Repeated Meta-Analysis

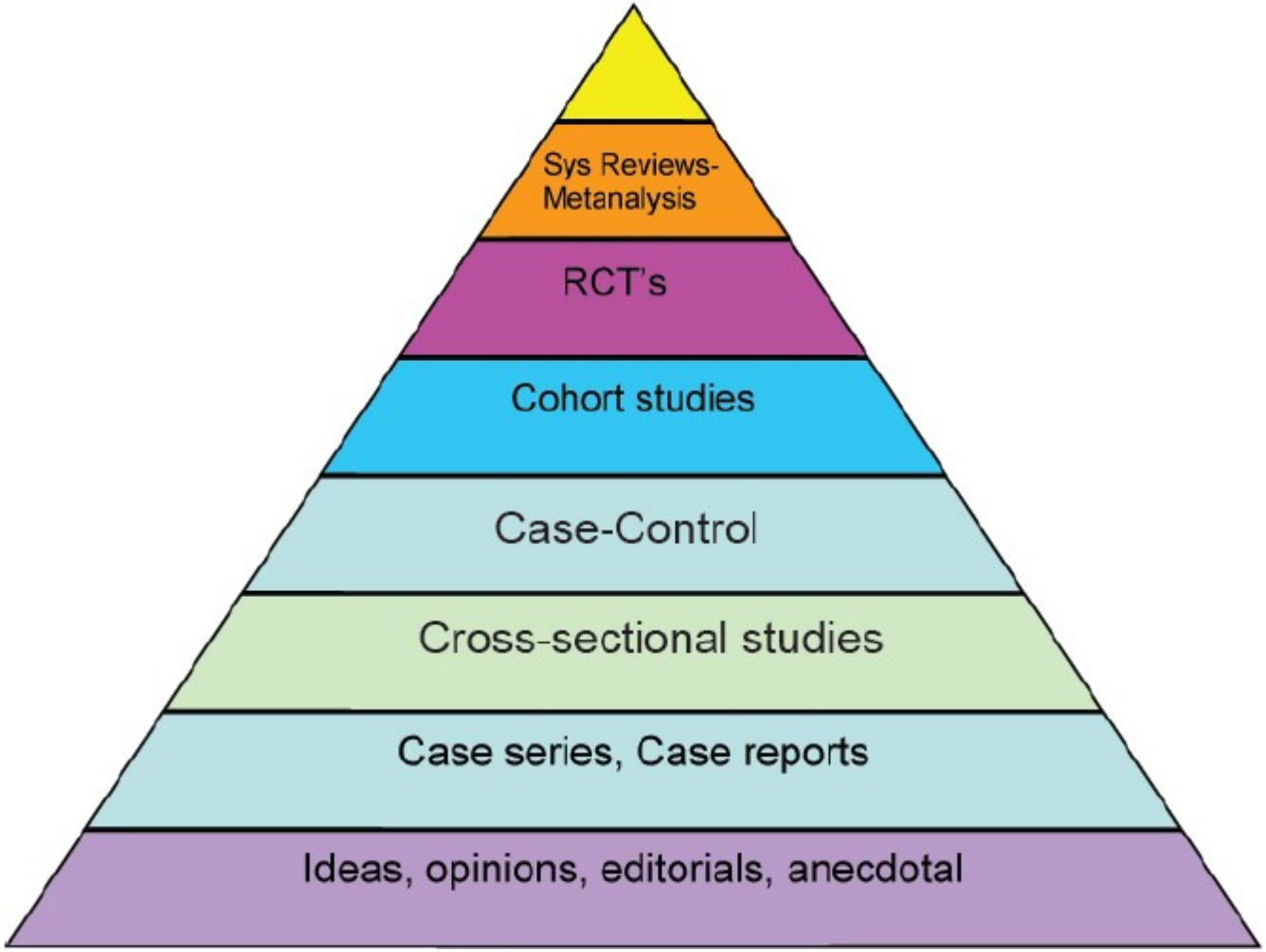
Pros and Cons of Multiplicity Adjustments

Martin Posch and Franz König

MEDIZINISCHE UNIVERSITÄT WIEN

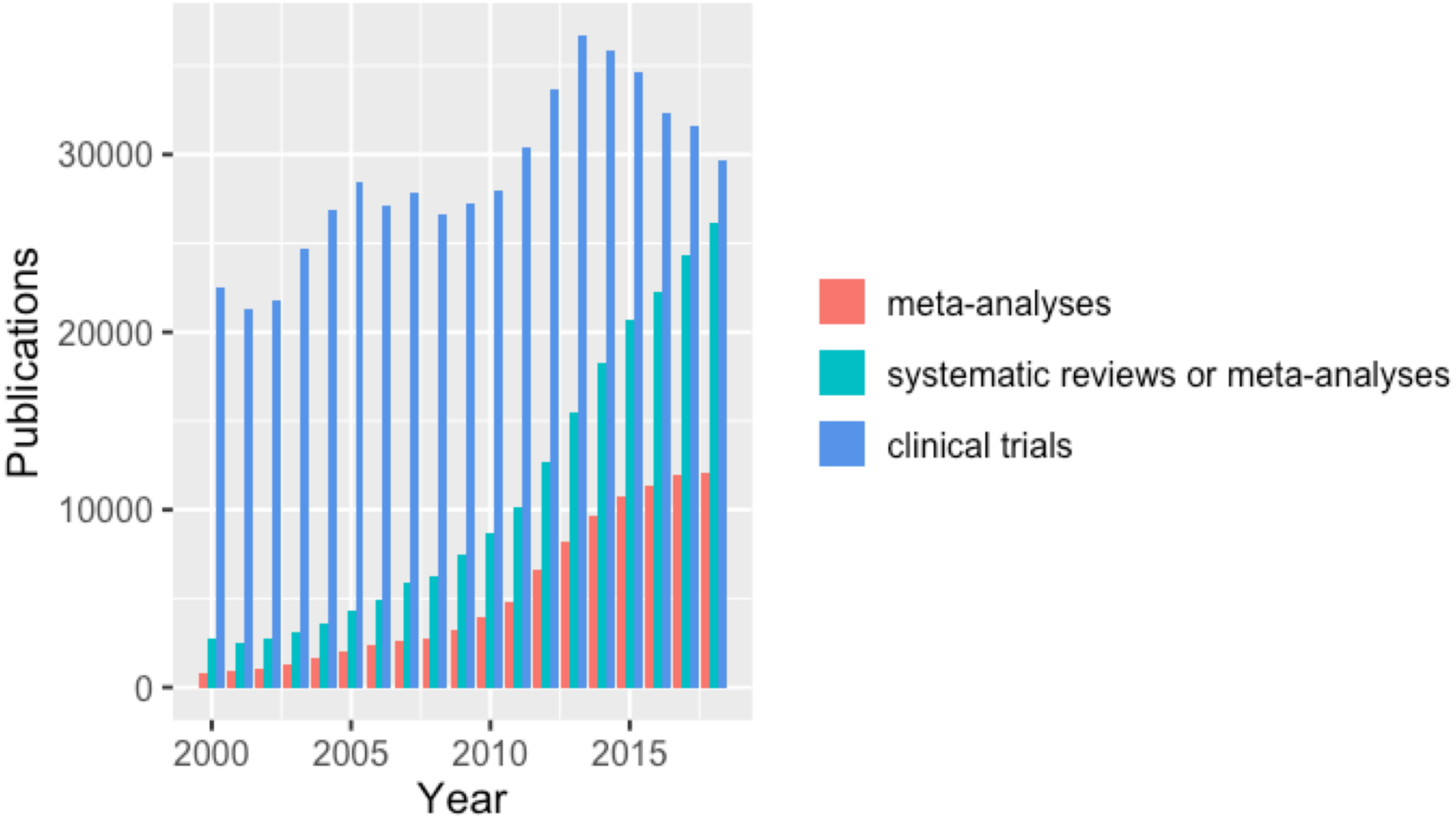
The Pyramid of Evidence

Guyatt et al JAMA (1954)



Source: https://blogs.bmj.com/adc/2014/11/03/the-crumbling-of-the-pyramid-of-evidence/

Publications by Type in PubMed



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The Mass Production of Redundant, Misleading, and Conflicted Systematic Reviews and Meta-analyses

JOHN P.A. IOANNIDIS

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Are systematic reviews and meta-analyses still useful research? We are not sure

Authors | Authors and affiliations

Morten Hylander Møller, John P. A. Ioannidis, Michael Darmon

What can go wrong with meta-analyses?

- Quality of the trials: “Garbage in – Garbage out”
- Publication bias
- Biased reporting of clinical trials (non-significant results less likely reported) (Goldacre, Nature, 2016)
- Conflicts of interest “Agenda Driven Bias”
- Meta-analyses are performed retrospectively
- Heterogeneity in analyses, inclusion exclusion criteria,….
- Underpowered meta-analyses
- Multiple meta-analyses on the same topic

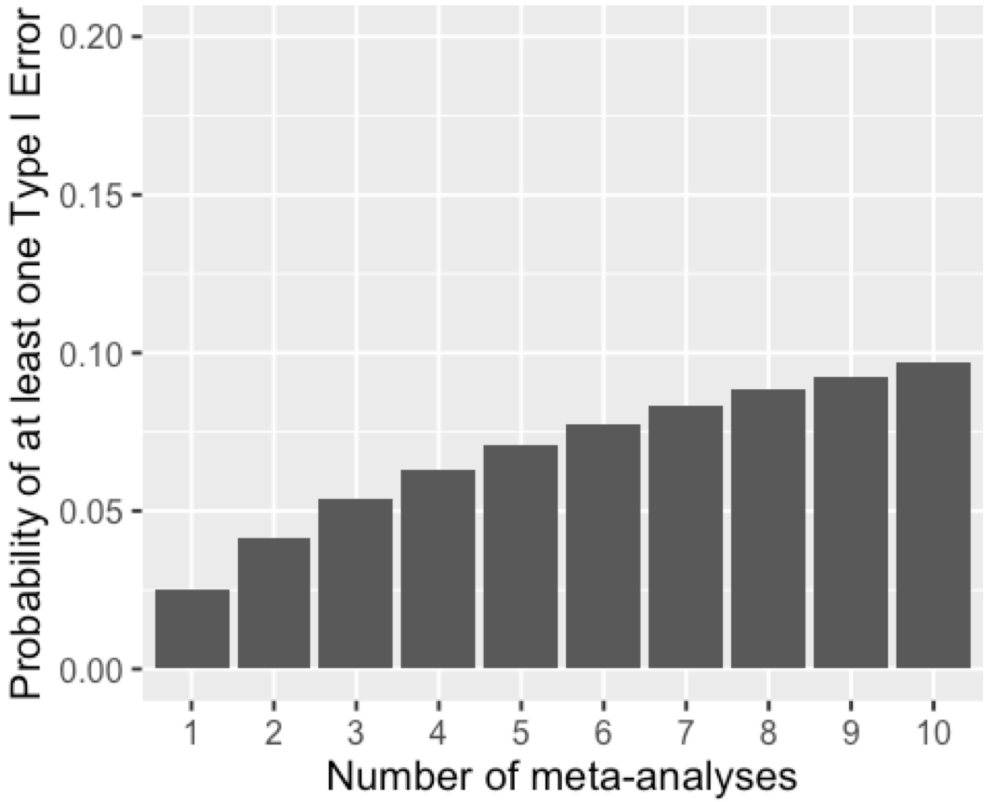
Multiple meta-analyses on the same topic

- Siontis et al (2013):
  Of 73 meta-analyses published in 2010
  - 49 (67%) at least 1 more meta-analysis published by 2012
  - Median: 2 meta-analyses, maximum 13 meta-analyses
- Many independent “overlapping” meta-analyses
- Updates of meta-analyses when there are
  - new relevant methods
  - new studies
  - new information on existing included studies

(Garner et al. 2016)

Updating meta-analyses and Type I Error

If meta-analysis are updated and a statistical test for each update is performed, the probability of at least one type I error increases:



Bias to false positive conclusions

- If meta-analyses are updated until a significant result is observed and then updates are stopped the probability to show a statistically significant treatment effect approaches one.
- To address this problem, statistical methods in analogy to group sequential trials have been developed
  - Trials sequential analysis (Wetterslev et al. 2008)
  - Sequential Meta-Analysis (Higgins et al. 2010)
  - The Law of the Iterated Logarithm (Hu et al. 2007)

Trial Sequential Analysis (Wetterslev et al. 2008)

- A maximum information and group sequential spending function (O'Brien Fleming) is pre-sepcified
- After each trial cumulative z-values are computed (with random or fixed effect model)
- Critical values depend on the information fraction at the analysis points
- Information = # of patients
- Controls the Type I and Type II error rate (for random effects model not exact)

Sequential Meta-Analysis (Higgins et al. 2010)

- In principle, similar to Trial Sequential Analysis,
- Information accounts for the heterogeneity between trials
- Bayesian estimation of information to avoid negative information increments

Law of the Iterated Logarithm approach (Hu et al. 2007)

- No maximum information to be specified
- More conservative
- Critical values need to be adjusted by simulation
- Information accounts for the heterogeneity between trials

Should Cochrane require adjustments for updated meta-analysis? (I)

- Status -2017: Members of Cochrane and others have developed techniques to manage Type I and II errors that can occur over time by updating and repeating meta-analyses.
- Some review authors used these techniques, Cochrane did neither encourage nor discourage their use at this point.
- Cochrane Scientific Committee recommendation (July 2017):

"Further technical examination of these two approaches is required before the Committee can decide whether there is a preferred approach or whether the methods provide added value to managing random error. An expert panel established will discuss further and report back to the Committee before arriving at a final decision."

Questions from Cochrane Scientific Committee recommendation statement/report July 2017

- "Is the problem with too little power in most meta-analysis when a required information is not reached with false positive support for the null hypothesis a sufficient problem that undermines the evidence produced by Cochrane reviews?
- Is the problem of false positive meta-analytic conclusions due to random error introduced by underpowered meta-analysis and the probability of repeated analyses rejecting the null hypothesis a sufficient problem that undermines the evidence produced by Cochrane Reviews?
- Is the current state of development for adjustment in cumulative meta-analyses to address, specifically, type II and type I errors sufficient to recommend their implementation in Cochrane Reviews?
- If so, can the CSC recommend one or more techniques?
- If not, what further knowledge or development does the CSC need to reach a satisfactory point to decide?"

Should Cochrane require adjustments for updated meta-analyses? (II)

Cochran Scientific Committee asked an expert panel whether Cochrane should **implement, and routinely adopt, sequential statistical** methods for its reviews

Expert Panel: **Christopher Schmid, Jackie Chandle**r, Stephen Senn, Jonathan Sterne, Elena Kulinskaya, Martin Posch, Kit Roes, Jo McKenzie

> **"The Expert Panel recommends against the use of sequential methods for updated meta-analyses in most circumstances within the Cochrane context. They should not be used for the main analyses, or to draw main conclusions."**

https://methods.cochrane.org/sites/default/files/public/uploads/tsa_expert_panel_guidance_and_recommendation_final.pdf (2018)

Main arguments

- Cochrane Reviews should provide the best summary of the evidence to date.
  The overall type I error is less relevant than the type I error at a specific analysis
- Cochrane authors should avoid binary interpretations (significant/not significant)
- A meta-analysis usually does not relate to a single decision
  - Different outcomes (benefit and harm)

Important differences between group sequential trials and updating meta-analysis

- The meta-analyst has **no control if and which trials are performed**. Group sequential stopping rules (for futility or superiority) will not be adhered to. Maximum information can hardly be pre-specified.
- Between trial heterogeneity estimates that determine the estimated information fractions may not be reliable.
- The design of later studies will depend on the results of earlier studies – thus, a sequential meta-analysis rather resembles an adaptive trial rather than a group sequential trial.

Tricky part

- *"Cochrane Review authors should interpret evidence on the basis of the estimated magnitude of the effect of intervention and its uncertainty (usually quantified using a confidence interval), rather than focusing primarily on the rejection of the null hypothesis of no treatment effect."*
- If the decision to update meta-analyses depends on the results of new trials, then the actual coverage probability of the conventional 95%-confidence interval is unknown …

Additional comments

- Bayesian Approaches: Formal decision analytic methods integrate effects of interventions estimated using meta-analyses and network meta-analyses with costs of the benefits and harm outcomes. Such methods **are now available and are more informative for decision makers than declarations of statistical significance** (whether adjusted or not).
- Sequential approaches may be considered **in the context of a prospectively planned meta-analysis** of a series of clinical trials.
- *For retrospective meta-analyses which are planned after trial results are available, type I error rates will not be reliable if adjusted or not.*

Conclusions of the Expert Panel

Cochrane should support the decision maker and end user by **providing the best and latest evidence, but that interpretation of that evidence should be left to the user** to make within their own context. The priority is to ensure the **decision maker is aware that the current estimate of the intervention effect may change** as further information becomes available. Most decision makers are well aware of this. Unless the evidence is overwhelmingly convincing, any decision may change or be reversed over time.

Addressing the challenges in meta-analyses

- Quality of the trials: “Garbage in – Garbage out”
  - *Grade Approach*
- Publication Bias
  - *Trial registration, publication of trial results in the registers*
- Biased reporting of clinical trials (non-significant results less likely reported) (Goldacre, Nature, 2016)
  - *Detailed prospective protocols with analysis plans, transparency*
- Conflicts of interest “Agenda Driven Bias” - *Transparency*
- Meta-analyses are performed retrospectively
  - *Register for meta-analyses (Prospero), Prospective meta-analyses*
- Heterogeneity in analyses, inclusion exclusion criteria,….
  - *Individual-level-meta-analyses*
- Multiple updated meta-analyses on the same topic
  - *For prospective analyses multiplicity adjustment*

Links

- https://methods.cochrane.org/methods-cochrane/repeated-meta-analyses
- **Cochrane Scientific Committee Recommendation statement/report (July 2017).** https://methods.cochrane.org/sites/default/files/public/uploads/scientific_committee_statement_report_cumulative_ma_final_301017.pdf
- **Expert panel consensus statement (December 2018):** https://methods.cochrane.org/sites/default/files/public/uploads/tsa_expert_panel_guidance_and_recommendation_final.pdf