Evidence based Dental Practice: Systematic Reviews

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Outline

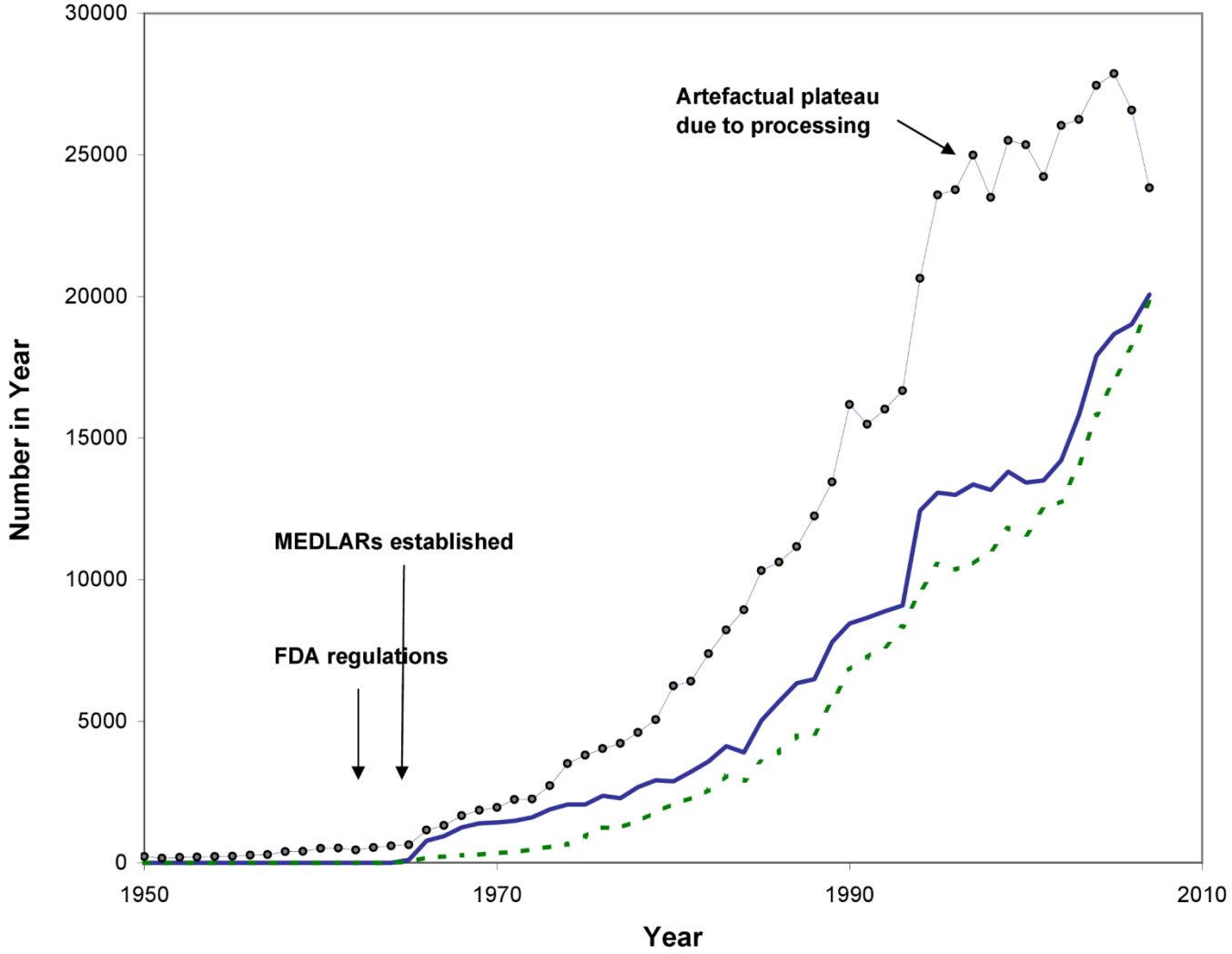
- Background
- Definition and importance of systematic review
- Steps in conducting a systematic review
- Bias in systematic reviews
- Concluding remarks

- Does flossing prevent dental caries?
- Does oral hygiene prevent periodontal diseases?
- Do oxalate treatments improve dentin hypersensitivity?

Where do you get the answers?

- Opinions of teachers and peers
- Expert opinion
- Journals
- Google
- Pubmed
- Cochrane Collaboration
- Evidence based dentistry websites: ADA EBD
- Journals of evidence based dentistry: JEBDP, JEBD

How to be informed?



Published per day in Pubmed:

2000 studies

75 RCTs

Bastian . PLoS Med. 2010;7(9):e1000326. PMID: 20877712.

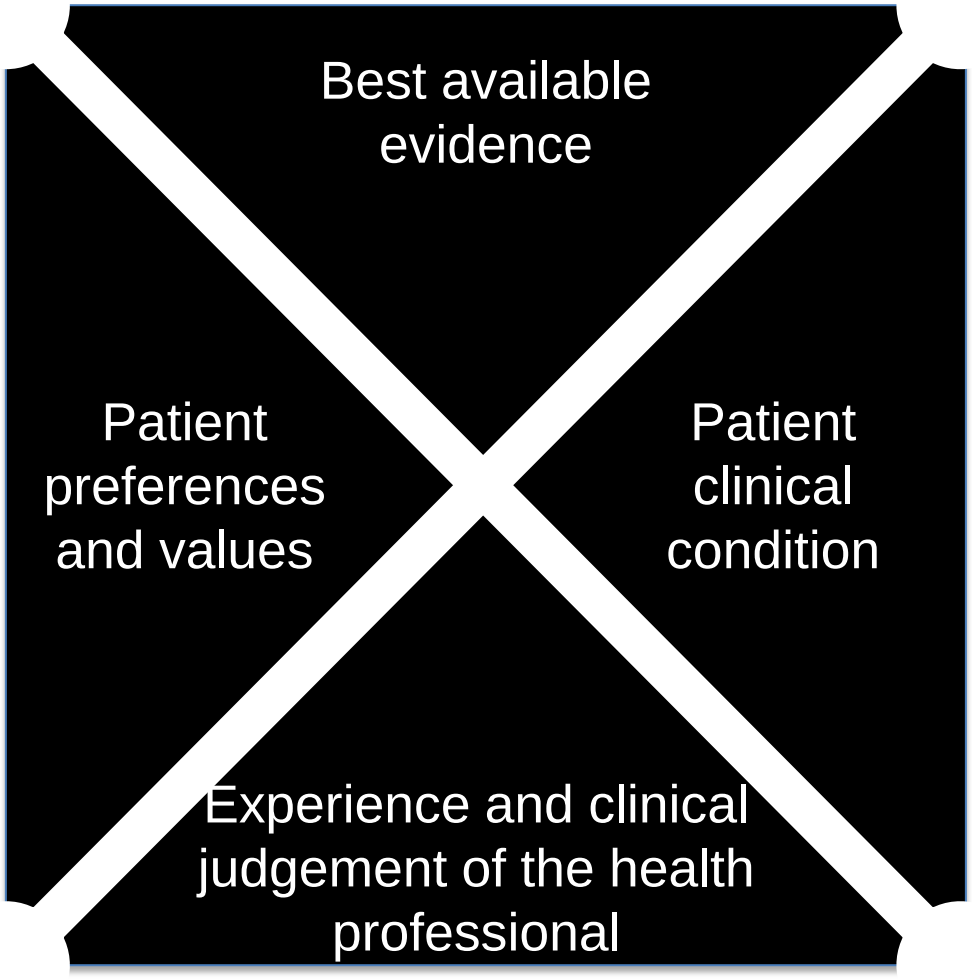
Need to be up-to-date

- 1/3 of evidence will eventually be refuted or attenuated
- 1/2 will never be implemented

How would you know what is worth of your time?

Ioannidis JP. JAMA. 2005 Jul 13;294(2):218-28. PMID: 16014596.

Evidence based dental practice



Generate the best evidence

Steps

- Ask
- Access: Exhaustive search
- Detailed appraisal
- Analyze & synthetize
- Apply

Time: 6 months

< 2000 papers

Systematic review

Use the best evidence

Steps

- Ask
- Access: Search
- Appraise
- Apply

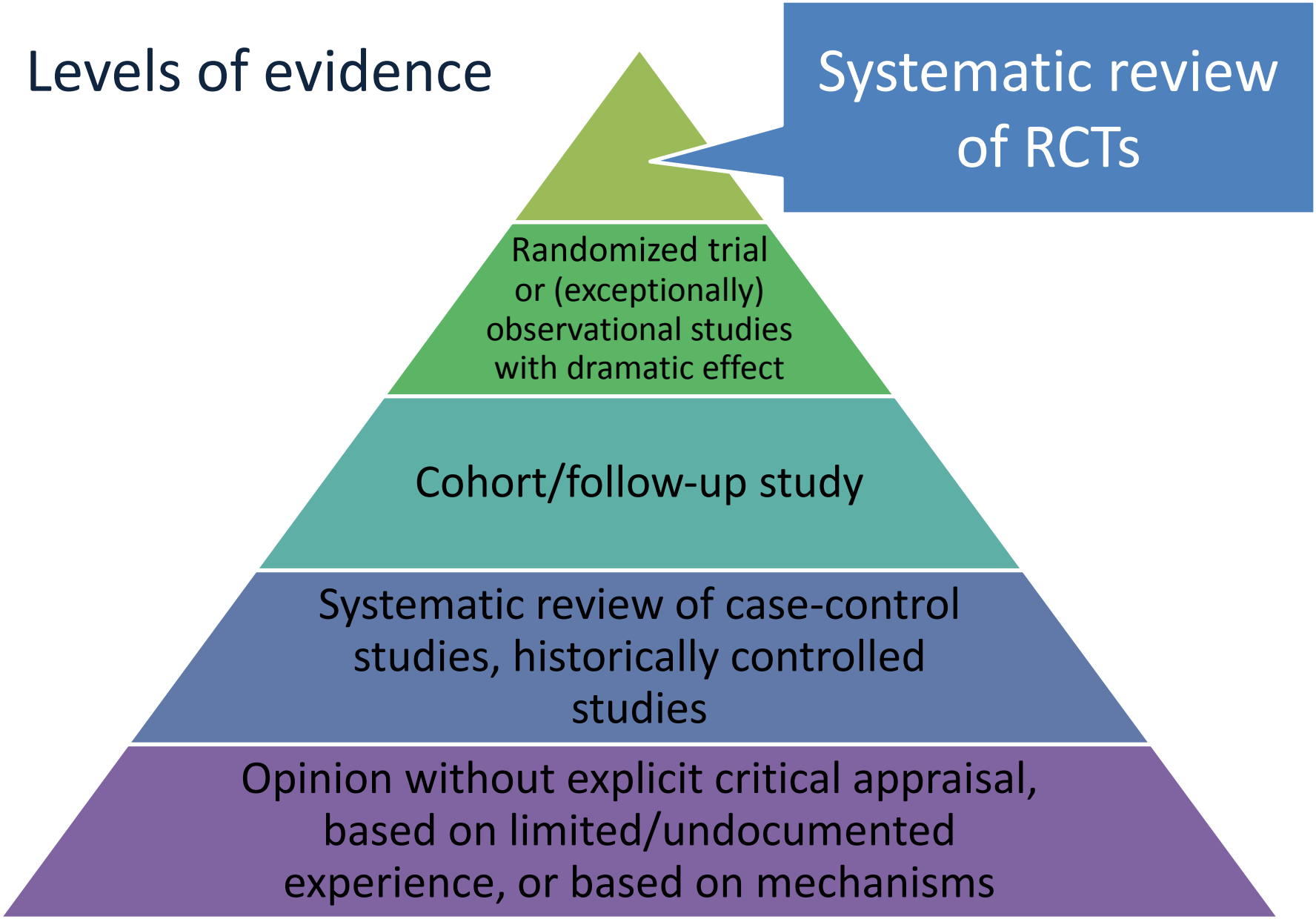
Time: 30 minutes

< 20 papers

CAT – critical appraisal tool

Search for a systematic review

Levels of evidence



What is a systematic review?

A review that attempts to collate all empirical evidence that fits pre-specified eligibility criteria in order to answer a specific research question using explicit, systematic methods to minimize bias, thus providing more reliable findings from which conclusions can be drawn and decisions made

(Altman 1992, Oxman 1993)

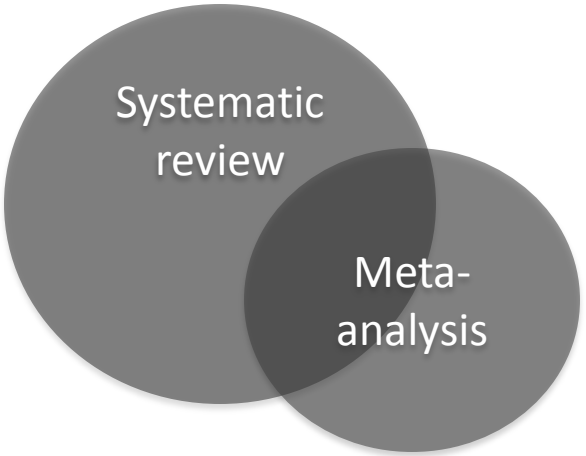
Moher. PLoS Med 2009; 6(7): e1000097. PMID: 19621072

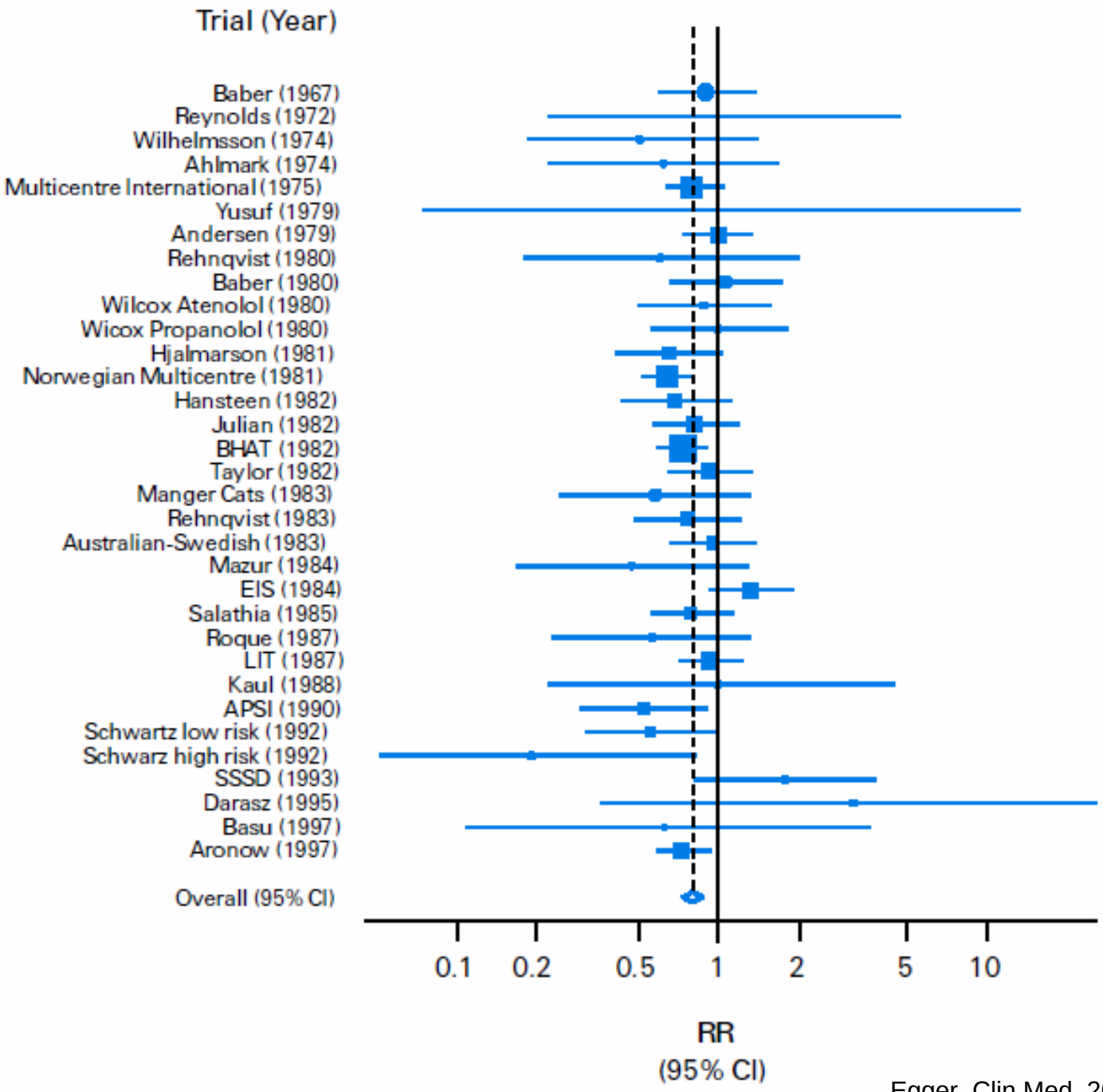
Systematic review

- a clearly stated set of objectives with pre-defined eligibility criteria for studies
- an explicit, reproducible methodology
- a systematic search of studies
- an assessment of the validity of the study findings
- a systematic presentation, and synthesis, of the characteristics and findings of the studies

Meta-analysis

- Estimates an ‘average’ or ‘common’ effect
- Improves the precision of an estimate by using all available data
- Optional part of a systematic review

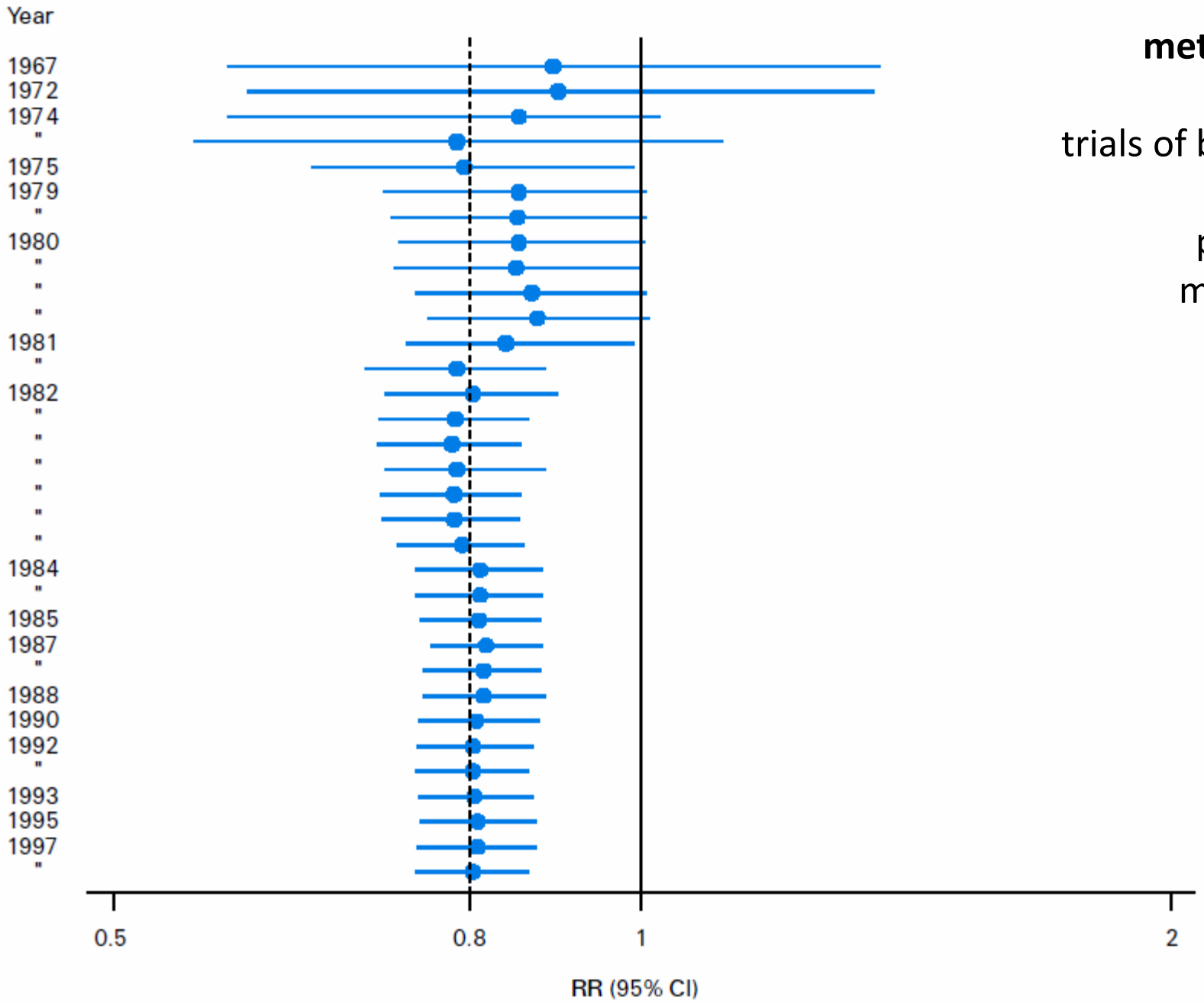




Meta-analysis of controlled trials of beta-blockers in secondary prevention of mortality after myocardial infarction.

Egger Clin Med. 2001, 1(6):478-84. PMID: 11792089.

Would any of you have agreed to participate in a placebo controlled trial of **beta-blockers after myocardial infarction** after 1981?



Cumulative meta-analysis of controlled trials of beta-blockers in secondary prevention of mortality after myocardial infarction.

Egger Clin Med. 2001, 1(6):478-84. PMID: 11792089.

Failure to review the cumulated evidence can lead to unnecessary duplication of research or to trial participants being deprived of effective interventions or exposed to harmful ones

Trial reports should begin and end with systematic review of evidence

- Only ½ of trial investigators were aware of a relevant existing review when they had designed their trial
- 44% of published trials did not mention a systematic review and only 1 had an updated systematic review integrating the new results

Clarke. Lancet. 2010;376(9734):20-1. PMID: 20609983.

Steps of a systematic review: 5 As

Ask: Define the question and inclusion criteria

Access: Search and select studies meeting inclusion criteria

Appraise: Describe the studies and appraise their quality/risk of bias

Analyze: Extract and synthetize the data

Apply: Report the findings and apply to your practice

Does this treatment help?

CONCISE REVIEW

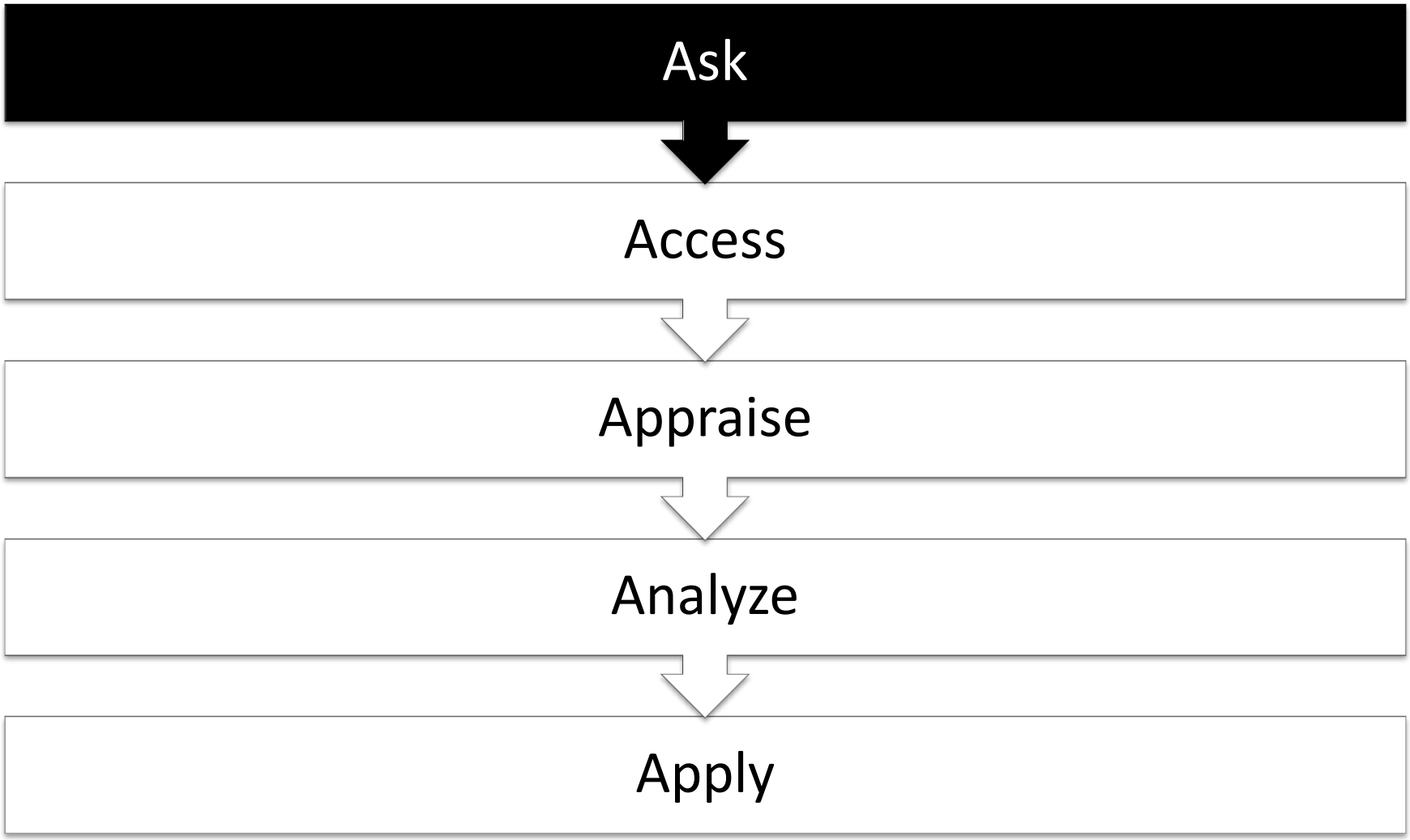
Dentin Hypersensitivity and Oxalates: a Systematic Review

J. Cunha-Cruz[1]*, J.R. Stout[2], L.J. Heaton[1], and J.C. Wataha[3] for Northwest PRECEDENT

[1]Dental Public Health Sciences, Box 357475, School of Dentistry, University of Washington, Seattle, WA 98195–7475, USA; [2]School of Dentistry, University of Washington, Seattle, WA, USA; and [3]Restorative Dentistry, School of Dentistry, University of Washington, Seattle, WA, USA; *corresponding author, silvajcc@u.washington.edu

J Dent Res 90(3):304-310, 2011

Systematic review



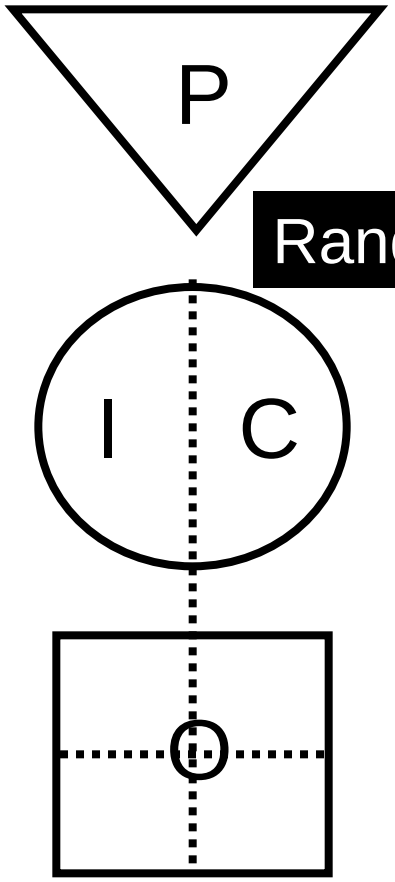
Do oxalate treatments improve dentin hypersensitivity?

PICO

In persons with dentin hypersensitivity, does oxalate treatment compared to placebo or no treatment reduce pain?

Participants

Persons with dentin hypersensitivity



Intervention

Oxalate treatment

Comparison

Placebo, or no treatment

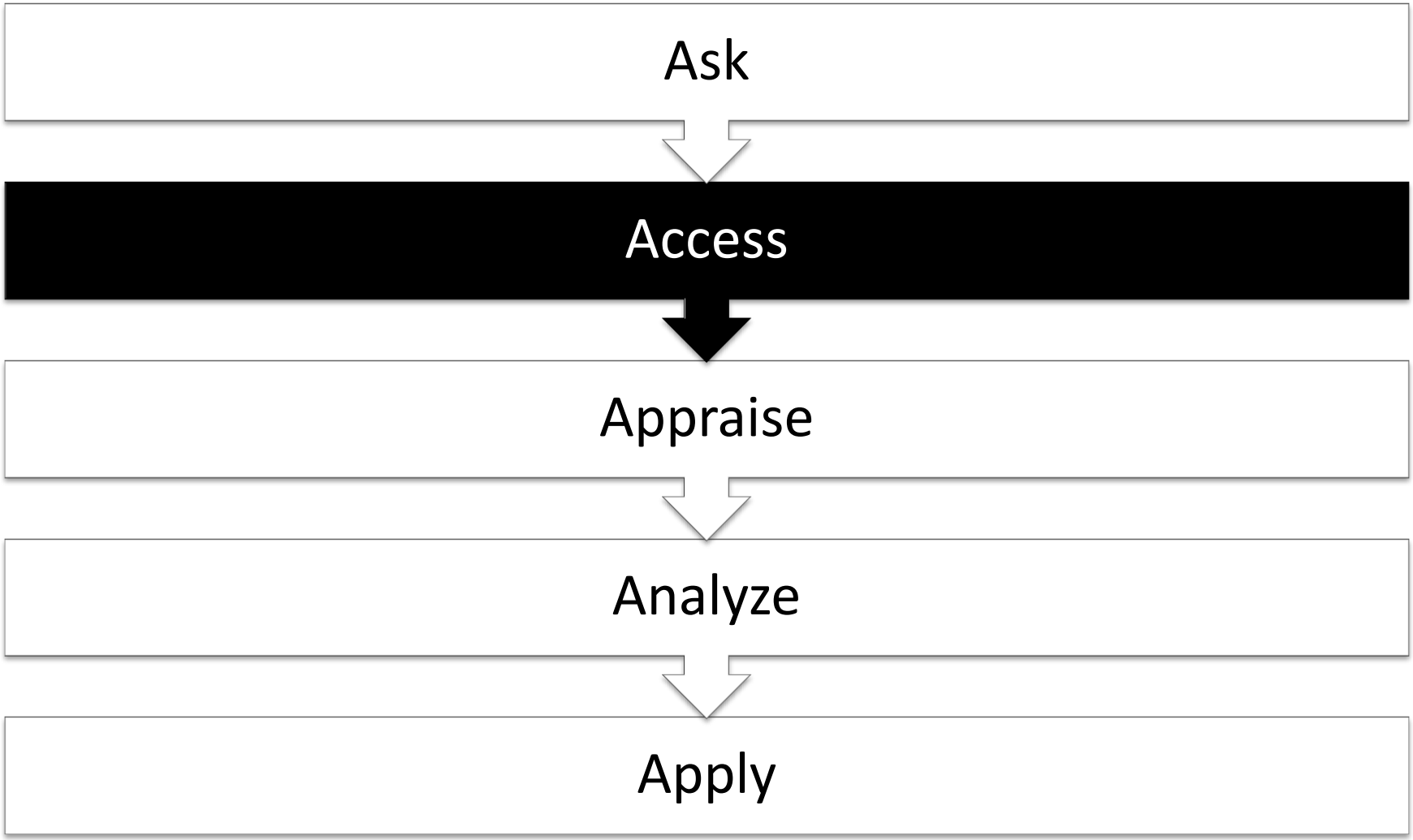
Outcomes

Any

Improvement on Dentin Hypersensitivity (Pain)

GATE:
a Graphic Appraisal Tool for Epidemiology
Rod Jackson *et al*. PMID: 16539343

Systematic review



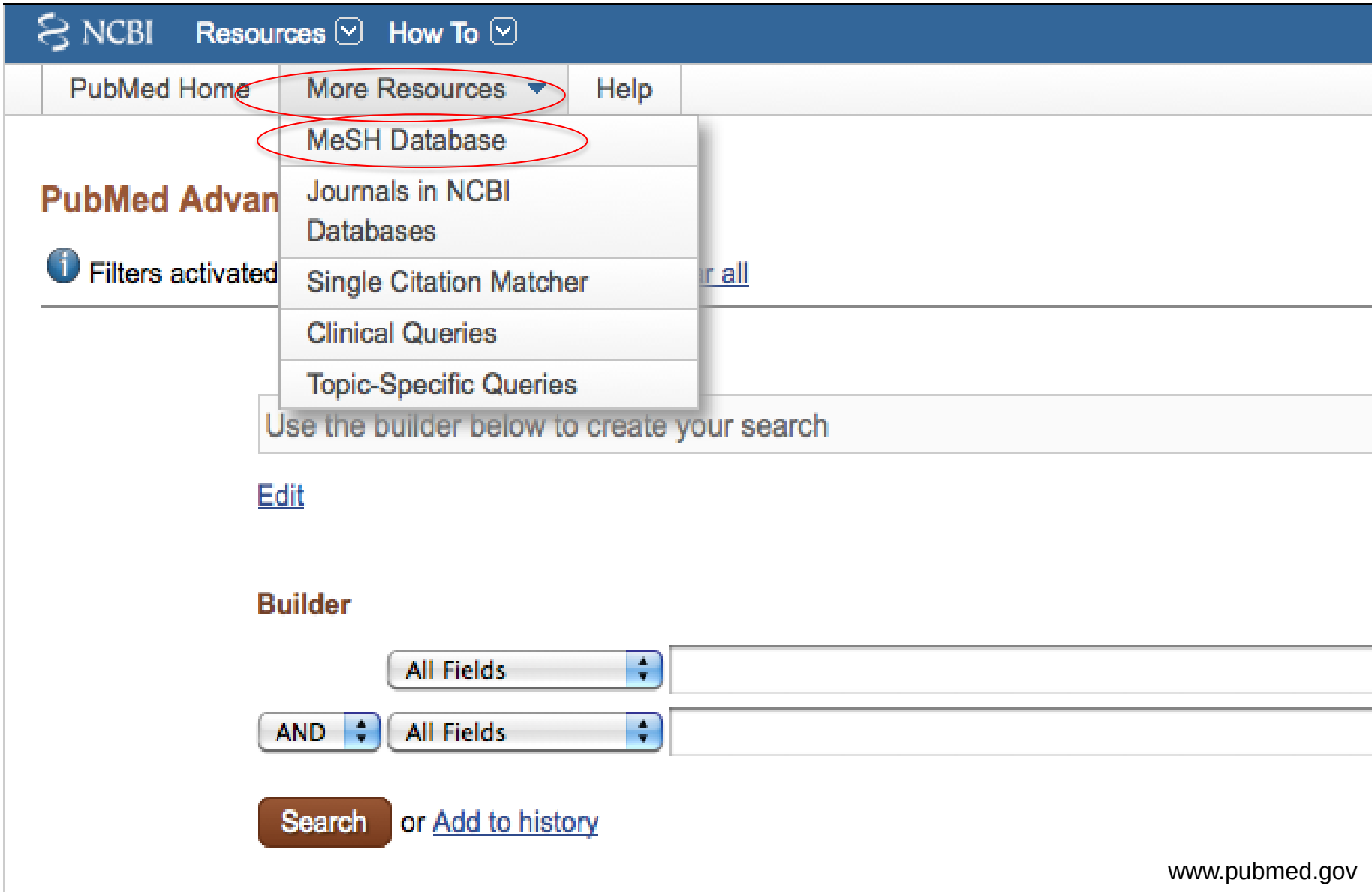
ACCESS

Search Strategy

- Period: 1966- Jul 2009
- No language restriction
- Electronic search
  - Pubmed
  - Cochrane Library (CENTRAL)
  - Grey literature (RCT registers, Theses database)
- Reference lists

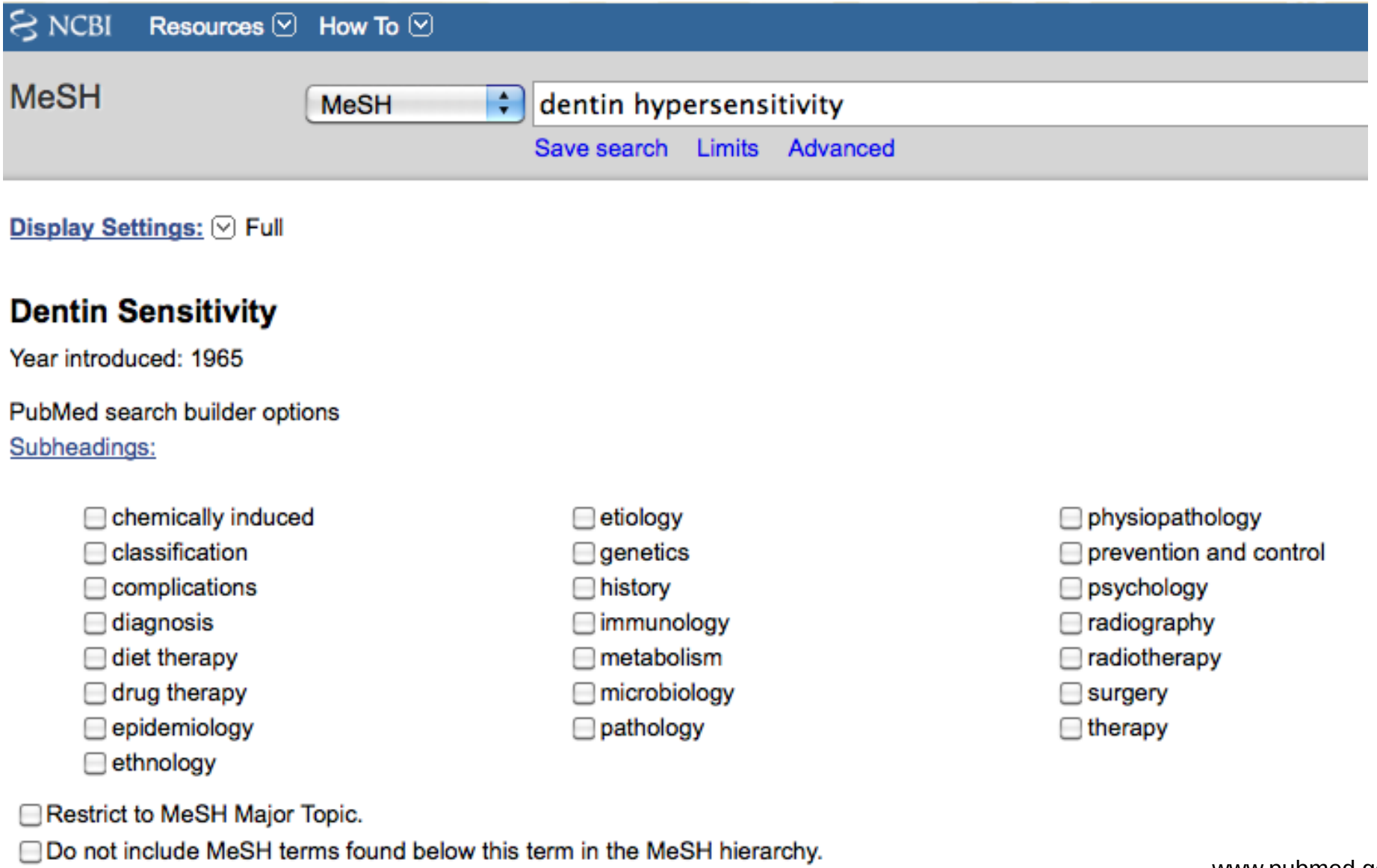
- Electronic search:
  - Boolean operators (OR, AND and NOT)
  - keywords: MeSH terms
  - limits and restrictions [ ]
  - Pubmed Clinical Queries

Keywords: MeSH terms



www.pubmed.gov

Search Strategy: MeSH terms



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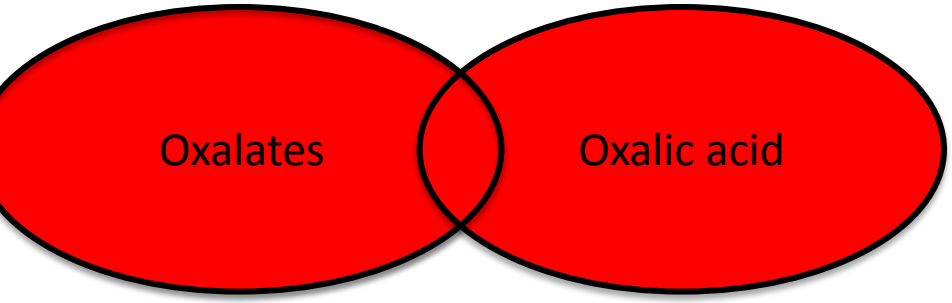
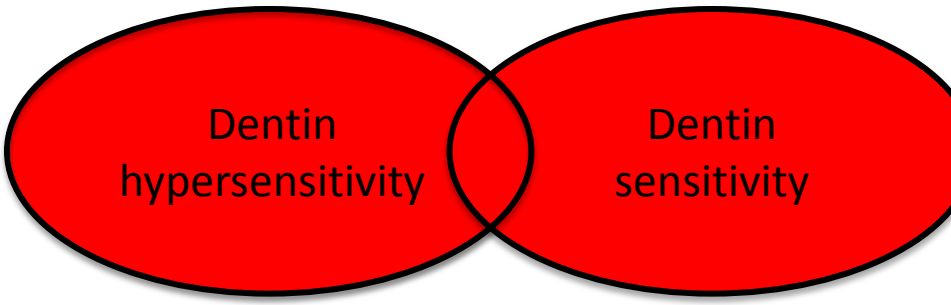
Boolean operators (AND, OR and NOT)

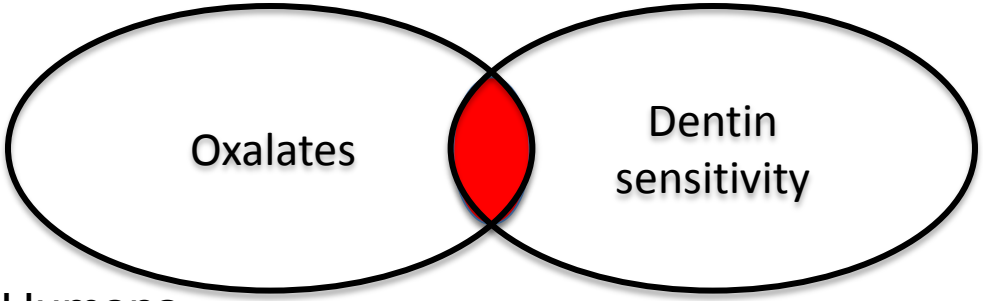
Oxalates **OR** Oxalic acid



Dentin hypersensitivity **OR** Dentin sensitivity

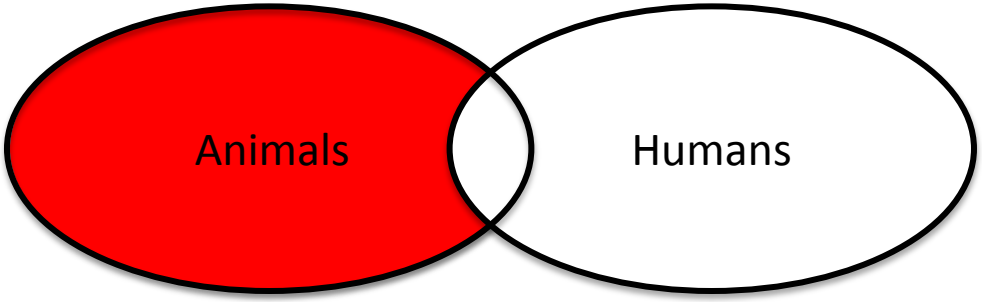


Oxalates **AND** Dentin sensitivity

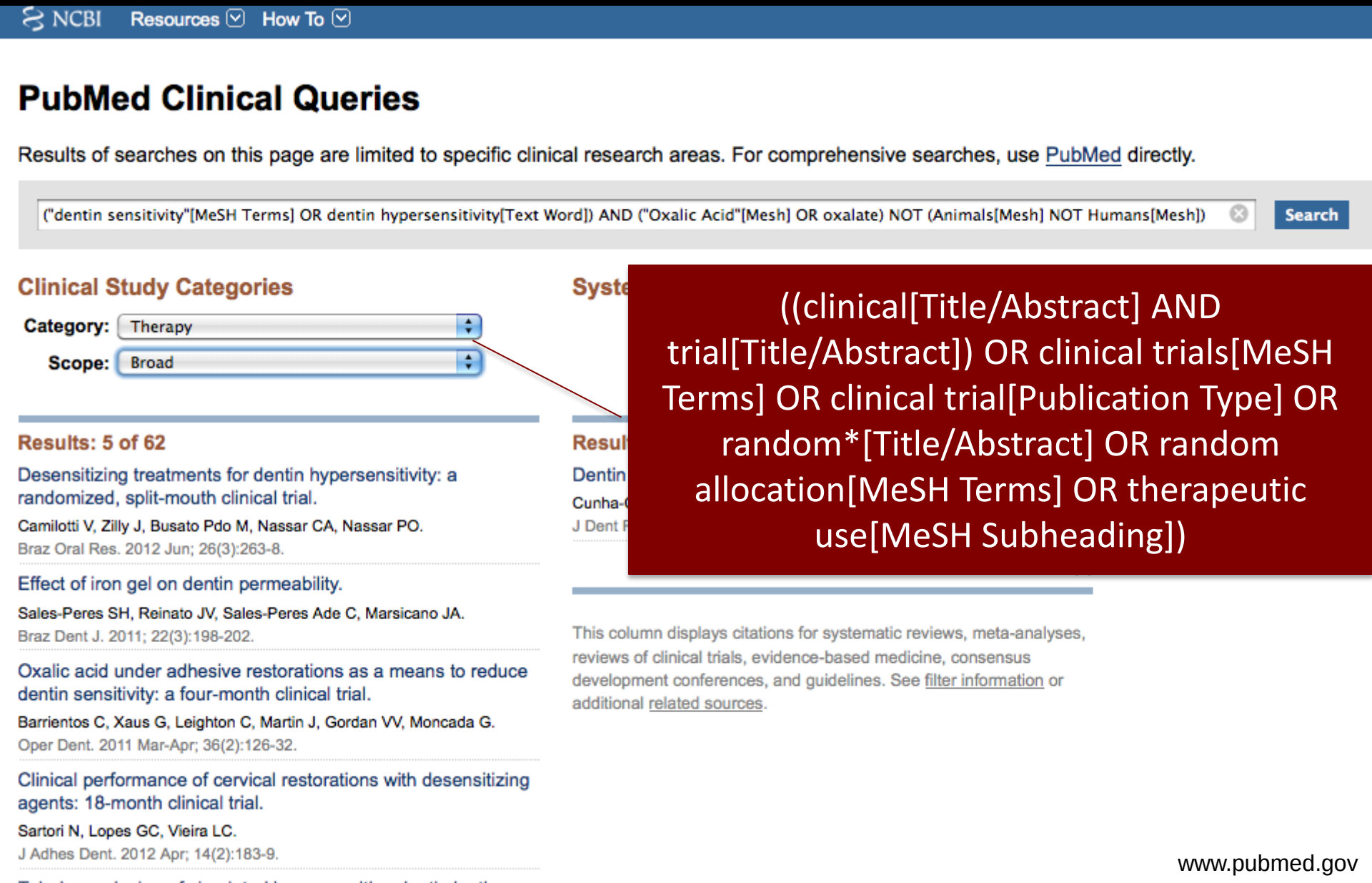


Exclude:

Animals **NOT** Humans

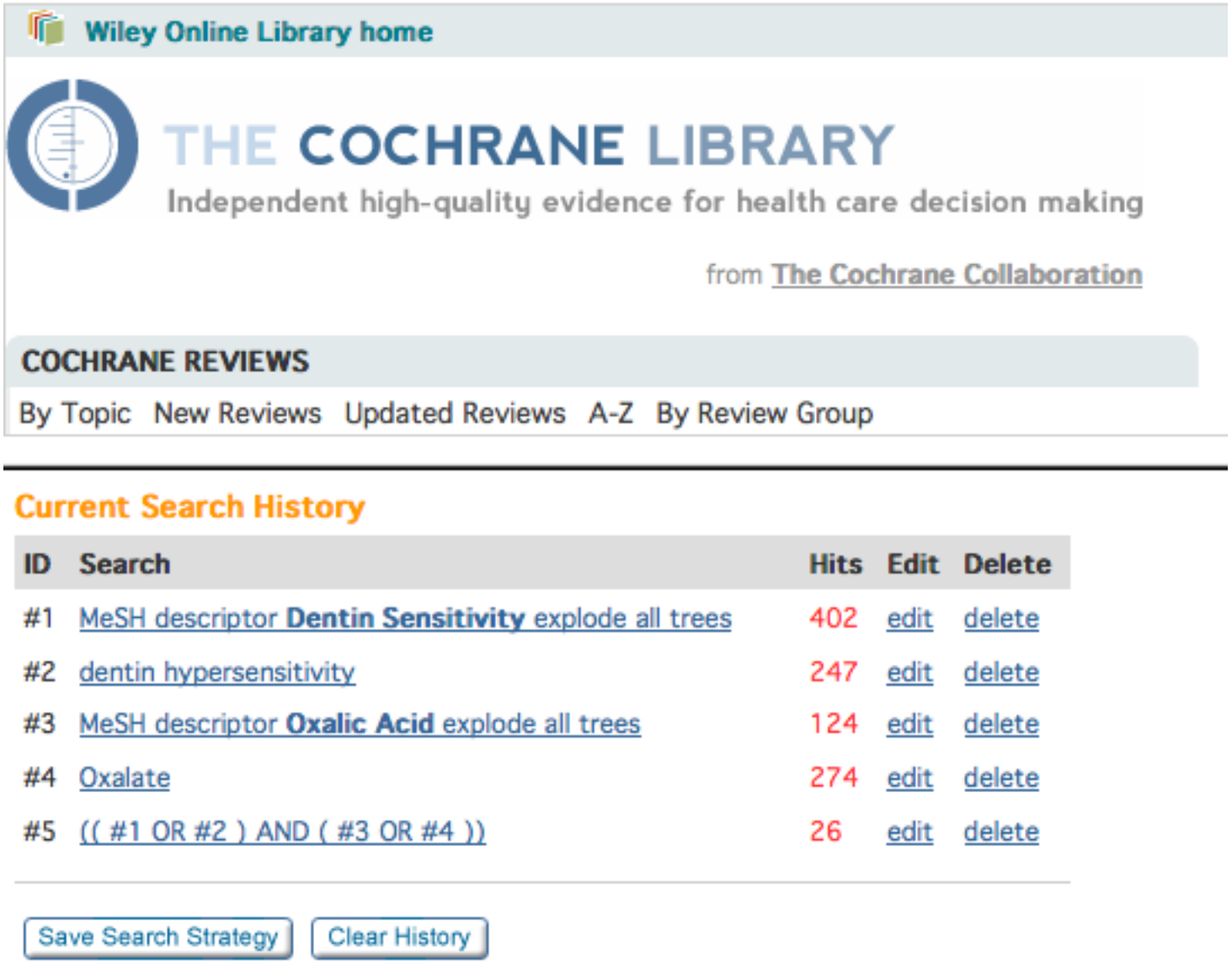


Restrict your search: Filters



www.pubmed.gov

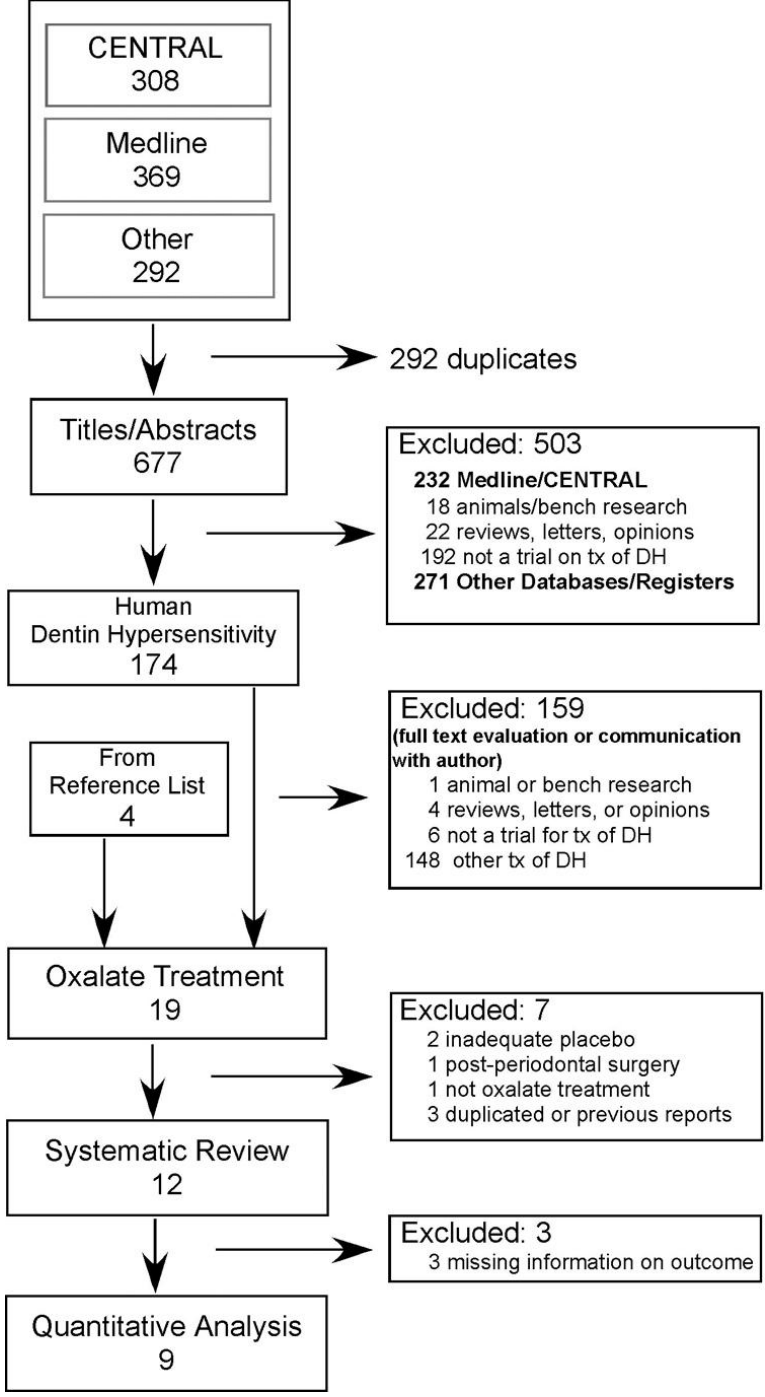
Search Strategy: Cochrane



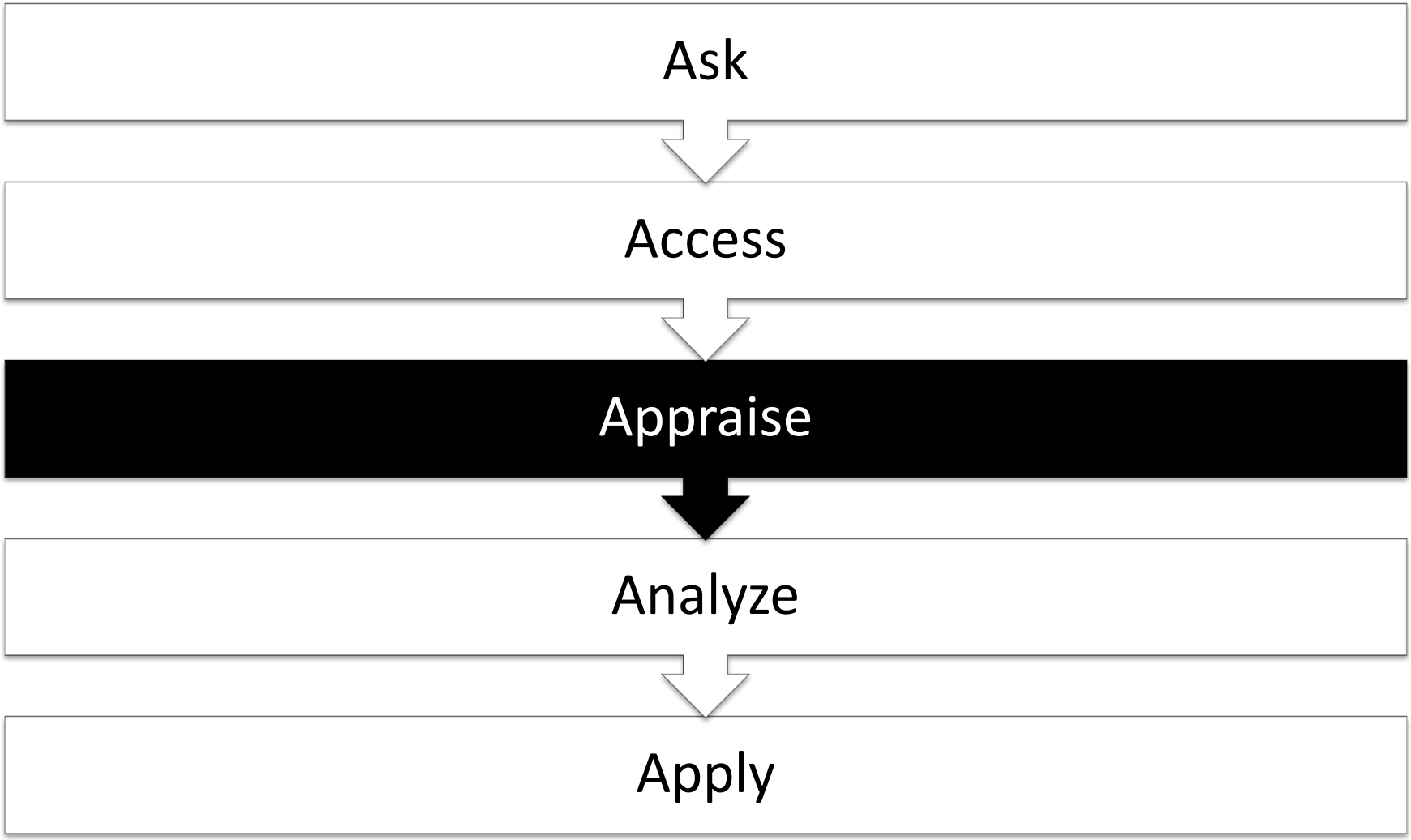
www.cochrane.org

ACCESS Study Selection

- Code all citations and state reason for exclusion
- Pilot test
- Reliability
  - Assessed the agreement of two reviewers
  - Considered adequate (*kappa*=0.79)



Systematic review



APPRAISE Study Description

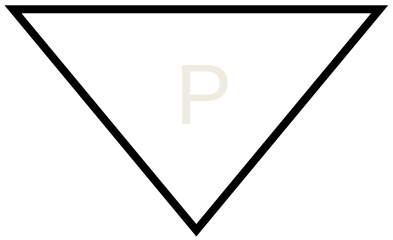
- Designed a data collection form
- Two reviewers collected information independently

	Pamir, 2007
Design	RCT
Follow-up duration	4 wk
Country	Turkey
Setting	University
Funding	Manufacturers (products only)
N of participants by group	30
N of teeth by group	15 + 15
Age	18-57
Gender (% female)	70
Experimental Intervention	*3% monohydrogen-monopotassium oxalate gel, pH 2
Control Intervention	placebo (distilled water)
Pain stimuli	Thermal, Evaporative
Outcomes	*Pain visual analog scale (cm)
Adverse Events	None

RCT: Randomized clinical trial, SD: standard deviation, NR

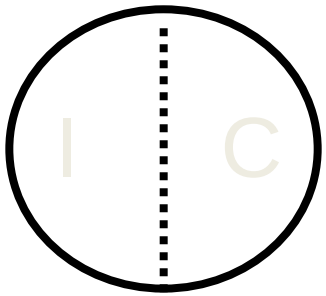
APPRAISE

Risk-of-Bias Assessment

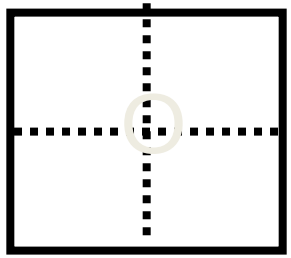


Recruitment

Allocation



Maintenance



Measurements:

Blind or

Objective

GATE:
a Graphic Appraisal Tool for Epidemiology
Rod Jackson *et al*. PMID: 16539343

APPRAISE Risk-of-Bias Assessment

- Biases
  - **R**ecruitment or Selection bias: systematic differences in the baseline characteristics of the comparison groups
  - **A**llocation: systematic differences in the allocation of participants to intervention and control groups
  - **M**aintenance:
    - Performance bias: systematic differences in **care** provided apart from the intervention being evaluated
    - Exclusion/Attrition bias: systematic differences in **withdrawals** from the trial
  - **M**easurement or Detection bias: systematic differences in outcome assessment (**b**lind or **o**bjective assessment)

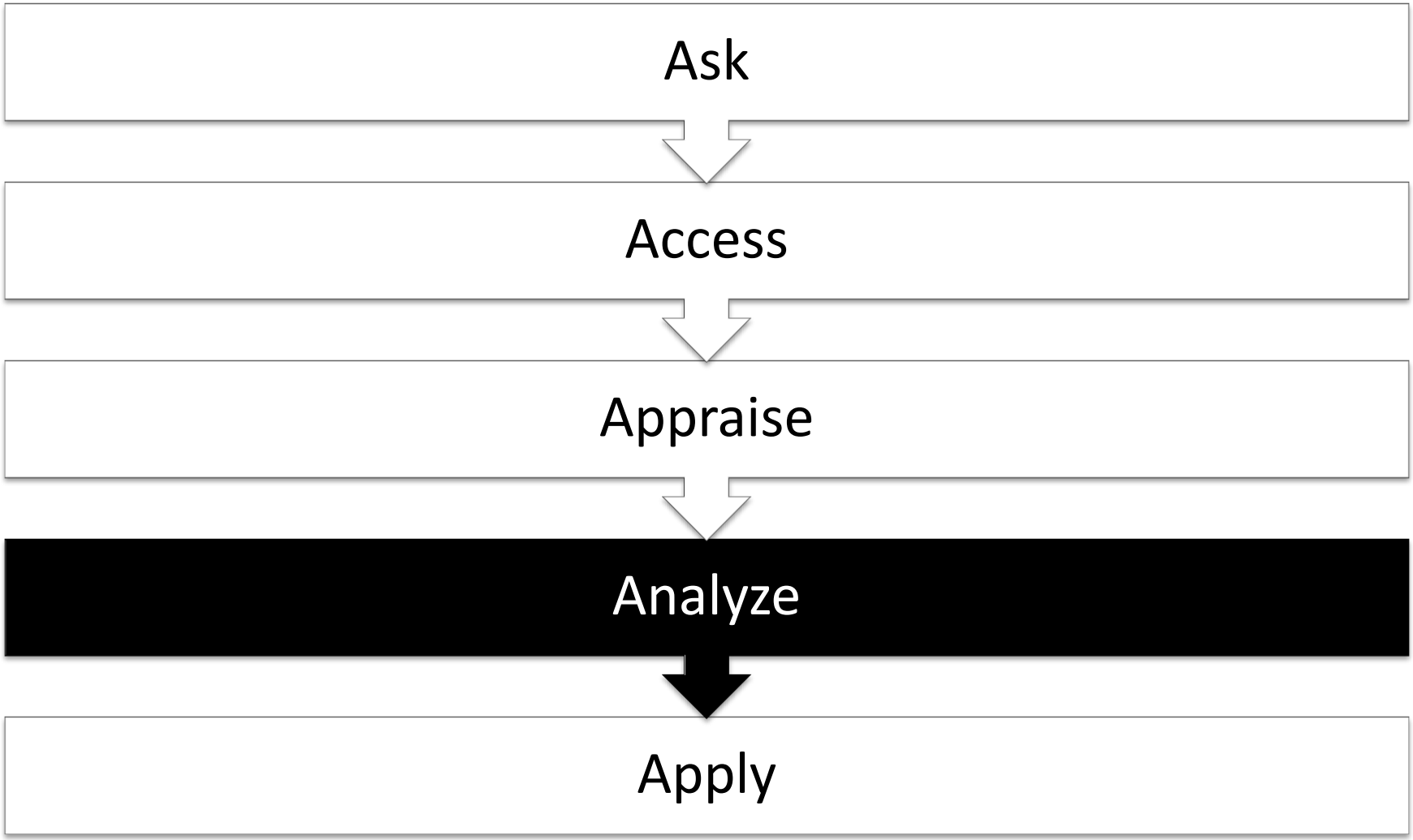
- Scales for RCT, cohort and case-control studies
- Methodological quality versus quality of reporting
  - Contact authors

APPRAISE Risk-of-Bias Assessment

Sequence generation	Assignment really random	Yes	Yes
Allocation concealment	Allocation concealed	Yes	Yes
Blinding of participants, care providers and outcome assessors	Patient blinded	Yes	Yes
	Care provider blinded	No	Yes
	Outcome assessor blinded	Yes	Yes
Incomplete outcome data	Point estimate and measure of variability presented	Yes	Yes
	Intention to treat analysis	NA	Unclear
Selective outcome reporting	Free of selective outcome reporting	Yes	Yes
Other sources of bias	Eligibility criteria specified	Yes	Yes
	Groups similar at baseline	Yes	Yes
	Split mouth (cross-over design) appropriate	NA	Unclear

NA: Not applicable

Systematic review



ANALYZE Data Extraction and Analysis

- Missing data and estimation
  - Need to assess previous publications of the same study
  - Contact the authors
  - Extract data in the text, tables and figures
  - Make assumptions

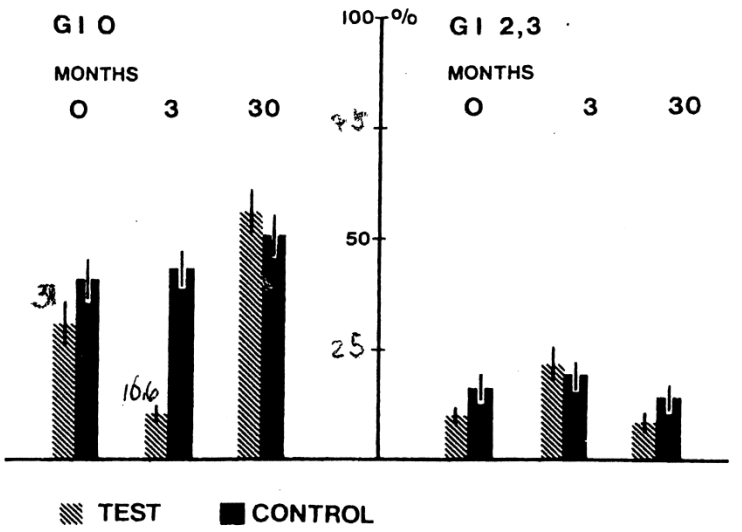
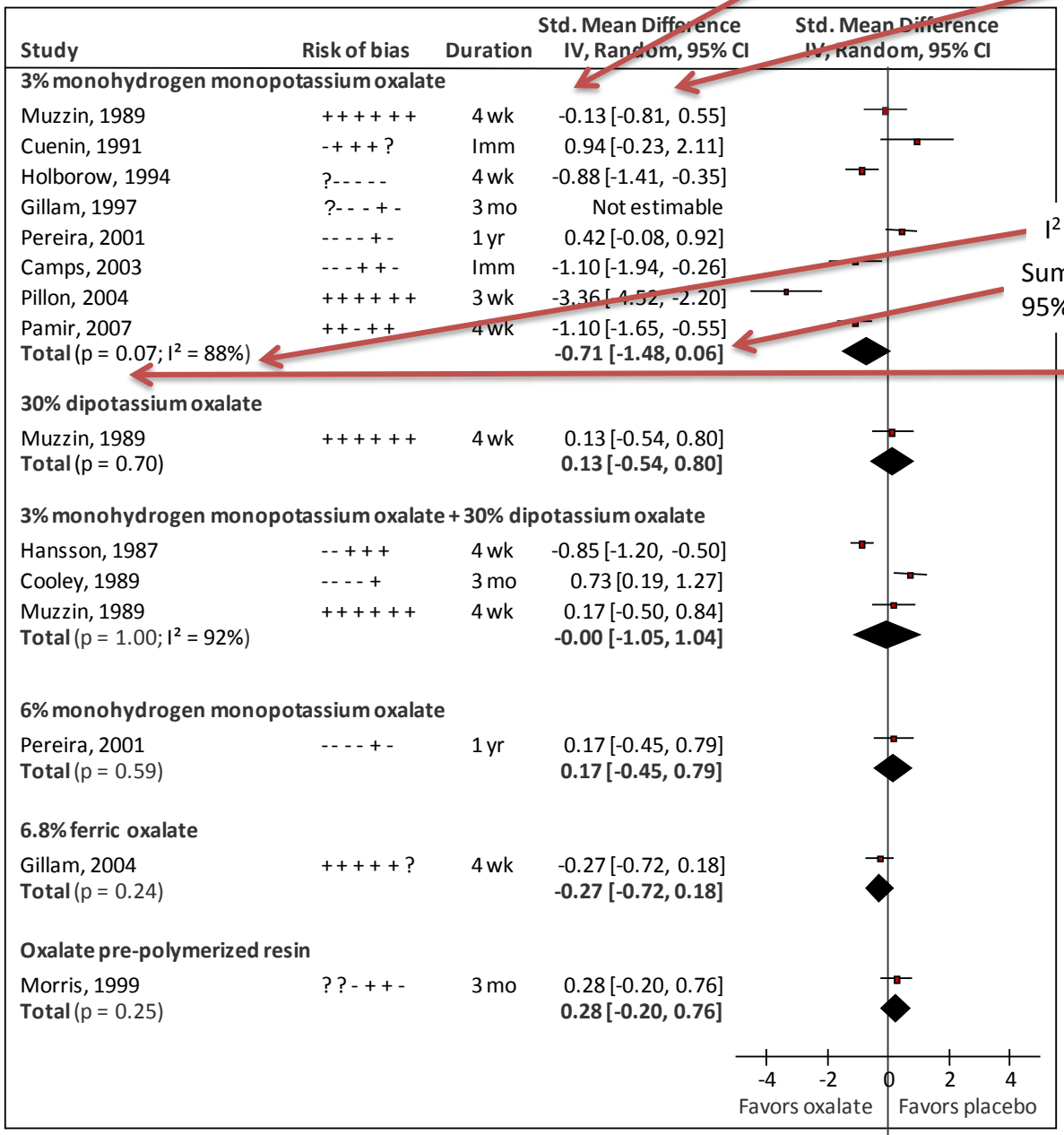


Fig. 3. Gingival status. Frequency of tooth surfaces scored 0 and 2+3 according to Gingival Index. Registrations are baseline, 3 and 30 months after oral hygiene education. Teeth examined are 16, 15, 13, 46, 45 and 43 (24 surfaces/individual).

ANALYZE Data Extraction and Analysis

- Heterogeneity
  - Proportion of variation not due to chance: I^2 Statistic
  - Test of "Null hypothesis" of no variation (p-value)
- Meta-analysis
  - If I^2 <70%
  - Summary estimate: standardized mean differences
- Analyses planned but not performed
  - Publication Bias Analysis
  - Sensitivity Analysis
  - Meta-regression

ANALYZE Results



Study	Risk of bias	Duration	Std. Mean Difference IV, Random, 95% CI
3% monohydrogen monopotassium oxalate			
Muzzin, 1989	+ + + + + +	4 wk	-0.13 [-0.81, 0.55]
Cuenin, 1991	- + + + ?	Imm	0.94 [-0.23, 2.11]
Holborow, 1994	?- - - - -	4 wk	-0.88 [-1.41, -0.35]
Gillam, 1997	?- - - + -	3 mo	Not estimable
Pereira, 2001	- - - - + -	1 yr	0.42 [-0.08, 0.92]
Camps, 2003	- - - + + -	Imm	-1.10 [-1.94, -0.26]
Pillon, 2004	+ + + + + +	3 wk	-3.36 [-4.52, -2.20]
Pamir, 2007	+ + - + +	4 wk	-1.10 [-1.65, -0.55]
Total (p = 0.07; I^2 = 88%)			**-0.71 [-1.48, 0.06]**
30% dipotassium oxalate			
Muzzin, 1989	+ + + + + +	4 wk	0.13 [-0.54, 0.80]
Total (p = 0.70)			**0.13 [-0.54, 0.80]**
3% monohydrogen monopotassium oxalate + 30% dipotassium oxalate			
Hansson, 1987	- - + + +	4 wk	-0.85 [-1.20, -0.50]
Cooley, 1989	- - - - +	3 mo	0.73 [0.19, 1.27]
Muzzin, 1989	+ + + + + +	4 wk	0.17 [-0.50, 0.84]
Total (p = 1.00; I^2 = 92%)			**-0.00 [-1.05, 1.04]**
6% monohydrogen monopotassium oxalate			
Pereira, 2001	- - - - + -	1 yr	0.17 [-0.45, 0.79]
Total (p = 0.59)			**0.17 [-0.45, 0.79]**
6.8% ferric oxalate			
Gillam, 2004	+ + + + + ?	4 wk	-0.27 [-0.72, 0.18]
Total (p = 0.24)			**-0.27 [-0.72, 0.18]**
Oxalate pre-polymerized resin			
Morris, 1999	? ? - + + -	3 mo	0.28 [-0.20, 0.76]
Total (p = 0.25)			**0.28 [-0.20, 0.76]**

12 RCTs with high risk of bias

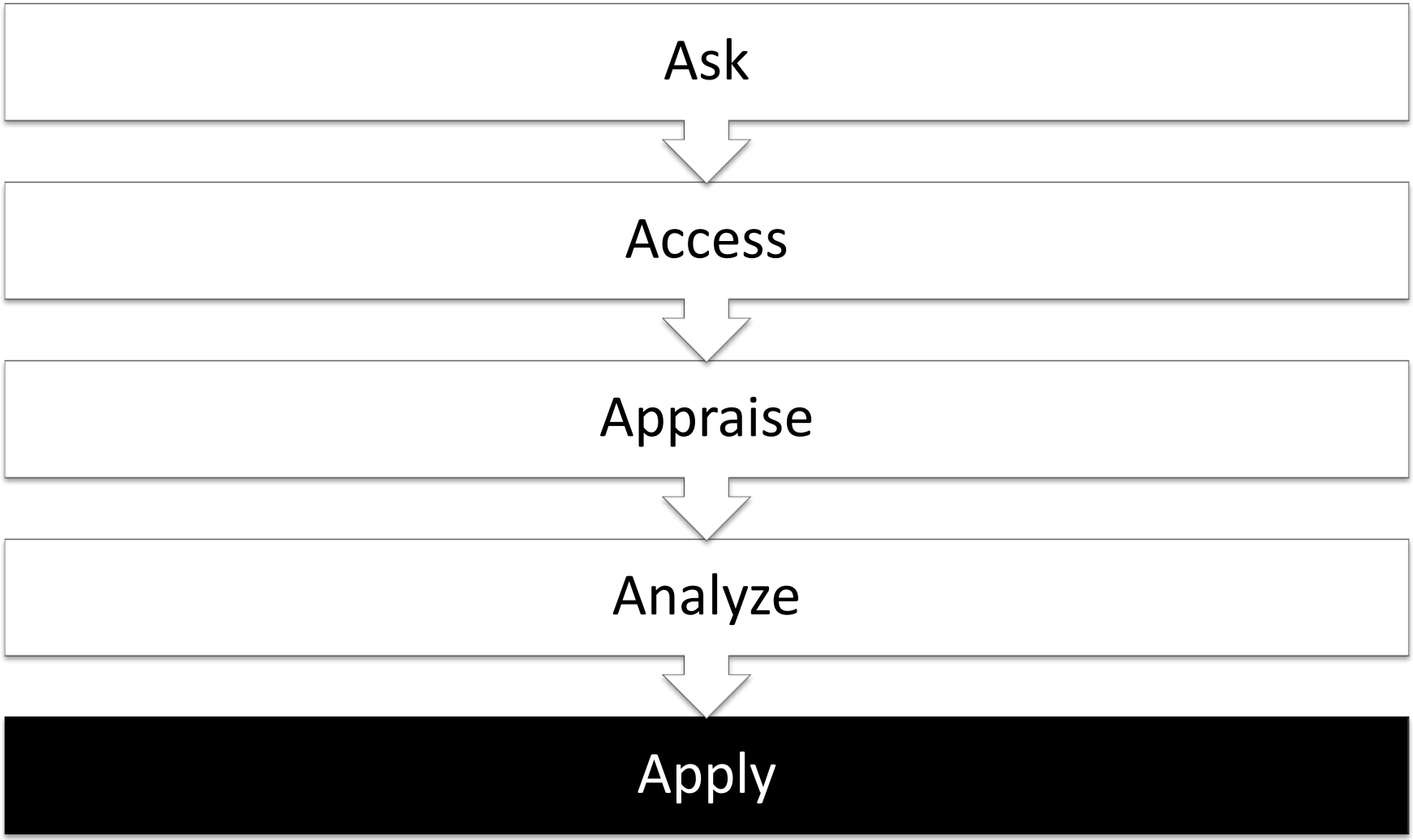
3% monohydrogen monopotassium oxalate

SMD =-0.71

(95%CI=-1.48-0.06, p=0.07)

Other treatments not associated with decreased dentin hypersensitivity when compared to placebo

Systematic review: 5 As



Bias in systematic reviews

Garbage in, garbage out?

- Meta-analysis without a systematic review
- Poor quality of studies or quality issues ignored
- Heterogeneity of studies not considered
- Indiscriminate data aggregation
- Reporting biases

Attention: small biases may be interpreted as real effects

Egger Clin Med. 2001, 1(6):478-84. PMID: 11792089.

Reporting biases

Statistically significant, "positive" results are more likely to be published:	**Publication bias**
rapidly	Time lag bias
in English	Language bias
more than once, and	Duplicate publication bias
more likely to be cited more than once	Outcome reporting bias

Egger Clin Med. 2001, 1(6):478-84. PMID: 11792089.

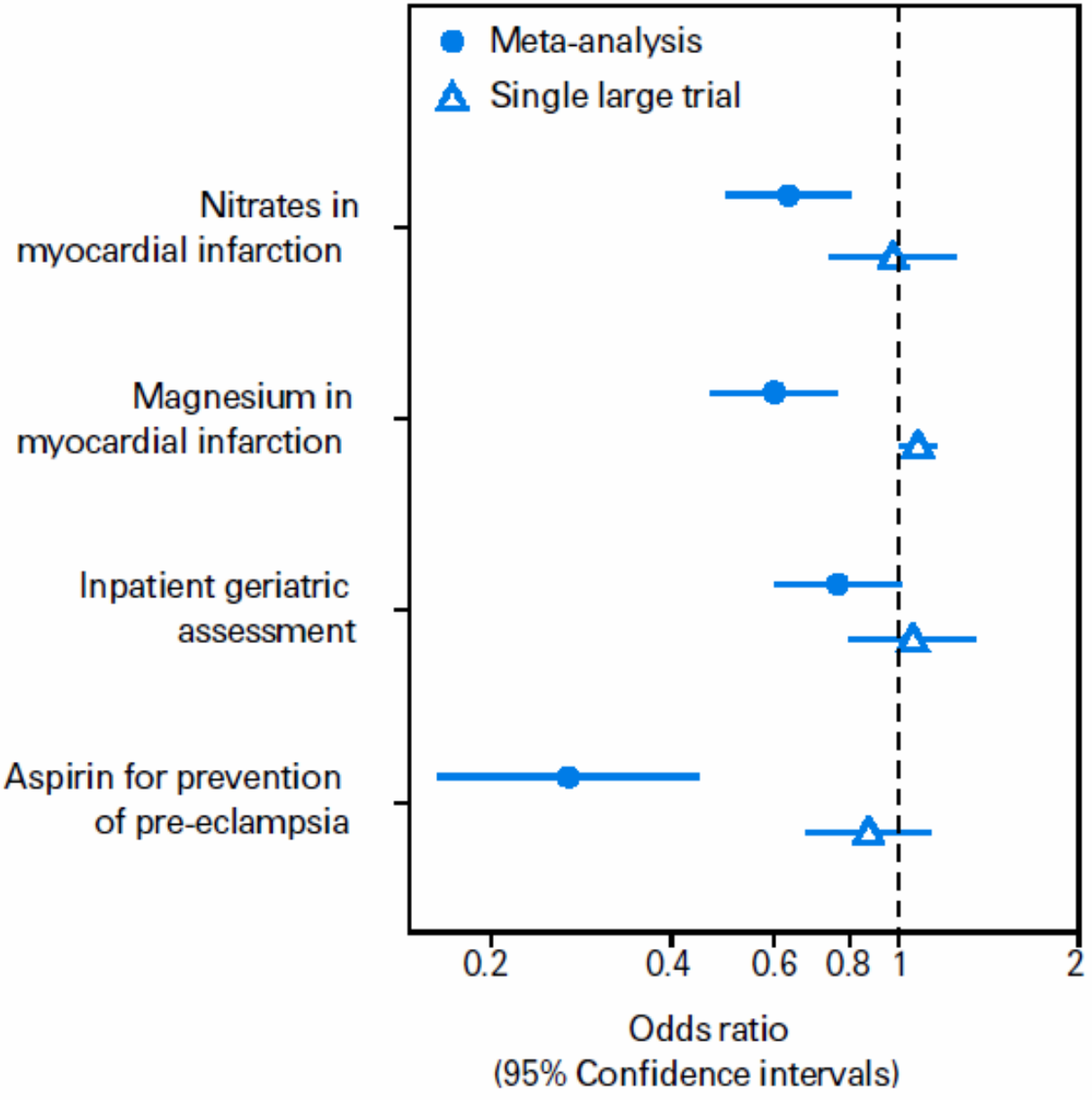
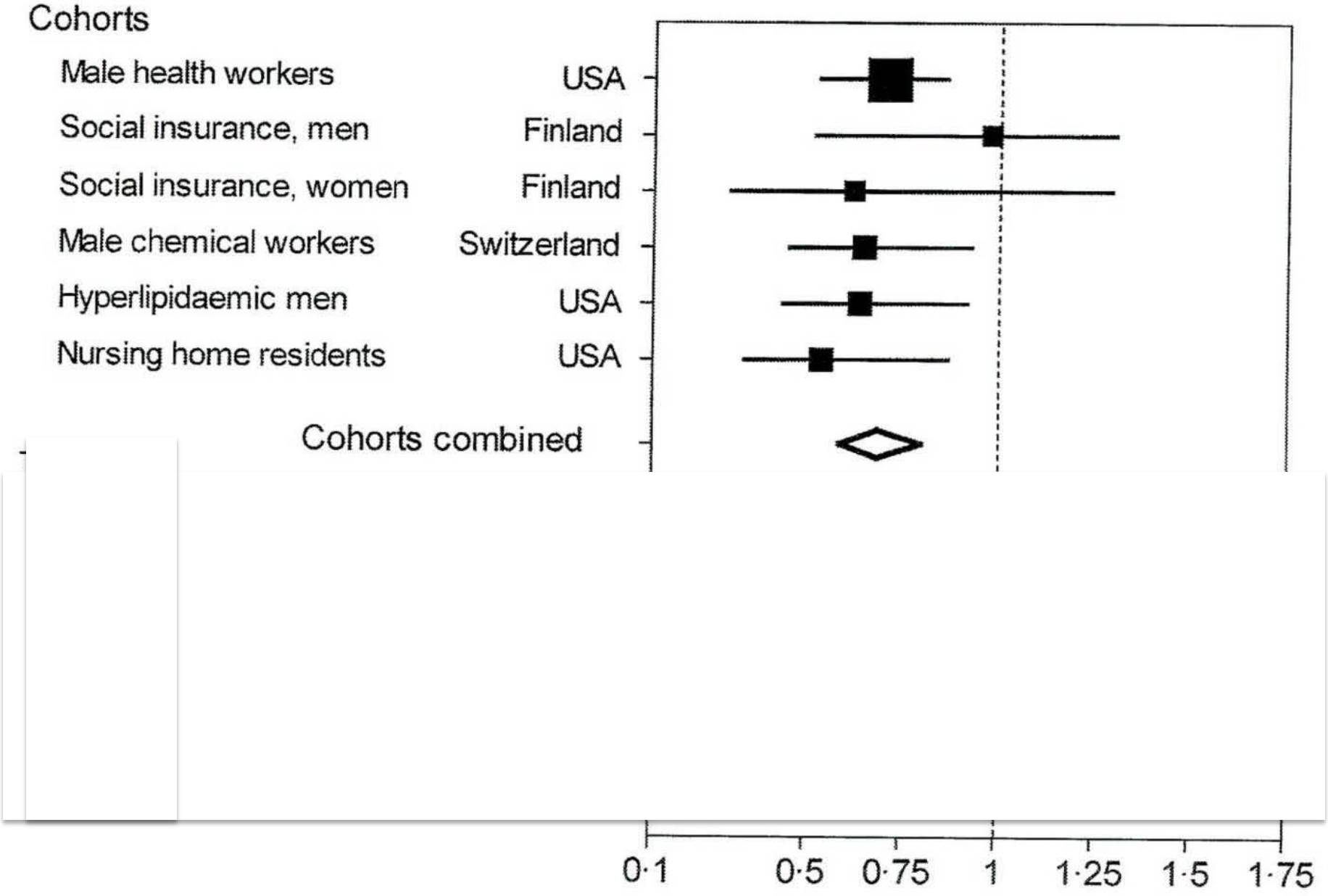


Fig 2. Results from discordant pairs of meta-analyses of small trials and single large trials.

Egger Clin Med. 2001, 1(6):478-84. PMID: 11792089.

Beta-carotene intake and cardiovascular mortality



Egger et al. Systematic reviews in health care. London: BMJ, 2001.

Concluding remarks: a systematic review can

- Refine unmanageable amounts of information
- Shorten the time between research discoveries and clinical implementation
- Investigate generalisability, consistency and inconsistency of studies
- Increase power and precision

Concluding remarks

- Motivation: time consuming tasks
- Focus: a clearly formulated question and a protocol
- Multidisciplinary review team
  - Content Specialist, epidemiologist, biostatistician, librarian
- Training
  - Methods: Cochrane handbook, books, etc
  - Software: Reference Manager, RevMan, Stata, etc

Resources

- Cochrane Collaboration: http://www.cochrane.org/
- Cochrane handbook: http://www.cochrane-handbook.org

- Guidelines for reporting Systematic Reviews of RCTs: PRISMA: Moher *et al*. PLoS Med 2009; 6(7): e1000097. PMID: 19621072
- Guidelines for reporting Systematic Reviews of non-experimental studies: MOOSE: Stroup *et al*. JAMA 2000;283:2008-12. PMID: 10789670
- Guidelines for interventional trials: SPIRIT: BMJ 2013;346:e7586. PMID: 23303884
- More guidelines: EQUATOR network: http://www.equator-network.org/resource-centre/library-of-health-research-reporting/

- Do oxalate treatments improve dentin hypersensitivity?
- Does flossing prevent interproximal dental caries?
- Does personal oral hygiene prevent periodontal diseases?

Does flossing prevent interproximal dental caries?

- Weak evidence from 6 RCTs with children 4 – 13 years old
- Flossing
  - performed by professionals in school days for 1.7 years: 40% reduction in dental caries (RR=0.6; 95%CI=0.48-0.76)
  - performed by professionals every 3 months for 3 years: no caries reduction (RR=0.93; 95%CI=0.73-1.19)
  - Self-performed by young adolescents for 2 years: no caries reduction (RR=1.01; 95%CI=0.85-1.20)
- No RCT in adults or unsupervised

J Dent Res 85(4):298-305, 2006

Does personal oral hygiene prevent periodontal diseases?

- Weak evidence from 3 RCT
- Oral hygiene did not prevent periodontal disease progression
  - Non-significant increase in alveolar bone loss in 13-yo children after 3 years (0.05 mm)
  - Not associated with tooth loss, probing depth or attachment loss in 60-90 yo seniors after 3 years
  - Not associated with periodontal index and attachment loss (0.09 mm) in 18 yo men after 46 months

Periodontology 2000, 37:29–34, 2005

Absence of evidence is not evidence of absence of effect

Systematic reviews also demonstrates where available evidence is insufficient and new trials are needed

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Thank you