Research synthesis
Methods, applications and challenges

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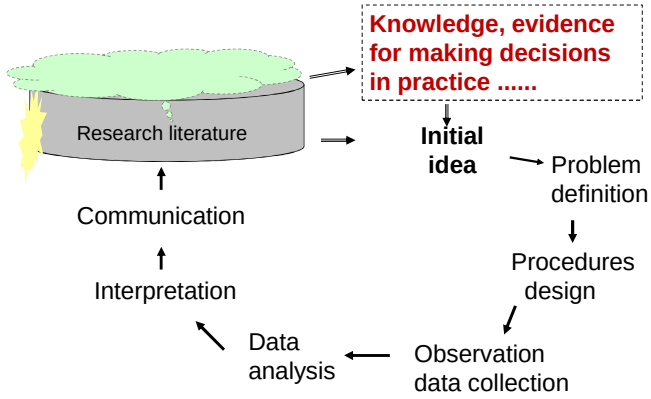
Research process



Adopted from: Graziano and Raulin, 2004

"The foundation of science is the cumulation of knowledge from the results of many studies"

"There are two steps to the cumulation of knowledge: (1**) the cumulation of results across studies to establish facts**, and (2) the formation of theories to organize the facts into a coherent and useful form."

Hunter & Schmidt. 2004

Chalmers I, Hedges LV, Cooper H:

*A brief history of **research synthesis***

Evaluation & the Health Professions, 2002, 25: 12-37)

"Although the need to synthesize research evidence has been recognized for well over two centuries, explicit methods for this form of research were not developed *until the 20th century*. The development of methods to reduce statistical imprecision using quantitative synthesis (meta-analysis) preceded the development of methods to reduce biases, the latter only beginning to receive proper attention during the *last quarter of the 20th century*."

Why Research Synthesis?

* Expanding volume of published literature
* Different or controversial results from studies on the same topic
  - insufficient statistical power
  - possible biases in research
  - diversity in study-level variables

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Information overload/explosion

75 trials and 11 systematic reviews a day: **How will we ever keep up?**

When Archie Cochrane reproached the medical profession for not having critical summaries of all RCTs, 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.

Bastian H, Glasziou P, Chalmers I (2010) Seventy-Five Trials and Eleven Systematic Reviews a Day: How Will We Ever Keep Up? PLoS Med 7(9): e1000326. doi:10.1371/journal.pmed.1000326

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READING BETWEEN THE LINES

On the impossibility of being expert

More scientific papers are being published than ever before. **Alan G Fraser** and **Frank D Dunstan** call for that new strategies to deal with this avalanche of information

Every doctor has an ethical duty to keep up to date. Is this just getting more difficult or has it already become impossible? Since Alvin Toffler coined the phrase "information overload" in 1970,[1] the growth of scientific and medical information has been inexorable. There are now 25 400 journals in science, technology, and medicine, and their number is increasing by 3.5% a year[2]; in 2009, they published 1.5 million articles.[3] PubMed now cites more than 20 million papers.

One response of the medical profession to the increasing scientific basis and clinical capacity of medicine has been to increase subspecialisation. This may restrict the breadth of knowledge of the ultraspecialist, but can such subspecialists maintain their depth of expertise? Taking one medical subspecialty as an example, we have examined the gap between information and human capacity, and we explore the implications for any doctor who wants to practise evidence based medicine.

tomography (CT), and coronary arteriography, as well as cardiovascular ultrasound (strategies 5-6, table).

All searches were performed for each year from 1966 (the year before ultrasonics was introduced as a search term in PubMed; echocardiography was added in 1973) to 2009. Trends in papers on echocardiography were modelled: a good fit—from a cubic model containing time, the square of time, and the cube of time—was used to predict the numbers of publications to the end of 2010 and annually to 2015.

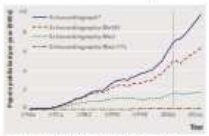

Fig 1: Trends in numbers of papers listed each year in PubMed, according to search strategies 1-6 in table. The numbers to the right of the vertical line, after 2009, are projected totals. MeSH=medical subject heading. Maj=as a main topic; CTs=controlled clinical trials

Results

which time at least 82 142 more papers would have been added, accounting for another eight years and 78 days. Before our recruit could catch up and start to read new manuscripts published the same day, he or she would—if still alive and even remotely interested—have read 408 049 papers and devoted (or served a sentence of) 40 years and 295 days. On the positive side, our recruit would finish just in time to retire.

Reading only the major studies would need more than four years for strategy 3 and more than five years for strategy 6. Alternatively, if only one year was allocated for study, then for strategy 3 our

The term '**meta-analysis**' was coined by Glass in 1976

Glass GV. *Primary, secondary, and meta-analysis of research. Educational Researcher 1976, 10:3-8*

"**the analysis of analyses**"

"the statistical analysis of a large collection of analysis results from individual studies for purposes of integrating the findings"

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Meta-analysis

To provide a **weighted** average, by quantitatively combining results of individual studies

To investigate heterogeneity across studies:

- subgroup analysis
- meta-regression

Weight in meta-analysis

Weight in meta-analysis: the contribution of the individual studies to the summary statistic

Larger studies are given more weight than smaller studies

- Sample size
- Inverse of variance
- Study validity

From **traditional literature review** to **systematic review**

Traditional literature review

- possible bias, errors
- inadequate use of available existing information

Systematic review

- reducing bias in research synthesis
- reducing statistical imprecision (meta-analysis)

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Systematic review -definition

A review of a clearly formulated question that uses *systematic* and *explicit* methods to identify, select and critically appraise relevant research, and to collect and analyse data from the studies that are included in the review.

Cochrane Reviewers' Handbook 4.1.5

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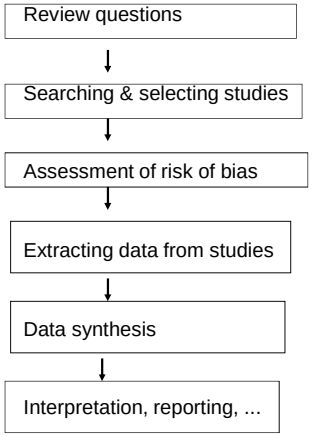
Systematic review: main steps



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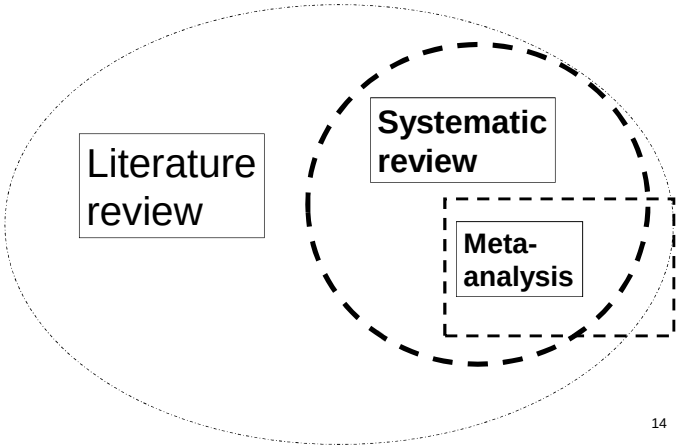
Literature review, systematic review, meta-analysis



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Using research synthesis:

- to answer the same research question as in primary studies
- to identify and, if possible, 'answer new questions with old data'

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Research synthesis in medicine and health science

- Evidence-based decision making and practice
- Recommending or proposing further research required
- Interpreting findings from new primary studies

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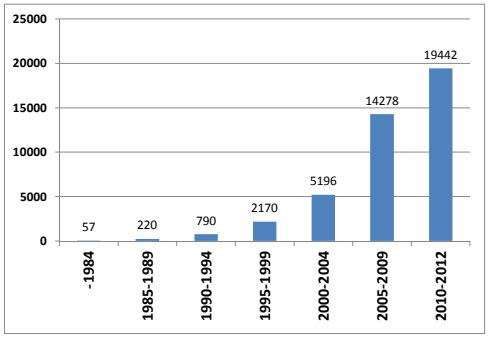
Number of articles with the term ‘systematic review’ or ‘meta-analysis’ in title

(a search of PubMed by 26-11-12)



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From systematic review to alternative approaches

Criticism of systematic review approach

Aggregative rather than interpretive

Not very useful for complex body of evidence

Alternative research synthesis approaches

Realist review (Pawson 1997)

Meta-narrative approach (Greenhalgh 2005)

Critical interpretive synthesis (Dixon-Woods 2006)

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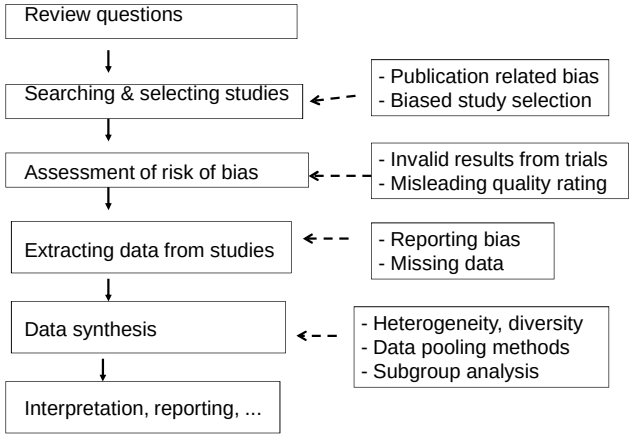
Research synthesis: main limitations

- Depending on published literature, and restricted by data reported

- Retrospective; bias may be introduced

Research synthesis process and related methodological challenges



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Publication Bias

The tendency to submit or accept studies for publication based on the direction or strength of the study findings.

Related biases:

Outcome reporting bias
Language bias
Grey literature bias
Time lag bias

Consequence of publication bias

- Significant or “positive” results are more likely to be published than non-significant or “negative” results.
- It threatens the validity of research synthesis

Open access, freely available online

Essay

Why Most Published Research Findings Are False

John P. A. Ioannidis

Summary

There is increasing concern that most current published research findings are false. The probability that a research claim is true may depend on study power and bias, the number of other studies on the same question, and, importantly, the ratio of true to no relationships among the relationships probed in each scientific field. In this framework, a research finding is less likely to be true when the studies conducted in a field are smaller; when effect sizes are smaller; when there is a greater number and lesser preselection of tested relationships; where there is greater flexibility in designs, definitions, outcomes, and analytical modes; when there is greater financial and other interest and prejudice; and when more teams are involved in a scientific field in chase of statistical significance. Simulations show that for most study designs and settings, it is more likely for

factors that influence this problem and some corollaries thereof.

Modeling the Framework for False Positive Findings

Several methodologists have pointed out [9–11] that the high rate of nonreplication (lack of confirmation) of research discoveries is a consequence of the convenient, yet ill-founded strategy of claiming conclusive research findings solely on the basis of a single study assessed by formal statistical significance, typically for a p-value less than 0.05. Research is not most appropriately represented and summarized by p-values, but, unfortunately, there is a widespread notion that medical research articles

It can be proven that most claimed research findings are false.

is characteristic of the field and can vary a lot depending on whether the field targets highly likely relationships or searches for only one or a few true relationships among thousands and millions of hypotheses that may be postulated. Let us also consider, for computational simplicity, circumscribed fields where either there is only one true relationship (among many that can be hypothesized) or the power is similar to find any of the several existing true relationships. The pre-study probability of a relationship being true is $R/(R+1)$. The probability of a study finding a true relationship reflects the power $1-\beta$ (one minus the Type II error rate). The probability of claiming a relationship when none truly exists reflects the Type I error rate, α. Assuming that c relationships are being probed in the field, the expected values of the 2×2 table are given in Table 1. After a research finding has been claimed based on

PLoS Med. 2007 Jun;4(6):e215.

Health Technology Assessment 2010; Vol. 14: No. 8

Dissemination and publication of research findings: an updated review of related biases

F Song, S Parekh, L Hooper, YK Loke, J Ryder, AJ Sutton, C Hing, CS Kwok, C Pang, and I Harvey

http://www.hta.ac.uk/fullmono/mon1408.pdf

February 2010
DOI: 10.3310/hta14080

Health Technology Assessment
NIHR HTA programme
www.hta.ac.uk

HTA

Diversity and heterogeneity across primary studies

Random error **(chance)**

Variations in **patients**

Variations in **interventions**

Different outcome measures

Methodological & reporting quality

. . . . .

Other methodological challenges

- Lack of directly relevant evidence
  - Indirect or mixed treatment comparison
  - Uncertain generalizability
  - Surrogate or intermediate outcome measures
- Overview of systematic reviews

  (analysis of analyses of analyses?)
- Systematic reviewing
  - observational studies
  - qualitative research studies
  - studies of diagnostic tests
  - studies of complex healthcare interventions

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Some practical issues

- Advanced information technology:
  space limitation is no longer an excuse for inadequate reporting
- Increasing access to data from primary studies
- Multiple systematic reviews of the same primary studies

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Methodological research on R.S. methods at MED

- Publication and related bias
- Indirect comparison of competing interventions
- Theory-orientated systematic reviews of complex interventions

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Thank you

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