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# Mixed-Effects Poisson Regression Models for Meta-Analysis of Follow-Up Studies with Constant or Varying Durations

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# Mixed-Effects Poisson Regression Models for Meta-Analysis of Follow-Up Studies with Constant or Varying Durations

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## Abstract

We present a framework for meta-analysis of follow-up studies with constant or varying duration using the binary nature of the data directly. We use a generalized linear mixed model framework with the Poisson likelihood and the log link function. We fit models with fixed and random study effects using Stata for performing meta-analysis of follow-up studies with constant or varying duration. The methods that we present are capable of estimating all the effect measures that are widely used in such studies such as the Risk Ratio, the Risk Difference (in case of studies with constant duration), as well as the Incidence Rate Ratio and the Incidence Rate Difference (for studies of varying duration). The methodology presented here naturally extends previously published methods for meta-analysis of binary data in a generalized linear mixed model framework using the Poisson likelihood. Simulation results suggest that the method is uniformly more powerful compared to summary based methods, in particular when the event rate is low and the number of studies is small. The methods were applied in several already published meta-analyses with very encouraging results. The methods are also directly applicable to individual patients' data offering advanced options for modeling heterogeneity and confounders. Extensions of the models for more complex situations, such as competing risks models or recurrent events are also discussed. The methods can be implemented in standard statistical software and illustrative code in Stata is given in the appendix.

**KEYWORDS:** meta-analysis, multivariate methods, random effects, Poisson regression, multilevel models

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# 1. Introduction

Meta-analysis constitutes a particular type of research, in which a set of original studies is synthesized and the potential diversity across them is explored using specific statistical methods (Glass, 1976; Greenland, 1998; Normand, 1999; Petiti, 1994). Although in medical research literature meta-analysis was initially applied in the field of randomized clinical trials (Chalmers et al, 1987; Sacks et al, 1987), it is nowadays considered a valuable tool for the combination of observational studies (Stroup et al, 2000) as well as for gene-disease association studies (Bagos, 2008; Trikalinos et al, 2008).

Traditionally, meta-analysis is being performed using summary or aggregate estimates calculated at a study-level. For binary outcomes, depending on the study design and the goals of a particular research, effect measures from each study (Table 1 and 2) are chosen and subsequently pooled taking into consideration the estimates of their variance. The method for calculating the overall estimates could rely on fixed or on random effects. Most of the summary-data techniques are based on large sample approximations for the variance and depend heavily on normality assumptions concerning the distribution of effect measures. Therefore, when these are violated, the commonly used methodology may be problematic. If the outcome of a study is measured on a continuous scale, methods based on the Weighted Mean Difference (WMD) are employed when the measures are on the same scale, whereas Standardized Mean Difference (SMD) methods are used when measures are not reported in the same units.

Bayesian methods have been proposed and used for years in applications in meta-analysis (Smith et al, 1995). In the classical setting, the chosen measure of association is the Odds Ratio (OR), although methods for the Risk Ratio (RR) and the Risk Difference (RD) have also been developed (Sutton & Abrams, 2001; Warn et al, 2002). Although Bayesian methods could be adopted easily for summary statistic data, their main advantage arises when it comes to using directly the binary structure of the data without assuming a normally distributed outcome (i.e. logOR). During the same period, frequentist methods that could also exploit the binary nature of the data have been developed. In one of the first attempts to carry out a statistical combination of binary data, a bivariate method was proposed, which models simultaneously the logits of exposed and non-exposed individuals (van Houwelingen et al, 1993). Later on, several approaches for random effects meta-analysis of binary outcomes were proposed in a multilevel framework (Thompson & Sharp, 1999; Thompson et al, 2001; Turner et al, 2000).

In all of the above-mentioned analyses though, the selected measure of association for binary data was the OR. Other approaches for multilevel modeling in meta-analysis include similar procedures with continuous outcomes (Higgins et al, 2001; Thompson et al, 2001), as well as methods for ordinal responses (Poon, 2004; Whitehead et al, 2001). Thus, it is clear that up to now no method has been proposed for performing meta-analysis using binary data in a frequentist framework estimating effects such as the RR and RD. Such measures could be preferable (compared to the OR) in the realm of prospective cohort studies or clinical trials and offer some advantages since they are more easily interpretable and might reflect better the clinical question. Furthermore, a common limitation of follow-up studies is the incomplete observation time of some individuals due to their withdrawal or loss before a point in calendar time that marks the termination of study. The incidence rate (IR) is a measure of disease frequency that is often used in observational studies with varying duration. The most likely value of the rate parameter is the total number of events divided by the total observation time added over all subjects included in the study with the latter known in epidemiology as person-time (Clayton & Hills, 1993). The estimate of effect is usually calculated in the form of the incidence rate ratio (IRR), while the attributable risk for an event (usually a disease) given the exposure can be estimated by the Incidence rate difference (IRD). Yet, little attention has been paid so far to the development of methodology tailored to the conduct of meta-analysis using IRRs or IRDs (Guevara et al, 2004). It is of relevance here to notice that the Cochrane Handbook of Systematic Reviews suggests pooling counts and rates using summary data methods (Deeks et al, 2008).

In this work, we discuss methods suitable for synthesizing measures of association such as RR, RD, IRD and IRR. We extend previously published multilevel methods that utilize a generalized linear mixed model framework, and apply models for count data using the Poisson likelihood. We argue that even though such methods are available, they have never been applied in meta-analysis within a frequentist framework mainly because of the dominant role played by the OR in the relevant literature. In Section 2 the newly proposed methods are presented in detail. Initially (Section 2.1) we formulate the problem and present briefly the well-known summary-based methods in order to establish notation. In Section 2.2, the general framework based on a mixed-effect Poisson regression model is illustrated, while in Section 2.3 we describe an alternative approach fitting a bivariate Poisson model. Section 2.4 deals with the implementation of Poisson regression models for meta-analysis of studies with individual patients' data and, finally, in Section 3 the above-mentioned techniques are applied in a simulation study in order to compute empirical power as well as in several published meta-analyses in order to assess their properties and compare the results.

# 2. Methods

## 2.1 Meta-analysis using summary measures

Let $c_{ij}$ denote the number of events in the $j^{th}$ group ($j$=0 control/unexposed group, $j$=1 intervention/exposed group) of the $i^{th}$ study and $n_{ij}$ the total number of individuals in the same group. The total person-time in the $j^{th}$ group of the $i^{th}$ study would be $T_{ij} = n_{ij}\overline{t_{ij}}$ where $\overline{t_{ij}}$ is the average person-time (Table 1).

**Table 1.** Typical layout of the data used in a meta-analysis of *k* observational studies or controlled clinical trials. If the duration of follow-up is constant the total person-time is irrelevant and only the number of events and the total number of persons in each arm of a study is used.

| | **Experimental arm** | | | **Control arm** | | |
|---|---|---|---|---|---|---|
| **study** | **Events** | **Persons** | **Person-time** | **Events** | **Persons** | **Person-time** |
| 1 | $c_{11}$ | $n_{11}$ | $T_{11}$ | $c_{10}$ | $n_{10}$ | $T_{10}$ |
| 2 | $c_{21}$ | $n_{21}$ | $T_{21}$ | $c_{20}$ | $n_{20}$ | $T_{20}$ |
| … | … | … | … | … | … | … |
| $k$ | $c_{k1}$ | $n_{k1}$ | $T_{k1}$ | $c_{k0}$ | $n_{k0}$ | $T_{k0}$ |

If the duration of the study varies between the two arms, as is the case in follow-up cohort studies, we would normally be interested in the IRR or in the IRD. When, on the other hand the duration is fixed for both arms, then, the measures of choice would be the RR or the RD. In retrospective case-control studies, the OR is the only available measure that can be used. However, the OR is also commonly used in prospective studies as an approximation to RR under the rare disease assumption. In Table 2, all the above mentioned estimates along with the large sample approximations for their standard errors are presented following the notation outlined above. We report the asymptotic standard errors that are based on large-sample theory as presented in standard textbooks (Clayton & Hills, 1993; Kleinbaum et al, 1982; Petiti, 1994), as well as in review papers (Normand, 1999; Sato, 1990).

In traditional fixed effects meta-analysis using summary measures, we assume that the individual estimates $\theta_i$ of each study are distributed normally around the true effect $\theta$ as:

$$\theta_i \sim N\left(\theta, s_i^2\right) \tag{2.1}$$

where $s_i^2$ is the estimated variance of each study. The combined estimate across $k$ studies can be calculated using:

$$\hat{\theta} = \sum_{i=1}^{k} w_i \theta_i \Big/ \sum_{i=1}^{k} w_i \tag{2.2}$$

with weights given by $w_i = 1/s_i^2$. In the presence of heterogeneity a preferable method is the random effects approach, which assumes that the true effect varies randomly between studies and consequently, we introduce a random component of the between studies variance $\tau^2$:

$$\theta_i \sim N\left(\theta, s_i^2 + \tau^2\right) \tag{2.3}$$

**Table 2.** The most commonly used summary measures of association used in observational studies and in controlled clinical trials. For each parameter we list its estimate and an approximate standard error that can be both expressed in terms of the counts denoted in Table 1.

| **Parameter** $(\theta)$ | **Estimate** $(\hat{\theta})$ | **Standard Error** $(se_{\hat{\theta}})$ |
|---|---|---|
| **RD** | $\frac{c_{i1}}{n_{i1}} - \frac{c_{i0}}{n_{i0}}$ | $\sqrt{\frac{c_{i1}(n_{i1}-c_{i1})}{n_{i1}^3} + \frac{c_{i0}(n_{i0}-c_{i0})}{n_{i0}^3}}$ |
| **logRR** | $\log\left(\frac{c_{i1}}{n_{i1}}\right) - \log\left(\frac{c_{i0}}{n_{i0}}\right)$ | $\sqrt{\frac{1}{c_{i1}} + \frac{1}{c_{i0}} - \frac{1}{n_{i1}} - \frac{1}{n_{i0}}}$ |
| **logOR** | $\log\left(\frac{c_{i1}}{n_{i1}-c_{i1}}\right) - \log\left(\frac{c_{i0}}{n_{i0}-c_{i0}}\right)$ | $\sqrt{\frac{1}{c_{i1}} + \frac{1}{c_{i0}} + \frac{1}{n_{i1}-c_{i1}} + \frac{1}{n_{i0}-c_{i0}}}$ |
| **IRD** | $\frac{c_{i1}}{T_{i1}} - \frac{c_{i0}}{T_{i0}}$ | $\sqrt{\frac{c_{i1}}{T_{i1}^2} + \frac{c_{i0}}{T_{i0}^2}}$ |
| **logIRR** | $\log\left(\frac{c_{i1}}{T_{i1}}\right) - \log\left(\frac{c_{i0}}{T_{i0}}\right)$ | $\sqrt{\frac{1}{c_{i1}} + \frac{1}{c_{i0}}}$ |

The most commonly used estimate of $\tau^2$ is the one proposed by DerSimonian and Laird (DerSimonian & Laird, 1986), which is calculated non-iteratively by the method of moments (MM). The weights $w_i^* = 1/\left(s_i^2 + \tau^2\right)$, if used in Eq. (2.2), will provide the random effects estimate of $\theta$. The methods described above can be easily extended in order to adjust for potential study-level covariates in a meta-regression (Thompson & Higgins, 2002). The non-iterative approaches based on summary data offer the advantage of simplicity since the estimates and their variances can be calculated using simple computations. Random effects estimates derived iteratively utilizing maximum likelihood (ML), restricted maximum likelihood (REML) or empirical Bayes (EB) methods have been proposed (Thompson & Sharp, 1999). In the Appendix, we describe how these models can be fitted in `Stata`.

The aforementioned summary based methods, despite being simple and easy to implement, suffer from some of serious disadvantages. First of all, they use normal approximations to draw inferences concerning the estimates. In several situations, the normality assumptions may be inappropriate, especially when we encounter zero events in one or both groups, in which case the estimates and their variances are not defined. In such instances, the only way to circumvent the problem would be to perform an ad-hoc correction adding a small quantity to the count in each cell of the 2x2 tables before the analysis (Sweeting et al, 2004). Secondly, the variances of the individual studies are considered known instead of being estimated from the data. Another important drawback is that the summary data methods cannot take advantage of individual patients' data (IPD). The collection and analysis of IPD is increasingly employed in pooled meta-analyses or multicenter trials and helps to discover significant confounders or effect modifiers acting at the individual level. Although meta-regression of summary estimates can also be substantially helpful, its use is limited on study-level covariates and the risk of ecological confounding resulting in spurious findings is not negligible (Higgins & Thompson, 2004; Thompson & Higgins, 2002).

## 2.2 Meta-analysis using Poisson regression on grouped data

In the present section, we describe a meta-analytical approach applying fixed and random effects Poisson regression models to grouped data, and we show their direct analogy with the summary data methods. Consequently, we will extend these models in case we have available IPD. When only summary (grouped) count data are available in the form reported in Table 1, Poisson regression models are directly applicable overcoming the problems discussed above. The relevance of the Poisson distribution is obvious, considering that the approximate variances described in the previous section can be derived by treating the counts in the contingency table as realization of Poisson random variables (Clayton & Hills, 1993; Kleinbaum et al, 1982). Formulation of the models, for incidence data, requires using the logarithm of the total number of counts ($c_{ij}$) as the dependent variable in the Poisson regression, with the inclusion of the logarithm of the total person-time $T_{ij}$ as an offset (a variable with coefficient constraint to be 1). The same model could be used for estimating RR, simply by substituting $T_{ij}$ by $n_{ij}$.

A fixed-effects meta-analysis using Poisson regression could be performed by fitting the model:

$$\log\left(c_{ij}\right) = \alpha_0 + \alpha_i + \theta z_{ij} + \log\left(T_{ij}\right) \tag{2.4}$$

where $z_{ij}$ is an indicator variable for the groups under comparison (taking values $z_{ij}$=0 for counts arising from the non-exposed group and $z_{ij}$=1 for counts observed in the intervention/exposed group for each study $i$). The parameter $\theta$ after being exponentiated yields the overall estimate of the IRR (or the RR if we use the total counts $n_{ij}$). This model incorporates dummy variables $\alpha_i$ ($i$=2, 3… $k$) as indicators for the study-specific fixed effects, in order to preserve the within studies comparison of exposed vs. non-exposed groups (stratification). The analogy to the measures reported in Table 2 is obvious if we re-arrange Eq. (2.4):

$$\log\left(c_{ij}/T_{ij}\right) = \alpha_0 + \alpha_i + \theta z_{ij} \tag{2.5}$$

The overall $\chi^2$ test for checking the significance of the study by group interaction is an analogue of the $\chi^2$ test for heterogeneity (Cochrane's $Q$) used in the summary data methods. Thus, fitting the model:

$$\log\left(c_{ij}\right) = \alpha_0 + \alpha_i + \theta z_{ij} + \sum_{i=2}^{k} \gamma_i a_i z_{ij} + \log\left(T_{ij}\right) \tag{2.6}$$

and testing the null hypothesis $H_0 : \gamma_i = 0, \forall\ i = 2,3,...k$ would result in a test statistic:

$$W = \sum_{i=2}^{k} \gamma_i^2 \sim \chi^2_{(k-1)} \tag{2.7}$$

Consequently, using $W$, a modified version of the $I^2$ measure of inconsistency (Higgins & Thompson, 2002; Higgins et al, 2003) can be easily calculated:

$$I^2 = \max\left\{0, \frac{W-(k-1)}{W}\right\} \tag{2.8}$$

It should be noted here, that Guevara and coworkers (Guevara et al, 2004), considered this model, but they incorrectly named it "random effects model". The particular mistake is apparent since they also considered a model (termed "fixed effects model") in which it was not included a study-specific fixed intercept. As discussed by Thompson and Sharp (Thompson & Sharp, 1999), such models are inadequate because they do not perform stratification by study and are equivalent to just pooling the data from the included trials without preserving the within-studies comparisons.

The random effects models provided below are extensions to the linear mixed (hierarchical) models described by Higgins and coworkers for the quantitative synthesis of continuous outcomes using individual patients' data (Higgins et al, 2001). The linear mixed model is extended here to a generalized linear mixed model using the Poisson distribution with the log link function. A similar methodology suitable for dichotomous outcomes using logistic regression has also been presented by Turner and coworkers (Turner et al, 2000). Introducing a study-specific random coefficient $\nu_i$, which represents the deviation of study's true effect ($y_i$) from the overall mean effect $\theta$, suggests an additive component of heterogeneity leading to a random coefficient Poisson regression. Thus:

$$\log\left(c_{ij}\right) = a_0 + \alpha_i + \left(\theta + \nu_i\right) z_{ij} + \log\left(T_{ij}\right),\ \nu_i \sim N\left(0, \tau^2\right) \tag{2.9}$$

With this model, the estimate for the between-studies variance is analogous to the one estimated by the random effects model of DerSimonian and Laird (MM) or its counterparts mentioned above (ML, REML or EB). However, the study-specific effects are still regarded as fixed. Alternatively, one can apply models with random study effects, assuming that the log-rates are random samples drawn from a normal distribution. This way, the fitted model as shown below, includes the effects $\upsilon_i$ of a study on the log-rate as well as the effects $\nu_i$ of study on the exposure effect.

$$\log\left(c_{ij}\right) = \alpha_0 + \upsilon_i + \left(\theta + \nu_i\right) z_{ij} + \log\left(T_{ij}\right),\ \begin{pmatrix} \nu_i \\ \upsilon_i \end{pmatrix} \sim MVN\left(\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{pmatrix} \sigma_\nu^2 & \sigma_{\nu\upsilon} \\ \sigma_{\upsilon\nu} & \sigma_\upsilon^2 \end{pmatrix}\right) \tag{2.10}$$

When fitting a model including a random intercept and a random coefficient like the one denoted in Eq. (2.10), we have to estimate also the covariance of the random terms. This should be equal to:

$$\operatorname{cov}\left(\nu_i, \upsilon_i\right) = \sigma_{\nu\upsilon} = \sigma_{\upsilon\nu} = \rho\sigma_\nu\sigma_\upsilon \tag{2.11}$$

If we force the covariance to be zero, we imply that the variance across studies for the control groups is always smaller than that of the intervention groups, and that the covariance of the estimate of the intervention and control groups is equal to the between-study variance of the estimate in the control groups (Higgins et al, 2001). These assumptions are unrealistic, and arise as a result of the coding scheme used for controls and cases (0/1). If however, we choose an encoding of ±½, we force the covariance of the random terms to be zero:

$$\begin{pmatrix} \nu_i \\ \upsilon_i \end{pmatrix} \sim MVN\left(\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{pmatrix} \sigma_\nu^2 & 0 \\ 0 & \sigma_\upsilon^2 \end{pmatrix}\right),\ \operatorname{cov}\left(\upsilon_i, \nu_i\right) = 0 \tag{2.12}$$

Although the issue regarding the use of each one of the previously mentioned methods is controversial, we applied them all to compare the results and reach safer conclusions. Discussion on this issue can be found in (Higgins & Whitehead, 1996; Higgins et al, 2001; Turner et al, 2000). If the duration is constant, using $n_{ij}$, a random effects estimate for the OR could be also calculated. Denoting by $\pi_{ij}=P(\delta_{ij}=1)$ the underlying risk (the probability of being a case) of an individual of the $j^{\text{th}}$ group of the $i^{\text{th}}$ study, we can fit a logistic regression model of the form:

$$\operatorname{logit}\left(\pi_{ij}\right)=\operatorname{logit}\left[P\left(\delta_{ij}=1 \mid j\right)\right]=a_0+\alpha_i+\left(\theta+\nu_i\right) z_{ij}, \nu_i \sim N\left(0, \tau^2\right) \quad (2.13)$$

Similar logistic regression models with or without random study effects have been used in the past by several authors (Agresti & Hartzel, 2000; Thompson & Sharp, 1999; Turner et al, 2000) and are presented here only for completeness.

Once the models of Eq. (2.4), (2.9) or (2.10) are fitted, we can calculate an estimate of IRD (or RD) making use of the relations, $IR_1$=exp($\theta$+$\alpha_0$) and $IR_0$=exp($\alpha_0$). Thus, we will have:

$$I\hat{R}D=I\hat{R}_1-I\hat{R}_0=\exp\left(\hat{\theta}\right)\exp\left(\hat{a}_0\right)-\exp\left(\hat{a}_0\right) \quad (2.14)$$

Using the delta method, it can be shown (Appendix I) that the variance of IRD is equal to:

$$\begin{aligned}\operatorname{var}\left(I\hat{R}D\right)=&\left[\exp\left(\hat{a}_0\right)\exp\left(\hat{\theta}\right)\right]^2\left\{\operatorname{var}\left(\hat{\theta}\right)+\operatorname{var}\left(\hat{a}_0\right)-2\operatorname{cov}\left(\hat{\theta},\hat{a}_0\right)\right\} \\ &+\left[\exp\left(\hat{a}_0\right)\right]^2\operatorname{var}\left(\hat{a}_0\right)\end{aligned} \quad (2.15)$$

Consequently, an approximate 95% confidence interval for $I\hat{R}D$ would be obtained using:

$$I\hat{R}D-1.96\sqrt{\operatorname{var}\left(I\hat{R}D\right)}, I\hat{R}D+1.96\sqrt{\operatorname{var}\left(I\hat{R}D\right)}$$

These models can be easily fitted in `Stata` using `gllamm`, or in SAS using `PROC NLMIXED`. They are expected to perform better compared to those presented in the previous sub-section in case where the normality assumptions may be invalid. In the Appendix III, `Stata` programs for fitting the models developed in this section are presented using the `gllamm` module (Rabe-Hesketh et al, 2002; Rabe-Hesketh et al, 2005). `gllamm` uses numerical integration by adaptive quadrature in order to integrate the latent variables and obtain the marginal log-likelihood. Afterwards, the log-likelihood is maximized by the Newton-Raphson method using numerical first and second derivatives.

We have to emphasize here, that the models considered in this work assume (similar to what is the case in the majority of methods for meta-analysis) that the random effects are normally distributed. One can also assume a discrete distribution for the random effects, which leads under certain circumstances to the so-called non-parametric maximum likelihood (NPML) approach (Aitkin, 1999; Biggeri et al, 2000). Even though such methods are not widely used, they can also be fitted using `gllamm` as described by the developers of the software (Rabe-Hesketh et al, 2003).

## 2.3 Bivariate Poisson meta-analysis

An alternative formulation of the random effects Poisson regression model could be described by modeling separately the counts of the control and intervention groups. Thus, we will consider a bivariate response ($c_{i0}$, $c_{i1}$) using indices $j$=0 for non-exposed and $j$=1 for the intervention/exposed group:

$$\left.\begin{aligned}\log\left(c_{i0}\right)&=\upsilon_{i0}+\theta_0+\log\left(T_{i0}\right)\\ \log\left(c_{i1}\right)&=\upsilon_{i1}+\theta_1+\log\left(T_{i1}\right)\end{aligned}\right\}\begin{pmatrix}\upsilon_{i0}\\ \upsilon_{i1}\end{pmatrix}\sim MVN\left(\begin{pmatrix}0\\0\end{pmatrix},\begin{pmatrix}\sigma_0^2 & \sigma_{10}\\ \sigma_{01} & \sigma_1^2\end{pmatrix}\right) \qquad (2.16)$$

The covariance of the random terms is defined as:

$$\operatorname{cov}\left(\upsilon_{i0},\upsilon_{i1}\right)=\sigma_{10}=\sigma_{01}=\rho\sigma_1\sigma_0$$

The bivariate technique is completely analogous to the bivariate logistic regression approach proposed by van Houwelingen and coworkers (van Houwelingen et al, 2002; van Houwelingen et al, 1993) and offers the advantage of modeling the baseline risk, which in some cases is considered an important source of heterogeneity. In general, the results obtained using the univariate multilevel model given by Eq. (2.10) and the bivariate model described here, are expected to be quite similar. Once the model is fitted, we can calculate the estimate of IRR using:

$$I\hat{R}R=\frac{I\hat{R}_1}{I\hat{R}_0}=\frac{\exp\left(\hat{\theta}_1\right)}{\exp\left(\hat{\theta}_0\right)}=\exp\left(\hat{\theta}_1-\hat{\theta}_0\right)=\exp\left(\hat{\theta}\right) \qquad (2.17)$$

The variance of $\hat{\theta}$ would be:

$$\operatorname{var}\left(\hat{\theta}\right)=\operatorname{var}\left(\hat{\theta}_1-\hat{\theta}_0\right)=\operatorname{var}\left(\hat{\theta}_1\right)+\operatorname{var}\left(\hat{\theta}_0\right)-2\operatorname{cov}\left(\hat{\theta}_1,\hat{\theta}_0\right) \qquad (2.18)$$

which can be easily calculated from the estimated covariance matrix. Thus, the significance of $\hat{\theta}$ under $H_0$: $\theta_1=\theta_0$ can be tested and a 95% approximate confidence interval for $I\hat{R}R$ could be computed according to:

$$\exp\left(\log I\hat{R}R-1.96\sqrt{\operatorname{var}\left(\log I\hat{R}R\right)}\right),\exp\left(\log I\hat{R}R+1.96\sqrt{\operatorname{var}\left(\log I\hat{R}R\right)}\right)$$

The model can be used in order to calculate an estimate for IRD in a similar manner:

$$I\hat{R}D=\exp\left(\hat{\theta}_1\right)-\exp\left(\hat{\theta}_0\right) \qquad (2.19)$$

The variance can be easily shown by the delta-method (Appendix II) to be equal to:

$$\begin{aligned}\operatorname{var}\left[\exp\left(\hat{\theta}_1\right)-\exp\left(\hat{\theta}_0\right)\right] &= \exp\left(\hat{\theta}_1\right)^2 \operatorname{var}\left(\hat{\theta}_1\right)+\exp\left(\hat{\theta}_0\right)^2 \operatorname{var}\left(\hat{\theta}_0\right) \\ &\quad -2\exp\left(\hat{\theta}_1\right)\exp\left(\hat{\theta}_0\right)\operatorname{cov}\left(\hat{\theta}_1,\hat{\theta}_0\right) \qquad (2.20) \\ &= \operatorname{var}\left(I\hat{R}D\right)\end{aligned}$$

Thus, an approximate 95% confidence interval for $I\hat{R}D$ could be obtained using:

$$I\hat{R}D-1.96\sqrt{\operatorname{var}\left(I\hat{R}D\right)}, I\hat{R}D+1.96\sqrt{\operatorname{var}\left(I\hat{R}D\right)}$$

The variance of Eq. (2.15) (2.18) and (2.20) can be computed by the `testnl` and `nlcom` commands in Stata using the general formulae for performing multivariate Wald tests for linear and non-linear hypotheses (Green, 2008; Judge et al, 1985). However, using Eq. (2.18) and (2.20) they are easily calculated in every statistical package.

The model of Eq. (2.16) is also useful for providing insights for other special cases often encountered. For instance, the univariate analogue of Eq. (2.16) could be used for meta-analysis of epidemiological studies reporting incidence of a disease (or any other proportion), without resorting to normal approximations or the need to perform transformations that will constrain the risk in the range [0-1]. Furthermore, extending the model of Eq. (2.9) in a bivariate situation when we have two different types of mutually exclusive counts (i.e. death from a particular disease vs. death from any other reason) will provide the means for performing meta-analysis of such mutually exclusive outcomes in a multilevel framework.

A similar model was recently proposed by Trikalinos and Olkin using bivariate modeling of two stochastically correlated outcomes (logORs, logRRs or RDs) calculated from summary data and analytical expressions for the covariance of the two outcomes were given (Trikalinos & Olkin, 2008). However, using the bivariate Poisson model, the correlation is inherently implied by the joint modeling and no additional calculation is needed. In the model of Eq. (2.9), we simply add a subscript for the $r^{th}$ outcome, ($r$=0,1,2…). In the work of Trikalinos and Olkin, there were 3 mutually exclusive outcomes (0=healthy, 1=death from breast cancer, 2=death from other causes); however, the methodology could be easily extended for any $r$>3. In the simpler formulation, for a single study $r$-1 Poisson regressions can be fitted, using the counts $c_{ij}^{r}$ as the dependent variables in each case, an indicator of the exposed/non-exposed status as the independent variable and the logarithm of the total number $n_{ij}$ for each arm as an offset to the model. Thus, it is straightforward to generalize this model in a meta-analysis of $i$=1,2,…$k$ studies, using $k$-1 indicator variables for the fixed studies effects.

Extending the model of Eq. (2.9), we can formulate a bivariate Poisson random-coefficient model:

$$\left.\begin{array}{l}\log\left(c_{ij}^{1}\right)=a_{01}+a_{i1}+\left(\theta_1+\nu_{i1}\right)z_{ij}+\log\left(n_{ij}\right)\\ \log\left(c_{ij}^{2}\right)=a_{02}+a_{i2}+\left(\theta_2+\nu_{i2}\right)z_{ij}+\log\left(n_{ij}\right)\end{array}\right\}\begin{pmatrix}\nu_{i1}\\ \nu_{i2}\end{pmatrix}\sim MVN\left(\begin{pmatrix}0\\0\end{pmatrix},\begin{pmatrix}\sigma_1^2 & \sigma_{12}\\ \sigma_{12} & \sigma_2^2\end{pmatrix}\right) \quad (2.21)$$

## 2.4 Meta-analysis using individual patients' data

If there are available individual patients' data (IPD), the total number of events $c_{ij}$ from the $j^{th}$ arm of the $i^{th}$ study will be equal to the sum of the counts of the $r$ individuals included in each arm, i.e. $c_{ij}=\sum_{r=1}^{n_{ij}}d_{ijr}$ . In such case, we will also have $T_{ij}=n_{ij}\overline{t}_{ij}=\sum_{r=1}^{n_{ij}}t_{ijr}$ and we can use the individual person-time $t_{ijr}$ to perform an IPD meta-analysis including individuals that gave rise to an event ($d_{ijr}$=1,2,3…) and individuals that were not ($d_{ijr}$=0). For instance, using this notation with grouped data the fixed-effects model of Eq. (2.4) can be rewritten:

$$\log\left(c_{ij}\right)=\log\left(\sum_{r=1}^{n_{ij}}d_{ijr}\right)=\alpha_0+\alpha_i+\theta z_{ij}+\log\left(\sum_{r=1}^{n_{ij}}t_{ijr}\right)$$

The same model, in case of IPD would be:

$$\log\left(d_{ijr}\right)=\alpha_0+\alpha_i+\theta z_{ijr}+\log\left(t_{ijr}\right) \quad (2.22)$$

Similarly, the random effects model of Eq. (2.9) becomes:

$$\log\left(d_{ijr}\right)=a_0+\alpha_i+\left(\theta+\nu_i\right)z_{ijr}+\log\left(t_{ijr}\right),\ \nu_i\sim N\left(0,\tau^2\right) \quad (2.23)$$

The same formulation could be also applied for the other models described in previous sections. The implementation of these models will provide useful results, since we can easily incorporate covariates $x_{ijr}$ measured at the individual level. Thus, the influential role of potential confounders or effect modifiers could be investigated in a pooled analysis. Furthermore, the model could be tailored to the characteristics of studies in which events occurred repeatedly. Multiple events per individual or recurrent events are known to produce over-dispersed counts; in other words, there is heterogeneity due to the within-individual correlation. The occurrence of an event multiple times in an individual requires special handling of over-dispersion and various approaches have been proposed (Glynn et al, 1993; Stukel et al, 1994; Sturmer et al, 2000).

A simple technique in the context of the methods discussed here is to use a random effects Poisson regression model, i.e. including a random intercept. The random intercept assumption is sensible since we expect individuals that already had an event to be at increased risk of having recurrence. The over-dispersion is apparent in the meta-analysis of Guevara et al (Guevara et al, 2004), which we will analyze in the next section. In the context of meta-analysis, this heterogeneity is at the individual level and should be distinguished from the usually encountered between-studies heterogeneity. The IPD methods presented here can accommodate such modeling utilizing a hierarchical model. Adding the random intercept $u_{ir}$ (i.e. for individuals $r$ in each study $i$) to Eq. (2.23), leads to a new equation:

$$\log\left(d_{ijr}\right) = a_0 + \alpha_i + u_{ir} + \left(\theta + v_i\right) z_{ijr} + \log\left(t_{ijr}\right),$$
$$v_i \sim N\left(0, \tau^2\right) \;\; u_{ir} \sim N\left(0, \sigma^2\right) \tag{2.24}$$

With this model, the between-subjects variability within each study can be separated from the between-studies variability, providing thereby a better way of exploring heterogeneity in an IPD meta-analysis. Adding in the model a random coefficient $v_{ir}$ for individuals $r$ in each study $i$, would imply that cases in each study are having a greater tendency to have a recurrence compared to controls, an assumption that needs to be investigated.

# 3. Application of the methods

We present here the application of the methods proposed based on Poisson regression and compare them against the established summary-based methods. We initially performed a simulation study to calculate empirical power and we also applied the methods in several published meta-analyses. We simulated hypothetical meta-analyses of studies with exposed and non-exposed persons drawn from a normal population with mean 100 individuals and variance of 50. We performed simulations using 5, 10, 15, 20 and 25 studies per meta-analysis with a Risk Ratio of 1.5 and 2.0 and we also varied the control group event rate taking values in the range 1%, 2.5%, 5%, 10% and 30%. Each simulation consisted of 1000 repetitions. Due to the excessive amount of computations needed, we evaluated only the fixed effects method of Eq. (2.5), assuming no between studies heterogeneity ($\tau^2$=0). The results of the simulation study are presented in Table 3 and Table 4, corresponding to a RR of 1.5 and 2.0 respectively. The empirical power of the Poisson regression method is uniformly higher compared to the summary based methods across the range of experimental conditions. Furthermore, the differences are more pronounced in cases of rare events (event rate ≤5%) and with small number of studies (≤10), results that highlight the potential usefulness of the newly proposed method.

We also analyzed four previously published meta-analyses. Two of these were also re-analyzed by Guevara and coworkers (Guevara et al, 2004) and revisit the effects of asthma self-management education on children. In particular, in the first meta-analysis involving 16 studies, the days of school absence were compared among intervention and control groups. In summary, the intervention group consisted of 867 individuals observed for a period of 6,171 person-months with 5,959 school absences. The corresponding values for the control arm were

766 subjects followed for 5,305 person-months with a total of 5,941 school absences (Wolf et al, 2003).

**Table 3.** The results of the simulation study comparing the empirical power of the proposed methods (using fixed effects Poisson regression) against the summary based methods. The results are based on 1000 repetitions with meta-analyses of varying number of studies (5, 10, 15, 20 and 25) and control group event rate (1%, 2.5%, 5%, 10% and 30%) using a Risk Ratio equal to 1.5.

| Poisson regression method (power) | Summary-based method (power) | Number of Studies (N) | Control Group Event Rate (%) |
|---|---|---|---|
| 0.061 | 0.051 | 5 | 1.0% |
| 0.129 | 0.074 | 10 | 1.0% |
| 0.192 | 0.107 | 15 | 1.0% |
| 0.274 | 0.124 | 20 | 1.0% |
| 0.313 | 0.179 | 25 | 1.0% |
| 0.169 | 0.136 | 5 | 2.5% |
| 0.323 | 0.220 | 10 | 2.5% |
| 0.441 | 0.310 | 15 | 2.5% |
| 0.552 | 0.378 | 20 | 2.5% |
| 0.647 | 0.495 | 25 | 2.5% |
| 0.308 | 0.284 | 5 | 5.0% |
| 0.548 | 0.478 | 10 | 5.0% |
| 0.701 | 0.667 | 15 | 5.0% |
| 0.829 | 0.732 | 20 | 5.0% |
| 0.900 | 0.841 | 25 | 5.0% |
| 0.548 | 0.559 | 5 | 10.0% |
| 0.845 | 0.827 | 10 | 10.0% |
| 0.950 | 0.930 | 15 | 10.0% |
| 0.981 | 0.937 | 20 | 10.0% |
| 0.998 | 0.957 | 25 | 10.0% |
| 0.942 | 0.949 | 5 | 30.0% |
| 0.997 | 0.963 | 10 | 30.0% |
| 1.000 | 0.982 | 15 | 30.0% |
| 1.000 | 0.992 | 20 | 30.0% |
| 1.000 | 0.997 | 25 | 30.0% |

The second meta-analysis that was presented in the same article encompassed 11 studies measuring the emergency room (ER) visits. The meta-analysis contained 630 individuals in the intervention group with 606 ER visits recorded over 6,831 person-months. In the control group, a total number of 484 subjects was observed for a period of 5,151 person-months with 597 ER visits totally (Wolf et al, 2003). Obviously, these two meta-analyses are dealing with recurrent events.

The third meta-analysis synthesized evidence from 10 studies that investigated the association between dietary fat intake and cardiovascular events including all available data on cardiovascular deaths, non-fatal myocardial infarction, stroke, angina, heart failure, peripheral vascular disease, angioplasty, and coronary artery bypass grafting (Hooper et al, 2001). In total, 6,636 individuals in the intervention group were monitored for a total period of 10,649 person-years yielding 553 combined cardiovascular events. In the control arm, 6,631 participants contributed 10,426 person-years of follow-up and experienced 653 cardiovascular events. This meta-analysis is characterized by the inclusion of two extremely large trials (including in total more than 11,000 cases and controls), whereas 4 other studies enrolled less than 200 cases and controls. The results of these three meta-analyses are reported in Table 5.

**Table 4.** The results of the simulation study comparing the empirical power of the proposed methods (using fixed effects Poisson regression) against the summary based methods. The results are based on 1000 repetitions with meta-analyses of varying number of studies (5, 10, 15, 20 and 25) and control group event rate (1%, 2.5%, 5%, 10% and 30%) using a Risk Ratio equal to 2.0.

| Poisson regression method (power) | Summary-based method (power) | Number of Studies (N) | Control Group Event Rate (%) |
|---|---|---|---|
| 0.160 | 0.094 | 5 | 1.0% |
| 0.377 | 0.225 | 10 | 1.0% |
| 0.556 | 0.314 | 15 | 1.0% |
| 0.682 | 0.404 | 20 | 1.0% |
| 0.778 | 0.499 | 25 | 1.0% |
| 0.458 | 0.368 | 5 | 2.5% |
| 0.750 | 0.603 | 10 | 2.5% |
| 0.902 | 0.811 | 15 | 2.5% |
| 0.968 | 0.894 | 20 | 2.5% |
| 0.988 | 0.938 | 25 | 2.5% |
| 0.759 | 0.693 | 5 | 5.0% |
| 0.962 | 0.921 | 10 | 5.0% |
| 0.998 | 0.968 | 15 | 5.0% |
| 0.999 | 0.982 | 20 | 5.0% |
| 1.000 | 0.985 | 25 | 5.0% |
| 0.946 | 0.950 | 5 | 10.0% |
| 0.998 | 0.984 | 10 | 10.0% |
| 1.000 | 0.980 | 15 | 10.0% |
| 1.000 | 0.989 | 20 | 10.0% |
| 1.000 | 0.997 | 25 | 10.0% |
| 1.000 | 0.988 | 5 | 30.0% |
| 1.000 | 0.990 | 10 | 30.0% |
| 1.000 | 0.998 | 15 | 30.0% |
| 1.000 | 1.000 | 20 | 30.0% |
| 1.000 | 1.000 | 25 | 30.0% |

Finally, we re-analyzed the data that were used by Warn and coworkers in the development of their Bayesian method (Warn et al, 2002). The data were obtained from a Cochrane Review investigating the effectiveness of single-dose

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ibuprofen (i.e. a non-steroidal anti-inflammatory analgesic) in reducing post-operative pain (Collins et al, 2000). The original review comprised 46 small trials of single-dose ibuprofen against placebo with doses ranging from 50mg to 800mg. Similarly to Warn and coworkers, we considered only the subset of 31 trials with dose of 400 mg. Since the length of follow-up is the same within trials, it is appropriate to consider the patient's 'risk' of experiencing pain relief and thus, we used this dataset to for applying methods that estimate OR, RR and RD. The results of this meta-analysis are reported in Table 6.

In all the datasets that we re-analyzed there was a moderate to severe degree of heterogeneity and thus, random effects models should provide more accurate results (Table 5 and 6). It should be noticed that even when we restrict the attention to summary data methods, the different methods (MM-DL, ML, REML) provide slightly different results, without changing though the overall conclusions. The differences of the fixed effects methods based on summary data compared to those using the Poisson regression are also non-negligible. All the random effects Poisson regression methods provide more convincing results for the significance of the intervention (exposure) compared to the summary data methods. In all analyses the bivariate Poisson regression and the mixed model with random study effects and 0/1 coding produce identical estimates. The model with fixed study effects produces slightly different results, which in the case of the meta-analysis for the effect of dietary fat intake on combined cardiovascular events (Hooper et al, 2001), lead to different conclusions when the IRD is the measure of choice. In this analysis, this model produces a marginally non-significant point estimate contradicting the other Poisson models, but is in agreement with summary data methods. The mixed model with zero covariance and the $\pm\frac{1}{2}$ coding, produces similar results compared to the mixed model with random study effects and 0/1 coding, although in the meta-analysis for the effect of ibuprofen on post-operating treatment of pain (Collins et al, 2000), the difference in the estimates is large in all effects measures (RR, RD, OR).

In the meta-analysis investigating the effectiveness of single-dose ibuprofen in reducing post-operative pain ibuprofen (Collins et al, 2000), we had the opportunity to compare the newly established methods against the Bayesian methods developed by Warn and coworkers (Warn et al, 2002). In general the Poisson model with fixed study effects produce estimates that are close to the ones produced by the Bayesian methods. Furthermore, in most of the cases, the 95% C.I. are wider compared to the Bayesian methods, on contrary to what generally one would expect. Besides the theoretical considerations behind the validity of the assumption that each model makes (i.e. zero covariance, coding scheme etc) some general conclusions could be drawn following previous studies (Higgins & Whitehead, 1996; Higgins et al, 2001; Turner et al, 2000). For instance, when the meta-analysis consists of a small number of studies, the most plausible model would be the one with fixed study effects. Random study effects could be preferable in cases of large number of included studies when the calculation of a large number of study-specific coefficients would be problematic. A large number of studies are also needed for a precise estimation of the covariance of the random terms in the model with the random study effects (Riley et al, 2007). The model with zero covariance potentially provides a compromise, but makes additional assumptions that may be untenable. In the particular meta-analyses that we analyzed, the meta-analysis for the effect of dietary fat intake on combined cardiovascular events (Hooper et al, 2001) included a small number of studies and two large influential studies; thus, the discrepancy of methods using fixed vs. random study effects is reasonable. On the other hand, in the meta-analysis for the effect of ibuprofen on post-operating treatment of pain which included 31 studies (Collins et al, 2000), large discrepancies arose by the use of zero covariance model.

# 4. Discussion

Meta-analyses are increasingly recognized as effective means of quantitatively synthesizing the results of primary research and exploring variability across studies (Petiti, 1994). Notwithstanding their simplicity, traditional summary-data methods used in most meta-analyses have many limitations. Therefore, the development of efficient methodology capable of exploiting the binary structure of the data and overcoming the shortcomings of traditional meta-analytical methods is needed (Bagos, 2008; Bagos & Nikolopoulos, 2007; Higgins et al, 2001; Thompson et al, 2001; Turner et al, 2000; Whitehead et al, 2001).

The current work describes various procedures based on Poisson regression and indicates their usefulness in pooling rates and ratios calculated in follow up studies. Although mixed-effects Poisson regression models have been used in the past in the biomedical literature (Gibbons et al, 2008; Pennello et al, 1999), according to the authors' knowledge they have never been described explicitly for meta-analysis. The methods proposed in this work can be useful in meta-analyses of count or rate data making use of the Poisson likelihood and thus, avoiding the continuity corrections in case of rare events that fit poorly to the normal approximation. The simulation study that we conducted revealed that the Poisson regression method is uniformly more powerful compared to the summary based method across a wide range of experimental conditions, especially in cases of rare events (event rate ≤5%) and small number of studies (≤10), results that highlight the potential usefulness of the newly proposed method. Consequently, the methods were successfully applied to the sparse data reported recently by Rucker and coworkers (Rucker et al, 2009) with very encouraging results (data not shown). In future studies, application of alternative methods such as the random-effects zero inflated Poisson regression models could be evaluated (Hall, 2000; Lee et al, 2006). The suggested methodology can be applied using widely available statistical software (SAS, STATA etc) whereas, especially in STATA, it can be easily implemented with the accompanied do file. The only limitation of the method is the increased computational demands required by the random coefficient models (several minutes for a standard meta-analysis).

We compared the proposed techniques with the commonly implemented models using data obtained from several published meta-analyses obtaining encouraging results. When the duration of follow-up is constant, estimates for the RR as well as for RD could be easily obtained in addition to the already established techniques for obtaining estimates of the OR. The choice of the particular measure that will be used in a meta-analysis as well as in primary research is however, an important issue that should be evaluated carefully (Deeks, 2002; Walter, 2000). When the duration varies, the proposed methodology naturally arises as a consequence of the properties of Poisson distribution. Nevertheless, events to person-time statistics should be used only when appropriate (Kraemer, 2009).

The new approach is also perceived to be suitable for the analysis of studies with recurrent events, which are common in medical research (Glynn & Buring, 1996; Glynn et al, 1993; Stukel et al, 1994; Sturmer et al, 2000). Overdispersion is often encountered in the case of multiple occurrences of an event in the same subject and our methodology accounts for this phenomenon adopting higher-level models. Emphasis has also been given to the analysis of individual patients data, whose synthesis offer many advantages over the meta-analysis based on summary statistics extracted from the published literature i.e. standardization of variables, sufficient control of confounding, collection of updated information and retrieval of unpublished data (Ioannidis et al, 2002; Steinberg et al, 1997). Our method could be an appropriate and flexible choice when meta-analysis of raw data from follow-up studies is planned in order to model heterogeneity and confounders directly at the individual level.

The mixed-effects Poisson regression model can also be used in meta-analyses of incidence or any other type of counts or rates. We have also shown that the model could be extended to handle situations of meta-analysis of mutually exclusive data (competing risks). The application of the method in the data used by Trikalinos and Olkin provided very encouraging results (data not shown). Furthermore, the models presented here based on Poisson regression can also be used very easily for providing estimates and confidence intervals for another useful measure, the Number Needed to Treat (NNT). NNT is defined as the inverse of RD (Nuovo et al, 2002; Walter & Sinclair, 2009) and thus, its confidence intervals can be easily produced by the Poisson model using the delta method. Since the large sample approximations for the variance of NNT are also prone to bias (Duncan & Olkin, 2005), we expect that the methods proposed here would compare favourably. Lastly, we have to mention that since Poisson regression models have been for long used for performing estimations on survival data (Laird & Olivier, 1981; Whitehead, 1980) another possible use of the mixed-effects Poisson model could be that of performing IPD meta-analysis with survival data.

Given the importance of conducting efficient research and the problems encountered in the statistical aspects of meta-analysis, the Poisson-based approach could be a promising and credible analytical tool in the synthesis of evidence from follow-up studies, in which a specific metric might be more relevant, while the period of observation will probably be incomplete in many participants or the outcome of interest might be observed repeatedly in the population. Therefore, using the suggested approach, analyses on scales other than the mathematically advantageous OR such as the RR or the RD are feasible. Common statistical software packages support the theoretical concept of combining studies with Poisson regression making fairly easy the implementation of the suggested methodology and we expect that this will be widely used.

**Table 5.** Results obtained using the various methods described in the text on the three published meta-analyses. We present the estimates for Incidence Rate Ratio (IRR) and Incidence Rate Difference (IRD) along with their respective 95% confidence intervals. IV: Inverse variance, MM-DL: Method of Moments of DerSimonian and Laird, ML: Maximum Likelihood, REML: Restricted Maximum Likelihood.

| | **Meta-analysis** | | | | | |
|---|---|---|---|---|---|---|
| | Dietary fat intake/ combined cardiovascular events (Hooper et al, 2001) | | Asthma self-management education in children / School absences (Wolf et al, 2003) | | Asthma self-management education in children / ER visits (Wolf et al, 2003) | |
| | | | | | | |
| | **IRR (95% CI)** | **IRD (95% CI)** | **IRR (95% CI)** | **IRD (95% CI)** | **IRR (95% CI)** | **IRD (95% CI)** |
| **Summary methods** | | | | | | |
| fixed effects (IV) | 0.825 (0.736, 0.924) | -0.005 (-0.011, 0.000) | 0.869 (0.838, 0.901) | -0.119 (-0.147, -0.091) | 0.678 (0.603, 0.762) | -0.013 (-0.020, -0.007) |
| random effects (MM-DL) | 0.754 (0.617, 0.921) | -0.016 (-0.031, -0.001) | 0.763 (0.671, 0.866) | -0.167 (-0.253, -0.082) | 0.561 (0.416, 0.756) | -0.053 (-0.080, -0.026) |
| random effects (ML) | 0.804 (0.701, 0.922) | -0.009 (-0.016, -0.001) | 0.743 (0.609, 0.905) | -0.166 (-0.248, -0.084) | 0.544 (0.384, 0.771) | -0.019 (-0.030, -0.009) |
| random effects (REML) | 0.787 (0.672, 0.921) | -0.009 (-0.017, -0.002) | 0.740 (0.599, 0.914) | -0.167 (-0.252, -0.082) | 0.539 (0.373, 0.779) | -0.020 (-0.031, -0.009) |
| | | | | | | |
| **Individual Data methods (Poisson Regression)** | | | | | | |
| Fixed effects | 0.819 (0.731, 0.917) | -0.015 (-0.023, -0.006) | 0.864 (0.834, 0.896) | -0.040 (-0.052, -0.029) | 0.659 (0.588, 0.739) | -0.051 (-0.074, -0.028) |
| Bivariate fixed effects | 0.829 (0.740, 0.929) | -0.011 (-0.017, -0.004) | 0.862 (0.832, 0.894) | -0.154 (-0.192, -0.117) | 0.765 (0.684, 0.857) | -0.027 (-0.039, -0.016) |
| Random effects (fixed study effects) | 0.819 (0.731, 0.917) | -0.015 (-0.023, -0.006) | 0.727 (0.587, 0.900) | -0.105 (-0.168, -0.042) | 0.516 (0.361, 0.739) | -0.090 (-0.143, -0.037) |
| Random effects (random study effects, z=0/1, cov≠0) | 0.746 (0.592, 0.940) | -0.026 (-0.059, 0.008) | 0.721 (0.579, 0.897) | -0.189 (-0.320, -0.058) | 0.525 (0.361, 0.764) | -0.056 (-0.104, -0.007) |
| Random effects (random study effects, z=±1/2, cov=0) | 0.779 (0.615, 0.987) | -0.019 (-0.038, 0.000) | 0.722 (0.581, 0.898) | -0.155 (-0.266, -0.043) | 0.521 (0.360, 0.754) | -0.041 (-0.069, -0.012) |
| Bivariate random effects | 0.746 (0.592, 0.940) | -0.026 ( -0.059, 0.008) | 0.721 (0.579, 0.897) | -0.189 (-0.320, -0.058) | 0.525 (0.361, 0.764) | -0.056 (-0.104, -0.007) |

**Table 6.** Results obtained using the various methods described in the text on re-analyzing the data from the meta-analysis investigating the effectiveness of single-dose ibuprofen in reducing post-operative pain (Collins et al, 2000). We present the estimates for Risk Ratio (RR), Risk Difference (RD) and Odds Ratio (OR) along with their respective 95% confidence intervals. For reasons of comparison we also list results obtained by Warn and coworkers using their Bayesian methods denoted by model a, b and c (Warn et al, 2002). IV: Inverse variance, MM-DL: Method of Moments of DerSimonian and Laird, ML: Maximum Likelihood, REML: Restricted Maximum Likelihood.

| | **RD (95% CI)** | **RR (95% CI)** | **OR (95% CI)** |
|---|---|---|---|
| **Summary data methods** | | | |
| fixed effects (IV) | 0.400 (0.371, 0.428) | 2.390 (2.106, 2.713) | 6.221 (4.988, 7.759) |
| random effects (MM-DL) | 0.395 (0.335, 0.454) | 3.385 (2.617, 4.378) | 8.021 (5.559, 11.575) |
| random effects (ML) | 0.393 (0.334, 0.452) | 3.412 (2.627, 4.431) | 8.048 (5.563, 11.643) |
| random effects (REML) | 0.393 (0.333, 0.453) | 3.447 (2.638, 4.503) | 8.129 (5.575, 11.854) |
| Bayesian method (model c) | 0.391 (0.328, 0.453) | 3.438 (2.602, 4.933) | 8.051 (5.481, 12.570) |
| | | | |
| **Individual Data methods (Poisson Regression, Logistic Regression)** | | | |
| Fixed effects | 0.367 (0.206, 0.527) | 3.451 (2.948, 4.040) | 8.421 (6.841, 10.367) |
| Bivariate fixed effects | 0.373 (0.331, 0.416) | 3.318 (2.840, 3.876) | 5.976 (4.983, 7.169) |
| Random effects (fixed study effects) | 0.367 (0.206, 0.527) | 3.451 (2.948, 4.040) | 9.818 (6.861, 14.051) |
| Random effects (random study effects, z=0/1, cov≠0) | 0.432 (0.375, 0.488) | 5.467 (3.623, 8.249) | 11.326 (7.017, 18.281) |
| Random effects (random study effects, z=±1/2, cov=0) | 0.774 (0.478, 1.070) | 4.093 (3.069, 5.458) | 9.985 (6.582, 15.149) |
| Bivariate random effects | 0.432 (0.375, 0.488) | 5.467 (3.623, 8.249) | 11.326 (7.017, 18.281) |
| Bayesian method (model a) | 0.375 (0.312, 0.440) | 3.864 (2.870, 5.263) | 8.670 (5.570, 12.94) |
| Bayesian method (model b) | 0.393 (0.333, 0.456) | 3.853 (3.045, 5.143) | 9.340 (6.300, 13.82) |

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# Appendix I

Once the models of Eq. (2.4), (2.9) or (2.10) are fitted, we can directly calculate an estimate of IRD (or RD) making use of the relations, $IR_1$=exp($\theta$+$\alpha$) and $IR_0$=exp($\alpha$). Thus, we will have:

$$I\hat{R}D = I\hat{R}_1 - I\hat{R}_0 = \exp\left(\hat{\theta}\right)\exp\left(\hat{a}_0\right) - \exp\left(\hat{a}_0\right)$$

The variance of IRD will be given by:

$$\mathrm{var}\left[\exp\left(\hat{a}_0\right)\exp\left(\hat{\theta}\right) - \exp\left(\hat{a}_0\right)\right] = \mathrm{var}\left[\exp\left(\hat{a}_0\right)\exp\left(\hat{\theta}\right)\right] + \mathrm{var}\left[\exp\left(\hat{a}_0\right)\right]$$

To calculate the variance of $\mathrm{var}\left[\exp\left(\hat{a}_0\right)\exp\left(\hat{\theta}\right)\right]$, we have to define a function $f(\theta,\ a_0)$=exp($a_0$)exp($\theta$) and approximate it using a bivariate 1st order Taylor expansion around the sample means of the parameters $\theta$, $a_0$ $\left(\hat{\mu}_\theta = \hat{\theta}, \hat{\mu}_{a_0} = \hat{a}_0\right)$ :

$$\hat{f}\left(\theta, a_0\right) = f\left(\hat{\theta}, \hat{a}_0\right) + \frac{\partial f\left(\hat{\theta}, \hat{a}_0\right)}{\partial \theta}\left(\theta - \hat{\theta}\right) + \frac{\partial f\left(\hat{\theta}, \hat{a}_0\right)}{\partial a_0}\left(a_0 - \hat{a}_0\right)$$

Then, using the delta method we will have:

$$\begin{aligned}
\mathrm{var}\left[f\left(\theta, a_0\right)\right] &\approx \mathrm{var}\left[\hat{f}\left(\theta, a_0\right)\right] \\
&= \mathrm{var}\left[\frac{\partial f\left(\hat{\theta}, \hat{a}_0\right)}{\partial \theta}\left(\theta - \hat{\theta}\right) + \frac{\partial f\left(\hat{\theta}, \hat{a}_0\right)}{\partial a_0}\left(a_0 - \hat{a}_0\right)\right] \\
&= \mathrm{var}\left[\frac{\partial f\left(\hat{\theta}, \hat{a}_0\right)}{\partial \theta}\left(\theta - \hat{\theta}\right)\right] + \mathrm{var}\left[\frac{\partial f\left(\hat{\theta}, \hat{a}_0\right)}{\partial a_0}\left(a_0 - \hat{a}_0\right)\right] \\
&\quad + 2\,\mathrm{cov}\left[\frac{\partial f\left(\hat{\theta}, \hat{a}_0\right)}{\partial \theta}\left(\theta - \hat{\theta}\right), \frac{\partial f\left(\hat{\theta}, \hat{a}_0\right)}{\partial a_0}\left(a_0 - \hat{a}_0\right)\right]
\end{aligned}$$

Thus:

$$\begin{aligned}
\mathrm{var}\left[f\left(\theta_1, \theta_0\right)\right] &\approx \left[\frac{\partial f\left(\hat{\theta}, \hat{a}_0\right)}{\partial \theta}\right]^2 \mathrm{var}\left(\theta\right) + \left[\frac{\partial f\left(\hat{\theta}, \hat{a}_0\right)}{\partial a_0}\right]^2 \mathrm{var}\left(a_0\right) \\
&\quad + 2\,\mathrm{cov}\left(\theta, a_0\right)\frac{\partial f\left(\hat{\theta}, \hat{a}_0\right)}{\partial \theta}\frac{\partial f\left(\hat{\theta}, \hat{a}_0\right)}{\partial a_0}
\end{aligned}$$

and after replacing the population values with the sample ones, the variance will be:

$$\begin{aligned}\mathrm{var}\left[\exp(\hat{a}_0)\exp(\hat{\theta})\right] &= \left[\exp(\hat{a}_0)\exp(\hat{\theta})\right]^2 \mathrm{var}(\hat{\theta}) + \left[\exp(\hat{a}_0)\exp(\hat{\theta})\right]^2 \mathrm{var}(\hat{a}_0) \\ &\quad - 2\left[\exp(\hat{a}_0)\exp(\hat{\theta})\right]\left[\exp(\hat{a}_0)\exp(\hat{\theta})\right]\mathrm{cov}(\hat{\theta},\hat{a}_0) \\ &= \left[\exp(\hat{a}_0)\exp(\hat{\theta})\right]^2 \left\{\mathrm{var}(\hat{\theta}) + \mathrm{var}(\hat{a}_0) - 2\,\mathrm{cov}(\hat{\theta},\hat{a}_0)\right\}\end{aligned}$$

$\mathrm{var}\left[\exp(\hat{a}_0)\right]$, can be calculated similarly to be equal to $\left[\exp(\hat{a}_0)\right]^2 \mathrm{var}(\hat{a}_0)$, and thus:

$$\begin{aligned}\mathrm{var}\left(I\hat{R}D\right) &= \left[\exp(\hat{a}_0)\exp(\hat{\theta})\right]^2 \left\{\mathrm{var}(\hat{\theta}) + \mathrm{var}(\hat{a}_0) - 2\,\mathrm{cov}(\hat{\theta},\hat{a}_0)\right\} \\ &\quad + \left[\exp(\hat{a}_0)\right]^2 \mathrm{var}(\hat{a}_0)\end{aligned}$$

# Appendix II

To calculate the variance of $I\hat{R}D$ from the bivariate model of Eq. (2.16), we have to define a function $f(\theta_1, \theta_0)=\exp(\theta_1)-\exp(\theta_0)$ and approximate it using a bivariate 1st order Taylor expansion around the sample means of the parameters $\theta_1$, $\theta_0$ $\left(\hat{\mu}_{\theta_1} = \hat{\theta}_1, \hat{\mu}_{\theta_0} = \hat{\theta}_0\right)$ :

$$\hat{f}(\theta_1,\theta_0) = f(\hat{\theta}_1,\hat{\theta}_0) + \frac{\partial f(\hat{\theta}_1,\hat{\theta}_0)}{\partial \theta_1}(\theta_1 - \hat{\theta}_1) + \frac{\partial f(\hat{\theta}_1,\hat{\theta}_0)}{\partial \theta_0}(\theta_0 - \hat{\theta}_0)$$

Then, using the delta method we will have:

$$\begin{aligned}\mathrm{var}\left[f(\theta_1,\theta_0)\right] &\approx \mathrm{var}\left[\hat{f}(\theta_1,\theta_0)\right] \\ &= \mathrm{var}\left[\frac{\partial f(\hat{\theta}_1,\hat{\theta}_0)}{\partial \theta_1}(\theta_1 - \hat{\theta}_1) + \frac{\partial f(\hat{\theta}_1,\hat{\theta}_0)}{\partial \theta_0}(\theta_0 - \hat{\theta}_0)\right] \\ &= \mathrm{var}\left[\frac{\partial f(\hat{\theta}_1,\hat{\theta}_0)}{\partial \theta_1}(\theta_1 - \hat{\theta}_1)\right] + \mathrm{var}\left[\frac{\partial f(\hat{\theta}_1,\hat{\theta}_0)}{\partial \theta_0}(\theta_0 - \hat{\theta}_0)\right] \\ &\quad + 2\,\mathrm{cov}\left[\frac{\partial f(\hat{\theta}_1,\hat{\theta}_0)}{\partial \theta_1}(\theta_1 - \hat{\theta}_1), \frac{\partial f(\hat{\theta}_1,\hat{\theta}_0)}{\partial \theta_0}(\theta_0 - \hat{\theta}_0)\right]\end{aligned}$$

Thus:

$$\operatorname{var}\left[f\left(\theta_1,\theta_0\right)\right] \approx \left[\frac{\partial f\left(\hat{\theta}_1,\hat{\theta}_0\right)}{\partial\theta_1}\right]^2 \operatorname{var}\left(\theta_1\right) + \left[\frac{\partial f\left(\hat{\theta}_1,\hat{\theta}_0\right)}{\partial\theta_0}\right]^2 \operatorname{var}\left(\theta_0\right) + 2\operatorname{cov}\left(\theta_1,\theta_0\right)\frac{\partial f\left(\hat{\theta}_1,\hat{\theta}_0\right)}{\partial\theta_1}\frac{\partial f\left(\hat{\theta}_1,\hat{\theta}_0\right)}{\partial\theta_0}$$

and after replacing the population values with the sample ones, the variance will be:

$$\begin{aligned}\operatorname{var}\left[\exp\left(\hat{\theta}_1\right)-\exp\left(\hat{\theta}_0\right)\right] &= \exp\left(\hat{\theta}_1\right)^2 \operatorname{var}\left(\hat{\theta}_1\right)+\exp\left(\hat{\theta}_0\right)^2 \operatorname{var}\left(\hat{\theta}_0\right) \\ &\quad -2\exp\left(\hat{\theta}_1\right)\exp\left(\hat{\theta}_0\right)\operatorname{cov}\left(\hat{\theta}_1,\hat{\theta}_0\right) \\ &= \operatorname{var}\left(I\hat{R}D\right)\end{aligned}$$

# Appendix III

```
*** calculation of IRR and IRD from studies with varying durations
*** we used the data of Wolf et al
*** the commands can be run interactively or in a do-file

input id personmonth1 events1 personmonth0 events0
1 132 7 120 24
2 324 8 180 3
3 1908 273 876 182
4 156 1 156 13
5 528 20 540 27
6 576 110 336 104
7 84 13 84 52
8 90 5 90 18
9 1368 8 1140 22
10 1212 55 1248 40
11 75 11 75 27
12 378 95 306 85
end

gen selogirr=sqrt(  1/events1 + 1/events0)
gen logirr=log( (events1/ personmonth1)/( events0/ personmonth0))

*** Summary data methods for IRR

*** Random effects (MM-DL)
metan logirr selogirr,random eform
*** Random effects (REML)
metareg logirr,wsse(selogirr) bse(reml)
*** Random effects (ML)
metareg logirr,wsse(selogirr) bse(ml)
```

```
gen seird=sqrt(  events1/ personmonth1^2 + events0/ personmonth0^2)
gen ird= (events1/ personmonth1) - ( events0/ personmonth0)

*** Summary data methods for IRD

*** Random effects (MM-DL
metan  ird seird,random
*** Random effects (REML)
metareg ird,wsse(seird) bse(reml)
*** Random effects (ML)
metareg ird,wsse(seird) bse(ml)


*** Poisson regression methods
reshape long personmonth events,i(id ) j(treat)

gen cons=1
gen logt=log(personmonth )

*** fixed effects Poisson regression (we use eform for obtaining the IRR)
xi: glm events treat i.id, fam(poisson)  link(log) offset(logt) eform
*** calculation of IRD with the delta method
nlcom exp(_b[_cons])*(exp(_b[treat ])-1)

*** random effects Poisson regression with random study effects
eq int:cons
eq slope:treat

gllamm events treat,fam(poisson) i(id ) link(log) eqs(int slope) nrf(2)
adapt offset(logt )
*** we use eform for obtaining the IRR
gllamm, eform /* IRR */
*** calculation of IRD with the delta method
nlcom exp(_b[_cons])*(exp(_b[treat ])-1)


*** random effects Poisson regression with random study effects
*** z=±1/2,cov=0
gen treat2=treat-0.5
eq slope2:treat2
gllamm  events  treat2  ,fam(poisson)  i(id  )  link(log)  eqs(int  slope2)
nocorr nrf(2) adapt offset(logt )
*** we use eform for obtaining the IRR
gllamm, eform
*** calculation of IRD with the delta method
nlcom exp(_b[_cons])*(exp(_b[treat2 ])-1)


*** random effects Poisson regression with fixed study effects
xi: gllamm events treat i.id, i(id) nrf(1) eqs(slope) l(log) fam(poisson)
adapt offset(logt)
*** we use eform for obtaining the IRR
gllamm, eform
*** calculation of IRD with the delta method
nlcom exp(_b[_cons])*(exp(_b[treat ])-1)
```

```
*** bivariate Poisson
tab treat,gen(c)

*** bivariate fixed effects Poisson
glm events c1 c2, nocons fam(poisson)  link(log) offset(logt ) eform
*** calculation of IRR with the delta method
nlcom _b[c2] - _b[c1]
*** calculation of IRD with the delta method
nlcom exp(_b[c2]) - exp(_b[c1])

*** bivariate random effects Poisson
eq c1 : c1
eq c2 : c2

gllamm events  c1 c2  , nocons fam(poisson) i(id ) link(log) eqs(c1 c2)
nrf(2) adapt offset(logt ) nip(12)
*** calculation of IRR with the delta method
nlcom _b[c2] - _b[c1]
*** calculation of IRD with the delta method
nlcom exp(_b[c2]) - exp(_b[c1])


*** calculation of RR, RD and OR from studies with constant durations
*** we used the data of Hooper et al
*** the commands can be run interactively or in a do-file

clear
set more off
input id r1 n1 r0 n0
1 19 32 2 30
2 2 15 0 14
3 57 80 31 82
4 20 40 6 40
5 22 38 5 46
6 19 37 6 43
7 37 61 9 64
8 21 28 3 28
9 15 32 0 34
10 18 37 1 39
11 20 38 0 38
12 26 42 0 38
13 40 81 2 39
14 9 41 7 39
15 15 40 5 40
16 19 49 0 51
17 9 12 6 16
18 9 49 0 47
19 33 49 17 48
20 39 39 14 37
21 29 42 24 41
22 6 30 0 11
23 124 306 5 85
24 67 98 1 40
25 13 30 5 32
26 27 36 13 38
27 42 63 10 32
```

```
28 42 62 7 30
29 22 31 2 19
30 21 30 3 30
31 16 38 11 40
end

gen logrr=log(r1/n1) -log(r0/n0)
gen selogrr=sqrt(1/r1+1/r0-1/n1-1/n0)

replace  logrr=log((r1+0.5)/(n1+0.5))  -log((r0+0.5)/(n0+0.5))  if  r1==0
|r0==0
replace selogrr= sqrt(1/(r1+0.5) +1/(r0+0.5) -1/(n1+0.5) -1/(n0+0.5)) if
r1==0 |r0==0

gen rd=r1/n1-r0/n0
gen serd=sqrt(r1*(n1-r1)/n1^3 +r0*(n0-r0)/n0^3 )

gen d1=n1-r1
gen d0=n0-r0

gen logor=log(r1/d1) -log(r0/d0)
gen selogor=sqrt(1/r1+1/r0+1/d1+1/d0)
replace  logor=log((r1+0.5)/(d1+0.5))  -log((r0+0.5)/(d0+0.5))  if  r1==0
|d0==0|r0==0|d1==0
replace selogor= sqrt(1/(r1+0.5) +1/(r0+0.5) +1/(d1+0.5) +1/(d0+0.5)) if
r1==0 |d0==0|r0==0|d1==0



*** Summary data methods for RR an RD using MM-DL
metan r1 d1 r0 d0,rd randomi nowt counts
metan r1 d1 r0 d0,rr randomi nowt counts

*** Summary data methods for RR an RD using MM-DL (alternative method)
metan rd serd,random nowt
metan logrr selogrr,random eform nowt

*** Summary data methods for RR an RD using REML
metareg logrr,wsse(selogrr) bse(reml)
metareg rd,wsse(serd)bse(reml)

*** Summary data methods for RR an RD using ML
metareg logrr,wsse(selogrr) bse(ml)
metareg rd,wsse(serd)bse(ml)


*** Poisson regression models
reshape long r n d, i(id) j(treat)
gen logt=log(n)
gen cons=1
eq int: cons
eq slop: treat
gen treat2=treat-0.5
eq slop2: treat2

*** random effects Poisson regression with fixed study effects
```

```
xi: gllamm r treat i.id, i(id) nrf(1) eqs(slop) l(log) fam(poisson) adapt
offset(logt) eform
**calculation of RD using the delta method
nlcom exp(_b[_cons])*(exp(_b[treat ])-1)

*** random effects Poisson regression with random study effects
gllamm r treat, i(id) nrf(2) eqs(int slop) l(log) fam(poisson) adapt
offset(logt) eform
**calculation of RD using the delta method
nlcom exp(_b[_cons])*(exp(_b[treat ])-1)

*** random effects Poisson regression with random study effects z=±1/2,
cov=0
gllamm r treat2 , i(id) nrf(2) eqs(int slop2) l(log) fam(poisson) nocorr
adapt offset(logt) eform
**calculation of RD using the delta method
nlcom exp(_b[_cons])*(exp(_b[treat ])-1)


*** the same models but using the binomial likelihood
*** in order to obtain the Odds Ratio
xi: gllamm r treat  i.id, i(id) nrf(1) eqs(slop) l(logit) fam(binom)
adapt denom(n) eform

gllamm r treat , i(id) nrf(2) eqs(int slop) l(logit) fam(binom) adapt
denom(n) eform

gllamm r treat2 , i(id) nrf(2) eqs(int slop2) l(logit) fam(binom) nocorr
adapt denom(n) eform

*** bivariate random effects Poisson
tab treat,gen(c)
eq c1: c1
eq c2 : c2

gllamm r  c1 c2, nocons fam(poisson) i(id) link(log) eqs(c1 c2) nrf(2)
adapt offset(logt )
**calculation of RR using the delta method
nlcom _b[c2] - _b[c1] /* RR */
**calculation of RD using the delta method
nlcom exp(_b[c2]) - exp(_b[c1]) /* RD */

*** alternative specification for fitting the same models
rename d y0
rename r y1
gen i=_n
reshape long y, i(i) j(case)
drop i
rename y wt1
eq int: cons
eq slop: treat

*** random effects Poisson regression with random study effects
gllamm case treat, i(id) nrf(2) eqs(int slop) l(log) fam(poisson)
w(wt)adapt eform
**calculation of RD using the delta method
```

```
nlcom exp(_b[_cons])*(exp(_b[treat ])-1)

*** bivariate random effects Poisson
tab treat,gen(cc)
eq c1: cc1
eq c2 : cc2

gllamm case  cc1 cc2, nocons fam(poisson) i(id ) link(log) eqs(c1 c2)
nrf(2) adapt w(wt)
**calculation of RR using the delta method
nlcom _b[cc2] - _b[cc1]
**calculation of RD using the delta method
nlcom exp(_b[cc2]) - exp(_b[cc1])

*** Logistic regression random effects model with fixed study effects
xi: gllamm case treat i.id, i(id) nrf(1) eqs(slop) l(logit) fam(binom)
w(wt)  adapt
```

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