Meta-analysis examples

Michail Belias

February 6, 2019

Berkey et al. (1995)

The Methods and Data

Berkey et al. (1995) describe the meta-analytic random- and mixed-effects models and provide the equation for the empirical Bayes estimator for the amount of (residual) heterogeneity (p. 398). The models and methods are illustrated with the BCG vaccine dataset (Colditz et al., 1994).

First, we load the package that contains the commands we will use later on. This can be done using the **library('name of the package')** command. The package that we will use is **metafor**. If the package is not installed in our computer we can use the **install.packages('name of the package')** command

The data are provided in the package and can be loaded straight from it using their name **dat.bcg**.

The contents of the dataset are:

```
   trial               author year tpos  tneg cpos  cneg ablat      alloc
1      1              Aronson 1948    4   119   11   128    44     random
2      2     Ferguson & Simes 1949    6   300   29   274    55     random
3      3      Rosenthal et al 1960    3   228   11   209    42     random
4      4    Hart & Sutherland 1977   62 13536  248 12619    52     random
5      5 Frimodt-Moller et al 1973   33  5036   47  5761    13  alternate
6      6      Stein & Aronson 1953  180  1361  372  1079    44  alternate
7      7     Vandiviere et al 1973    8  2537   10   619    19     random
8      8           TPT Madras 1980  505 87886  499 87892    13     random
9      9     Coetzee & Berjak 1968   29  7470   45  7232    27     random
10    10      Rosenthal et al 1961   17  1699   65  1600    42 systematic
11    11       Comstock et al 1974  186 50448  141 27197    18 systematic
12    12   Comstock & Webster 1969    5  2493    3  2338    33 systematic
13    13       Comstock et al 1976   27 16886   29 17825    33 systematic
```

Per trial, a 2x2 matrix looks like the following.

Exposure \ Event	Yes	No	Total	
Yes	a	b	N1= a+b	Rexp = a/(a+b), Odds1 = a/b
No	c	d	N2=c+d	Rnexp=c/(c+d), Odds2 = c/d
Total			N=a+b+c+d	

Relative Risk: Rexp/Rnexp
Absolute Relative Risk difference = Rexp - Rnexp
Relative Risk Ratio: (Rexp - Rnexp)/ Rnexp
Odds Ratio: Odds1/Odds2 = (a*d)/(c*b)
PETO odds ratio = exp((observed - expected events)/variance)
where,
Observed events = a, and Expected events = $\left(\frac{n_e}{N}\right) \times (a + c)$ and variance = $\frac{n_e\, n_c\, (a + c)\,(b + d)}{N^2\,(N - 1)}$

As a first step we will calculate the log risk-ratios and corresponding sampling variances with **escalc()** function:

```
   trial                 author year tpos  tneg cpos  cneg ablat      alloc
1      1                Aronson 1948    4   119   11   128    44     random
2      2      Ferguson & Simes 1949    6   300   29   274    55     random
3      3       Rosenthal et al 1960    3   228   11   209    42     random
4      4     Hart & Sutherland 1977   62 13536  248 12619    52     random
5      5 Frimodt-Moller et al 1973   33  5036   47  5761    13  alternate
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7      7      Vandiviere et al 1973    8  2537   10   619    19     random
8      8            TPT Madras 1980  505 87886  499 87892    13     random
9      9      Coetzee & Berjak 1968   29  7470   45  7232    27     random
10    10       Rosenthal et al 1961   17  1699   65  1600    42 systematic
11    11        Comstock et al 1974  186 50448  141 27197    18 systematic
12    12     Comstock & Webster 1969    5  2493    3  2338    33 systematic
13    13        Comstock et al 1976   27 16886   29 17825    33 systematic
        yi     vi
1  -0.8893 0.3256
2  -1.5854 0.1946
3  -1.3481 0.4154
4  -1.4416 0.0200
5  -0.2175 0.0512
6  -0.7861 0.0069
7  -1.6209 0.2230
8   0.0120 0.0040
9  -0.4694 0.0564
10 -1.3713 0.0730
11 -0.3394 0.0124
12  0.4459 0.5325
13 -0.0173 0.0714
```
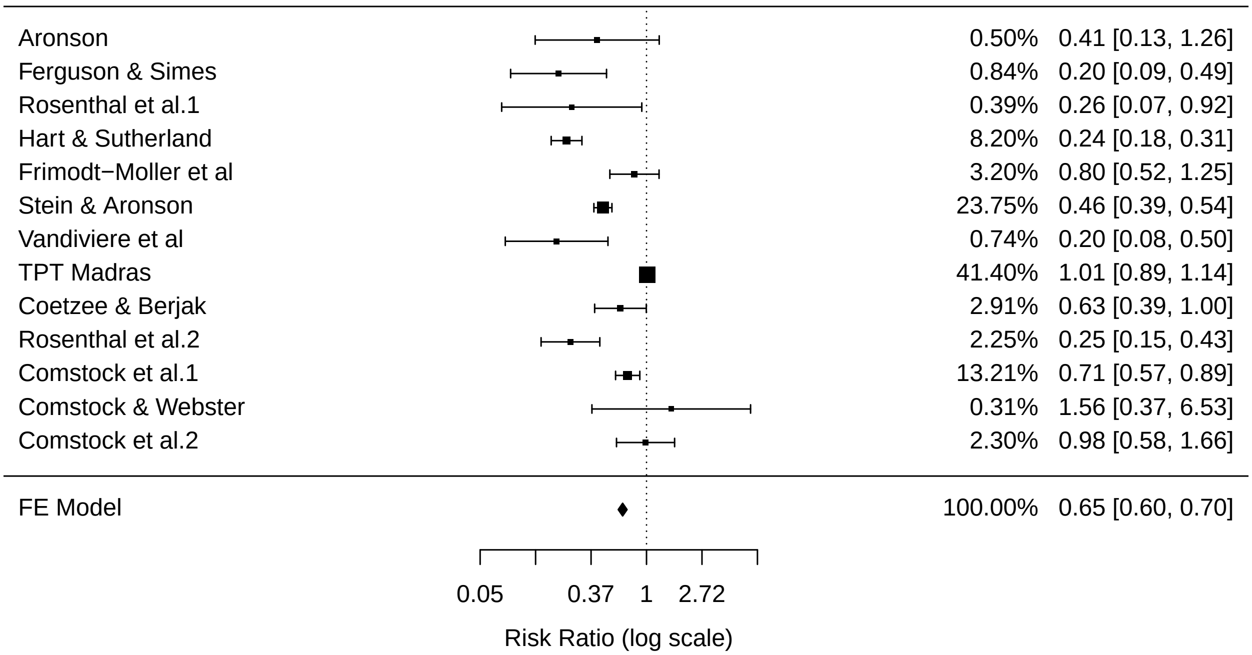

The metafor package calculates the sampling variances of the log risk ratios as described by Berkey et al. (1995) on page 399 (right under the 2×2 table). If we want to cross-validate the risk ratios we can calculate them manually.

Fixed-effect model

Now we can fit a fixed-effect model to these data. We can save the summary into an object using the <- or = signs. using the **rma()** function we can estimate the pooled risk-ratio.

```
Fixed-Effects Model (k = 13)

Test for Heterogeneity:
Q(df = 12) = 152.2330, p-val < .0001

Model Results:

estimate      se       zval    pval    ci.lb    ci.ub
 -0.4303  0.0405  -10.6247  <.0001  -0.5097  -0.3509  ***

---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

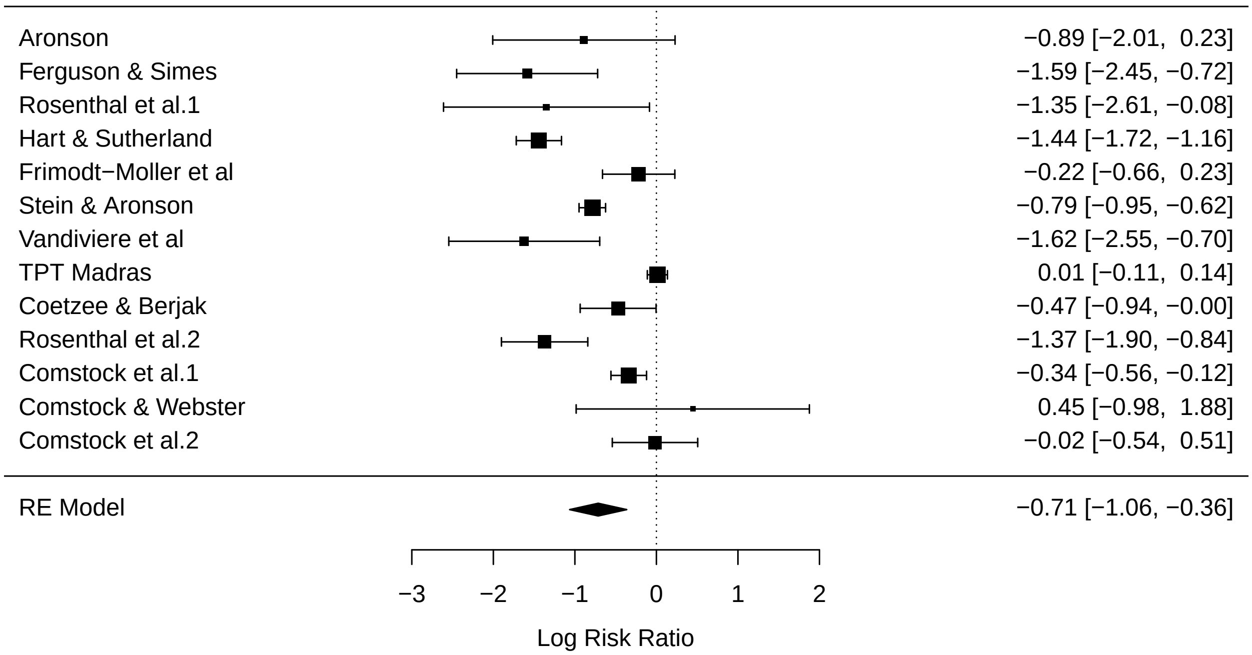
Also we can observe the forest plot.



Random-Effects Model

Now we can fit a random-effects model to these data, using the DerSimonian-Laird estimator for the amount of heterogeneity with:

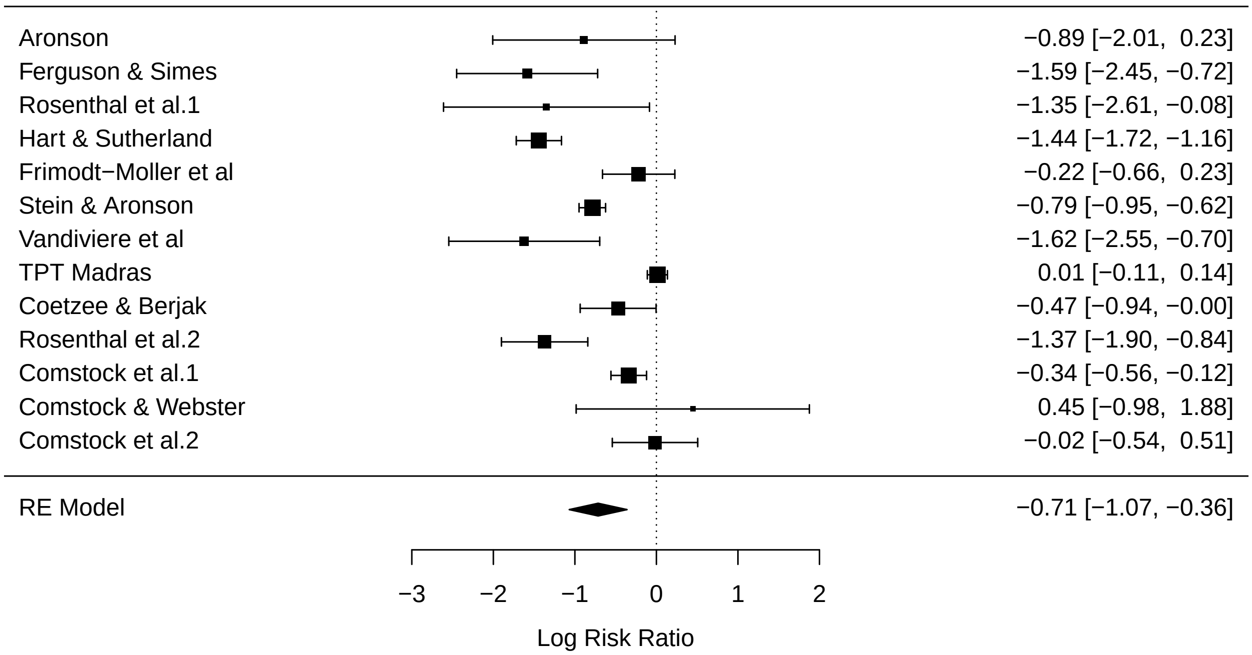
```
Random-Effects Model (k = 13; tau^2 estimator: DL)

tau^2 (estimated amount of total heterogeneity): 0.3088 (SE = 0.2299)
tau (square root of estimated tau^2 value):      0.5557
I^2 (total heterogeneity / total variability):   92.12%
H^2 (total variability / sampling variability):  12.69

Test for Heterogeneity:
Q(df = 12) = 152.2330, p-val < .0001

Model Results:

estimate      se     zval    pval    ci.lb    ci.ub
 -0.7141  0.1787  -3.9952  <.0001  -1.0644  -0.3638  ***

---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```



If we use the *?* sign in front of a function we can go to the help file of the function.

Here we can observe that there are various types of $\hat{\tau}^2$ estimators. For instance, the empirical Bayes estimator.

```
Random-Effects Model (k = 13; tau^2 estimator: EB)

tau^2 (estimated amount of total heterogeneity): 0.3181 (SE = 0.1737)
tau (square root of estimated tau^2 value):      0.5640
I^2 (total heterogeneity / total variability):   92.33%
H^2 (total variability / sampling variability):  13.04

Test for Heterogeneity:
Q(df = 12) = 152.2330, p-val < .0001

Model Results:

estimate      se     zval    pval    ci.lb    ci.ub
 -0.7150  0.1809  -3.9525  <.0001  -1.0695  -0.3604  ***

---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```



These results match exactly what Berkey et al. (1995) report on page 408: The amount of heterogeneity (“between-trial variance”) is estimated to be $\hat{\tau}^2 = 0.268$ and the pooled estimate is $\hat{\mu} = -0.5429$ with a standard error of $SE[\hat{\mu}] = 0.1842$.

Mixed-Effects Model

As we can see we slightly reducing the heterogeneity present in our estimates. Nevertheless, we may assume that there is another variable that is modifying our estimates. Then we can use a mixed-effects model with absolute latitude (centered at 33.46 degrees) as moderator. In this case, we assume that part of the variability see into our estimated is due to the place that the trial has been conducted and can be fitted with:

```
Mixed-Effects Model (k = 13; tau^2 estimator: EB)

tau^2 (estimated amount of residual heterogeneity):     0.1421 (SE = 0.0975)
tau (square root of estimated tau^2 value):             0.3770
I^2 (residual heterogeneity / unaccounted variability): 80.11%
H^2 (unaccounted variability / sampling variability):   5.03
R^2 (amount of heterogeneity accounted for):            55.31%

Test for Residual Heterogeneity:
QE(df = 11) = 30.7331, p-val = 0.0012

Test of Moderators (coefficient(s) 2):
QM(df = 1) = 9.9178, p-val = 0.0016

Model Results:

                  estimate      se     zval    pval    ci.lb    ci.ub
intrcpt            -0.7339  0.1335  -5.4981  <.0001  -0.9955  -0.4722  ***
I(ablat - 33.46)   -0.0286  0.0091  -3.1493  0.0016  -0.0463  -0.0108   **

---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

Again, the results match the findings from Berkey et al. (1995): The residual amount of heterogeneity is now $\hat{\tau}^2 = 0.142$ and the estimated model is $log(RR) =$ -0.734 -0.029 $\times(x - 33.46)$, where x is the distance from the equator (in degrees latitude). The standard errors of the model coefficients are $SE[b_0] = 0.133$ and $SE[b_1] = 0.009$.

The amount of variance (heterogeneity) accounted for by the absolute latitude moderator is provided in the output above. It can also be obtained with the **anova()** function:

```
        df     AIC     BIC    AICc   logLik    LRT   pval       QE  tau^2
Full     3 23.2048 24.8997 25.8715  -8.6024                 30.7331 0.1421
Reduced  2 29.3647 30.4946 30.5647 -12.6823 8.1598 0.0043 152.2330 0.3088
           R^2
Full
Reduced 53.97%
```

df AIC BIC logLik LRT pval QE tau^2 R^2 Full 3 29.3011 30.9960 -11.6506 35.8827 0.1572
Reduced 2 32.2578 33.3877 -14.1289 4.9566 0.0260 85.8625 0.2682 41.38% The value below R^2 indicates that approximately 41% of the heterogeneity has been accounted for.

The predicted average risk ratios at 33.46 and 42 degrees reported by Berkey et al. (1995) can be computed with:

```
  pred ci.lb ci.ub cr.lb cr.ub
1 0.48  0.37  0.62  0.22  1.05
2 0.38  0.27  0.52  0.17  0.84
```

Fixed-Effects Model with moderator

The results from a fixed-effects model with absolute latitude as the predictor can be obtained with:

```
Fixed-Effects with Moderators Model (k = 13)

Test for Residual Heterogeneity:
QE(df = 11) = 30.7331, p-val = 0.0012

Test of Moderators (coefficient(s) 2):
QM(df = 1) = 121.4999, p-val < .0001

Model Results:

                  estimate      se      zval    pval    ci.lb    ci.ub
intrcpt            -0.6347  0.0445  -14.2492  <.0001  -0.7220  -0.5474
I(ablat - 33.46)   -0.0292  0.0027  -11.0227  <.0001  -0.0344  -0.0240

intrcpt           ***
I(ablat - 33.46)  ***

---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

The predicted risk ratios at 33.46 and 42 degrees are now:

```
  pred ci.lb ci.ub
1 0.53  0.49  0.58
2 0.41  0.37  0.46
```

References

Berkey, C. S., Hoaglin, D. C., Mosteller, F., & Colditz, G. A. (1995). A random-effects regression model for meta-analysis. //Statistics in Medicine, 14//(4), 395–411.

Colditz, G. A., Brewer, T. F., Berkey, C. S., Wilson, M. E., Burdick, E., Fineberg, H. V., et al. (1994). Efficacy of BCG vaccine in the prevention of tuberculosis: Meta-analysis of the published literature. //Journal of the American Medical Association, 271//(9), 698–702.