

Multivariate meta-analysis

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SUMMARY

Meta-analysis is now a standard statistical tool for assessing the overall strength and interesting features of a relationship, on the basis of multiple independent studies. There is, however, recent acknowledgement of the fact that in many applications responses are rarely uniquely determined. Hence there has been some change of focus from a single response to the analysis of multiple outcomes. In this paper we propose and evaluate three Bayesian multivariate meta-analysis models: two multivariate analogues of the traditional univariate random effects models which make different assumptions about the relationships between studies and estimates, and a multivariate random effects model which is a Bayesian adaptation of the mixed model approach. Our preferred method is then illustrated through an analysis of a new data set on parental smoking and two health outcomes (asthma and lower respiratory disease) in children. Copyright © 2003 John Wiley & Sons, Ltd.

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1. INTRODUCTION

Meta-analysis is a statistical method used to amalgamate the findings of individual studies that are strongly related in order to deal with issues that cannot be answered by the results of a single study alone. Hitherto, emphasis has been primarily on a single response of interest. Indeed, this univariate situation has been explored and evaluated in a very wide variety of modelling situations and statistical paradigms. For example, the Bayesian models of Carlin [1] and Smith *et al.* [2] may be contrasted with the generalized linear mixed model approach of Platt *et al.* [3], while Mengersen *et al.* [4] and Brockwell and Gordon [5] examine more general questions of method choice. In particular, the two latter papers find favour with models that admit between-study heterogeneity (random effects models) but demonstrate concerns about the coverage probabilities of some methods commonly used in practice.

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Critical debate on appropriate interpretation and implementation of meta-analysis also continues to occupy a large literature; see, for example, Mosteller and Chalmers [6] and Henry and Wilson [7] for earlier commentary, Thornton and Lee [8] as a representative of the vexed issue of publication bias, Thompson and Spector [9] for caveats and an entire issue of *Statistics in Medicine* in 1997 devoted to the topic. A comprehensive contemporary review by Sheehan [10] provides a wide coverage of meta-analysis methods and issues in contexts relevant to medicine.

The problem identified and addressed in this paper, however, is that often the attention is not on a single response but on multiple outcomes. This is strongly evident in many epidemiological and medical studies, especially when the focus is on broad health effects associated with a specific agent. There are two scenarios that might induce consideration of a multivariate approach to meta-analysis. First, technically equivalent outcomes may not be considered as a single entity because of differences in study design, aims or definition. Second, outcomes may be known to be strongly related, so that an evaluation of the agent should 'borrow strength' not only across studies, as in traditional meta-analysis models, but also across outcomes.

Consider, as a concrete example, the potential health effects among children exposed to environmental tobacco smoke (ETS), or passive smoking. This has been a topic of growing international interest, as evidenced in Australia by the recent NHMRC Report on 'The Health Effects of Passive Smoking' [11]. Here, as in previous similar reports [12], numerous outcomes were considered individually, despite the recognized fact that most studies provided information about multiple outcomes and that many of these were known to be highly related.

For example, two common chronic illnesses of interest in the context of ETS are asthma and lower respiratory disease (LRD). Both childhood diseases are well known causes of morbidity and of mortality worldwide [13, 14]. Moreover, the known strong relationship between them is exacerbated by the lack of precise definition as discussed in Section 2. How does one more formally acknowledge such relationships in a quantitative evaluation of this important association? Although standard meta-analysis facilitates conclusions on the basis of the accumulated evidence across studies, they deny such accumulation across the spectrum of measured health outcomes.

In this paper we examine and evaluate three multivariate meta-analysis models, designed to estimate the association of each outcome with the agent of interest, the overall association with the agent based on both outcomes and the relationship between the outcomes themselves in this context. A preferred approach is fully developed under a Bayesian paradigm, using the software package BUGS (Bayesian inference using Gibbs sampling) [15]. Although this package currently condones only conjugate priors in a multivariate setting and offers a wide but limited range of likelihoods, its appeal lies in its accessibility, increasing popularity, free distribution and ongoing development. The models in this paper are thus constructed in light of the requirements of this package; the various implications of this are discussed as required. Our approach is then favourably compared with two alternatives and then illustrated in the context of the case study described above: eliciting the association between asthma and LRD with ETS among children, based on diverse epidemiological studies which report results for either or both responses.

This study builds on a growing body of interest in multivariate approaches to meta-analysis. This is discussed and the various methods compared in Section 3.3. The contribution of the current paper is to consolidate and extend this focus, through evaluation of general multivariate models and their application to a new data set of current medical interest.

2. TRADITIONAL META-ANALYSIS MODELS

2.1. Notation

For each analysis and without loss of information, all models in this paper are based on the reported log-odds ratios (LOR) and corresponding variances. Assume that there are J outcomes of interest and that I_j independent studies contribute data to the j th outcome, $j = 1, \dots, J$. For the i th study in the j th outcome, an LOR y_{ij} and corresponding variance $\text{var}(y_{ij})$ are observed. Let θ_{ij} and θ_j represent the true LOR for the i jth study population and the true overall LOR for the j th outcome. The set of observed LORs for the j th outcome is denoted by $\mathbf{y}_j = (y_{1j}, \dots, y_{I_j j})'$ with the corresponding set of true LORs denoted by $\theta_j = (\theta_{1j}, \dots, \theta_{I_j j})'$. Throughout, ϕ_{ij} , ϕ_j and ψ_j will denote parameters representing variances multiplied by known constants, and v_{ij} , v_j and δ_j will denote their associated degrees of freedom. The exact definition of these quantities will vary with the model and this also applies to X , which will denote a design matrix, and to B and C , which are square matrices of constants. The diagonal terms of C_j , say, are denoted by $c_{ii(j)}$. Matrices are written in upper case and the estimator of a parameter is denoted by a carat over the particular symbol; for example, the estimator of θ_j is $\hat{\theta}_j$.

The design matrix X_j mentioned above contains covariate information. The first column is a column of 1s, while every other column relates to a covariate and is centred to have an average value of 0.

The multivariate normal distribution is denoted as MVN. The notation $D \rightarrow \infty$ indicates that the elements of D are very large and tending to infinity.

2.2. Frequentist analysis

The traditional fixed effects (FE) and random effects (RE) models for meta analysis provide the starting point for the development of our methodology. Under the FE model, for the j th outcome from the i th study, we take $y_{ij} \sim N(\theta_j, \phi_{ij})$, where ϕ_{ij} is estimated by the observed variance and θ_j is then estimated as a simple weighted average [16]

$$\hat{\theta}_j = \frac{\sum_{i=1}^{I_j} \hat{\phi}_{ij}^{-1} y_{ij}}{\sum_{i=1}^{I_j} \hat{\phi}_{ij}^{-1}}$$

The RE model further allows for between-study variation by taking $y_{ij} \sim N(\theta_{ij}, \phi_{ij})$ and $\theta_{ij} \sim N(\theta_j, \psi_j)$, so that now $\hat{\theta}_j$ uses weights $\phi_{ij}^* = \phi_{ij} + \psi_j$ with the ϕ_{ij} estimated as before and ψ_j estimated in the meta-analysis [17].

The relative merits of these approaches are discussed by numerous authors. For example, whereas Mengersen *et al.* [4], Smith *et al.* [1] and Brockwell and Gordon [5] report a preference for an RE model, Thompson [18] argues that unrealistic assumptions about the between-study variance imply that the RE model cannot be regarded as a robust solution to the problem of statistical heterogeneity but more as a basis for sensitivity analysis [19].

Although some of the odds ratios used in our analysis were already adjusted for various sets of covariates in the original studies, there may still be a need to take further account of them in the meta-analyses. One simple approach to covariate adjustment is suggested by Thompson *et al.* [20]. Let \mathbf{z}_j be the vector of covariates that are of interest for outcome j and let z_{ij} be the values it takes for study i . We model $E(y_{ij}) = \alpha_j + \gamma_j' \mathbf{z}_{ij}$ and use the estimate of γ_j to compute adjusted values $y_{ij}^* = y_{ij} - \hat{\gamma}_j(z_{ij} - \bar{z}_j)$, where $\bar{z}_j = \sum_{i=1}^{I_j} z_{ij}/I_j$ is the overall mean for

the covariates. A covariate that is categorical is represented by binary-valued components of \mathbf{z}_j , the number of components being one less than the number of categories. Some continuous variables are more sensibly fit as categorical. Age, for example, takes a median value for each study and is better described by grouping the values into two or three subgroups. This also helps the presentation of results, as the estimated odds ratio can be given for each category.

Computation of confidence intervals, variances and hypothesis tests under the above models make various strong assumptions about normality. The FE model assumes that the y_{ij} are normally distributed around θ_j ; the RE model makes analogous assumptions that the y_{ij} and θ_{ij} are normally distributed around θ_{ij} and θ_j , respectively. Although the assumptions about y_{ij} are generally supported by the size of most of the studies, it is useful to verify the sensitivity of the results to any of these premises [18].

Normality may be assessed via q-q plots of variance-weighted residuals and associated Weisberg–Bingham statistics [20]. If this assumption is found to be unsustainable, a heavy tailed distribution [20] or a non-parametric distribution [21] may be substituted.

2.3. Bayesian analysis

Bayesian approaches to meta-analysis are becoming more established and elaborate, especially given the greater access to computational means for analysis through Markov chain Monte Carlo (MCMC), as discussed in Section 3.3. Following DuMouchel [22], a hierarchical Bayesian meta-analysis model analogous to the above RE model may be constructed.

2.3.1. Independent model. Consider first the simpler and common situation in which all studies are independent. Here, the observed variance covariance C_j is diagonal and $y_{ij} \sim N(\theta_{ij}, \phi_j c_{ii(j)})$. Priors are placed on the unknown parameters. It is reasonable to assume that the θ_{ij} are also normally distributed with variance proportional to a prior diagonal variance–covariance matrix. The mean of the θ_{ij} may depend on the covariates in the matrix X , so can be expressed as a linear combination $\mathbf{x}'_{ij} \boldsymbol{\beta}_j$ where \mathbf{x}'_{ij} is the i th row of X_j . The first component of the set $\boldsymbol{\beta}_j$ is made equal to θ_j , which is the quantity of primary interest for outcome j . Thus $\theta_{ij} \sim N(\mathbf{x}'_{ij} \boldsymbol{\beta}_j, \psi_j b_{ii(j)})$.

Typically, there is little information about the unknown coefficients $\boldsymbol{\beta}_j$. Hence a weak prior is adopted for this set of parameters: $\boldsymbol{\beta}_j \sim \text{MVN}(0, D \rightarrow \infty)$. In the absence of other information, $b_{ii(j)}$ is set equal to b_j for all i , where b_j is the method of moments estimate of between-study variance for outcome j . An alternative would be to impose a flat or very diffuse prior on this term as well, but this may lead to identifiability problems. Priors must now be placed on the unknown variables ψ_j and ϕ_j . It is typical to allow their inverses to have conjugate chi-square distributions with means of 1 and constants δ_j and v_j indicating the degree of ‘belief’ in these priors, so that $\phi_j^{-1} \sim \chi^2_{v_j}/v_j$ and $\psi_j^{-1} \sim \chi^2_{\delta_j}/\delta_j$. DuMouchel [22] provides some guidance in the choice of δ_j and v_j .

In this model, three major sources of variance are described: the study-level characteristics (through X); between-study variance (through $\psi_j B_j$), and within-study variance (through $\phi_j C_j$).

2.3.2. General model. In some situations the studies may not be independent as assumed in Section 2.3.1. For example, in the ETS case study considered in Section 4 it may be reasonable to consider clusters of studies according to country group. This might be represented as an additional hierarchy in the model or through a spatial term indicating increased correlation

between studies that are geographic neighbours. An alternative is to generalize the model in Section 2.3.2 to directly accommodate the lack of independence.

In this situation, the set of observed LORs for the j th outcome is assumed to have an MVN distribution with mean θ_j , and variance based on ϕ_j and the observed variance–covariance matrix C_j . Hence $y_j \sim \text{MVN}(\theta_j, \phi_j C_j)$.

Priors are again placed on the unknown parameters. It is reasonable to assume that the θ_j also have an MVN distribution, with variance proportional to a prior variance–covariance matrix B_j , and mean again specified by a linear combination of the covariates: $\theta_j \sim \text{MVN}(X_j \beta_j, \psi_j B_j)$.

As in the independent model, chi-square distributions are adopted for the following terms: $\phi_j^{-1} \sim \chi^2_{v_j}/v_j$ and $\psi_j^{-1} \sim \chi^2_{\delta_j}/\delta_j$.

3. MULTIVARIATE MODELS

3.1. A preferred approach

To give a very general multivariate extension of the model described in Section 2.3.2, let $y^* = (y_{11}, \dots, y_{l1}, \dots, y_{1J}, \dots, y_{lJ})'$ so y^* contains the LORs for all outcomes from all studies. Similarly, put $\theta^* = (\theta_{11}, \dots, \theta_{l1}, \dots, \theta_{1J}, \dots, \theta_{lJ})'$ and $\beta^* = (\beta_{11}, \dots, \beta_{l1}, \dots, \beta_{1J}, \dots, \beta_{lJ})'$. Thus it is assumed that $y^* \sim \text{MVN}(\theta^*, \Gamma^*)$. As before, the priors for θ^* and β^* are given MVN distributions, so that $\theta^* \sim \text{MVN}(X^* \beta^*, \Lambda^*)$, $\beta^* \sim \text{MVN}(0, D^* \rightarrow \infty)$.

Prior distributions for the variance matrices Γ^* and Λ^* must also be specified and this requires care; in particular, many components of Γ^* and Λ^* should usually be zero and so, for example, Γ^* and Λ^* should not be given inverse Wishart distributions.

Following from Section 2.3.1, results from different studies are often independent of each other. In this case the following simpler formulation is appropriate. Suppose the i th study reported LORs for all the J outcomes and put $y_i = (y_{i1}, \dots, y_{iJ})'$ and $\theta_i = (\theta_{i1}, \dots, \theta_{iJ})'$. We should note that here y_i and θ_i give values for the i th study, while in Section 2.3 y_j and θ_j give values for the j th disease. Under the assumption that studies are independent, the natural generalization of the univariate meta-analysis is to assume $y_i \sim \text{MVN}(\theta_i, \Gamma_i)$ and $\theta_i \sim \text{MVN}((x'_{i1} \beta_1, \dots, x'_{iJ} \beta_J)', \Lambda)$, where the j th diagonal elements of Γ_i and Λ are set equal to $\phi_j c_{ii(j)}$ and $\psi_j b_j$, respectively, and x_{ij} and β_j have the same definitions as in Section 2.3. (Thus y_{ij} and θ_{ij} have the same marginal distributions as in the univariate Bayesian analysis of Section 2.3.1.)

We further assume that the Γ_i have a common correlation structure so that the (j, k) off-diagonal element of Γ_i may be written as $\rho_{jk}(c_{ii(j)} c_{ii(k)})^{1/2}$, where ρ_{jk} does not vary with i . We denote the off-diagonal elements of Λ by σ_{jk} and its diagonal elements by $\psi_j b_j$. As in Section 2.3, we give β_j a diffuse prior distribution, $\beta_j \sim \text{MVN}(0, D^* \rightarrow \infty)$. We have that $\Gamma_i = G_i \Phi G_i$, where $G_i = \text{diag}\{c_{ii(1)}^{1/2}, \dots, c_{ii(J)}^{1/2}\}$ and

$$\Phi = \begin{pmatrix} \phi_I & \rho_{12} & \cdots & \rho_{1J} \\ \rho_{12} & \phi_2 & & \vdots \\ \vdots & & \ddots & \vdots \\ \rho_{1J} & \cdots & \cdots & \phi_J \end{pmatrix}$$

We assume that G_i and the b_i are known. (Their values were needed for the univariate approach described above.) Hence the increase in the number of parameters is minimal; for two outcomes the additional parameters are ρ_{12} and σ_{12} .

We must specify prior distributions for Φ and Λ , and the natural choice is to give each a Wishart distribution. However, at the present time off-the-shelf software such as BUGS can only handle multivariate distributions that are conjugate. The example we consider has only two outcomes so the Wishart prior distribution is approximated by giving each diagonal element a gamma distribution and each correlation a uniform distribution on the interval $[-1, 1]$. We again suppose $\phi_j^{-1} \sim \chi_{v_j}^2/v_j$ and $\psi_j^{-1} \sim \chi_{\delta_j}^2/\delta_j$. We acknowledge that this is more difficult for three- or higher-dimensional normal distributions as correlations must follow various constraints for the variance matrix to be positive-definite.

When an odds ratio is not given for an outcome one can either treat it as a missing value or, alternatively, consider the marginal distribution for the odds ratios that have been observed. In principle, these two options give identical answers but the second has much better convergence properties. With our model it is straightforward to take marginal distributions for the appropriate components of \mathbf{y}_i and $\boldsymbol{\theta}_i$. For example, to fit a two-outcome model using BUGS, it may be easiest to consider three separate model specifications:

- (a) for studies that examine both outcomes;
- (b) for studies that examine only the first outcome; and
- (c) for studies that examine only the second outcome.

The models will be:

(a)

$$\begin{pmatrix} y_{i1} \\ y_{i2} \end{pmatrix} \sim \text{MVN} \left(\begin{pmatrix} \theta_{i1} \\ \theta_{i2} \end{pmatrix}, \begin{pmatrix} c_{ii(1)}^{1/2} & 0 \\ 0 & c_{ii(2)}^{1/2} \end{pmatrix} \begin{pmatrix} \phi_1 & \rho_{12} \\ \rho_{12} & \phi_2 \end{pmatrix} \begin{pmatrix} c_{ii(1)}^{1/2} & 0 \\ 0 & c_{ii(2)}^{1/2} \end{pmatrix} \right)$$

and

$$\begin{pmatrix} \theta_{i1} \\ \theta_{i2} \end{pmatrix} \sim \text{MVN} \left(\begin{pmatrix} \mathbf{x}'_{i1} \boldsymbol{\beta}_1 \\ \mathbf{x}'_{i2} \boldsymbol{\beta}_2 \end{pmatrix}, \begin{pmatrix} \psi_1 b_1 & \sigma_{12} \\ \sigma_{12} & \psi_2 b_2 \end{pmatrix} \right)$$

(b)

$$y_{i1} \sim N(\theta_{i1}, \phi_1 c_{ii(1)}), \quad \theta_{i1} \sim N(\mathbf{x}'_{i1} \boldsymbol{\beta}_1, \psi_1 b_1)$$

(c)

$$y_{i2} \sim N(\theta_{i2}, \phi_2 c_{ii(2)}), \quad \theta_{i2} \sim N(\mathbf{x}'_{i2} \boldsymbol{\beta}_2, \psi_2 b_2)$$

The models are linked because the expressions in (b) and (c) use the parameters that occur in (a).

The above depiction of the problem does not allow for the possibility that a study may offer more than one statistic of interest for an outcome. For example, outcomes can be expressed as log-odds ratios, standardized differences or rates. Suppose a study has two statistics for the

first outcome and three for the second. Then we might put

$$\Phi = \begin{pmatrix} \phi_1 & \tau_1 & \rho_{12} & \rho_{12} & \rho_{12} \\ \tau_1 & \phi_1 & \rho_{12} & \rho_{12} & \rho_{12} \\ \rho_{12} & \rho_{12} & \phi_2 & \tau_2 & \tau_2 \\ \rho_{12} & \rho_{12} & \tau_2 & \phi_2 & \tau_2 \\ \rho_{12} & \rho_{12} & \tau_2 & \tau_2 & \phi_2 \end{pmatrix}$$

so τ_1 reflects correlation between the two statistics for the first outcome and τ_2 reflects correlation between any pair of statistics for the second outcome. The form of Λ when there are multiple outcome statistics would obviously be similar to Φ .

The difficulty with this approach is to coerce BUGS to allow specification of Φ as having a multivariate distribution with specific components that are equal. In order to overcome this, we again specify inverse gamma distributions for the elements on the main diagonal (the same distributions as for the univariate models) and a uniform distribution on the interval $(-1, 1)$ for their correlation. Constraints must be imposed to ensure that the matrix is positive-definite. As above, the multivariate normal distribution may be separated into a univariate marginal distribution and a univariate conditional distribution, thus retaining the bivariate normal model.

The issue of identifiability needs to be addressed. Since $y_i | \theta_i, \Gamma_i \sim \text{MVN}(\theta_i, \Gamma_i)$ and $\theta_i | \beta_1, \dots, \beta_J, \Lambda \sim \text{MVN}((x'_{i1}\beta_1, \dots, x'_{iJ}\beta_J)', \Lambda)$, it follows that

$$y_i | \beta_1, \dots, \beta_J, \Lambda \sim \text{MVN}((x'_{i1}\beta_1, \dots, x'_{iJ}\beta_J)', \Lambda + \Gamma_i) \quad (1)$$

Estimates of the diagonal elements of Γ_i are provided by the i th study and inter-study variation provides estimates of the $\Lambda + \Gamma_i$. Thus the diagonal elements of Λ can be estimated. Now, $\Gamma_i = G_i \Phi G_i$, with G_i known so, in principle, the off-diagonal elements of $\Lambda + G_i \Phi G_i$ may be estimated from just the inter-study variation provided the G_i vary between studies. However, unless there are a large number of studies and the G_i differ substantially, it will be very difficult to separate which of the variation in the y_i should be attributed to Λ and which to $G_i \Phi G_i$. In particular, if the G_i are identical, then there is an identifiability problem in separating out the covariance between Λ and $G_i \Phi G_i$. We must note, though, that this need not cause problems in determining β_1, \dots, β_J . For example, if the G_i are identical then equation (1) shows that this estimation becomes a standard multivariate regression problem.

3.2. Alternative approaches

3.2.1. Alternative model 1. An alternative multivariate scenario is to develop expressions in terms of vectors of the same outcome, rather than corresponding to the same study as in Section 3.1. This situation is thus a direct application of the model in Section 2.3, with off-diagonal elements in C and B now describing the relationships between studies and outcomes which were before taken to be independent. Again, Wishart priors may be imposed on the precision terms in the model, but now these must be fully specified. In the case study described in Section 4, this would involve a description of all 67×67 components. Of course, it is much simpler to assume independence with a consequent reduction to a 2×2 matrix as in Section 3.1, but in this situation the approach of Section 3.1 is clearly better since the covariance terms are taken to be estimated instead of known.

There are four further concerns with this model. First, the model cannot formally accommodate any differences between the LORs from the studies providing data for all outcomes

and those LORs from studies reporting on only a subset of outcomes. Second, the estimated correlation between the occurrences of the outcomes of interest changes as the value assigned to the degrees of freedom of the precision matrix for θ_j changes, so that only a rough indicator of the nature of the association can be obtained. Third, the estimated correlation between the occurrences of the outcomes are different according to whether they are adjusted for potential risk factors or not, suggesting that it is almost impossible to provide a reasonable prior beforehand, under this model formulation. Finally, this framework can only accommodate one statistic per study for each outcome.

In application, the input of the covariance terms in the model would be based on correlation information available for all studies, but these are not generally available. Therefore, a symmetric matrix based on a covariance which is a little smaller than the observed covariances may be adopted. If diagonal matrices are adopted, the elements of the matrix corresponding to the variance of θ_j represent the between-study variance of each of the outcomes and might be estimated through a frequentist RE model.

3.2.2. Alternative model 2. This approach may be considered as a Bayesian adaptation of a mixed model scheme for multi-centre trials and is constructed as $y \sim N(Z_B \beta_B, \omega C)$, $\beta_B \sim N(X\mu + Z_A \beta_A, c_B V_B)$, where $\mu \sim N(0, D)$ and $\beta_A \sim N(0, c_A V_A)$ and the modifiers c_A and c_B are derived from inverse chi-square distributions as $c^{-1} \sim \chi^2(v_c)/v_c$ where the degrees of freedom reflect the magnitude of belief given to the corresponding matrices. Here the between-study effect and the between-study-and-outcome effect are denoted by the subscripts A and B, respectively. Z is a design matrix which identifies LORs from the same studies, and is similar in structure to X which specifies the outcomes from which the LORs arise.

For example, suppose that there are two outcomes M and N . If there are three log-odds ratios, with the first one for outcome M and the remainder for outcome N , then the relevant fixed effect design matrix X is

$$X^T = \begin{bmatrix} 1 & 0 & 0 \\ 0 & 1 & 1 \end{bmatrix}$$

and $\mu = (\mu_M, \mu_N)$ comprises the overall LORs for the two outcomes. Likewise, if there is a covariate of interest (say, age), and if the first two log-odds ratios are from one age group and the third is from the other age group, then the corresponding X is

$$X = \begin{bmatrix} 1 & 0 & 0 \\ 0 & 1 & 1 \\ 0 & 1 & 0 \end{bmatrix}$$

and $\mu = (\mu_M, \mu_N, \mu_a)$ with the last term representing the covariate effect. Similarly, Z is another design matrix for random effects. In the analysis, $Z\beta$ is split into $Z_A \beta_A$ and $Z_B \beta_B$, where the former component specifies study effects and the latter classifies study + outcome effects. The vector μ is fitted as fixed in this model since this approach offers clear variance structure.

Note that, unlike the model of Section 3.2.1, this structure allows for more than one odds ratio for each outcome for each study. Multiple LORs for a particular outcome, arising perhaps from analyses of different subgroups of children, different types of covariate adjustment or different sources of exposure, are specified in the design matrix Z_A . Moreover, for a given outcome of interest, there is no need for the responses from the studies providing data for

both outcomes to be similar to those from the studies providing data only for the outcome of interest. Finally, since the variance matrix D is fitted as fixed, the estimated correlation between asthma and LRD obtained by the analysis is more credible than the one produced under the previous model.

However, there remains a strong concern with this model. Importantly, the approach is unsuitable when interest does not centre on the difference between means. In multi-centre trials the model is $y = \text{mean} + \text{treatment} + \text{centre} + \text{error}$ and the main interest is on the difference between treatments, not the mean. In meta-analysis, however, the model is $y = \text{treatment} + \text{study} + \text{error}$ and the main interest is the actual effect of each treatment. As a consequence, there is clearly confounding between the treatment and study effects. One might insist that the mean of the study effects must be zero, but the prior variances attached to ‘studies’ and ‘treatments’ could well make a big difference to parameter estimates.

3.3. *The new approaches in context*

It is useful to consider the above approaches in light of other published methods for multivariate analysis of multiple response measures. In this section we briefly review several representative papers.

An early example of a Bayesian hierarchical normal random effects model for 2×2 tables with a single response of interest is given by Carlin [1]. Here, as in the approaches described above, exchangeable priors are adopted for comparable studies. The Bayesian paradigm is exploited as a vehicle for formal assessment of uncertainty in the conclusions. A Monte Carlo approach is used for numerical computation, as opposed to the MCMC methodology adopted here.

A similar model is considered in a bivariate framework by van Houwelingen *et al.* [21]. Again, a random effects model for the log-odds ratios is adopted, but the Normal approximation is replaced by a conditional non-central hypergeometric distribution that arises from the paired binomial sampling model and the bivariate focus appears through a joint distribution between the parameters of the two treatments under consideration (θ_A and θ_B in their notation; θ_t and θ_r in McIntosh’s, described below). An EM algorithm is employed for analysis. This random effects model is formulated as a regression by Berkey *et al.* [23] in which the treatment effects form the response and covariates are added that may explain heterogeneity. A claimed advantage of these models is that the original units of the measured outcomes are retained rather than creating standardized effect sizes and consequently the interpretation of the results is enhanced.

Under a frequentist paradigm, generalized linear mixed models are developed and explored by Platt *et al.* [3]. Here, the odds ratio is modelled as a linear combination of study-specific covariates and random effects representing between-study variation. Normal approximations to the hypergeometric are employed and the suggestions of Berkey *et al.* [23] are used to reduce correlation between odds ratio and variance estimates. The regression coefficients and dispersion parameters are estimated by penalized quasi-likelihood and a linear model is fitted by weighted least squares to the observed log-odds ratios. They conclude that both approaches are reasonable in many circumstances but caution against using such approximate inference if the data are highly sparse.

McIntosh [24] also adopts a random effects regression model in which the treatment effects are assessed using the observed control group event rates as covariates. McIntosh then adds

a multivariate component to this model through a bivariate two-level hierarchical model. This is imposed in order to avoid the bias demonstrated to occur by including as fixed effects the estimates of population risk to explain treatment homogeneity. Both maximum likelihood and Bayesian platforms are discussed, with estimation for the former undertaken via the EM algorithm and a data augmentation (MCMC) algorithm for the latter.

Under McIntosh's formulation θ_{ii} represents the true treatment effect (for example, log-odds ratio) for trial (or study) i and θ_{ri} represents the true risk of the treated population (for example, mortality rate) in this trial. Both values are functions of treatment and control group parameters and are related through the Bayesian regression model $\theta_{ii} | \theta_{ri} \sim N(\mu_t + \beta_\theta(\theta_{ri} - \mu_r), \tau_t^2)$ with prior $\theta_{ri} \sim N(\mu_r, \tau_r^2)$. The trials yield observations Y_{ii} and Y_{ri} and an estimate of the covariance σ_{tri} . The bivariate measurement error model is then used as the sampling model

$$\begin{pmatrix} Y_{ii} \\ Y_{ri} \end{pmatrix} \sim N_2 \left(\begin{pmatrix} \theta_{ii} \\ \theta_{ri} \end{pmatrix}, \begin{pmatrix} \sigma_{ii}^2 & \sigma_{tri}^2 \\ \sigma_{tri}^2 & \sigma_{ri}^2 \end{pmatrix} \right)$$

This problem has recently been examined by Arends *et al.* [25] with the inclusion of explicit descriptions of the underlying baseline risk. As in Section 4, computation is through Markov chain Monte Carlo (MCMC) using the BUGS [15] software package. Emphasis is given to the flexibility of MCMC in allowing exact likelihoods, handling many different treatment effects measures and baseline risks, and obtaining additional information such as confidence bands for the underlying relationship between true effect measure and baseline risk.

In all of the above papers, the multivariate nature of the model arises through the description of the relationship between two treatment groups or a treatment and control in the analysis of a single response outcome. Other authors, such as Raudenbush *et al.* [26] and Berkey *et al.* [27, 28] take a similar focus to that adopted in the present paper in their consideration of multiple outcomes. Fixed-effects approaches are adopted by Raudenbush *et al.* who propose a fixed-effects generalized-least-squares multiple-regression model that allows adjustment for study-level covariates, and Berkey *et al.* [27] who extend their model described above.

An extension of the latter meta-regression approach to include a random effects component to account for unexplained heterogeneity, described by Berkey *et al.* [28] gives a model that is closely aligned to those described in Sections 3.1 and 3.2. This so-called general random-effects multiple-outcomes meta-regression model is represented as $y_i = X_i\beta + \delta_i + e_i$ where y_i is the vector of outcomes reported by trial i , X_i is a matrix containing the observed trial-level covariates for trial i , β is the vector of regression coefficients to estimate and δ_i is a vector of random effects associated with trial i . It is assumed (but not necessary) that $\delta_i \sim \text{MVN}(0, D)$ with D an unknown covariance matrix representing between-study covariance that is unexplained by the regression. For independent studies D has zero off-diagonal entries. Under the assumption of large sample sizes, e_i is $\text{MVN}(0, S_i)$ so that $\text{cov}(y_i) = D + S_i$ and $y_i \sim \text{MVN}(X_i\beta, D + S_i)$. A variety of methods for estimation is described, including iteratively weighted least-squares and multivariate maximum likelihood.

The methods described in the present paper are essentially analogues of the last approach, based on a Bayesian perspective and employing MCMC for analysis. The software used for the case study in Section 4 is BUGS. Available software for frequentist paradigms includes ML Win, SAS Proc Mixed and lme from S-plus.

4. CASE STUDY

ETS and its association with children's health has been an issue of concern for nearly a decade and has been a topic for analysis by such groups as the Australian National Health and Medical Research Council and the U.S. Environmental Protection Agency. We use this as our case study, asking the question: since childhood health outcomes such as asthma and lower respiratory disease (LRD) are correlated, and since the odds ratios for each outcome separately are relatively small in number and size, is there an advantage in combining the outcomes as well as the studies in an overall assessment of the association between ETS and children's respiratory illness?

4.1. Data source

The majority of studies considered for inclusion in our analysis were cited in the NHMRC Report [11]. Key references in this list of papers were then also accessed. Papers were then examined for their ability to provide required data on LRD and/or asthma in children which met the definitions given below. A total of 59 papers were identified as relevant to the current analysis: 27 contained LRD data only; 24 contained asthma data only, and 8 contained data on both outcomes.

Where available, data relating to covariates of interest were also extracted. These comprised study size, mean age, gender, year of publication, country group (coded 1–6), household or parental ETS, and whether reported estimates were adjusted or unadjusted for covariates.

While it is acknowledged that the NHMRC Report does not include all available studies on these associations and that our selection strategy may thus be biased, this compilation represents an accessible set of studies from a commissioned report. None the less, possible publication bias is assessed in Section 4.3 below.

4.2. Definition of outcomes

The definitions of asthma and LRD were problematic. In our analysis, the symptoms that were defined as asthma were bronchial asthma, allergic bronchitis and spastic bronchitis. The events defined as LRD were wheeze, persistent wheeze, bronchial obstruction, obstructive bronchitis, wheezing bronchitis, wheezy bronchitis, bronchiolitis, bronchitis and pneumonia.

There is no standard definition of asthma which is suitable for epidemiological studies [29] and there is considerable variation in opinion about the diagnosis of LRD. Asthma is manifested by wheezing in response to a variety of stimuli, including respiratory infection. In young children in particular, it is difficult to distinguish LRD, wheezing and asthma [30]. Moreover, a wheeze is often used as a surrogate measure of asthma, but the studies variously define wheeze. These difficulties are exacerbated by between-study differences such as sampling techniques and awareness of the two diseases. Hence although studies may advertise that their study concerns a particular outcome, the actual event measured may reflect a different outcome according to the definitions above. For example, Strachan and Carey [31] claim to study asthma but the measured outcome is wheeze and consequently it enters our analysis as LRD data.

Although the ideal source of diagnosis is the physician, most studies relied upon parental reporting. In our analysis, where the former was not available the latter source was used,

although it is acknowledged that this may induce bias. In particular, Burchfiel *et al.* [32] suggest that parents who smoke and report their own respiratory symptoms or illnesses may also tend to over-report respiratory conditions in their children.

The preferred measure was a cumulative count of the events rather than a current count, as the latter can only provide a snapshot of the association of interest. However, when the former was not available in any particular study, the latter was accepted.

Association between outcomes and ETS was most commonly reported as an odds ratio, so this was taken as the measure of interest. For a study to be included in the analysis, then, it had to provide an estimate of an odds ratio or equivalent and a corresponding variance, or information enabling these computations.

4.3. Definition of ETS

In most studies, exposure to ETS was defined through the smoking habits of parents and other persons living with the subject. However, there was great variation between studies with respect to their definition of ETS. For instance, Park and Kim [33] define a non-smoker as a person who had not smoked for one month prior to the interview, whereas, O'Connor *et al.* [34] define current cigarette smoking as currently smoking at least one cigarette per day or having quit such a habit within the past twelve months. Some papers did not even proffer a definition of a smoker [35]. This nebulous definition of smoking may contribute to the considerable variation shown in the results from otherwise comparatively analogous studies. For example, Ehrlich *et al.* [34] illustrated the effect of using different definitions of maternal smoking on the contribution of ETS to the final model of predictors of current asthma and wheeze.

Consequently, for our analysis a smoker was defined simply as one who was not a non-smoker, thus effectively adopting the various rules of the individual papers. Again, it is acknowledged that this may induce some bias or, perhaps more probably, additional noise in our results.

4.4. Inspection of data

Tables I, II and III provide the final data set, comprising study ID, sample size, average age and gender of subjects, country group in which the study was conducted, source of exposure (parental or household), reported odds ratios and whether these are adjusted for covariates, and the corresponding standard error of the log-odds ratios. The tables subset the studies into those providing results for asthma only (Table I), LRD only (Table II) and both outcomes (Table III). The corresponding box plots of the observed log-odds ratios and 95 per cent confidence intervals are shown in Figures 1 and 2 for asthma and LRD, respectively.

Inspection of these figures indicates that most of the reported odds ratios are greater than unity, suggesting that passive smoking may be positively associated with increased odds of asthma and of LRD. However, the standard errors of the individual estimates are sufficiently broad to induce suspicion about whether chance can be discounted as an explanation of these raised odds. Moreover, the results from a single table are less compelling than the impression from the data overall. Since there is a strong correlation of 0.84 between the log-odds ratios in those studies which report both outcomes, a meta-analysis which appropriately combines the data from both responses appears attractive. It is acknowledged, however, that

Table I. Data gathered from studies reporting odds ratios for asthma only.

ID	Size	Age	Sex	Year	Country	Smoke	Adj.	OR	SE(logOR)
3	1285	1.1	3	1987	1	0	0	1.47	0.27
6	1077	6.7	3	1995	1	0	0	1.42	0.15
10	850	9.4	3	1996	6	0	0	1.28	0.23
11	892	10.9	3	1996	2	0	1	0.98	0.22
14	1232	9.5	3	1996	5	0	1	0.91	0.27
17	2216	8.6	3	1997	1	1	0	0.76	0.15
19	535	6.5	3	1995	5	0	0	1.35	0.60
25	318	8.2	3	1995	6	0	0	1.40	0.36
38	511	2.5	3	1995	3	0	0	1.69	0.17
56	2554	9.5	3	1995	3	1	0	0.57	0.33
601	9653	9.0	3	1997	3	1	1	1.56	0.14
603	3769	9.0	3	1997	3	1	1	1.10	0.23
603	2540	9.0	3	1997	3	1	1	0.70	0.43
71	8585	7.0	3	1993	4	0	0	1.21	0.04
78	3072	8.5	3	1982	2	0	1	1.49	0.16
79	4331	2.5	3	1990	2	0	1	2.10	0.23
80	1215	2.0	3	1993	1	1	1	2.20	0.21
81	708	10.5	3	1994	4	1	1	1.40	0.19
82	620	10.0	3	1995	3	0	1	2.80	0.39
83	126	9.0	3	1991	3	0	0	2.56	0.37
84	228	8.5	3	1992	2	1	1	2.00	0.29
85	914	3.5	3	1993	2	0	1	1.43	0.18
114	207	9.3	3	1992	2	1	0	1.43	0.33
122	700	7.9	3	1992	2	0	0	1.42	0.19

ID: study identification number; Size: total number of valid subjects in study; Sex: 3 = both genders; Age: average age of subjects; Year: year of publication; Country: country code, 1 = England or Scotland, 2 = USA or Canada, 3 = Scandinavia or Netherlands, 4 = New Zealand or Australia, 5 = Japan, Hong Kong or Malaysia, 6 = Other (Israel, Turkey, South Africa, Mexico or U. Arab Emirates); Smoke: 0 = parental exposure, 1 = household exposure; Adj.: reported odds ratio is adjusted for covariates; OR: odds ratio; SE(logOR): standard error of log-odds ratio.

this attractiveness could be illusory, given the small number of studies on which this estimate is based and the possibility that it is caused primarily by intra-study correlation.

4.5. Publication bias

A visual assessment of potential publication bias in asthma and LRD associations may be obtained from a comparison of the reported log-odds ratios and their standard errors. The premise is that larger studies should provide similar estimates, and that random variation should induce a symmetric number of larger and smaller estimates from the smaller studies. Thus a plot of the log-odds ratio versus the inverse standard error for each study should have a symmetric funnel shape [37]. The funnel plots for the asthma and LRD associations are depicted in Figures 3 and 4, respectively. In both figures there is a distinct lack of small studies with comparatively small odds ratios in the left corner, strongly indicating the possibility of publication bias. The number of possible missing studies could be estimated using various methods; there is strong dissention about this in the NHMRC Report [11] due to dispute over the relative quality of estimates taken from unpublished reports. Here, we simply acknowledge the consequent potential for overestimation of the overall association.

Table II. Data gathered from studies reporting odds ratios for LRD only.

ID	Size	Age	Sex	Year	Country	Smoke	Adj.	OR	SE(logOR)
4	470	9.0	3	1994	3	0	1	1.04	0.20
8	550	1.7	3	1995	3	0	0	1.84	0.18
16	3048	1.0	3	1997	3	0	1	1.52	0.12
20	5953	0.5	3	1987	3	0	1	2.70	0.20
22	159	1.0	3	1986	2	0	0	2.00	0.24
26	343	9.5	3	1995	2	0	1	2.34	0.28
29	10106	7.5	3	1984	2	0	0	0.98	0.06
32	443	3.8	3	1992	4	0	0	6.91	0.46
36	12727	2.5	3	1987	1	0	0	1.46	0.10
37	257	7.5	3	1989	1	1	1	2.70	0.37
40	253	1.0	3	1995	4	0	0	0.72	0.51
43	1503	13.0	3	1997	1	0	0	1.13	0.14
49	1001	7.0	3	1988	1	1	0	1.04	0.19
50	961	13.5	3	1995	1	0	1	1.02	0.13
51	1138	9.0	3	1983	2	0	1	1.01	0.11
57	4665	13.5	3	1997	5	1	0	1.04	0.07
61	1143	1.0	3	1981	4	0	1	1.04	0.01
63	483	1.0	3	1989	1	0	1	1.61	0.23
65	8154	4.6	3	1995	4	0	1	1.22	0.04
69	2077	0.5	3	1974	1	0	0	1.65	0.21
75	301	1.0	3	1988	2	1	0	1.99	0.35
76	153	10.9	3	1989	2	0	0	2.52	0.39
88	16562	8.0	3	1991	1	0	1	1.35	0.30
89	15712	5.0	3	1995	1	0	0	1.33	0.19
105	192	0.8	3	1992	3	0	0	3.28	0.50
109	726	16.3	3	1996	6	0	1	4.36	0.47
111	372	7.0	3	1980	2	0	0	5.89	1.03

Terms defined in Table I.

Table III. Data gathered from studies reporting odds ratios for both outcomes.

ID	Size	Age	Sex	Year	Country	Smoke	Adj.	OR	SE(logOR)
Asthma									
24	9670	5.0	3	1989	1	0	0	0.96	0.12
28	11534	9.5	3	1996	2	1	1	0.98	0.11
44	7677	14.0	3	1995	6	0	0	1.17	0.06
52	5412	9.2	3	1997	6	1	1	1.35	0.09
54	925	7.0	3	1997	2	1	1	1.60	0.28
59	1501	9.5	3	1991	5	1	1	1.10	0.11
93	3482	8.4	3	1986	2	0	0	1.15	0.13
113	684	9.0	3	1988	3	1	1	0.93	0.04
LRD									
24	9670	5.0	3	1989	1	0	1	1.05	0.09
28	11534	9.5	3	1996	2	1	1	1.13	0.06
44	7677	14.0	3	1995	6	0	0	1.15	0.02
52	5412	9.2	3	1997	6	1	1	1.25	0.09
54	925	7.0	3	1997	2	1	1	1.70	0.32
59	1501	9.5	3	1991	5	1	1	1.20	0.15
93	3482	8.4	3	1986	2	0	0	1.24	0.08
113	684	9.0	3	1988	3	1	1	1.25	0.11

Terms defined in Table I.

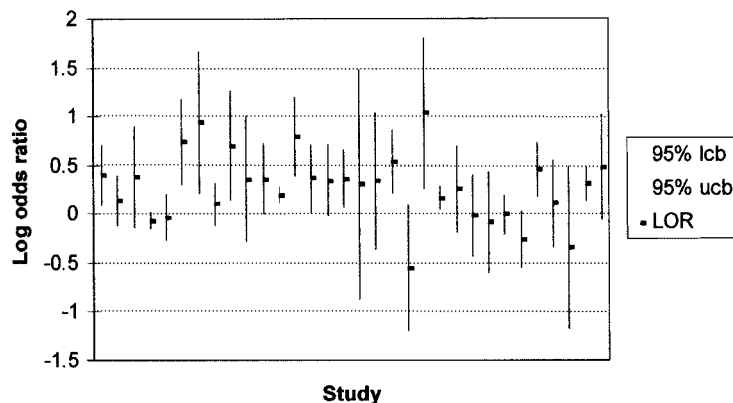


Figure 1. Point estimates and 95 per cent confidence intervals for the log-odds ratios for asthma, ordered by year of publication, from 1982 to 1997.

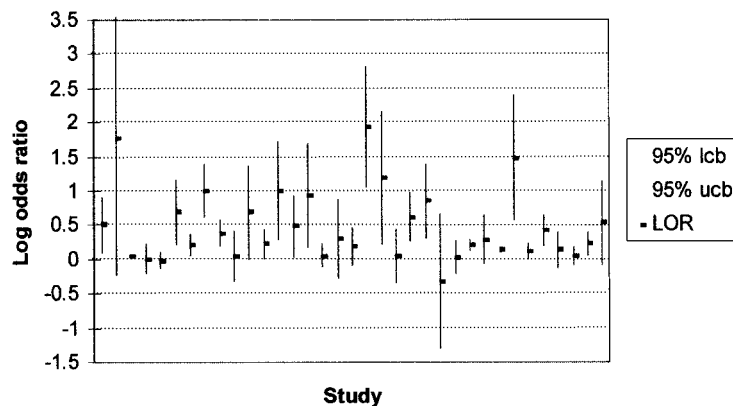


Figure 2. Point estimates and 95 per cent confidence intervals for the log-odds ratios for LRD, ordered by year of publication, from 1974 to 1997. Note that the scale is different from Figure 1. The truncated upper bound is 3.79, for study 111.

5. RESULTS

5.1. Covariate adjustment

An exploratory analysis of significant risk factors for asthma and LRD separately was undertaken through a series of normal linear models, with log odds as the dependent variable and using the following series of factors: country; smoke; adjusted; size; country + smoke; country + adjusted; smoke + adjusted; country + smoke + adjusted; size + smoke + adjusted. For each outcome, no combination of risk factors was statistically significant, with the smallest p -value of 0.08 for a model of asthma comprising the two variables 'smoke' (parental or household) and 'adjusted' (reported estimates adjusted or unadjusted for covariates). However, age was found to be strongly significant and, after exploration, the most informative

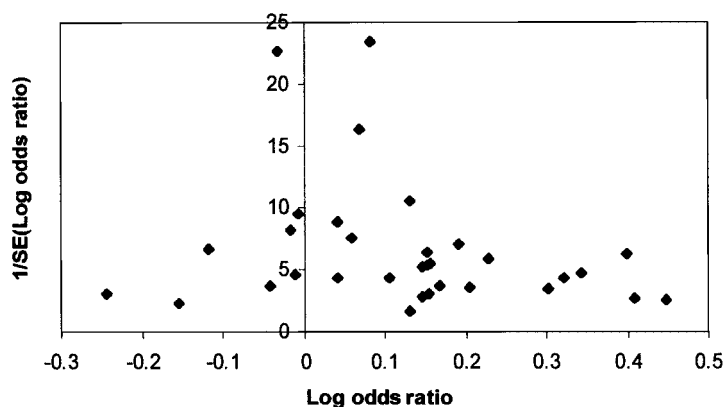


Figure 3. Funnel plot of the asthma log-odds ratios.

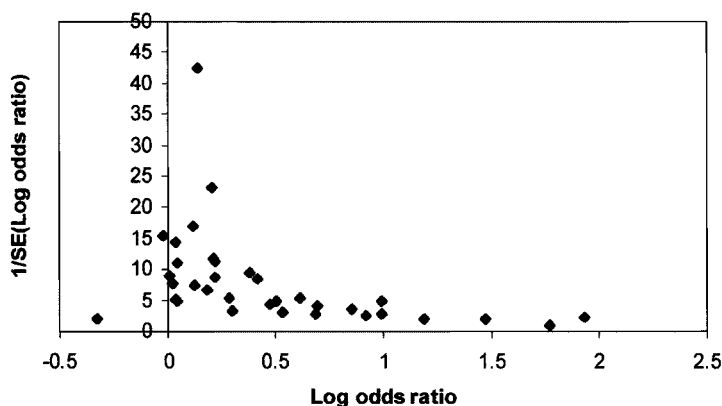


Figure 4. Funnel plot of the LRD log-odds ratio. Study 111 with a comparatively very large standard error of 1.03 for the log-odds ratio is omitted from the plot.

split was based on whether the median age of the subjects is greater or less than four years ($p = 0.0005$ for LRD, $p = 0.0038$ for asthma). The second best split, not further reported in this paper, was with a categorization around three years, for which estimates were different but the inference was not altered. No other variable was found to make a statistically significant contribution after age was entered into the model in this way.

5.2. Univariate analysis

5.2.1. Frequentist approach. Table IV provides summary statistics generated under the frequentist univariate FE and RE models. As expected, the standard errors generated under the RE model are slightly larger than their counterparts in the FE model. All analyses indicate a significant positive association between ETS and the two outcomes, but the increase is much more pronounced after study heterogeneity is taken into account under the RE model. The

Table IV. Summary statistics for univariate frequentist meta-analyses of the reported odds ratios under fixed effects (FE) and random effects (RE) models. The between-study variance is estimated using the approach of DerSimonian and Laird.

Outcome	Method	Odds ratio	95 per cent CI	Between-study variance	Homogeneity statistic (Q)
Asthma	FE	1.15	(1.10, 1.20)	0.036	98.8, 31 d.f.
	RE	1.26	(1.15, 1.38)		
LRD	FE	1.09	(1.07, 1.11)	0.019	155.3, 34 d.f.
	RE	1.28	(1.19, 1.37)		

Table V. Decomposition of data under a frequentist univariate random effects (RE) model.

		Asthma			LRD		
		OR	95 per cent CI	Number of studies	OR	95 per cent CI	Number of studies
Overall		1.26	(1.15, 1.38)	32	1.28	(1.19, 1.37)	35
Size	<1000	1.44	(1.17, 1.76)	14	1.84	(1.45, 2.33)	16
	1000+	1.20	(1.08, 1.33)	18	1.18	(1.11, 1.26)	19
Age	<4	1.74	(1.46, 2.07)	5	1.77	(1.37, 2.28)	12
	4+	1.18	(1.08, 1.30)	27	1.16	(1.09, 1.24)	23
Year published	Pre-1990	1.11	(0.92, 1.34)	5	1.33	(1.17, 1.50)	16
	1990+	1.29	(1.17, 1.43)	27	1.27	(1.16, 1.39)	19
Country group	1.00	1.24	(0.88, 1.76)	5	1.27	(1.10, 1.46)	10
	2.00	1.34	(1.14, 1.59)	10	1.32	(1.11, 1.56)	10
	3.00	1.27	(0.93, 1.74)	8	1.63	(1.24, 2.13)	6
	4.00	1.22	(1.12, 1.32)	2	1.22	(0.98, 1.52)	4
	5.00	1.08	(0.88, 1.31)	3	1.06	(0.94, 1.20)	2
	6.00	1.23	(1.11, 1.35)	4	1.29	(1.02, 1.62)	3
Exposure	Parental	1.30	(1.18, 1.43)	18	1.31	(1.20, 1.42)	2
	Household	1.18	(1.01, 1.39)	14	1.19	(1.07, 1.33)	9
Adjusted	No	1.20	(1.07, 1.34)	15	1.34	(1.18, 1.51)	17
	Yes	1.32	(1.13, 1.54)	17	1.27	(1.15, 1.40)	18

Terms are defined in Table I.

overall statistic for testing homogeneity between studies, $Q = \sum_{i=1}^J (y_{ij} - \hat{\theta}_j)^2 / \phi_{ij}$, is statistically significant for both outcomes (LRD: $Q = 155.3$, 34 d.f.; asthma: $Q = 98.8$, d.f. = 31), indicating support for the RE model. The implication of accounting for this heterogeneity is particularly evident in the results for LRD, where the FE and RE results are very different.

It is also of interest to examine meta-analyses of particular categories of subjects and papers. In Table V, summary statistics under the RE model are provided for selected subgroups. These are graphically depicted in Figures 5 and 6 for asthma and LRD, respectively. From these tables and figures, we observe that there is strong similarity in overall odds ratios for asthma (1.26) and LRD (1.28) and in the size of the confidence intervals. The combined odds ratios from smaller studies (with less than 1000 subjects) are substantially higher than those from larger studies. Younger children have higher odds ratios than older children, and the association is greater when exposure is measured in terms of parental smoking than general household smoking. Country group 5 (Japan, Hong Kong, Malaysia) has noticeably smaller

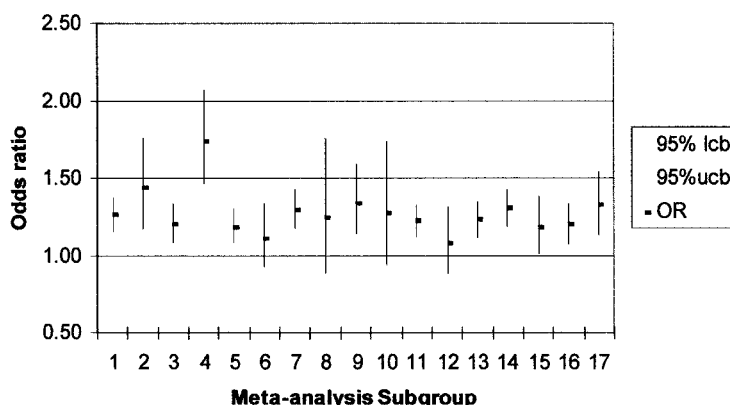


Figure 5. Odds ratios and 95 per cent confidence intervals for various subsets of the asthma data, under a frequentist univariate RE model. 1 = overall; number of subjects: 2 = <1000, 3 = 1000+; average age: 4 = <4 years, 5 = 4+ years; year published: 6 = pre-1990, 7 = 1990+; country group: 8 = 1, 9 = 2, 10 = 3, 11 = 4, 12 = 5, 13 = 6; source of exposure: 14 = parental, 15 = household; adjusted for covariates: 16 = no, 17 = yes.

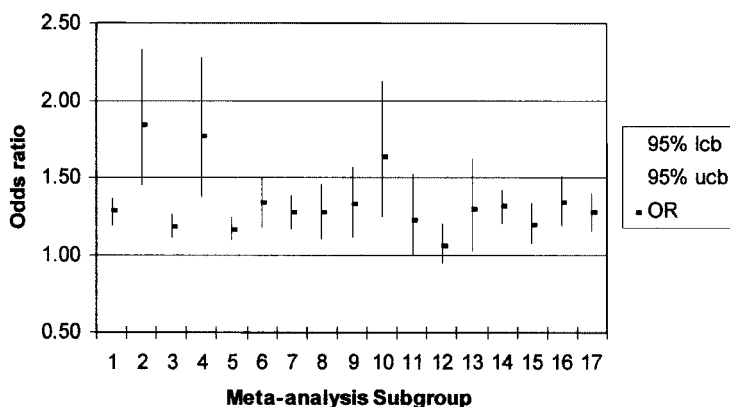


Figure 6. Odds ratios and 95 per cent confidence intervals for various subsets of the LRD data, under a frequentist univariate RE model. 1 = overall; number of subjects: 2 = <1000, 3 = 1000+; average age: 4 = <4 years, 5 = 4+ years; year published: 6 = pre-1990, 7 = 1990+; country group: 8 = 1, 9 = 2, 10 = 3, 11 = 4, 12 = 5, 13 = 6; source of exposure: 14 = parental, 15 = household; adjusted for covariates: 16 = no, 17 = yes.

odds ratios for both outcomes than the other country groups, for whom the estimates are reasonably consistent. There is no bias demonstrated over both outcomes for pre- or post-1990 papers, or for estimates adjusted or unadjusted for covariates.

Model checking in the ETS example was undertaken through quantile–quantile plots and goodness-of-fit tests. This provided support for normality of the y_{ij} for both outcomes for both FE or RE models. However, under the RE model, the assumption that the between-

Table VI. Summary statistics for the posterior distributions of certain measures under a univariate Bayesian random effects model, for two age categories (split at 4 years), based on an MCMC sample of 100 000 cycles. Within- and between-study weights are the estimates of ϕ and ψ , respectively.

Outcome	Measure	Estimate	95 per cent CI
Asthma	Overall odds ratio	1.27	1.14, 1.42
	OR for older age group	1.20	1.07, 1.35
	OR for younger age group	1.75	1.33, 2.31
	Within-study weight	0.99	0.67, 1.39
	Between-study weight	8.02	3.57, 15.0
	Age covariate	-0.38	-0.68, -0.08
LRD	Overall odds ratio	1.39	1.23, 1.59
	OR for older age group	1.24	1.08, 1.45
	OR for younger age group	1.71	1.37, 2.15
	Within-study weight	0.88	0.59, 1.25
	Between-study weight	12.93	6.02, 23.23
	Age covariate	-0.32	0.58, 0.05

study error for LRD has a normal distribution is not supported and a t -distribution better describes this variation. An RE analysis of the LRD data using this modification revealed that the overall odds ratio and confidence bounds decreased by about one percentage point. Moreover, after adjustment for age, there was considerably more support for normality of the between-study error for LRD. Given these considerations, a normal distribution was retained in further analyses.

5.2.2. Bayesian approach. In our analysis of the ETS data, B_j and C_j are diagonal matrices so the distributions of y_j and θ_j were re-expressed as $y_{ij} \sim N(\theta_{ij}, \phi_j c_{ii(j)})$ and $\theta_{ij} \sim N(x'_{ij} \beta_j, \psi_j b_j)$. As indicated in Section 2.3, $c_{ii(j)}$ was set equal to the within-study estimate of $\text{var}(y_{ij})$ and b_j was equated to the method of moments estimate of between-study variance for outcome j ($j = 1, 2; i = 1, \dots, I_j$). For the prior distributions of ϕ_j and ψ_j we put $v_j = 50$ to reflect the number of exposed cases in a typical large ETS study and $\delta_j = 3$ to acknowledge negligible information about between study-behaviour. Further analyses not shown here indicated reasonable lack of sensitivity to these choices. The first component of x_{ij} equals 1 and the second component reflected the structure of the age covariate. The latter was centred to have a mean of 0. Putting $\beta_j \sim \text{MVN}(\mathbf{0}, D \rightarrow \infty)$ completed the model specification. The effect of giving θ_{ij} a univariate t -distribution was also examined, in keeping with the results of the previous section.

Analysis was undertaken using BUGS as described in Sections 2 and 3. BUGS code for all analysis discussed in this paper and notes on its implementation may be obtained from the corresponding author. For each analysis, estimates were based on a collection period of 100 000 iterations after a burn-in of 150 000 cycles, with thinning intervals of one to five cycles where advised by CODA convergence diagnostics, particularly the Raftery–Lewis assessment [38].

Table VI provides results (posterior odds ratios and 95 per cent credible intervals) after age adjustment (split at 4 years). For asthma, the posterior mean odds ratios for the individual

Table VII. Summary statistics for the posterior distributions of certain measures under a multivariate Bayesian model (Section 3.1) adjusted for age and using all data. Estimates are based on 90 000 MCMC cycles.

Outcome	Measure	Estimate	95 per cent CI
Asthma	Overall odds ratio	1.27	1.14, 1.42
	OR for the older age group	1.20	1.07, 1.35
	OR for the younger age group	1.75	1.31, 2.34
	Age covariate	-0.38	-0.69, -0.07
Asthma and LRD	Correlation between the two outcomes for the younger age group	0.31	-0.87, 0.98
	Correlation between the two outcomes for the older age group	0.55	-0.80, 0.99
LRD	Overall odds ratio	1.40	1.24, 1.60
	OR for the older age group	1.27	1.10, 1.47
	OR for the younger age group	1.71	1.38, 2.14
	Age covariate	-0.30	-0.68, -0.05

studies (θ_{ii}) and overall (θ_i) are similar to those obtained under the frequentist RE approach, but the Bayesian model produces slightly larger credible intervals in keeping with the more flexible modelling of the between-study variation and hence the uncertainty in the age effect.

All analyses indicate that the association between each outcome and ETS is substantially greater in younger age groups. Considering the parameter associated with the covariate, age, the log-odds ratio for asthma is 0.380 smaller, on average, for the older age group. For LRD, the mean log-odds ratio is 0.316 smaller for the older age group. Because the age factor has been adjusted to have an average value of 0, the covariate parameter is approximately uncorrelated with θ_j , so the width of the posterior credible interval for θ_j is smaller than before. The results also indicate that the LRD odds ratios adjusted for the age covariate give greater support for the normality assumptions than before.

5.3. Multivariate analysis

It was assumed that studies were independent of each other and, using the preferred model of Section 3.1, we put $\mathbf{y}_j \sim \text{MVN}(\boldsymbol{\theta}_j, \Gamma_i)$ and $\boldsymbol{\theta} \sim \text{MVN}((\mathbf{x}'_{i1}\boldsymbol{\beta}_1, \dots, \mathbf{x}'_{ij}\boldsymbol{\beta}_j)', \Lambda)$. The diagonal elements of the 2×2 matrices Γ_i and Λ are $\phi_j c_{ii(j)}$ and $\psi_j v_j$, respectively, and it was assumed that the off-diagonal elements of Γ_i could be written as $\rho_{12}(c_{ii(1)}c_{ii(2)})^{1/2}$. Uniform distributions on the interval $[-1, 1]$ were taken as the prior distributions for the correlations $\sigma_{12}/\{\psi_1 b_1 \psi_2 b_2\}^{1/2}$ and $\rho_{12}/\{\phi_1 \phi_2\}^{1/2}$, that are derived from Λ and Φ . Other quantities and variables were given the same values and prior distributions as they were given in the univariate Bayesian analysis.

The model was implemented in BUGS with no difficulty and the multivariate models had noticeably better convergence properties than the corresponding univariate models. Moreover, inspection of the residuals revealed better support for the assumptions of normality. There is an identifiability problem between Γ_i and Λ but sensitivity analysis given in the next section shows that this had almost no effect on estimates of the parameters of main interest. Summary statistics are provided in Table VII.

In this analysis, the estimated within-study-and-outcome variance terms were close to the observed residual variance, indicating that there was little unexplained variability in the data

Table VIII. Summary statistics for the posterior distributions of certain measures under a multivariate Bayesian model (Section 3.1), adjusted for age and after excluding studies that reported only LRD.

Outcome	Measure	Estimate	95 per cent CI
Asthma	Overall odds ratio	1.27	1.14, 1.43
	OR for the older age group	1.20	1.06, 1.36
	OR for the younger age group	1.75	1.31, 2.34
LRD	OR for the older age group	1.25	0.97, 1.60

under this model. An overall strong association between ETS and each outcome was observed, but this was more dominant in the younger age group.

Compared with the univariate results, small studies suffered slightly greater shrinkage and the posterior credible intervals of the LORs under the multivariate models were consequently shorter. However, the overall summary estimates for the multivariate models are almost identical to those under the univariate approach and the credible intervals for the correlations are extremely wide, indicating that the multivariate extension has not contributed substantially to this analysis. This is perhaps expected because there are only eight studies that examine both asthma and LRD and many studies that examine one or other of the outcomes. Indeed, it is anticipated that the benefits of the multivariate model would be clearer under circumstances where ‘borrowing strength’ appears imperative because data are limited.

To this end the analyses were repeated but with some data omitted. Specifically, the studies in which only LRD had been examined were excluded. This seems to have had the desired effect in that the univariate and multivariate results for LRD now differ clearly, as illustrated in Table VIII. For comparison, a univariate analysis on the same dataset yields a mean odds ratio of 1.21 with 95 per cent credible interval from 0.94 to 1.58. Under the multivariate model, the means are quite different and the standard deviation is a touch smaller. This is interesting, since the *a priori* expectation was that the difference would be in the standard errors, but in fact it is the point estimates of log-odds ratios that differ most. If one takes the results based on all the data as the ‘true’ value, which seems the best one can do, then the multivariate point estimate is much the better.

It may be that the data set is such that missingness on LRD is associated with the LOR of asthma. As soon as missingness is not completely at random, the complete cases analysis (that is, only based on the studies with asthma and LRD available) is biased. This is corroborated by the observation from Table VII that the posterior distribution of the correlation is very flat.

Of course, the lack of results for LRD for the younger age group reflects the lack of data for this cohort. In fact, the MCMC estimates for this group were an odds ratio of 38 and a 95 per cent credible interval covering effectively the whole real line.

5.4. Sensitivity assessment

The discussion in Sections 3 and 4 highlights the identifiability of the correlations as a potentially important issue in the adoption of this model. In particular, the choice of prior for the correlations may impact on the estimates of important variables.

It would be reasonable to argue that more information could be extracted from the individual studies to assist in the definition of within-study correlations, thus providing greater stability to the estimation of between-study correlation. In this case study, however, only eight studies reported estimates of both outcomes of interest and relevant information about the within-study correlation between the measures was scant. Moreover, adjustment was made for age in the above analysis. It is acknowledged that relevant information might be obtained from the corresponding authors, but this was not pursued for this case study.

A different approach to assessing the impact of choice of prior for correlations was adopted here. A sensitivity analysis was undertaken using the full data set from the case study described in Section 4, based on the following model from Section 3.1:

$$\begin{pmatrix} y_{i1} \\ y_{i2} \end{pmatrix} \sim \text{MVN} \left(\begin{pmatrix} \theta_{i1} \\ \theta_{i2} \end{pmatrix}, \begin{pmatrix} c_{ii(1)}^{1/2} & 0 \\ 0 & c_{ii(2)}^{1/2} \end{pmatrix} \begin{pmatrix} \phi_1 & \rho_{12} \\ \rho_{12} & \phi_2 \end{pmatrix} \begin{pmatrix} c_{ii(1)}^{1/2} & 0 \\ 0 & c_{ii(2)}^{1/2} \end{pmatrix} \right)$$

and

$$\begin{pmatrix} \theta_{i1} \\ \theta_{i2} \end{pmatrix} \sim \text{MVN} \left(\begin{pmatrix} \mathbf{x}'_{i1} \boldsymbol{\beta}_1 \\ \mathbf{x}'_{i2} \boldsymbol{\beta}_2 \end{pmatrix}, \begin{pmatrix} \psi_1 b_1 & \sigma_{12} \\ \sigma_{12} & \psi_2 b_2 \end{pmatrix} \right)$$

with the correlations (cor1 and cor2) defined by $\text{cor1} = \rho_{12} / \sqrt{(\phi_1 \phi_2)}$ and $\text{cor2} = \sigma_{12} / \sqrt{(\psi_1 b_1 \psi_2 b_2)}$.

The following priors were examined:

Prior 1. The original prior: $\text{cor1} \sim U(-1, 1)$ and $\text{cor2} \sim U(-1, 1)$.

Prior 2. Making cor1 positive with tiny weight for negative values:
 $\text{cor1a} \sim U(0, 1)$; $\text{cor1b} \sim U(-1, 0)$; $y \sim \text{Bernoulli}(0.9999)$;
 $\text{cor1} = y \times \text{cor1a} + (1 - y) \times \text{cor1b}$; $\text{cor2} \sim U(-1, 1)$.

Prior 3. Making both cor1 and cor2 positive with tiny weight for negative values:
 $\text{cor1a} \sim U(0, 1)$; $\text{cor1b} \sim U(-1, 0)$; $y1 \sim \text{Bernoulli}(0.9999)$; $\text{cor1} = y1 \times \text{cor1a} + (1 - y1) \times \text{cor1b}$;
 $\text{cor2a} \sim U(0, 1)$; $\text{cor2b} \sim U(-1, 0)$; $y2 \sim \text{Bernoulli}(0.9999)$; $\text{cor2} = y2 \times \text{cor2a} + (1 - y2) \times \text{cor2b}$.

Prior 4. Making cor2 positive with tiny weight for negative values:
 $\text{cor1} \sim U(-1, 1)$, $\text{cor2a} \sim U(0, 1)$; $\text{cor2b} \sim U(-1, 0)$; $y2 \sim \text{Bernoulli}(0.9999)$;
 $\text{cor2} = y2 \times \text{cor2a} + (1 - y2) \times \text{cor2b}$.

Prior 5. Making cor1 and cor2 equal to each other, with $\text{cor1} \sim U(-1, 1)$, $\text{cor2} = \text{cor1}$.

Under every scenario described above, the choice of prior made almost no difference to any of the estimates other than those of cor1 and cor2. The estimates for every other parameter varied by less than 0.01.

One interpretation of the above results is that the method described is useful even though in this example the correlations are difficult to identify. Another interpretation is that in this study, the overlap between asthma and LRD seems so small that the correlation hardly plays a role in the bivariate analysis with respect to the estimates of the overall odds ratios and their credible intervals. Hence there is little impact of misspecification of correlation priors.

However in other situations this impact may be substantial. More general investigation is required to further investigate this.

6. DISCUSSION

This paper has focused on approaches to combining information not only from different studies, but also from different outcomes. Natural extensions of the common univariate models are explored, including fully multivariate approaches and adaptations of mixed models for multi-centre trials. Modifications to the multivariate framework are suggested for ease of computation and greater flexibility in application to situations in which different studies offer different degrees of information about the outcomes of interest.

It was natural to adopt a Bayesian platform for these multivariate models, for the following reasons. 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. Second, there is an ease in adjusting for covariates and, third, the posterior estimates and probabilities are easily interpreted.

By performing a multivariate Bayesian random effect analysis, we are able to not only estimate the association between ETS and individual respiratory health outcomes, but also estimate the overall association between the outcomes in the context of their associations with passive smoking. Although it was anticipated that the 'borrowing of strength' from multiple outcomes would positively influence the posterior estimates for each outcome, this was not observed in the ETS data set studied here. In fact, the posterior credible intervals for the odds ratios were very similar to those obtained under the univariate analyses and, somewhat surprisingly, where anything was affected it was the odds ratios themselves. It is believed that this is due to both outcomes having fairly equivalent numbers of observations. This is supported by secondary analyses in which a large subset of data was removed, resulting in a noticeable difference between the univariate and multivariate estimates. Indeed, the overall conclusion from this sensitivity analysis was that the multivariate models are most influential when the data sets are small.

Of course, caveats on the applicability and interpretation of meta-analyses apply to the multivariate situation perhaps even more strongly than to the univariate framework. As intimated in Section 1, there is now a wealth of prescriptive, descriptive and cautionary literature to this effect. In addition, improvements to the meta-analysis models described here may be obtained by greater effort in extracting important information such as within-study correlations between measures in those studies that report both outcomes. On the basis of the sensitivity analysis, it is arguable that this additional information would not affect the current conclusions, although it may be invaluable in other applications.

Overall, the association between ETS and asthma, and ETS and lower respiratory disease was found to be statistically significant but small, with posterior estimates of odd-ratios around 1.3, and up to 1.7 after adjustment for age, and none of the upper 95 per cent credible bounds exceeded 2.0. This covariate was found to be the most influential of those covariates considered, with children under three or four years of age associated with a substantially larger overall odds-ratio than older children. One country group (Japan, Hong Kong, Malaysia) was found to have a smaller, and non-significant, odds ratio for both outcomes, although possible explanations for this are not pursued in this paper.

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