Bayesian implementation of a genetic model-free approach to the meta-analysis of genetic association studies

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SUMMARY

A genetic model-free method for the meta-analysis of genetic association studies is described that estimates the mode of inheritance from the data rather than assuming that it is known. For a bi-allelic polymorphism, with G as risk allele and g as wild-type, the genetic model depends on the ratio of the two log odds ratios, \( \lambda = \log \text{OR}_{Gg}/\log \text{OR}_{GG} \), where \( \text{OR}_{GG} \) compares GG with gg and \( \text{OR}_{Gg} \) compares Gg with gg. Modelling \( \log \text{OR}_{GG} \) as a random effect creates a hierarchical model that can be implemented within a Bayesian framework.

In Bayesian modelling, vague prior distributions have to be specified for all unknown parameters when no external information is available. When the data are sparse even supposedly vague prior distributions may have an influence on the posterior estimates. We investigate the impact of different vague prior distributions for the between-study standard deviation of \( \log \text{OR}_{GG} \) and for \( \lambda \), by considering three published meta-analyses and associated simulations. Our results show that depending on the characteristics of the meta-analysis the results may indeed be sensitive to the choice of vague prior distribution for either parameter.

Genetic association studies usually use a case-control design that should be analysed by the corresponding retrospective likelihood. However, under some circumstances the prospective likelihood has been shown to produce identical results and it is usually preferred for its simplicity. In our meta-analyses the two likelihoods give very similar results. Copyright © 2005 John Wiley & Sons, Ltd.

KEY WORDS: Bayesian methods; case–control study; genetic association studies; meta-analysis; prior distributions; retrospective likelihood

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1. INTRODUCTION

1.1. Bayesian models for meta-analysis

Meta-analysis is the quantitative synthesis of results from multiple studies [1]. If the results for the individual studies are similar they can be pooled using a fixed effects model, but where the studies show heterogeneity it is important to use a random effects model that allows for the between-study variability [1]. Ideally the reasons for the heterogeneity should then be investigated [2]. A random effects meta-analysis is an example of a two-level hierarchical (or multilevel) model. By assuming exchangeability between studies, each can ‘borrow strength’ from the others. This results in the estimated effects for the individual studies being shrunk towards the overall mean and usually gives increased precision. More importantly, the precision of the estimate of that overall mean will allow for the variability between studies [3,4].

The Bayesian approach to hierarchical modelling has been advocated for theoretical and practical reasons [4]. Bayesian analysis allows researchers to use external information either in the form of subjective beliefs or based on other data sources, and enables them to produce subjective probability statements about the model parameters [4]. Fitting Bayesian models by Markov chain Monte Carlo (MCMC) methods is particularly flexible and makes it practical to use relatively complex hierarchical models while allowing for uncertainty in all parameters [5,6]. Although possible, inclusion of uncertainty for variance parameters in an equivalent likelihood analysis is not straightforward and this source of variability is often ignored [7].

The main practical problem in undertaking a Bayesian meta-analysis is to specify appropriate prior distributions for the model parameters based on external information. When expert opinion is available it can be difficult to use this to derive probability distributions, especially for parameters such as variances or correlations [8,9]. When there is no external information we are left with the equally difficult problem of trying to specify non-informative prior distributions for all of the model parameters, including the hyperparameters if the model is hierarchical [3]. Although a number of such prior distributions have been proposed, and routinely used, strictly speaking ‘non-informative’ prior distributions, i.e. prior distributions that formally represent ignorance, and thus do not favour any particular parameter values, do not exist [10,11]. In fact, any prior distribution exerts some influence on the shape of the posterior distribution, the more so in the presence of sparse data. The real aim is to identify a prior distribution that has minimal effect on the final inference relative to the data [12]. For this reason, the term non-informative prior distribution is better replaced by ‘vague’ prior distribution [13,14], which indicates a density with high spread that gives similar prior probability to a wide range of parameter values. The problem of choosing vague prior distributions has been demonstrated to be particularly critical for hierarchical variance parameters, since prior distributions proposed as vague might in fact influence the analysis due to limited data [13,15–17]. Thus, sensitivity analyses that examine the robustness of the choice of prior distributions are an essential part of a Bayesian hierarchical analysis.

1.2. Meta-analysis of genetic association studies: a genetic model-free approach

The meta-analysis of genetic association studies introduces specific methodological problems [18], among which the most characteristic is the presence of at least three possible
genotypes as exposure groups and the fact that these are related by the underlying mode of inheritance. In the simplest case of a bi-allelic genetic polymorphism, with a wild-type allele, g, and a mutant allele, G, thought to be associated with the disease of interest, association studies will collect information on the relative frequency of disease in subjects with each of the three genotypes (gg, Gg and GG). There are thus two relative risks or odds ratios to be estimated, GG and Gg, each compared with the wild genotype gg. The relationship between these two relative risks is dependent on the mode of inheritance, also called the genetic model.

Methods currently used for the meta-analysis of such studies usually reduce the three groups to two by assuming a specific genetic model and thus combining the groups accordingly (e.g. assuming a recessive model to justify combining Gg and gg) or assigning to the heterozygous group Gg half the effect, on the log scale, of the GG group (co-dominant model or ‘per-allele’ analysis) [18].

Since the underlying genetic model is usually not known, we propose a method that avoids the assumption of a specific genetic model, but which takes into account the correlation between the two estimates of the odds ratios [19]. The model treats the log odds ratio of Gg versus gg (log OR\textsubscript{Gg}) as an unknown proportion, λ, of the log odds ratio of GG versus gg (log OR\textsubscript{GG}), i.e. λ = log OR\textsubscript{Gg}/log OR\textsubscript{GG}, and thus OR\textsubscript{Gg} = (OR\textsubscript{GG})\textsuperscript{λ}. Under this model the ratio, λ, is assumed constant across studies. We refer to this approach as ‘genetic model-free’, a term already in use in genetic epidemiology to indicate that no underlying genetic model is assumed, though the analyses are still based on an assumed statistical model. Values of λ equal to 0, 0.5 and 1 correspond to the recessive, co-dominant and dominant genetic model, respectively, but we allow λ to take any value between 0 and 1. In very rare situations a gene may be over-dominant, that is the risk of the Gg group can be higher or lower than either of the homozygous groups [20]. This would be characterized by values of λ higher than 1 or lower than 0. This rare situation is not considered in this particular investigation.

1.3. Overview of the paper

In this paper we consider the statistical aspects of a Bayesian implementation of the genetic model-free approach by applying the model to three previously published meta-analyses and to simulations based on those three scenarios.

When adopting a Bayesian approach to a hierarchical model that allows heterogeneity in OR\textsubscript{GG}, unless there is prior knowledge, we have the problem of specifying vague prior distributions for the between-study variance of log OR\textsubscript{GG} and for the parameter λ. Since we rule out the over-dominant case in our examples, we need vague prior distributions for λ which are constrained to cover the range between 0 and 1. The sensitivity of the analysis to the choice of vague prior distributions is investigated for the three published meta-analyses introduced in Section 2 and then for the simulated data in Section 3.

By far the majority of genetic association studies use a case–control design that requires a retrospective likelihood based on the probability of exposure given disease. Prentice and Pyke [21] showed that a maximum likelihood analysis based on the corresponding prospective likelihood gives the same results as an analysis of the retrospective likelihood for a single study. Because the form of the prospective likelihood is simpler, it is very widely used. Equivalence within the Bayesian framework does not generally exist and has only been established for very particular choices of prior distributions [22]. Although not exactly equivalent, the results of Prentice and Pyke would suggest that with vague prior distributions the
retrospective and prospective Bayesian analyses should give similar answers. This issue is investigated in the context of meta-analysis in Section 4.

2. ILLUSTRATIVE EXAMPLES

2.1. Illustrative meta-analyses

For illustrative purposes, the genetic model-free method and all sensitivity analyses are applied to three previously published meta-analyses. In all cases, the polymorphism is bi-allelic, and we will call the two alleles G and g, where G is the one thought to be associated with the disease. The examples are

(a) *AGT* gene and essential hypertension, reported by Kato et al. [23]. The meta-analysis includes 7 case–control studies, with an average number of cases and controls per study of 191 and 175, respectively, and an average frequency of the G allele of 0.75.

(b) *KIR6.2* gene and type II diabetes, reported by Hani et al. [24]. This meta-analysis includes 4 case–control studies, with an average number of cases and controls per study of 130 and 92, respectively, and an average frequency of the G allele of 0.34.

(c) *PONI* Q192R polymorphism and myocardial infarction, reported by Wheeler et al. [25]. This is a meta-analysis including 19 studies, 17 of which are case–control and 2 cohort studies. The average number of cases and controls per study is 301 and 424, respectively, and the average frequency of the G allele is 0.33.

The variation between the three meta-analyses in terms of the number and sizes of the studies and the frequency of the allele of interest allows us to assess whether the sensitivity to the choice of prior distributions varies according to these characteristics.

2.2. The meta-analytical model based on retrospective likelihood

The meta-analysis is based on a retrospective likelihood that mirrors the method of sampling in case–control studies. Subjects are selected dependent on their disease status and then their exposure status is ascertained.

Denoting by $y_{0j}$ and $y_{1j}$ the number of controls and cases, respectively, in genotype group $j$, with $j = 1, 2, 3$ (corresponding to gg, Gg and GG), the retrospective likelihood ($L_R$) for each study included in the meta-analysis is derived from a pair of multinomial distributions

$$y_{0j} \sim \text{Multinomial}(n_0, p_{0j}) \quad y_{1j} \sim \text{Multinomial}(n_1, p_{1j})$$

where $n_0$ and $n_1$ are the total number of controls and cases, respectively

$$p_{dj} = \frac{\beta_j \exp(d \delta_j)}{\sum_{k=1}^{3} \beta_k \exp(d \delta_k)}, \quad j = 1, 2, 3$$

and $d$ is an indicator of the disease status, taking the value of 0 for controls and 1 for cases. The probability that a control has exposure $j$ is $\beta_j / \sum_{k=1}^{3} \beta_k$, with $\beta_1 = 1$. The log odds ratios of disease for the exposure groups Gg and GG compared to no exposure (gg) are represented by $\delta_2$ and $\delta_3$, respectively, while $\delta_1$ is zero by definition. The likelihood for each study will
thus take the form

\[ L_R(\beta, \delta; y) = \prod_{d=0}^{3} \prod_{j=1}^{3} \left\{ \frac{\beta_j \exp(d\delta_j)}{\sum_{k=1}^{3} \beta_k \exp(d\delta_k)} \right\}^{y_{dj}} \]  

(1)

In the meta-analysis, the full likelihood is then obtained as the product of likelihoods (1) over the \( i \) studies, under the assumption of independence of the studies. The study-specific log odds ratios for GG versus gg, \( \delta_{3i} \), are modelled as normally distributed random effects parameters, which vary about an overall mean, \( \theta \), with variance, \( \tau^2 \)

\[ \delta_{3i} \sim N(\theta, \tau^2) \]

The study-specific log odds ratios for Gg versus gg, \( \delta_{2i} \), are equal to the product of \( \delta_{3i} \) and \( \lambda \), i.e. \( \lambda = \delta_{2i}/\delta_{3i} \), and the mode of inheritance, \( \lambda \), is assumed constant across studies and thus modelled as a fixed effect parameter. It is usually not possible to model both \( \delta_{3i} \) and \( \lambda \) as random effects because, without extra information, it is very difficult to simultaneously estimate the heterogeneity of the two parameters. However, if there are reasons to believe that \( \lambda \) differs across populations, the model could be generalized to include subgroups of studies within which \( \lambda \) is constant.

Prior distributions have to be specified for the unknown model parameters \( \theta \), \( \tau \) and \( \lambda \). While a diffuse normal distribution is used for \( \theta \) in all models, i.e. \( \theta \sim \text{Normal}(0, 10^{4}) \), prior distributions for \( \tau \) and \( \lambda \) are discussed in the following paragraphs. Corresponding posterior distributions are obtained using MCMC methods implemented using WinBUGS 1.4.1 [26], and details on the WinBUGS code for fitting this model can be found on our website, www.hs.le.ac.uk/research/HCG/AppendixSiM2005.doc. The number of simulations was varied and the traces were inspected for evidence of non-convergence before deciding on a ‘burn-in’ of 5000 iterations followed by chains of length 10,000.

2.2.1. Prior distributions for the heterogeneity term. Three prior distributions were considered for the between-study standard deviation, \( \tau \). Figure 1(a) shows the densities for the three prior distributions, all presented on the standard deviation scale.

The first prior distribution is a gamma distribution for the precision parameter (the inverse of the variance),

\[ \frac{1}{\tau^2} \sim \text{Gamma}(0.001, 0.001) \]

This corresponds to an inverse-gamma distribution on the between-study variance, and is approximately uniform apart from a ‘spike’ of probability mass close to zero. Although this is perhaps the most commonly used vague prior distribution for the heterogeneity parameter, it has been recently criticized and prior distributions on the standard deviation parameter have been recommended, as they are more directly interpretable [15, 26].

The second prior distribution for the standard deviation, \( \tau \), is a standardized half-normal distribution truncated at zero,

\[ \tau \sim \text{Half-Normal}(0, 1) \quad \tau > 0 \]

This prior distribution gives a low probability to values greater than 2.

Finally, the third prior distribution considered is a uniform distribution over the range 0 to 2 and excludes the possibility that the standard deviation can be over 2

$$\tau \sim \text{Uniform}(0, 2)$$

### 2.2.2. Prior distributions for $\lambda$

We consider two beta prior distributions for the parameter, $\lambda$. Both are constrained to cover the range between 0 and 1, and have been used for modelling vague prior beliefs about proportions [4]. Figure 1(b) shows the densities for the two prior distributions.

The first prior is a beta distribution with both parameters equal to one

$$\lambda \sim \text{Beta}(1, 1)$$

This distribution is uniform between 0 and 1. However, when parameters have values very close to the extremes, i.e. 0 or 1, and the data are sparse, this prior distribution will tend to pull the posterior estimates towards 0.5. For instance, for a near recessive model where the true value of $\lambda$ is very close to 0, this prior distribution will tend to distort the posterior estimates because it gives 90 per cent prior probability to values greater than 0.1.

The second prior is a beta distribution with both parameters equal to 0.5

$$\lambda \sim \text{Beta}(0.5, 0.5)$$

and corresponds to a Jeffreys’ prior distribution for a binomial likelihood. This distribution gives greater prior probability to values of $\lambda$ close to the extremes [27], i.e. to models which are close to recessive or dominant. However, if the genetic model is actually close to co-dominant, i.e. $\lambda = 0.5$, and the data are sparse, this distribution may tend to inflate the uncertainty surrounding $\lambda$.

### 2.3. Results

The results for the 6 combinations of prior distributions for $\tau$ and $\lambda$ for the meta-analyses of Kato, Hani and Wheeler are illustrated in Figures 2(a), (b) and (c), respectively. Point
Figure 2. Plots of the results for the four parameters (OR_{GG}, OR_{Gg}, \lambda, and \tau) obtained by applying models with different prior distributions to the original meta-analyses by: (a) Kato; (b) Hani; and (c) Wheeler. The models are based on retrospective likelihood.
estimates (medians) and 95 per cent credible intervals (CrI) of the four parameters of interest, OR$_Gg$, OR$_{GG}$, $\lambda$ and $\tau$, are plotted for each model.

The gamma distribution, with its spike close to zero, tends to produce lower estimates of $\tau$ with narrower credible intervals, which in turn tends to be reflected in the widths of the credible intervals for the odds ratios. This is particularly pronounced in Hani’s meta-analysis, where the data are sparse because there are only 4 studies. Here the estimate of $\tau$ is 53 and 51 per cent lower with the gamma prior distribution compared with the uniform and the credible interval is 33 and 38 per cent narrower, for beta(1,1) and beta(0.5,0.5), respectively.

The impact of the two different beta prior distributions for $\lambda$ varies according to the characteristics of the meta-analysis. As expected the beta(0.5,0.5) tends to pull the point estimates for $\lambda$ towards the extremes, i.e. 0 and 1, and the beta(1,1) tends to provide more precise estimates of $\lambda$, when $\lambda$ is near 0.5, as in Wheeler.

3. SIMULATIONS

Simulated data sets were created based on the three meta-analyses described in Section 2, in order to investigate the posterior parameter estimates in situations where the true values were known. The total number of studies and study sizes were kept the same as in the original meta-analyses, while values for the model parameters were taken from a profile maximum
likelihood approach previously used to analyse these data [19]. For each of the three meta-analyses, 1000 new data sets were randomly generated and each was analysed in WinBUGS using the different prior distributions described in Section 2.2. It was not possible to check the convergence of all 18000 analyses so we selected data sets that gave a large discrepancy in results when analysed with different prior distributions and checked convergence for those by running longer chains (‘burn-in’ 50,000, chain length 100,000) with different starting values. In all cases the results confirmed the original analyses.

The median of the corresponding MCMC simulations was taken as the point estimate for each of the four parameters OR_{Gg}, OR_{GG}, \lambda, and \tau. The medians from the analyses with the different prior distributions were compared in terms of their mean, their root mean square error (RMSE), and the coverage of the 95 per cent CrIs, that is the percentage of intervals that included the true value. These three measures describe the average properties of the estimators across the 1000 data sets.

### 3.1. Results

For the four parameters OR_{Gg}, OR_{GG}, \lambda, and \tau, the mean, RMSE, and coverage of the 95 per cent CrIs are summarized in Table I. For the scenarios based on Wheeler’s and Kato’s meta-analyses, the number of data sets effectively analysed was in fact 995 and 998, respectively, since a few simulated meta-analyses contained studies with 0 cells for both cases and controls in a genotype group, and the MCMC algorithm did not converge.

In all cases the half-normal and uniform prior distributions caused the heterogeneity, \tau, to be overestimated on average, although only in the case of the Hani-based simulations was the RMSE also appreciably larger. The beta prior distributions for \lambda caused the average estimate of \lambda to move towards 0.5, the more so in the presence of sparse data. This behaviour is caused by the constraint that \lambda must lie between 0 and 1, and the choice of symmetrical prior distributions such as the beta(0.5,0.5) or the beta(1,1). Such a situation is illustrated by the Kato-based simulations where the true value of \lambda is 0.13, so that underestimates had to lie between 0 and 0.13 while overestimates could lie between 0.13 and 1, and the average consequently tends to be too high. Under these circumstances the mean, or corresponding bias, is not an appropriate indicator of the quality of the estimator. A better indicator is the RMSE which favours the beta(0.5,0.5) prior distribution when \lambda is small and the beta(1,1) when \lambda is close to 0.5. On average the odds ratios are relatively insensitive to the choice of prior distributions.

Good average performance is reassuring but may not be a reliable guide to the sensitivity to the choice of prior distributions for any particular single data set. For this reason we used Bland–Altman style plots, originally described as a way to assess agreement between two methods of clinical measurement [28], in order to graphically evaluate the difference in results when comparing different prior distributions in all 1000 data sets (Figure 3). The difference in estimates based on any two prior distributions is plotted against the average of the two estimates. Plots for the Kato-based simulations are shown in Figure 3 and include a line drawn at the mean difference. Two dotted lines are drawn at the mean difference plus and minus 1.96 times the standard deviation of the difference, in order to both quantify the difference that can be observed when using different prior distributions on the same data set, and detect patterns in the difference which are related to the size of the parameter estimate. Plots for the other two scenarios showed similar results (data not shown).
Table I. Results of the sensitivity analyses to different prior distributions for $\lambda$ and $\tau$, for the simulated meta-analyses based on each of the 3 scenarios: (a) Kato; (b) Hani; and (c) Wheeler. RMSE = Root Mean Square Error.

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<th>$\text{OR}_{GG}$</th>
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**Statistics**

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<td>0.195</td>
<td>96.26</td>
<td>0.113</td>
<td>0.040</td>
<td>98.69</td>
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<tr>
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<td>1.076</td>
<td>0.041</td>
<td>94.43</td>
<td>1.154</td>
<td>0.053</td>
<td>97.87</td>
<td>0.529</td>
<td>0.196</td>
<td>96.46</td>
<td>0.114</td>
<td>0.040</td>
<td>98.79</td>
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<td>1.078</td>
<td>0.037</td>
<td>94.75</td>
<td>1.16</td>
<td>0.054</td>
<td>97.17</td>
<td>0.532</td>
<td>0.153</td>
<td>97.98</td>
<td>0.097</td>
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<td>0.037</td>
<td>95.86</td>
<td>1.16</td>
<td>0.054</td>
<td>97.98</td>
<td>0.521</td>
<td>0.158</td>
<td>97.47</td>
<td>0.116</td>
<td>0.041</td>
<td>98.59</td>
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<tr>
<td>Uniform</td>
<td>1.077</td>
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<td>95.35</td>
<td>1.16</td>
<td>0.054</td>
<td>98.08</td>
<td>0.521</td>
<td>0.159</td>
<td>97.58</td>
<td>0.117</td>
<td>0.042</td>
<td>98.59</td>
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</table>
Figure 3. Plots of the difference in the estimates for Kato meta-analysis obtained by models with different prior distribution against their average value (Bland–Altman plot) for: (a) OR_{ceg}; (b) OR_{GG}; (c) λ; and (d) τ. Horizontal lines are drawn at the mean difference, and at the mean difference plus and minus 1.96 times the standard deviation of the differences. The models are based on retrospective likelihood.

Figure 3(b) shows the effects of the different prior distributions on the estimate of OR_{GG} in individual data sets generated under the conditions of the Kato meta-analysis. The posterior estimates of OR_{GG} with different prior distributions for τ are usually very close, mostly within
±0.1 for estimates that are rarely over 3, and the agreement tends to be better in data sets where the posterior estimates of the odds ratio is close to 1. However, on rare occasions the difference can be as large as 0.3 when the average estimate is 3, a 10 per cent difference. Unfortunately there seems to be no way of distinguishing in advance if the prior distributions will have a large impact on a particular simulated data set. If a 10 per cent difference might be of importance, then sensitivity to the choice of prior distributions needs to be checked in any meta-analysis.
The impact on \( \lambda \) of the choice of the prior distribution is shown in Figure 3(c) and once again the differences tend to be small, but can, for particular data sets, be very large. For instance, data sets which produce estimates that average 0.6 can produce estimates that differ with the choice of prior distribution by up to 0.2. Figure 3(c) also shows some of the systematic effects noted in the average results. As might be anticipated, the impact of the choice of prior distribution is most marked in the estimate of \( \tau \), shown in Figure 3(d). Not only are there strong systematic patterns, but the differences can also be large. For instance, when comparing a gamma prior distribution and a uniform prior distribution the estimates can vary by as much as 0.4 when the average estimate is 0.5, that is one estimate is 0.3 while the other is 0.7.

4. PROSPECTIVE VERSUS RETROSPECTIVE LIKELIHOOD

Although the retrospective likelihood reflects the method of sampling in case–control studies, a prospective likelihood based on the probability of disease given exposure, gives the same odds ratio, in both maximum likelihood [21] and some Bayesian analyses [22]. The advantage of using the prospective likelihood is that the outcome variable, disease, is binary, whereas in the retrospective analysis the outcome, exposure, can have many levels. In the case of genetic association studies, the exposure, i.e. genotype, has three categories even in the simplest case of a bi-allelic polymorphism.

Although the equivalence of the two likelihoods for fixed effects meta-analyses follows from the analogy with a stratified case–control study, there is no reason to suppose that exactly equivalent results will be obtained with more complex hierarchical models. Nonetheless, where the heterogeneity is small or the data are not sparse, we might expect the results to be similar.

Denoting by \( y_{0j} \) and \( y_{1j} \) the number of controls and cases, respectively, in genotype group \( j \), with \( j = 1, 2, 3 \) (i.e. gg, Gg and GG), the prospective likelihood \( (L_P) \) for each study included in the meta-analysis is derived from three binomial distributions, which leads to the following likelihood:

\[
L_P(\lambda, \delta, y) = \prod_{j=1}^{3} \prod_{d=0}^{1} \left\{ \frac{\lambda^d \exp(d\delta_j)}{\sum_{k=0}^{1} \lambda^k \exp(d\delta_j)} \right\}^{y_{dj}}
\]

where the parameter \( \lambda \) is the baseline odds of disease (no exposure), i.e. the odds of disease when \( j = 1 \) (genotype gg), and \( \delta \) is the log odds ratio of interest (\( \delta_2 \) for log OR_{Gg} and \( \delta_3 \) for log OR_{GG}).

In the meta-analysis the full likelihood is obtained as the product of the likelihoods (2) over the \( i \) studies, assuming that the studies are independent. As in the retrospective meta-analysis (Section 2.2), the study-specific log odds ratios \( \delta_{3i} \) are modelled as normally distributed random effects parameters, with an overall mean \( \theta \) and between-study variance \( \tau^2 \). The underlying study-specific log odds ratios, \( \delta_{2i} \), are again derived as the product of \( \delta_{3i} \) and \( \lambda \). A diffuse normal distribution, \( \theta \sim \text{Normal}(0, 10000) \), is used in all models, while the different prior distributions for \( \tau \) and \( \lambda \) are as discussed in Sections 2.2.1 and 2.2.2. Corresponding posterior distributions are obtained using MCMC methods implemented using WinBUGS 1.4.1 [26], and details on the WinBUGS code for fitting this model can be found on our website, www.hs.le.ac.uk/research/HCG/AppendixSiM2005.doc. The number of simulations was varied.
and the traces were inspected for evidence of non-convergence before deciding on a ‘burn-in’ of 5000 iterations followed by chains of length 10 000 for the retrospective model and 50 000 for the prospective model.

4.1. Results

We compared the retrospective and the prospective likelihoods by applying them to the three meta-analyses described in Section 2.1 and then to the simulated data sets described in Section 3.

Table II shows the results for the models with beta(0.5,0.5) and uniform(0,2) as vague prior distributions for $\lambda$ and $\tau$, respectively. The results are nearly identical for all meta-analyses and parameters of interest, both in terms of the point estimates (medians) and the width of the credible intervals. Different prior distributions for $\lambda$ and $\tau$ gave similar results (data not shown). These findings were confirmed by the results of the simulations (data not shown). The only difference in the two approaches was a tendency to a slower convergence for the prospective models, even after the use of hierarchical centring in the specification of the prospective models [29]. This is the reason why the results for the prospective models (Table II) were based on longer chains, as described in the previous section.

<table>
<thead>
<tr>
<th>Meta-analysis</th>
<th>Likelihood</th>
<th>OR$_{GG}$ (95% CrI)</th>
<th>OR$_{GG}$ (95% CrI)</th>
<th>$\lambda$ (95% CrI)</th>
<th>$\tau$ (95% CrI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kato</td>
<td>Retrospective</td>
<td>1.087 (1.001,1.705)</td>
<td>1.828 (1.057,3.598)</td>
<td>0.166 (0.001,0.538)</td>
<td>0.564 (0.236,1.373)</td>
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<tr>
<td></td>
<td>Prospective</td>
<td>1.083 (1.000,1.736)</td>
<td>1.814 (1.053,3.660)</td>
<td>0.159 (0.000,0.542)</td>
<td>0.560 (0.239,1.425)</td>
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<tr>
<td>Hani</td>
<td>Retrospective</td>
<td>1.163 (0.997,1.797)</td>
<td>2.029 (0.959,3.956)</td>
<td>0.238 (0.002,0.785)</td>
<td>0.294 (0.017,1.513)</td>
</tr>
<tr>
<td></td>
<td>Prospective</td>
<td>1.162 (0.998,1.773)</td>
<td>2.013 (0.968,4.095)</td>
<td>0.240 (0.001,0.815)</td>
<td>0.306 (0.015,1.492)</td>
</tr>
<tr>
<td>Wheeler</td>
<td>Retrospective</td>
<td>1.083 (1.001,1.207)</td>
<td>1.148 (1.019,1.337)</td>
<td>0.618 (0.028,0.997)</td>
<td>0.108 (0.009,0.332)</td>
</tr>
<tr>
<td></td>
<td>Prospective</td>
<td>1.083 (1.000,1.210)</td>
<td>1.147 (1.009,1.330)</td>
<td>0.627 (0.032,0.998)</td>
<td>0.106 (0.005,0.331)</td>
</tr>
</tbody>
</table>

5. DISCUSSION

The genetic model-free approach to the meta-analysis of genetic association studies is an integrated way of synthesizing the evidence on the genetic association, which captures both the magnitude of the genetic effect and information about the genetic mode of inheritance. Although the method can be implemented using maximum likelihood [19], the Bayesian framework is an attractive alternative with both philosophical and practical advantages. From
a philosophical point of view, Bayesian analysis allows explicit inclusion of prior distribution information on the genetic effect and on the genetic mode of inheritance. Although this possibility has not been explored in this paper, the models presented could incorporate prior knowledge when it is available. Such knowledge might be based on evidence from studies not included in the meta-analysis or on expert opinion. While in the first instance the inclusion of prior information would often be straightforward, in the second case it can be difficult to use expert opinion to derive appropriate probability distributions [8, 9]. From a practical point of view, the flexibility offered by Bayesian models estimated by MCMC algorithms makes it relatively straightforward to implement complex hierarchical models. The combination of increased computing power together with the availability of free software, particularly WinBUGS [26], to implement MCMC models represents one of the main driving forces behind the increasing use of Bayesian methods in medical research. However, the increased flexibility leads to a greater requirement to consider the issue of model choice [4, 30].

In situations where external information is not available, prior distributions still have to be specified for all parameters. Although such prior distributions may be intended to be non-informative, this is in fact an impossible aim as Figure 1 illustrates. Rather, we must hope that the prior distributions will not be influential, in the sense that the use of alternative vague prior distributions will not change the conclusions. This may be an impossible aim if the data are sparse, especially when specifying prior distributions for scale parameters, such as the between-study heterogeneity in a random effects meta-analysis. If the results are sensitive to the choice of supposedly vague prior distributions, then we have no option but to consider that any prior distribution is informative and so must be chosen with care and subject to a sensitivity analysis [4]. The problem of statistical inference in the presence of sparse data is not limited to the Bayesian approach, and an analogous non-Bayesian analysis would find a very flat likelihood and would produce wide confidence intervals. In such circumstances, the ideal solution might be to incorporate subjective prior information or other external evidence in the Bayesian analysis [11].

The hierarchical model for the meta-analysis of genetic association studies involving the ratio, $\lambda$, requires many large studies if the choice of prior distribution for $\lambda$ is not to have an undue influence on the posterior estimates. In much the same way, the prior distribution for the between-study variation, $\tau$, can also influence the results. Recent research has suggested that the gamma prior distribution is not a good choice for the between-study precision in a hierarchical model and that the half-normal or uniform may be better [15]. Our findings do not support such a conclusion in this situation, where in general the gamma performs well. Of course, part of the problem is to do with the scaling of the prior distributions. Had we taken a half-normal with a smaller standard deviation, or a uniform distribution over a shorter range, then the corresponding estimates would have been more similar to those obtained using a gamma prior distribution. This very fact emphasizes the impossibility of defining a generic vague prior distribution when data are sparse, and the importance of careful specification even when using vague prior distributions.

Our analysis illustrates the importance of an investigation of sensitivity to the choice of prior distributions in any Bayesian analysis in which the prior distributions are not based on external knowledge. The sensitivity analysis will depend on the range of vague prior distributions that are considered reasonable in any given situation and the size of the change in the final estimate or its credible interval that is of practical importance. Thus, it will not be possible to find a single vague prior distribution that is always the least informative, so in
complex models the desire to use vague prior distributions does not free the researchers from the need to tailor their prior distributions to their particular problem.

In our analyses the prospective and retrospective likelihoods gave very similar results for all examples considered and for all the different vague prior distributions considered for $\tau$ and $\lambda$. It may well be that in practice the prospective likelihood could be used when synthesizing evidence from case–control studies. However, the approximate equivalence of the two likelihoods for a particular combination of data set and model can only be established by using both, which rather removes the benefits of the simpler, but theoretically inappropriate, prospective model. The retrospective likelihood has the further advantage that it can easily incorporate the assumption of Hardy–Weinberg equilibrium in the controls [31,32]. Given these considerations it will often be more appropriate to use the retrospective likelihood unless there is considerable evidence of approximate equivalence from similar analyses.

Although not explored in this paper, informative prior distributions, based on expert opinion or external evidence, could be used for the different model parameters. In a more general meta-analysis context, empirical data-based prior distributions have been advocated for the heterogeneity term, $\tau$, and might be an attractive option, especially when the number of studies included in the meta-analysis is small [33]. For the parameter $\lambda$, there might well be data from studies evaluating the effect of the same polymorphism on similar disease pathways. The increase in the precision of the estimated $\lambda$ due to the use of an informative prior distribution would in turn increase the precision in the estimates of the odds ratios of interest, $\text{OR}_{GG}$ and $\text{OR}_{Gg}$, and so might be very beneficial.

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REFERENCES

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