Meta-analysis in R

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Contents

1 Preparation

Please install the R package "meta" first:

```
#install.packages("meta", dependencies=TRUE)
library(meta)
```

```
## Loading 'meta' package (version 6.1-0).
## Type 'help(meta)' for a brief overview.
## Readers of 'Meta-Analysis with R (Use R!)' should install
## older version of 'meta' package: https://tinyurl.com/dt4y5drs
```

Help on meta-analysis functions in R is obtained by:

```
?metabin # meta-analysis of binary outcome data
?metagen # a function for generic inverse variance meta-analysis
```

Load a toy data set and print it:

```
data(Fleiss93cont)
Fleiss93cont
```

```
##     study year n.e mean.e sd.e n.c mean.c  sd.c
## 1   Davis 1973  13    5.0 4.70  13   6.50  3.80
## 2 Florell 1971  30    4.9 1.71  50   6.10  2.30
## 3   Gruen 1975  35   22.5 3.44  35  24.90 10.65
## 4    Hart 1975  20   12.5 1.47  20  12.30  1.66
## 5  Wilson 1977   8    6.5 0.76   8   7.38  1.41
```

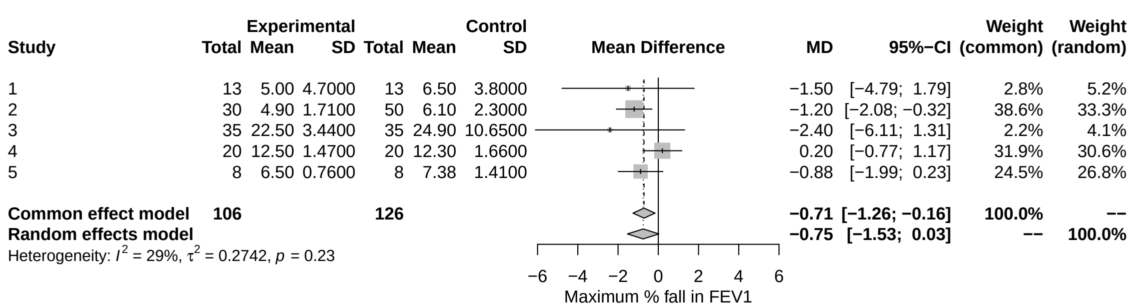
2 Meta-analysis for continuous outcome data

2.1 Basic meta-analysis

```
m1 <- metacont(n.e, mean.e, sd.e, n.c, mean.c, sd.c,
data = Fleiss93cont, sm = "MD")
```

2.2 Forest plot

```
forest(m1, xlab="Maximum % fall in FEV1")
```



2.3 Stratification by (fictitious) grouping variables

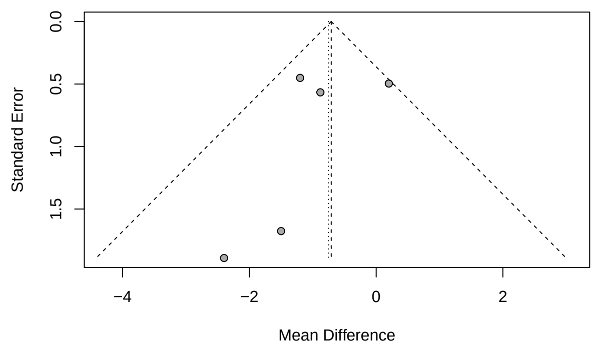
```
Fleiss93cont$age <- c(55, 65, 55, 65, 55)
Fleiss93cont$region <- c("Europe", "Europe", "Asia", "Asia", "Europe")
```

2.4 Subgroup analysis

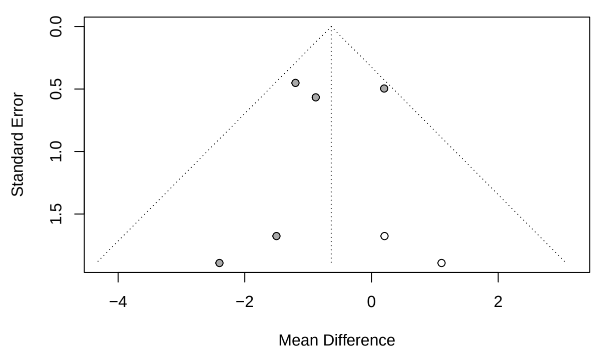
```
m2 <- metacont(n.e, mean.e, sd.e, n.c, mean.c, sd.c, studlab=paste(study, year),
 data=Fleiss93cont, subgroup=region, print.byvar=FALSE, sm = "MD")
forest(m2, xlab="Maximum % fall in FEV1, stratified by region")
```

2.5 Publication bias

```
funnel(m2)
```




```
funnel(trimfill(m2))
```




```
trimfill(m2)
```

```
## Number of studies combined: k = 7 (with 2 added studies)
## Number of observations: o = 328
##
##                              MD             95%-CI     z p-value
## Random effects model -0.6362 [-1.3542; 0.0818] -1.74  0.0824
##
```

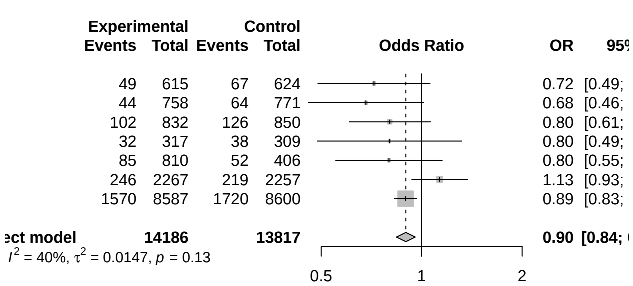
```
## Quantifying heterogeneity:
##  tau^2 = 0.2267 [0.0000; 4.2154]; tau = 0.4762 [0.0000; 2.0531]
##  I^2 = 12.1% [0.0%; 74.3%]; H = 1.07 [1.00; 1.97]
##
## Test of heterogeneity:
##     Q d.f. p-value
##  6.83    6  0.3371
##
## Details on meta-analytical method:
## - Inverse variance method
## - Restricted maximum-likelihood estimator for tau^2
## - Q-Profile method for confidence interval of tau^2 and tau
## - Trim-and-fill method to adjust for funnel plot asymmetry
```

3 Meta-analysis of binary outcomes

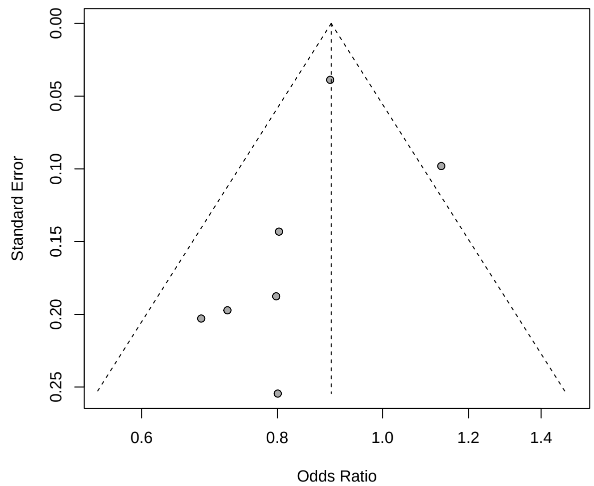
```
data(Fleiss1993bin)
```

- study: study label
- year: year of publication
- d.asp: number of deaths in aspirin group
- n.asp: number of observations in aspirin group
- d.plac: number of deaths in placebo group
- n.plac: number of observations in placebo group

```
m3 <- metabin(d.asp, n.asp, d.plac, n.plac, data = Fleiss1993bin,
  studlab = paste(study, year), sm = "OR", random = FALSE)
forest(m3)
```



```
funnel(m3)
```




```
summary(m3)
```

```
##                   OR           95%-CI %W(common)
## MRC-1 1974  0.7197 [0.4890; 1.0593]        3.2
## CDP 1976    0.6808 [0.4574; 1.0132]        3.1
## MRC-2 1979  0.8029 [0.6065; 1.0629]        5.7
## GASP 1979   0.8007 [0.4863; 1.3186]        1.8
## PARIS 1980  0.7981 [0.5526; 1.1529]        3.2
## AMIS 1980   1.1327 [0.9347; 1.3728]       10.2
## ISIS-2 1988 0.8950 [0.8294; 0.9657]       72.9
##
## Number of studies combined: k = 7
## Number of observations: o = 28003
## Number of events: e = 4414
##
##                           OR           95%-CI     z p-value
## Common effect model 0.8969 [0.8405; 0.9570] -3.29  0.0010
##
## Quantifying heterogeneity:
##  tau^2 = 0.0147 [0.0000; 0.1145]; tau = 0.1214 [0.0000; 0.3384]
##  I^2 = 39.7% [0.0%; 74.6%]; H = 1.29 [1.00; 1.99]
##
## Test of heterogeneity:
##     Q d.f. p-value
##  9.95    6  0.1269
##
## Details on meta-analytical method:
## - Mantel-Haenszel method
## - Restricted maximum-likelihood estimator for tau^2
## - Q-Profile method for confidence interval of tau^2 and tau
```

4 Meta-analysis if only RR, OR, or HR, and confidence intervals are known

```
data2 <- data.frame(matrix(nrow=13, ncol=0)) #columns will be added subsequently
data2$Study <- LETTERS[1:13] #just an example, better use real author names here
data2$rr <- c(0.1952, 0.1890, 0.2331, 0.2463, 0.2500, 0.3911, 0.3836, 0.6239, 0.7112,
0.8032, 0.9828, 1.0121, 1.5630)
data2$lcl <- c(0.0774, 0.0797, 0.1766, 0.1450, 0.0707, 0.1280, 0.3272, 0.3917, 0.5717,
0.5155, 0.5821, 0.8946, 0.3740)
data2$ucl <- c(0.4925, 0.4482, 0.3075, 0.4182, 0.8838, 1.1950, 0.4497, 0.9939, 0.8847,
1.2515, 1.6593, 1.1450, 6.5331)
#Compute the log(RR) and its standard error SElog(RR):
data2$log.rr <- log(data2$rr)
data2$se.log.rr <- (log(data2$ucl) - log(data2$lcl)) / (2*1.96)
#Meta-analysis using the metagen-function (generic meta-analysis):
ma2 <- metagen(TE = log.rr, seTE = se.log.rr, studlab = Study, data = data2, sm = "RR")
summary(ma2)
```

```
##       RR           95%-CI %W(common) %W(random)
## A 0.1952 [0.0774; 0.4924]        0.7        6.1
## B 0.1890 [0.0797; 0.4482]        0.8        6.5
## C 0.2331 [0.1767; 0.3076]        8.1        9.6
## D 0.2463 [0.1450; 0.4183]        2.2        8.4
## E 0.2500 [0.0707; 0.8839]        0.4        4.6
## F 0.3911 [0.1280; 1.1950]        0.5        5.2
## G 0.3836 [0.3272; 0.4497]       24.6       10.0
## H 0.6239 [0.3917; 0.9938]        2.9        8.7
## I 0.7112 [0.5717; 0.8847]       13.1        9.8
## J 0.8032 [0.5155; 1.2515]        3.2        8.8
## K 0.9828 [0.5821; 1.6593]        2.3        8.4
## L 1.0121 [0.8946; 1.1450]       40.9       10.0
## M 1.5630 [0.3740; 6.5324]        0.3        4.0
##
## Number of studies combined: k = 13
##
##                          RR           95%-CI      z  p-value
## Common effect model  0.6187 [0.5717; 0.6695] -11.93 < 0.0001
## Random effects model 0.4730 [0.3287; 0.6806]  -4.03 < 0.0001
##
## Quantifying heterogeneity:
##  tau^2 = 0.3393 [0.1322; 1.1849]; tau = 0.5825 [0.3636; 1.0885]
##  I^2 = 93.3% [90.2%; 95.4%]; H = 3.86 [3.20; 4.65]
##
## Test of heterogeneity:
##       Q d.f.  p-value
##  178.41   12 < 0.0001
##
## Details on meta-analytical method:
## - Inverse variance method
## - Restricted maximum-likelihood estimator for tau^2
## - Q-Profile method for confidence interval of tau^2 and tau
```

```
#See also: https://training.cochrane.org/handbook/current/chapter-06#section-6-3-1
```

Sensitivity analysis: exclude one study at a time

```
metainf(ma2)
```

```
## Influential analysis (common effect model)
##
##                       RR            95%-CI  p-value   tau^2     tau    I^2
## Omitting A        0.6239 [0.5764; 0.6754] < 0.0001  0.3222  0.5676  93.6%
## Omitting B        0.6249 [0.5773; 0.6764] < 0.0001  0.3145  0.5608  93.6%
## Omitting C        0.6743 [0.6210; 0.7321] < 0.0001  0.3010  0.5486  91.3%
## Omitting D        0.6318 [0.5833; 0.6842] < 0.0001  0.3288  0.5734  93.4%
## Omitting E        0.6209 [0.5737; 0.6720] < 0.0001  0.3481  0.5900  93.8%
## Omitting F        0.6201 [0.5729; 0.6712] < 0.0001  0.3643  0.6035  93.8%
## Omitting G        0.7233 [0.6604; 0.7921] < 0.0001  0.3811  0.6173  91.7%
## Omitting H        0.6185 [0.5709; 0.6701] < 0.0001  0.3762  0.6134  93.8%
## Omitting I        0.6059 [0.5567; 0.6594] < 0.0001  0.3656  0.6046  93.8%
## Omitting J        0.6134 [0.5661; 0.6646] < 0.0001  0.3524  0.5936  93.8%
## Omitting K        0.6121 [0.5651; 0.6629] < 0.0001  0.3267  0.5716  93.7%
## Omitting L        0.4400 [0.3971; 0.4876] < 0.0001  0.2952  0.5434  85.3%
## Omitting M        0.6169 [0.5700; 0.6677] < 0.0001  0.3322  0.5764  93.8%
##
## Pooled estimate   0.6187 [0.5717; 0.6695] < 0.0001  0.3393  0.5825  93.3%
##
## Details on meta-analytical method:
## - Inverse variance method
## - Restricted maximum-likelihood estimator for tau^2
```

5 Meta-analysis of diagnostic tests

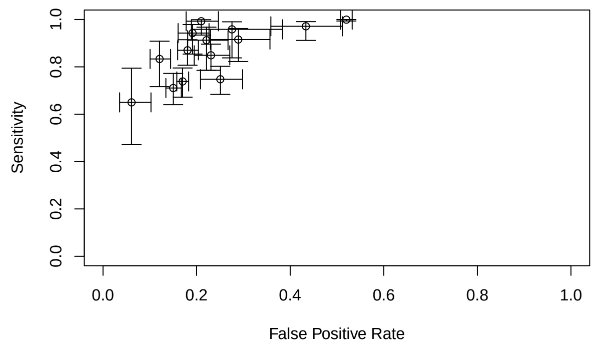
5.1 Descriptive plots: sensitivity and specificity of individual studies

```
data("AuditC")
print(AuditC)
```

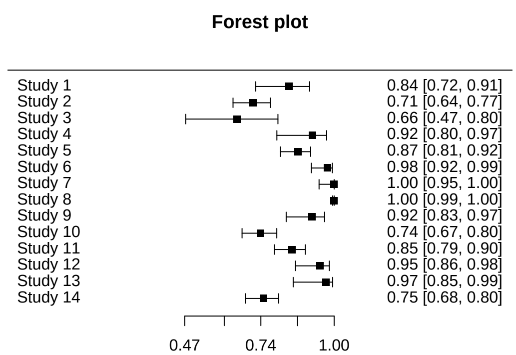
```
##     TP FN   FP   TN
## 1   47  9  101  738
## 2  126 51  272 1543
## 3   19 10   12  192
## 4   36  3   78  276
## 5  130 19  211  959
## 6   84  2   68   89
## 7   68  0  112  423
## 8  752  0 3226 2977
## 9   59  5   55  136
## 10 142 50  571 2788
## 11 137 24  107  358
```

```
## 12  57  3  103  437
## 13  34  1   21   56
## 14 152 51   88  264
```

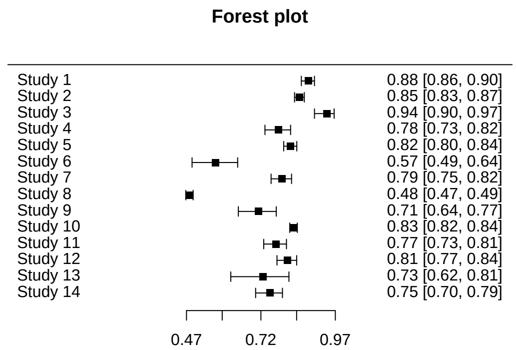
```r
crosshair(AuditC) #To be applied to the original data set,
```




```r
#containing TP, TN, FP, FN for every study
AuditC_desc <- madad(AuditC, correction.control="single", correction=0)
mada::forest(AuditC_desc, type = "sens")
```

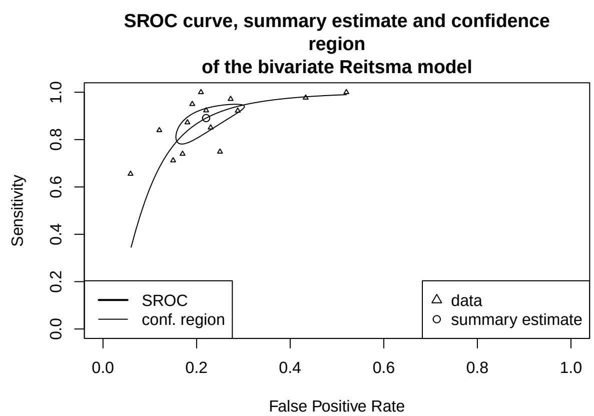



```r
#To be applied to the object returned by the madad() function
mada::forest(AuditC_desc, type = "spec")
```



5.2 Bivariate meta-analysis

```r
reitsma_model <- reitsma(AuditC)
plot(reitsma_model, main="SROC curve, summary estimate and confidence\nregion
of the bivariate Reitsma model")
points(fpr(AuditC), sens(AuditC), pch=2, cex=0.5)
legend("bottomright", c("data", "summary estimate"), pch = c(2,1))
legend("bottomleft", c("SROC", "conf. region"), lwd = c(2,1))
```




```r
summary(reitsma_model)
```

```
## Call:  reitsma.default(data = AuditC)
##
## Bivariate diagnostic random-effects meta-analysis
## Estimation method: REML
##
## Fixed-effects coefficients
##                     Estimate Std. Error      z Pr(>|z|) 95%ci.lb 95%ci.ub
## tsens.(Intercept)      2.100      0.338  6.215    0.000    1.438    2.762 ***
## tfpr.(Intercept)      -1.264      0.174 -7.249    0.000   -1.605   -0.922 ***
## sensitivity            0.891          -      -        -    0.808    0.941
```

```
## false pos. rate      0.220          -      -        -    0.167    0.285
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Variance components: between-studies Std. Dev and correlation matrix
##       Std. Dev tsens  tfpr
## tsens    1.175 1.000     .
## tfpr     0.638 0.854 1.000
##
##  logLik     AIC     BIC
##  31.564 -53.128 -46.467
##
## AUC:  0.887
## Partial AUC (restricted to observed FPRs and normalized):  0.861
##
## I2 estimates
## Zhou and Dendukuri approach:  40.4 %
## Holling sample size unadjusted approaches:  35.6 - 79.3 %
## Holling sample size adjusted approaches:  0.2 - 2.4 %
```

6 References

R software:

```
citation()
```

```
##
## To cite R in publications use:
##
##   R Core Team (2022). R: A language and environment for statistical
##   computing. R Foundation for Statistical Computing, Vienna, Austria.
##   URL https://www.R-project.org/.
##
## Ein BibTeX-Eintrag für LaTeX-Benutzer ist
##
##   @Manual{,
##     title = {R: A Language and Environment for Statistical Computing},
##     author = {{R Core Team}},
##     organization = {R Foundation for Statistical Computing},
##     address = {Vienna, Austria},
##     year = {2022},
##     url = {https://www.R-project.org/},
##   }
##
## We have invested a lot of time and effort in creating R, please cite it
## when using it for data analysis. See also 'citation("pkgname")' for
## citing R packages.
```

R package "meta":

```r
citation("meta")
```

```
##
## To cite package 'meta' in publications use:
##
##   Balduzzi S, Rücker G, Schwarzer G (2019), How to perform a
##   meta-analysis with R: a practical tutorial, Evidence-Based Mental
##   Health; 22: 153-160.
##
## Ein BibTeX-Eintrag für LaTeX-Benutzer ist
##
##   @Article{,
##     title = {How to perform a meta-analysis with {R}: a practical tutorial},
##     author = {Sara Balduzzi and Gerta Rücker and Guido Schwarzer},
##     journal = {Evidence-Based Mental Health},
##     year = {2019},
##     number = {22},
##     pages = {153--160},
##   }
##
## DOI: 10.1136/ebmental-2019-300117
```

R package "mada":

```r
citation("mada")
```

```
##
## Um Paket 'mada' in Publikationen zu zitieren, nutzen Sie bitte:
##
##   Sousa-Pinto PDwcfB (2022). _mada: Meta-Analysis of Diagnostic
##   Accuracy_. R package version 0.5.11,
##   <https://CRAN.R-project.org/package=mada>.
##
## Ein BibTeX-Eintrag für LaTeX-Benutzer ist
##
##   @Manual{,
##     title = {mada: Meta-Analysis of Diagnostic Accuracy},
##     author = {Philipp Doebler with contributions from Bernardo Sousa-Pinto},
##     year = {2022},
##     note = {R package version 0.5.11},
##     url = {https://CRAN.R-project.org/package=mada},
##   }
##
## ACHTUNG: Diese Zitationsinformation wurde aus der DESCRIPTION-Datei
## automatisch generiert. Evtl. ist manuelle Nachbearbeitung nötig, siehe
## 'help("citation")'.
```

Session info:

```r
sessionInfo()
```

```
## R version 4.2.2 (2022-10-31 ucrt)
```

```
## Platform: x86_64-w64-mingw32/x64 (64-bit)
## Running under: Windows 10 x64 (build 19045)
##
## Matrix products: default
##
## locale:
## [1] LC_COLLATE=German_Germany.utf8  LC_CTYPE=German_Germany.utf8
## [3] LC_MONETARY=German_Germany.utf8 LC_NUMERIC=C
## [5] LC_TIME=German_Germany.utf8
##
## attached base packages:
## [1] stats     graphics  grDevices utils     datasets  methods   base
##
## other attached packages:
## [1] mada_0.5.11   metafor_3.8-1 metadat_1.2-0 Matrix_1.5-3  mvmeta_1.0.3
## [6] ellipse_0.4.3 mvtnorm_1.1-3 meta_6.1-0
##
## loaded via a namespace (and not attached):
##  [1] Rcpp_1.0.9         compiler_4.2.2     nloptr_2.0.3       highr_0.10
##  [5] mathjaxr_1.6-0     tools_4.2.2        boot_1.3-28.1      digest_0.6.31
##  [9] lme4_1.1-31        evaluate_0.20      lifecycle_1.0.3    nlme_3.1-161
## [13] lattice_0.20-45    rlang_1.0.6        cli_3.6.0          rstudioapi_0.14
## [17] yaml_2.3.6         CompQuadForm_1.4.3 xfun_0.36          fastmap_1.1.0
## [21] stringr_1.5.0      knitr_1.41         xml2_1.3.3         vctrs_0.5.1
## [25] grid_4.2.2         glue_1.6.2         rmarkdown_2.19     mixmeta_1.2.0
## [29] minqa_1.2.5        magrittr_2.0.3     htmltools_0.5.4    MASS_7.3-58.1
## [33] splines_4.2.2      stringi_1.7.12
```