MI260: Introduction to model-based meta-analysis

Hands-on Exercise: Fixed effects meta-analysis

Introduction

In this exercise, together we'll use the LDL data to work through a fixed-effects meta-analysis of the effect of 80 mg atorvastatin compared to placebo. In the process, we'll learn the basics of using some of the plotting functions in the `metafor` package, fit a fixed-effects meta-analysis 'by hand', and finally use the `metafor` package to fit the model for us. Using what you learned in the first exercise, you will then perform a meta-analysis for the pancreatic cancer 12 month mortality incidence.

Files Provided

Datasets:

- AtorvastatinStudies.csv – LDL data for placebo-controlled studies with atorvastatin arms
- CochranePancreaticData12months.csv– mortality incidence data from 15 studies comparing gemcitabine to a gemcitabine+chemotherapy regimen

R code:

1. FixedEffectsExercise-Part1.r – code for reading and doing fixed effects analysis of the atorvastatin data
2. FixedEffectsExercise-Part2.r – code for reading and doing fixed effects analysis of the pancreatic cancer 12 month mortality incidence

Part 1:
LDL data from 8 placebo-controlled atorvastatin studies

1. Read the data and review the variables in the dataset. The variable `ldlPcfb` and `seLdlPcfb` are the mean percent change from baseline LDL and its standard error. The associated sample size is in the variable `n`.

```
d <- read.csv('AtorvastatinStudies.csv')
print(d)
```

2. We'll be working primarily with the difference from placebo. Derive the difference in means and the corresponding standard error. Note, you'll need to do some data manipulation in order to get the data in an easily usable form.

```
ator <- d[d$dose1>0,]
pbo <- d[d$dose1==0,c("trial","n","ldlPcfb","ldl0",
                      "seLdl0","seLdlPcfb")]
names(pbo) <- paste(names(pbo),".pbo",sep='')

ator <- merge(ator, pbo, by.x="trial",by.y="trial.pbo", all=T)

ator$diff <- ator$ldlPcfb - ator$ldlPcfb.pbo
ator$seDiff <- sqrt(ator$seLdlPcfb^2 + ator$seLdlPcfb.pbo^2
```

3. Make a forest plot of the mean difference from placebo. Is there anything else you'd like to add to the plot?

```
ator80 <- ator[ator$dose1==80,]
# Basic plot
forest(x=ator80$diff, sei=ator80$seDiff)
# Add axis and study labels
forest(x=ator80$diff, sei=ator80$seDiff,
      slab=ator80$trial, refline=NULL,
      xlab="Mean Difference",
      main="Difference in %CFB LDL for 80 mg atorvastatin")
# Add column labels and plot the data in order
ator80 <- ator80[rev(order(ator80$diff)),]
forest(x=ator80$diff, sei=ator80$seDiff,
      slab=ator80$trial, refline=NULL,
      at=seq(-80,-30,by=10),ylim=c(0,9),
      xlab="Mean Difference",
      main="Difference in %CFB LDL for 80 mg atorvastatin")
text(-120.5, 7.5, "Study", cex=0.95, adj=0, font=2)
text(-30, 7.5, "Mean Diff. + 95%CI",cex=0.95, adj=0, font=2)
```

4. Calculate the fixed effects meta-analysis weights for each study. Are there any studies that are getting an extremely large or small weight? Use these weights to calculate the fixed effects estimate of the mean difference and an approximate 95% CI. How does this estimate compare to the estimate based on the atorvastatin 10 mg data in the notes?

```
ator80$w <- 1/ator80$seDiff^2
print(ator80$w/sum(ator80$w))

feEst <- sum(ator80$diff * ator80$w) / sum(ator80$w)
seFeEst <- sqrt( 1/sum(ator80$w) )
feCI <- feEst + c(-1.96, 0, 1.96)*seFeEst
names(feCI) <- c("LCL95","Estimate","UCL95")
print(feCI)
```

5. Make another forest plot of the mean difference values and add the fixed effect estimate to the plot

```
forest(x=ator80$diff, sei=ator80$seDiff,
       slab=ator80$trial, refline=NULL,
       at=seq(-80,-30,by=10),ylim=c(-2.5,nrow(ator80)+3),
       xlab="Mean Difference",
       main="Difference in %CFB LDL for 80 mg atorvastatin")
text(-120.5, 7.5, "Study", cex=0.95, adj=0, font=2)
text(-30, 7.5, "Mean Diff. + 95%CI",cex=0.95, adj=0, font=2)
addpoly(x=feEst, sei=seFeEst, mlab="Fixed Effects Estimate",
row=-1)
```

6. Now use the rma function to fit the fixed effects meta-analysis model for the difference from placebo and make related plots.

```
fema <- rma(yi=diff, sei=seDiff, data=ator80, method="FE",
slab=trial)

print(fema)
plot(fema)
forest(fema)

forest(fema, refline=NULL,
       at=seq(-80,-30,by=10),
       ylim=c(-2.5,nrow(ator80)+3),
       xlab="Mean Difference",
       main="Difference in %CFB LDL for 80 mg atorvastatin")
text(-120.5, 7.5, "Study", cex=0.95, adj=0, font=2)
```

7. If you have time, try fitting a similar meta-analysis model to the atorvastatin 80 mg percent change from baseline (i.e., not the difference from placebo). Looking at the forest plot, do you think there is substantial between-study variability in the response?

Part 2:

Month 12 Mortality Incidence in pancreatic cancer from Cochrane Collaboration

Repeat the same sort of analysis as above using the Month 12 Mortality incidence data. We'll focus on the odds ratio of the Gemcitabine+Chemotherapy arms relative to gemcitabine alone.

1. Read the data and review the variables. The variables `d.GC` and `N.GC` correspond to the number of deaths and number randomized in the Gemcitabine+Chemotherapy arm. The variables `d.G` and `N.G` correspond to the number of deaths and number randomized in the Gemcitabine alone arm.

2. Derive the log odds ratio and the variance for the log odds ratio from each study. Recall that the odds ratio estimate is given by $OR = \frac{d.GC/\left(N.GC - d.GC\right)}{d.G/\left(N.G - d.G\right)}$ and the variance of the estimated log odds ratio is given by $\text{var}\left(\ln\left(OR\right)\right) = d.GC^{-1} + \left(N.GC - d.GC\right)^{-1} + d.G^{-1} + \left(N.G - d.G\right)^{-1}$

3. Using the forest function, make a forest plot of the ***log odds ratios***. Look at the help file for the `forest.default` function (in R, type `?forest.default`). Now, using the `atransf` argument to the `forest` function, make a forest plot for the odds ratio using the log odds ratio as the input. Your code might look like the snippet below.

```
forest(x=d$lor, vi=d$var.lor, slab=d$study,
       refline=0, atransf=exp)
```

4. Calculate the fixed effects meta-analysis weights for each study and use these to calculate the fixed effects estimate of the log odds ratio and an approximate 95% CI. What do you think about the relative weights for the studies? Which studies get the most weight? Which get the least?

5. Use the `rma` function to fit the fixed effects meta-analysis model and make a forest plot. Do the results using the `rma` function match what you calculated by hand?

<u>If you have time</u>

6. Fit the fixed effects meta-analysis model for the odds ratio using the observed number of deaths and number randomized, instead of the derived log odds ratio and its standard error. To understand how to do this, look at the help file for `rma.uni`.