Passive smoking in the workplace: classical and Bayesian meta-analyses

Abstract There are currently several classical and Bayesian methods of meta-analysis available for combining epidemiological results. We describe and compare these in a consistent framework, and apply them to published studies of the relative risk of lung cancer associated with exposure to environmental tobacco smoke in the workplace. We find that although all methods give reasonably similar combined estimates of relative risk of lung cancer associated with this exposure (none of which is significantly raised above unity, in either a frequentist or a Bayesian sense), the approximations arising from classical methods appear to be nonconservative and should be used with caution. The Bayesian methods, which account more explicitly for possible inhomogeneity in studies, give slightly lower estimates again of relative risk and wider posterior credible intervals, indicating that inference from the non-Bayesian approaches might be optimistic.

Key words Passive smoking · Meta-analysis Environmental tobacco smoke (ETS) · Hierarchical Bayes · Random effects

Introduction

Meta-analysis is an increasingly popular statistical technique for combining information from separate studies [9, 22]. There are, however, well-documented concerns about the way in which data can be combined if the collection of studies is not homogeneous by design [9, 20]. Some of these concerns are matters of judgment and relate to such issues as differing aims of studies or differing study quality; others can be quantified objectively, and relate to the underlying variability in the information presented, and different statistical approaches have been developed to attempt to deal with these. In this paper we describe a coherent framework for the application of several such meta-analysis techniques in the context of case-control studies in epidemiology and consider the sensitivity of the conclusions to the different methods.

In the epidemiological literature it has been standard (see [33, 37]) to combine relative risks using a so-called “fixed-effects” model. This essentially ignores heterogeneity between studies. A more general “random effects” model, which introduces parameters to allow for some interstudy variation, seems to be preferable and is recommended in [23].

We describe how the random effects method can also be interpreted within an empirical Bayes paradigm and can then be compared in a natural and systematic way to fully Bayesian methods for combining information, such as those recently proposed by DuMouchel [6] and Carlin [4]. This gives more freedom to introduce parameters describing uncertainty in the underlying collection of studies, and thus, within a consistent hierarchical model framework, one can consider whether the extra model description necessary for fitting Bayesian models leads to different inferences about the underlying processes.

In this situation the Bayesian models are not used to describe “prior information” in any strong sense (although in the context we consider there is some appropriate prior information that can be used). Rather, one can view the models as describing in more detail the way in which the studies might be heterogeneous, and this methodology allows one to account more explicitly for greater variability in the underlying collection of studies than is done in the fixed or even the random effects models.

We illustrate and compare these methods through an assessment of the overall association between lung cancer and exposure to environmental tobacco smoke (ETS, or “passive smoking”) in the workplace. There have been many meta-analyses of the individual studies of ETS exposure associated with spousal smoking [17, 24, 25, 31,
33) but there has been limited assessment of the current set of 13 papers addressing general workplace exposure, apart from those of Lee ([17] p. 117) who reports an estimated relative risk and 95% confidence interval of 0.98 (0.89, 1.08) of published results in the nine studies available in 1986, and discussion of these issues using fixed and random effect models ([19] Tables 4, 5). Lee [19] addresses almost the same data set as we use, and our analysis can be compared to his.

The workplace ETS studies seem appropriate for meta-analysis for several reasons. Although the association between lung cancer and ETS is an issue of public and legal concern, there has been a tendency to extrapolate results for spousal smoking to the workplace arena. By utilizing all current information about workplace exposure itself, an overall estimate of the relative risk and its variability may be constructed directly and compared with the spousal exposure estimates.

Because we use both frequentist and Bayesian (including empirical Bayesian) methods below, it will be convenient to define the phrase “significantly different from unity” to cover either the situation in which there is a constructed 95% confidence interval which does not cover unity or a Bayesian 95% credible interval which does not cover unity: the context should make it clear which is meant. The sizes of the individual studies are relatively small, so that although individual relative risks have been found to be statistically insignificant (in either of these senses), combining them by means of the meta-analyses increases power to indicate such significance if it exists.

Our main goal is to give a coherent approach to using the Bayesian hierarchical model description and to indicate whether such choices can influence the outcome. In particular, we assess the use of approximate methods of analysis in the individual studies, and the next section describes these problems, which logically precede the problems of combining the information.

**Methods**

**Individual study estimates**

The statistical quantities of interest in the individual studies, and combined in our meta-analyses, are estimates of the relative risk (RR) of outcome in a population with some defined exposure compared with outcome for an unexposed population, and associated variances or interval estimates for RR.

We use the following notation throughout: we suppose that we have k studies, and that

\[ \text{RR}_i = \text{observed estimate of relative risk in study } i, \]

\[ \theta_i = \text{true log relative risk in study } i, \]

\[ W_i = \text{an appropriate estimate of } \left( \text{Var}(Y_{i}) \right)^{-1}. \]

In the traditional setting for case-control studies, the empirical odds ratio provides a point estimate of the true relative risk for each study.

In order to implement the meta-analysis methods below, we need to estimate the individual parameters \( \theta_i \) and to calculate corresponding variances for these estimates. We shall compare three such methods:

1. Fisher’s exact method ([11] p. 124), which gives a point estimate and a non-parametric confidence interval (CI) but no variance estimate for RR.
2. The Mantel-Haenszel (M-H) point estimate ([11] p. 141) and an approximate CI for RR, given by applying a result recently derived by Sato [27] for the CI of a combined estimator to a single-study situation (note that this method gives no variance estimate for RR, and although an approximate variance estimate has been obtained for the M-H estimate [26], no corresponding confidence interval may be obtained without making generally unacceptable distributional assumptions about RR.)
3. The logit method ([11] pp. 129–130), which gives a point estimate \( Y_i \) and approximate variance, with a corresponding CI based on an assumption of normality which is known to be reasonable, at least for large sample sizes

One outcome of our analyses below is a comparison of the accuracy of the M-H and logit approaches for the individual studies, using Fisher’s exact method as a benchmark. Combined estimates using the exact Fisher approach are unavailable, however, without some modification to the method, so similar comparisons cannot be made of the resultant meta-analyses.

The classical paradigm for meta-analysis

In order to develop a random effects model (of which a fixed effects model is a particular case) we consider the formulation

\[ Y = \theta + \varepsilon \]

\[ \theta = X \mu + \varepsilon, \quad \mu \]

where \( Y = (Y_1, ..., Y_k) \), \( \theta = (\theta_1, ..., \theta_k) \), \( \varepsilon = (\varepsilon_1, ..., \varepsilon_k) \), \( \mu \) is a \( p \times 1 \) vector of parameters. We shall take \( X \) to be the \( k \times 1 \)-vector of \( 1 \)'s, and so \( \mu \) to be a scalar parameter, representing the true underlying log RR over all studies.

In (Eq. 1) the log relative risks \( Y_i \) are used since they can be shown to be asymptotically normal; and accordingly we assume that the \( \varepsilon_i \) are independently and identically distributed \( N(0, \sigma^2) \) random variables, that the \( \varepsilon_i \) are independently and identically distributed \( N(0, \tau^2) \) random variables, and that the \( \varepsilon_i \) and \( \varepsilon_i \) are mutually independent. The quantities \( \sigma^2 \) represent the within-study variabilities, while the quantity \( \tau^2 \) provides a measure of the between- or across-study variability. This meta-analytic interpretation differs from the “random-effects” model in traditional analysis of variance, in which it is assumed that the \( \theta_i \) are random draws from a population: for further discussion see [23]. In the special case in which \( \tau^2 = 0 \), indicating homogeneity between studies, the random effects model reduces to the well-known but less adaptable fixed effects model (see [33, 37] and others).

As is common practice [23], if we assume we know the individual study variances \( \sigma_i^2 \), which we then equate to the estimates \( W_i^{-1} \) from the studies, a point estimate \( \hat{\mu}_w^* \) and its variance \( V(\hat{\mu}_w^*) \) are given by

\[ \hat{\mu}_w^* = \frac{\sum W_i Y_i}{\sum W_i}, \quad (2) \]

\[ V(\hat{\mu}_w^*) = \frac{1}{\sum W_i^*}, \quad (3) \]

with

\[ W_i^* = W_i^{-1} + \tau^2. \quad (4) \]