Nonparametric estimation of effect heterogeneity in rare events meta-analysis: bivariate, discrete mixture model

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Abstract—Meta-analysis provides an integrated analysis and summary of the effects observed in k independent studies. The conventional analysis proceeds by first calculating a study-specific effect estimate, and then provides further analysis on the basis of the available k independent effect estimates associated with their uncertainty measures. Here we consider a setting where counts of events are available from k independent studies for a treatment and a control group. We suggest to model this situation with a study-specific Poisson regression model, and allow the study-specific parameters of the Poisson model to arise from a nonparametric mixture model. This approach then allows the estimation of the heterogeneity variance of the effect measure of interest in a nonparametric manner. A case study is used to illustrate the methodology throughout the paper.

Keywords and phrases: *Heterogeneity Variance; Count Data Analysis; Nonparametric Mixture Models; Meta-Analysis; Rare Events*

1. INTRODUCTION

Meta-analyses are used to analyze and integrate the results of several studies investigating the same research question, providing a cheaper and more powerful alternative to a large new single study. For a general introduction into meta-analysis design refer to Schulze *et al.* (2003) or Borenstein *et al.* (2009), for example. The following special meta-analytic setting was considered in Böhning *et al.* (2015), and shall be the focus of this paper. In k independent studies, counts of events are observed in an intervention and control group. This setting can be described by a count random variable Y_{ij}. The index i indicates the study i for $i = 1, 2, ..., k$, where k denotes the number of available studies. Also, $j = 1$ denotes an intervention group and $j = 0$ a control group. Y_{ij} represents the number of events in study i and group j, whereas T_{ij} denotes the person-time at risk in study i and group j. The latter is considered as non-random and reduces to the number at risk, n_{ij}, if all members in study i share the same person-time. Furthermore, conditional upon study i we have that $E(Y_{ij}) = \lambda_{ij} T_{ij}$, where λ_{ij} denotes the event occurrence risk in study i and group j. We are interested in settings where the probability of no events is large, so that often low

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frequency counts such as 0, 1, or 2 are observed. In this situation, the Poisson assumption comes into play and assumes that

$$Y_{ij} \sim Po(\lambda_{ij} T_{ij}), \tag{1}$$

for study i and group j, where $Po(\theta)$ denotes the Poisson distribution with the density $e^{-\theta}\theta^y/y!$ for count $y = 0, 1, 2, ...$ Here, the mean and variance of Y_{ij} are $E(Y_{ij}) = \lambda_{ij} T_{ij} = \mathrm{Var}(Y_{ij})$.

We emphasise that (1) is conditional upon study i and treatment group j, and as such uses a study-group specific parameter λ_{ij}. Hence, it is a reasonable but untestable assumption as we only have one count Y_{ij} observed per study and group combination. In addition, the count Y_{ij} will often be very small, to the extreme of having no events in one or both groups.

The *major objective* of this work is to consider the frequently used log-linear model

$$\log E(Y_{ij}) = \log \lambda_{ij} + \log T_{ij} = \alpha_i + \beta_i \times j + \log T_{ij}$$

and to model the (latent) distribution of the treatment effect β_i. In contrast to the standard mixed model approach, which takes $\beta_i \sim N(\beta, \sigma^2_\beta)$, we will present a *nonparametric* approach which leaves the distribution of β_i unspecified.

The paper is organised as follows. Section 2 contains a case study which will help the reader to understand the setting and its issues. Section 3 presents the modelling, followed by Section 4 which discusses how effect heterogeneity can be detected and estimated. Section 5 illustrates the modelling and diagnosis of heterogeneity for the case study, before the paper ends in Section 6 with a short discussion.

2. CASE STUDY

In this work, we used a systematic review of the effectiveness of prophylactic antibiotic treatment on infectious complications in women undergoing caesarean delivery (Smaill and Hofmeyr, 2002; Cooper *et al.*, 2003). The data are provided in Table 1. They included 61 independent studies with counts of occurrence of wound infection as outcome in women undergoing caesarean delivery. The intervention group used prophylactic antibiotics, whereas the control group had no prophylactic antibiotics (placebo). Many of the component studies were small in size, with average sample sizes being 80 persons per trial in the treatment arm and 63 persons per trial in the control arm. The occurrence of wound infection was observed relatively rarely and there were zero events present in each of the two arms. For studies with no event in one (single-zero) or both (double-zero) treatment arms, the study-specific risk ratio (or relative risk) $\widehat{RR}_i = \frac{Y_{i1}/T_{i1}}{Y_{i0}/T_{i0}}$ and its associated variance estimate $1/Y_{i0} + 1/Y_{i1}$ are undefined since there exist some Y_{ij} equal to zero. As a result of this, the double- or single-zero studies would need to be excluded prior to conducting this analysis.

Table 1: Meta-analytic data on prophylactic antibiotics in caesarean section

	Treatment		Placebo	
Report, Year	Events	Total	Events	Total
Adeleye et al., 1981	11	58	14	48
Bibi et al., 1994	4	133	28	136
Chan et al., 1989	27	299	12	101
Conover et al., 1984	2	68	1	56
Cormier et al., 1989	5	55	8	55
Dashow et al., 1986	3	100	0	33
Dashow et al., 1986	4	183	3	44

Continued on next page

Table 1 Continued

	Treatment		Placebo	
Report, Year	Events	Total	Events	Total
De Boer et al., 1989	1	11	5	17
De Boer et al., 1989	10	80	21	74
Dillon et al., 1981	0	46	4	55
Duff et al., 1980	0	26	1	31
Duff et al., 1982	0	42	0	40
Elliot et al., 1986	0	119	1	39
Engel et al., 1986	1	50	9	50
Fugere et al., 1983	2	60	6	30
Gall, 1979	1	46	1	49
Gerstner et al., 1980	3	53	9	50
Gibbs et al., 1972	0	33	4	28
Gibbs et al., 1973	0	34	6	34
Gibbs et al., 1981	0	50	2	50
Gordon et al., 1979	0	78	1	36
Hager et al., 1983	1	43	1	47
Hagglund et al., 1989	0	80	3	80
Harger et al., 1981	2	196	14	190
Hawrylyshyn et al., 1983	2	124	2	58
Ismail et al., 1990	2	74	8	78
Jakobi et al., 1994	4	167	5	140
Karhunen et al., 1985	2	75	9	77
Kreutner et al., 1978	0	48	2	49
Kristensen et al., 1990	0	102	1	99
Lapas et al., 1989	1	50	10	50
Leonetti et al., 1989	0	100	1	50
Levin et al., 1983	0	85	3	43
Lewis et al., 1990	1	36	1	25
Lewis et al., 1990	2	76	4	75
Mahomed et al., 1988	12	115	15	117
Mallaret et al., 1990	6	136	16	130
McCowan et al., 1980	9	35	7	38
Miller et al., 1968	13	150	23	150

Continued on next page

Table 1 Continued

	Treatment		Placebo	
Report, Year	Events	Total	Events	Total
Moodley et al., 1981	2	40	4	20
Moro et al., 1974	0	74	2	74
Padilla et al., 1983	0	34	5	37
Phelan et al., 1979	2	61	2	61
Polk et al., 1982	3	146	9	132
Rehu et al., 1980	4	88	4	40
Roex et al., 1986	1	64	7	65
Ross et al., 1984	7	57	7	58
Rothbard et al., 1975	0	16	1	16
Rothbard et al., 1975	2	31	6	37
Ruiz-Moreno et al., 1991	1	50	4	50
Saltzman et al., 1985	1	50	2	49
Schedvins et al., 1986	2	26	0	27
Stage et al., 1983	3	133	12	66
Stiver et al., 1983	6	244	17	117
Tully et al., 1983	1	52	2	61
Tzingounis et al., 1982	2	46	4	50
Weissberg et al., 1971	0	40	3	40
Wong et al., 1978	2	48	3	45
Work et al., 1977	3	40	1	40
Yip et al., 1997	1	160	1	160
Young et al., 1983	1	50	4	50

The results of a meta-analysis on the risk ratio based on the data on prophylactic antibiotics in caesarean treatment is presented by a forest plot in Figure 1 (one study is excluded due to the above mentioned issue of zero count occurrence). It can be concluded that a woman undergoing caesarean delivery appears to have a lower risk for infectious complications if in the prophylactic antibiotic treatment group compared to being in the placebo or no prophylactic antibiotic treatment group. One of the primary questions in a meta-analysis of effects is whether there is homogeneity of effect. In the next section we will present a modelling approach that can help answer this question.

3. THE LOG-LINEAR MODEL WITH HETEROGENEITY

The modelling approach that we are presenting for heterogeneity estimation is detailed as follows. Given the Poisson model (1) we may re-parameterise the mean as follows:

$$\log E(Y_{ij}) = \log \lambda_{ij} + \log T_{ij} = \alpha_i + \beta_i \times j + \log T_{ij}.$$

This re-parameterisation has the benefit that the log-risk ratio in the i-th study is given by β_i and corresponds to $\log RR_i$. In addition, heterogeneity can be now separated into *baseline* heterogeneity – the variability in the intercept α_i – and the heterogeneity in the effect measure –

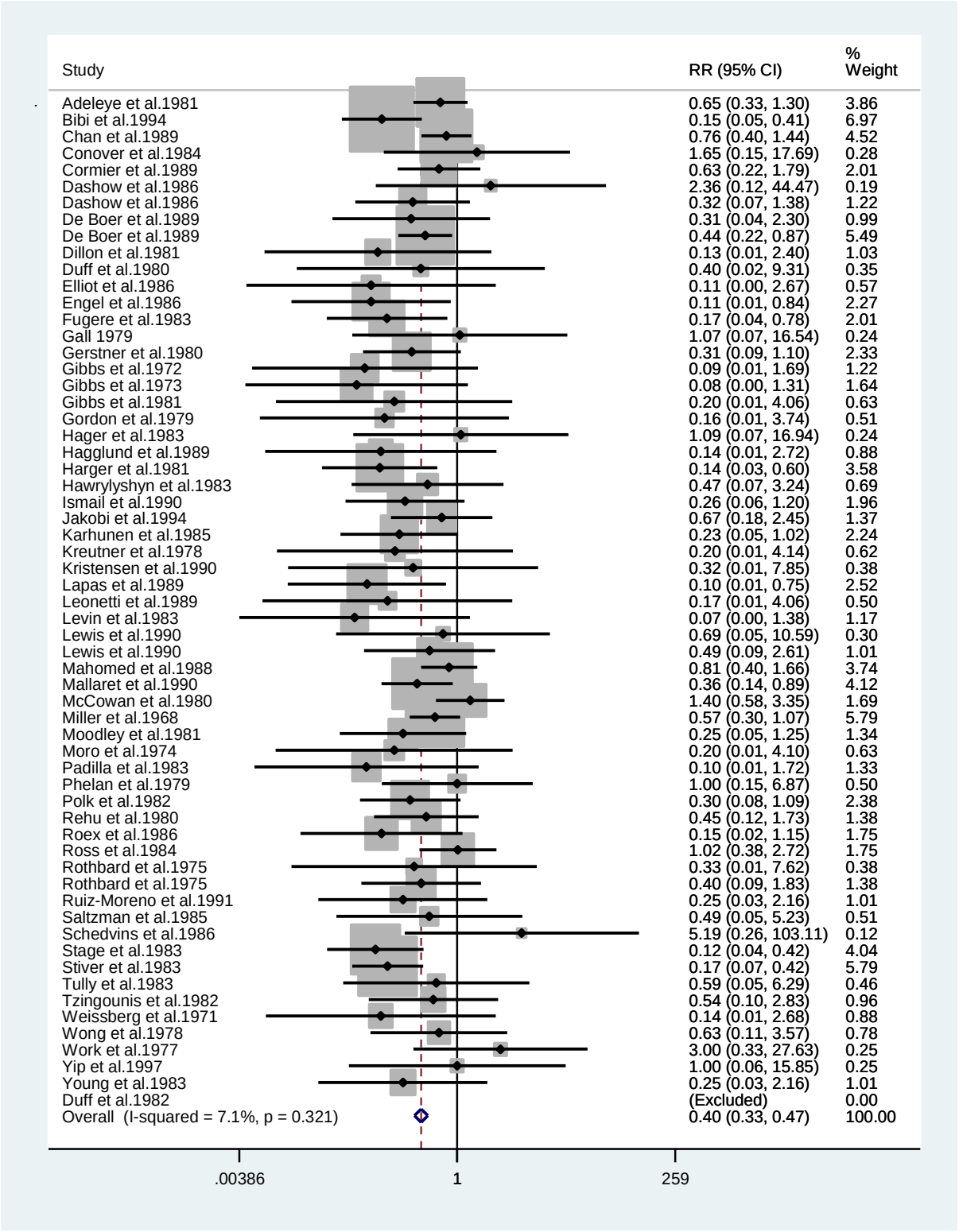

Figure 1. Forest plot of prophylactic antibiotics in caesarean section

the variability in the slope β_i. The scenario of no effect homogeneity is characterised by $\beta_i = 0$ for all studies $i = 1, 2, ..., k$. To model heterogeneity, the typical generalised liner mixed model approach takes $\alpha_i \sim N(\alpha, \sigma_\alpha^2)$ and $\beta_i \sim N(\beta, \sigma_\beta^2)$. Here, instead of assuming a normal (or other parametric) distribution, we leave the distribution of (α_i, β_i) unspecified. From the foundations of nonparametric maximum likelihood estimation, the maximum likelihood estimator maximising the mixture log-likelihood with mixing distribution Q

$$\ell(Q) = \sum_{i,j} \log \int p(y_{ij}; \exp(\alpha_i + \beta_i \times j + \log T_{ij}))Q(d\alpha_i, d\beta_i) \tag{2}$$

is always discrete (Lindsay, 1982, 1995). Here $p(y; \lambda) = \exp(-\lambda)\lambda^y/y!$ is the Poisson discrete mass function for $y = 0, 1, ...$ and $\lambda > 0$. Hence, there is no limitation of generality if we replace (2) by

$$\ell(Q) = \sum_{i,j} \log \sum_{s=1}^{S} p(y_{ij}; \exp(\alpha_s + \beta_s \times j + \log T_{ij}))q_s. \tag{3}$$

The log-likelihood (3) is evidently a discrete mixture log-likelihood with weights $q_1, q_2, ..., q_S$ being positive and summing up to 1. Unfortunately, it is not known which values for S should be chosen however. This is known as *the number of components problem*. A typical solution is to start with $S = 1$ and then sequentially increase the number of components by one until no further increase in the log-likelihood is detected. Specifically, for a given value of S, the log-likelihood (3) is maximised using the EM algorithm (Dempster *et al.*, 1977; McLachlan and Krishnan, 2007). More details on computational and algorithmic approaches for mixture likelihood problems are given on Böhning (2000).

We will denote the maximum likelihood estimate of the parameters α_s, β_s and q_s for $s = 1, 2, ..., S$ as

$$\hat{Q} = \begin{pmatrix} \hat{\alpha}_1 & \cdots & \hat{\alpha}_S \\ \hat{\beta}_1 & \cdots & \hat{\beta}_S \\ \hat{q}_1 & \cdots & \hat{q}_S \end{pmatrix}.$$

Note that $\hat{Q}$ is a mixing distribution jointly on the intercept α and the slope (log-risk ratio) β. Having the maximum likelihood estimate available, we are then able to give a nonparametric estimate of the heterogeneity variance of the log-risk ratio as

$$\hat{\tau}^2 = \sum_{s=1}^{S} (\hat{\beta}_s - \bar{\beta})^2 \hat{q}_s,$$

where $\bar{\beta} = \sum_{s=1}^{S} \hat{q}_s \hat{\beta}_s$. This variance is of particular interest in meta-analysis as its size indicates the amount of heterogeneity in effect size across studies. Of course, other variances such as the baseline heterogeneity variance in the α_s can also be considered.

4. DIAGNOSING HETEROGENEITY

Our interest lies in detecting heterogeneity in the log-risk ratio β. The issue of broad interest relates to the question "Is there homogeneity of relative risk across studies or not?" To investigate this question we first focus on the general model M_1.

$$\sum_{s=1}^{S_1} p(y_{ij}; \exp(\alpha_s + \beta_s \times j + \log T_{ij}))q_s.$$

Note that this model has *baseline* heterogeneity (α_s) and *effect heterogeneity* (β_s). This model needs to be contrasted to the model allowing for baseline heterogeneity but constraining on effect

Table 2. Model evaluation under heterogeneity and homogeneity of effect

S	log-likelihood	AIC	BIC	$\hat{\tau}^2$	$\bar{\beta}$
bivariate mixture model M_1					
1	-359.2	722.5	726.8	0	-0.96
2	-289.9	589.7	600.5	0.04	-0.77
3	-284.3	584.6	601.8	0.99	-1.02
4	-283.4	588.8	612.6	1.03	-1.02
univariate mixture model M_0 keeping $\beta_s = \beta$					
1	-359.2	722.5	726.8	-	-0.96
2	-291.7	591.3	599.9	-	-0.64
3	-289.9	591.8	604.8	-	-0.66
4	-289.9	595.8	613.1	-	-0.66

homogeneity. This alternate model, denoted as M_0, can be written as

$$\sum_{s=1}^{S_0} p(y_{ij}; \exp(\alpha_s + \beta \times j + \log T_{ij}))q_s.$$

We emphasise here that these models are not necessarily nested, for example if $S_0 > S_1$. For this reason we will not focus on likelihood ratio testing, but rather concentrate on model selection criteria such as Akaike information criterion (AIC) defined as $-2\ell(\hat{Q}) + 2p$ and Bayesian information criterion (BIC) defined as $-2\ell(\hat{Q}) + p \log k$, where p are the number of parameters in the model under consideration, k is the number of studies and $\ell(\hat{Q})$ is the maximised mixture log-likelihood under the model of consideration. If model M_1 is considered there are $p = 3S_1 - 1$ independent parameters due to the constraint $\sum_{s=1}^{S_1} \alpha_s = 1$. If model M_0 is considered there are $p = 2S_0$ independent parameters. The model is chosen according to the smallest value of AIC and BIC. If both criteria lead to substantial contradictory choices then we will put more focus on the BIC, as the AIC is considered less reliable in choosing the number of components (Naik *et al.*, 2007; Ray and Lindsay, 2008).

5. CASE STUDY (CONTINUED)

We now continue with the discussion of the case study, where our interest is in the structure and form of the heterogeneity in the log-risk ratio across studies. In Table 2, we consider in its upper subtable the modelling of the mixture distribution of the bivariate intercept and slope parameters (α_s, β_s), while in the lower subtable we consider only heterogeneity in the baseline parameter α_s while keeping the slope parameter homogeneous. We can see from Table 2 that the best model for the bivariate mixture model M_1 is given by $S = 2$ (according to the BIC) or $S = 3$ (according to the AIC) components, respectively. Given the arguments in the previous section to follow the BIC in inconclusive cases, ultimately we go with $S = 2$ as this is what the BIC suggests. The associated value estimated for τ^2 is $\hat{\tau}^2 = 0.04$.

For the univariate mixture with homogeneity in the log-risk ratio, the best model has $S = 2$ components (both AIC and BIC agree independently). It is interesting that according to the BIC the best model is the homogeneous risk ratio model with two component heterogeneity in the baseline parameter. Alternatively, according to the AIC the best model is a risk ratio heterogeneity model with 3 components. We interpret this as having here a meta-analysis with a very mild form of effect heterogeneity.

6. DISCUSSION AND CONCLUSIONS

It is of interest to compare our approach with a conventional, two-stage approach in meta-analysis. In the latter, study-specific log-relative risks are computed as

$$\widehat{RR}_i = \exp(\hat{\beta}_i) = \frac{y_{i1}/T_{i1}}{y_{i0}/T_{i0}}.$$

Furthermore, the observed effect measure $\hat{\beta}_i$ is partitioned according to $\hat{\beta}_i = \beta_i + \epsilon_i$ into a true study effect β_i of study i and a random error ϵ_i. These have variances corresponding to $\mathrm{Var}(\hat{\beta}_i) = \mathrm{Var}(\beta_i) + \mathrm{Var}(\epsilon_i)$, assuming independence between random error ϵ_i and random effect β_i. Here, $\mathrm{Var}(\beta_i) = \tau^2$ is the heterogeneity variance and measures the variation of the true effect across studies. $\mathrm{Var}(\epsilon_i) = 1/(Y_{i0} + 0.5) + 1/(Y_{i1} + 0.5)$ is the study variance and measures the within-study variance.

An example of an alternate overall or summary estimator is the so-called Mantel–Haenszel estimator

$$\widehat{RR}_{\mathrm{MH}} = \frac{\sum_i y_{i1} T_{i0}/T_i}{\sum_i y_{i0} T_{i1}/T_1},$$

where $T_i = T_{i1} + T_{i0}$. For this average effect measure the heterogeneity measuring statistic

$$Q = \sum_i w_i (\hat{\beta}_i - \bar{\beta})^2$$

can be considered where $w_i = 1/\mathrm{Var}(\hat{\beta}_i)$ and $\bar{\beta} = \log \widehat{RR}_{\mathrm{MH}}$. A normalised heterogeneity measure is given by $I^2 = \frac{Q-(k-1)}{Q}$, as suggested by Higgins and Thompson (2002). This measure reports what proportion of the variation we detect is due to the variation of the log-relative risk across studies. If it is 0, there is no heterogeneity and all variation is due to random error within the studies. Alternatively, if it is 1, all variation is due to the heterogeneity of the log-relative risk across studies. This is what can be seen in Figure 1 with an $I^2 = 0.071$ or 7.1%, which confirms our result of very low effect heterogeneity in this meta-analysis. The conventional two-stage meta-analysis approach also provides an estimate of τ^2, which in this case takes the value of 0.0405, comparing favourably with the value we have derived in Table 2 using the bivariate mixture model with $S = 2$. Of course, here this comparison was reasonably justified as all component studies had large sample sizes and many studies had non-sparse events. However, 19 studies in the meta-analysis had zero events in at least one treatment arm (so-called single-zero and double-zero studies), and in these cases study-specific relative risks could only be computed by replacing zeros with a smoothing constant of 0.5. This can lead to considerable bias, and as such one of the benefits of our approach is that it avoids the use of smoothing constants.

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Appendix: STATA code

All computations were done using the package `STATA16` (StataCorp 2019). In the following we demonstrate how to fit a two-component, bivariate mixture model. Different numbers of components can be achieved by replacing 2 with any desired number of components. The log-relative risks for the components are -0.1581758 and -0.743582. The associated weights can be found using the command `estat lcprob` which is provided at the end of the output below. y are the counts of events and $\log n$ is the log-size of the study. *treat* is a binary treatment indicator with 1 denoting being in the treatment group and 0 otherwise.

```
. fmm 2 : poisson y treat, exposure(logn)

Finite mixture model                              Number of obs     =        122
Log likelihood = -307.22036

Class          : 1
Response       : y
Model          : poisson

------------------------------------------------------------------------------
             |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
y            |
       treat |  -.1581758   .1603739    -0.99   0.324    -.4725029    .1561514
       _cons |   1.128934   .1005598    11.23   0.000     .9318403    1.326027
    ln(logn) |          1  (exposure)
------------------------------------------------------------------------------

Class          : 2
Response       : y
Model          : poisson

------------------------------------------------------------------------------
             |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
y            |
       treat |   -.743582   .1821602    -4.08   0.000    -1.100609   -.3865546
       _cons |  -.2447636   .1432094    -1.71   0.087    -.5254488    .0359217
    ln(logn) |          1  (exposure)
```

```
------------------------------------------------------------------------------

. estat lcprob

Latent class marginal probabilities             Number of obs     =        122

------------------------------------------------------------------
             |            Delta-method
             |     Margin   Std. Err.     [95% Conf. Interval]
-------------+----------------------------------------------------
       Class |
          1  |   .2027119   .0486684      .1235069    .3144862
          2  |   .7972881   .0486684      .6855138    .8764931
------------------------------------------------------------------
```

The `fmm` module also has the option to keep certain parameters homogeneous, i.e. not to involve them in the mixture. This can be achieved with the optional parameter `coef` as shown below. Here we keep the parameter of the log-relative risk estimated constant over the components.

```
. fmm 2 , lcinvariant(coef) : poisson y treat, exposure(logn)

Finite mixture model                            Number of obs     =        122
Log likelihood = -311.15859

Class          : 1
Response       : y
Model          : poisson

------------------------------------------------------------------------------
             |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
y            |
       treat |  -.3426311   .1499642    -2.28   0.022    -.6365555   -.0487067
       _cons |   1.094218   .0881464    12.41   0.000     .9214543    1.266982
    ln(logn) |          1  (exposure)
------------------------------------------------------------------------------

Class          : 2
Response       : y
Model          : poisson

------------------------------------------------------------------------------
             |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
y            |
       treat |  -.3426311   .1499642    -2.28   0.022    -.6365555   -.0487067
       _cons |  -.5363991   .1513947    -3.54   0.000    -.8331272   -.2396709
    ln(logn) |          1  (exposure)
------------------------------------------------------------------------------
```

A conventional two-stage meta-analysis can be accomplished by using the `STATA`-package `metan`. The data format needs to be of the so-called $a-b-c-d$-type:

- a number of events in the treatment group
- b number of non-events in the treatment group
- c number of events in the control group

- d number of non-events in the control group.

We yield the following output (the parameter `random` produces a random effects analysis including an estimte of τ^2):

```
. metan a b c d, random
```

Study	RR	[95% Conf.	Interval]	% Weight
1	0.650	0.326	1.298	6.18
2	0.146	0.053	0.405	3.27
3	0.760	0.400	1.444	6.89
4	1.647	0.153	17.694	0.67
5	0.625	0.218	1.791	3.09
6	2.356	0.125	44.467	0.44
7	0.321	0.074	1.381	1.71
8	0.309	0.041	2.304	0.93
9	0.440	0.222	0.872	6.28
10	0.132	0.007	2.396	0.46
11	0.395	0.017	9.306	0.39
13	0.111	0.005	2.673	0.38
14	0.111	0.015	0.845	0.92
15	0.167	0.036	0.777	1.55
16	1.065	0.069	16.537	0.51
17	0.314	0.090	1.096	2.28
18	0.095	0.005	1.687	0.46
19	0.077	0.005	1.314	0.48
20	0.200	0.010	4.063	0.42
21	0.156	0.007	3.742	0.38
22	1.093	0.071	16.941	0.51
23	0.143	0.007	2.722	0.44
24	0.138	0.032	0.601	1.69
25	0.468	0.068	3.239	1.00
26	0.264	0.058	1.201	1.59
27	0.671	0.184	2.450	2.13
28	0.228	0.051	1.021	1.63
29	0.204	0.010	4.143	0.42
30	0.324	0.013	7.851	0.38
31	0.100	0.013	0.752	0.92
32	0.168	0.007	4.059	0.38
33	0.073	0.004	1.384	0.44
34	0.694	0.046	10.589	0.52
35	0.493	0.093	2.614	1.33
36	0.814	0.399	1.662	5.87
37	0.358	0.145	0.888	4.00
38	1.396	0.582	3.347	4.25
39	0.565	0.298	1.073	6.90
40	0.250	0.050	1.251	1.42
41	0.200	0.010	4.096	0.42
42	0.099	0.006	1.721	0.47
43	1.000	0.146	6.873	1.01
44	0.301	0.083	1.090	2.16
45	0.455	0.120	1.727	2.02
46	0.145	0.018	1.146	0.88
47	1.018	0.381	2.716	3.49
48	0.333	0.015	7.619	0.39
49	0.398	0.086	1.833	1.57
50	0.250	0.029	2.159	0.81
51	0.490	0.046	5.231	0.68

```
52                  |  5.185       0.261   103.110          0.43
53                  |  0.124       0.036     0.425          2.34
54                  |  0.169       0.069     0.418          4.02
55                  |  0.587       0.055     6.286          0.68
56                  |  0.543       0.104     2.828          1.36
57                  |  0.143       0.008     2.679          0.45
58                  |  0.625       0.109     3.569          1.22
59                  |  3.000       0.326    27.631          0.77
60                  |  1.000       0.063    15.849          0.50
61                  |  0.250       0.029     2.159          0.81
12                  |  (Excluded)
--------------------+-------------------------------------------------
D+L pooled RR       |  0.429       0.352     0.523        100.00
--------------------+-------------------------------------------------

  Heterogeneity chi-squared =  63.49 (d.f. = 59) p = 0.321
  I-squared (variation in RR attributable to heterogeneity) =   7.1%
  Estimate of between-study variance Tau-squared =  0.0405

  Test of RR=1 : z=   8.39 p = 0.000
```