Evaluation of underlying risk as a source of heterogeneity in meta-analyses

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Abstract

Two Bayesian models for evaluating the association between underlying risk and observed treatment effects in a meta-analysis were compared using one simulated and one real dataset. Based on the simulated data (n=50 observations), Model 1 produced a reasonably precise estimate of the coefficient for the underlying risk, but it was negatively biased. The posterior distribution of the underlying risk coefficient from Model 2 was extremely wide and left skewed. The analysis of the real dataset confirmed there was little evidence of heterogeneity (between study variance) and no significant effect of underlying risk on the treatment effect from this particular study.

Introduction

One of the primary objectives of a meta-analysis is to produce a summary estimate of a treatment effect from a set of clinical trials. A second, and in some cases, equally important objective is to evaluate the amount of variation (heterogeneity) among the observed treatment effects. It is necessary to determine if the variation between studies exceeds that due to chance, and, if this is the case, it is important to determine what factors contribute to that variation.

A multi-level approach to meta-analysis uses individual study 2x2 tables and the total variation between observed study effects is partitioned into variation due to sampling and between-study variance. The former is derived from the within-study variance and the sample size in each study and is therefore derived from the data and not estimated (Hox and DeLeeuw, 2003). The between study variance is estimated using multi-level analysis procedures. The variation in study populations across studies is an important potential contributor to heterogeneity. Some of these population characteristics may be measured and evaluated using procedures such as meta-regression (Egger et al, 2001). In other cases, the factor may be unmeasured (if data not reported) or unmeasurable. After adjustment for measured factors, the underlying risk can be viewed as a summary of the effects of unmeasured population characteristics. It can also readily be determined from the control group data, so it is a logical candidate for evaluation as a source of heterogeneity.

Unfortunately, there are two problems with the use of traditional methods to evaluate the contribution that underlying risk makes to the observed heterogeneity. The first is that there is a structural dependency between the underlying risk (risk in control group) and the outcome (RR) which includes the underlying risk in its computation. Consequently, it is not appropriate to use underlying risk as a predictor in a procedure such as meta-regression. Secondly, both the underlying risk and the RR are likely to be measured with error and consequently, the phenomenon of regression toward the mean will result in the relationship between the two being underestimated (Egger et al, 2001). Recently, two methods for evaluating the effect of underlying risk on between-study heterogeneity have been evaluated (Sharp and Thompson, 2000).

The objectives of this manuscript are: to demonstrate the effect of the structural dependency between underlying risk and RR using simulated data, to describe (in non-technical terms) the two models referred to above, and to evaluate the performance of the two models using simulated data and real data. A more complete manuscript will extend the simulation studies of the performance of these models, compare the results from the Bayesian analyses to a frequentist implementation of the models, and evaluate a slightly modified version of one model.

Materials and Methods

Structural dependency

A simulated dataset containing 20,000 observations (10,000 control and 10,000 treated subjects) was created with the risk of the outcome being 0.2 in control subjects and 0.6 in treated subjects (RR=3). Pairs of subjects (1 treated and 1 control) were randomly assigned to one of 200 studies (100 subjects per study) so that the expected RR was 3 in each study. A scatterplot and a lowess smoothed curve were generated to show the relationship between the RR and the underlying risk (risk in control group).

Models for heterogeneity dependent on underlying risk

Both models (Sharp and Thompson, 2000) have the same basic form (Equation 1)

$$\bullet_i = \bullet_i' + \bullet(\bullet_i - \bullet) \qquad \text{Equation 1}$$

where $\bullet_i$ = treatment effect on log scale (lnOR), $\bullet_i'$ = true treatment effect after having adjusted for effect of underlying risk, $\bullet$ = coefficient for effect of underlying risk, and $\bullet_i$ = underlying risk (log odds in control group) centred by subtracting the mean underlying risk ($\bullet$). Both models assume that across studies, the true treatment effects are distributed normally ($\bullet_i' \sim N(\bullet, \bullet.^2)$). Model 1 (Thompson, 1997) assumes that the number of positive events in the control and treatment groups are both binomially distributed. Model 2 (McIntosh, 1996) assumes that the log odds in the control group and the lnOR are both distributed Normally (with means $\bullet_i$ and $\bullet_i$ respectively) . Neither model requires an explicit assumption about the distribution of the underlying risks ($\bullet_i$) although their standard formulations (as presented in Sharp and Thompson, 2000) assume no specific distribution for Model 1 and a Normal distribution ($\bullet_i \sim N(\bullet, \bullet.^2)$) for Model 2. If the $\bullet_i$ are Normally distributed (as in Model 2), the $\bullet_i$ will be as well.

A simulated dataset consisting of 50 hypothetical studies with between 20 and 200 subjects per study and underlying risks uniformly distributed between 0.1 and 0.5 was created. The true treatment effect (lnOR) was drawn from a normal distribution with a mean of 1.099 (equivalent to an OR of 3) and a variance of 1. The actual number of events in the treatments and control groups were binomially distributed with the risk in the treatment group being a function of the underlying risk and the treatment effect. The coefficient for the underlying risk ($\bullet$) was set to 2. A real dataset from a meta-analysis of the effect of recombinant bovine somatotropin (rBST) on the risk of clinical mastitis in dairy cows was also evaluated using both models. The data came from 29 studies reported in 20 manuscripts (Dohoo et al, 2003). All analyses were carried out using WinBUGS (code available in paper by Sharp and Thompson (2000) or from the primary author). Uninformative priors were used in all analyses. Estimates were derived from 10,000 samples drawn from the posterior distribution and the median and 95% credibility intervals were reported.

Results and Discussion

Structural dependency

The structural dependency between a treatment effect and the underlying risk is demonstrated in Figure 1. Although the data were simulated with a constant RR=3, there appears to be a strong association with underlying risk. A traditional meta-regression also incorrectly identifies a significant association (results not shown).

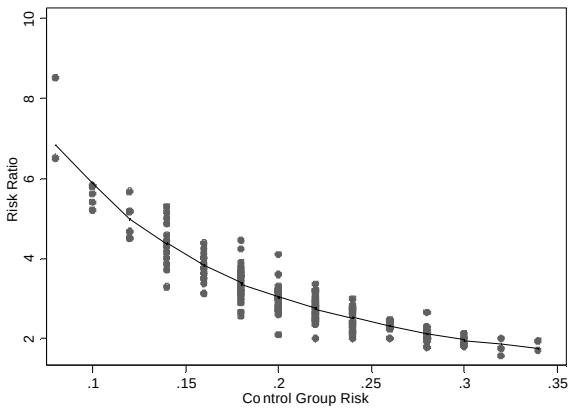

Figure 1 Relationship between treatment and effect and underlying risk as a result of their structural dependency.

Models for heterogeneity dependent on underlying risk

Table 1 shows the results from the analysis of each of the two datasets by each of the two models. For

the simulated data, Model 1 underestimated the value of •, but the estimates had reasonable credibility intervals. The variance of $•_i$ ($•.^2$) was somewhat underestimated. Model 2 overestimated the value of •, but the credibility interval was extremely wide and highly skewed to the left. With this distribution, any individual estimate could be highly misleading. Model 1 also has the advantage that the assumption of binomial distributions of counts in the treatment and exposed groups may be easier to justify than the assumption of normally distributed log odds and lnOR (Model 2). On the other hand, assuming a distribution for underlying risks (as done in this case in Model 2), as opposed to estimating each value individually (as done in Model 1) might be advantageous if there were many studies in the meta-analysis.

Table 1 Medians and 95% credibility intervals in () of key parameters from the models for evaluating the effect of underlying risk on estimates of treatment effect in simulated and real data.

	Simulated Data			rBST Data	
Parameter	Simulated Value	Model 1	Model 2	Model 1	Model 2
•	2	1.42	2.48	-0.15	-0.07
		(0.75 , 2.08)	(-65.4 , 3.39)	(-0.37 , 0.10)	(-0.39 , 0.24)
•'	1.28	1.15	1.19	0.34	0.33
		(0.86 , 1.45)	(1.02 , 1.38)	(0.14 , 0.50)	(0.16 , 0.49)
•	-0.97	-0.96	-0.91	-1.38	-1.38
		(-1.07 , -0.86)	(-1.01 , -0.23)	(-1.54 , -1.22)	(-1.54 , -1.20)
$•.^2$	0.90	0.68	1.28	0.01	0.01
		(0.09 , 1.75)	(0.88 , 1.80)	(0 , 0.09)	(0 , 0.07)

For the real (rBST) data both models indicated no significant effect of underlying risk on the treatment effect (credibility interval for both estimates of • included 0). There was also little evidence of heterogeneity in the treatment effect as both estimates of $•.^2$ were very small (0.01). These results agreed very closely with the original meta-analysis which reported no significant heterogeneity between studies (P-value for Q statistic was 0.95) and an identical estimate of treatment effect (•' = 0.34).

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