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The identity of two meta-analytic likelihoods and the ignorability of double-zero studies

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Summary

In meta-analysis, the conventional two-stage approach computes an effect estimate for each study in the first stage and proceeds with the analysis of effect estimates in the second stage. For counts of events as outcome, the risk ratio is often the effect measure of choice. However, if the meta-analysis includes many studies with no events the conventional method breaks down. As an alternative one-stage approach a Poisson regression model and a conditional binomial model can be considered where no event studies do not cause problems. The conditional binomial model excludes double-zero studies, whereas this is seemingly not the case for the Poisson regression approach. However, we show here that both models lead to the same likelihood inference and double-zero studies (in contrast to single-zero studies) do not contribute in either case to the likelihood.

Key words: Conditional binomial likelihood; data fusion; double-zero studies; Poisson likelihood; meta-

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analysis

1. Introduction

Meta-analysis and data fusion of studies with rare events has become recently a matter of prime interest. An example is the post-admission surveillance of the anti-diabetes drug *Rosiglitazone* where concern arose in terms of adverse events. A meta-analysis of Nissen & Wolski (2007, 2010) showed an increased risk ratio for myocardial infarction while being on treatment. This meta-analysis started a debate on how to deal with rare event studies in a meta-analysis. For a review on this debate see Böhning et al. (2015). The central problem is the occurrence of *single-zero* and *double-zero* trials, former being a trial where exactly in one arm a zero count occurs, the latter being a trial where both arms contain zero counts as study outcome. To demonstrate the problem we look at a meta-analysis on perinatal death in post-term pregnancy comparing selective induction with routine induction. The data are taken from Piaget-Rossel & Taffé (2019a) (originally stemming from Crowley (2010)) and provided in Table 1 for convenience. The meta-analysis consists only of zero-studies, eleven double-zero studies and eight single-zero studies. Note that the studies are not small in arm size, the smallest having ten at risk while the largest has 1706 at risk. It is clear that a conventional two-stage meta-analysis is not possible for these kind of data. Recall that a two-stage meta-analysis proceeds, in principle, as follows. In the first stage an effect measure such as the risk ratio is determined *for each study* which generates a sample of study statistics which are in a second stage further analyzed by computing a summary statistic, for example, and performing heterogeneity analysis. For a review of the approach see, for example, the recent works by Borenstein et al. (2009) or Schwarzer et al. (2015). The two-stage approach fails for the data of Table 1 as for none of the nineteen studies the risk ratio can be reliably estimated. For a discussion and review of rare event meta-analysis including zero-counts see also Lane (2013) and for an alternative approach based on the arcsine-transformation which

Table 1. Meta-analytic data set of 19 studies on perinatal death in post-term pregnancy comparing selective with routine induction

	Selective induction		Routine induction	
Study i	Deaths	At risk	Deaths	At risk
1	0	55	2	57
2	0	118	0	119
3	0	131	1	134
4	0	57	0	55
5	0	481	0	235
6	1	78	0	78
7	0	66	0	53
8	0	76	0	90
9	0	195	1	207
10	0	214	0	195
11	0	152	1	150
12	0	103	0	97
13	0	94	1	94
14	0	188	1	168
15	0	12	0	10
16	0	109	0	129
17	0	1701	2	1706
18	0	57	0	51
19	0	235	0	175

can cope with zero-event studies as well see Rücker et al. (2009). Other recent contributions include the works of Piaget-Rossel & Taffé (2019a) and Piaget-Rossel & Taffé (2019b).

We consider the one-stage approach based upon generalized linear models. It appears reasonable to use a Poisson regression model for the data of Table 1, treating the count of deaths as Poisson outcome, conditional on a linear predictor which includes a binary covariate for the type of induction, a fixed effect for each study as well as the log-number at risk as offset. This approach has been suggested, for example, in Cai et al. (2010).

Yet, another approach (also mentioned in Cai et al. (2010), Stijnen at al. (2010) or Böhning et al. (2015)) considers the fact that the count in the intervention conditional upon the sum of both outcome over the study arms is binomial with the sum of both count outcomes as size parameter and the event parameter only involving the parameter of interest. This is an attractive

approach as it does not involve a main effect for each study any more, hence eliminates the baseline parameter and only involves the parameter of interest, RR. It can be seen as moving from a two-sample problem to an equivalent one-sample problem. However, it is often argued against this approach that double-zero studies do not play any role as for those the binomial denominator is zero, whereas it is felt that they contribute in the Poisson regression approach mentioned in the previous paragraph (see also Kuss (2015) for this aspect). See also Piaget-Rossel & Taffé (2019c) for an investigation of the role of zero-event studies in rare-events meta-analysis.

We have implemented both approaches, the Poisson regression and the conditional, binomial model for the data of Table 1 and present the results in Table 2. We find the result, potentially surprising, that the inference based upon the Poisson regression model and the conditional, binomial coincides entirely. Hence also double-zero studies do not contribute to the Poisson regression model, potentially, in contrast to common belief.

Table 2. One-stage estimates of the risk ratio for the meta-analytic data set of 19 studies on perinatal death in post-term pregnancy comparing selective with routine induction (Table 1); the main effects for the Poisson regression model are not given here for brevity; note also that the conditional binomial approach requires no other estimate than the intercept given here

Model	Risk ratio	SE	z	P-value	CI
Poisson regression	0.1114	0.1174	-2.08	0.037	0.0141 – 0.8795
conditional binomial	0.1114	0.1174	-2.08	0.037	0.0141 – 0.8795
Mantel-Haenszel	0.1113				0.0141 – 0.8799

This short note is organized as follows. In section 2 we introduce notations and models in the context of a single study. In section 3 we discuss the general meta-analytic setting and show the identity of the log-likelihoods for the Poisson regression model with the conditional, binomial model. Section 4 closes with a short discussion including the connection to Mantel-Haenszel estimation.

2. A Poisson likelihood

For simplicity, we start with the situation of one study. To be slightly more general, we allow units to be different with respect to their times under risk and denote with T_0 and T_1 the person-times in control and intervention arm. If all units are under risk for the same time period, the person-time reduces to the number of units under risk as this is the case for the meta-analytic data presented in Table 1. Let X_0 denote a Poisson count for a control arm with mean $\mu_0 > 0$ and person-time T_0 so that

$$\log E(X_0) = \log \mu_0 = \log T_0 + \alpha \tag{2.1}$$

with α being a real number. Also, let X_1 denote a Poisson count for an intervention arm with mean $\mu_1 > 0$ and person-time T_1 so that

$$\log E(X_1) = \log \mu_1 = \log T_1 + \alpha + \beta \tag{2.2}$$

with β being also a real numbers. In fact, e^β denotes the *risk ratio*

$$RR = e^\beta = \frac{\mu_1/T_1}{\mu_0/T_0}.$$

It is assumed that X_1 and X_0 are independent. We also emphasize that, from our perspective, the Poisson assumption in the rare event situation is reasonable, at least a wide-spread assumption. For an approach utilizing the negative-binomial distribution see Piaget-Rossel & Taffé (2019b).

For a single study, the associated log-likelihood corresponds up to an additive constant independent of α and β

$$\log L = -T_1 e^\alpha e^\beta + x_1(\log T_1 + \alpha + \beta) - T_0 e^\alpha + x_0(\log T_0 + \alpha) \tag{2.3}$$

$$= -e^\alpha(T_0 + T_1 e^\beta) + x\alpha + x_1\beta = -e^\alpha T_0(1 + re^\beta) + x\alpha + x_1\beta,$$

where the last equality is valid up to an additive constant again, $x = x_0 + x_1$ and $r = T_1/T_0$. Keeping β fixed, (2.3) is maximised for $e^{\hat{\alpha}} = x/[T_0(1+re^\beta)]$ and the resulting *profile log-likelihood*

function is given as

$$\ell(\beta) = x_1\beta - x\log(1+re^{\beta}), \tag{2.4}$$

again up to some additive constant independent of β.

3. A conditional likelihood

We refer to a well-known result (Ross, 1985) that X_1 conditional upon $X_1 + X_0 = x$ is binomial with size parameter x and event parameter $q = \frac{\mu_1}{\mu_1+\mu_0}$:

$$P(X_1 = x_1 | X_1 + X_0 = x) = \binom{x}{x_1} q^{x_1}(1-q)^{x_0}, \tag{3.5}$$

using the fact that X_1 and X_0 are independent Poisson counts with parameters μ_1 and μ_0, respectively. The binomial likelihood (3.5) has the benefit that the baseline parameter α is eliminated. This can be seen by considering

$$q = \frac{\mu_1}{\mu_1+\mu_0} = \frac{T_1 e^{\alpha}e^{\beta}}{T_1 e^{\alpha}e^{\beta} + T_0 e^{\alpha}} = \frac{re^{\beta}}{1+re^{\beta}} = \frac{rRR}{1+rRR}.$$

Hence the main effect of the factor study drops out. In the case of balanced studies ($T_1 = T_0$ or $r = 1$) the binomial event parameter q is simply $RR/(1+RR)$ where RR is the risk ratio.

The associated log-likelihood function (up to an additive constant independent of β) is

$$\ell(\beta) = x_1\beta - x\log(1+re^{\beta}), \tag{3.6}$$

which is evidently identical to (2.4). Both likelihoods show that a double-zero study (in contrast to a single-zero study) does not provide any information as their associated log-likelihood is zero.

4. Major result

We now consider the more general meta-analytic setting of k studies with independent Poisson counts X_{ij} for study $i = 1, 2, \cdots, k$ and arm $j = 0, 1$. The notation $j = 1$ identifies the treatment

arm and $j = 0$ the control arm. We assume the model

$$\log E(X_{ij}) = \log T_{ij} + \alpha_i + \beta \times j, \tag{4.7}$$

where T_{ij} is the person-time in study i and arm j, $i = 1, 2, \cdots, k$ and $j = 0, 1$. Note that model (4.7) has study-specific intercepts but a common risk ratio e^{β} across studies. It is important to include study-specific intercept terms as one would like to retain the within-study intervention comparison. The log-likelihood is then (up to an additive constant)

$$\log L = -\sum_i e^{\alpha_i} T_{i0}(1 + r_i e^{\beta}) + \sum_i x_i \alpha_i + \sum_i x_{i1}\beta, \tag{4.8}$$

where $x_i = x_{i0} + x_{i1}$ and $r_i = T_{i1}/T_{i0}$. The log-likelihood (4.8) is maximized for fixed β by $e^{\hat{\alpha}_i} = x_i/[T_{i0}(1 + r_i e^{\beta})]$. We achieve the *profile log-likelihood function*

$$\ell(\beta) = \sum_i x_{i1}\beta - \sum_i x_i \log(1 + r_i e^{\beta}). \tag{4.9}$$

The conditional binomial likelihood generalizes for k studies to

$$\prod_i \binom{x_i}{x_{i1}} q_i^{x_{i1}} (1 - q_i)^{x_{i0}}, \tag{4.10}$$

where $q_i = \frac{r_i e^{\beta}}{1 + r_i e^{\beta}}$. The log-likelihood associated with (4.10) is identical to (4.9) up to an additive constant independent of β. Note that

$$\text{logit}(q_i) = \log q_i - \log(1 - q_i) = \log r_i + \beta, \tag{4.11}$$

so that (4.10) is easily maximized by means of a logistic regression model with event count x_{i1} and binomial denominator $x_i = x_{i0} + x_{i1}$ as dependent variable and linear predictor $\log r_i + \beta$, the latter being only an intercept model with offset term $\log r_i$, the log-ratios of the person-times of intervention and control arm in study i. Note that the intercept term in (4.11) is still the original log-risk ratio, in contrast to the usual interpretation in logistic regression. Table 3 presents the data in a way that they can be readily analyzed using a logistic regression fit with

Table 3. Conditional, binomial representation of meta-analytic data set of 19 studies on perinatal death in post-term pregnancy comparing selective with routine induction

Study i	x_{1i}	x_i	r_i
1	0	2	0.97
2	0	0	0.99
3	0	1	0.98
4	0	0	1.04
5	0	0	2.05
6	1	1	1.00
7	0	0	1.25
8	0	0	0.84
9	0	1	0.94
10	0	0	1.10
11	0	1	1.01
12	0	0	1.06
13	0	1	1.00
14	0	1	1.12
15	0	0	1.20
16	0	0	0.85
17	0	2	1.00
18	0	0	1.12
19	0	0	1.34

only an intercept term, the log-relative risk, and the log-ratio of the person-times. Finally, we can think of the conditional, binomial likelihood as a profile likelihood for a Poisson regression model where the main effect of study has been eliminated by means of profiling.

5. Discussion

We close with a few remarks. The suggested approach has a close connection to Mantel-Haenszel estimation which is popular in epidemiology. Consider the score w.r.t. (4.9) which is given as

$$\sum_i x_{i1} - \sum_i x_i \frac{r_i RR}{1 + r_i RR} = \sum_i \frac{x_{i1} T_{i0}}{T_{i0} + T_{i1} RR} - \sum_i \frac{x_{i0} T_{i1}}{T_{i0} + T_{i1} RR} RR.$$

Equating this score to zero leads to

$$RR = \frac{\sum_i T_{i0} x_{i1} / (T_{i0} + T_{i1} RR)}{\sum_i T_{i1} x_{i0} / (T_{i0} + T_{i1} RR)}. \tag{5.12}$$

Equation (5.12) cannot only be seen as an implicit characterization of the maximum likelihood estimator, it also provides an iterative scheme for generating it by starting with some value for RR such as $RR = 1$, generating a new value by computing the right-hand side of (5.12), plugging that in and so forth. The first iterate when starting with $RR = 1$ is the Mantel-Haenszel estimate $\sum_i w_i T_{i0} x_{i1} / \sum_i w_i T_{i1} x_{i0}$, where $w_i = 1/(T_{i0} + T_{i1})$. Note that maximum likelihood and Mantel-Haenszel estimator coincide if all studies are balanced ($r_i = 1$). This explains why for the data of Table 1 both estimators are very close as the studies are nearly balanced (see also Tables 2 and 3). Note that the Mantel-Haenszel estimator is always defined (unless one arm has only zeros in all studies) and is also invariant to the inclusion or exclusion of double-zero studies (whereas it can change its value when single-zero studies are excluded as pointed out in Böhning et al. (2015)). Mantel-Haenszel estimation is popular but has limitations when it comes to the inclusion of further covariates. The latter would be easily possible for the conditional logistic regression model by extending the linear predictor by further covariates such a time of place of study, intervention modification or size of study.

The conditional binomial can also easily be extended to include a parametric random effect for the intervention as follows

$$\prod_i \binom{x_i}{x_{i1}} \int_{\beta_i} \left(\frac{r_i e^{\beta_i}}{1 + r_i e^{\beta_i}}\right)^{x_{i1}} \left(\frac{1}{1 + r_i e^{\beta_i}}\right)^{x_{i0}} \phi(\beta_i | \beta_0, \tau^2) d\beta_i,$$

where $\phi(\beta_i | \beta_0, \tau^2)$ could be the normal density with mean β_0 and variance τ^2. This would allow investigating for heterogeneity of the intervention effect across studies. This is clearly simpler than using the Poisson regression model where two nested marginals have to be considered.

6. Software and data

We have used the package `STATA` (version 16) for the analysis of the meta-analytic data in this paper. Code and data can be found at `https://github.com/boehning/meta_likelihood`. The provided code will reproduce all analysis in this paper and can also be used for similar meta-

analytic event data and analysis.

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