BMS 18 SR & MA

Introduction

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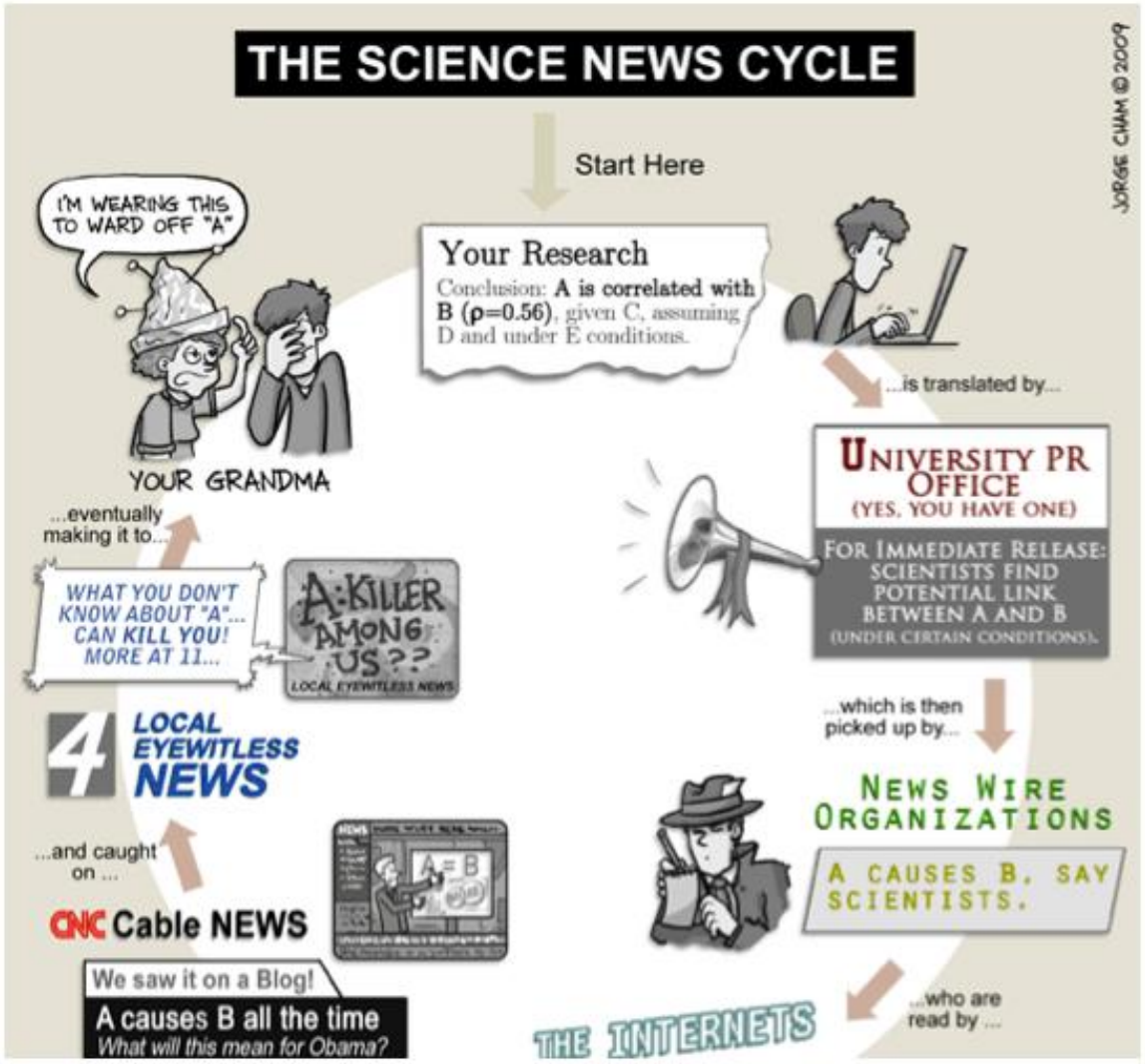
Radboudumc


Smoking is riskier than ever
Despite recent reports of sev-
Flu Outbreak
Few health issues are as imbued
The Childhood Obesity
When considering the health of
they do agree that problems will most
companies haven
exchange is esse
EFFECTS OF STRESS ON YOUR HE

The answer to your scientific question



https://www.wired.com/2011/06/the-science-news-cycle/

Your expectations

BMS18 - Teachers

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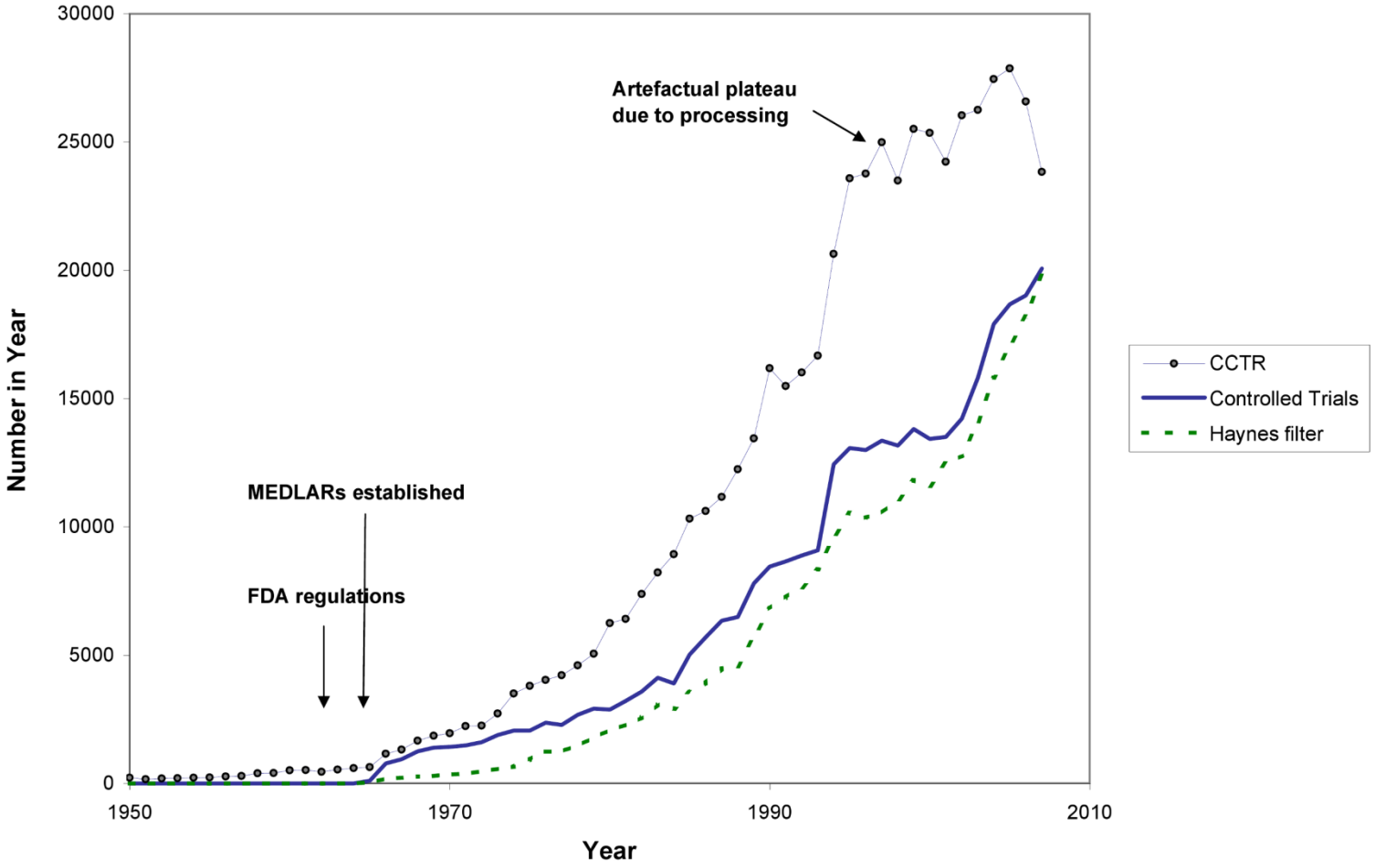
First edition !

- Start-up problems ???

- Tell us
- Or contact omt3@student.ru.nl if not satisfied with our solution

- Please help us to improve this course!

Number of published trials, 1950-2007



CCTR is the Cochrane Controlled Trials Registry
Haynes filter uses the “narrow” version of the Therapy filter in PubMed: ClinicalQueries

Bastian H, et al. (2010).

The answer to your scientific question… ?

OPEN ACCESS Freely available online

PLoS MEDICINE

Policy Forum

Seventy-Five Trials and Eleven Systematic Reviews a Day: How Will We Ever Keep Up?

Hilda Bastian[1]*, **Paul Glasziou**[2], **Iain Chalmers**[3]

1 German Institute for Quality and Efficiency in Health Care (IQWiG), Cologne, Germany, **2** Centre for Research in Evidence-Based Practice, Faculty of Health Sciences, Bond University, Gold Coast, Australia, **3** James Lind Library, James Lind Initiative, Oxford, United Kingdom

Thirty years ago, and a quarter of a century after randomised trials had become widely accepted, Archie Cochrane reproached the medical profession for not having managed to organise a "critical summary, by speciality or subspeciality, adapted periodically, of all relevant randomised controlled trials" [1]. Thirty years after Cochrane's reproach we feel it is timely to consider the extent to which

Summary Points

- When Archie Cochrane reproached the medical profession for not having critical summaries of all randomised controlled trials, about 14 reports of trials were being published per day. There are now 75 trials, and 11 systematic reviews of trials, per day and a plateau in growth has not yet been reached.
- Although trials, reviews, and health technology assessments have undoubtedly had major impacts, the staple of medical literature synthesis remains the non-systematic narrative review. Only a small minority of trial reports are being

Bastian H, Glasziou P, Chalmers I (2010) Seventy-Five Trials and Eleven Systematic Reviews a Day: How Will We Ever Keep Up?. PLOS Medicine 7(9): e1000326. https://doi.org/10.1371/journal.pmed.1000326
https://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1000326

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There is variation in study results

- Nowadays, an abundance of information on medical therapies is available, for example in the literature, where many clinical studies are reported.

- Results of different studies will show **variation**,
  and even worse:
  information can become contradictory or misleading along the way.

  - Three studies saying ‘yes’ versus one saying ‘no’: should this result in a positive conclusion?
  - The one that says “no” might outweigh the others in validity and power.
  - It is clearly too simple to just perform a head count.

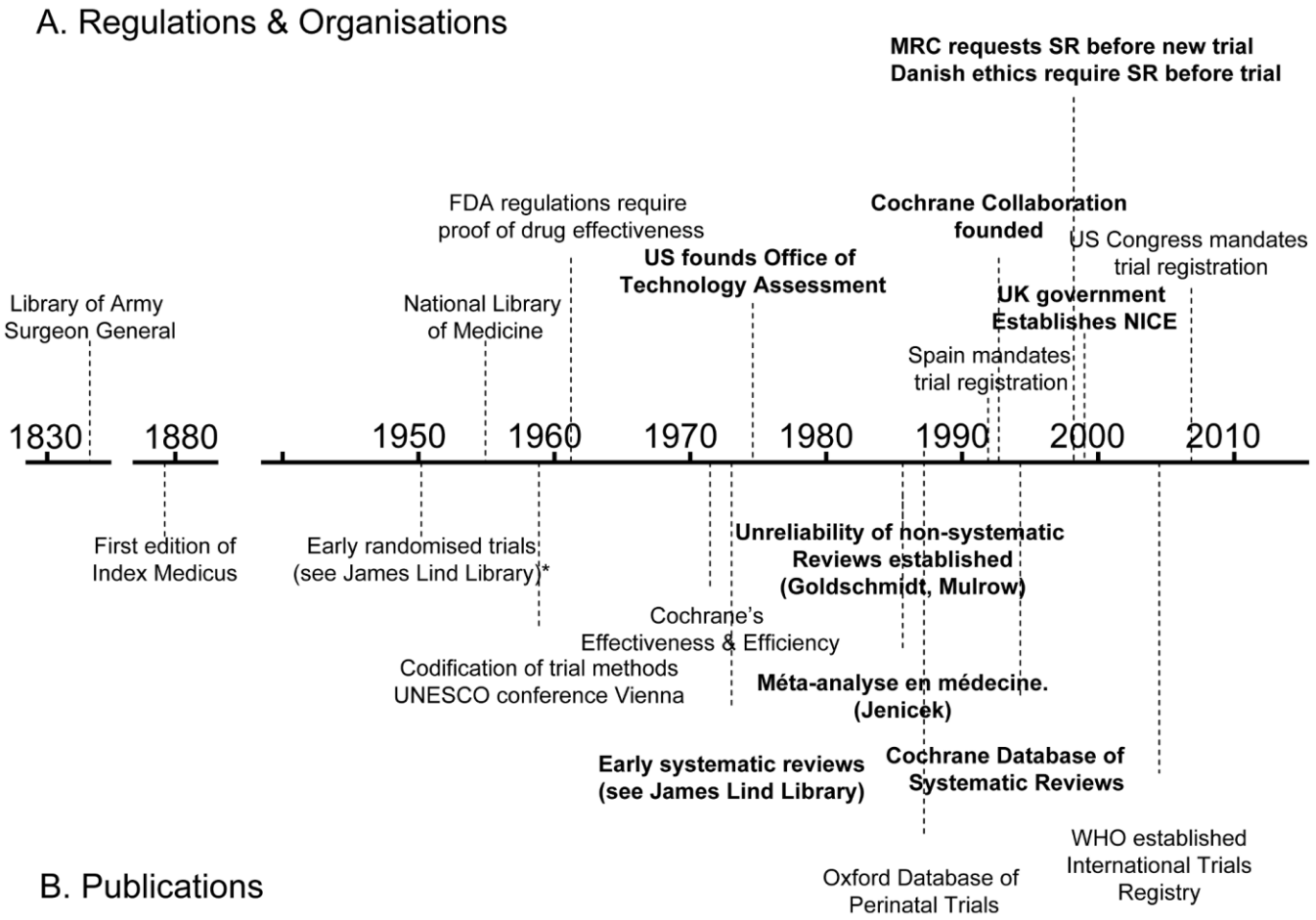
How to deal with all this?

Combine study results

If you want to summarize information that is available
in studies on some therapy or diagnostic test,
you can perform a (systematic) review
and/or a meta-analysis

Some history

Milestones in the development of trials and the science of reviewing trials

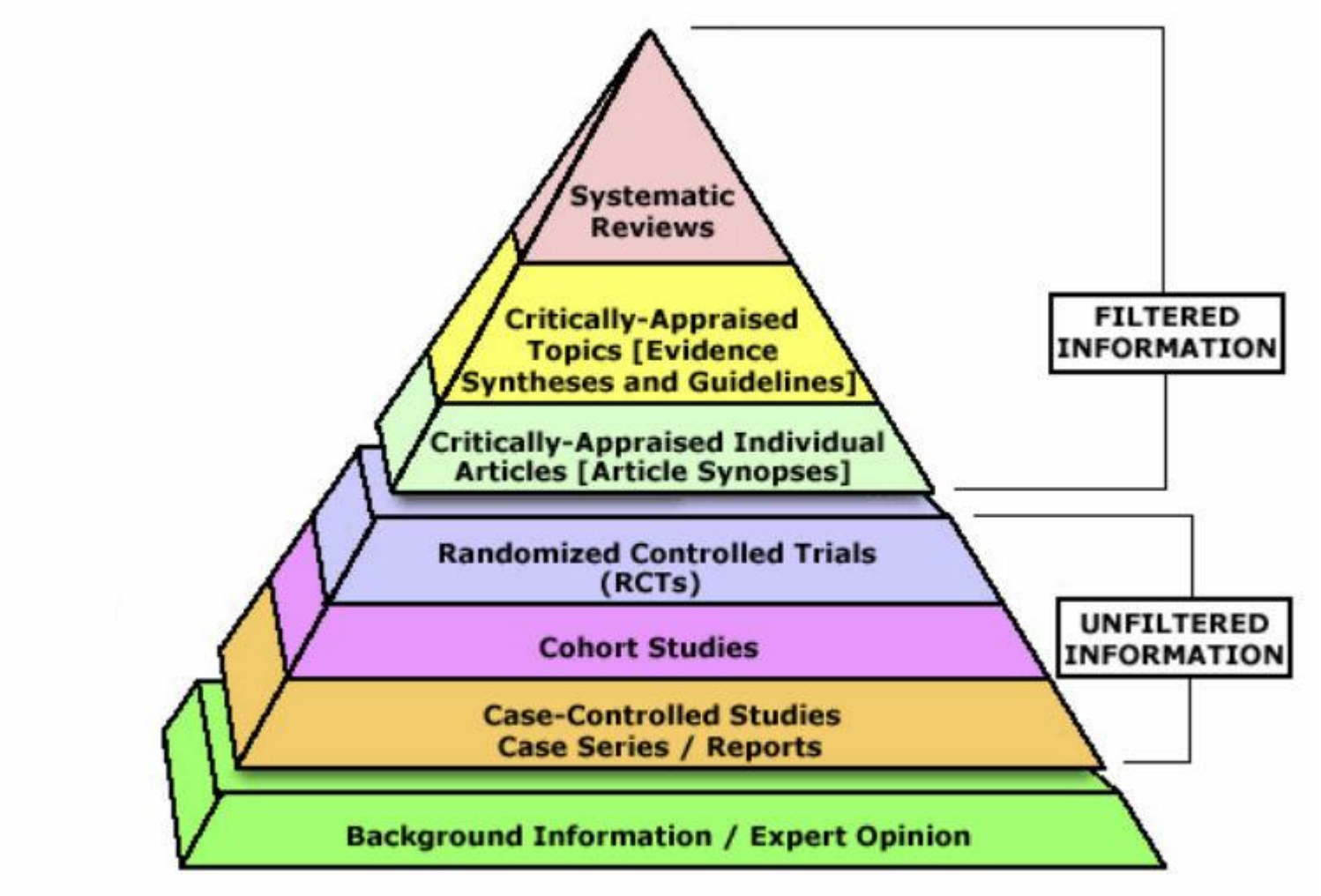


Bastian H, et al. (2010).

If quality of evidence would be considered a pyramid, what category should be placed at the peak?

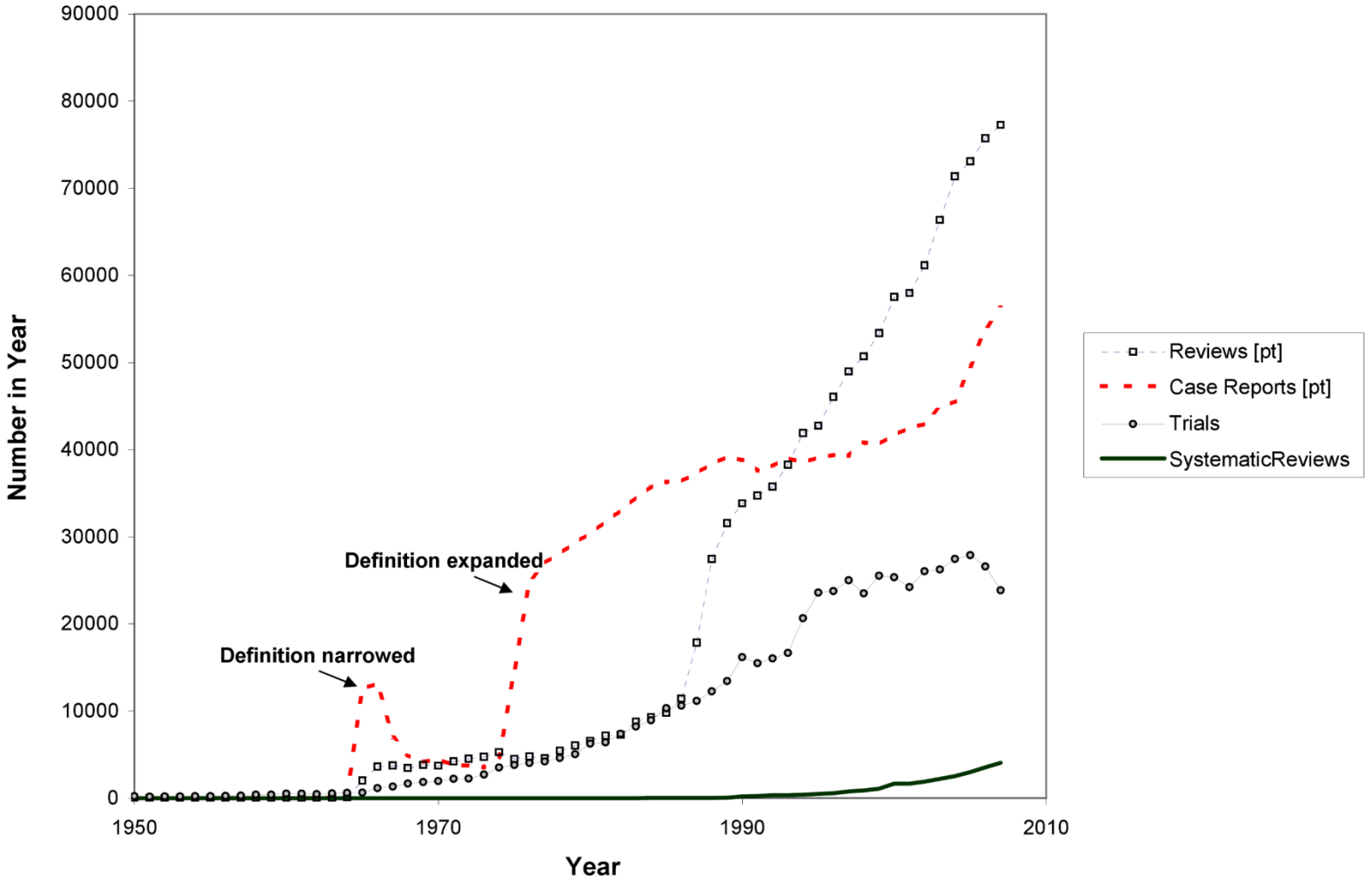
Egypt: the pyramids at Giza and the Sphinx. Credit: Wellcome Library, London. Wellcome Images

The Evidence-Based Medicine Pyramid



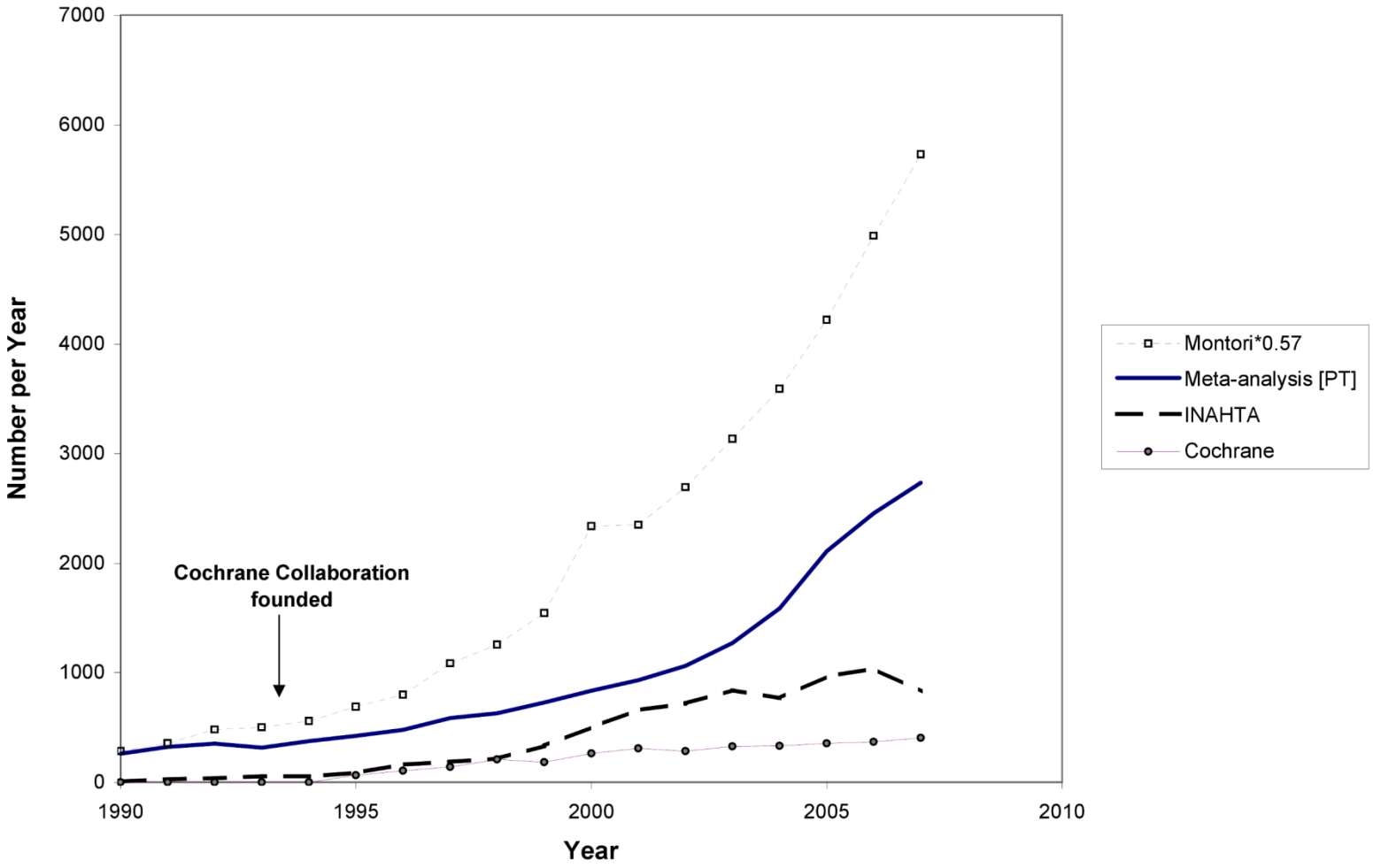
https://www.students4bestevidence.net/the-evidence-based-medicine-pyramid/

Increasing number of reviews, case reports, trials, and SRs, 1950-2007



Bastian H, et al. (2010).

Number of SRs in health care, 1990-2007



Bastian H, et al. (2010).

Systematic Review

- If you want to summarize information that is available in studies on some therapy or diagnostic test, you can perform a **systematic review**

- Systematic methods

- Transparant:
  - Inclusion- / exclusion criteria
  - Literature search strategies
  - Methods of analysis (meta-analysis)
  - Interpretation of results
  - Presentation of results

Systematic Review

Meta-analysis

- **Meta-analysis** is the quantitative method of combining and analyzing data from more than one study at once, and has its own statistical techniques.

- The **statistical technique** will have its effect on the final conclusion.

  - A **random effects** model may lead to a somewhat different conclusion than a fixed effects model.

  - **Subgroups** of patients might be of special interest, but bring their own statistical techniques.

Publication bias

Selective reporting can bias the conclusion seriously.

PB occurs when the likelihood of publication differs between studies, based on certain characteristics of the study or its results.

E.g. less publication of:

- Neutral (or negative) results
- Results based on small sample sizes
- Results which contradict current ideology

Often in combination with selective outcome reporting

RCTs suffer from bias

BMJ large meta-epidemiological study, 2008

Objective

- To examine whether the association of inadequate or unclear allocation concealment and lack of blinding with biased estimates of intervention effects varies with the nature of the intervention or outcome.

Data sources

- 146 MAs including 1346 trials, wide range of interventions and outcomes.

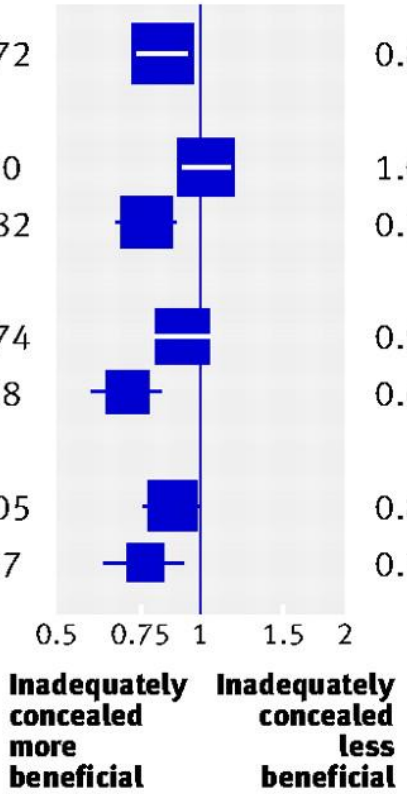
Main outcome measures

- Ratios of odds ratios quantifying the degree of bias associated with
  - inadequate or unclear allocation concealment
  - lack of blinding
  - for trials with different types of intervention and outcome.
- A ratio of odds ratios <1 implies exaggerated intervention effect estimates.

Wood L, et al., BMJ 2008; 336:601

Ratios of odds ratios comparing estimates of intervention effects in 532 trials with inadequate or unclear allocation concealment versus 272 trials with adequate concealment

Comparison (No of meta-analyses)	No of trials*	Ratio of odds ratios	Ratio of odds ratios (95% CI)	P value of test of interaction	Variability in bias† (P value)
Overall (102)	532 *v* 272		0.83 (0.74 to 0.93)	–	0.11 (<0.001)
All cause mortality (23)	119 *v* 90		1.01 (0.90 to 1.15)	0.002	0.02 (0.24)
Other outcomes (79)	415 *v* 182		0.76 (0.66 to 0.87)		0.14 (<0.001)
Objective outcomes (62)	310 *v* 174		0.91 (0.80 to 1.03)	0.009	0.11 (<0.001)
Subjective outcomes (40)	222 *v* 98		0.69 (0.59 to 0.82)		0.07 (0.011)
Drug intervention (65)	411 *v* 205		0.87 (0.76 to 1.00)	0.27	0.09 (<0.001)
Other intervention (37)	121 *v* 67		0.77 (0.64 to 0.93)		0.16 (<0.001)



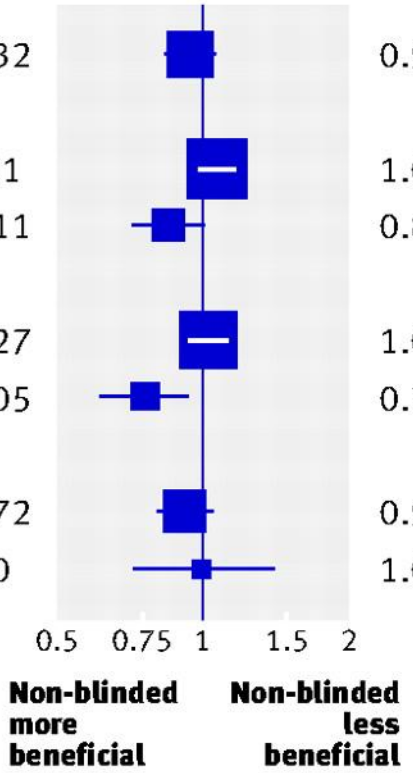
* Inadequately or unclearly concealed *v* adequately concealed

† Between-meta-analysis heterogeneity variance

Wood L, et al., BMJ 2008; 336:601

Ratios of odds ratios comparing intervention effect estimates in 314 non-blinded trials versus 432 blinded trials

Comparison (No of meta-analyses)	No of trials*	Ratio of odds ratios	Ratio of odds ratios (95% CI)	P value of test of interaction	Variability in bias† (P value)
Overall (76)	314 *v* 432		0.93 (0.83 to 1.04)	–	0.11 (<0.001)
All cause mortality (18)	79 *v* 121		1.04 (0.95 to 1.14)	0.011	0.01 (0.27)
Other outcomes (58)	235 *v* 311		0.83 (0.70 to 0.98)		0.18 (<0.001)
Objective outcomes (44)	210 *v* 227		1.01 (0.92 to 1.10)	0.01	0.08 (<0.001)
Subjective outcomes (32)	104 *v* 205		0.75 (0.61 to 0.82)		0.14 (0.001)
Drug intervention (57)	250 *v* 372		0.92 (0.81 to 1.05)	0.66	0.10 (<0.001)
Other intervention (19)	64 *v* 60		1.00 (0.71 to 1.39)		0.22 (0.003)



* Non-blinded *v* blinded

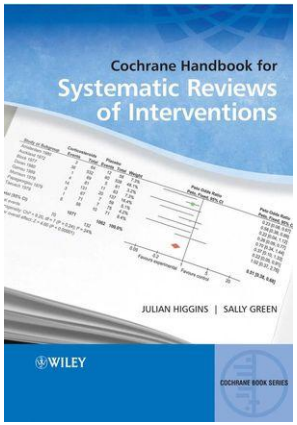
† Between-meta-analysis heterogeneity variance

Grading the evidence

- In the end, your findings must be based on the **grading** of the full body of evidence.
- Efforts to minimise bias are particularly important when objective measurement of outcomes is not feasible
- Authors of systematic reviews, and those critically appraising trials, should routinely assess the risk of bias in results associated with the way each trial was done.
- Such assessments should be outcome specific.
  The Cochrane Collaboration has formulated detailed guidance on how to do this (see www.cochrane. org/resources/handbook)
- Systematic reviewers should report meta-analyses restricted to trials at low risk of bias either as the primary analysis or in conjunction with less restrictive analyses.

Literature

- ***Cochrane Handbook for Systematic Reviews of Interventions***
  https://training.cochrane.org/handbook
  - All basics available in a free online book
  - The handbook used by the Cochrane Review authors and recommended by the Cochrane Collaboration



- **Cochrane** is a global independent network of researchers, professionals, patients, caregivers and people interested in healthcare.

- It's the largest, international organization, that produces systematic reviews. They study all of the best available evidence generated through research, and make it easier to inform decisions about health. It is a not for profit organization with collaborations from more than 120 countries.

- **Finding What Works in Health Care.**
  - By the Institute of Medicine. They outline the standards for doing systematic reviews.
  - This book is freely available online (use Google or another search engine).

- **Borenstein at al. Introduction to Meta-Analysis**
  - More technical details, but very readable. Not for free, but several chapters can be found online.
  - https://onlinelibrary.wiley.com/doi/book/10.1002/9780470743386

BMS18 - Content

Wednesday track: Peer-review of systematic review paper

- On Wednesdays (self study time) you will be involved in the peer review of a systematic review. Aims of this exercise are two-fold: you will learn to critically read a systematic review paper and to peer review.

Thursday / Friday track: conducting an SR and MA and evaluating the results

- We will practice with many aspects that are related to conducting an SR/MA, starting from the formulation of the research question, the literature search and evaluation of the study validity, data extraction, the actual meta-analysis, and the summary of the results.

Week	Peer review	Conducting an SR & MA	
	Wednesday	**Thursday**	**Friday**
1	Introduction SR article	• Introduction • How to peer-review • PICO • Literature search	• How to conduct an MA (fixed & random effects models, sensitivity analyses, frequently used software)
2	Peer review part 1	• Study validity and data extraction	• Heterogeneity • Subgroup analysis and meta-regression • Ecological fallacy
3	Peer review part 2	• Publication bias • Descriptive vs. quantitative summary • Meta-analysis in various fields (not only in humans!)	• Grading the evidence
4	Peer review part 3 including recommendation on paper acceptance	• Outlook to other types of SRs/Mas (diagnostic tests, prognostic studies, networks of interventions, individual participant data) • Question hour	• Exam 9:30-12:30 • Hand in peer-review before 24:00

After completion of the course, you are able to

- Explain the importance of systematic reviews and meta-analysis in preclinical and clinical health research, including their strengths and limitations
- Distinguish several types of systematic reviews and meta-analyses, i.e. based on
  - animal or human data
  - prognostic, diagnostic or intervention studies,
  - aggregate or individual participant data,
  - paired comparisons or networks of comparisons of interventions
- Design a research question, that can be answered with a systematic research and meta-analysis
- Select relevant studies, asses their validity and extract relevant data from these studies
- Apply the techniques for meta-analysis, including meta-regression and subgroup meta-analysis with use of digital ruler and meta-analysis software.
- Evaluate critically the evidence as provided by a systematic review and meta-analysis using the Grade system.
- Create a peer-review of a scientific paper on a systematic review and meta-analysis.