Solutions Practical: Dose-response meta-analysis

Background

Second-generation antidepressants are the first-line options for the pharmacological treatment for depression. The therapeutic dose is at least 20 mg of fluoxetine or equivalent on a daily basis. However, there is still an ongoing debate about whether and how much antidepressants should be titrated up in order to maximize their effect as the side effects increase with increased dosage. The aim here is to find an optimal dose range where both the efficacy and acceptability are optimised.

R packages

We will use the packages **meta**, **readxl**, **dosresmeta** and **rms** to run and plot dose-response analyses.

If you haven't already installed **dosresmeta** and **rms**, please do so by typing

```
install.packages("dosresmeta")
install.packages("rms")
```

Next, we make the R packages available.

```
library(dosresmeta)
library(rms)
library(meta)
library(readxl)
```

Dataset

We will import the Excel dataset AntidepressantsDOSE.xls.

```
AntidepressantsDOSE = read_excel("AntidepressantsDOSE.xls", na = "NA")
AntidepressantsDOSE = as.data.frame(AntidepressantsDOSE)
```

This has RCTs that compare the outcomes with antidepressants at various dosages. How many studies are available?

```
length(unique(AntidepressantsDOSE$Study_No))
```

```
## [1] 71
```

How many different doses as observed? Which is the most frequently studies dose?

```
table(AntidepressantsDOSE$dose)
```

```
##
##     0  3.35     4     5   6.7     8    10 10.05  12.5  13.4  19.8    20
##    71     1     1     1     1     1     3     6     2     1     7    40
##  20.1    25  26.8    30 30.15    40  40.2  53.6    56    60    80  80.4
##     9     3     3     5     3    17     1     2     1     3     4     1
##   160
##     3
```

```
length(table(AntidepressantsDOSE$dose))
```

```
## [1] 25
```

Take some time to browse the column logRR in the dataset. How are these numbers calculated?

Run a dose-response analysis for the response outcome

Linear association

We will use the dosresmeta function to investigate the association between the dose and the response to antidepressants. Use the help to understand the arguments in the function and its output. Although the shape is expected to be non-linear, we will start with a linear model.

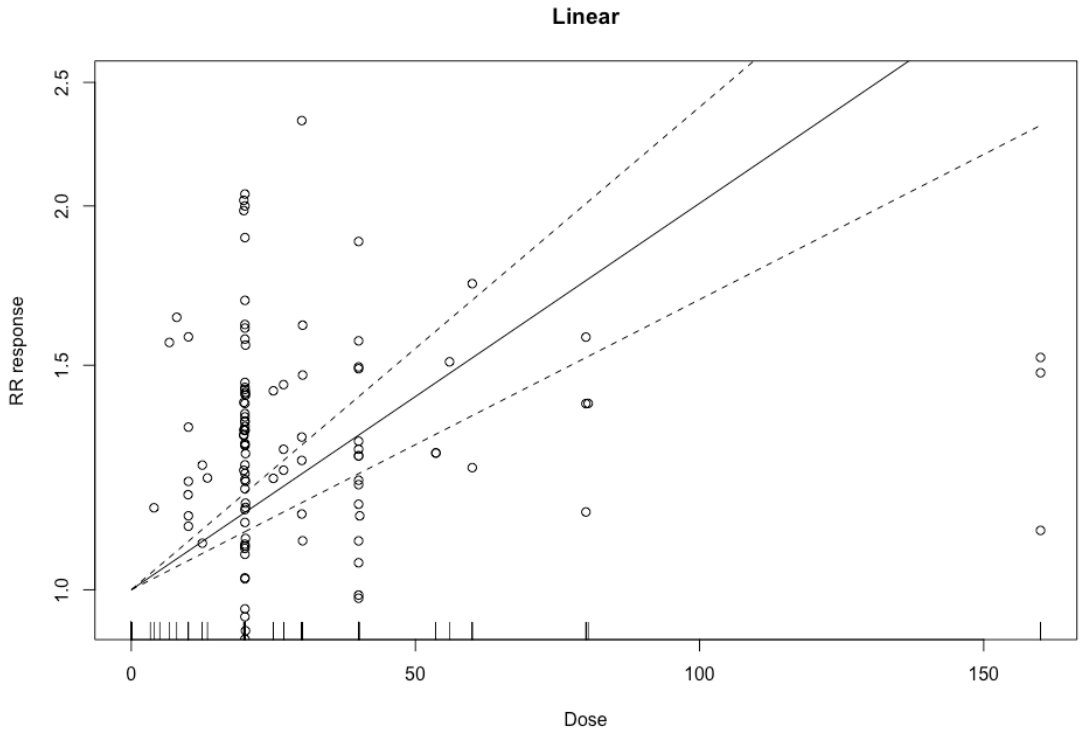
```
doseresRR = dosresmeta(logRR ~ dose, Study_No, data = AntidepressantsDOSE,
                       cases = Responders, n = No_randomised,
                       type = type, se = selogRR, method = "reml")
summary(doseresRR)
```

```
## Call:  dosresmeta(formula = logRR ~ dose, id = Study_No, type = type,
##     cases = Responders, n = No_randomised, data = AntidepressantsDOSE,
##     se = selogRR, method = "reml")
##
## Two-stage random-effects meta-analysis
## Estimation method: REML
## Covariance approximation: Greenland & Longnecker
##
## Chi2 model: X2 = 61.9556 (df = 1), p-value = 0.0000
##
## Fixed-effects coefficients
##               Estimate  Std. Error       z  Pr(>|z|)  95%ci.lb  95%ci.ub
## (Intercept)    0.0070      0.0009  7.8712    0.0000    0.0052    0.0087
##
## (Intercept)  ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
##
## Between-study random-effects (co)variance components
##   Std. Dev
##     0.0047
##
## Univariate Cochran Q-test for residual heterogeneity:
## Q = 164.9894 (df = 70), p-value = 0.0000
## I-square statistic = 57.6%
##
## 71 studies, 71 values, 1 fixed and 1 random-effects parameters
##    logLik        AIC        BIC
##  223.6956  -443.3912  -438.8942
```

Now, let us plot the results

```
with(predict(doseresRR, exp = TRUE, order = TRUE), {
     plot(dose, pred, log = "y", type = "l",
          xlim = c(0, 160), ylim = c(0.95, 2.5),
          xlab = "Dose", ylab = "RR response", main = c("Linear"))
     lines(dose, ci.lb, lty = 2)
     lines(dose, ci.ub, lty = 2)
     rug(dose, quiet = TRUE)
     })
with(AntidepressantsDOSE, points(dose[logRR != 0], exp(logRR[logRR != 0])))
with(AntidepressantsDOSE, rug(dose, quiet = TRUE))
```



What do the points represent in the graph?

Splines

The anticipated dose-response shape is expected to increase up a certain dose and then flaten out. We can use the rcs function for such a shape and will need to define some knots (at least 3).

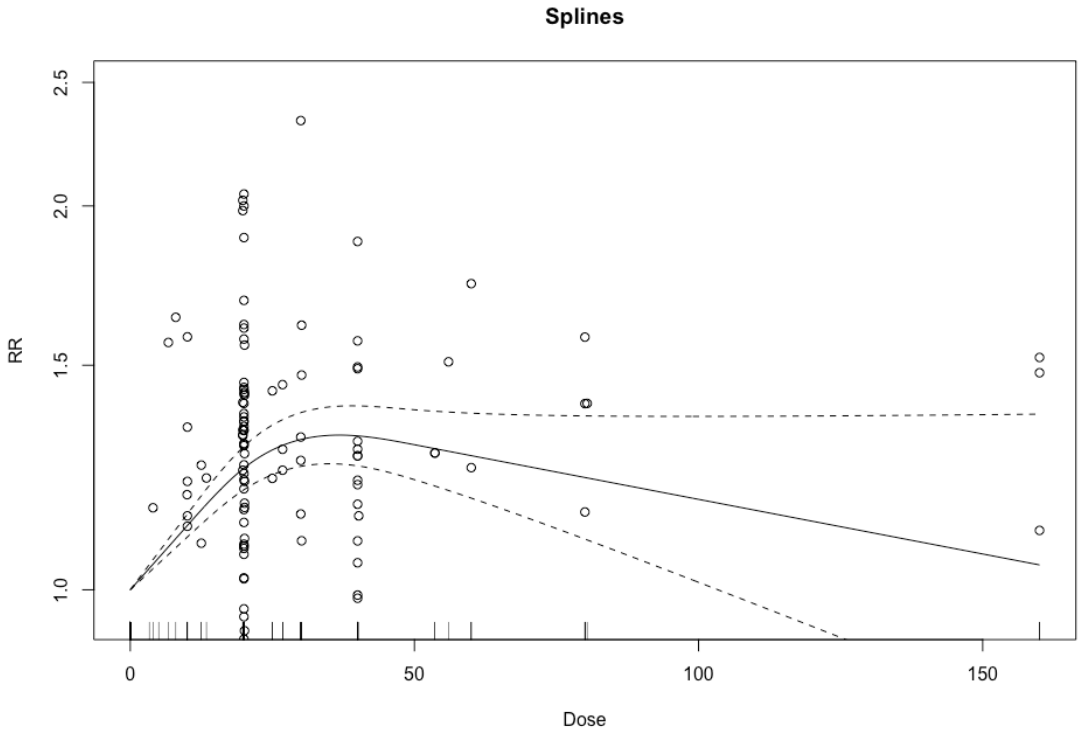
```
knots = c(10, 20, 50)
doseresRR = dosresmeta(logRR ~ rcs(dose, knots), Study_No,
                       data = AntidepressantsDOSE,
                       cases = Responders, n = No_randomised,
                       type = type, se = selogRR, proc = "1stage")
summary(doseresRR)
```

```
## Call:  dosresmeta(formula = logRR ~ rcs(dose, knots), id = Study_No,
##     type = type, cases = Responders, n = No_randomised, data = Antidepress
antsDOSE,
##     se = selogRR, proc = "1stage")
##
## One-stage random-effects meta-analysis
## Estimation method: REML
## Covariance approximation: Greenland & Longnecker
##
## Chi2 model: X2 = 122.0041 (df = 2), p-value = 0.0000
##
## Fixed-effects coefficients
##                          Estimate  Std. Error        z  Pr(>|z|)  95%ci.lb
## rcs(dose, knots)dose      0.0115      0.0011  10.9792    0.0000    0.0095
## rcs(dose, knots)dose'    -0.0180      0.0023  -7.9541    0.0000   -0.0225
##                          95%ci.ub
## rcs(dose, knots)dose      0.0136  ***
## rcs(dose, knots)dose'    -0.0136  ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Between-study random-effects (co)variance components
##                          Std. Dev                  Corr
## rcs(dose, knots)dose      0.0038  rcs(dose, knots)dose
## rcs(dose, knots)dose'     0.0029                    -1
##
## 71 studies, 119 values, 2 fixed and 3 random-effects parameters
##   logLik       AIC       BIC
##  18.9244  -27.8489  -14.0380
```

Now, let us plot the results.

```
newdata = data.frame(dose = seq(0, 160))
xref = min(AntidepressantsDOSE$dose)
with(predict(doseresRR, newdata, xref, exp = TRUE), {
     plot(get("rcs(dose, knots)dose"), pred, log = "y", type = "l",
          xlim = c(0, 160), ylim = c(0.95, 2.5),
```

```
          xlab = "Dose", ylab = "RR", main = c("Splines", text))
     matlines(get("rcs(dose, knots)dose"), cbind(ci.ub, ci.lb),
              col = 1, lty = "dashed")
     })
with(AntidepressantsDOSE, points(dose[logRR != 0], exp(logRR[logRR != 0])))
with(AntidepressantsDOSE, rug(dose, quiet = TRUE))
```



Now, change the knots; put more knots at different places and plot the results to see if the shape changes a lot. Note the AIC and select the set of knots that provides the best AIC.

Run dose-dropout due to adverse events analyses

Now modify the codes provided to estimate the dose-dropout due to adverse events associations. The variables logRRdrop and logRRdropAE contain the respective outcomes information. Use knots at 10, 20 and 50 mg. Note also that dosresmeta does not accept studies with missing values. Hence you have to exclude any studies not providing information on dropout. This is denoted in columns excdropAE.

After obtaining the plot, interpret them in conjunction with the dose-response plot to estimate the optimal dose for antidepressants.

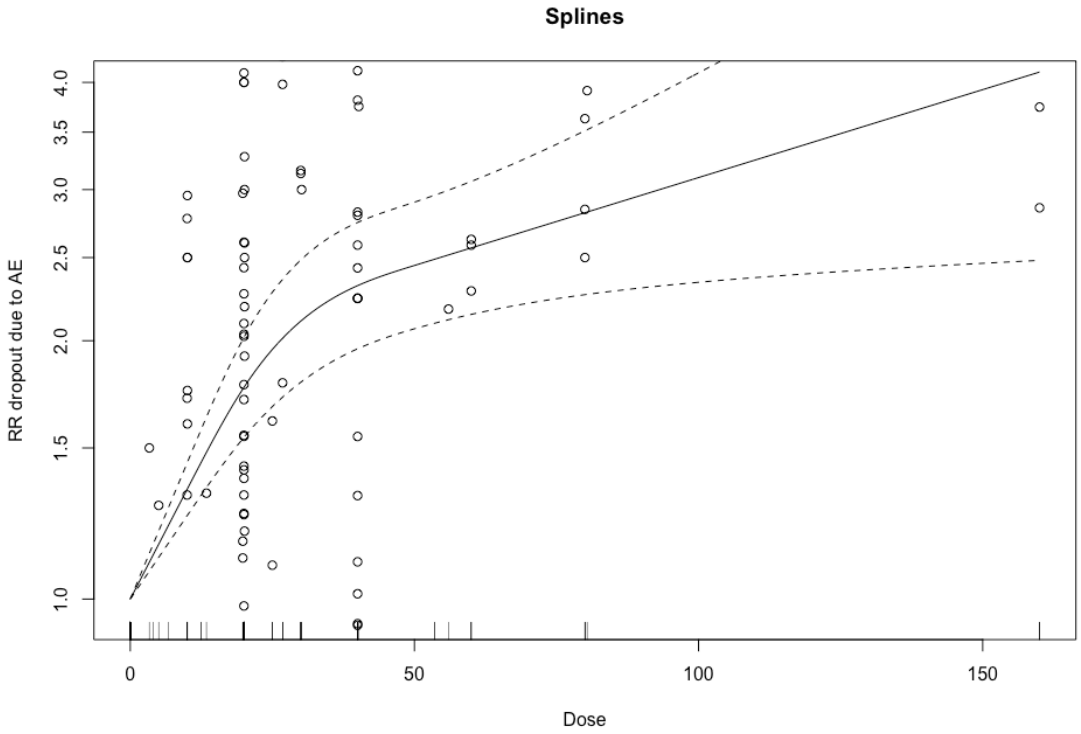
Here, we run the analysis for dose-dropout due to adverse events.

```
knots = c(10, 20, 50)
AntidepressantsDOSE1 = subset(AntidepressantsDOSE, excdropAE == FALSE)
```

```r
doseresRRAE = dosresmeta(logRRdropAE ~ rcs(dose, knots), Study_No,
                         data = AntidepressantsDOSE1,
                         cases = Dropouts_sideeffects, n = No_randomised,
                         type = type, se = selogRRdropAE, proc = "1stage")
summary(doseresRRAE)
```

```
## Call:  dosresmeta(formula = logRRdropAE ~ rcs(dose, knots), id = Study_No,
##     type = type, cases = Dropouts_sideeffects, n = No_randomised,
##     data = AntidepressantsDOSE1, se = selogRRdropAE, proc = "1stage")
##
## One-stage random-effects meta-analysis
## Estimation method: REML
## Covariance approximation: Greenland & Longnecker
##
## Chi2 model: X2 = 108.4251 (df = 2), p-value = 0.0000
##
## Fixed-effects coefficients
##                         Estimate  Std. Error        z  Pr(>|z|)  95%ci.lb
## rcs(dose, knots)dose     0.0294      0.0036   8.1510    0.0000    0.0224
## rcs(dose, knots)dose'   -0.0330      0.0066  -4.9965    0.0000   -0.0459
##                         95%ci.ub
## rcs(dose, knots)dose     0.0365  ***
## rcs(dose, knots)dose'   -0.0200  ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Between-study random-effects (co)variance components
##                         Std. Dev                  Corr
## rcs(dose, knots)dose     0.0090  rcs(dose, knots)dose
## rcs(dose, knots)dose'    0.0168                    -1
##
## 58 studies, 102 values, 2 fixed and 3 random-effects parameters
##   logLik       AIC       BIC
## -90.0737  190.1474  203.1733
```

```r
xref1 = min(AntidepressantsDOSE1$dose)
with(predict(doseresRRAE, newdata, xref1, exp = TRUE), {
     plot(get("rcs(dose, knots)dose"), pred, log = "y", type = "l",
          xlim = c(0, 160), ylim = c(c(0.95, 4)),
          xlab = "Dose", ylab="RR dropout due to AE", main=c("Splines", text)
)
     matlines(get("rcs(dose, knots)dose"), cbind(ci.ub, ci.lb),
              col = 1, lty = "dashed")
     })
with(AntidepressantsDOSE1,
     points(dose[logRRdropAE != 0], exp(logRRdropAE[logRRdropAE != 0])))
with(AntidepressantsDOSE1, rug(dose, quiet = TRUE))
```


Splines
RR dropout due to AE
1.0
1.5
2.0
2.5
3.0
3.5
4.0
0
50
100
150
Dose