Meta-Analysis with R
Meta-Analysis of Other Outcomes

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Subgroup Analysis

- From time to time we need to work with subgroups of studies in a meta-analysis. The various “R” commands for meta-analysis in the “R” package meta support a “byvar” option, i.e. conduct a subgroup analysis by a variable.

```
> # 1. Read in the data:
> data3 <- read.csv("dataset03.csv")
> # 2. As usual, to view an object, type its name:
> data3
        author year  Ne   Me   Se  Nc   Mc   Sc    duration
1   Bontognali 1991  30 0.70 3.76  30 1.27 4.58 <= 3 months
2  Castiglioni 1986 311 0.10 0.21 302 0.20 0.29 <= 3 months
3    Cremonini 1986  21 0.25 0.23  20 0.71 0.29 <= 3 months
4       Grassi 1994  42 0.16 0.29  41 0.45 0.43 <= 3 months
5      Jackson 1984  61 0.11 0.00  60 0.13 0.00 <= 3 months
6      Allegra 1996 223 0.07 0.11 218 0.11 0.14  > 3 months
7     Babolini 1980 254 0.13 0.18 241 0.33 0.27  > 3 months
8        Boman 1983  98 0.20 0.27 105 0.32 0.30  > 3 months
9       Borgia 1981  10 0.05 0.08   9 0.15 0.17  > 3 months
10    Decramer 2005 256 0.10 0.11 267 0.11 0.16  > 3 months
11      Grassi 1976  35 0.14 0.15  34 0.27 0.21  > 3 months
12    Grillage 1985  54 0.10 0.00  55 0.12 0.00  > 3 months
13      Hansen 1994  59 0.11 0.15  70 0.16 0.19  > 3 months
14     Malerba 2004 115 0.06 0.08 119 0.07 0.08  > 3 months
15     McGavin 1985  72 0.42 0.34  76 0.52 0.35  > 3 months
16     Meister 1986  90 0.15 0.15  91 0.20 0.19  > 3 months
17     Meister 1999 122 0.06 0.15 124 0.10 0.15  > 3 months
18     Moretti 2004  63 0.12 0.14  61 0.17 0.17  > 3 months
19       Nowak 1999 147 0.03 0.06 148 0.06 0.12  > 3 months
20    Olivieri 1987 110 0.18 0.31 104 0.33 0.41  > 3 months
21        Parr 1987 243 0.18 0.21 210 0.21 0.21  > 3 months
22        Pela 1999  83 0.17 0.18  80 0.29 0.32  > 3 months
23   Rasmussen 1988  44 0.13 0.21  47 0.14 0.19  > 3 months
```

Subgroup Analysis

- The result of the meta-analysis is given by

```
> mc3 <- metacont(Ne, Me, Se, Nc, Mc, Sc, data=data3,
+                  studlab=paste(author, year))
Warning message:
```

```
> print(summary(mc3), digits=2)
Number of studies combined: k=21

                         MD         95%-CI       z  p-value
Fixed effect model    -0.05 [-0.05; -0.04] -10.06 < 0.0001
Random effects model -0.08 [-0.11; -0.05]  -5.82 < 0.0001

Quantifying heterogeneity:
tau^2 = 0.0027; H = 2.63 [2.19; 3.15]; I^2 = 85.5% [79.1%; 89.9%]

Test of heterogeneity:
      Q d.f.  p-value
 138.08   20 < 0.0001
Details on meta-analytical method:
- Inverse variance method
- DerSimonian-Laird estimator for tau^2
```

- The results indicate significant between-study heterogeneity ($Q = 138, p < 0.0001$) with $I^2 = 85.5\%$. Here subgroup information is available for study duration: studies whose duration was greater or less than three months.

Subgroup Analysis

- A subgroup analysis can be done by using argument "byvar" in the original call of the "metacont" function:

```
> mc3s <- metacont(Ne, Me, Se, Nc, Mc, Sc, data=data3,
+                  studlab=paste(author, year),
+                  byvar=duration, print.byvar=FALSE)
```

- Another more convenient way is to update the original meta-analysis by using the "update.meta" function from "R" package "meta".

```
> mc3s <- update(mc3, byvar=duration, print.byvar=FALSE)
```

Subgroup Analysis

```
> print(summary(mc3s), digits=2)
Number of studies combined: k=21

                        MD           95%-CI      z  p-value
Fixed effect model   -0.05 [-0.05; -0.04] -10.06 < 0.0001
Random effects model -0.08 [-0.11; -0.05]  -5.82 < 0.0001

Quantifying heterogeneity:
tau^2 = 0.0027; H = 2.63 [2.19; 3.15]; I^2 = 85.5% [79.1%; 89.9%]

Test of heterogeneity:
      Q d.f.  p-value
 138.08   20 < 0.0001

Results for subgroups (fixed effect model):
              k    MD         95%-CI     Q   tau^2   I^2
<= 3 months   4 -0.13 [-0.17; -0.09] 22.43   0.035 86.6%
> 3 months   17 -0.04 [-0.05; -0.03] 94.92   0.002 83.1%

Test for subgroup differences (fixed effect model):
                    Q d.f.  p-value
Between groups  20.73    1 < 0.0001
Within groups  117.35   19 < 0.0001

Results for subgroups (random effects model):
              k    MD         95%-CI     Q   tau^2   I^2
<= 3 months   4 -0.28 [-0.50; -0.05] 22.43   0.035 86.6%
> 3 months   17 -0.06 [-0.09; -0.04] 94.92   0.002 83.1%

Test for subgroup differences (random effects model):
                    Q d.f.  p-value
Between groups   3.41    1   0.0647

Details on meta-analytical method:
```

Subgroup Analysis

- The results for the fixed effect model show that between-group heterogeneity is highly statistically significant ($Q = 20.73$ on 1 degrees of freedom) as well as within-group heterogeneity ($Q = 117.35$, 19 degrees of freedom).
- Further, the fixed effect estimates (-0.13, short duration -0.04, long duration) are not that different. While short duration studies seem to have far fewer patients, the effect appears similar; study duration does not appear to be the source of the high degree of heterogeneity in these data.
- This observation is supported by the results for the random effects model (between-study heterogeneity: $Q = 3.41$, 1 degrees of freedom).

Meta-Analysis with Survival Outcomes

- A meta-analysis with survival time outcomes is typically based on the hazard ratio as measure of treatment effect.
- Accordingly, the logarithm of the hazard ratio and its standard error are the basic quantities utilised in meta-analysis.
- The generic inverse variance method can be used straightforward with log hazard ratio $\hat{\theta}_k$ and its standard error $S.E.(\hat{\theta}_k)$, for study k, $k = 1, \cdots, K$.

Meta-Analysis with Survival Outcomes

- Using these quantities, all methods described before can be used for meta-analysis. In the following example we consider the most basic case, i.e. fixed effect and random effects meta-analysis using the DerSimonian-Laird method to estimate the between-study variance $\hat{\tau}^2$.

```
> # 1. Read in the data
> data4 <- read.csv("dataset04.csv")
> # 2. Print data
> data4
       author year  Ne  Nc   logHR selogHR
1 FCG on CLL 1996  53  52 -0.5920  0.3450
2  Leporrier 2001 341 597 -0.0791  0.0787
3        Rai 2000 195 200 -0.2370  0.1440
4      Robak 2000 133 117  0.1630  0.3120
```

Meta-Analysis with Survival Outcomes

- Columns “logHR” and “selogHR” correspond to the log hazard ratio and its standard error.

```
> mg1 <- metagen(logHR, selogHR,
+                 studlab=paste(author, year), data=data4,
+                 sm="HR")
```

```
> print(mg1, digits=2)
                    HR        95%-CI %W(fixed) %W(random)
FCG on CLL 1996 0.55 [0.28; 1.09]      3.68        5.85
Leporrier 2001  0.92 [0.79; 1.08]     70.70       59.76
Rai 2000        0.79 [0.59; 1.05]     21.12       27.32
Robak 2000      1.18 [0.64; 2.17]      4.50        7.08

Number of studies combined: k=4

                        HR        95%-CI     z  p-value
Fixed effect model    0.89 [0.78; 1.01] -1.82   0.0688
Random effects model 0.87 [0.74; 1.03] -1.58   0.1142

Quantifying heterogeneity:
tau^2 = 0.0061; H = 1.1 [1; 2.81]; I^2 = 17.2% [0%; 87.3%]
```

Meta-Analysis with Survival Outcomes

```
Test of heterogeneity:
    Q d.f.  p-value
 3.62    3   0.3049

Details on meta-analytical method:
- Inverse variance method
- DerSimonian-Laird estimator for tau^2
```