SOLUTIONS to Computer Practical - Basic Meta-Analysis in R

R packages

We will use the package **foreign** to import data and the package **meta** to run meta-analyses.

```
library(meta)
library(foreign)
```

Dataset

Dataset diuretic.dta contains the data from the review of diuretics in pregnancy. Open the dataset in R, either by using *Import Dataset* tab or type:

```
# First set the directory to where the data is saved
setwd("C:/Users/kc19o338/Desktop/Stata Practicals/data/")
#Then load the data
DiureticData <- read.dta("diuretic.dta")
```

Use the **str()** or **summary ()** command to obtain details of the dataset.

```
str(DiureticData)
```

```
## 'data.frame':    9 obs. of  6 variables:
##  $ trial  : int  1 2 3 4 5 6 7 8 9
##  $ trialid: chr  "Weseley" "Flowers" "Menzies" "Fallis" ...
##  $ nt     : int  131 385 57 38 1011 1370 506 108 153
##  $ nc     : int  136 134 48 40 760 1336 524 103 102
##  $ pet    : int  14 21 14 6 12 138 15 6 65
##  $ pec    : int  14 17 24 18 35 175 20 2 40
##  - attr(*, "datalabel")= chr "Diuretics and pre-eclampsia"
##  - attr(*, "time.stamp")= chr "18 Jan 2010 12:00"
##  - attr(*, "formats")= chr  "%8.0g" "%9s" "%8.0g" "%8.0g" ...
##  - attr(*, "types")= int  251 9 252 252 252 252
##  - attr(*, "val.labels")= chr  "" "" "" "" ...
##  - attr(*, "var.labels")= chr  "trial identity number" "trial first author
" "total treated patients" "total control patients" ...
##  - attr(*, "expansion.fields")=List of 10
##   ..$ : chr  "trialid" "note1" "name of first author of trial"
##   ..$ : chr  "trialid" "note0" "1"
##   ..$ : chr  "pec" "note1" "number of control patients with pre-eclampsia"
##   ..$ : chr  "pec" "note0" "1"
##   ..$ : chr  "pet" "note1" "number of treated patients with pre-eclampsia"
##   ..$ : chr  "pet" "note0" "1"
##   ..$ : chr  "_dta" "note3" "They examine the prevention of pre-eclampsia
```

```
with diuretics."
##   ..$ : chr  "_dta" "note0" "3"
##   ..$ : chr  "_dta" "note2" "(British Medical Journal, 290, 17-23)."
##   ..$ : chr  "_dta" "note1" "These data are from the meta analysis publish
ed by Collins et al."
##  - attr(*, "version")= int 8
```

```
summary(DiureticData)
```

```
##      trial     trialid                nt               nc
##  Min.   :1   Length:9           Min.   :  38.0   Min.   :  40.0
##  1st Qu.:3   Class :character   1st Qu.: 108.0   1st Qu.: 102.0
##  Median :5   Mode  :character   Median : 153.0   Median : 134.0
##  Mean   :5                      Mean   : 417.7   Mean   : 353.7
##  3rd Qu.:7                      3rd Qu.: 506.0   3rd Qu.: 524.0
##  Max.   :9                      Max.   :1370.0   Max.   :1336.0
##       pet              pec
##  Min.   :  6.00   Min.   :  2.00
##  1st Qu.: 12.00   1st Qu.: 17.00
##  Median : 14.00   Median : 20.00
##  Mean   : 32.33   Mean   : 38.33
##  3rd Qu.: 21.00   3rd Qu.: 35.00
##  Max.   :138.00   Max.   :175.00
```

These data are from the meta analysis published by Collins et al. (British Medical Journal, 290, 17-23). They examine the prevention of pre-eclampsia with diuretics.

trialid: name of first author of trial

pet: number of treated patients with pre-eclampsia

pec: number of control patients with pre-eclampsia

We will start by calculating log odds ratio and its standard error for each study, for use in meta-analyses. (We will see in question 2 that these calculations can be done automatically). First, derive the number of healthy mothers (those who did not experience pre-eclampsia) in the treatment and control arm of each trial

```
DiureticData$hc<-DiureticData$nc-DiureticData$pec
DiureticData$ht<-DiureticData$nt-DiureticData$pet
DiureticData
```

```
##   trial   trialid   nt   nc pet pec   hc   ht
## 1     1   Weseley  131  136  14  14  122  117
## 2     2   Flowers  385  134  21  17  117  364
## 3     3   Menzies   57   48  14  24   24   43
## 4     4    Fallis   38   40   6  18   22   32
## 5     5   Cuadros 1011  760  12  35  725  999
## 6     6 Landesman 1370 1336 138 175 1161 1232
## 7     7     Kraus  506  524  15  20  504  491
```

```
## 8     8   Tervila  108  103   6   2  101  102
## 9     9  Campbell  153  102  65  40   62   88
```

Now derive the odds ratio, then the log odds ratio and its corresponding standard error for each study.

```
DiureticData$or=(DiureticData$pet/DiureticData$ht)/(DiureticData$pec/Diuretic
Data$hc)
DiureticData$logor=log(DiureticData$or)
DiureticData$selogor=sqrt(1/DiureticData$pet+1/DiureticData$ht+1/DiureticData
$pec+1/DiureticData$hc)
DiureticData
```

```
##   trial   trialid   nt   nc pet pec   hc   ht        or       logor
## 1     1   Weseley  131  136  14  14  122  117 1.0427350  0.04184711
## 2     2   Flowers  385  134  21  17  117  364 0.3970588 -0.92367084
## 3     3   Menzies   57   48  14  24   24   43 0.3255814 -1.12214279
## 4     4    Fallis   38   40   6  18   22   32 0.2291667 -1.47330574
## 5     5   Cuadros 1011  760  12  35  725  999 0.2488202 -1.39102454
## 6     6 Landesman 1370 1336 138 175 1161 1232 0.7431262 -0.29688945
## 7     7     Kraus  506  524  15  20  504  491 0.7698574 -0.26154993
## 8     8   Tervila  108  103   6   2  101  102 2.9705882  1.08875999
## 9     9  Campbell  153  102  65  40   62   88 1.1448864  0.13530539
##     selogor
## 1 0.3995008
## 2 0.3431280
## 3 0.4219215
## 4 0.5467420
## 5 0.3380608
## 6 0.1209697
## 7 0.3474010
## 8 0.8284755
## 9 0.2605327
```

In the above list, which trials have the smallest standard errors and which have the biggest standard errors?

Answer: Trial number 6 has the smallest standard error, with trial 9 the next smallest; trial number 8 has the biggest standard error, with 4 the next biggest.

Meta-analysis

We will now use the **metagen** command to perform a fixed and then a random-effects meta-analysis and the **forest** command to obtain the forest plots, using inverse-variance weighting. The basic output is produced by typing:

```
metagen(DiureticData$logor, DiureticData$selogor, comb.random = FALSE, comb.f
ixed = TRUE)
```

```
##                         95%-CI %W(fixed)
## 1  0.0418 [-0.7412;  0.8249]       5.0
## 2 -0.9237 [-1.5962; -0.2512]       6.8
## 3 -1.1221 [-1.9491; -0.2952]       4.5
## 4 -1.4733 [-2.5449; -0.4017]       2.7
## 5 -1.3910 [-2.0536; -0.7284]       7.0
## 6 -0.2969 [-0.5340; -0.0598]      54.5
## 7 -0.2615 [-0.9424;  0.4193]       6.6
## 8  1.0888 [-0.5350;  2.7125]       1.2
## 9  0.1353 [-0.3753;  0.6459]      11.8
##
## Number of studies combined: k = 9
##
##                                        95%-CI     z  p-value
## Fixed effect model -0.3980 [-0.5731; -0.2229] -4.45 < 0.0001
##
## Quantifying heterogeneity:
## tau^2 = 0.2297; H = 1.85 [1.31; 2.60]; I^2 = 70.7% [41.8%; 85.2%]
##
## Test of heterogeneity:
##      Q d.f. p-value
##  27.26    8  0.0006
##
## Details on meta-analytical method:
## - Inverse variance method
```

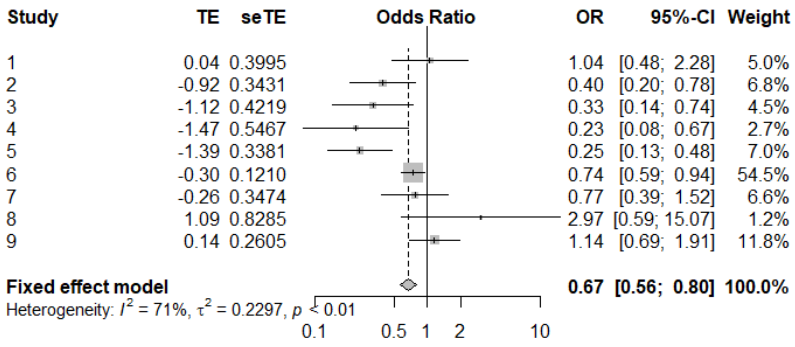
To display the output on the odds ratio scale, type:

```
fixed.effect<-metagen(DiureticData$logor, DiureticData$selogor, sm= "OR", com
b.random = FALSE, comb.fixed = TRUE)
print(fixed.effect)
```

```
##       OR            95%-CI %W(fixed)
## 1 1.0427 [0.4766;  2.2815]       5.0
## 2 0.3971 [0.2027;  0.7779]       6.8
## 3 0.3256 [0.1424;  0.7444]       4.5
## 4 0.2292 [0.0785;  0.6692]       2.7
## 5 0.2488 [0.1283;  0.4827]       7.0
## 6 0.7431 [0.5863;  0.9420]      54.5
## 7 0.7699 [0.3897;  1.5210]       6.6
## 8 2.9706 [0.5857; 15.0675]       1.2
## 9 1.1449 [0.6871;  1.9078]      11.8
##
## Number of studies combined: k = 9
##
##                         OR           95%-CI     z  p-value
## Fixed effect model 0.6717 [0.5638; 0.8002] -4.45 < 0.0001
##
## Quantifying heterogeneity:
## tau^2 = 0.2297; H = 1.85 [1.31; 2.60]; I^2 = 70.7% [41.8%; 85.2%]
```

```
##
## Test of heterogeneity:
##      Q d.f. p-value
##  27.26    8  0.0006
##
## Details on meta-analytical method:
## - Inverse variance method
```

```
forest(fixed.effect)
```

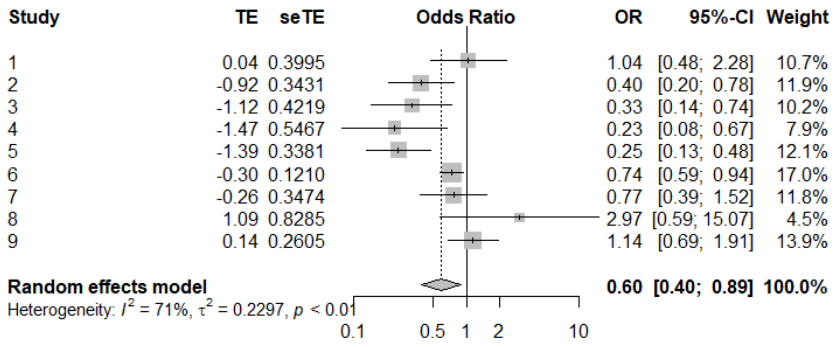


To derive a random-effects analysis:

```
random.effects<-metagen(DiureticData$logor,DiureticData$selogor, sm="OR", com
b.fixed=FALSE, comb.random = TRUE)
print(random.effects)
```

```
##       OR            95%-CI %W(random)
## 1 1.0427 [0.4766;  2.2815]       10.7
## 2 0.3971 [0.2027;  0.7779]       11.9
## 3 0.3256 [0.1424;  0.7444]       10.2
## 4 0.2292 [0.0785;  0.6692]        7.9
## 5 0.2488 [0.1283;  0.4827]       12.1
## 6 0.7431 [0.5863;  0.9420]       17.0
## 7 0.7699 [0.3897;  1.5210]       11.8
## 8 2.9706 [0.5857; 15.0675]        4.5
## 9 1.1449 [0.6871;  1.9078]       13.9
##
```

```
## Number of studies combined: k = 9
##
##                          OR           95%-CI     z p-value
## Random effects model 0.5964 [0.4001; 0.8891] -2.54  0.0112
##
## Quantifying heterogeneity:
## tau^2 = 0.2297; H = 1.85 [1.31; 2.60]; I^2 = 70.7% [41.8%; 85.2%]
##
## Test of heterogeneity:
##      Q d.f. p-value
##  27.26    8  0.0006
##
## Details on meta-analytical method:
## - Inverse variance method
## - DerSimonian-Laird estimator for tau^2

forest(random.effects)
```

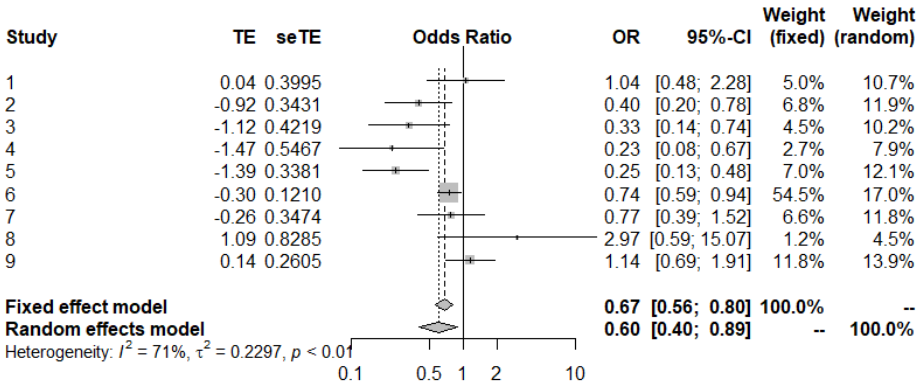


Check that these results agree with those in the handout. What happens to the squares in the forest plot when you conduct a random-effects analysis?

It is possible to display both the fixed and random-effects estimates. If you don't specify the comb.fixed or comb.random parameters, default is to display both the fixed and random-effects estimates.

```
both.models<-metagen(DiureticData$logor,DiureticData$selogor, sm="OR")
print(both.models)
```

```
##       OR            95%-CI %W(fixed) %W(random)
## 1 1.0427 [0.4766;  2.2815]       5.0       10.7
## 2 0.3971 [0.2027;  0.7779]       6.8       11.9
## 3 0.3256 [0.1424;  0.7444]       4.5       10.2
## 4 0.2292 [0.0785;  0.6692]       2.7        7.9
## 5 0.2488 [0.1283;  0.4827]       7.0       12.1
## 6 0.7431 [0.5863;  0.9420]      54.5       17.0
## 7 0.7699 [0.3897;  1.5210]       6.6       11.8
## 8 2.9706 [0.5857; 15.0675]       1.2        4.5
## 9 1.1449 [0.6871;  1.9078]      11.8       13.9
##
## Number of studies combined: k = 9
##
##                         OR           95%-CI     z  p-value
## Fixed effect model   0.6717 [0.5638; 0.8002] -4.45 < 0.0001
## Random effects model 0.5964 [0.4001; 0.8891] -2.54   0.0112
##
## Quantifying heterogeneity:
## tau^2 = 0.2297; H = 1.85 [1.31; 2.60]; I^2 = 70.7% [41.8%; 85.2%]
##
## Test of heterogeneity:
##      Q d.f. p-value
##  27.26    8  0.0006
##
## Details on meta-analytical method:
## - Inverse variance method
## - DerSimonian-Laird estimator for tau^2

forest(both.models)
```



There are a large number of options to derive a forest plot, which you can examine by typing:

```
?forest
```

Experiment with the use graphics options of the **forest** command. The following options are likely to be useful:

xlab - label the horizontal axis (Odds Ratio)

prediction=TRUE - add prediction interval for random-effects model

layout = "JAMA" - a specific layout of the forest plot

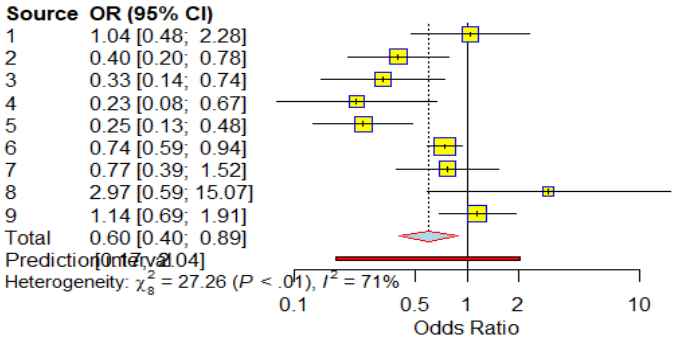
col.diamond = "green" - The colour of diamonds representing the results for fixed effect and random effects models.

col.diamond.lines = "red" - The colour of the outer line of diamonds representing the results for fixed effect and random effects models.

col.square = "yellow" - The colour for squares reflecting study's weight in the meta-analysis

col.square.lines = "blue" - The colour for the outer lines of squares reflecting study's weight in the meta-analysis

```
forest(random.effects, prediction = TRUE, xlab="Odds Ratio", layout = "JAMA",
col.diamond = "green", col.diamond.lines = "red",
       col.square = "yellow", col.square.lines = "blue")
```

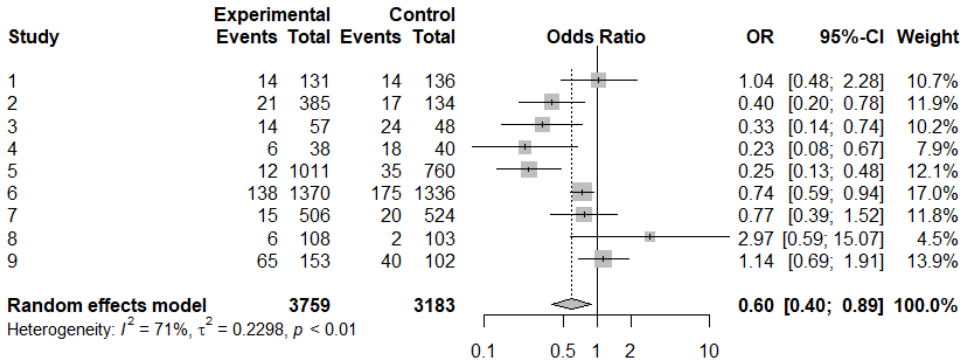


Exercise 2

The **metabin** command will use the raw (2X2) data from each study to calculate a range of treatment effect estimates and then derive meta-analyses using either Mantel-Haenszel or inverse-variance weights, for odds ratios, risk ratios and risk differences, also the Peto method for odds ratios, and generalized linear mixed model are available for pooling. The default is to use the Mantel-Haenszel method. The user supplies the names of variables containing the number of: i) events in treatment group, ii) observations in treatment group, iii) events in control group and iv) observations in control group. This means that you do not need to start by deriving the treatment effect and its standard error in each study. For example (random effects):

```
?metabin
random.effects.or = metabin(pet, nt, pec, nc, comb.fixed = FALSE,
                    data = DiureticData, sm = "OR")
summary(random.effects.or)

## Number of studies combined: k = 9
##
##                          OR           95%-CI     z p-value
## Random effects model 0.5964 [0.4001; 0.8892] -2.54  0.0112
##
```

```
## Quantifying heterogeneity:
## tau^2 = 0.2298; H = 1.85 [1.31; 2.60]; I^2 = 70.7% [41.8%; 85.2%]
##
## Test of heterogeneity:
##      Q d.f. p-value
##  27.27    8  0.0006
##
## Details on meta-analytical method:
## - Mantel-Haenszel method
## - DerSimonian-Laird estimator for tau^2

forest(random.effects.or)
```



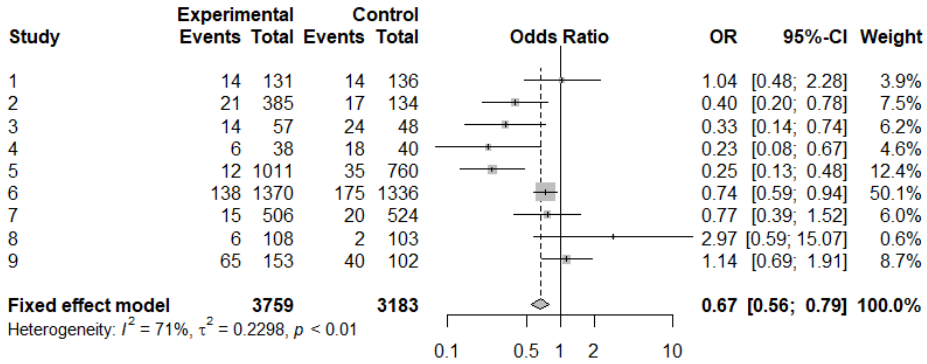
As well as the graph options used for question 1, you can use the options available for the forest plot.

Use this command to derive the same analysis as in question 1, by using the comb.random=FALSE for fixed effect model:

```
fixed.effect.or = metabin(pet, nt, pec, nc, comb.random=FALSE,
                    data = DiureticData, sm = "OR")
summary(fixed.effect.or)

## Number of studies combined: k = 9
##
##                         OR           95%-CI     z  p-value
## Fixed effect model 0.6677 [0.5620; 0.7932] -4.60 < 0.0001
```

```
##
## Quantifying heterogeneity:
## tau^2 = 0.2298; H = 1.85 [1.31; 2.60]; I^2 = 70.7% [41.8%; 85.2%]
##
## Test of heterogeneity:
##      Q d.f. p-value
##  27.27    8  0.0006
##
## Details on meta-analytical method:
## - Mantel-Haenszel method
```

```
forest(fixed.effect.or)
```

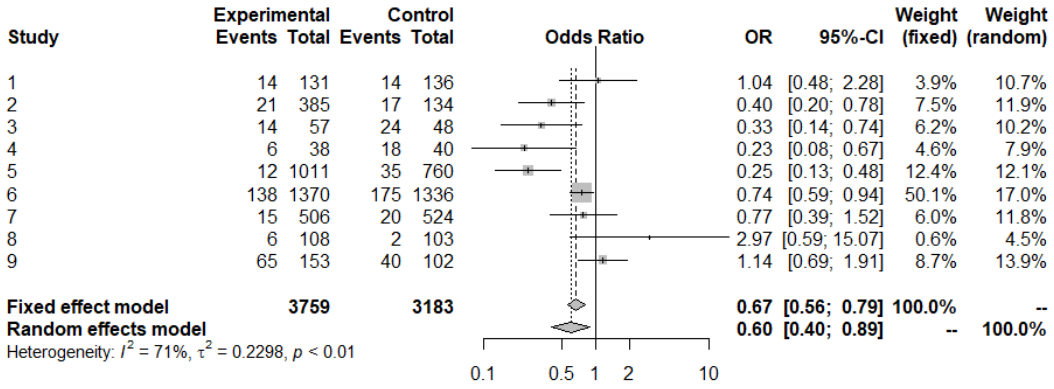


Use this command to derive the same analysis as in question 1 for both fixed effect model and random effects model:

```
both.models.or = metabin(pet, nt, pec, nc,
                   data = DiureticData, sm = "OR")
summary(both.models.or)
```

```
## Number of studies combined: k = 9
##
##                          OR           95%-CI     z  p-value
## Fixed effect model   0.6677 [0.5620; 0.7932] -4.60 < 0.0001
## Random effects model 0.5964 [0.4001; 0.8892] -2.54   0.0112
##
## Quantifying heterogeneity:
```

```
## tau^2 = 0.2298; H = 1.85 [1.31; 2.60]; I^2 = 70.7% [41.8%; 85.2%]
##
## Test of heterogeneity:
##      Q d.f. p-value
##  27.27    8  0.0006
##
## Details on meta-analytical method:
## - Mantel-Haenszel method
## - DerSimonian-Laird estimator for tau^2

forest(both.models.or)
```



Compare the results using Mantel-Haenszel and inverse variance weights, for odds ratios and risk ratios, and using the Peto method for odds ratios. You can choose different method to be used for pooling the studies by **"method"** parameter and different summary measure by **"sm"** parameter. See helpfile for metabin (**?metabin**) for more information.

```
pooledOR.MH = metabin(pet, nt, pec, nc,
                      data = DiureticData, sm = "OR")
summary(pooledOR.MH)

## Number of studies combined: k = 9
##
##                          OR           95%-CI     z  p-value
## Fixed effect model   0.6677 [0.5620; 0.7932] -4.60 < 0.0001
## Random effects model 0.5964 [0.4001; 0.8892] -2.54   0.0112
##
```

```
## Quantifying heterogeneity:
## tau^2 = 0.2298; H = 1.85 [1.31; 2.60]; I^2 = 70.7% [41.8%; 85.2%]
##
## Test of heterogeneity:
##      Q d.f. p-value
##  27.27    8  0.0006
##
## Details on meta-analytical method:
## - Mantel-Haenszel method
## - DerSimonian-Laird estimator for tau^2
```

```
pooledOR.Inverse = metabin(pet, nt, pec, nc, method="Inverse",
                   data = DiureticData, sm = "OR")
summary(pooledOR.Inverse)
```

```
## Number of studies combined: k = 9
##
##                          OR           95%-CI     z  p-value
## Fixed effect model   0.6717 [0.5638; 0.8002] -4.45 < 0.0001
## Random effects model 0.5964 [0.4001; 0.8891] -2.54   0.0112
##
## Quantifying heterogeneity:
## tau^2 = 0.2297; H = 1.85 [1.31; 2.60]; I^2 = 70.7% [41.8%; 85.2%]
##
## Test of heterogeneity:
##      Q d.f. p-value
##  27.26    8  0.0006
##
## Details on meta-analytical method:
## - Inverse variance method
## - DerSimonian-Laird estimator for tau^2
```

```
pooledRR.MH = metabin(pet, nt, pec, nc,
                   data = DiureticData, sm = "RR")
summary(pooledRR.MH)
```

```
## Number of studies combined: k = 9
##
##                          RR           95%-CI     z  p-value
## Fixed effect model   0.7140 [0.6188; 0.8237] -4.62 < 0.0001
## Random effects model 0.6458 [0.4637; 0.8996] -2.59   0.0097
##
## Quantifying heterogeneity:
## tau^2 = 0.1570; H = 1.90 [1.35; 2.66]; I^2 = 72.2% [45.4%; 85.9%]
##
## Test of heterogeneity:
##      Q d.f. p-value
##  28.81    8  0.0003
##
## Details on meta-analytical method:
```

```
## - Mantel-Haenszel method
## - DerSimonian-Laird estimator for tau^2

pooledRR.Inverse = metabin(pet, nt, pec, nc, method="Inverse",
                   data = DiureticData, sm = "RR")
summary(pooledRR.Inverse)

## Number of studies combined: k = 9
##
##                          RR           95%-CI     z  p-value
## Fixed effect model   0.7370 [0.6383; 0.8511] -4.16 < 0.0001
## Random effects model 0.6459 [0.4642; 0.8988] -2.59   0.0095
##
## Quantifying heterogeneity:
## tau^2 = 0.1556; H = 1.89 [1.35; 2.65]; I^2 = 72.0% [45.0%; 85.8%]
##
## Test of heterogeneity:
##      Q d.f. p-value
##  28.62    8  0.0004
##
## Details on meta-analytical method:
## - Inverse variance method
## - DerSimonian-Laird estimator for tau^2

pooledOR.MH = metabin(pet, nt, pec, nc,
                  data = DiureticData, sm = "OR")
summary(pooledOR.MH)

## Number of studies combined: k = 9
##
##                          OR           95%-CI     z  p-value
## Fixed effect model   0.6677 [0.5620; 0.7932] -4.60 < 0.0001
## Random effects model 0.5964 [0.4001; 0.8892] -2.54   0.0112
##
## Quantifying heterogeneity:
## tau^2 = 0.2298; H = 1.85 [1.31; 2.60]; I^2 = 70.7% [41.8%; 85.2%]
##
## Test of heterogeneity:
##      Q d.f. p-value
##  27.27    8  0.0006
##
## Details on meta-analytical method:
## - Mantel-Haenszel method
## - DerSimonian-Laird estimator for tau^2

pooledOR.Peto = metabin(pet, nt, pec, nc, method="Peto",
                  data = DiureticData, sm = "OR")
summary(pooledOR.Peto)

## Number of studies combined: k = 9
##
```

```
##                           OR           95%-CI     z  p-value
## Fixed effect model   0.6640 [0.5588; 0.7890] -4.65 < 0.0001
## Random effects model 0.5980 [0.3999; 0.8942] -2.50   0.0123
##
## Quantifying heterogeneity:
## tau^2 = 0.2438; H = 1.92 [1.37; 2.68]; I^2 = 72.7% [46.6%; 86.1%]
##
## Test of heterogeneity:
##      Q d.f. p-value
##  29.34    8  0.0003
##
## Details on meta-analytical method:
## - Peto method
## - DerSimonian-Laird estimator for tau^2
```

The **metabin** command stores the estimated log of treatment effect and the standard error of the log effect with following variable names ***random.effects.or*$*TE*.*random***, ***random*.*effects*.*or$seTE.random***

These estimates should match the result we get from metagen (note in metagen inverse variance method was used)

```
random.effects.or$TE.random
```

```
## [1] -0.5167641
```

```
random.effects.or$seTE.random
```

```
## [1] 0.2037271
```

Some R meta-analysis commands require the user to provide the log odds ratio and its standard error: the metabin command is useful for deriving these variables.

Exercise 3

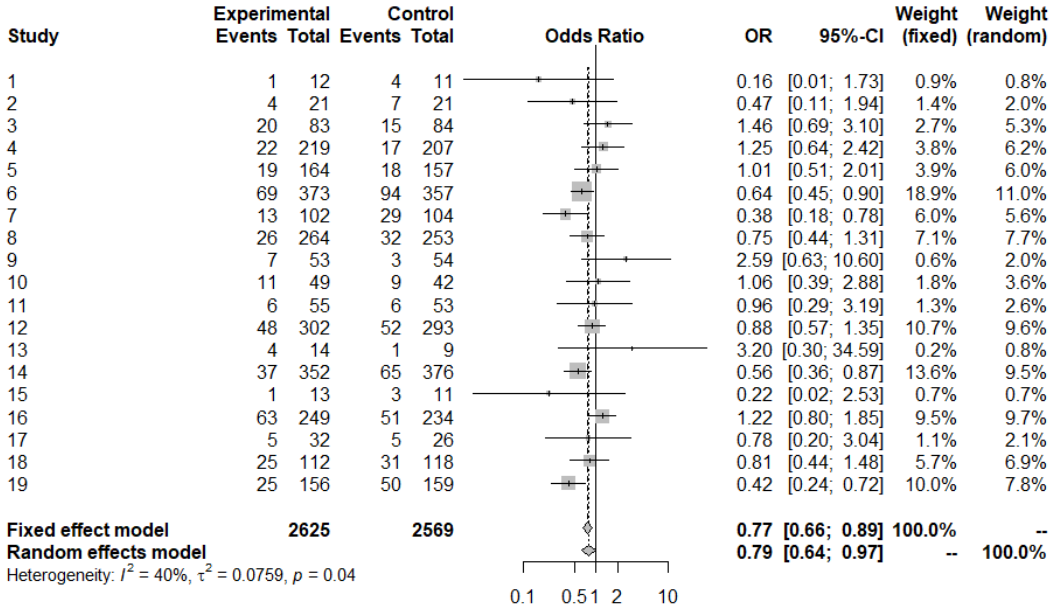
Datasets streptok.dta and magnes.dta give the effects (from all known trials) of streptokinase and magnesium respectively on the prevention of mortality after acute myocardial infarction.

```
# First set the directory to where the data is saved
setwd("C:/Users/kc19o338/Desktop/Stata Practicals/data/")
StreptokData <- read.dta("streptok.dta")

MagnesData <- read.dta("magnes.dta")
```

For the streptokinase data, perform meta-analyses on all studies: a) performed up to and including 1977

```
pooledOR = metabin(cases1, pop1, cases0, pop0, subset= year<=1977,
                   data = StreptokData, sm = "OR")
summary(pooledOR)
```

```
## Number of studies combined: k = 19
##
##                           OR           95%-CI     z p-value
## Fixed effect model   0.7686 [0.6645; 0.8890] -3.54  0.0004
## Random effects model 0.7868 [0.6355; 0.9743] -2.20  0.0279
##
## Quantifying heterogeneity:
## tau^2 = 0.0759; H = 1.29 [1.00; 1.70]; I^2 = 40.1% [0.0%; 65.3%]
##
## Test of heterogeneity:
##      Q d.f. p-value
##  30.03   18  0.0371
##
## Details on meta-analytical method:
## - Mantel-Haenszel method
## - DerSimonian-Laird estimator for tau^2

forest(pooledOR)
```



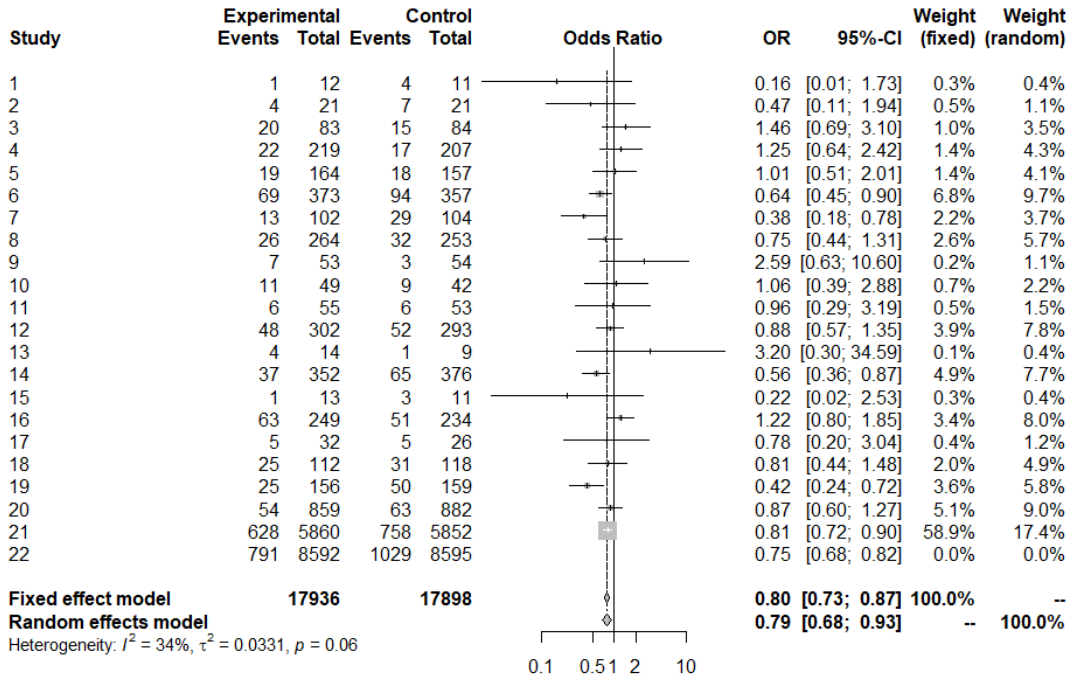
There is a clear effect of streptokinase using trials reported up to and including 1977.

b) excluding the ISIS-2 trial, trial's number = 22 - (hint: ?metabin, use exclude=…)

```
pooledOR = metabin(cases1, pop1, cases0, pop0, exclude =22,
                   data = StreptokData, sm = "OR")
summary(pooledOR)
```

```
## Number of studies combined: k = 21
##
##                           OR           95%-CI     z  p-value
## Fixed effect model   0.7962 [0.7301; 0.8683] -5.15 < 0.0001
## Random effects model 0.7929 [0.6784; 0.9266] -2.92   0.0035
##
## Quantifying heterogeneity:
## tau^2 = 0.0331; H = 1.23 [1.00; 1.61]; I^2 = 34.4% [0.0%; 61.3%]
##
## Test of heterogeneity:
##      Q d.f. p-value
##  30.49   20  0.0623
##
## Details on meta-analytical method:
## - Mantel-Haenszel method
## - DerSimonian-Laird estimator for tau^2
```

```
forest(pooledOR)
```



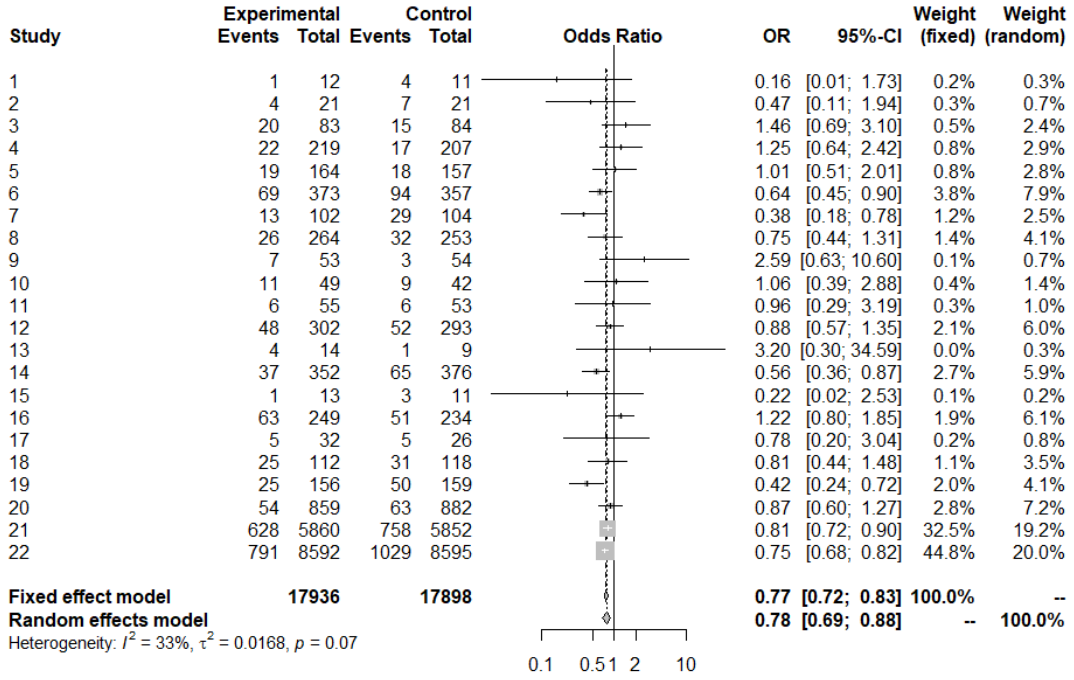
c)

including all trials

```
pooledOR = metabin(cases1, pop1, cases0, pop0,
                   data = StreptokData, sm = "OR")
summary(pooledOR)
```

```
## Number of studies combined: k = 22
##
##                           OR           95%-CI     z  p-value
```

```
## Fixed effect model   0.7735 [0.7249; 0.8254] -7.76 < 0.0001
## Random effects model 0.7825 [0.6927; 0.8840] -3.94 < 0.0001
##
## Quantifying heterogeneity:
## tau^2 = 0.0168; H = 1.22 [1.00; 1.59]; I^2 = 33.3% [0.0%; 60.3%]
##
## Test of heterogeneity:
##      Q d.f. p-value
##  31.50   21  0.0657
##
## Details on meta-analytical method:
## - Mantel-Haenszel method
## - DerSimonian-Laird estimator for tau^2

forest(pooledOR)
```

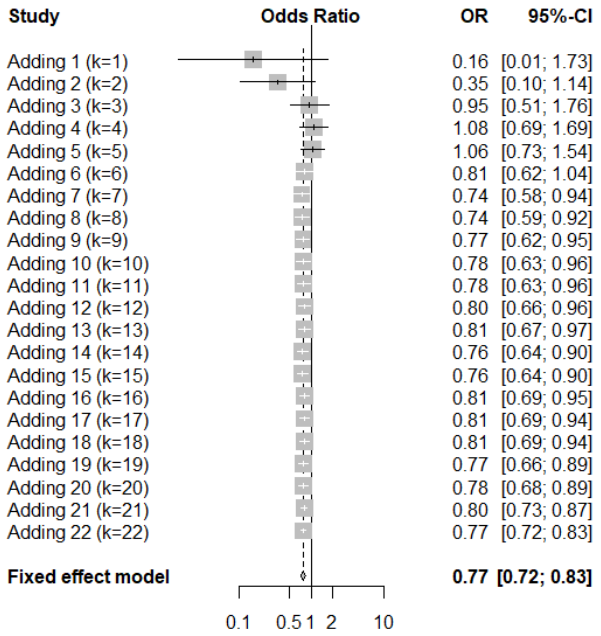


Although the evidence is much stronger, and the precision of the estimate greater, following the large trials published in the late 1980s, the magnitude of the estimate is very similar to that using evidence available in 1977. This can be seen using cumulative meta-analysis.

Is there any evidence of heterogeneity between studies? Examine how the evidence for an effect of streptokinase accumulated using the **metacum** (cumulative meta-analysis) command. For example:

```
CumulativeMA<-metacum(pooledOR)
CumulativeMA
```

```
##
## Cumulative meta-analysis (Fixed effect model)
##
##                         OR           95%-CI  p-value   tau^2    I^2
## Adding 1 (k=1)     0.1591 [0.0146; 1.7318]   0.1313
## Adding 2 (k=2)     0.3450 [0.1043; 1.1414]   0.0813  0.0000   0.0%
## Adding 3 (k=3)     0.9516 [0.5144; 1.7604]   0.8743  0.5848  54.0%
## Adding 4 (k=4)     1.0792 [0.6880; 1.6929]   0.7400  0.1432  34.7%
## Adding 5 (k=5)     1.0585 [0.7266; 1.5420]   0.7672  0.0335  13.7%
## Adding 6 (k=6)     0.8056 [0.6239; 1.0401]   0.0973  0.0965  41.8%
## Adding 7 (k=7)     0.7369 [0.5799; 0.9365]   0.0125  0.1385  51.5%
## Adding 8 (k=8)     0.7397 [0.5939; 0.9214]   0.0071  0.0899  43.4%
## Adding 9 (k=9)     0.7650 [0.6163; 0.9497]   0.0152  0.1176  47.7%
## Adding 10 (k=10)   0.7764 [0.6286; 0.9590]   0.0188  0.1005  42.6%
## Adding 11 (k=11)   0.7814 [0.6346; 0.9620]   0.0201  0.0833  36.7%
## Adding 12 (k=12)   0.7984 [0.6621; 0.9628]   0.0184  0.0559  31.3%
## Adding 13 (k=13)   0.8069 [0.6697; 0.9722]   0.0240  0.0587  30.6%
## Adding 14 (k=14)   0.7614 [0.6419; 0.9032]   0.0018  0.0595  33.5%
## Adding 15 (k=15)   0.7561 [0.6377; 0.8965]   0.0013  0.0590  31.8%
## Adding 16 (k=16)   0.8084 [0.6906; 0.9463]   0.0081  0.0733  39.2%
## Adding 17 (k=17)   0.8080 [0.6910; 0.9448]   0.0076  0.0647  35.2%
## Adding 18 (k=18)   0.8079 [0.6943; 0.9400]   0.0058  0.0529  31.1%
## Adding 19 (k=19)   0.7686 [0.6645; 0.8890]   0.0004  0.0759  40.1%
## Adding 20 (k=20)   0.7813 [0.6822; 0.8949]   0.0004  0.0618  37.5%
## Adding 21 (k=21)   0.7962 [0.7301; 0.8683] < 0.0001  0.0331  34.4%
## Adding 22 (k=22)   0.7735 [0.7249; 0.8254] < 0.0001  0.0168  33.3%
##
## Pooled estimate    0.7735 [0.7249; 0.8254] < 0.0001  0.0168  33.3%
##
## Details on meta-analytical method:
## - Mantel-Haenszel method

forest(CumulativeMA)
```



Although the confidence intervals became progressively narrower, there was clear evidence that streptokinase was effective from the mid-1970s, and the point estimate changed only marginally after that time.

Routine treatment with streptokinase after myocardial infarction was not recommended in the majority of textbooks and reviews until the late 1980s.

Exercise 4

(Optional - solutions not provided)

For the magnesium data, perform meta-analyses on all studies: a) performed up to and including 1991

b) excluding the ISIS-4 trial

c) including all trials