R practice: Meta-analysis (4)

Minato Nakazawa

7 March 2011

1 Meta-analysis to integrate odds ratios by Peto's method

Last week we have seen the example of Peto's method as the study which Yusuf et al. (1985) applied the Peto's design to secondary preventive effect of beta blocker against heartattack.

Table 1.3 shows the result of meta-analysis of 15 RCTs about the preventive effect (reduction of mortality) of long-term administration of beta-blocker by Peto's method. In R, it is supported by `metafor` package.

Table 1.3

studyid	bbdeath	bbno	cntldeath	cntlno
reynolds	3	38	3	39
wilhelmsson	7	114	14	116
ahlmark	5	69	11	93
multicentre	102	1533	127	1520
baber	28	355	27	365
rehnqvist	4	59	6	52
norwegian	98	945	152	939
taylor	60	632	48	471
hansteen	25	278	37	282
bhat	138	1916	188	1921
julian	64	873	52	583
australianswedish	45	263	47	266
mangercats	9	291	16	293
eis	57	858	45	883
rehnqvist2	25	154	31	147

Using the data entered this as tab-delimited text file `yusuf1985.txt`, fitting the random effects model and integrated by Peto's method and checking heterogeneity can be done by the following script (it was done last week).

```
x <- read.delim("yusuf1985.txt")
library(metafor)
res <- rma(measure="PETO",ai=bbdeath,n1i=bbno,ci=cntldeath,n2i=cntlno,data=x)
forest(res,atransf=exp,slab=paste(x$studyid),xlim=log(c(0.01,50)),at=log(c(1:10/10,2:10)))
summary(res)
exp(res$b)
```

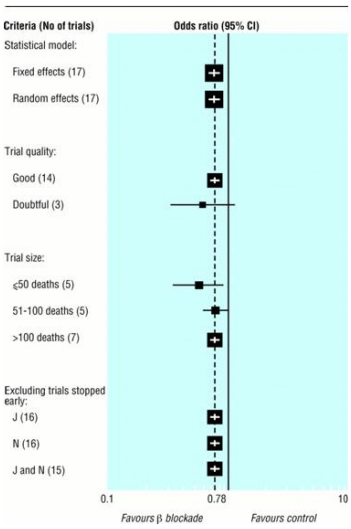
We can get forest plot for random effects model (integrated odds ratio is shown as 0.78 at the bottom of the plot). `summary(res)` gives the result of heterogeneity test and the model fitting test. Heterogeneity test is to test the null-hypothesis that the result of studies are homogeneous. Here we get p-value of 0.2927 so that we cannot reject the null-hypothesis. `exp(res$b)` shows the estimated odds ratio by Peto's method. And it should be noted that the random effects model fitting is significant (p-value is 0.0006).

```
> summary(res)

Random-Effects Model (k = 15; tau^2 estimator: REML)

  logLik  Deviance       AIC       BIC
 -4.3403    8.6806   12.6806   13.9587

tau^2 (estimate of total amount of heterogeneity): 0.0173 (SE = 0.0238)
tau (sqrt of the estimate of total heterogeneity): 0.1315
I^2 (% of total variability due to heterogeneity): 26.22%
H^2 (total variability / within-study variance):   1.36

Test for Heterogeneity:
Q(df = 14) = 16.3466, p-val = 0.2927

Model Results:

estimate       se     zval     pval    ci.lb    ci.ub
 -0.2422   0.0704  -3.4424   0.0006  -0.3801  -0.1043      ***

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

> exp(res$b)
             [,1]
intrcpt 0.7849175
```

2 Sensitivity Analysis

Here I cite the explanation from Egger et al. (1997). This paper basically uses the data by Yusuf et al. (1985) but added 2 new studies (details are not available) so that the analysis may slightly differ from our practice.

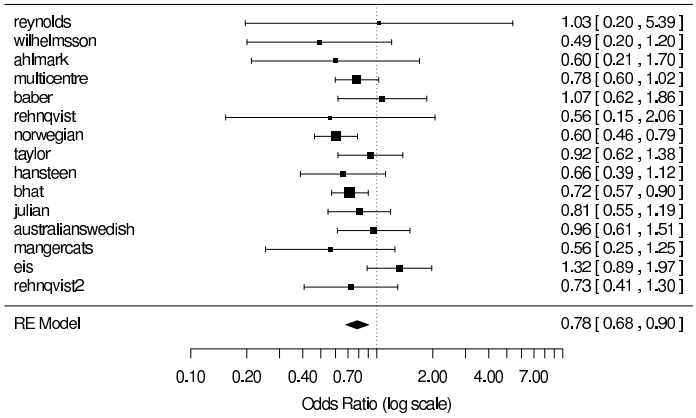
> Opinions will often diverge on the correct method for performing a particular meta-analysis. The robustness of the findings to different assumptions should therefore always be examined in a thorough sensitivity analysis. This is illustrated in [figure 4] (see below) for the meta-analysis of β blockade after myocardinal infarction. Firstly, the overall effect was calculated by different statistical methods, by using both a fixed and a random effects model. The [figure 4] shows that the overall estimates are virtually identical and that confidence intervals are only slightly wider with the random effects model. This is explained by the relatively small amount of variation between trials in this meta-analysis.

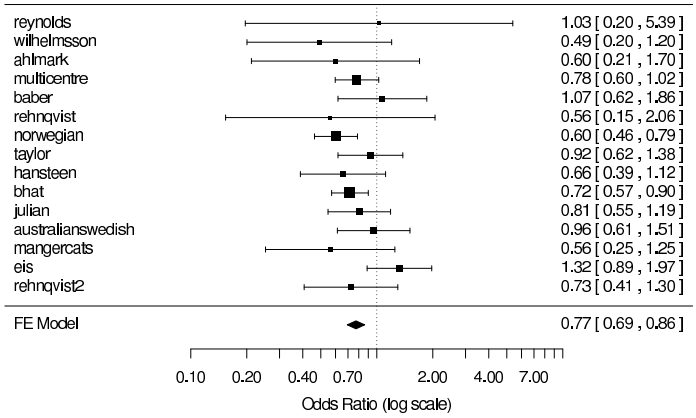


In our practice using R, the following script generates the result of fitting fixed effects model and its forest plot.

```
res.fixed <- rma(measure="PETO",ai=bbdeath,n1i=bbno,ci=cntldeath,n2i=cntlno,data=x,method="FE")
forest(res.fixed,atransf=exp,slab=paste(x$studyid),xlim=log(c(0.01,50)),at=log(c(1:10/10,2:10)))
summary(res.fixed)
exp(res.fixed$b)
```

The forest plot with the case of previous one (random effects model) are shown below.



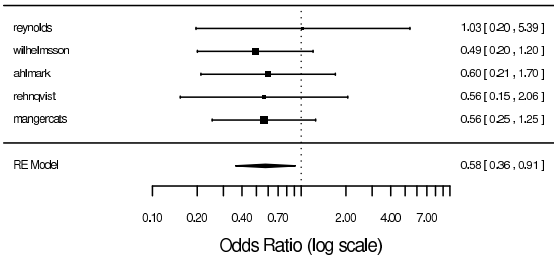


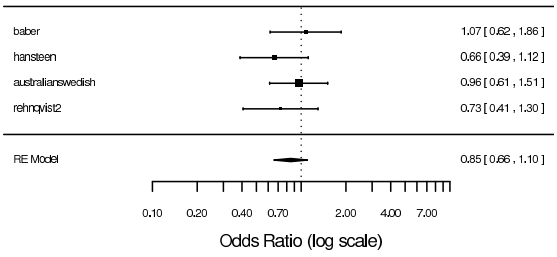
Besides the effect of model, the effects of trial quality, trial size, and the exclusion of trials stopped early should be examined as sensitivity analysis. It can be done by using `subset()` function to limit trials to meet with specified conditions and comparing them. I will cite Eggar et al.'s explanation again.

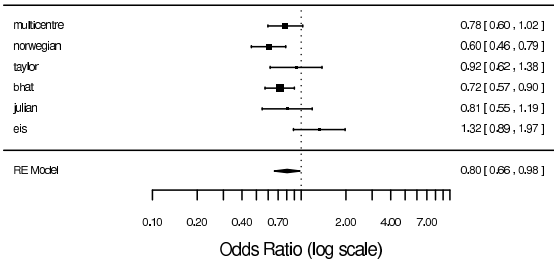
> Secondly, methodological quality was assessed in terms of how patients were allocated to active treatment or control groups, how outcome was assessed, and how the data were analysed. The maximum credit of nine points was given if patient allocation was truly random, if assessment of vital status was independent of treatment group, and if data from all patients initially included were analysed according to the intention to treat principle (Note: we cannot practice this because of lack of such detailed information). [Figure 4] shows that the three low quality studies ($\leq$ 7 points) showed more benefit than the high quality trials. Exclusion of these three studies, however, leaves the overall effect and the confidence intervals practically unchanged.
>
> Thirdly, significant results are more likely to get published than non-significant findings, and this can distort the findings of meta-analysis. The presense of such publication bias can be identified by stratifying the analysis by study size — smaller effects can be significant in larger studies. If publication bias is present, it is expected that, of published studies, the largest ones will report the smallest effects. [Figure 4] shows that this is indeed the case, with the smallest trials (50 or fewer deaths) showing the largest effect. However, exclusion of the smallest studies has little effect on the overall estimate.
>
> Finally, two studies were stopped earlier than anticipated on the grounds of the results from interim analyses. Estimates of treatment effects from trials that were stopped early are liable to be biased away from the null value. Bias may thus be introduced in a meta-analysis that include such trials. Exclusion of these trials, however, affects the overall estimate only marginally.
>
> The sensitivity analysis thus shows that the results from this meta-analysis are robust to the choice of the statistical method and to the exclusion of trials of poorer quality or of studies stopped early. It also suggests that publication bias is unlikely to have distorted its findings.

In our practice, the effect of sample size (its meaning implys publication bias) can be tested by the following script.

```
x$death <- x$bbdeath+x$cntldeath
A <- subset(x,death<=50)
B <- subset(x,((death>50)&(death<=100)))
C <- subset(x,death>100)
resA <- rma(measure="PETO",ai=bbdeath,n1i=bbno,ci=cntldeath,n2i=cntlno,data=A)
resB <- rma(measure="PETO",ai=bbdeath,n1i=bbno,ci=cntldeath,n2i=cntlno,data=B)
resC <- rma(measure="PETO",ai=bbdeath,n1i=bbno,ci=cntldeath,n2i=cntlno,data=C)
pdf("sizeeffect.pdf",width=4,height=8)
layout(1:3)
forest(resA,atransf=exp,slab=paste(A$studyid),xlim=log(c(0.01,50)),at=log(c(1:10/10,2:10)))
forest(resB,atransf=exp,slab=paste(B$studyid),xlim=log(c(0.01,50)),at=log(c(1:10/10,2:10)))
forest(resC,atransf=exp,slab=paste(C$studyid),xlim=log(c(0.01,50)),at=log(c(1:10/10,2:10)))
dev.off()
```







3 Reference

- Egger M, Smith GD, Phillips AN (1997) Meta-analysis: Principles and procedures. *BMJ*, 315: 1533-. [http://www.bmj.com/content/315/7121/1533]