Biostatistics & Epidemiological Data Analysis using R

12

Meta-analysis

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Motivation

Results from a PubMed search for papers with "meta-analysis" or "meta analysis" or "systematic review" in the title:
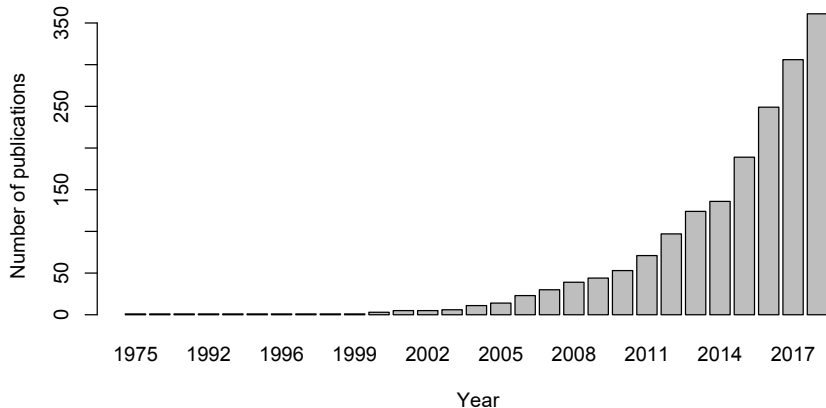
What is a systematic review?

Systematic review

- Collection and description of empirical evidence to a specific research question, with specified criteria.
- Yields a systematic list of the entire published literature for a research question, in contrary to a simple review, which is often based on an arbitrary selection of studies.
- Can always be done.

$\longrightarrow$ qualitative description of all relevant studies and results.

What is a meta-analysis?

Meta-analysis

- Statistical analysis and "pooling" of the collected results of a systematic review.
- Should be based on a systematic review.
- Is not always possible - only if the studies can be meaningfully aggregated.

$\longrightarrow$ quantitative summary of the studies (if meaningful).

Steps of a systematic review/meta-analysis

1. Specify research question, search strategy, filtering steps.

   Prospectively register the protocol.
2. Search articles.
3. Filter articles.
4. Extract information from the selected articles (and present in table).
5. Judge the quality of the extracted studies.
6. Judge the heterogeneity of the articles.
7. Estimate pooled total effect.
8. Determine publication bias.
9. Analyze subgroups.

Publish results after completion.

Overview of ressources in R

- Overview of R packages for meta-analysis: `https://cran.r-project.org/web/views/MetaAnalysis.html`

- R package for helping with systematic review, extracting information, and e.g. creating PRISMA plots: `https://cran.r-project.org/web/packages/metagear/`

- Different functions for meta-analysis: `https://cran.r-project.org/web/views/MetaAnalysis.html`

Doing a meta-analysis in R

Use `metafor` R package, see `R_12b_meta_analysis.Rmd`.

Reminder

- Studies are too different
  $\longrightarrow$ no meta-analysis, only systematic review.
- All studies are collected and their results homogeneous
  $\longrightarrow$ fixed-effect meta-analysis.
- Studies are not complete/only a sample
  $\longrightarrow$ random-effect meta-analysis.

Step 6: estimate the heterogeneity of the articles

Measures of heterogeneity

- τ^2 = heterogeneity
  = variance of the effect estimates (e.g. log relative risk) between studies

- I^2 = heterogeneity / total variance
  = heterogeneity / (variance between + within studies)

  Possible orientation: small 25% / moderate 50% / large 75%

- H^2 = heterogeneity / variance within studies

- Cochran's heterogeneity statistic Q = weighted quadratic difference between study effects and summary effect

- Q can be used to test heterogeneity (χ^2-distribution with $K-1$ degrees of freedom, $K=$ number of studies).

- all directly computed in `rma()` function in `metafor` package.

Step 7: estimate pooled total effect

- Estimate the total effect as weighted mean of the study effects ...
- ... in a statistical model, in which the studies are the observations and their effect measures are the outcome (y), through the intercept of the model, which only contains the intercept as fixed effect and potentially also a random intercept.
- Default weights in rma() function: 1/variance
- Analogously: estimate the variance of the total effect estimate.

Step 7: estimate pooled total effect

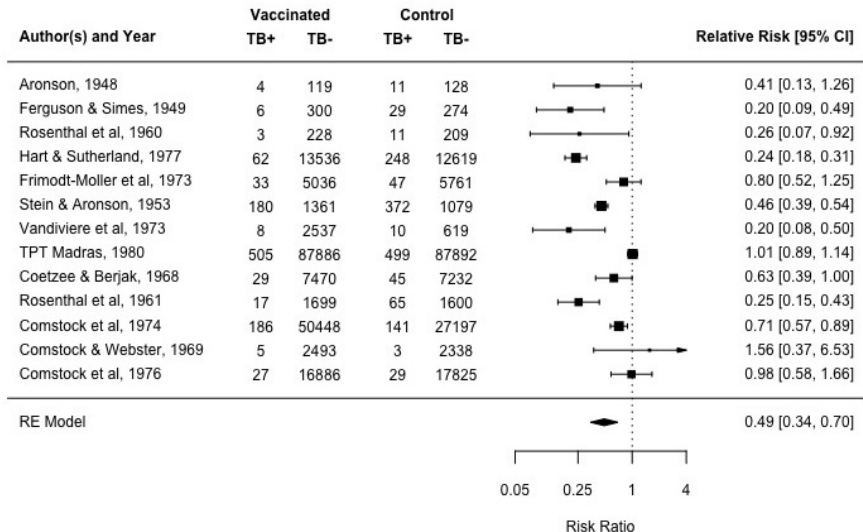### Implemented in `metafor`:

- Relative risk, odds ratio, risk difference, ...
- Mean difference, standardized mean difference
- Different transformations of correlation coefficients
- Different transformations of proportions
- Extract the effect measures with the `escalc()` function, pool with the `rma()` function
- ...

For further measures, see `meta` package and the overview in `help(meta)`.

Step 7: visualize the results: forest plot

Author(s) and Year	Vaccinated		Control		Relative Risk [95% CI]
	TB+	TB-	TB+	TB-	
Aronson, 1948	4	119	11	128	0.41 [0.13, 1.26]
Ferguson & Simes, 1949	6	300	29	274	0.20 [0.09, 0.49]
Rosenthal et al, 1960	3	228	11	209	0.26 [0.07, 0.92]
Hart & Sutherland, 1977	62	13536	248	12619	0.24 [0.18, 0.31]
Frimodt-Moller et al, 1973	33	5036	47	5761	0.80 [0.52, 1.25]
Stein & Aronson, 1953	180	1361	372	1079	0.46 [0.39, 0.54]
Vandiviere et al, 1973	8	2537	10	619	0.20 [0.08, 0.50]
TPT Madras, 1980	505	87886	499	87892	1.01 [0.89, 1.14]
Coetzee & Berjak, 1968	29	7470	45	7232	0.63 [0.39, 1.00]
Rosenthal et al, 1961	17	1699	65	1600	0.25 [0.15, 0.43]
Comstock et al, 1974	186	50448	141	27197	0.71 [0.57, 0.89]
Comstock & Webster, 1969	5	2493	3	2338	1.56 [0.37, 6.53]
Comstock et al, 1976	27	16886	29	17825	0.98 [0.58, 1.66]
RE Model					0.49 [0.34, 0.70]

In the `metafor` package with the `forest()` function.

Exercises

1. Do a meta-analysis with the dat.bcg dataset with all steps as in R_12b_meta_analysis.Rmd, but with the risk difference as effect measure.
2. Do a meta-analysis with the dataset dat.begg1989 in the metafor package.
3. Do a meta-analysis with the dataset dat.bourassa1996 in the metafor package.
4. For help with the last two exercises, see the vignette https://cran.r-project.org/web/packages/metafor/metafor.pdf

Questions?

References

- `www.ccace.ed.ac.uk/research/software-resources/systematic-reviews-and-meta-analyses`.
- Handbuch für Cochrane Handbook for Systematic Reviews of Interventions: `https://training.cochrane.org/handbook`
- Pigott (2012). Advances in Meta-Analysis. Springer.
- Chen & Peace (2013). Applied Meta-Analysis with R. CRC Press.