MEDCIDS
DEPARTAMENTO DE MEDICINA DA COMUNIDADE, INFORMAÇÃO E DECISÃO EM SAÚDE

U.PORTO

CINTESIS
Health. Research.

HEADS
PhD PROGRAMME IN HEALTH DATA SCIENCE

DECIDE

Introduction to Health Interventions, Policy and Services

Coordinator:

Luís Filipe Azevedo

MEDCIDS
DEPARTAMENTO DE MEDICINA DA COMUNIDADE, INFORMAÇÃO E DECISÃO EM SAÚDE

U.PORTO

CINTESIS
Health. Research.

HEADS
PhD PROGRAMME IN HEALTH DATA SCIENCE

DECIDE

Introduction to Health Interventions, Policy and Services

Methods in Evidence Synthesis – Part III

Authors

Luís Filipe Azevedo

Bernardo Sousa Pinto

Summary

- Meta-analysis for binary and continuous outcomes using R:
  - metafor package:
    - Calculating effect sizes
    - Performing meta-analysis
    - Interpreting and plotting results
    - Exploring sources of heterogeneity
  - meta package:
    - Calculating effect sizes
    - Performing meta-analysis
    - Interpreting and plotting results
    - Exploring sources of heterogeneity

Meta-analysis using metafor package

Meta-analysis using metafor package

metafor package

We will use metafor as the main package to perform meta-analysis for binary and continuous outcomes

```
> install.packages("metafor")
  library(metafor)
```

Meta-analysis using metafor package

Meta-analysis for binary outcomes: BCG dataset

Includes 13 primary studies assessing the effectiveness of the BCG vaccine against tuberculosis

Two groups (vaccinated *versus* non-vaccinated) being compared

Binary outcome (tuberculosis diagnosis - positive *vs* negative)

	Tuberculosis +	Tuberculosis -
Vaccinated group	tpos	tneg
Control group	cpos	cneg

Meta-analysis using metafor package

Meta-analysis for binary outcomes: BCG dataset

	Tuberculosis +	Tuberculosis -
Vaccinated group	tpos	tneg
Control group	cpos	cneg

Effect measures that could be used to assess the effectiveness of BCG vaccine: risk ratio, odds ratio, risk difference…

Meta-analysis using metafor package

Meta-analysis for binary outcomes: Effect size calculation

We will perform meta-analysis to estimate the pooled risk ratio

As we only have raw data, we firstly need to calculate the effect size and sampling variance for each primary study.

For that, we will use the `escalc()` function

Let's start to check its arguments!

```
> ?escalc
```

Meta-analysis using metafor package

```
escalc(measure, formula, ai, bi, ci, di, n1i, n2i, x1i, x2i, t1i, t2i,
       m1i, m2i, sd1i, sd2i, xi, mi, ri, ti, sdi, r2i, ni, yi, vi, sei,
       data, slab, subset,
       add=1/2, to="only0", drop00=FALSE, vtype="LS",
       var.names=c("yi","vi"), add.measure=FALSE,
       append=TRUE, replace=TRUE, digits=4, ...)
```

The options for the `measure` argument are then:

- `"RR"` for the *log risk ratio*.
- `"OR"` for the *log odds ratio*.
- `"RD"` for the *risk difference*.
- `"AS"` for the *arcsine square root transformed risk difference* (Rücker et al., 2009).
- `"PETO"` for the *log odds ratio* estimated with Peto's method (Yusuf et al., 1985).

Measures for Dichotomous Variables

In various fields (such as the health and medical sciences), the response or outcome variable measured is often dichotomous (binary), so that the data from a study comparing two different groups can be expressed in terms of a *2x2* table, such as:

	outcome 1	outcome 2	total
group 1	ai	bi	n1i
group 2	ci	di	n2i

where `ai`, `bi`, `ci`, and `di` denote the cell frequencies (i.e., the number of people falling into a particular category) and `n1i` and `n2i` the row totals (i.e., the group sizes).

	Tuberculosis +	Tuberculosis -
Vaccinated group	tpos	tneg
Control group	cpos	cneg

Meta-analysis using metafor package

Meta-analysis for binary outcomes: Effect size calculation

```
# Computation of the effect size (log risk ratio) and of the
corresponding sampling variance for each primary study
> bcg <- escalc(measure="RR", ai=tpos, bi=tneg, ci=cpos,
      di=cneg, data=bcg)
```

The bcg dataset now contains two more variables:

- yi – computed effect sizes
- vi – computed sampling variances

Please note that in this dataset we have no group with zero events. Otherwise, we would have to include additional arguments…

Meta-analysis using metafor package

Effect size calculation

The existence of cells with zero counts is particularly troublesome:

	Event	No event
Experimental	0	b
Control	c	d

$$RR = \frac{\frac{0}{0+b}}{\frac{c}{c+d}} = 0 \quad \ln(0) = -\infty \qquad SE_{lnRR} = \sqrt{\frac{b}{0} + \frac{d}{c(c+d)}}$$

$$OR = \frac{0 \times d}{b \times c} = 0 \quad \ln(0) = -\infty \qquad SE_{lnOR} = \sqrt{\frac{1}{0} + \frac{1}{b} + \frac{1}{c} + \frac{1}{d}}$$

To circumvent this issue, it is possible to add a small increment – known as continuity correction – so that there are no cells with zero counts left.

Meta-analysis using metafor package

Effect size calculation

In the `escalc()` function, the `add=` and `to=` arguments are used to define continuity corrections:

- `add=` indicates the amount to add to zero cells. The default value is 0.5
- `to=` indicates to which cells the continuity correction is to be added:
  - `"only0"` : Default option. Continuity correction is only added to cells with zero counts
  - `"all"` : Continuity correction is added to all cells
  - `"if0all"` : Continuity correction is added to all cells if there are any with zero counts
  - `"none"` : Continuity correction is not added

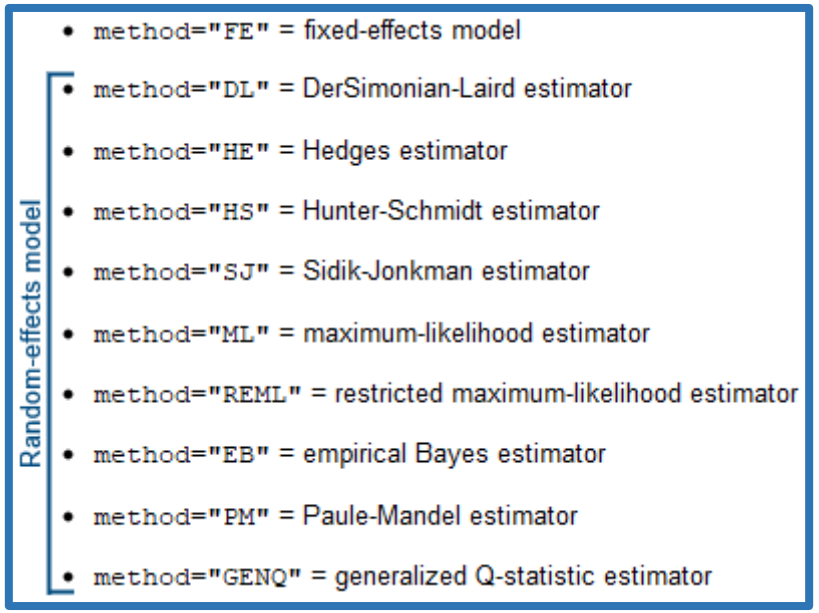
Meta-analysis using metafor package

Performing meta-analysis

To perform meta-analysis, we apply `rma` function.

We only need to define the following arguments:

- data: Dataset
- yi: Effect size variable
- vi: Variance variable
- slab: Primary studies identification
- method: Defines the model and, in case of a random-effects model, the method for estimating heterogeneity



Meta-analysis using metafor package

Meta-analysis for binary outcomes: Meta-analysis

```
# Meta-analysis following a random-effects model with the
restricted maximum-likelihood estimator method for the amount of
heterogeneity

> ma01 <- rma(yi=yi, vi=vi, data=bcg, slab=paste(author, year,
sep=", "), method="REML")
```

```
# In fact, we could have done it all in just one step!

> ma01 <- rma(measure="RR", ai=tpos, bi=tneg, ci=cpos, di=cneg, data=bcg,
slab=paste(author, year, sep=", "), method="REML")
```

Meta-analysis using metafor package

```
> ma01

Random-Effects Model (k = 13; tau^2 estimator: REML)

  logLik  deviance       AIC       BIC      AICc
-12.2024   24.4047   28.4047   29.3746   29.7381

tau^2 (estimated amount of total heterogeneity): 0.3132 (SE = 0.1664)
tau (square root of estimated tau^2 value):      0.5597
I^2 (total heterogeneity / total variability):   92.22%
H^2 (total variability / sampling variability):  12.86

Test for Heterogeneity:
Q(df = 12) = 152.2330, p-val < .0001

Model Results:

estimate      se     zval    pval    ci.lb    ci.ub
 -0.7145  0.1798  -3.9744  <.0001  -1.0669  -0.3622  ***
```

Meta-analysis using metafor package

```
> ma01

Random-Effects Model (k = 13; tau^2 estimator: REML)

  logLik  deviance       AIC       BIC      AICc
-12.2024   24.4047   28.4047   29.3746   29.7381

tau^2 (estimated amount of total heterogeneity): 0.3132 (SE = 0.1664)
tau (square root of estimated tau^2 value):      0.5597
I^2 (total heterogeneity / total variability):   92.22%
H^2 (total variability / sampling variability):  12.86

Test for Heterogeneity:
Q(df = 12) = 152.2330, p-val < .0001

Model Results:

estimate      se     zval     pval    ci.lb    ci.ub
 -0.7145  0.1798  -3.9744  <.0001  -1.0669  -0.3622  ***
```

k = 13 → Number of primary studies

Estimates for the log(risk ratio) and for the corresponding lower and upper bounds of the confidence interval. To convert these values back into the natural scale, the exp() function must be applied.

p-value

Meta-analysis using metafor package

Meta-analysis for binary outcomes: Results interpretation

```
# For obtaining the pooled estimate and the respective
confidence interval bounds transformed into the natural scale:

> exp(c(ma01$beta, ma01$ci.lb, ma01$ci.ub))
[1] 0.4894209 0.3440743 0.6961661
```

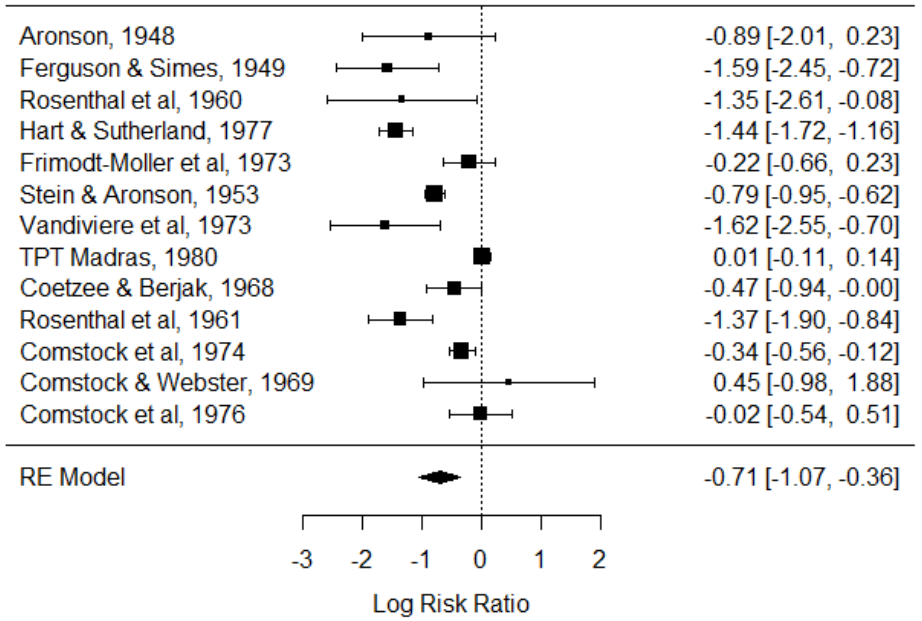
We observed that the BCG associates with decreased risk of tuberculosis (RR=0.5; 95%CI=0.3-0.7; p<0.001)

Meta-analysis using metafor package

Meta-analysis for binary outcomes: Forest plot

The `forest()` function creates a forest plot. The only mandatory argument is the meta-analysis object.

```
> forest(ma01)
```



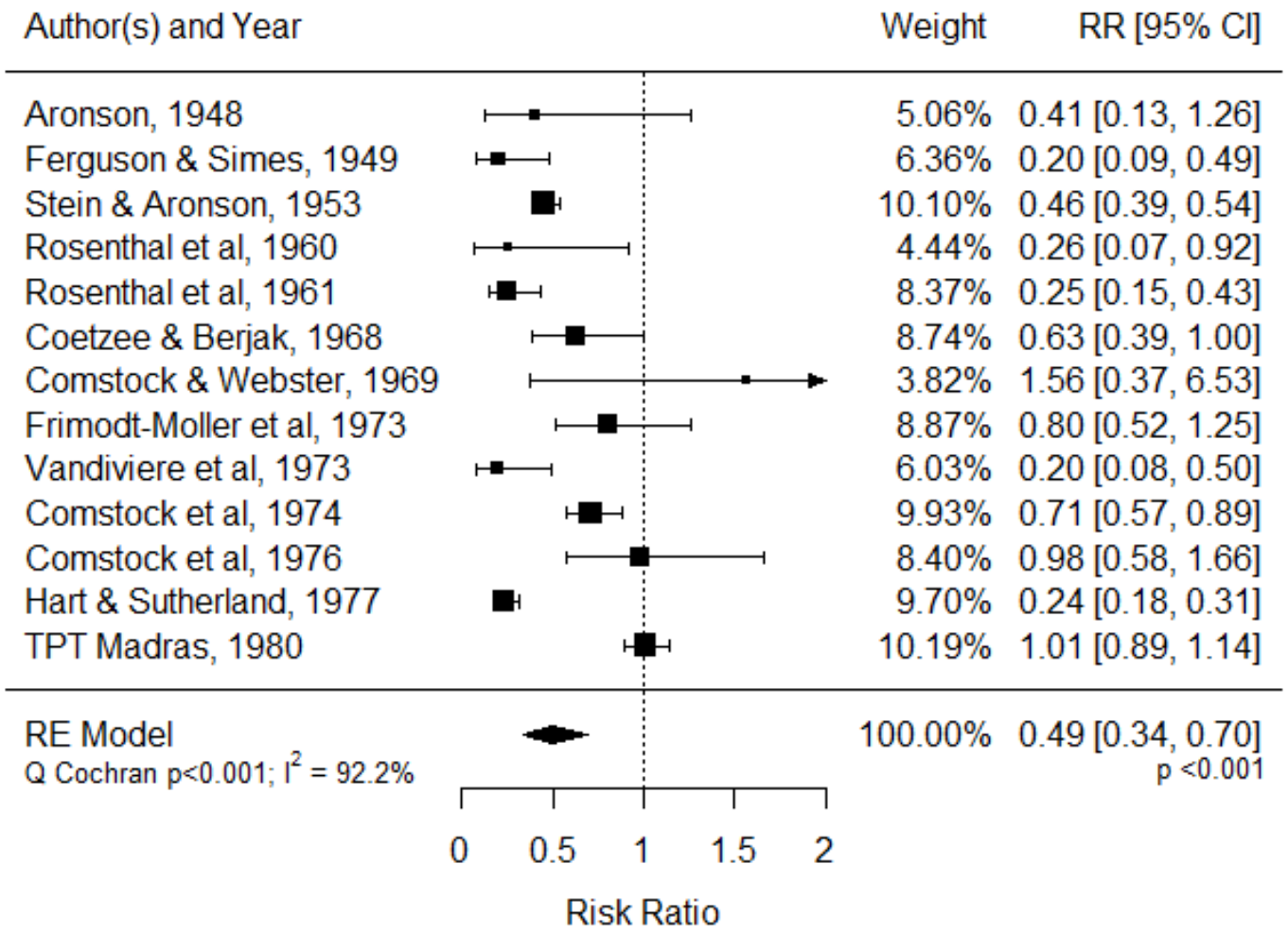
What can be done to improve this plot?

Meta-analysis using metafor package

Meta-analysis for binary outcomes: Forest plot

```
# "alim" corresponds to the limit of the xx axis of the forest plot;
"xlim" concerns the width of the plot; "at" locates the xx axis marks;
"refline" locates the reference line.
> forest.rma(ma01, transf=exp, showweights=TRUE, alim =c(0,2), xlim=c(-
2.5,4.5), at=c(0,0.5,1,1.5,2), order = order(bcg$year), refline=1)
# To add a top legend
text(-2.5,15, "Author(s) and Year",  pos=4)
text(3,15, "Weight", pos=2)
text(4.5,15, "RR [95% CI]", pos=2)
# To add text for the effect size p-value and for heterogeneity
text(3.7, -1.85, pos=4, cex=0.8, bquote(paste("p <0.001")))
text(-2.5, -1.85, pos=4, cex=0.8, bquote(paste("Q Cochran p<0.001", ";
", I^2, " = ", .(formatC(ma01$I2, digits=1, format="f")), "%")))
```

Meta-analysis using metafor package

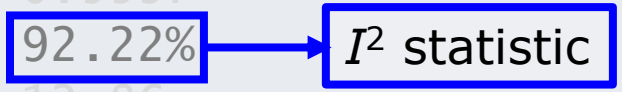


forestplot package can be used to further personalize the presentation of forest plots – you can find an online script guiding its use

Meta-analysis using metafor package

Meta-analysis for binary outcomes: Heterogeneity

```
> ma01

Random-Effects Model (k = 13; tau^2 estimator: REML)

  logLik  deviance       AIC       BIC      AICc
-12.2024   24.4047   28.4047   29.3746   29.7381

tau^2 (estimated amount of total heterogeneity): 0.3132 (SE = 0.1664)
tau (square root of estimated tau^2 value):      0.5597
I^2 (total heterogeneity / total variability):   92.22%
H^2 (total variability / sampling variability):  12.86

Test for Heterogeneity:
Q(df = 12) = 152.2330, p-val < .0001
```



Meta-analysis using metafor package

Meta-analysis for binary outcomes: Sensitivity analysis

Leave-one-out sensitivity analysis is a special form of sensitivity analysis consisting in removing each study at a time. The `leave1out()` function allows for such type of sensitivity analysis.

```
#The leave1out function can be applied to the meta-analysis model:

> leave1out(ma01)

                  estimate     se    zval   pval   ci.lb   ci.ub       Q      Qp   tau2      I2      H2
Aronson            -0.7071 0.1900 -3.7223 0.0002 -1.0794 -0.3348 151.5826 0.0000 0.3362 93.2259 14.7622
Ferguson & Simes   -0.6540 0.1807 -3.6195 0.0003 -1.0082 -0.2999 145.3176 0.0000 0.2926 92.2540 12.9098
Rosenthal et al.1  -0.6856 0.1857 -3.6916 0.0002 -1.0495 -0.3216 150.1970 0.0000 0.3207 92.9354 14.1551
```

Each output line corresponds to the results obtained when the respective study was not included in the meta-analysis

Meta-analysis using metafor package

Meta-analysis for binary outcomes: Meta-regression

To perform meta-regression, we need to introduce covariates after the effect size and the character ~

```
# Univariable meta-regressions with different covariates
(latitude, year and allocation):

> mreg01_lat <- rma(yi=yi~ablat, vi=vi, data=bcg, method="REML")

> mreg01_year <- rma(yi=yi~year, vi=vi, data=bcg, method="REML")

> mreg01_alloc <- rma(yi=yi~alloc, vi=vi, data=bcg, method="REML")
```

Meta-analysis using metafor package

```
# Results of the univariable meta-regression analysis with the latitude as covariate:

> mreg01_lat

Mixed-Effects Model (k = 13; tau^2 estimator: REML)

tau^2 (estimated amount of residual heterogeneity):     0.0764 (SE = 0.0591)
tau (square root of estimated tau^2 value):             0.2763
I^2 (residual heterogeneity / unaccounted variability): 68.39%
H^2 (unaccounted variability / sampling variability):   3.16
R^2 (amount of heterogeneity accounted for):            75.62%

Test for Residual Heterogeneity:
QE(df = 11) = 30.7331, p-val = 0.0012

Test of Moderators (coefficient(s) 2):
QM(df = 1) = 16.3571, p-val < .0001

Model Results:

         estimate      se     zval    pval    ci.lb    ci.ub
intrcpt    0.2515  0.2491   1.0095  0.3127  -0.2368   0.7397
ablat     -0.0291  0.0072  -4.0444  <.0001  -0.0432  -0.0150  ***
```

Meta-analysis using metafor package

```
# Results of the univariable meta-regression analysis with the latitude as covariate:

> mreg01_lat

Mixed-Effects Model (k = 13; tau^2 estimator: REML)

tau^2 (estimated amount of residual heterogeneity):     0.0764 (SE = 0.0591)
tau (square root of estimated tau^2 value):             0.2763
I^2 (residual heterogeneity / unaccounted variability): 68.39%
H^2 (unaccounted variability / sampling variability):   3.16
R^2 (amount of heterogeneity accounted for):            75.62%

Test for Residual Heterogeneity:
QE(df = 11) = 30.7332, p-val = 0.0012

Test of Moderators (coefficient(s) 2):
QM(df = 1) = 16.3571, p-val < .0001

Model Results:

         estimate      se     zval    pval    ci.lb    ci.ub
intrcpt   0.2515  0.2491   1.0095  0.3127  -0.2368   0.7397
ablat    -0.0291  0.0072  -4.0444  <.0001  -0.0432  -0.0150  ***
```

Exponentials of meta-regression coefficients can be interpreted as odds ratio (RR). In this case, RR=0.97 (95%CI=0.96-0.99)

Meta-analysis using metafor package

Meta-analysis for binary outcomes: Subgroup analysis

To perform subgroup analysis, we need to define the argument `subset=` in the `rma()` function

```
# Subgroup analysis in relation to the allocation type:

> ma01_random <- rma(yi=yi, vi=vi, data=bcg, method="REML",
slab=paste(author, year, sep=", "), subset=alloc=="random")

> ma01_alternate <- rma(yi=yi, vi=vi, data=bcg, method="REML",
slab=paste(author, year, sep=", "), subset=alloc=="alternate")

> ma01_system <- rma(yi=yi, vi=vi, data=bcg, method="REML",
slab=paste(author, year, sep=", "), subset=alloc=="systematic")
```

Meta-analysis using metafor package

```
# Results for the subgroup of primary studies with random allocation:

> ma01_random

Random-Effects Model (k = 7; tau^2 estimator: REML)

tau^2 (estimated amount of total heterogeneity): 0.3925 (SE = 0.3029)
tau (square root of estimated tau^2 value):      0.6265
I^2 (total heterogeneity / total variability):   89.93%
H^2 (total variability / sampling variability):  9.93

Test for Heterogeneity:
Q(df = 6) = 110.2133, p-val < .0001

Model Results:

estimate      se     zval    pval    ci.lb    ci.ub
 -0.9710  0.2760  -3.5186  0.0004  -1.5118  -0.4301  ***
```

Meta-analysis using metafor package

Meta-analysis for binary outcomes: Funnel plot

The possibility of publication bias can be assessed by means of the rank correlation test of Begg `ranktest()` and of funnel plot visual inspection.

```
> ranktest(ma01)

Rank Correlation Test for Funnel Plot Asymmetry

Kendall's tau = 0.0256, p = 0.9524
```

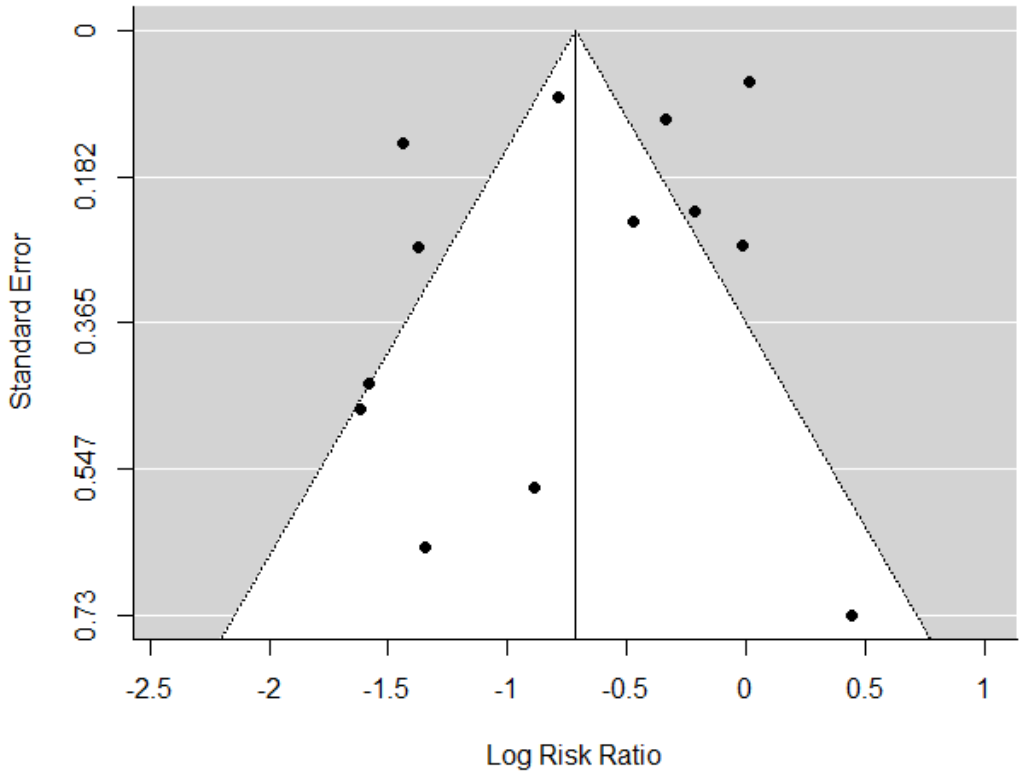
Meta-analysis using metafor package

```
# Obtention of the funnel plot
> funnel(ma01)

# Obtention of the funnel plot with trim-and-fill
> (ma01_tf <- trimfill(ma01))
  funnel(ma01_tf)

Estimated number of missing studies on the right side: 1 (SE = 2.4528)

Random-Effects Model (k = 14; tau^2 estimator: REML)

tau^2 (estimated amount of total heterogeneity): 0.3313 (SE = 0.1701)
tau (square root of estimated tau^2 value):      0.5756
I^2 (total heterogeneity / total variability):   92.14%
H^2 (total variability / sampling variability):  12.72

Test for Heterogeneity:
Q(df = 13) = 154.6750, p-val < .0001

Model Results:

estimate      se     zval    pval    ci.lb    ci.ub
 -0.6571  0.1785  -3.6805  0.0002  -1.0070  -0.3072  ***
```

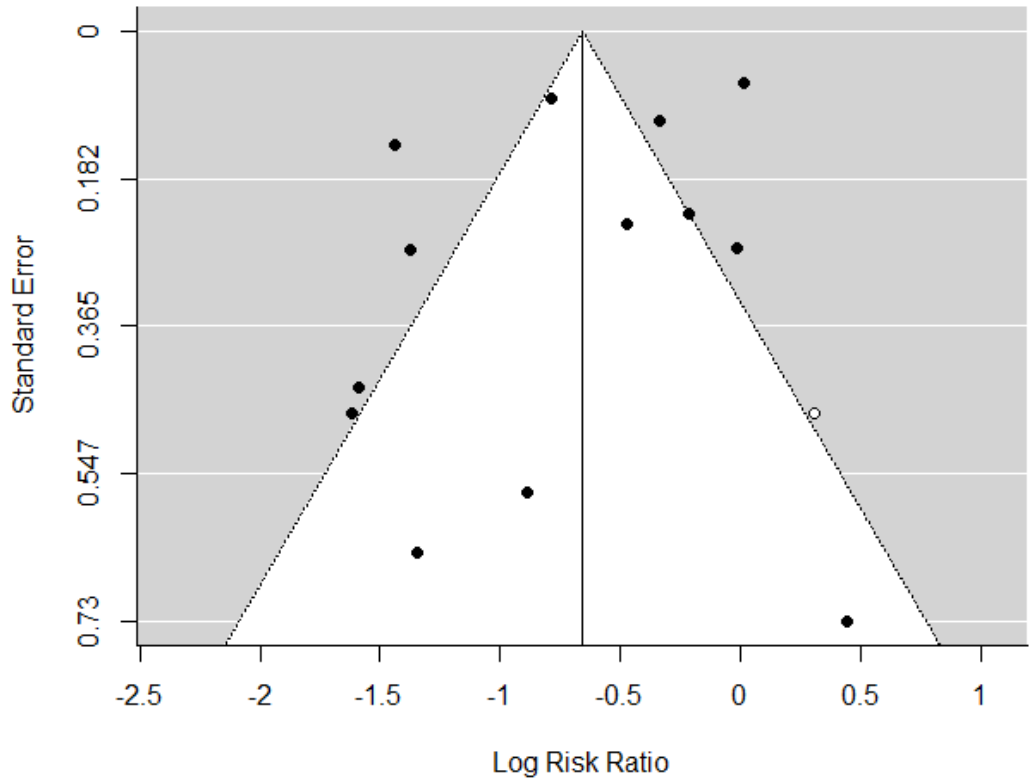
Meta-analysis using metafor package

Meta-analysis for binary outcomes: Funnel plot

"Standard" funnel plot



Funnel plot with trim-and-fill



Meta-analysis using metafor package

Meta-analysis for continuous outcomes: stroke dataset

Includes 9 primary studies comparing the length of stay between stroke patients receiving specialized care *versus* those receiving routine care

Two groups (specialized *versus* routine care) being compared

Continuous outcome: Length of stay (LOS)

Effect measures that could be used: mean difference, standardized mean difference…

Meta-analysis using metafor package

Meta-analysis for continuous outcomes: Effect size calculation

As we only have raw data, we firstly need to calculate the effect size and sampling variance for each primary study.

Once again, we will use the `escalc()` function

Let's check again its arguments!

```
> ?escalc
```

Meta-analysis using metafor package

```
escalc(measure, formula, ai, bi, ci, di, n1i, n2i, x1i, x2i, t1i, t2i,
       m1i, m2i, sd1i, sd2i, xi, mi, ri, ti, sdi, r2i, ni, yi, vi, sei,
       data, slab, subset,
       add=1/2, to="only0", drop00=FALSE, vtype="LS",
       var.names=c("yi","vi"), add.measure=FALSE,
       append=TRUE, replace=TRUE, digits=4, ...)
```

The options for the `measure` argument are then:

- `"MD"` for the *raw mean difference*.
- `"SMD"` for the *standardized mean difference*.
- `"SMDH"` for the *standardized mean difference* with heteroscedastic population variances in the two groups (Bonett, 2008, 2009).
- `"ROM"` for the *log transformed ratio of means* (Hedges et al., 1999; Lajeunesse, 2011).

Measures for Quantitative Variables

When the response or dependent variable assessed in the individual studies is measured on some quantitative scale, it is customary to report certain summary statistics, such as the mean and standard deviation of the scores. The data layout for a study comparing two groups with respect to such a variable is then of the form:

	mean	standard deviation	group size
group 1	m1i	sd1i	n1i
group 2	m2i	sd2i	n2i

	Mean LOS	Standard-deviation	Group size
Specialized care	los_spec	sd_spec	n_spec
Routine care	los_rout	sd_rout	n_rout

Meta-analysis using metafor package

Meta-analysis for continuous outcomes: Effect size calculation

```
# Computation of the effect size (mean difference) and of
the corresponding sampling variance for each primary study
> stroke <- escalc(measure="MD", n1i=n_spec, m1i=los_spec,
sd1i=sd_spec, n2i=n_rout, m2i=los_rout, sd2i=sd_rout,
data=stroke)
```

The stroke dataset now contains two more variables:

- yi – computed effect sizes
- vi – computed sampling variances

Meta-analysis using metafor package

Meta-analysis for continuous outcomes: Meta-analysis

```
# Meta-analysis following a random-effects model with the restricted maximum-likelihood estimator method for the amount of heterogeneity

> ma02 <- rma(yi=yi, vi=vi, data=stroke, slab=paste(study, year, sep=", "), method="REML")
```

```
# Once again, we could have done it all in just one step!

> ma02 <- rma(measure="MD", n1i=n_spec, m1i=los_spec, sd1i=sd_spec, n2i=n_rout, m2i=los_rout, sd2i=sd_rout, data=stroke, slab=paste(study, year, sep=", "), method="REML")
```

Meta-analysis using metafor package

```
> ma02

Random-Effects Model (k = 9; tau^2 estimator: REML)

tau^2 (estimated amount of total heterogeneity): 684.6462 (SE = 359.7541)
tau (square root of estimated tau^2 value):      26.1657
I^2 (total heterogeneity / total variability):   98.97%
H^2 (total variability / sampling variability):  97.21

Test for Heterogeneity:
Q(df = 8) = 238.9158, p-val < .0001

Model Results:

estimate      se     zval    pval     ci.lb   ci.ub
-15.1060  8.9466  -1.6885  0.0913  -32.6409  2.4289  .
```

Specialized care associates with a trend towards decreased LOS (pooled meta-analytic estimate: -15.1 days; 95%CI=-32.6;2.43; p=0.091). However, severe heterogeneity was observed (p<0.001; I^2=99.0%)

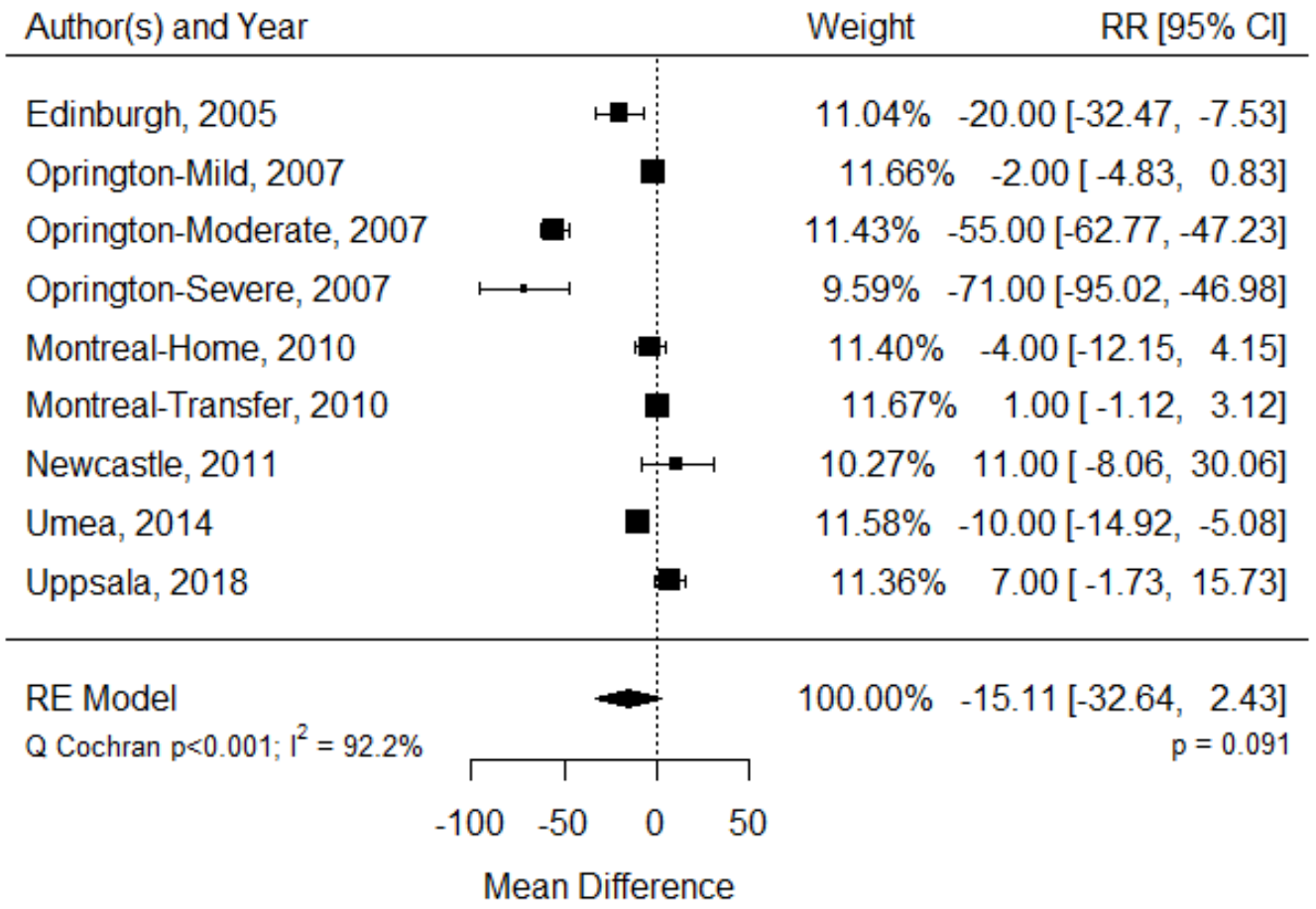
Meta-analysis using metafor package

Meta-analysis for continuous outcomes: Forest plot

```
# Forest plot presenting relative weights, p-value for the effect size and heterogeneity statistics.
> forest.rma(ma02, showweights=TRUE, order = order(stroke$year), xlim=c(-350,350))
text(-350,10.5, "Author(s) and Year",  pos=4)
text(150,10.5, "Weight", pos=2)
text(350,10.5, "RR [95% CI]", pos=2)
text(265, -1.85, pos=4, cex=0.8, bquote(paste("p = ", .(formatC(ma02$pval, digits=3, format="f")))))
text(-350, -1.8, pos=4, cex=0.8, bquote(paste("Q Cochran p<0.001", "; ", I^2, " = ", .(formatC(ma01$I2, digits=1, format="f")), "%")))
```

Meta-analysis using metafor package

Meta-analysis for continuous outcomes: Forest plot



Meta-analysis using meta package

Meta-analysis using meta package

Other packages: meta package

There are other packages to perform "classical" meta-analysis.

We will redo our analyses using meta package.

```
> install.packages("meta")
  library(meta)
```

You can also find an online script guiding the use of rmeta.

Meta-analysis using meta package

Meta-analysis for binary outcomes: Meta-analysis

Again, we will use bcg dataset to perform meta-analysis to estimate the pooled risk ratio

Given the raw data, meta-analysis of binary outcomes can be performed using the `metabin()` function

Let's start to check its arguments!

```
> ?metabin
```

Meta-analysis using meta package

```
metabin(event.e, n.e, event.c, n.c, studlab,
        data=NULL, subset=NULL, exclude=NULL,
        method=ifelse(tau.common, "Inverse", gs("method")),
        sm=
        ifelse(!is.na(charmatch(tolower(method), c("peto", "glmm"),
                                nomatch = NA)),
                      "OR", gs("smbin")),
        incr=gs("incr"), allincr=gs("allincr"),
        addincr=gs("addincr"), allstudies=gs("allstudies"),
        MH.exact=gs("MH.exact"), RR.cochrane=gs("RR.cochrane"),
        model.glmm = "UM.FS",
        level=gs("level"), level.comb=gs("level.comb"),
        comb.fixed=gs("comb.fixed"), comb.random=gs("comb.random"),
        hakn=gs("hakn"),
        method.tau=
        ifelse(!is.na(charmatch(tolower(method), "glmm", nomatch = NA)),
               "ML", gs("method.tau")),
        tau.preset=NULL, TE.tau=NULL,
        tau.common=gs("tau.common"),
        prediction=gs("prediction"), level.predict=gs("level.predict"),
        method.bias=ifelse(sm=="OR", "score", gs("method.bias")),
        backtransf=gs("backtransf"), pscale = 1,
        title=gs("title"), complab=gs("complab"), outslab="",
        label.e=gs("label.e"), label.c=gs("label.c"),
        label.left=gs("label.left"), label.right=gs("label.right"),
        byvar, bylab, print.byvar=gs("print.byvar"),
        byseparator = gs("byseparator"),
        print.CMH=gs("print.CMH"),
        keepdata=gs("keepdata"),
        warn=gs("warn"),
        control=NULL,
        ...)
```

	Tuberculosis +	Tuberculosis -	Total
Vaccinated group	tpos	tneg	tpos + tneg
Control group	cpos	cneg	cpos + cneg

Pooling method

Effect measure

Method to estimate tau – DerSimonian and Laird is the default method. REML and other methods rely on metafor package.

With meta package, fixed effects and random effects meta-analysis results are simultaneously presented

Meta-analysis using meta package

If there are cells with zero counts, the following function may be defined:

- `incr=` indicates the amount to add to zero cells. It can be defined as a numerical value or as `"TACC"` (treatment arm continuity correction - to correct for unbalanced sample sizes in the experimental *versus* control group). The default value is 0.5.

By default, continuity correction is added only to zero cells. This can be modified by setting as TRUE one of the following arguments:

- `allincr=` If TRUE, continuity correction is added to all cells if there are any zero counts.
- `addincr=` If TRUE, continuity correction is added to all cells.

Meta-analysis using meta package

Meta-analysis for binary outcomes: Meta-analysis

```
# Meta-analysis weighting by the inverse variance and with the
restricted maximum-likelihood estimator method for the amount
of heterogeneity. The prediction argument allows for obtention
of estimates of a hypothetical future study.

> ma04 <- metabin(data=bcg, event.e=tpos, n.e=tpos+tneg,
event.c=cpos, n.c=cpos+cneg, method="Inverse", sm="RR",
method.tau="REML", prediction=TRUE, studlab=paste(author,year))
```

Meta-analysis using meta package

```
> ma04
                              RR           95%-CI %W(fixed) %W(random)
Aronson 1948              0.4109 [0.1343; 1.2574]       0.5        5.1
Ferguson & Simes 1949     0.2049 [0.0863; 0.4864]       0.8        6.4
Rosenthal et al 1960      0.2597 [0.0734; 0.9186]       0.4        4.4
Hart & Sutherland 1977    0.2366 [0.1793; 0.3121]       8.2        9.7
Frimodt-Moller et al 1973 0.8045 [0.5163; 1.2536]       3.2        8.9
...

Number of studies combined: k = 13

                         RR           95%-CI      z  p-value
Fixed effect model   0.6503 [0.6007; 0.7040] -10.62 < 0.0001
Random effects model 0.4894 [0.3441; 0.6962]  -3.97 < 0.0001
Prediction interval         [0.1342; 1.7848]

Quantifying heterogeneity:
tau^2 = 0.3132; H = 3.56 [2.93; 4.34]; I^2 = 92.1% [88.3%; 94.7%]

Test of heterogeneity:
      Q d.f.  p-value
 152.23   12 < 0.0001

Details on meta-analytical method:
- Inverse variance method
- Restricted maximum-likelihood estimator for tau^2
```

Meta-analysis using meta package

metafor package

```
> ma04
                                RR           95%-CI %W(fixed) %W(random)
Aronson 1948                0.4109 [0.1343; 1.2574]       0.5        5.1
Ferguson & Simes 1949       0.2049 [0.0863; 0.4864]       0.8        6.4
Rosenthal et al 1960        0.2597 [0.0734; 0.9186]       0.4        4.4
Hart & Sutherland 1977      0.2366 [0.1793; 0.3121]       8.2        9.7
Frimodt-Moller et al 1973   0.8045 [0.5163; 1.2536]       3.3        8.0
...

Number of studies combined: k = 13

                         RR           95%-CI      z  p-value
Fixed effect model   0.6503 [0.6007; 0.7040] -10.62 < 0.0001
Random effects model 0.4894 [0.3441; 0.6962]  -3.97 < 0.0001
Prediction interval         [0.1342; 1.7848]

Quantifying heterogeneity:
tau^2 = 0.3132; H = 3.56 [2.93; 4.34]; I^2 = 92.1% [88.3%; 94.7%]

Test of heterogeneity:
     Q d.f.  p-value
 152.23   12 < 0.0001

Details on meta-analytical method:
- Inverse variance method
- Restricted maximum-likelihood estimator for tau^2
```

Estimates for the risk ratio and for the corresponding confidence interval and *p*-value

Estimates for the risk ratio of a future study

Estimates of the I^2 and of *p*-value for the Q Cochran test

Meta-analysis using meta package

Meta-analysis for binary outcomes: Forest plot

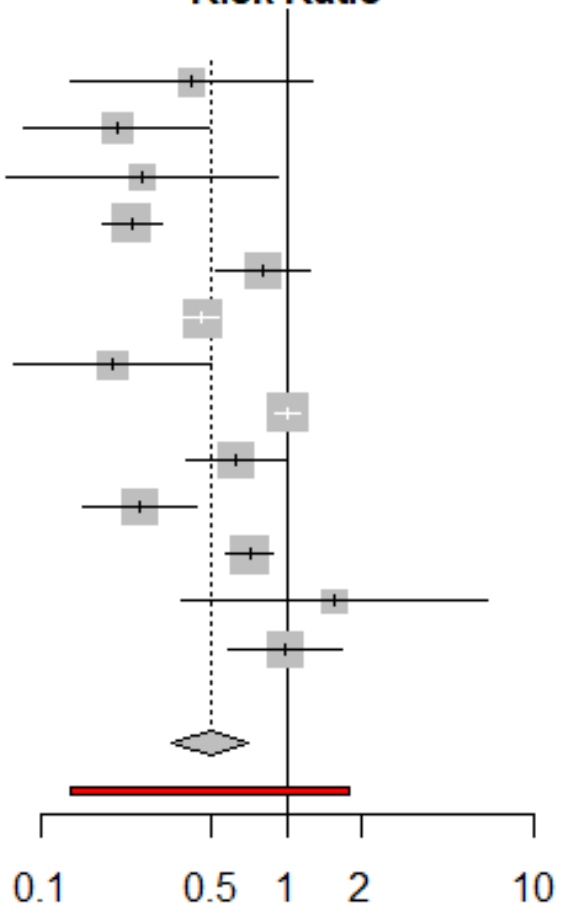
The function `forest()` creates a forest plot.

```
# The "common=FALSE" expression is used to hide fixed effects model
results. To hide random effects model results, we would use the
expression "random=FALSE". The "prediction" argument orders the
presentation of the predicted interval. The number of decimal places is
set by the "digits" argument.
> forest(ma04, common=FALSE, prediction = TRUE, digits = 1)
```

Meta-analysis using meta package

Study	Experimental Events	Experimental Total	Control Events	Control Total	RR	95%-CI	Weight
Aronson 1948	4	123	11	139	0.4	[0.1; 1.3]	5.1%
Ferguson & Simes 1949	6	306	29	303	0.2	[0.1; 0.5]	6.4%
Rosenthal et al 1960	3	231	11	220	0.3	[0.1; 0.9]	4.4%
Hart & Sutherland 1977	62	13598	248	12867	0.2	[0.2; 0.3]	9.7%
Frimodt-Moller et al 1973	33	5069	47	5808	0.8	[0.5; 1.3]	8.9%
Stein & Aronson 1953	180	1541	372	1451	0.5	[0.4; 0.5]	10.1%
Vandiviere et al 1973	8	2545	10	629	0.2	[0.1; 0.5]	6.0%
TPT Madras 1980	505	88391	499	88391	1.0	[0.9; 1.1]	10.2%
Coetzee & Berjak 1968	29	7499	45	7277	0.6	[0.4; 1.0]	8.7%
Rosenthal et al 1961	17	1716	65	1665	0.3	[0.1; 0.4]	8.4%
Comstock et al 1974	186	50634	141	27338	0.7	[0.6; 0.9]	9.9%
Comstock & Webster 1969	5	2498	3	2341	1.6	[0.4; 6.5]	3.8%
Comstock et al 1976	27	16913	29	17854	1.0	[0.6; 1.7]	8.4%
Random effects model		**191064**		**166283**	**0.5**	**[0.3; 0.7]**	**100.0%**
Prediction interval						**[0.1; 1.8]**	

Heterogeneity: $I^2 = 92\%$, $\tau^2 = 0.3132$, $p < 0.01$



Meta-analysis using meta package

Meta-analysis for binary outcomes: Meta-regression

To perform meta-regression, we need to apply the `metareg()` function to an already existent meta-analysis object

```
# Univariable meta-regressions with different covariates (latitude, year and allocation):
> mreg04_lat <- metareg(ma04, ablat)
> mreg04_year <- metareg(ma04, year)
> mreg04_alloc <- metareg(ma04, alloc)

# Multivariable meta-regression with latitude and year as covariates:
> mreg04_multi <- metareg(ma04, ablat+year)
```

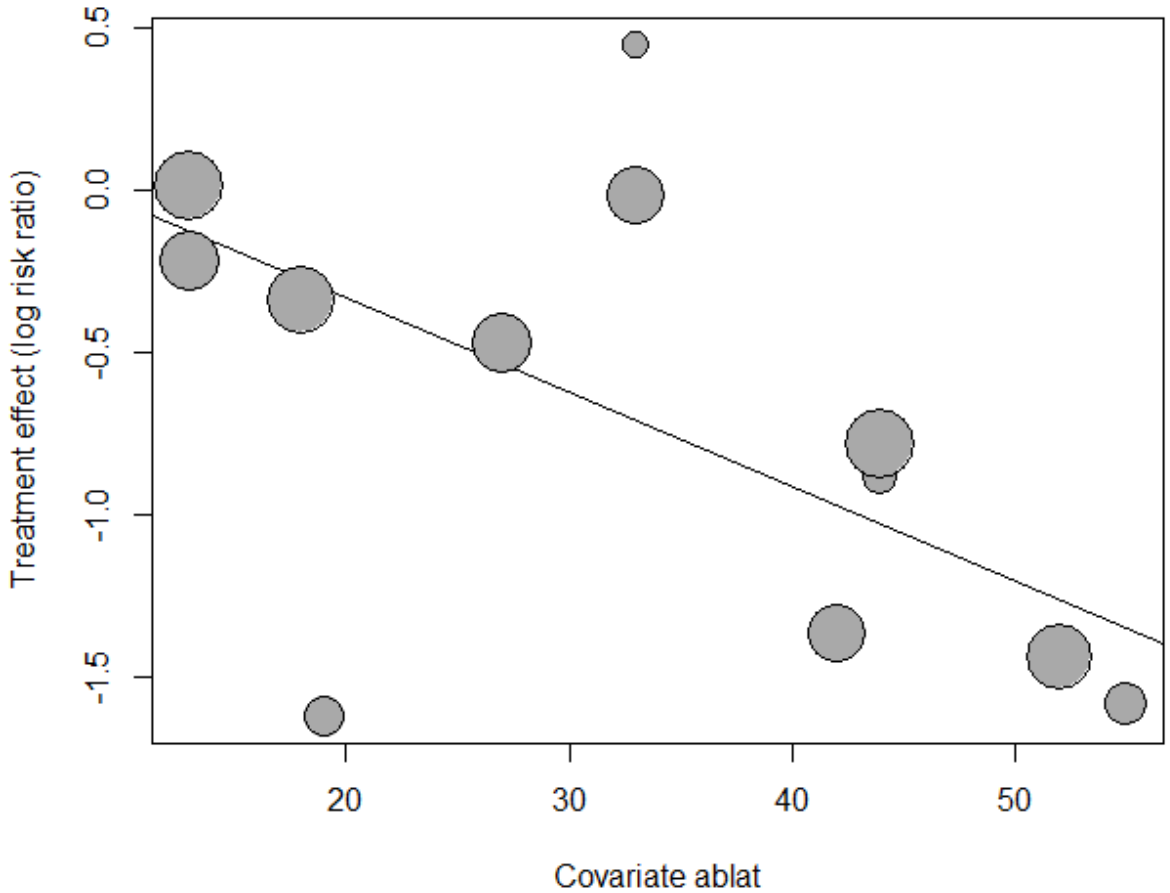
Meta-analysis using meta package

```
# Results of the univariable meta-regression analysis with the latitude as covariate:

> mreg04_lat

Mixed-Effects Model (k = 13; tau^2 estimator: REML)

tau^2 (estimated amount of residual heterogeneity):     0.0764 (SE = 0.0591)
tau (square root of estimated tau^2 value):             0.2763
I^2 (residual heterogeneity / unaccounted variability): 68.39%
H^2 (unaccounted variability / sampling variability):   3.16
R^2 (amount of heterogeneity accounted for):            75.62%

Test for Residual Heterogeneity:
QE(df = 11) = 30.7331, p-val = 0.0012

Test of Moderators (coefficient(s) 2):
QM(df = 1) = 16.3571, p-val < .0001

Model Results:

         estimate      se     zval    pval    ci.lb    ci.ub
intrcpt   0.2515  0.2491   1.0095  0.3127  -0.2368   0.7397
ablat    -0.0291  0.0072  -4.0444  <.0001  -0.0432  -0.0150  ***
```

meta relies on metafor to perform meta-regression

Meta-analysis using meta package

```
# Plotting the results of a meta-regression for a continuous covariate:
> bubble(mreg04_lat)
```



Meta-analysis using meta package

Meta-analysis for binary outcomes: Subgroup analysis

To perform subgroup analysis, we use the `byvar` argument

```
# Subgroup analysis (based on the allocation type) in a meta-analysis de novo:

> ma04_sub <- metabin(data=bcg, event.e=tpos, n.e=tpos+tneg, event.c=cpos, n.c=cpos+cneg, method="Inverse", sm="RR", method.tau="REML", prediction=TRUE, studlab=paste(author,year), byvar=alloc)

# Update of an existent meta-analysis

> ma04_sub <- update(ma04, byvar=alloc)
```

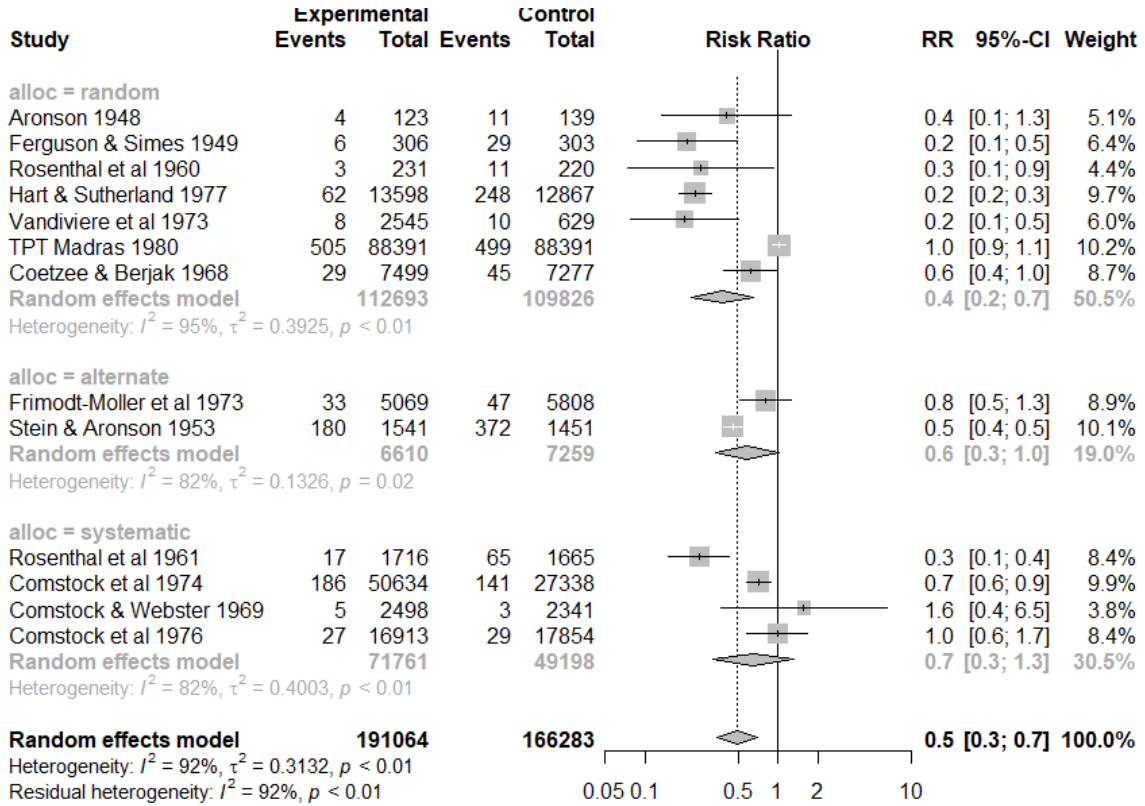
Meta-analysis using meta package

```
# Results for the subgroup analysis based on the allocation:

> ma04_sub

                            RR           95%-CI %W(fixed) %W(random)      alloc
Aronson 1948            0.4109 [0.1343; 1.2574]       0.5         5.1     random
Ferguson & Simes 1949   0.2049 [0.0863; 0.4864]       0.8         6.4     random
...

Results for subgroups (random effects model):
                     k     RR           95%-CI      Q  tau^2   I^2
alloc = random       7 0.3787 [0.2205; 0.6504] 110.21 0.3925 94.6%
alloc = alternate    2 0.5823 [0.3353; 1.0112]   5.56 0.1326 82.0%
alloc = systematic   4 0.6543 [0.3233; 1.3243]  16.59 0.4003 81.9%

Test for subgroup differences (random effects model):
                    Q d.f. p-value
Between groups   1.86    2  0.3943
```

In the output, both fixed effects and random effects meta-analysis results are presented

Meta-analysis using meta package

```
# Plotting the results of a subgroup analysis:

> forest(ma04_sub, prediction=FALSE, common=FALSE,
xlim=c(0.05,10), digits=1, digits.sd=1)
```



Meta-analysis using meta package

Meta-analysis for binary outcomes: Funnel plot

The possibility of publication bias can be assessed by means of hypothesis tests (`metabias()` function) and of funnel plot visual inspection.

```
#To perform Begg's rank correlation test, the argument "method" must be set to "rank".
For Egger's linear regression test: method="linreg". Particularly for binary outcomes,
Harbord's test (method="score") and Peter's test (method="peters") may be particularly
interesting.
> metabias(ma04, method="rank")

Rank correlation test of funnel plot asymmetry

data:  ma04
z = 0.12202, p-value = 0.9029
alternative hypothesis: asymmetry in funnel plot
sample estimates:
      ks    se.ks
 2.00000 16.39105
```

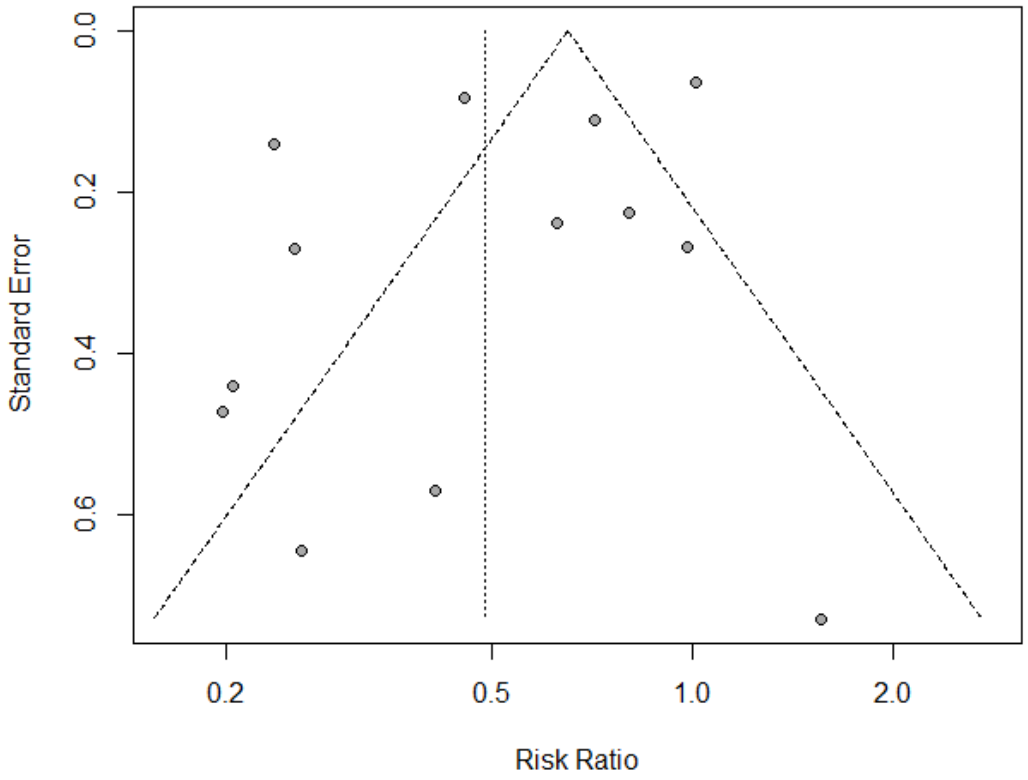
Meta-analysis using meta package

```
# To obtain a funnel plot
> funnel(ma04, common=FALSE)

# To obtain a funnel plot with trim-and-fill
> (ma04_tf <- trimfill(ma04, common=FALSE))
  funnel(ma04_tf)
...
Filled: Rosenthal et al 1961   2.2018 [1.2965; 3.7394]        6.3
Filled: Hart & Sutherland 1977 2.3620 [1.7901; 3.1166]        6.7
Filled: Ferguson & Simes 1949  2.7274 [1.1489; 6.4747]        5.4
Filled: Vandiviere et al 1973  2.8260 [1.1199; 7.1309]        5.3

Number of studies combined: k = 17 (with 4 added studies)

                         RR            95%-CI     z p-value
Random effects model 0.7102 [0.4593; 1.0981] -1.54  0.1237
Prediction interval         [0.1100; 4.5860]

Quantifying heterogeneity:
tau^2 = 0.7164; H = 4.05 [3.46; 4.75]; I^2 = 93.9% [91.6%; 95.6%]

Test of heterogeneity:
      Q d.f.  p-value
 262.73   16 < 0.0001
```

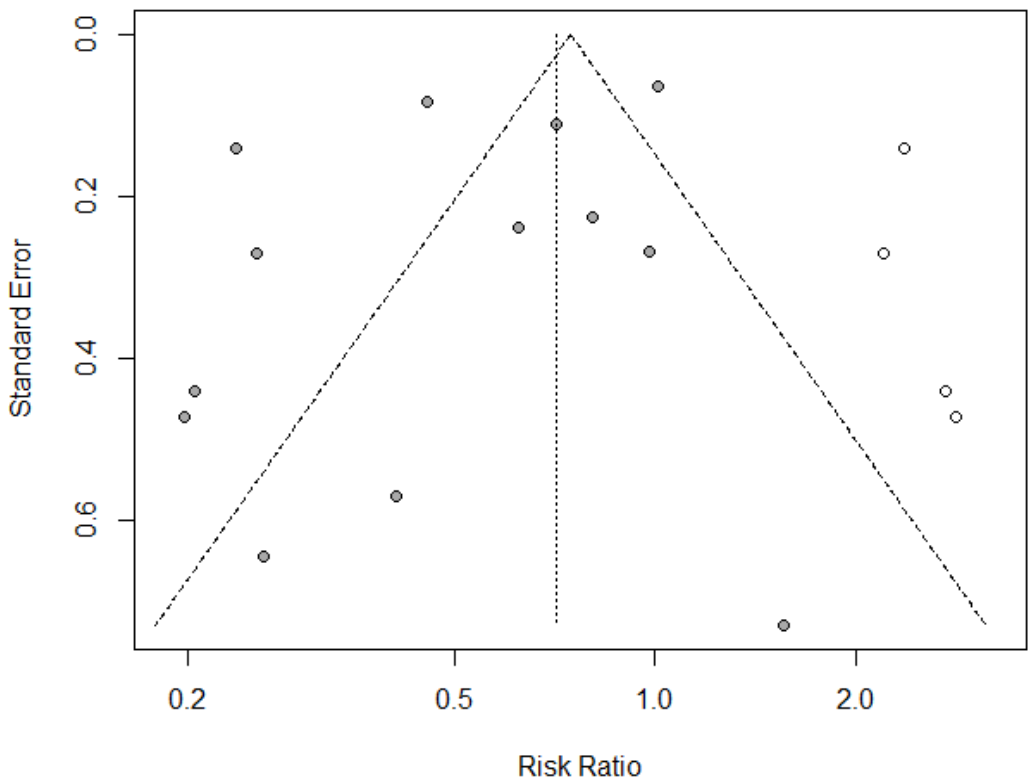
Meta-analysis using meta package

Meta-analysis for binary outcomes: Funnel plot

"Standard" funnel plot



Funnel plot with trim-and-fill



Meta-analysis using meta package

Meta-analysis for continuous outcomes: Meta-analysis

Again, we will use stroke dataset to perform meta-analysis to estimate the pooled mean difference

Given the raw data, meta-analysis of continuous outcomes can be performed using the `metacont()` function

Let's start to check its arguments!

```
> ?metacont
```

Meta-analysis using meta package

Effect measure

Method to estimate tau – DerSimonian and Laird is the default method. REML and other methods rely on metafor package.

```
metacont(n.e, mean.e, sd.e, n.c, mean.c, sd.c, studlab,
         data=NULL, subset=NULL, exclude=NULL,
         sm=gs("smcont"), pooledvar=gs("pooledvar"),
         method.smd=gs("method.smd"), sd.glass=gs("sd.glass"),
         exact.smd=gs("exact.smd"),
         level=gs("level"), level.comb=gs("level.comb"),
         comb.fixed=gs("comb.fixed"), comb.random=gs("comb.random"),
         hakn=gs("hakn"),
         method.tau=gs("method.tau"), tau.preset=NULL, TE.tau=NULL,
         tau.common=gs("tau.common"),
         prediction=gs("prediction"), level.predict=gs("level.predict"),
         method.bias=gs("method.bias"),
         backtransf=gs("backtransf"),
         title=gs("title"), complab=gs("complab"), outclab="",
         label.e=gs("label.e"), label.c=gs("label.c"),
         label.left=gs("label.left"), label.right=gs("label.right"),
         byvar, bylab, print.byvar=gs("print.byvar"),
         byseparator=gs("byseparator"),
         keepdata=gs("keepdata"),
         warn=gs("warn"),
         control=NULL)
```

	Mean LOS	Standard-deviation	Group size
Specialized care	los_spec	sd_spec	n_spec
Routine care	los_rout	sd_rout	n_rout

In meta package, fixed effects and random effects meta-analysis results are simultaneously presented

Meta-analysis using meta package

Meta-analysis for continuous outcomes: Meta-analysis

```
# Meta-analysis for the mean difference with the amount of
heterogeneity estimated by the restricted maximum-likelihood
method. The prediction argument allows for obtention of estimates
of a hypothetical future study.

> ma05 <- metacont(data=stroke, n.e=n_spec, mean.e=los_spec,
sd.e=sd_spec, n.c=n_rout, mean.c=los_rout, sd.c=sd_rout, sm="MD",
method.tau="REML", prediction=TRUE, studlab=paste(study,year))
```

Meta-analysis using meta package

```
> ma05
                              MD               95%-CI %W(fixed) %W(random)
Edinburgh 2005          -20.0000 [-32.4744;  -7.5256]       1.4       11.0
Oprington-Mild 2007      -2.0000 [ -4.8271;   0.8271]      28.1       11.7
Oprington-Moderate 2007 -55.0000 [-62.7656; -47.2344]       3.7       11.4
Oprington-Severe 2007   -71.0000 [-95.0223; -46.9777]       0.4        9.6
...

Number of studies combined: k = 9

 MD                95%-CI     z  p-value
Fixed effect model    -3.4636 [ -4.9626; -1.9646] -4.53 < 0.0001
Random effects model -15.1060 [-32.6409;  2.4289] -1.69   0.0913
Prediction interval           [-80.4949; 50.2829]

Quantifying heterogeneity:
tau^2 = 684.6462; H = 5.46 [4.54; 6.58]; I^2 = 96.7% [95.2%; 97.7%]

Test of heterogeneity:
      Q d.f.  p-value
 238.92    8 < 0.0001
```

Specialized care associates with a trend towards decreased LOS (pooled meta-analytic estimate: -15.1 days; 95%CI=-32.6;2.4; p=0.091). However, severe heterogeneity was observed (p<0.001; I^2=96.7%)

Meta-analysis using meta package

Meta-analysis for continuous outcomes: Forest plot

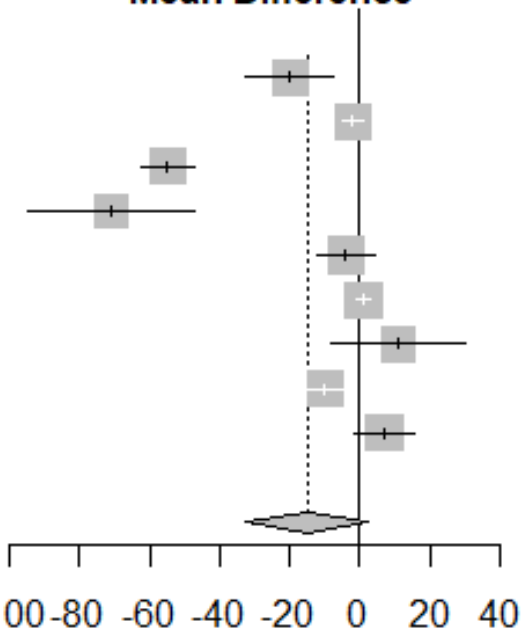
The function `forest()` creates a forest plot.

```
# The "common=FALSE" argument is used to hide fixed effects model
results. In this example, the predicted interval will not be presented
("prediction=FALSE"). The "xlim" argument sets the limits of the xx axis
of the forest plot. The number of decimal places is set by the "digits"
arguments.
> forest(ma05, common=FALSE, prediction=FALSE, xlim=c(-75,50), digits=1,
digits.sd=1)
```

Meta-analysis using meta package

Study	Experimental Total	Mean	SD	Control Total	Mean	SD	MD	95%-CI	Weight
Edinburgh 2005	155	55.0	47.0	156	75.0	64.0	-20.0	[-32.5; -7.5]	11.0%
Oprington-Mild 2007	31	27.0	7.0	32	29.0	4.0	-2.0	[-4.8; 0.8]	11.7%
Oprington-Moderate 2007	75	64.0	17.0	71	119.0	29.0	-55.0	[-62.8; -47.2]	11.4%
Oprington-Severe 2007	18	66.0	20.0	18	137.0	48.0	-71.0	[-95.0; -47.0]	9.6%
Montreal-Home 2010	8	14.0	8.0	13	18.0	11.0	-4.0	[-12.2; 4.2]	11.4%
Montreal-Transfer 2010	57	19.0	7.0	52	18.0	4.0	1.0	[-1.1; 3.1]	11.7%
Newcastle 2011	34	52.0	45.0	33	41.0	34.0	11.0	[-8.1; 30.1]	10.3%
Umea 2014	110	21.0	16.0	183	31.0	27.0	-10.0	[-14.9; -5.1]	11.6%
Uppsala 2018	60	30.0	27.0	52	23.0	20.0	7.0	[-1.7; 15.7]	11.4%
Random effects model	**548**			**610**			**-15.1**	**[-32.6; 2.4]**	**100.0%**

Heterogeneity: $I^2 = 97\%$, $\tau^2 = 684.6462$, $p < 0.01$



Meta-analysis using meta package

Meta-analysis for the generic inverse variance method: stroke2 dataset

In meta package, `metagen()` function allows to perform meta-analysis based on the generic inverse variance method :

```
> ma06 <-  metagen(data=stroke2, TE=mean_diff, seTE=sem,
sm="MD", prediction=TRUE, studlab=paste(study, year))
```

Meta-analysis using meta package

```
> ma06

                       MD             95%-CI %W(fixed) %W(random)
Edinburgh 2005 -10.5000 [-14.4199; -6.5801]      20.8       20.8
Newcastle 2011 -11.0000 [-15.5079; -6.4921]      15.7       15.7
Umea 2014       -9.6000 [-13.1279; -6.0721]      25.6       25.6
Uppsala 2018    -8.3000 [-14.1799; -2.4201]       9.2        9.2
Oslo 2019      -11.4000 [-14.7319; -8.0681]      28.7       28.7

Number of studies combined: k = 5

                           MD             95%-CI      z  p-value
Fixed effect model   -10.4035 [-12.1891; -8.6179] -11.42 < 0.0001
Random effects model -10.4035 [-12.1891; -8.6179] -11.42 < 0.0001
Prediction interval           [-13.3028; -7.5041]

Quantifying heterogeneity:
tau^2 = 0; H = 1.00 [1.00; 1.15]; I^2 = 0.0% [0.0%; 24.7%]

Test of heterogeneity:
    Q d.f. p-value
 1.10    4  0.8936
```

Meta-analysis using meta package

```
> forest(ma06, common=FALSE, prediction=TRUE,
xlim=c(-16,5), digits=1, digits.se = 1)
```