UMC Utrecht

Meta-analysis of prognosis studies

Introduction of a new R package

Thomas Debray

Background

Prediction modeling research

Assessment of model impact

Identification of predictive factors

Development of prediction model(s)

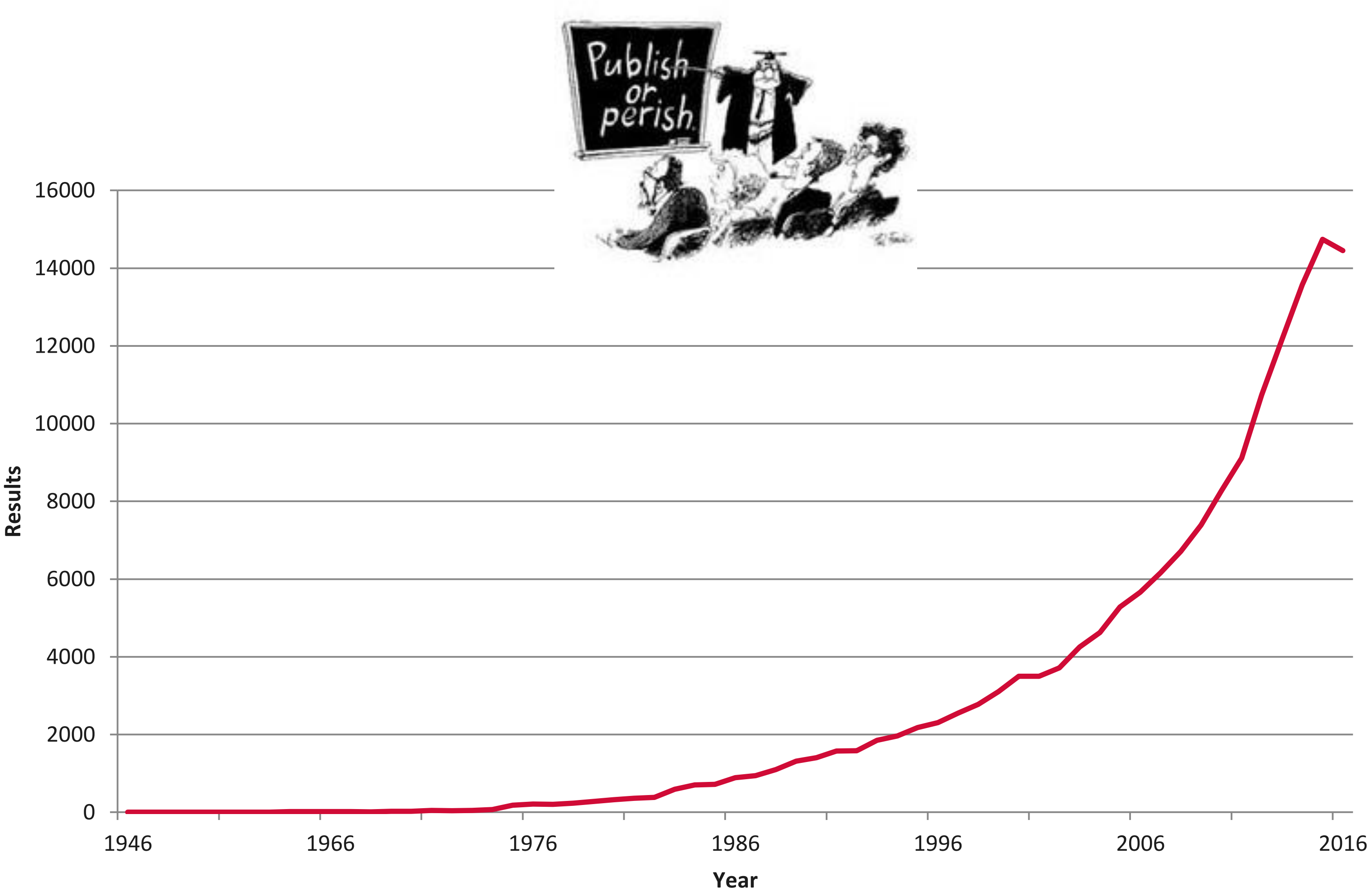
Validation of prediction model(s)

Identification of prognostic factors

Background

PubMed

predict* prognos*



R-package: metamisc

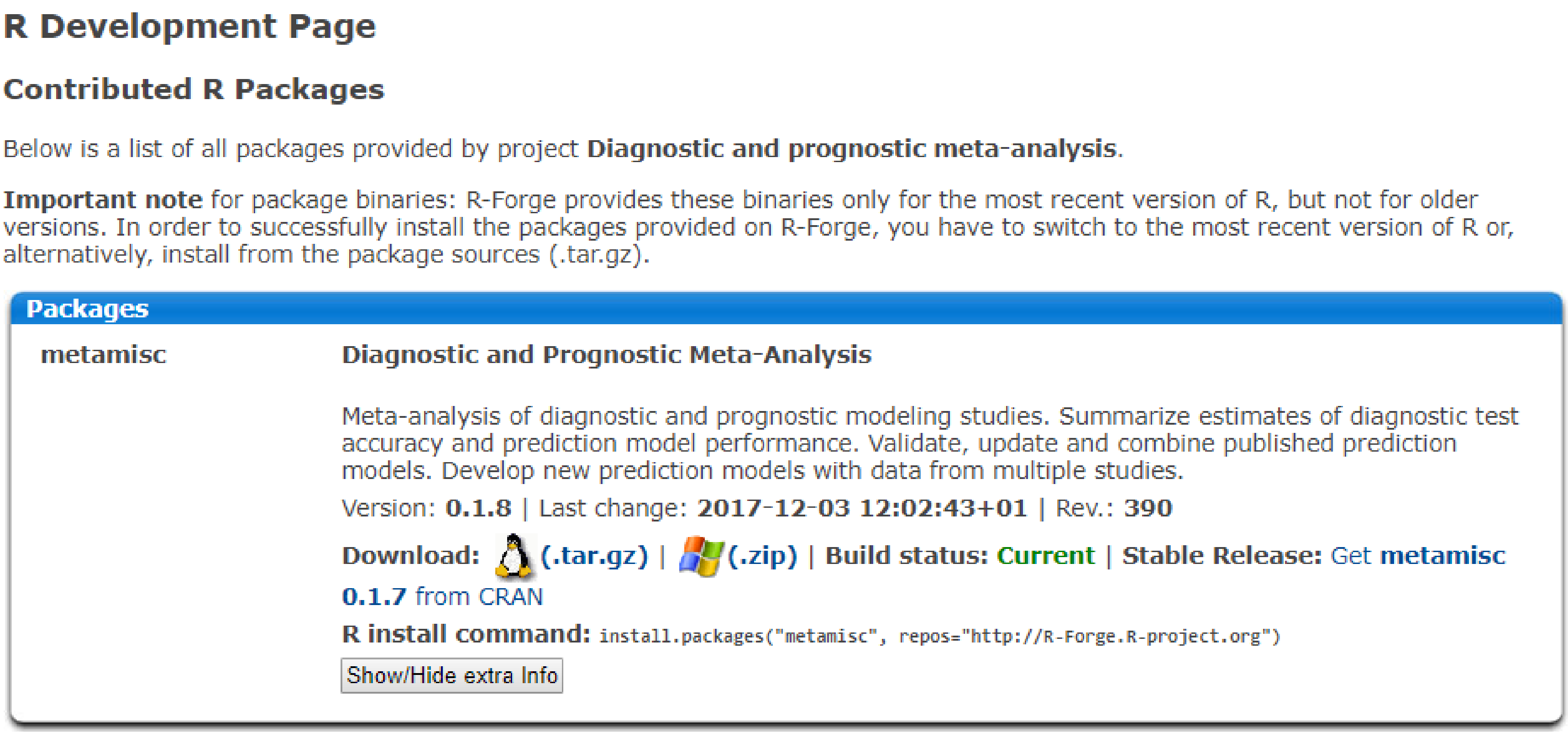
by Thomas Debray & Valentijn de Jong

Motivation

- Synthesis of prognostic factors and models
  - Relevant parameters often poorly reported
  - Statistical methodology relatively complex
  - Many methods (still) not being used
  - Lack of (user-friendly) software

- Existing meta-analysis software not always helpful
  - Focus on extracting & summarizing relative effects
  - Focus on likelihood functions with Normality assumptions
  - Focus on modeling aggregate data

“metamisc”



R Development Page

Contributed R Packages

Below is a list of all packages provided by project **Diagnostic and prognostic meta-analysis**.

Important note for package binaries: R-Forge provides these binaries only for the most recent version of R, but not for older versions. In order to successfully install the packages provided on R-Forge, you have to switch to the most recent version of R or, alternatively, install from the package sources (.tar.gz).

Packages

metamisc

Diagnostic and Prognostic Meta-Analysis

Meta-analysis of diagnostic and prognostic modeling studies. Summarize estimates of diagnostic test accuracy and prediction model performance. Validate, update and combine published prediction models. Develop new prediction models with data from multiple studies.

Version: **0.1.8** | Last change: **2017-12-03 12:02:43+01** | Rev.: **390**

Download: **(.tar.gz)** | **(.zip)** | **Build status:** **Current** | **Stable Release:** Get **metamisc 0.1.7** from CRAN

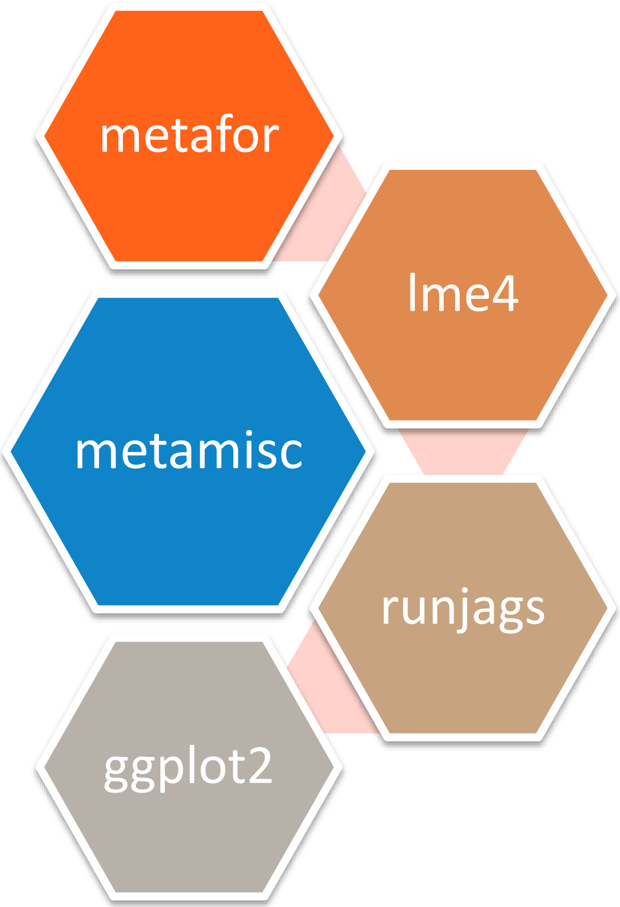
R install command: `install.packages("metamisc", repos="http://R-Forge.R-project.org")`

https://CRAN.R-project.org/package=metamisc

Functionalities

- Bivariate meta-analysis methods
- Testing of funnel plot asymmetry
- Extract, restore and summarize estimates of prediction model performance
- Validate, update and combine published prediction models [In progress]
- Develop new prediction models with data from multiple studies [In progress]

Key building blocks



metafor

lme4

metamisc

runjags

ggplot2

Example datasets

- Fibrinogen
  (31 associations between plasma fibrinogen concentration and CHD)
- EuroSCORE
  (22 validations of EuroSCORE II)
- Framingham
  (21 validations of Framingham Wilson)
- DVTmodels
  (5 published models for predicting presence of DVT)
- DVTipd
  (hypothetical dataset with 500 subjects suspected of having DVT)
- …

Validation of prediction models

Research Methods & Reporting

A guide to systematic review and meta-analysis of prediction model performance

BMJ 2017 ; 356 doi: https://doi.org/10.1136/bmj.i6460 (Published 05 January 2017)
Cite this as: *BMJ* 2017;356:i6460

valmeta()

- Meta-analysis of prediction model performance
  - Restoring of missing information
  - Estimation of weighted average
  - Generation of forest plots
- Approximate and “exact” likelihood functions
  - normal/identity
  - normal/log (O:E ratio)
  - normal/logit (c-stat)
  - poisson/log (O:E ratio)
- Estimation
  - MLE, REML, empirical Bayes, … (see metafor)
  - Bayes MCMC (weakly informative priors)

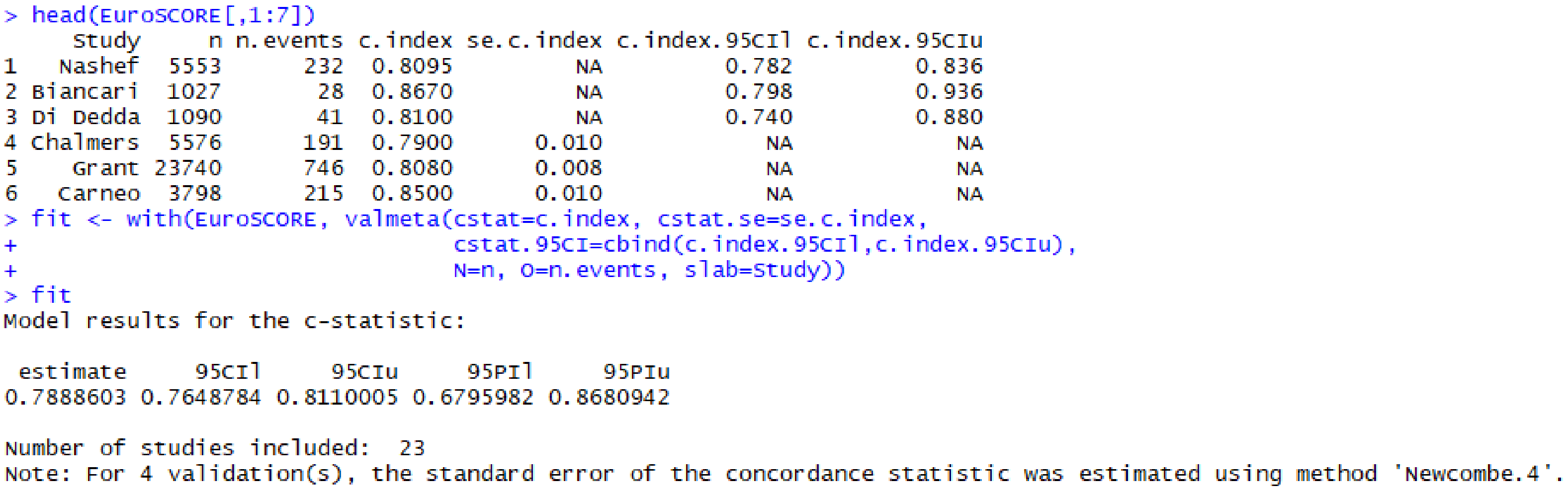
Usage

```
valmeta(measure = "cstat", cstat, cstat.se, cstat.95CI, OE, OE.se, OE.95CI,
  citl, citl.se, N, O, E, Po, Po.se, Pe, t.val, t.ma, t.extrapolate = FALSE,
  method = "REML", test = "knha", verbose = FALSE, slab, n.chains = 4, pars, …)
```

```
# Meta-analysis of the c-statistic (random effects)
valmeta(cstat=cstat, cstat.se= cstat.se, cstat.95CI=cbind(95CIl, 95CIu), N=n, O=n.events))
valmeta(cstat=c.index,  N=n, O=n.events)
valmeta(cstat=cstat, cstat.se=cstat.se, cstat.95CI=cbind(95CIl,95CIu),N=n, O=n.events,
method="BAYES") # Bayesian meta-analysis
```

```
# Meta-analysis of the total O:E ratio (random effects)
valmeta(measure="OE", O=n.events, E=e.events, N=n)
valmeta(measure="OE", O=n.events, E=e.events)
valmeta(measure="OE", Po=Po, Pe=Pe, N=n)
valmeta(measure="OE", O=n.events, E=e.events, pars=list(model.oe="poisson/log"))
```

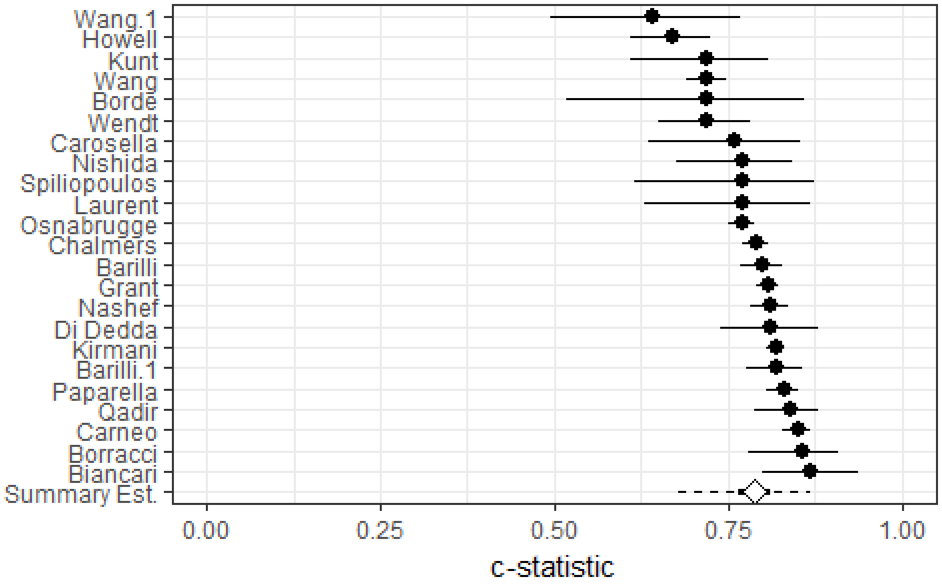
Example



```
> head(EuroSCORE[,1:7])
     Study     n n.events c.index se.c.index c.index.95CIl c.index.95CIu
1   Nashef  5553      232  0.8095         NA         0.782         0.836
2 Biancari  1027       28  0.8670         NA         0.798         0.936
3 Di Dedda  1090       41  0.8100         NA         0.740         0.880
4 Chalmers  5576      191  0.7900      0.010            NA            NA
5    Grant 23740      746  0.8080      0.008            NA            NA
6   Carneo  3798      215  0.8500      0.010            NA            NA
> fit <- with(EuroSCORE, valmeta(cstat=c.index, cstat.se=se.c.index,
+                               cstat.95CI=cbind(c.index.95CIl,c.index.95CIu),
+                               N=n, O=n.events, slab=Study))
> fit
Model results for the c-statistic:

 estimate     95CIl     95CIu     95PIl     95PIu 
0.7888603 0.7648784 0.8110005 0.6795982 0.8680942 

Number of studies included:  23
Note: For 4 validation(s), the standard error of the concordance statistic was estimated using method 'Newcombe.4'.
```



Bivariate meta-analysis

Volume 9, Issue 1
January 2008

An alternative model for bivariate random-effects meta-analysis when the within-study correlations are unknown FREE

Richard D. Riley ✉, John R. Thompson, Keith R. Abrams

Biostatistics, Volume 9, Issue 1, 1 January 2008, Pages 172–186, https://doi.org/10.1093/biostatistics/kxm023

Published: 11 July 2007 **Article history** ▾

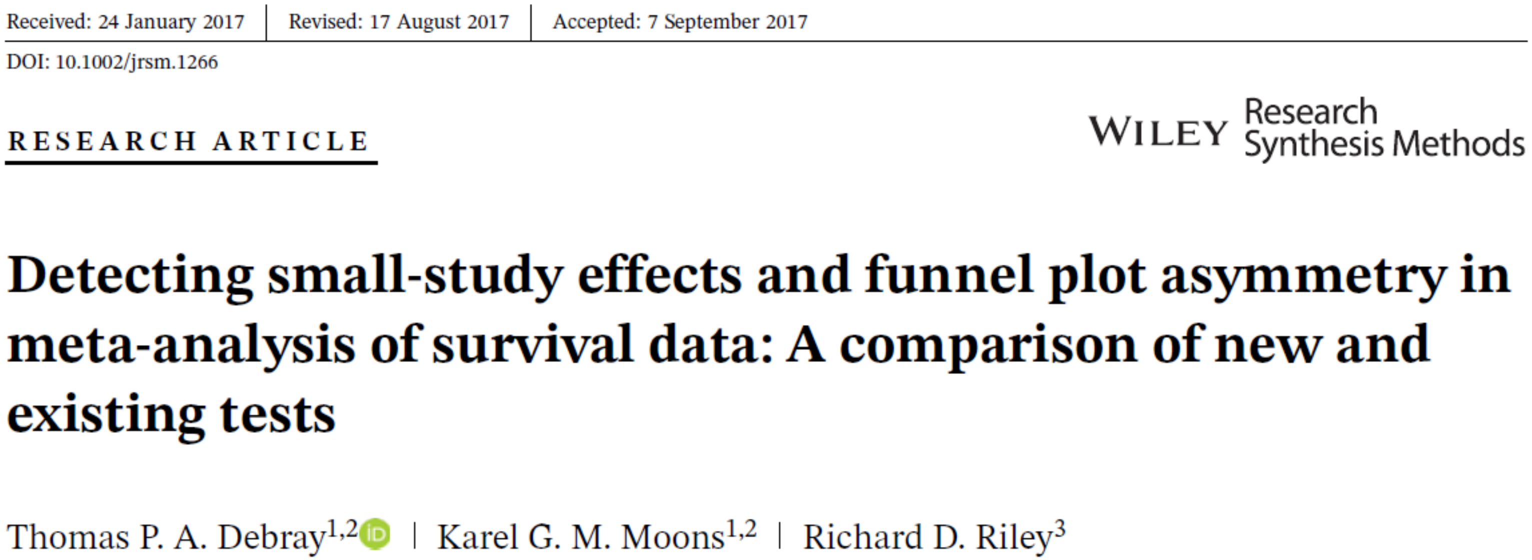
riley()

- Synthesis of 2 correlated endpoints
  - Estimation of an overall correlation parameter
  - Estimation of weighted average
  - Generation of forest plots

- Estimation
  - REML
  - Bayes MCMC (in progress)

- Usage
  - riley(X, optimization = "Nelder-Mead", control = list(), ...)

Evaluation of publication bias



Received: 24 January 2017 | Revised: 17 August 2017 | Accepted: 7 September 2017
DOI: 10.1002/jrsm.1266

RESEARCH ARTICLE

WILEY Research Synthesis Methods

Detecting small-study effects and funnel plot asymmetry in meta-analysis of survival data: A comparison of new and existing tests

Thomas P. A. Debray[1,2] | Karel G. M. Moons[1,2] | Richard D. Riley[3]

fat() for funnel plot asymmetry tests

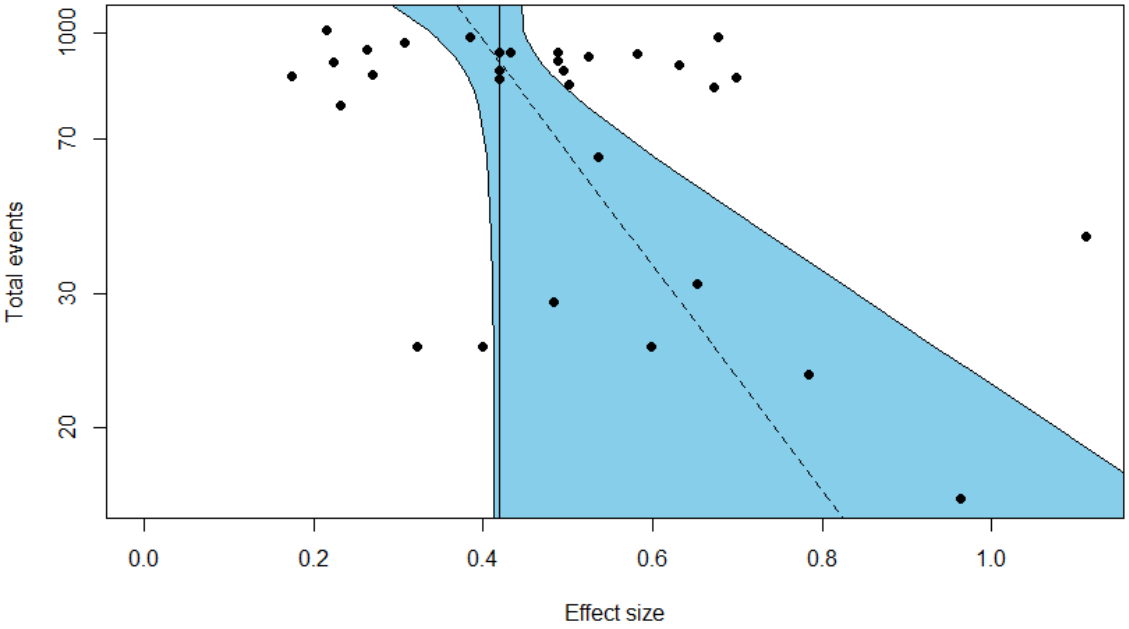
- Assess selective reporting of predictor-outcome associations (e.g. hazard ratio)

- Regression tests with multiplicative heterogeneity
  - Egger *et al.*
  - Macaskill *et al.*
  - Peters *et al.*
  - Debray *et al.*

- Usage
  - `fat(b, b.se, n.total, d.total, d1, d2, method = "E-FIV")`

Example

```
# Inverse variance weighted regression test
data(Fibrinogen)
b <- log(Fibrinogen$HR)
b.se <- ((log(Fibrinogen$HR.975) - log(Fibrinogen$HR.025))/(2*qnorm(0.975)))
d.total <- Fibrinogen$N.events
fit <- fat(b=b, b.se=b.se, d.total=d.total, method="D-FIV")
plot(fit)
```



Model development in IPD-MA

metapred

- Entire GLM, including non-linear functions
- Stepwise selection possible
- Any performance measure
- Internal-external cross-validation
- Currently only two-stage models

metapred(), similar to glm() :

- metapred(data, strata = “s“)
- metapred(data, strata = “s“, Y ~ X1 + I(X2^2) +I(log(X3))
- metapred(data, strata = “s“, family = binomial)
- metapred(data, strata = “s“, family = quasipoisson)

metapred() has extra options:

- metapred(data, strata = “s“, cvFUN = “bootstrap”)
- metapred(data, strata = “s“, stepwise = FALSE)
- metapred(data, strata = “s“, meta.method = “DL“)
- metapred(data, strata = “s“, recal.int = TRUE)

metapred()

- While metapred is in development:

```
metamisc:::metapred(data, strata = “s“)
```

Final remarks

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Future work

- Improve customization
    - Estimation methods
    - Forest plots

- Add more examples
    - Fabricated IPD-MA data sets
    - Data generation algorithm (based on MCMC)

- Add functionalities
    - Development of prediction models in IPD-MA
    - Validation of prediction models in IPD-MA
    - Updating of prediction models in IPD-MA
    - Aggregation & meta-analysis of prediction models