

What is a systematic review?

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BRITAIN'S BEST-SELLING QUALITY DAILY

Wednesday, April 16, 2008 No 47,546 80p

Vitamin pills 'can increase the risk of early death'

By Kate Devlin
Medical Correspondent

WHAT IS THE GOOD

men's increased the risk of an early death by four per cent.

Pope tells of his shame



I mean to continue, insists bruised Brown

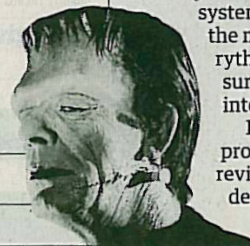
By Andrew Porter,
Robert Winnett
and Myers Butterworth

GORDON Brown was forced to defend his premiership and in particular his economic record yesterday as he faced mounting criticism over the credit crisis.
 As the biggest mortgage lenders embroiled his calls to reduce the cost of borrowing.



Bad science Celebs decry evidence on vitamin pills

Ben Goldacre



And so our ongoing project to learn about evidence through nonsense enters its sixth improbable year. This week the assembled celebrity community and vitamin pill industry will walk us through the pitfalls of reading through a systematic review and meta-analysis from the Cochrane Collaboration, an international not-for-profit organisation set up 20 years ago to create transparent, systematic, unbiased reviews of the medical literature on everything from drugs, through surgery, to community interventions.

Last week Cochrane produced a gold-standard review, looking at 67 trials describing the experiences



Review said vitamin pills may increase risk of dying Photograph: Fiona Hanson/PA

Antioxidant supplements for prevention of mortality in healthy participants and patients with various diseases (Review)

Bjelakovic G, Nikolova D, Gluud LL, Simonetti RG, Gluud C



This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2010, Issue 1

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en.wikipedia.org/wiki/Systematic_review
 A **systematic review** is a literature review focused on a research question that tries to identify, appraise, select and synthesize all high quality research evidence ...
 Characteristics - Cochrane Collaboration - Strengths and weaknesses - See also
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 by P Hemingway - Related articles
 research evidence. ○ **Systematic reviews** attempt to bring the same level of rigour to ...
 one review it is called a mixed-method **systematic review**. ○ Systematic ...

[PDF] **Systematic Reviews: CRD's guidance for ...** University of York

Where do I find the best evidence?

The Literature

- Information overload
- 2 million articles published a year
- 20,000 biomedical journals
- 500 dental journals
- Unpublished studies
- Language

Where do I find the best evidence?

Textbooks/Reviews

- Written by “experts”
- Quickly out of date

Where do I find the evidence?

- Ask someone
- Look in filing cabinet
- Consult a text book
- Search an electronic database
 - Bibliographic- *Medline, Embase, Lilacs*
 - Secondary publications- *Cochrane, Database of Systematic Reviews*

Where do I find the best evidence?

Electronic Databases

- Identify <50% of available relevant articles
- Most missed citations are on Medline
- Indexing is poor
- Title, abstract and ‘key words’
- Structured abstracts

Where do I find the best evidence?

Hand Searching

- Only reliable way to identify all relevant articles
- Boring, tedious and time consuming
- Must try to avoid duplication of effort

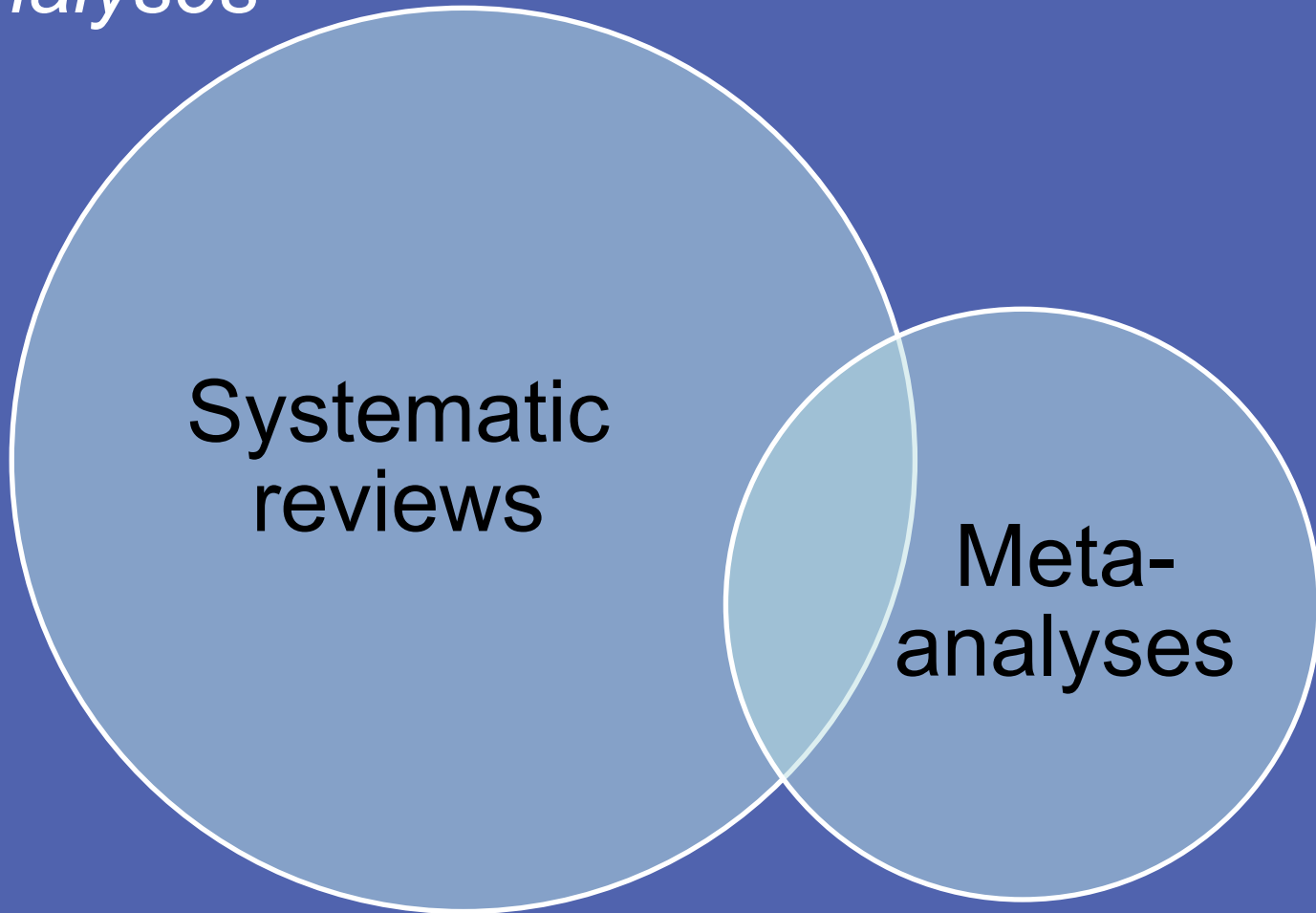


One solution to this problem is using
systematic reviews of the evidence

What are systematic reviews?

- A systematic review is the process of systematically locating, appraising and synthesising evidence from scientific studies in order to obtain a reliable overview

Terminology: systematic review & meta analyses



How are Systematic Reviews different?

Traditional reviews

- Individual opinions based on haphazardly selected data rather than comprehensive systematic assessment
- Inconsistent, prone to error and unconvincing

Systematic reviews

- Prepared as methodically and as carefully as a piece of primary research
- Describe how trials were identified, selected and evaluated
- Checked and verified

Why are they important ?

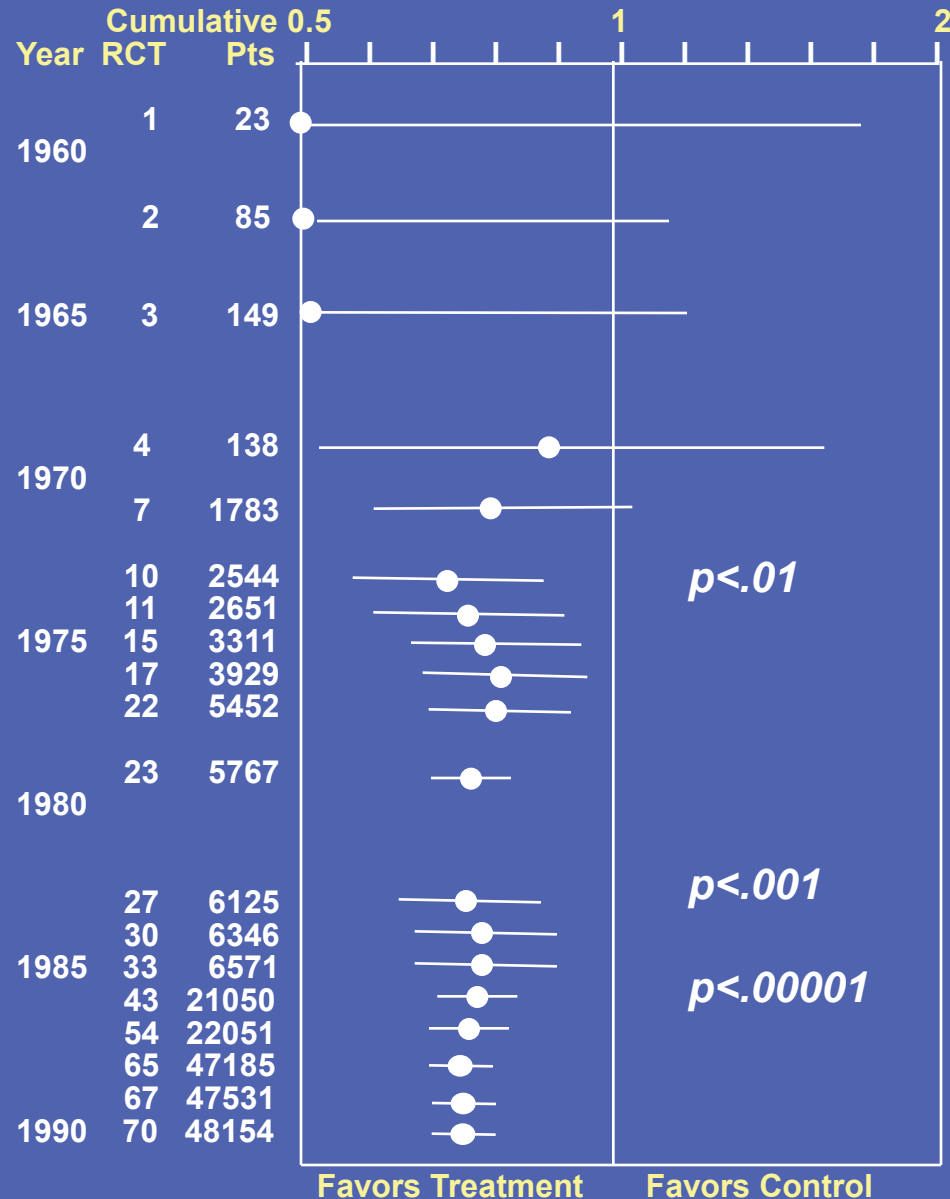
- Reduce large quantities of information into manageable portions
- Formulate policy and develop guidelines
- Efficient use of resources
- Increased power/precision
- Limit bias and improve accuracy

Antman 1992 examined the treatment of acute myocardial infarction and compared:

- Recommendations in textbooks and reviews
- Results of meta analysis (if they had been done)

A. Thrombolytic Therapy (clot-busters)

Odds Ratio (Log Scale)



Textbook/Review Recommendations

Routine	Specific	Rare/Never	Experimental	Not Mentioned
				21
				8
			1	10
			1	2
			2	8
				7
				8
	1			12
	1		8	4
	1		7	3
5	2		2	1
15	8			1
6	1			

Results

- Discrepancies between meta- analysis and recommendations by reviewers
- Review articles failed to mention important new advances and delayed recommending effective preventive measures
- Harmful treatments continued to be recommended by experts

Systematic review process

- **Structured process involving several steps (all described in review protocol):**
 1. Well formulated question
 2. Comprehensive data search
 3. Unbiased selection and abstraction process
 4. Assessment of papers
 5. Synthesis of data

1. Well formulated question

How effective is flossing in addition to toothbrushing, as compared with toothbrushing alone, in the management of bleeding gums and tooth decay?

1. Well formulated question

- **P**articipants
- **I**nterventions (**E**xposure)
- **C**omparisons
- **O**utcomes

This question is...

- The lynchpin of a systematic review protocol
- Leads on to inclusion and exclusion criteria
- Helps build up a search strategy
- Gets authors thinking about what data to extract, and what quality criteria are important
- Allows authors to decide on their analysis now

Inclusion criteria | Specifics

- **Participants**

- *All ages? People with restricted dexterity? orthodontic patients?*

- **Interventions**

- *Self performed (supervised)? Mouthrinses?*

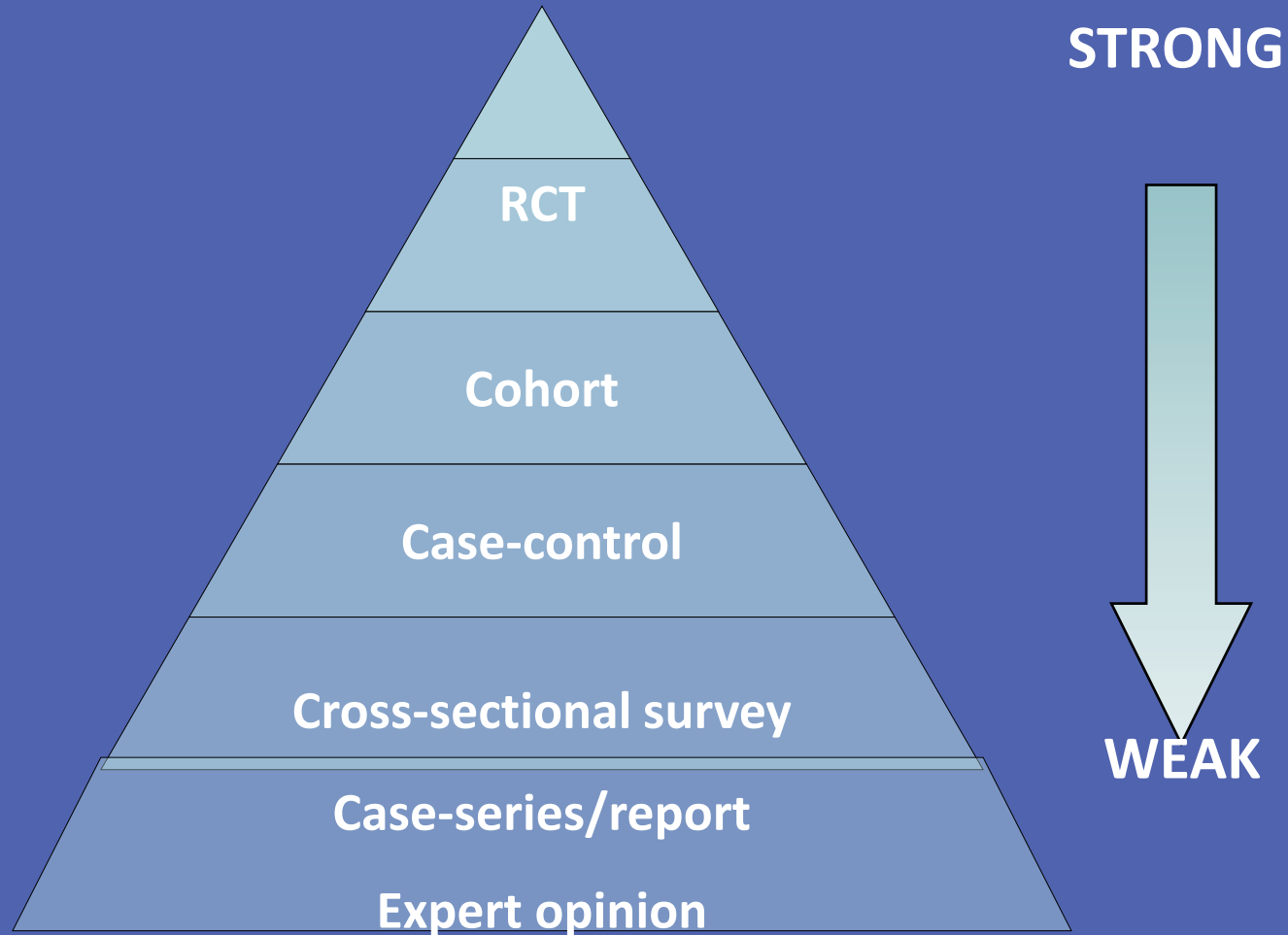
- **Comparisons**

- *Toothbrushing with out flossing- is rinsing OK*

- **Outcomes**

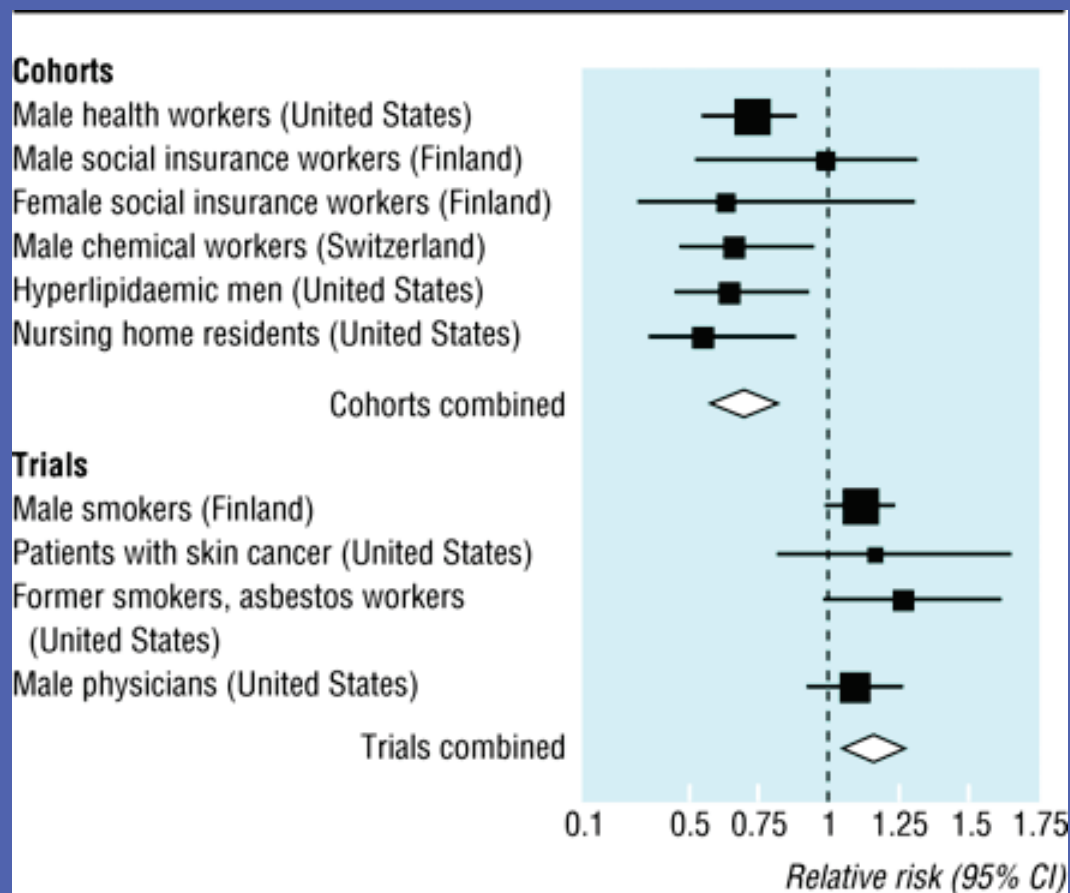
- *number of bleeding sites, side effects? costs?*

Hierarchy of evidence



Meta-analysis of association between β carotene intake and cardiovascular mortality

Egger 1998 BMJ



Meta-analysis of association between β carotene intake and cardiovascular mortality

- Results from observational studies show considerable benefit, whereas the findings from randomised controlled trials show an increase in the risk of death

Possible scenarios

- **Question not related to effectiveness of an intervention**
 - Associations between gum disease and risk of heart disease, low birth weight babies and stroke.
- **RCTs not feasible in area of study**
 - Water fluoridation
- **No/limited RCTs**
 - Effectiveness of physiotherapy, occupational therapy, and speech pathology for people with Huntington's disease.

2. Search strategy

- Needs to be as **comprehensive** as possible
- **Consider:**
 - Electronic databases (Cochrane Controlled Trials Register, Medline, Embase);
 - Reference lists;
 - Handsearching;
 - English language/non-English language;
 - Sources of ongoing and/or unpublished studies

Reporting biases

- **Statistically significant ‘positive’ results are:**
 - more likely to be published
 - **publication bias**
 - more likely to be published rapidly
 - **time lag bias**
 - more likely to be published in English
 - **language bias**
 - more likely to be cited by others
 - **citation bias**

Publication bias | an example

- Systematic review of reboxetine, a third-generation anti-depressant
- **13 trials**, published and unpublished data
- **74%** of patient data **previously unpublished**
- Reboxetine is “*overall an ineffective and potentially harmful antidepressant*”
- **Contradicts findings of previous reviews** which considered only published data

Eyding et al, BMJ 2010

Registered trials

- **Trials registries**

- clinicaltrials.gov

- **The Declaration of Helsinki states:**

- “Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.”*

- **International Committee of Medical Journal Editors (ICMJE)**

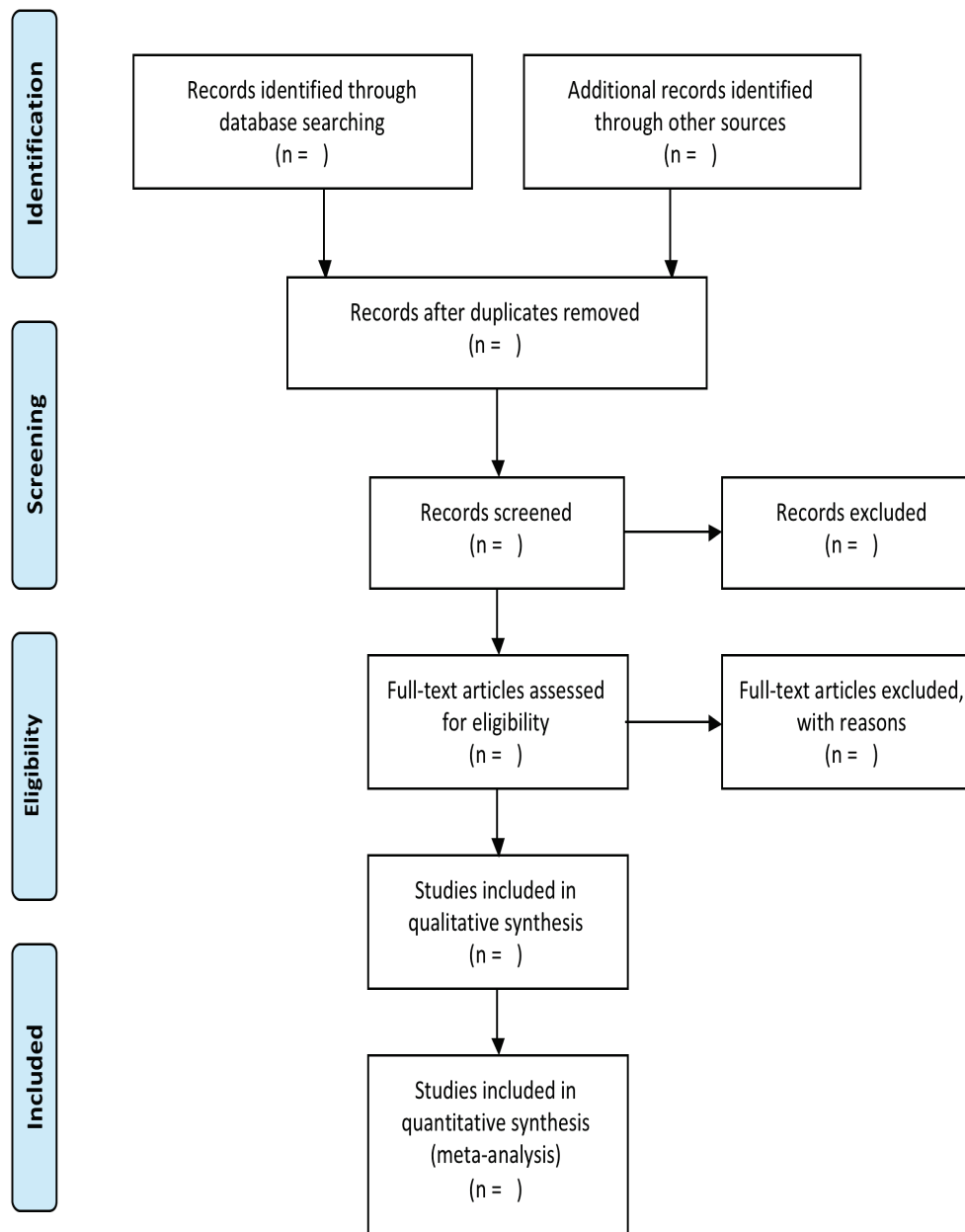
Registered trials

- **50% of trials supporting drugs that are approved by the U.S. Food and Drug Administration (FDA) remain unpublished 5 years after drug approval**

Bourgeois et al, Ann Intern Med. 2010



PRISMA 2009 Flow Diagram



3. Unbiased selection and data extraction process

- Selection of relevant papers
- Data extraction using predefined data extraction form
- Process should be conducted independently by at least two reviewers

4. 'Quality' assessment of included studies

- Process should be conducted independently by at least two reviewers
- Results of the assessment should be reflected in the analysis

‘Quality’ assessment tools

- **Composite scales**
 - assign numerical value to individual items to provide overall estimate of quality – **problematic**
- **Component approach**
 - assesses relevant methodological aspects individually (*e.g. randomisation, blinding, drop-outs*) - **preferred**

Risk of bias assessment

- Bias determines the **extent to which results of studies can be believed**.
A study conducted to the highest possible standards can still have risk of bias.
- **Direction of bias:** causes overestimation or underestimation of effect
- Magnitude of bias

Study Risk of Bias Table | Finkelstein 1990

Bias	Authors' judgement	Support for judgement
Random sequence generation (<i>selection bias</i>)	Unclear risk	"Subjects were randomly assigned to one of the five test groups..."
Allocation concealment (<i>selection bias</i>)	Unclear risk	Not reported
Blinding - Outcome assessors	Unclear risk	Not reported
Blinding - Participants	Unclear risk	Unclear
Incomplete outcome data (<i>attrition bias</i>)	Low risk	Exact number of subjects lost to follow-up in each of the groups cannot be ascertained from the report. The total number of subjects lost to follow-up was 3 out of 161, so attrition seems low and therefore unlikely to affect the results
Selective reporting (<i>reporting bias</i>)	Low risk	No protocol available. All primary outcomes in the 'Methods' section were addressed in the 'Results'
Other bias	Unclear risk	Compliance was not assessed, breakdown by gender not reported.

Risk of Bias

Summary Table

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding - Outcome assessors	Blinding - Participants	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Finkelstein 1990	?	?	?	?	+	+	?
Hague 2007	+	?	+	?	+	+	?
Jared 2005	+	?	+	?	+	?	?
Schiff 2006	?	?	?	?	+	+	?
Vogel 1975	?	?	+	?	?	-	-
Walsh 1985	?	?	+	?	+	-	?
Zimmer 2006	-	+	+	-	+	+	?

Random sequence generation (selection bias)

Allocation concealment (selection bias)

Blinding - Outcome assessors

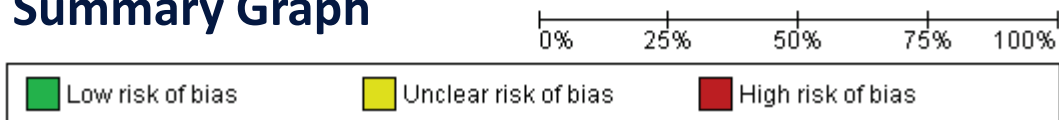
Blinding - Participants

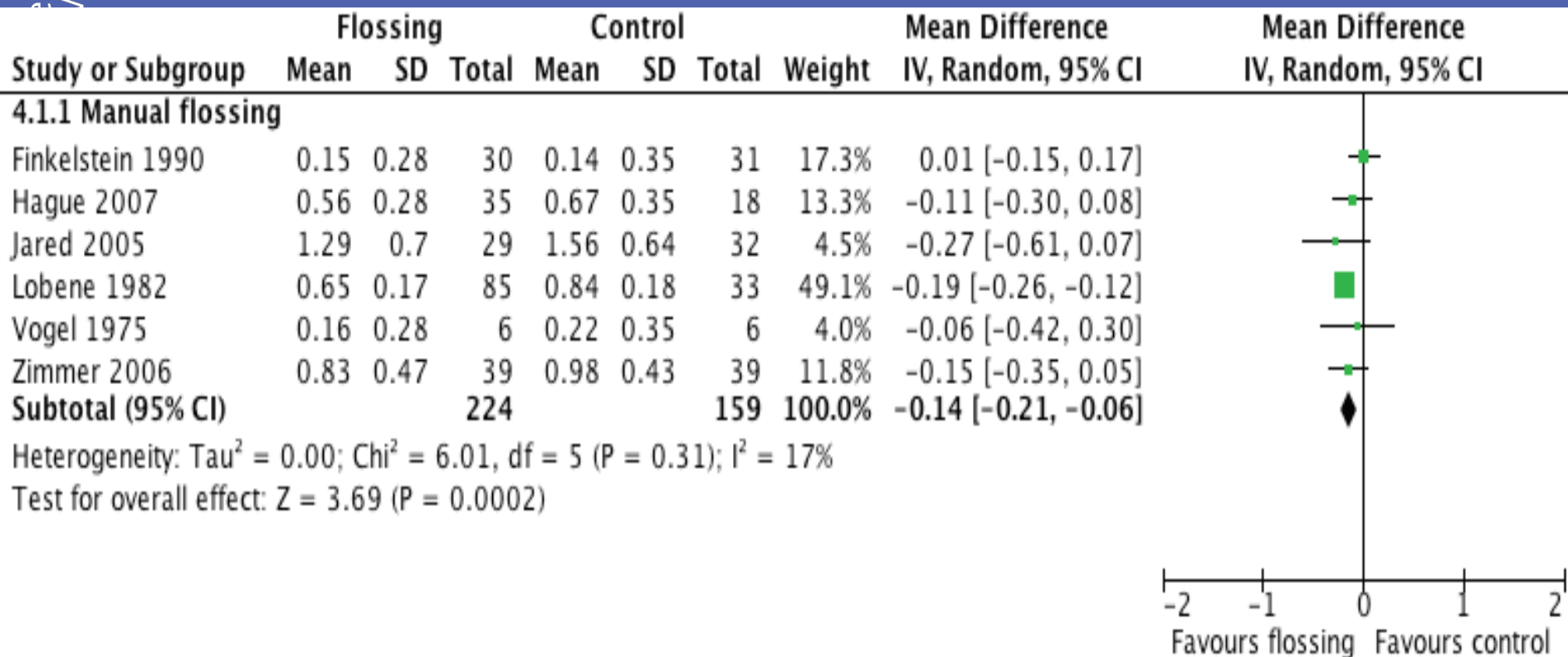
Incomplete outcome data (attrition bias)

Selective reporting (reporting bias)

Other bias

Summary Graph







THE COCHRANE COLLABORATION

Cochrane Collaboration

An international organisation that aims to help people make well-informed decisions about healthcare by preparing, maintaining and promoting the accessibility of systematic reviews of the effects of health care interventions.

- ***The Cochrane Collaboration is an enterprise that rivals the Human Genome Project in its potential implications for modern medicine."***
- **- The Lancet ¹**

Further reading

- Cochrane Handbook (Higgins 2011)
<http://www.cochrane-handbook.org/>
- Systematic reviews. Egger M, Davey Smith G, Altman DG, BMJ books 2001
- PRISMA
<http://www.prisma-statement.org>