (0.58, 5.76)	3.78 (1.25, 11.37)	11.06 (3.87, 31.62)	1.32
12	Meurman	6.27 (0.82, 48.25)	0.83 (0.05, 13.22)	6.16 (0.85, 44.78)	2.72
13	Selikoff and Hammond	7.13 (4.20, 12.11)	8.47 (1.92, 37.25)	73.73 (40.47, 134.33)	1.07
14	Selikoff	8.67 (5.11, 14.71)	25.00 (9.00, 69.41)	40.63 (22.30, 74.01)	1.07
15	Hammond	10.85 (6.39, 18.41)	5.17 (2.17, 12.32)	53.24 (31.11, 91.12)	1.06
16	Berry, 1971–1980 M + F	7.13 (4.20, 12.11)	7.27 (2.39, 22.09)	17.25 (9.75, 30.52)	1.06
17	Liddell	4.94 (0.14, 172.43)	2.98 (0.07, 127.77)	8.21 (0.24, 279.28)	24.62
18	Berry, 1960–1970 F	7.13 (4.20, 12.11)	5.00 (0.66, 38.02)	52.56 (25.06, 110.25)	1.06

where C and V are $k \times k$ observed and prior variance–covariance matrices, respectively, and the degrees of freedom df_σ and df_τ indicate how well C and V, respectively, are known. Again following Dumouchel, we assume the studies are independent and take V to be the $k \times k$ identity matrix, and we take C to be a diagonal matrix with the corresponding diagonal entries the variances of the individual observations Y_i. For a general discussion on these assumptions see Tweedie *et al.* [27]. X is a vector of 1's and μ is the mean log synergy index for all studies combined. The notation $D \to \infty$ indicates that the elements of D are very large and tending to infinity.

The hierarchical model for V is the same as that for S, with obvious changes of notation.

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We initially conservatively assume that $df_\sigma = 79$, to reflect the average number of jointly exposed cases, and $df_\tau = 10$ to acknowledge there is little information about study–behaviour. In Section 4.1 we test the sensitivity of these assumptions.

The models were run using a Gibbs sampling algorithm in the software package WinBUGS [28]. For each analysis, estimates were based on 30 000 iterations, after a burn in of 20 000 cycles. Convergence was assessed by examining Monte-Carlo error estimates and Gelman–Rubin statistics [29].

3.2.2. Bayesian multivariate analysis of relative risks. Here Y_i is a vector $(\log(\mathrm{RR_{AS}}), \log(\mathrm{RR_A}), \log(\mathrm{RR_S}))$ observed for each study i, $i = 1, \ldots, k$. The multivariate normal distribution is denoted as MVN.

For the multivariate analysis, we make the following distributional assumptions:

$$Y_i \sim \mathrm{MVN}(\theta_i, C_i)$$

$$\theta_i \sim \mathrm{MVN}(\mu, \Sigma)$$

$$C_i^{-1} \sim \mathrm{Wishart}(R, 3)$$

and

$$\mu \sim \mathrm{MVN}(0, D)$$

$$\Sigma^{-1} \sim \mathrm{Wishart}(V, 3)$$

where θ_i are μ are the study-specific and overall posterior estimates, respectively. C_i^{-1} and Σ^{-1} are precision matrices, and R and V are scale matrices for the prior variance–covariance matrices. R consists of the observed variance–covariance matrix for y_i, and V is taken to be a diagonal matrix suggesting *a priori* independence between the risk factors and little *a priori* information about the size of the variances. D is a variance–covariance matrix of diagonal elements approaching ∞. The covariances of observed relative risk estimates for case–control studies were estimated via logistic regression, and for cohort studies from a Poisson model [30].

4. RESULTS

Table III provides the observed study-specific estimates of S and V and the corresponding posterior estimates based on the univariate Bayesian model described in Section 3.2.1. Most of the observed study-specific estimates for S are greater than 1, indicating a more than additive relationship. The study-specific posterior estimates for S show evidence of shrinkage towards the overall mean. Overall, by 'borrowing strength' across studies the posterior mean of S is 1.70 with a 95 per cent credible interval (CI) of (1.09, 2.67) indicating (overall) strong evidence in favour of a more than additive relationship. Inclusion of Study 11 by assuming a relatively small variance does not change the overall result greatly (1.74 (1.13, 2.70)).

The estimated value of API, given an overall observed estimate for S of 1.74, was 0.41 (0.08, 0.63). This suggests that for smokers also exposed to asbestos, approximately 40 per cent of lung cancer cases can be attributed to the synergistic behaviour of the two carcinogens, as

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Table III. Results (univariate): test of synergy (S) and multiplicativity (V).

		Synergy index (S)		Multiplicativity index (V)	
Study	Author	Observed estimates*	Posterior estimates**	Observed estimates*	Posterior estimates**
1	deKlerk	2.33 (0.90, 6.06)	2.08 (0.83, 5.25)	1.25 (0.19, 8.15)	1.00 (0.29, 3.51)
2	Martischnig	5.30 (1.23, 22.80)	2.77 (0.86, 9.29)	2.89 (0.87, 9.61)	1.87 (0.70, 5.04)
3	Pastorino, no PAH	1.41 (0.64, 3.12)	1.48 (0.66, 3.26)	0.64 (0.10, 4.08)	0.75 (0.22, 2.58)
4	Pastorino, PAH	2.03 (0.86, 4.79)	1.92 (0.83, 4.50)	1.01 (0.13, 7.89)	0.91 (0.25, 3.40)
5	Bovenzi	1.49 (1.14, 1.96)	1.50 (1.08, 2.09)	0.86 (0.31, 2.39)	0.85 (0.36, 2.01)
6	Kjuus	3.24 (1.36, 7.72)	2.63 (1.11, 6.26)	1.52 (0.39, 5.93)	1.20 (0.42, 3.42)
7	Blot, Georgia	1.65 (1.07, 2.55)	1.65 (1.01, 2.69)	1.26 (0.54, 2.93)	1.15 (0.55, 2.44)
8	Blot, Virginia	1.30 (0.75, 2.24)	1.35 (0.74, 2.45)	0.84 (0.39, 1.81)	0.84 (0.42, 1.69)
9	Blot, Florida	1.17 (0.73, 1.87)	1.23 (0.72, 2.07)	0.72 (0.22, 2.36)	0.76 (0.29, 2.00)
10	McDonald	0.86 (0.56, 1.31)	0.90 (0.59, 1.38)	0.61 (0.25, 1.49)	0.66 (0.31, 1.44)
11	Zhu			1.60 (0.43, 5.93)	1.25 (0.45, 3.46)
12	Meurman	1.01 (0.45, 2.25)	1.13 (0.56, 2.33)	1.19 (0.07, 20.33)	0.93 (0.22, 4.03)
13	Selikoff and Hammond	5.35 (0.63, 45.16)	2.50 (0.70, 9.18)	1.22 (0.21, 6.96)	1.01 (0.30, 3.37)
14	Selikoff	1.31 (0.62, 2.78)	1.38 (0.70, 2.70)	0.19 (0.06, 0.56)	0.29 (0.12, 0.71)
15	Hammond	3.73 (1.71, 8.11)	3.15 (1.55, 6.39)	0.95 (0.44, 2.06)	0.93 (0.47, 1.84)
16	Berry, 1971–1980 M+F	1.31 (0.22, 7.68)	1.52 (0.47, 4.99)	0.33 (0.10, 1.07)	0.46 (0.18, 1.18)
17	Liddell	1.22 (0.84, 1.77)	1.25 (0.82, 1.91)	0.56 (0.20, 1.56)	0.64 (0.27, 1.51)
18	Berry, 1960–1970 F	5.09 (0.28, 91.59)	2.16 (0.54, 8.91)	1.47 (0.09, 24.74)	0.98 (0.23, 4.21)
Overall			1.70 (1.09, 2.67)		0.86 (0.52, 1.41)
Overall (incl. Study 11)			1.74 (1.13, 2.70)		
Attributable proportion due to interaction (API)			0.41		
		(0.08, 0.63)			

Note: Estimates quoted are the mean estimate, below which is the * 95 per cent Confidence Interval or ** 95 per cent credible interval.

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distinct from their separate effects. Note that this 'attribution' is descriptive only and, without other analyses, indicates association rather than cause.

The observed study-specific estimates for V in Table III vary from 0.19 for Study 14 to 2.89 for Study 2. On the basis of the observed 95 per cent confidence intervals, most of the studies except for Study 14 show evidence consistent with a multiplicative relationship. Combining the studies, the overall posterior estimate for V is 0.86 (0.52, 1.41). This is consistent with Lee's results of 0.83 (0.63, 1.08) [24]. Both the observed and posterior estimates for V indicate conformity with the hypothesis of a multiplicative relationship.

Table IV provides the results of the multivariate analysis. The study-specific posterior estimates of the relative risk of exposure to smoking alone (RR_S) range from 4.07 to 8.13. We find an overall posterior estimate for RR_S of 5.51 (3.78, 7.89). For the relative risk of exposure to asbestos alone (RR_A), the posterior estimates range from 1.77 to 6.92. Overall, the posterior estimate for RR_A is 3.13 (1.80, 5.41). For the combined exposure of asbestos and smoking, the posterior estimates range considerably from 5.50 to 50.86. Overall, the posterior estimate for RR_{AS} is 13.69 (8.20, 22.76). On the basis of the relative risk estimates, the multivariate estimates for S and V are 1.94 and 0.83, respectively. For each study, we also calculate the probability that either S is greater than 1 (indicating more than additive) or V is less than 1 (indicating less than multiplicative). Overall, the multivariate analysis indicates overwhelming support for a value of S greater than 1 ($P(S>1) \simeq 1$), and a very high probability that V is less than 1 ($P(V<1) = 0.79$). Considering the two tests together, there is very strong evidence the relationship is more than additive but less than multiplicative. Table V provides the overall results for S and V under the univariate and multivariate models and probability estimates that S and V are greater than selected thresholds.

A comparison of the overall results for S and V from the univariate and multivariate analyses in Table V does not reveal a large difference in either the point estimates or the confidence range. The results for V from Studies 2 and 5 (the largest study) can be compared in Figures 1 and 2. For Study 2 the relative risk and covariance estimates are low compared to higher estimates for Study 5. These figures again reveal relatively minor differences in the point estimates, but the multivariate analysis supports a wider credible interval.

Figures 3 and 4 show bivariate density plots for S and V based on the results of the multivariate analysis from Studies 2 and 5, respectively. Lower relative risk and covariance estimates for Study 2 results in a bivariate density plot, which is more evenly spread, compared to Study 5. Table VI provides a test of the variance–covariance matrix for the multivariate analysis. Higher covariance estimates for the relative risk estimates appear to result in a tightening of the 95 per cent credible intervals for S and V.

4.1. Sensitivity of the results

A meta-analysis provides an opportunity to investigate subgroups of studies. Table VII provide the results for S and V by type of study, classification for non-smoker, use of external reference, type of asbestos, classification used for no asbestos exposure, and study size. There appears to be strong evidence for a less than multiplicative relationship among the following subsets: prospective studies ($P(V<1) = 0.86$); studies which classify only those who never smoked as non-smokers ($P(V<1) = 0.86$); studies based on exposure to crocidolite or amosite ($P(V<1) = 0.85$); and studies with number of cases less than 150 ($P(V<1) = 0.78$). The difference between types of asbestos is based on only two studies (1 and 14) for crocidolite and amosite, and strongly influenced by a low estimate for V from study 14 (Observed $V = 0.19$ (0.06, 0.56)).

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Table IV. Results for multivariate RR analysis.

Study No.	Author	Posterior estimates*						
		RR_S	RR_A	RR_{AS}	S	V	$P(S)>1$	$P(V)<1$
1	deKlerk	4.73 (2.16, 10.74)	2.88 (1.11, 7.81)	12.30 (5.19, 31.47)	2.16 (0.98, 4.23)	1.04 (0.31, 2.51)	0.97	0.58
2	Martischnig	3.43 (1.54, 8.79)	2.29 (0.72, 8.05)	9.56 (3.61, 31.66)	3.05 (0.75, 7.51)	1.51 (0.31, 4.19)	0.94	0.37
3	Pastorino, no PAH	5.57 (2.34, 13.24)	2.78 (0.82, 9.16)	10.75 (3.82, 30.30)	1.62 (0.69, 3.44)	0.85 (0.20, 2.46)	0.87	0.73
4	Pastorino, PAH	5.89 (2.38, 14.61)	2.87 (0.82, 9.87)	13.45 (4.47, 40.69)	1.94 (0.77, 4.12)	0.98 (0.23, 2.82)	0.93	0.65
5	Bovenzi	6.80 (2.70, 16.56)	2.25 (0.69, 7.20)	11.00 (4.16, 27.72)	1.50 (0.80, 2.45)	0.86 (0.22, 2.37)	0.91	0.72
6	Kjuus	5.51 (2.90, 10.50)	3.03 (1.16, 8.35)	17.37 (6.47, 43.08)	2.67 (0.98, 5.34)	1.21 (0.33, 2.99)	0.97	0.45
7	Blot, Georgia	5.20 (2.87, 9.87)	2.02 (0.76, 5.91)	8.80 (4.28, 20.88)	1.56 (0.76, 2.83)	0.96 (0.28, 2.28)	0.90	0.63
8	Blot, Virginia	4.07 (2.16, 8.93)	2.29 (0.96, 6.23)	6.99 (3.16, 21.20)	1.52 (0.62, 3.27)	0.85 (0.26, 2.05)	0.81	0.74
9	Blot, Florida	5.94 (2.71, 12.53)	2.25 (0.74, 6.84)	8.39 (3.56, 21.18)	1.25 (0.62, 2.37)	0.74 (0.20, 1.99)	0.71	0.80
10	McDonald	5.08 (2.81, 10.25)	1.92 (0.87, 4.88)	5.50 (2.93, 13.72)	0.94 (0.56, 1.70)	0.62 (0.23, 1.36)	0.25	0.92
11	Zhu	3.74 (1.50, 10.00)	4.70 (1.61, 12.94)	15.93 (5.94, 44.48)	2.42 (1.10, 4.50)	1.04 (0.30, 2.45)	0.98	0.56
12	Meurman	6.27 (2.47, 15.17)	1.77 (0.49, 6.36)	7.22 (2.67, 20.53)	1.03 (0.51, 2.28)	0.80 (0.19, 2.33)	0.47	0.77
13	Selikoff and Hammond	6.25 (2.97, 11.15)	6.53 (1.82, 20.45)	50.86 (12.28, 104.27)	4.91 (1.55, 9.24)	1.49 (0.36, 3.97)	0.99	0.33
14	Selikoff	6.39 (2.80, 12.76)	6.92 (1.65, 26.60)	26.71 (7.80, 64.91)	2.43 (0.93, 5.40)	0.78 (0.16, 2.46)	0.97	0.76
15	Hammond	8.13 (3.51, 14.44)	4.62 (1.67, 11.48)	36.16 (10.94, 72.31)	3.38 (1.44, 5.54)	1.09 (0.34, 2.59)	0.99	0.53
16	Berry, 1971–1980 M+F	6.37 (3.46, 10.68)	4.56 (1.61, 10.99)	15.83 (7.85, 29.22)	1.71 (0.94, 3.10)	0.63 (0.22, 1.64)	0.96	0.88
17	Liddell	5.42 (2.15, 13.41)	2.93 (0.95, 8.80)	9.62 (3.40, 27.36)	1.45 (0.71, 2.90)	0.72 (0.20, 1.90)	0.84	0.82
18	Berry, 1960–1970 F	6.46 (3.42, 10.80)	5.10 (1.59, 15.99)	37.08 (10.90, 76.17)	3.98 (1.34, 7.52)	1.34 (0.33, 3.51)	0.99	0.41
Overall		5.51 (3.78, 7.89)	3.13 (1.80, 5.41)	13.69 (8.20, 22.76)	1.94 (1.29, 2.84)	0.83 (0.46, 1.40)	1.00	0.79

Note: *Estimates quoted are the mean estimate, below which is the 95 per cent Credible Interval.

The sensitivity of the Bayesian univariate estimates to the distributional assumptions in the model is provided in Table VIII. Plausible ranges for the degrees of freedom for σ and τ, a tighter precision estimate for μ and a robust analysis excluding the smallest and largest studies were tested. The overall results appear to be robust to these alternative assumptions.

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Table V. Combined results for S and V.

	Test of synergy (S)				Test of multiplicativity (V)			
Analysis	Overall (95% CI)	$P(S)>1$	$P(S)>1.5$	$P(S)>2$	Overall (95% CI)	$P(V)<0.5$	$P(V)<1$	$P(V)<1.5$
Bayesian univariate	1.70 (1.09, 2.67)	0.99	0.70	0.23	0.86 (0.52, 1.41)	0.02	0.74	0.98
Bayesian multivariate	1.94 (1.29, 2.84)	1.00	1.00	1.00	0.83 (0.46, 1.40)	0.05	0.79	0.98

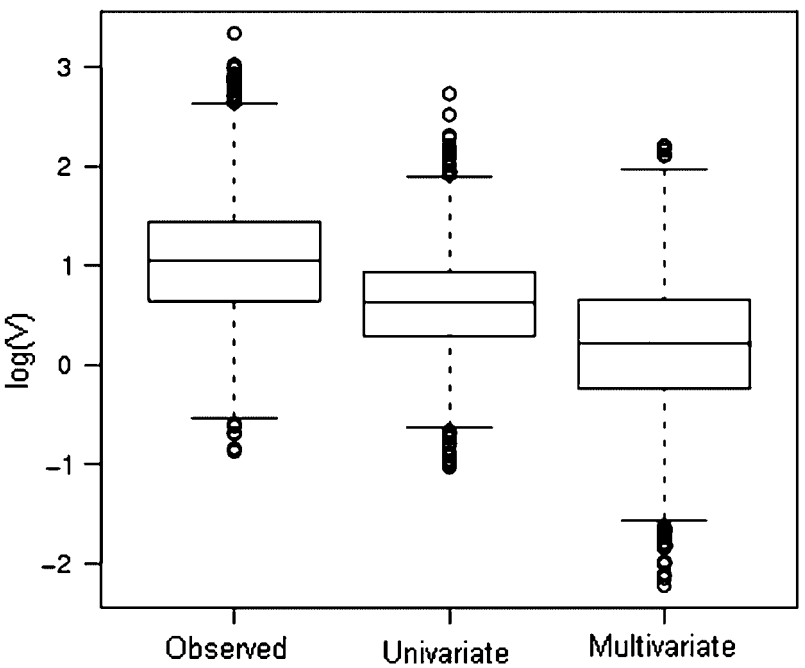

Figure 1. Box plots of V from Study 2.

The sensitivity of the Bayesian multivariate estimates is summarized in Table IX. Results by study type, a tighter precision for μ and exclusion of the smallest and largest study are shown. As previously indicated by the univariate results, there appears to be more evidence for a multiplicative relation for case–control studies ($P(V<1)=0.37$) compared to cohort studies ($P(V<1)=0.90$), although support for a simple multiplicative relation for cohort studies ($V=0.64$ (0.23, 1.42)) cannot be ruled out.

5. DISCUSSION

We reviewed the literature on the combined effect of exposure to asbestos and smoking on lung cancer, and explored a Bayesian approach to assess evidence of interaction. A Bayesian approach

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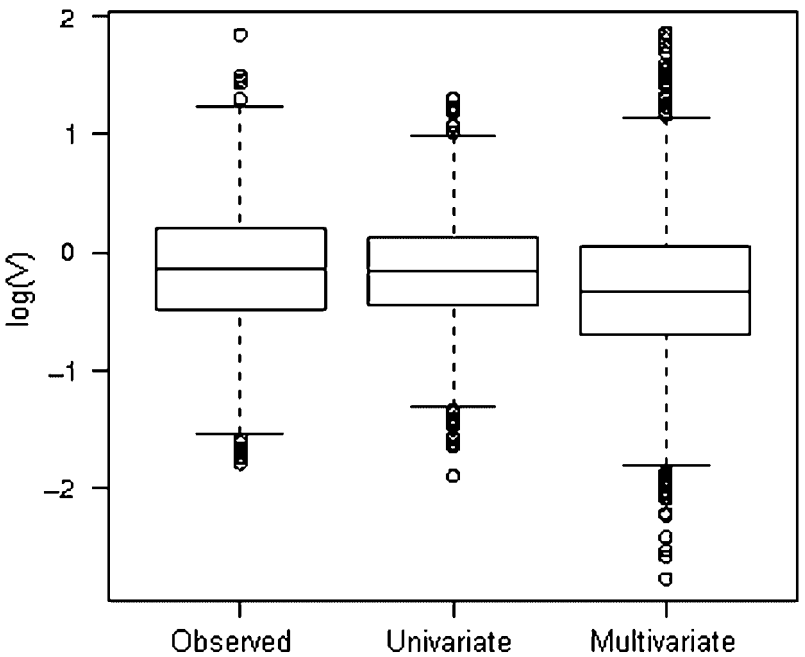

Figure 2. Box plots of V from Study 5.

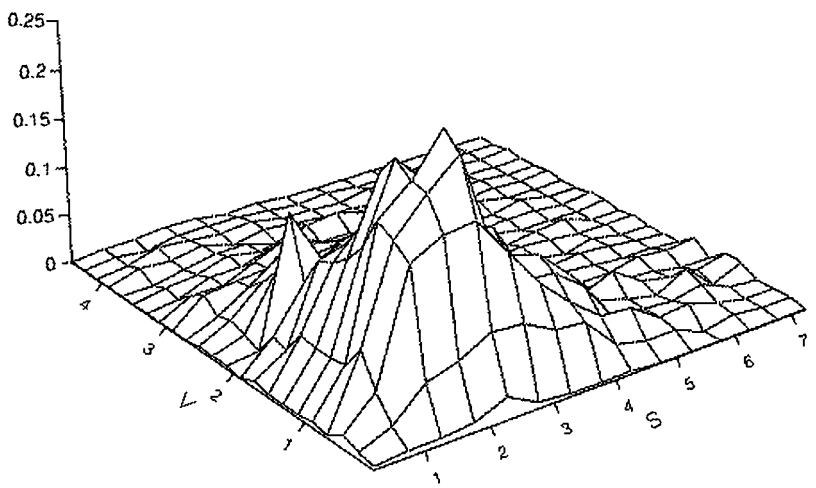

Figure 3. Density plot of V and S from multivariate analysis for Study 2.

using estimates of S and V indicates that the relation is closer to multiplicative than additive, a result consistent with recent reviews of the literature.

The results highlight two issues. First, estimates from the univariate and multivariate analysis were similar but with wider credible intervals on the latter. Although we have more information

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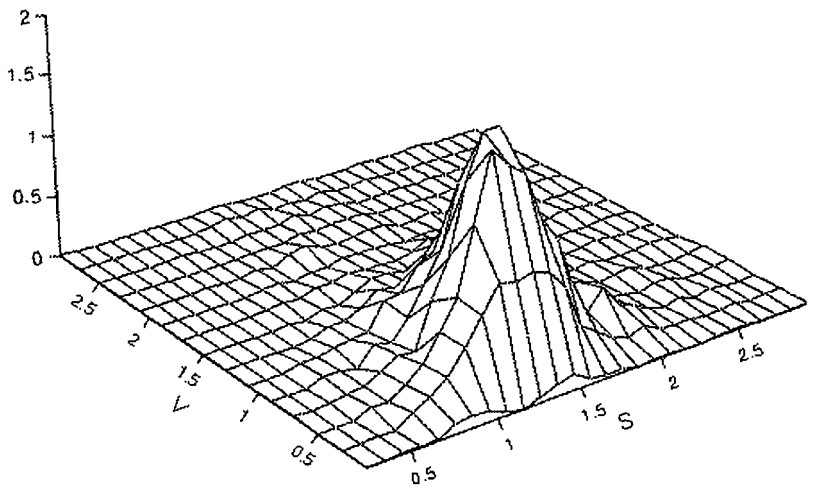

Figure 4. Density plot of V and S from multivariate analysis for Study 5.

Table VI. Sensitivity of estimates from the variance/covariance matrix for the multivariate analysis.

Analysis	S (95% CI)	V (95% CI)
Main	1.94 (1.29, 2.84)	0.83 (0.46, 1.40)
Low variance (0.20), low covariance (0.15)	2.07 (1.38, 2.99)	0.97 (0.60, 1.50)
High variance (1.00), high covariance (0.90)	2.10 (1.36, 3.16)	1.00 (0.53, 1.74)
High variance (1.00), low covariance (0.15)	2.08 (1.07, 3.67)	0.99 (0.45, 1.92)

about our parameters, the effect of incorporating covariance information is to increase the number of parameters of interest, and we only indirectly estimate these parameters. The wider credible interval of each estimate may thus be a more accurate reflection of the uncertainty we have in these estimates. Second, while there was support from a few of the studies for a multiplicative relation, the same studies also supported an additive relation. It is thus important to both allow for this uncertainty in the modelling and directly assess competing hypotheses of interest by analysing the evidence jointly.

Several explanations have been postulated for the biological mechanisms underlying evidence for a multiplicative relation. One is that cancer may be a multi-stage process, with the two carcinogens acting at different stages [31]. It is postulated that early stage carcinogenesis by asbestos supplies a population of initiated cells that the powerful late-stage actions of tobacco carcinogens then promote to overt cancer [32]. In contrast, when two carcinogens affect the same stage of carcinogenesis, then the relative risks are additive, and there is no interaction [33]. Another explanation is that smoking may impair clearance of asbestos particles from the lung [34].

The main emphasis of our review is on studies included in two recent reviews of the literature [2, 3]. A search of the MEDLINE reference database (1998–May 2004) and cited references for more recent studies revealed a number of papers with information relating to occupational exposure to asbestos, smoking habits, and the association of these factors with lung cancer risks. However, only one study provided quantitative information about relative risks for each exposure

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Table VII. Results for S and V by factor.

Analysis		Synergy index (S) Posterior estimate (95% CI)	$P(S)>1$	No. studies	Multiplicativity index (V) Posterior estimate (95% CI)	$P(V)<1$	No. studies
Main		1.70 (1.09, 2.67)	0.99	17	0.86 (0.52, 1.41)	0.74	18
1. Study type	Prospective	1.6 (0.75, 3.55)	0.89	8	0.66 (0.30, 1.46)	0.86	9
	Case–control	1.82 (0.96, 3.50)	0.97	9	1.10 (0.53, 2.33)	0.40	9
2. Classification for non-smoker	Never smoked	1.58 (0.79, 3.26)	0.90	9	0.68 (0.33, 1.39)	0.86	10
	Light smoker	1.88 (0.93, 3.88)	0.96	8	1.14 (0.51, 2.56)	0.37	8
3. By group (external reference)	Data compared to external ref.	2.48 (0.81, 7.74)	0.95	5	0.55 (0.18, 1.69)	0.86	5
	otherwise	1.54 (0.91, 2.61)	0.95	12	1.01 (0.56, 1.85)	0.49	13
4. Type of asbestos	Any type	2.03 (1.14, 3.68)	0.99	12	0.98 (0.53, 1.83)	0.53	12
	Crocidolite or amosite	1.69 (0.33, 8.56)	0.75	2	0.40 (0.06, 2.56)	0.85	2
	Chrysotile	1.01 (0.22, 4.54)	0.51	2	0.79 (0.20, 3.10)	0.64	3
5. Classification for no asbestos exposure	No exposure	1.97 (0.66, 6.12)	0.89	4	1.25 (0.42, 3.75)	0.34	5
	Low exposure	1.53 (0.68, 3.51)	0.85	7	0.76 (0.30, 1.95)	0.72	7
	Population exp.	1.81 (0.77, 4.22)	0.92	6	0.73 (0.29, 1.78)	0.76	6
6. Study size	No. cases <150	1.76 (0.80, 3.97)	0.92	8	0.71 (0.30, 1.75)	0.78	9
	No. cases >150	1.69 (0.90, 3.26)	0.95	9	0.97 (0.49, 1.93)	0.54	9

category [19]. The results from one study were based on a cohort previously included [35]. Some studies provided insufficient information on smoking habits [36–39], while other studies were underpowered to assess evidence of a joint effect [40] or were genetically based [41]. The study by Goldberg [38] found that 'the probability that a cancer is due to asbestos is the same among smokers and non-smokers', implying a multiplicative relation was found.

The study by Gustavsson *et al.* [19] investigated the association between low-dose exposure to asbestos and lung cancer, and in the analysis of the combined effect of asbestos and smoking, found evidence indicating a less than multiplicative yet slightly more than additive effect. Relative risk estimates (with 95 per cent confidence intervals) are reported as $RR_S = 21.8(14.4, 32.8)$, $RR_A = 4.2$ $(1.6, 11.1)$, $RR_{AS} = 28.6$ $(19.9, 48.3)$. Departure from multiplicativity was investigated in the study by including an interaction term in a logistic regression ($\beta_{12} = 0.31$ $(0.11, 0.86)$), and departure from additivity was evaluated using the synergy index $(1.15$ $(0.77, 1.72))$.

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Table VIII. Sensitivity of the posterior estimates (univariate): test of S and V.

Analysis		Posterior estimates* S	Posterior estimates* V	$P(S)>1$	$P(V)<1$
Main		1.70 (1.09, 2.67)	0.86 (0.52, 1.41)	0.99	0.74
1. df(σ)	14	1.71 (1.09, 2.70)	0.86 (0.53, 1.41)	0.99	0.74
	268	1.70 (1.09, 2.67)	0.85 (0.52, 1.42)	0.99	0.74
2. df(τ)	20	1.72 (1.07, 2.79)	0.86 (0.51, 1.44)	0.99	0.73
	2	1.63 (1.15, 2.36)	0.84 (0.55, 1.31)	1.00	0.79
3. Precision (μ)	1/15	1.69 (1.09, 2.66)	0.86 (0.52, 1.41)	0.99	0.74
4. Robust (excl. smallest and largest studies)		1.69 (1.04, 2.75)	0.84 (0.49, 1.43)	0.98	0.74

Note: *Estimates quoted are the mean estimate, below which is the 95 per cent credible interval.

Table IX. Sensitivity of the posterior estimates (multivariate analysis).

Analysis	RR_S	RR_A	RR_{AS}	S	V	$P(S)>1$	$P(V)<1$
Main	5.51 (3.78, 7.89)	3.13 (1.80, 5.41)	13.69 (8.20, 22.76)	1.94 (1.29, 2.84)	0.83 (0.46, 1.40)	1.00	0.79
SA1 CC	4.22 (2.39, 7.53)	1.72 (0.85, 3.55)	8.39 (4.75, 15.18)	1.99 (0.99, 3.79)	1.28 (0.48, 2.79)	0.97	0.37
PP	7.14 (4.06, 12.39)	5.63 (2.51, 12.85)	23.08 (10.33, 48.28)	2.13 (1.01, 3.98)	0.64 (0.23, 1.42)	0.98	0.90
SA2 restrictive prior	5.22 (3.57, 7.45)	2.90 (1.67, 4.92)	12.54 (7.48, 20.59)	1.92 (1.26, 2.80)	0.86 (0.48, 1.45)	1.00	0.75
SA3 robust (excl. smallest and largest studies)	5.13 (3.39, 7.67)	3.05 (1.71, 5.54)	12.33 (7.24, 21.16)	1.87 (1.20, 2.78)	0.83 (0.43, 1.44)	1.00	0.79

Note: Estimates quoted are the mean estimate, below which is the 95 per cent credible interval.

There are, of course, limitations associated with combining studies in the form of a meta-analysis. Meta-analysis is designed to enable a combination of results from studies which are comparable in outcome and exposure. Here we have combined studies with variability in, but not limited to: definitions of non-smokers; exposure times to asbestos; and exposure to different types and size of asbestos particles. In the first case, approximately half of the studies (ten) defined a non-smoker as 'never smoked', with the rest combining non-smokers and 'light smokers'. Although, as Lee points out, it could still be possible to observe a multiplicative relation regardless of the smoking definition, the magnitude of the effect may be somewhat diminished [3]. Across studies there is also a difference in the duration and level of exposure to asbestos. A recent study by Gustavsson

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et al. [19] examining the risk of low-dose exposure to asbestos, found evidence for a multiplicative relation with a magnitude of interaction lower than that previously reported for higher doses. The studies also differ in the type of asbestos and the size of asbestos particles to which subjects are likely to be exposed. Another recent study by Hodgson found the risk differential between chrysotile and crocidolite or amosite for lung cancer to be between 1:10 and 1:50 [42]. Further, there is evidence that the size of asbestos particles is important. Landrigan [43] found evidence that the risk of lung cancer in the mining and milling industry is 10–50 fold lower than in industries that process and use asbestos, such as textile manufacture and insulation. In industries that use and process asbestos, bundles of fibres are broken up into shorter, thinner fibres that are readily inhaled and retained in the alveoli.

There are also limitations to assessing interaction. First, in the case of studies on exposure to asbestos and smoking, the small number of lung cancer cases for non-smokers greatly increases the uncertainty of establishing any relation unless study populations are very large or specifically targeted. For example, in study 9, we found support for a multiplicative relation using our test of multiplicativity ($V = 0.72$ $(0.22, 2.36)$). A hypothetical increase in the number of lung cancer cases occurring in the asbestos-exposed population from 5 to 10 would only be needed to obtain a result which is not supportive of a multiplicative relation. Greenland and Rothman [12] suggest that even with large data sets we may not have enough information to establish relations among variables while controlling for confounding. Second, consistent with a multi-stage model of carcinogenesis, the form of interaction observed may be influenced by the length of follow-up time in studies [44].

An assessment of interaction is also a function of dosage levels for each risk factor, both in the nature of the functional form assumed for dose–response relationships for each factor and the dosage levels at which they combine. In the case of continuous covariates, care must be taken to consider the appropriate dose–response relationship for each factor individually before an assessment of the combined effect. Here we have used categorical covariates (exposed *versus* not exposed) on the dosage levels for each factor, and the dose–response relationship is difficult to explicitly model. Our main interest is then the extent to which the risk factors combine at this binary level. Although the definitions of those exposed and not exposed are subject to cut-off points we should still be able to see evidence for a multiplicative or additive relation provided the definitions are consistent across studies. However, a limitation of such a binary classification is that the power to test interactions is essentially determined by the size of the smallest category, so few lung cancer cases for non-smokers suggests that an analysis based on a binary classification is likely to be weaker than one based on continuous data.

APPENDIX A: CALCULATIONS FOR THE VARIANCE OF S AND V

A.1. Variance of S

We calculated the variance of S based on Rothman [15]. A large sample interval estimator for S based on a log-Gaussian sampling distribution would be

$$\begin{aligned} S_L &= \exp(\ln(\hat{S}) - Z_{1-\alpha/2}\mathrm{SE}(\ln(\hat{S}))) \\ S_U &= \exp(\ln(\hat{S}) + Z_{1-\alpha/2}\mathrm{SE}(\ln(\hat{S}))) \end{aligned} \tag{A1}$$

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The evaluation of $\mathrm{SE}(\ln(\hat{S}))$ depends upon the type of study. For case–control studies,

$$\hat{\mathrm{SE}}(\ln(\hat{S})) = \left[\frac{\hat{\mathrm{var}}(\mathrm{R}\hat{\mathrm{R}}_{\mathrm{AS}})}{(\mathrm{R}\hat{\mathrm{R}}_{\mathrm{AS}} - 1)^2} + \frac{\hat{\mathrm{var}}(\mathrm{R}\hat{\mathrm{R}}_{\mathrm{S}}) + \hat{\mathrm{var}}(\mathrm{R}\hat{\mathrm{R}}_{\mathrm{A}}) + 2\,\hat{\mathrm{cov}}(\mathrm{R}\hat{\mathrm{R}}_{\mathrm{S}}, \mathrm{R}\hat{\mathrm{R}}_{\mathrm{A}})}{(\mathrm{R}\hat{\mathrm{R}}_{\mathrm{S}} + \mathrm{R}\hat{\mathrm{R}}_{\mathrm{A}} - 2)^2} - \frac{2\,\hat{\mathrm{cov}}(\mathrm{R}\hat{\mathrm{R}}_{\mathrm{AS}}, \mathrm{R}\hat{\mathrm{R}}_{\mathrm{S}} + \mathrm{R}\hat{\mathrm{R}}_{\mathrm{A}})}{(\mathrm{R}\hat{\mathrm{R}}_{\mathrm{AS}} - 1)(\mathrm{R}\hat{\mathrm{R}}_{\mathrm{S}} + \mathrm{R}\hat{\mathrm{R}}_{\mathrm{A}} - 2)} \right]^{1/2} \tag{A2}$$

where

$$\hat{\mathrm{var}}(\mathrm{R}\hat{\mathrm{R}}_{ij}) = \mathrm{R}\hat{\mathrm{R}}_{ij}^2 \left(\frac{1}{a_{ij}} + \frac{1}{c_{ij}} + \frac{1}{b} + \frac{1}{d} \right) \tag{A3}$$

$$\hat{\mathrm{cov}}(\mathrm{R}\hat{\mathrm{R}}_{\mathrm{S}}, \mathrm{R}\hat{\mathrm{R}}_{\mathrm{A}}) = \mathrm{R}\hat{\mathrm{R}}_{\mathrm{S}}\mathrm{R}\hat{\mathrm{R}}_{\mathrm{A}} \left(\frac{1}{b} + \frac{1}{d} \right) \tag{A4}$$

$$\hat{\mathrm{cov}}(\mathrm{R}\hat{\mathrm{R}}_{\mathrm{AS}}, \mathrm{R}\hat{\mathrm{R}}_{\mathrm{S}} + \mathrm{R}\hat{\mathrm{R}}_{\mathrm{A}}) = \mathrm{R}\hat{\mathrm{R}}_{\mathrm{AS}}(\mathrm{R}\hat{\mathrm{R}}_{\mathrm{S}} + \mathrm{R}\hat{\mathrm{R}}_{\mathrm{A}}) \left(\frac{1}{b} + \frac{1}{d} \right) \tag{A5}$$

and b and d denote the frequencies of cases and controls in the low-risk category for both risk indicators, and a_{ij} and c_{ij} denote the frequencies of cases and controls in (non-referent) risk category i, j.

For cohort studies (with small effects), using first-order Taylor series approximations,

$$\hat{\mathrm{SE}}(\ln(\hat{S})) = \left[\frac{\hat{\mathrm{var}}(\hat{R}_{\mathrm{AS}}) + \hat{\mathrm{var}}(\hat{R}_{00})}{(\hat{R}_{\mathrm{AS}} - \hat{R}_{00})^2} + \frac{\hat{\mathrm{var}}(\hat{R}_{\mathrm{S}}) + \hat{\mathrm{var}}(\hat{R}_{\mathrm{A}}) + 4\,\hat{\mathrm{var}}(\hat{R}_{00})}{(\hat{R}_{\mathrm{S}} + \hat{R}_{\mathrm{A}} - 2\hat{R}_{00})^2} - \frac{4\,\hat{\mathrm{var}}(\hat{R}_{00})}{(\hat{R}_{\mathrm{AS}} - \hat{R}_{00})(\hat{R}_{\mathrm{S}} + \hat{R}_{\mathrm{A}} - 2\hat{R}_{00})} \right]^{1/2} \tag{A6}$$

where $\hat{\mathrm{var}}(\hat{R}_{ij})$ can be taken as $\hat{R}_{ij}/M_{ij}$ with M_{ij} denoting the total number of observations in the joint risk indicator category i, j.

A.2. Variance of V

For case–control studies, V can also be expressed as $\mathrm{RR}_{\mathrm{AS}}$ compared to $\mathrm{RR}_{\mathrm{S}}(X_2)$ divided by $\mathrm{RR}_{\mathrm{A}}(X_1)$. $V = X_2/X_1$.

$$\begin{aligned} \mathrm{var}(\log(X_1)) &= 1/a + 1/b + 1/c + 1/d \\ \mathrm{var}(\log(X_2)) &= 1/e + 1/f + 1/g + 1/h \\ \mathrm{var}(\log(V)) &= \mathrm{var}(\log(X_1)) + \mathrm{var}(\log(X_2)) \end{aligned} \tag{A7}$$

where a to h denote the frequency of cases and controls for each risk category, and X_1 and X_2 are assumed to be independent.

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For cohort studies with background risk not externally referenced,

$$\text{var}(\log(V)) = 1/a + 1/b + 1/e + 1/f \tag{A8}$$

For cohort studies with background risk externally referenced, we used the variance for the ratio of two standardized ratios found in Gardner and Altman [45].

REFERENCES

1. Saracci R, Boffetta P. Interactions of tobacco smoking with other causes of lung cancer. In *Epidemiology of Lung Cancer*: *Lung Biology in Health and Disease*, Samet JM (ed.). 1994.
2. Liddell F. The interaction of asbestos and smoking in lung cancer. *Annals of Occupational Hygiene* 2001; **45**(5):341–356.
3. Lee P. Relation between exposure to asbestos and smoking jointly and the risk of lung cancer. *Occupational and Environmental Medicine* 2001; **58**:145–153.
4. Roy P, Esteve J. Using relative risk models for estimating synergy between two risk factors. *Statistics in Medicine* 1998; **17**:1357–1373.
5. van der Linde A, Osius G. Estimation of non-parametric multivariate risk functions in matched case-control studies with application to the assessment of interactions of risk factors in the study of cancer. *Statistics in Medicine* 2001; **20**:1639–1662.
6. Selikoff I, Hammond E, Churg J. Asbestos exposure, smoking and neoplasia. *Journal of the American Medical Association* 1968; **204**:104–110.
7. Erren T, Jacobsen M, Piekarski C. Synergy between asbestos and smoking on lung cancer risks. *Epidemiology* 1999; **10**(4):405–411.
8. Vainio H, Boffetta P. Mechanisms of the combined effect of asbestos and smoking in the etiology of lung cancer. *Scandinavian Journal of Work Environment and Health* 1994; **20**:235–242.
9. Steenland K, Thun M. Interaction between tobacco smoking and occupational exposures in the causation of lung cancer. *Journal of Occupational Medicine* 1986; **28**:110–118.
10. Waage H, Vatten L, Opedal E. Smoking intervention in subjects at risk of asbestos-related lung cancer. *American Journal of Industrial Medicine* 1997; **31**:705–712.
11. Guidotti T. Apportionment in asbestos-related disease for purposes of compensation. *Industrial Health* 2002; **40**:295–311.
12. Greenland S, Rothman KJ. *Modern Methods in Epidemiology* (2nd edn). Lippincott-Raven: Philadelphia, PA, 1998.
13. UNSCEAR. Ionizing radiation: sources and biological effects. *Technical Report*, United Nations Scientific Committee on the Effects of Atomic Radiation, 1982.
14. Hallqvist J, Ahlbom A, Diderichsen F *et al.* How to evaluate interaction between causes: a review of practices in cardiovascular epidemiology. *Journal of Internal Medicine* 1996; **239**:377–382.
15. Rothman K. The estimation of synergy or antagonism. *American Journal of Epidemiology* 1976; **103**:506–511.
16. Rothman K. Synergy and antagnism in cause–effect relationships. *American Journal of Epidemiology* 1974; **99**:385–388.
17. Wildner M, Markuzzi A. Interaction and model selection. *Journal of Internal Medicine* 1997; **241**(6):535–536.
18. Walker A. Proportion of disease attributable to the combined effect of two factors. *International Journal of Epidemiology* 1981; **10**:81–85.
19. Gustavsson P, Nyberg F, Pershagen G *et al.* Low-dose exposure to asbestos and lung cancer: dose-response relations and interaction with smoking in a population-based case-referent study in Stockholm, Sweden. *American Journal of Epidemiology* 2002; **155**(11):1016–1022.
20. Doll R. The age distribution of cancer: implications for models of carcinogenesis. *JRSS* (*A*) 1971; **134**:133–166.
21. Saracci R. Asbestos and lung cancer: an analysis of the epidemiological evidence on the asbestos-smoking interaction. *International Journal of Cancer* 1977; **20**:323–331.
22. Saracci R. The interactions of tobacco smoking and other agents in cancer etiology. *Epidemiology Review* 1987; **9**:175–193.
23. Berry G, Newhouse ML, Antonis P. Combined effect of asbestos and smoking on mortality from lung cancer and mesothelioma in factory workers. *British Journal of Industrial Medicine* 1985; **42**:12–18.

DOI: 10.1002/sim

24. Lee P. Author's Reply: joint action of smoking and asbestos exposure on lung cancer. *Occupational and Environmental Medicine* 2002; **59**:495–496.
25. Liddell F. Letter: joint action of smoking and asbestos exposure on lung cancer. *Occupational and Environmental Medicine* 2002; **59**:494–495.
26. Dumouchel W. Bayesian meta-analysis. In *Statistical Methodology in the Pharmaceutical Sciences*, vol. 206. Marcel Dekker: New York, 1990; 509–529.
27. Tweedie RL, Biggerstaff B, Scott D, Mengersen K. Bayesian meta-analysis with application to studies of ETS and lung cancer. *Lung Cancer* 1996; **14**(Suppl. 1):S171–S194.
28. Spiegelhalter DJ, Thomas A, Best NG. Winbugs version 1.4 user manual. *Research Report*, Medical Research Council Biostatistics, Cambridge, 2002.
29. Brooks SP, Gelman A. Alternative methods for monitoring convergence of iterative simulations. *Journal of Computational and Graphical Statistics* 1998; **7**:434–455.
30. Breslow NE, Day NE. *Statistical Methods in Cancer Research. Vol. 2*: *The Design and Analysis of Cohort Studies.* IARC, 1987.
31. Peto R, Lopez AD, Boreham J, Thun M, Heath JC, Doll R. Mortality from smoking worldwide. *British Medical Bulletin* 1996; **52**:12–21.
32. Reif A, Heeren T. Consensus on synergism between cigarette smoke and other environmental carcinogens in the causation of lung cancer. *Advances in Cancer Research* 1999; **76**:161–186.
33. Brown CC, Chu KC. Additive and multiplicative models and multistage carcinogenesis theory. *Risk Analysis* 1989; **9**:99–105.
34. Cohen D, Arai SF, Brain JD. Smoking impairs long-term dust clearance from the lung. *Science* 1979; **204**:514–516.
35. Liddell FDK, Armstrong BG. The combination of effects on lung cancer of cigarette smoking and exposure in quebec Chrysotile miners and millers. *Annals of Occupational Hygiene* 2002; **46**(1):5–13.
36. Rafnsson V, Sulem P. Cancer incidence among marine engineers, a population based study (Iceland). *Cancer Causes and Control* 2003; **14**(1):29–35.
37. Ulvestad B, Kjaerheim K, Martinsen JI *et al.* Cancer incidence among workers in the asbestos-cement producing industry in Norway. *Scandinavian Journal of Work Environment and Health* 2002; **28**(6):411–417.
38. Goldberg M. Asbestos and cancer risk: the exposure-effect relationship for populations with occupational exposure. *Revue Des Maladies Respiratoires* 1999; **16**:1278–1285.
39. Stayner LT, Smith R, Bailer J *et al.* Exposure-response analysis of risk of respiratory disease associated with occupational exposure to chrysotile asbestos. *Occupational and Environmental Medicine* 1997; **54**:646–652.
40. Rosamilia K, Wong O, Raabe GK. A case-control study of lung cancer among refinery workers. *Journal of Occupational and Environmental Medicine* 1999; **41**(12):1091–1103.
41. Schabath MB, Spitz MR, Delclos GL, Gunn GB, Whitehead LW, Wu X. Association between asbestos exposure, cigarette smoking, myeloperoxidase (MPO) genotypes, and lung cancer risk. *American Journal of Industrial Medicine* 2002; **42**:29–37.
42. Hodgson J, Darnton A. The quantitative risks of mesothelioma and lung cancer in relation to asbestos exposure. *Annals of Occupational Hygiene* 2000; **44**(8):565–601.
43. Landrigan P. Editorial: asbestos—still a carcinogen. *New England Journal of Medicine* 1998; **338**:1618–1619.
44. Archer V. Lung cancer risks of underground miners. *The Yale Journal of Biology and Medicine* 1988; **61**:183–193.
45. Gardner MJ, Altman DG. *Statistics With Confidence*. BMJ: London, 1989.

DOI: 10.1002/sim