MI260: Introduction to model-based meta-analysis

Hands-on Exercise: Meta-regression and diagnostic plots

Introduction

In this exercise, we'll make funnel and radial plots to examine small-study effects and fit meta-regression model to the LDL.

Files Provided

Dataset:

- AtorvastatinStudies.csv – LDL data for placebo-controlled studies with atorvastatin arms

R code:

- MetaRegressionExercise.r – code for plotting and meta-regression analysis of the atorvastatin LDL data

Part 1:

Funnel and radial plots to examine small-study effects

1. Make funnel and radial plots of the difference from placebo. Do the plots look symmetric to you? Do you think there is evidence of publication bias?

```
fema <- rma(yi=diff, vi=seDiff^2, data=ator80, method="FE",
            slab=trial)

# Funnel plot
funnel(fema, xlab="Difference in %CFB LDL", ylab="Standard Error")

# Radial plot
radial(fema)
```

Part 2:

Meta-regression of the difference from placebo in percent change from baseline LDL

1. Plot the observed mean difference against baseline LDL in the active group (`ldl0`) score using both a scatter plot and a forest plot. Which type of plot do you prefer? Does this variable seem promising to explain some of the heterogeneity of effect? Try the same using the change from baseline in the placebo group (`ldlPcfb.pbo`).

```
xyplot(diff~base.c, data=d, pch=19, cex=0.4/d$se.d^2,
      xlab="Baseline WOMAC score", ylab="Difference from placebo",
      sub="Size of points proportional to meta-analysis weight")

# Forest plot with baseline WOMAC score added
d <- d[rev(order(d$base.c)),]

forest(x=d$diff, vi=d$se.d^2,
      slab=d$ref, refline=NA,
      ilab=signif(d$base.c,3),
      ilab.xpos=-6,
      at=seq(-6,1,by=1),
      ylim=c(0,10),
      main="Difference from Placebo in WOMAC at Week 6")
text(-11, 9.5, "Study", cex=0.95, adj=0, font=2)
text(-7, 9.5, "Baseline", cex=0.95, adj=0, font=2)
text(2, 9.5, "Mean diff. + 95%CI",cex=0.95, adj=0, font=2)
```

2. Fit a fixed effects meta-regression model using the covariate you feel might explain more of the variability in the difference from placebo. How would you interpret the coefficients in this meta-regression? Is there a statistically significant effect of the covariate? Is the estimated effect clinically meaningful? What might we conclude about the impact of the covariate the drug effect? Is there any residual heterogeneity of effect based on the Q statistic? Plot the results using a forest plot.

```
feReg <- rma(yi=diff, sei=seDiff, mods=(ldlPcfb.pbo), data=ator80,
      method="FE", slab=trial)

forest(feReg, refline=NA, #order='obs',
      ilab=signif(ator80$ldlPcfb.pbo,2),
      ilab.xpos=-90,
      ylim=c(0,nrow(ator80)+3),
      main="Difference from Placebo in %CFB LDL")
text(-120, 7.5, "Study", cex=0.95, adj=0, font=2)
text(-95, 7.75, "Placebo\n%CFB LDL", cex=0.95, adj=0, font=2)
text(-30, 7.5, "Mean diff. + 95%CI",cex=0.95, adj=0, font=2)
```

3. Perform the same meta-regression but using a random effects model. Do your conclusions change? Plot the results using a forest plot, adding prediction intervals for placebo response of -4%, -2%, 0%, and 2%.

```
reReg <- rma(yi=diff, sei=seDiff, mods=(ldlPcfb.pbo),
data=ator80,
      method="REML", slab=trial)

predVals <- predict(reReg, newmods=c(-2,0,2,4))

forest(reReg, refline=NA, #order='obs',
      ilab=signif(ator80$ldlPcfb.pbo,2),
      ilab.xpos=-90,
      ylim=c(-4,nrow(ator80)+3),
      main="Difference from Placebo in %CFB LDL")
text(-120, 7.5, "Study", cex=0.95, adj=0, font=2)
text(-95, 7.75, "Placebo\n%CFB LDL", cex=0.95, adj=0, font=2)
text(-30, 7.5, "Mean diff. + 95%CI",cex=0.95, adj=0, font=2)
addpoly(x=predVals$pred, sei=predVals$se,col='red',  cex=0.9,
      mlab=paste("Placebo response =",c(-2,0,2,4),"%"))
```