EBM SERIES

Systematic review
&Meta-analyses

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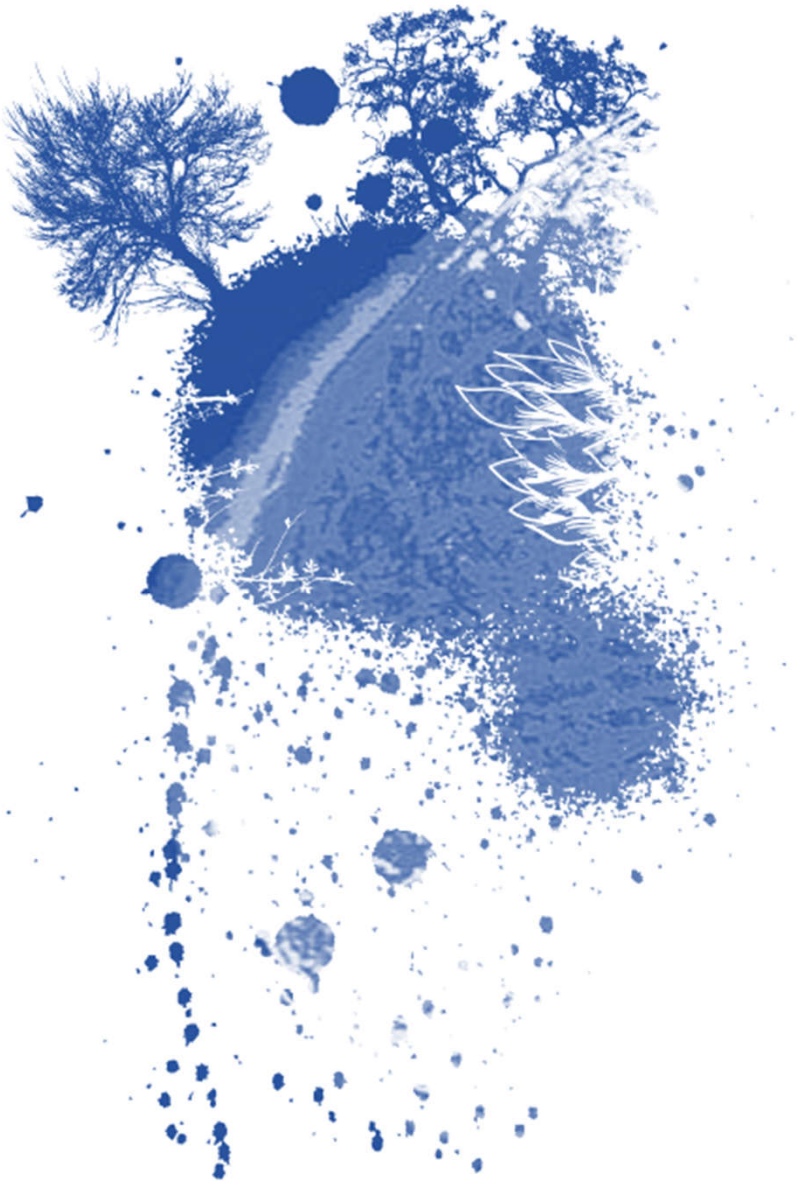
Today's Topics

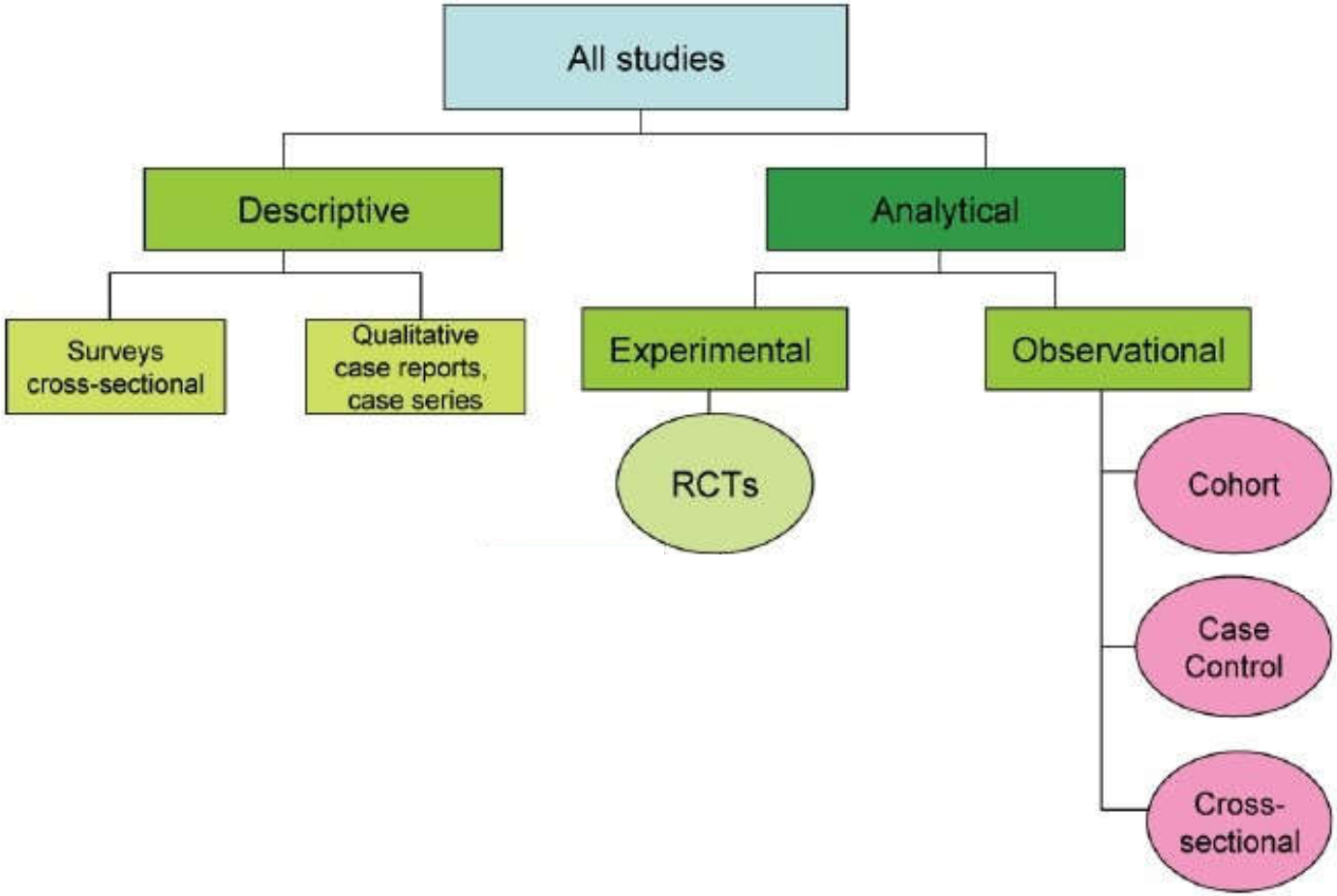
- Systematic reviews
- Meta-analyses
- Critical Appraisal of SR&MA ☆ ☆

Basic concepts

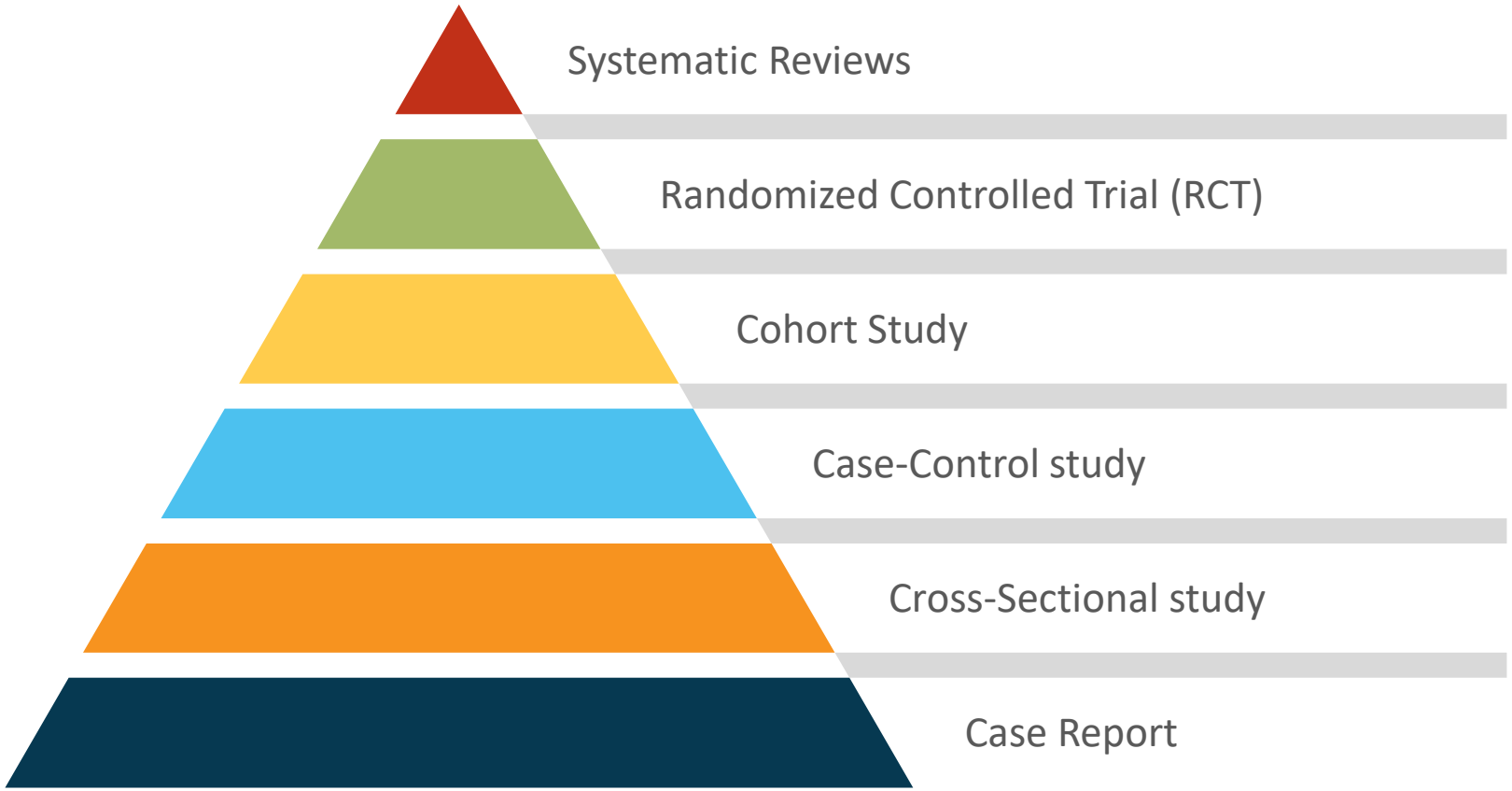


Types of study design

Methods to answer the research question



Hierarchy of evidences



Systematic review &Meta-analyses

Types of analyses (evidences)

Primary analysis (Primary research):

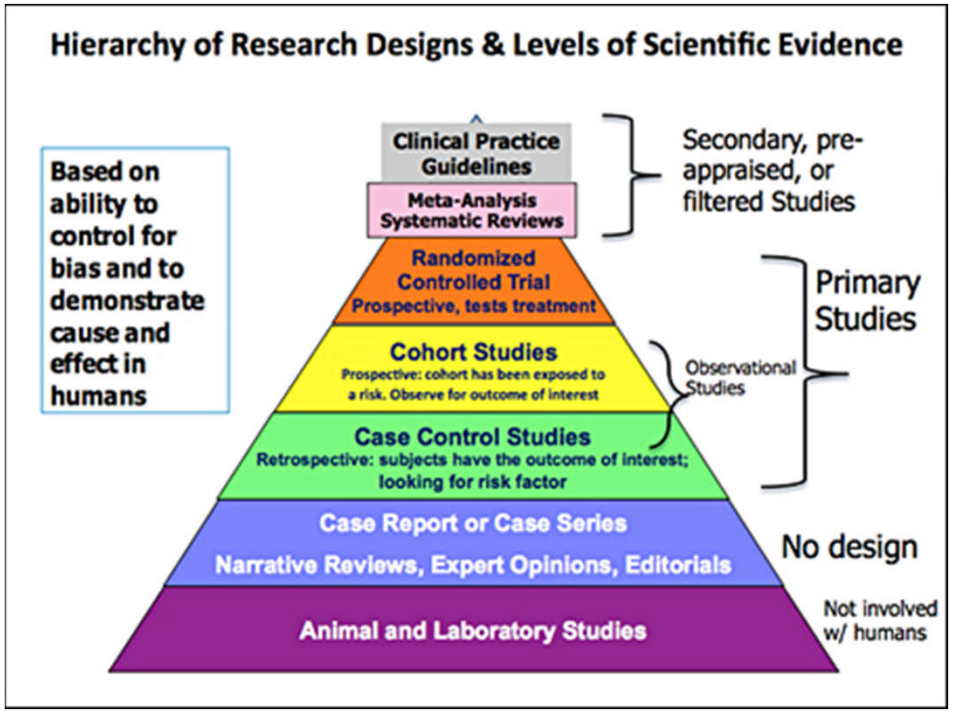
Original studies

Original analysis of research data

Secondary analysis (Secondary research):

Summary (Review, SA), Synopses, System

Re-analysis of the original data either using another statistical technique or answering new questions with previously obtained data (Meta-analysis)



Systematic review &Meta-analyses

Narrative review VS Systematic review

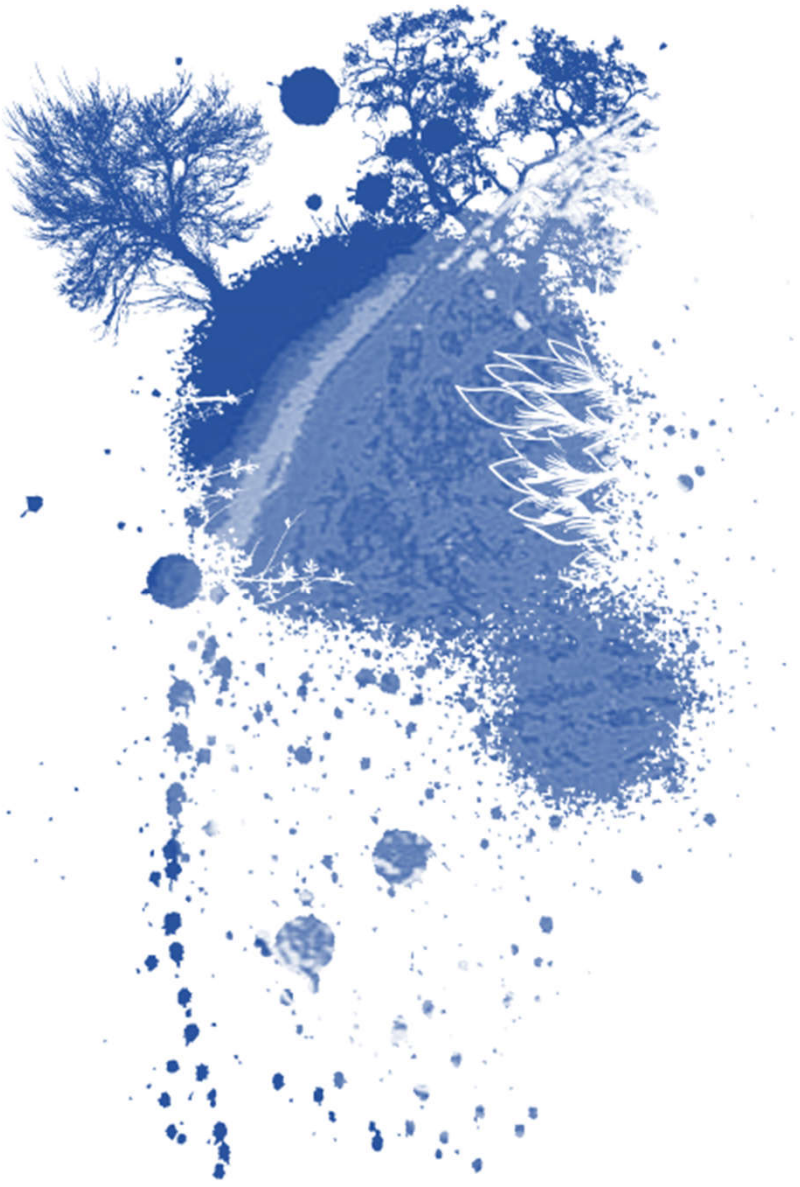
Characteristic	Narrative Review	Systematic Review
Clinical question	Seldom reported, or address several questions	Focused question: PICO
Search for primary articles	Seldom reported, not comprehensive	Comprehensive search of several sources
Selection of primary articles	Seldom reported, often biased	Explicit inclusion and exclusion criteria
Evaluation of quality of primary studies	Seldom reported, not usually systematic	Methodological quality of primary articles is assessed
Summary of results of primary studies	Usually qualitative, nonsystematic	Synthesis is systematic, meta-analysis

Systematic review
&Meta-analyses

Narrative review VS Systematic review

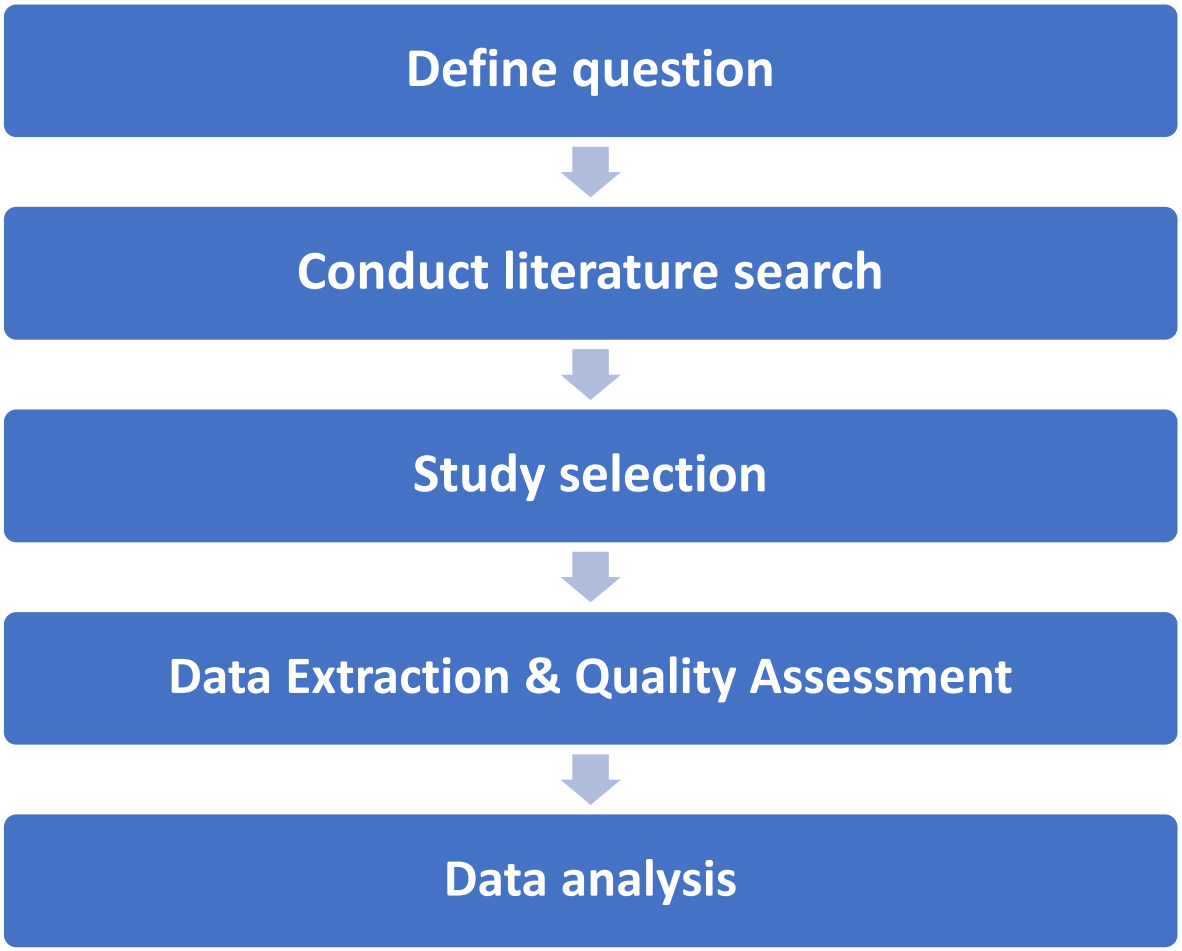
Steps of SR

Steps of MA



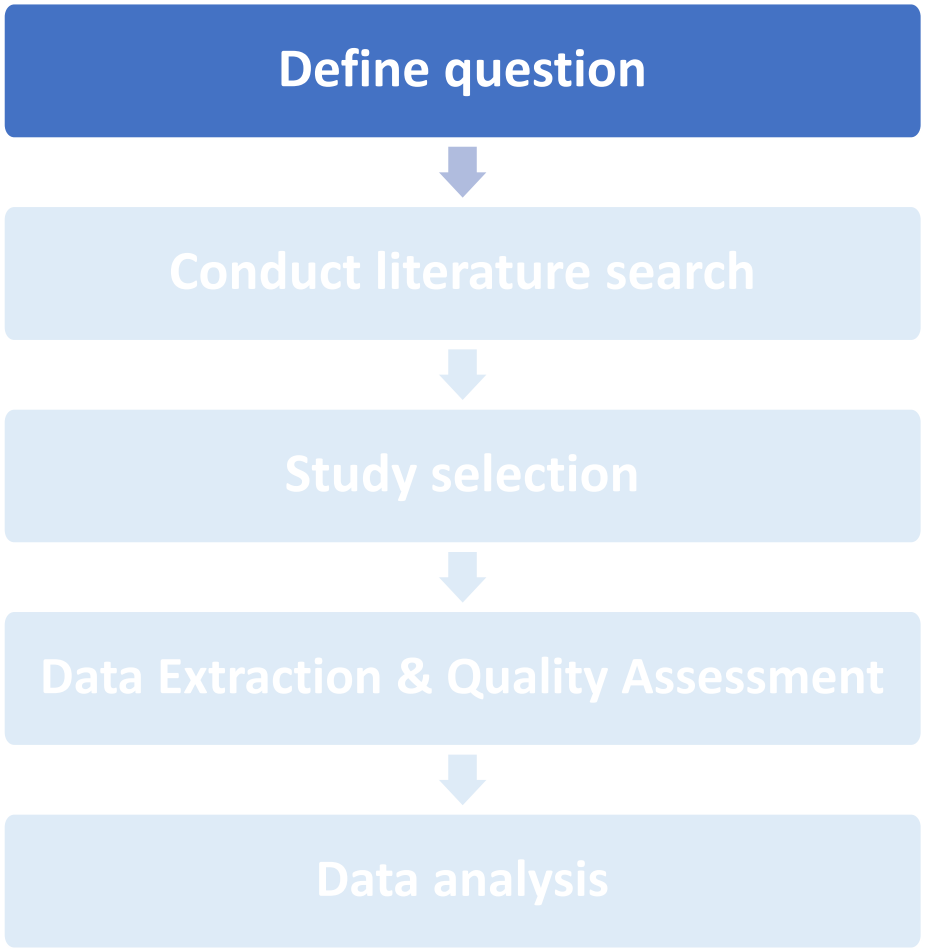
Systematic review &Meta-analyses

Steps of SR



Systematic review &Meta-analyses

Steps of SR



Structural research question:

Population
Intervention/Exposure
Comparison
Outcome

Methodology

- time
- language
- publication restriction

Systematic review &Meta-analyses

Steps of SR

- Define question
- **Conduct literature search**
- Study selection
- Data Extraction & Quality Assessment
- Data analysis

Steps for searching

1. Decide on information source
   - At least 2 databases
2. Define search terms
3. Searching Strategies
4. Identify titles and abstract

Systematic review &Meta-analyses

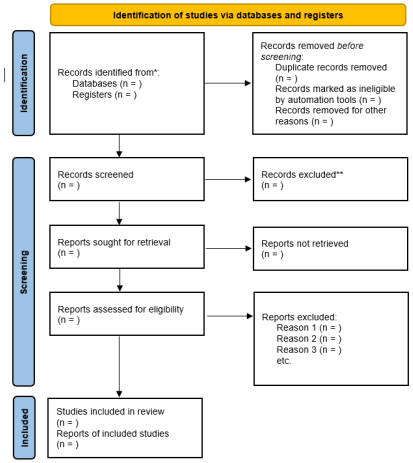
Steps of SR

- Define question
- Conduct literature search
- **Study selection**
- Data Extraction & Quality Assessment
- Data analysis

Define inclusion Criteria
Define exclusion Criteria
Define ineligible Criteria

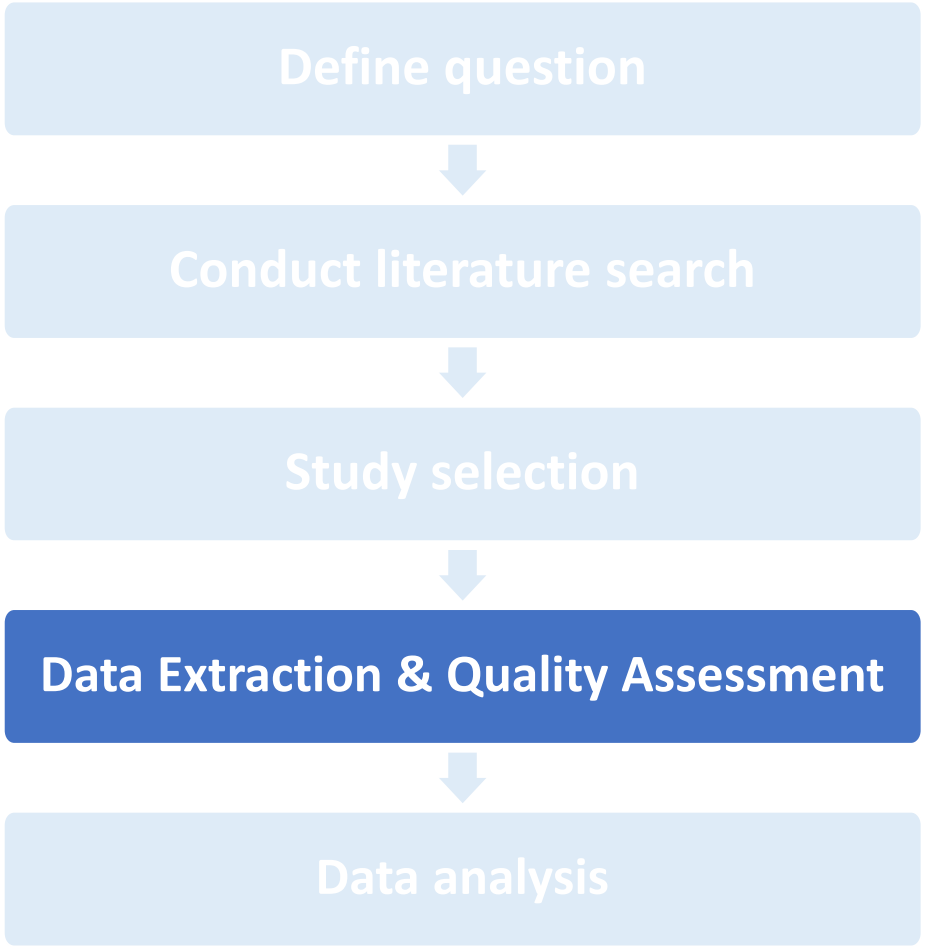
↓

Study selection
From At least 2 reviewers
(including Assess agreement on study selection)



Systematic review &Meta-analyses

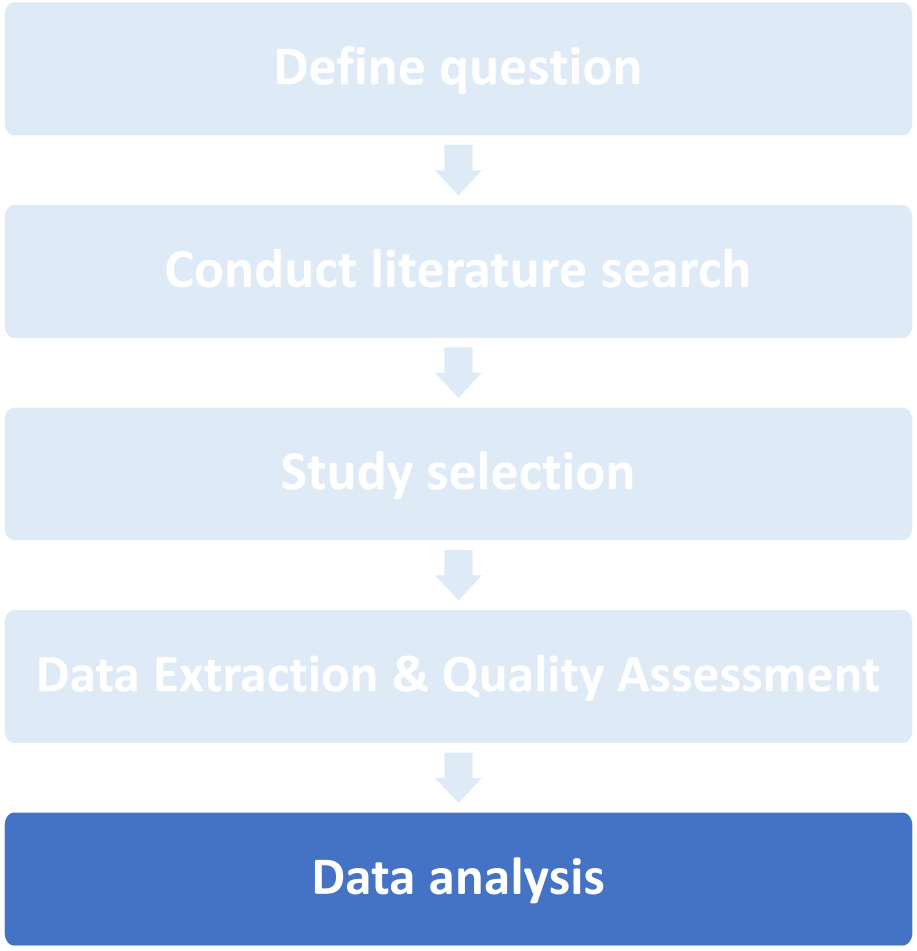
Steps of SR



- Data abstraction
  - PICOM (incl. Characteristic study)
  - Author, years, email
- Result
  - Proportion: Incidence, Prevalence
  - Mean: Mean, Mean difference
  - Ratios: Relative risks, Odds ratio
  - Diagnostic performances: Sn, Sp
  - Etc.
- Methodologic quality
  - Depends on Types of primary studies
  - Risk of Bias of each study
- Assess agreement on validity assessment

Systematic review &Meta-analyses

Steps of SR

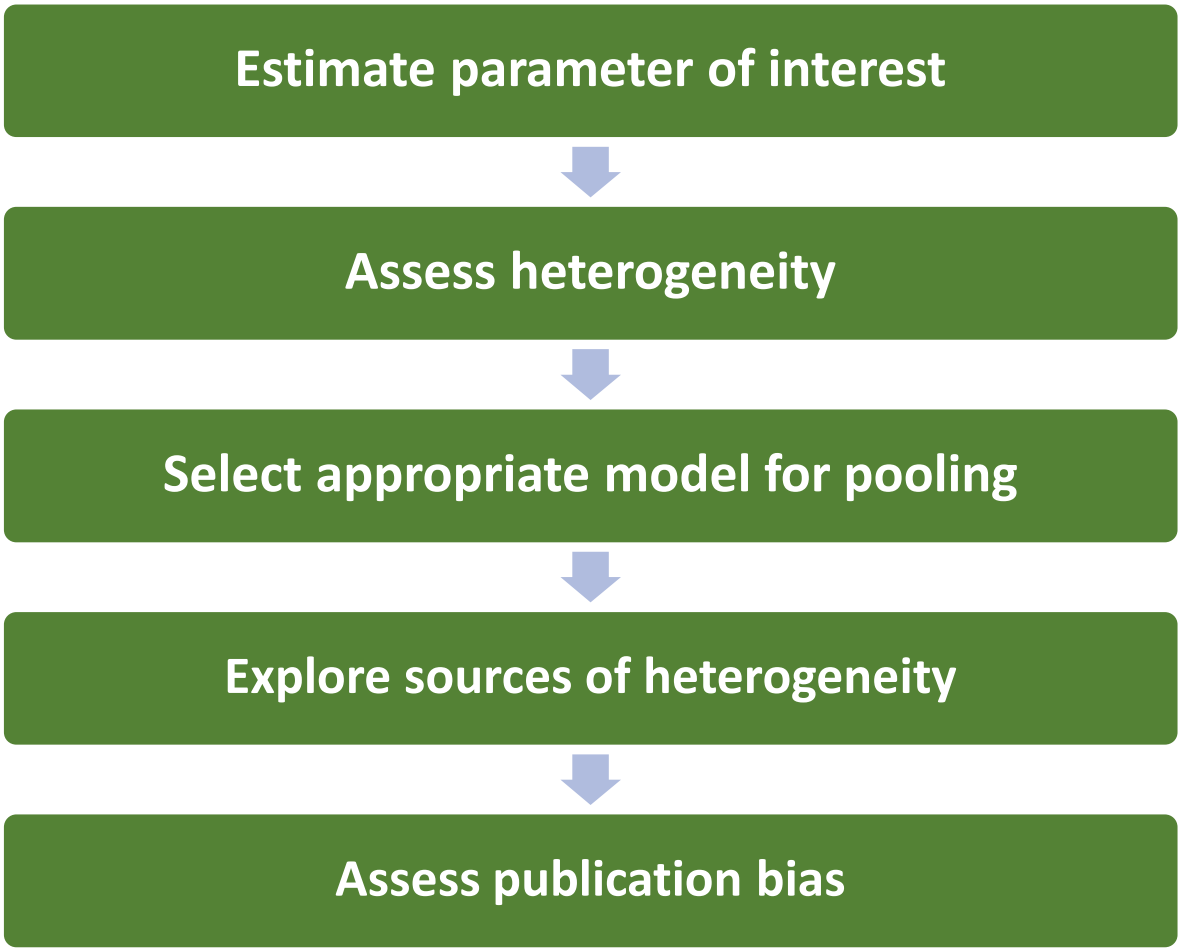


Meta-Analysis

- Select method of generating pooled estimates across studies
- Pool treatment effect estimates (if appropriate)
- Explore heterogeneity
- Conduct subgroup analysis if appropriate
- Explore possibility of publication bias

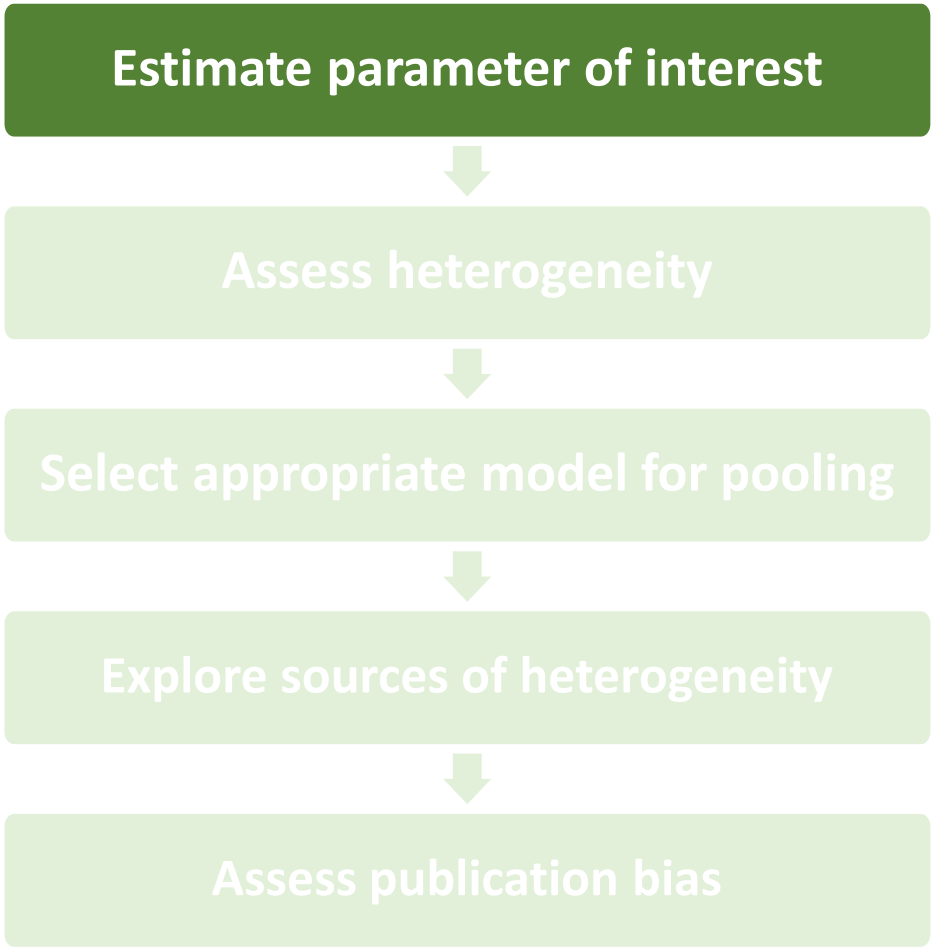
Systematic review &Meta-analyses

Steps of MA



Systematic review &Meta-analyses

Steps of MA



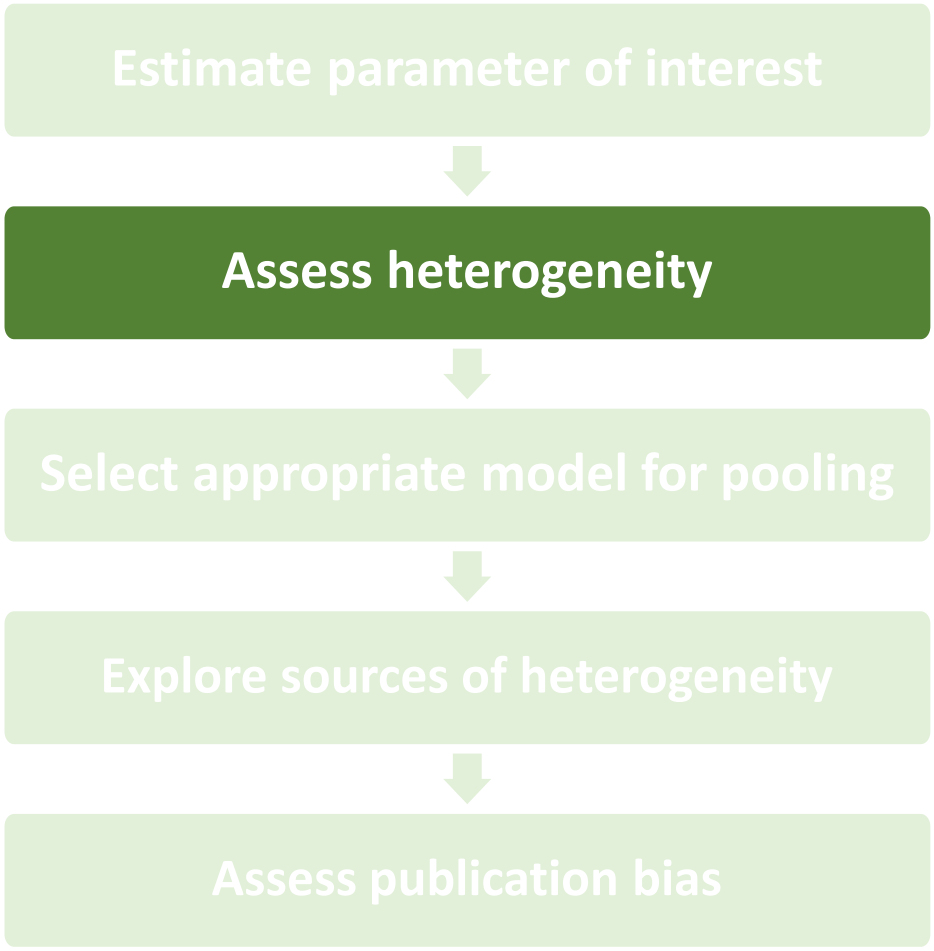
Estimate parameter of interest

- Proportion: Incidence, Prevalence
- Mean: Mean, Mean difference
- Ratios: Relative risks, Odds ratio
- Diagnostic performances: Sn, Sp
- Etc.

Comparative studies	Dichotomous outcome
	Continuous outcome
Estimated studies	Dichotomous outcome
	Continuous outcome

Systematic review &Meta-analyses

Steps of MA



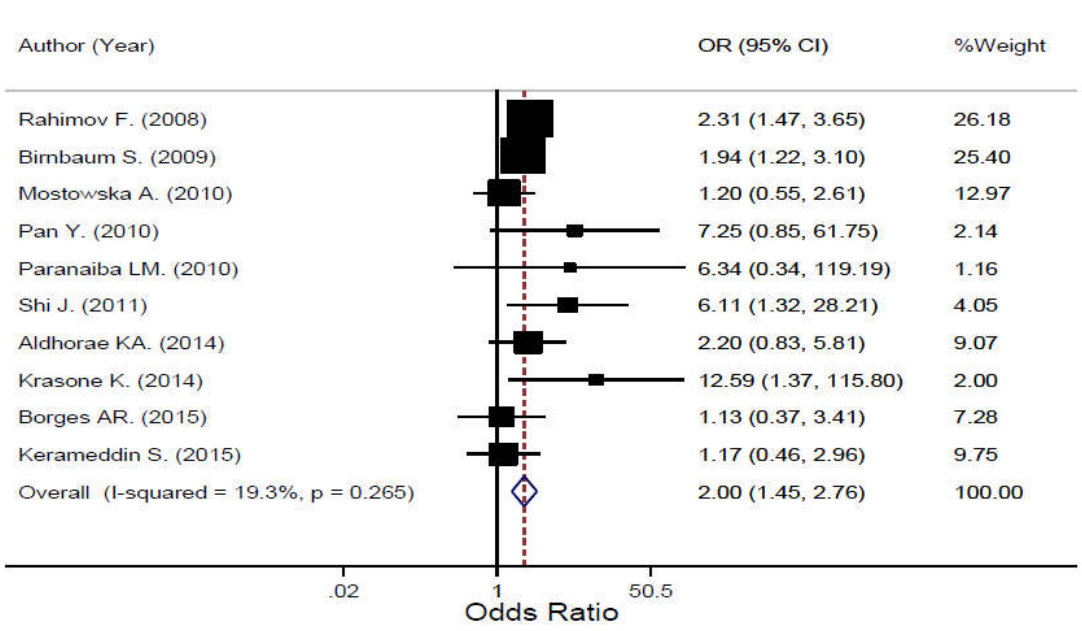
Assess Heterogeneity among studies

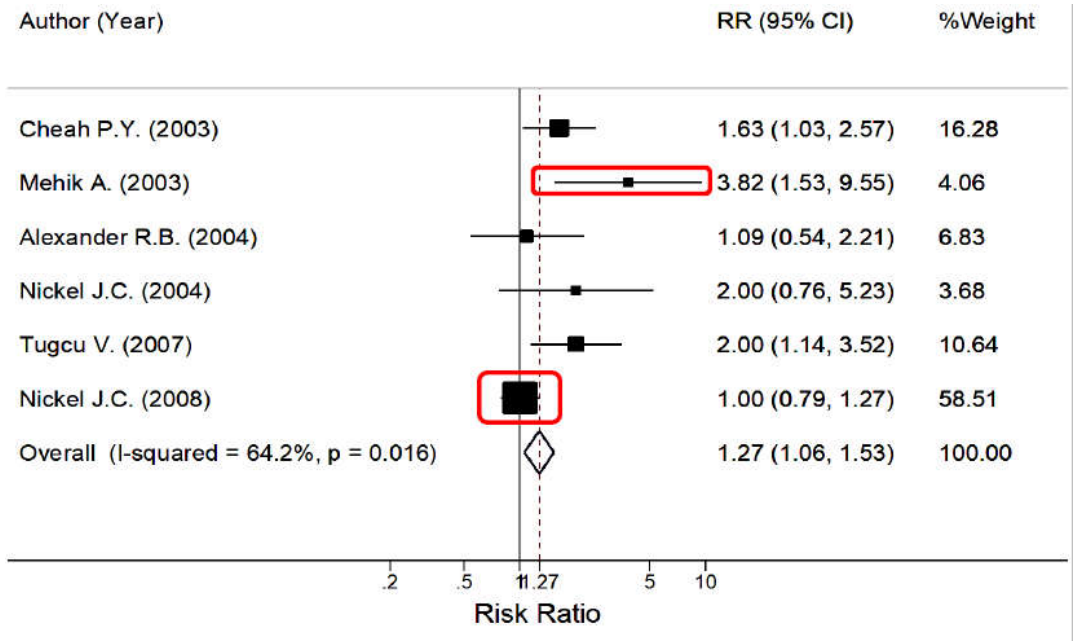
- Forest Plot
  - By visual
- Cochrane's Q Test
  - Yes/No
- Higgin's I^2
  - Degree of heterogeneity
  - %, Scale (How much)

Systematic review &Meta-analyses

Steps of MA: Assess Heterogeneity among studies

- **Forest Plot**
- Cochrane's Q Test
- Higgin's I^2





Low heterogeneity

High heterogeneity

Systematic review &Meta-analyses

Steps of MA: Assess Heterogeneity among studies

- Forest Plot
- **Cochrane's Q Test**
- Higgin's I^2

Cochrane's Q Test

The statistical hypotheses

H0: $no\ heterogeneity\ (homogeneity\ among\ studies)$

- underlying effect is the same
- underlying assumption of pooling holds true

H1: $heterogeneity\ among\ study$

- Less sensitive when the number of studies is low (<25 studies)
- The level of significance is recommended to be at least 0.10

Systematic review &Meta-analyses

Steps of MA: Assess Heterogeneity among studies

- Forest Plot
- Cochrane's Q Test
- **Higgin's I^2**

Higgin's I^2

$$I^2 = \frac{Q - df}{Q} \times 100$$

df = Degree of freedom

For random-effect meta-analysis: df = K-1

Percentage of "unexplained" variance

Higher degree of heterogeneity – consider between-study variations

Higgin's I^2	Degree of heterogeneity
< 25%	Low
25%-75%	Moderate
>75%	High

Moderate or higher degree should be considered to account for between study's variation.

Systematic review &Meta-analyses

Steps of MA

Estimate parameter of interest

↓

Assess heterogeneity

↓

Select appropriate model for pooling

↓

Explore sources of heterogeneity

↓

Assess publication bias

Heterogeneity among studies when

- Forest Plot
  - Not concordance
- Cochrane's Q Test
  - P-value<0.10
- Higgin's I^2
  - $\geq$ 25%

Systematic review &Meta-analyses

Steps of MA

- Estimate parameter of interest
- Assess heterogeneity
- **Select appropriate model for pooling**
- Explore sources of heterogeneity
- Assess publication bias

Model for pooling data

No variation between studies (Homogeneity)

- Fixed effect model
  - Inverse variance
  - Mantel-Haenzel
  - Peto

Variations between studies (Heterogeneity)

- Random effect model
  - Der-Simonian and Laird

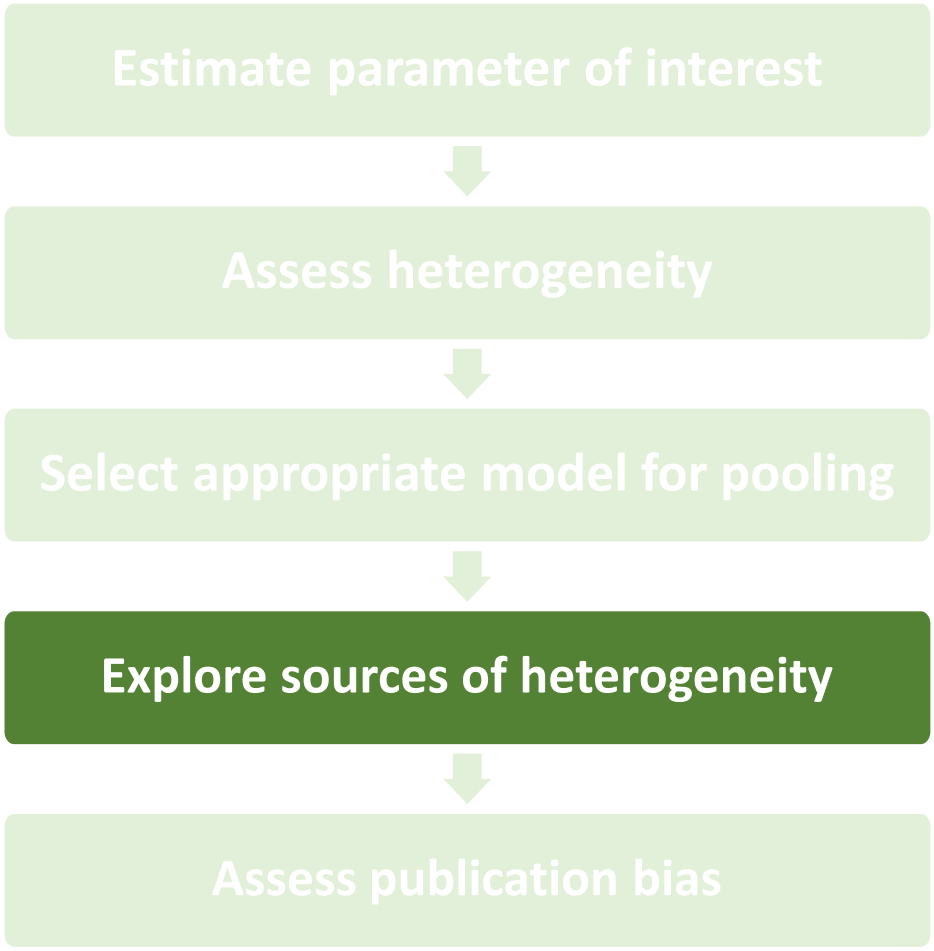
Systematic review &Meta-analyses

Steps of MA: Select appropriate model for pooling

Issues	Fixed Effect Model	Random Effect Model
Underlying assumption	All trials estimate the same size of treatment effect	Varying underlying effect
Computational method	Error term comes from “within trial” (ignore between-study variability)	Error term comes from “within trial” and “between trial”
Practical consequences	Narrower confidence interval	Wider confidence interval

Systematic review &Meta-analyses

Steps of MA



Sources of heterogeneity

- Clinical variation
  - Population Characteristic
- Methodological variation
  - Type of study design
  - Type of outcome
  - Type of outcome measurement
  - Type of treatment

Systematic review &Meta-analyses

Steps of MA

Estimate parameter of interest

↓

Assess heterogeneity

↓

Select appropriate model for pooling

↓

Explore sources of heterogeneity

↓

Assess publication bias

How to access sources of heterogeneity

Meta regression

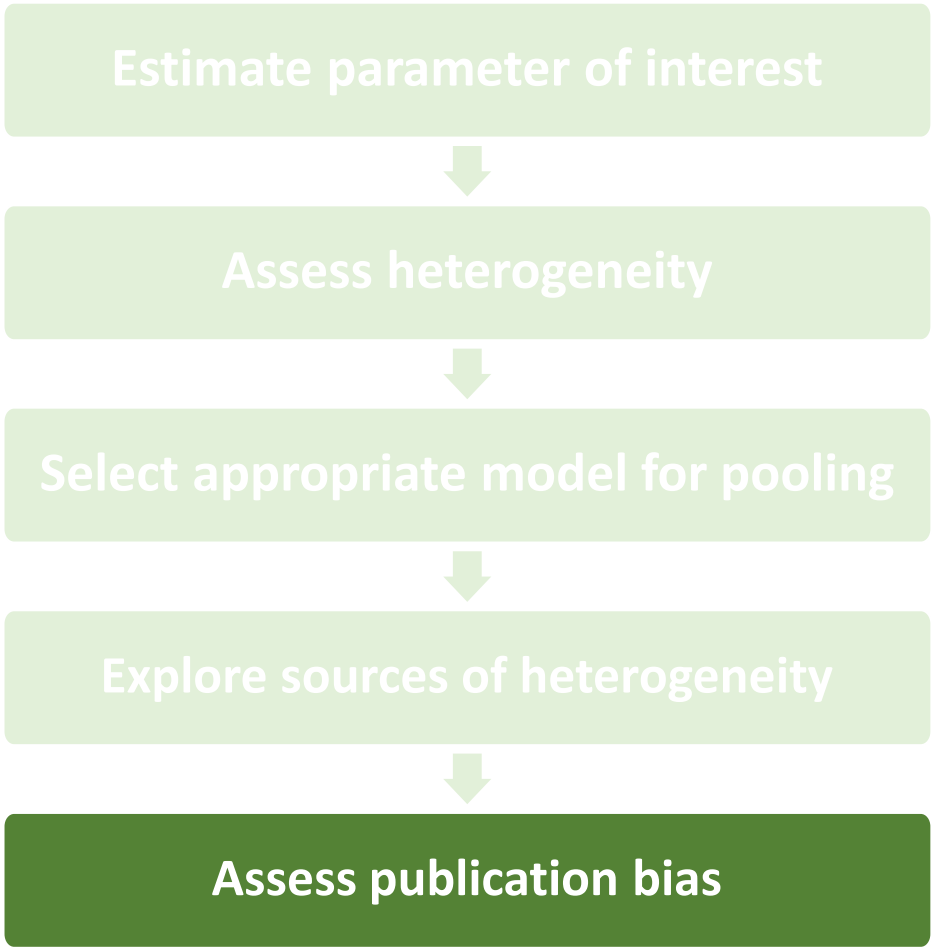
- Moment method (Der-Simonian and Laird)
- Restricted maximum likelihood (REML)
- Empirical Bayes method

Subgroup analysis

Sensitivity analysis

Systematic review &Meta-analyses

Steps of MA



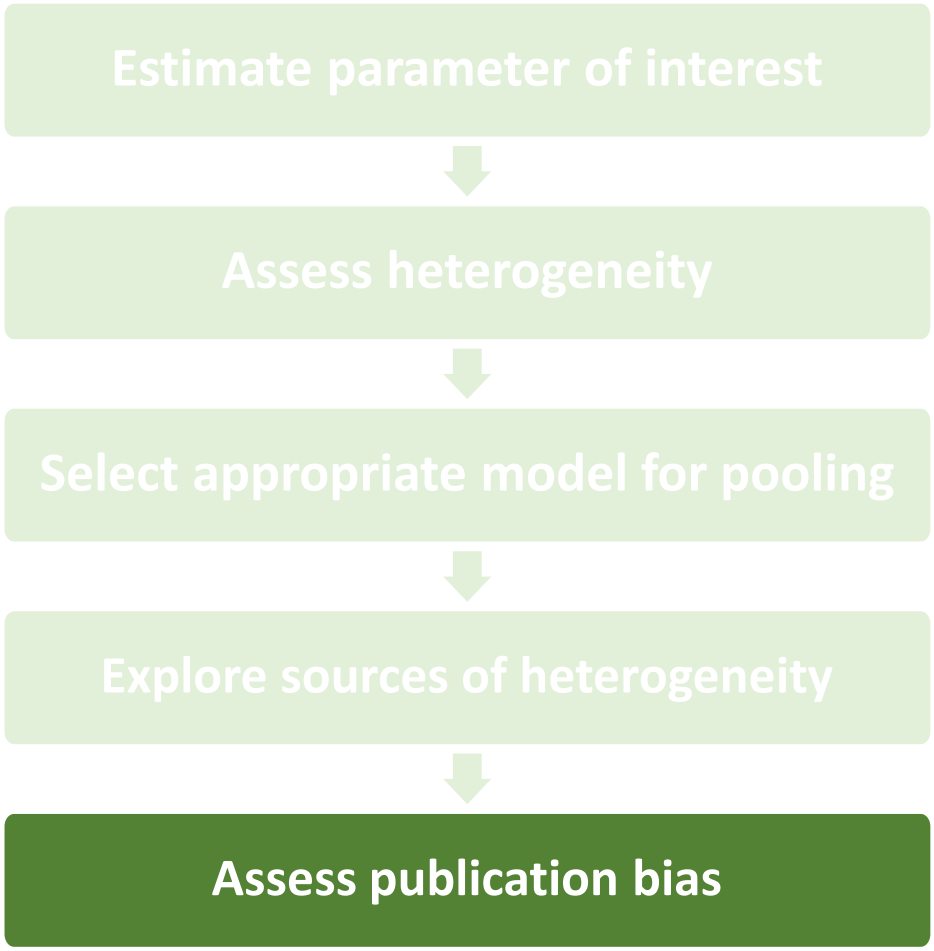
Publication bias

Publication bias and other related biases can be summarized as statistically significant, 'positive' results being:

- published positive results (publication bias)
- published rapidly (time lag bias)
- published in English (language bias)
- be published more than once (multiple publication bias)
- cited by others (citation bias)

Systematic review &Meta-analyses

Steps of MA

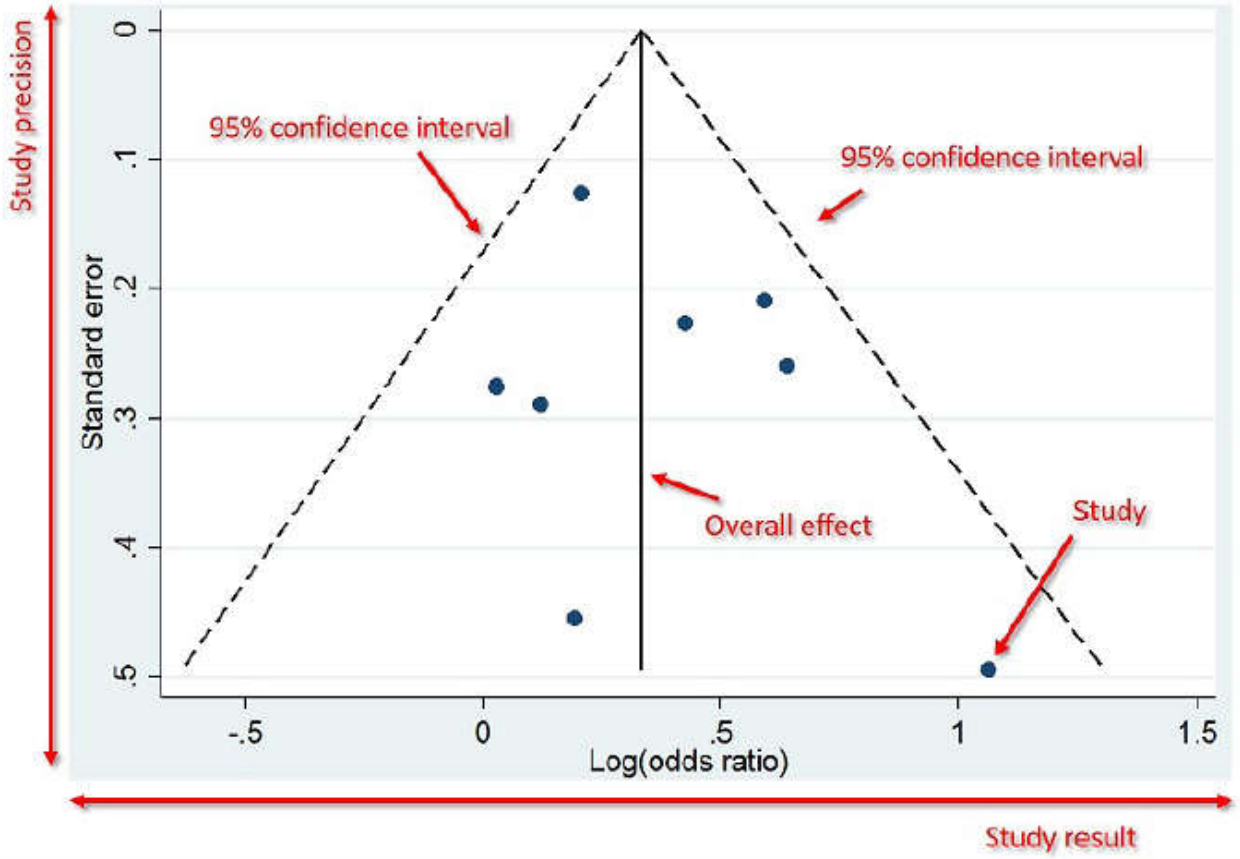


Assess publication bias

- Funnel plot
  - By visual
- Egger's test
  - Yes/No For Asymmetry of funnel plot
- Contour enhanced-funnel plot
  - By visual but with area of significance

Systematic review &Meta-analyses

Steps of MA: Assess publication bias

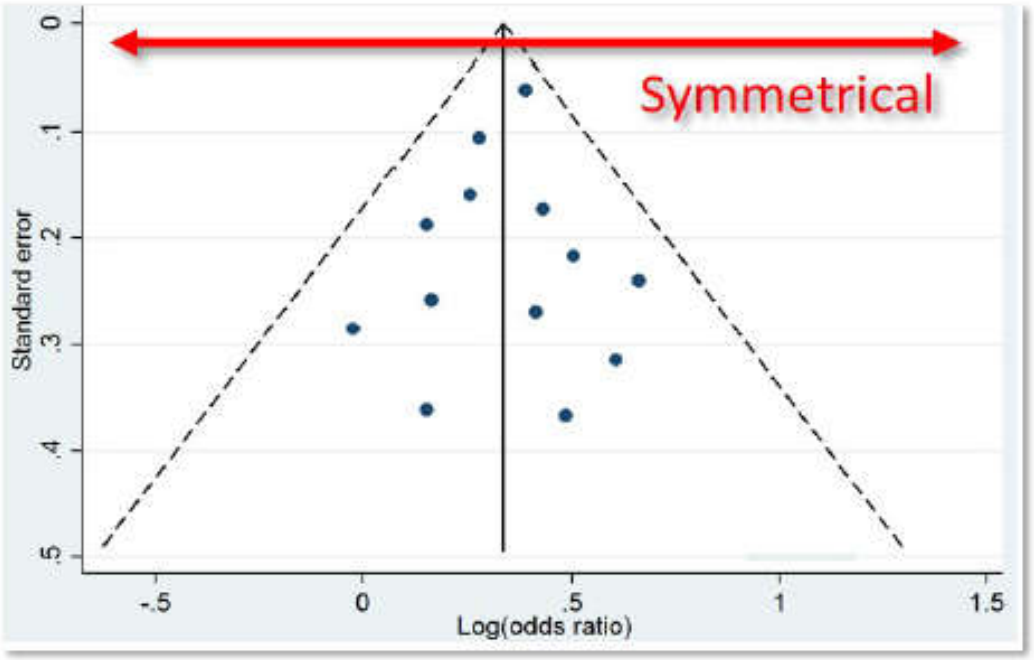


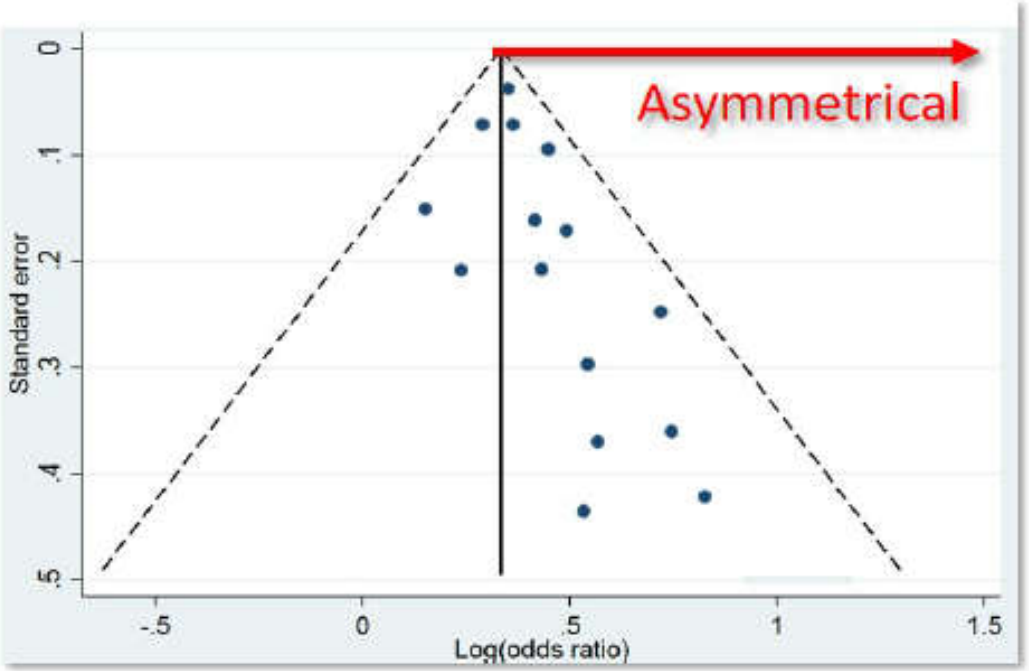
Funnel plot

- Funnel plot
  - By visual
- Contour enhanced-funnel plot
  - By visual but with area of significance
- Egger's test
  - Yes/No

Systematic review &Meta-analyses

Steps of MA: Assess publication bias





Systematic review &Meta-analyses

Steps of MA: Assess publication bias

Egger's test

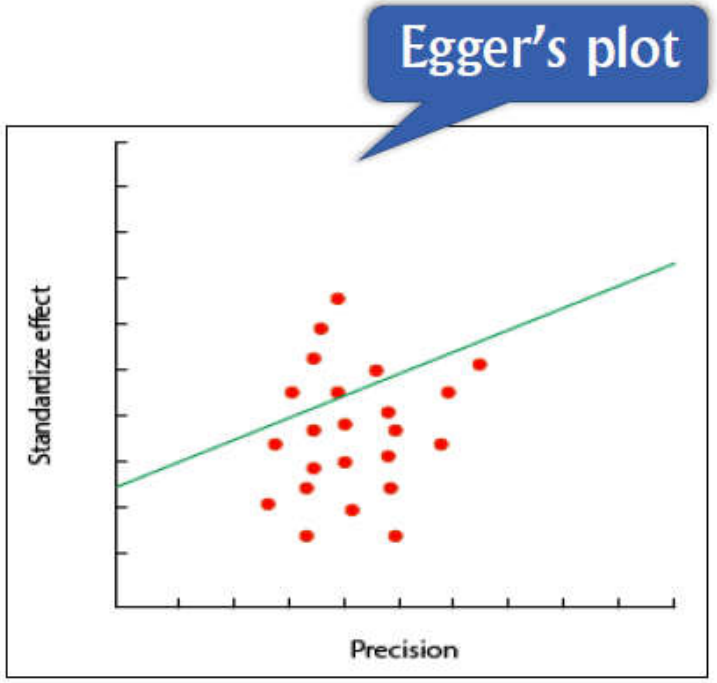
A parametric test for assessing asymmetry of the funnel plot using linear regression analysis

The statistical hypotheses

H0: $Funnel\ plot\ is\ symmetic$al

- No association between standardized effect and variance
- No small-study effect

H1: $Funnel\ plot\ is\ Asymmetic$al



Systematic review &Meta-analyses

Steps of MA: Assess publication bias

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. metabias lnrr selnrr,egger

Note: data input format theta se_theta assumed.

Egger's test for small-study effects:
Regress standard normal deviate of intervention
effect estimate against its standard error

Number of studies =  6                                  Root MSE      =   1.095
------------------------------------------------------------------------------
     Std_Eff |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       slope |  -.2821979   .2148871    -1.31   0.259    -.8788202    .3144244
        bias |   2.575638   .9318214     2.76   0.051    -.0115133    5.162789
------------------------------------------------------------------------------

Test of H0: no small-study effects              P = 0.051
```

Systematic review &Meta-analyses

Steps of MA: Assess publication bias

Causes of asymmetry

Heterogeneity of effect sizes

Selection bias

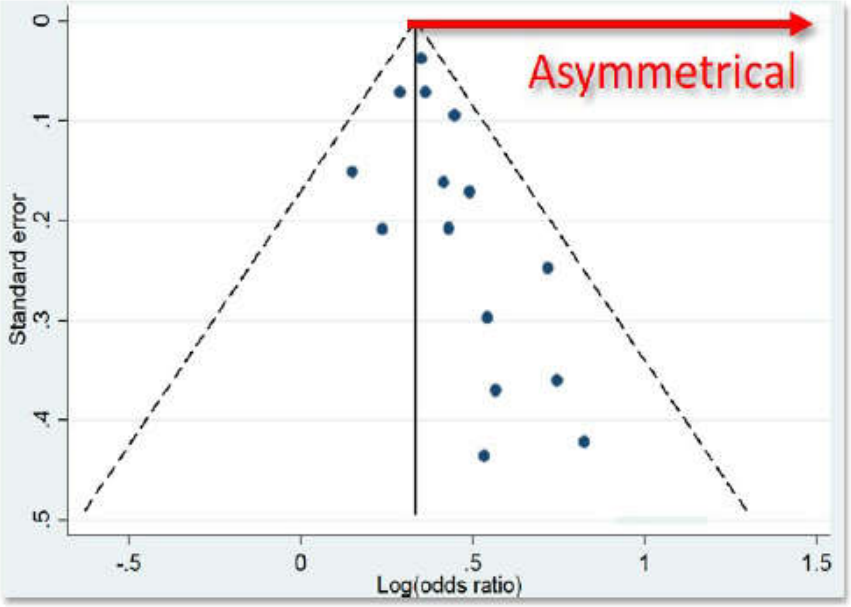
- Some studies with negative findings are not selected.

Poor quality of research

- Studies design, measurement bias, etc.

Publication bias

- Missing small or negative studies

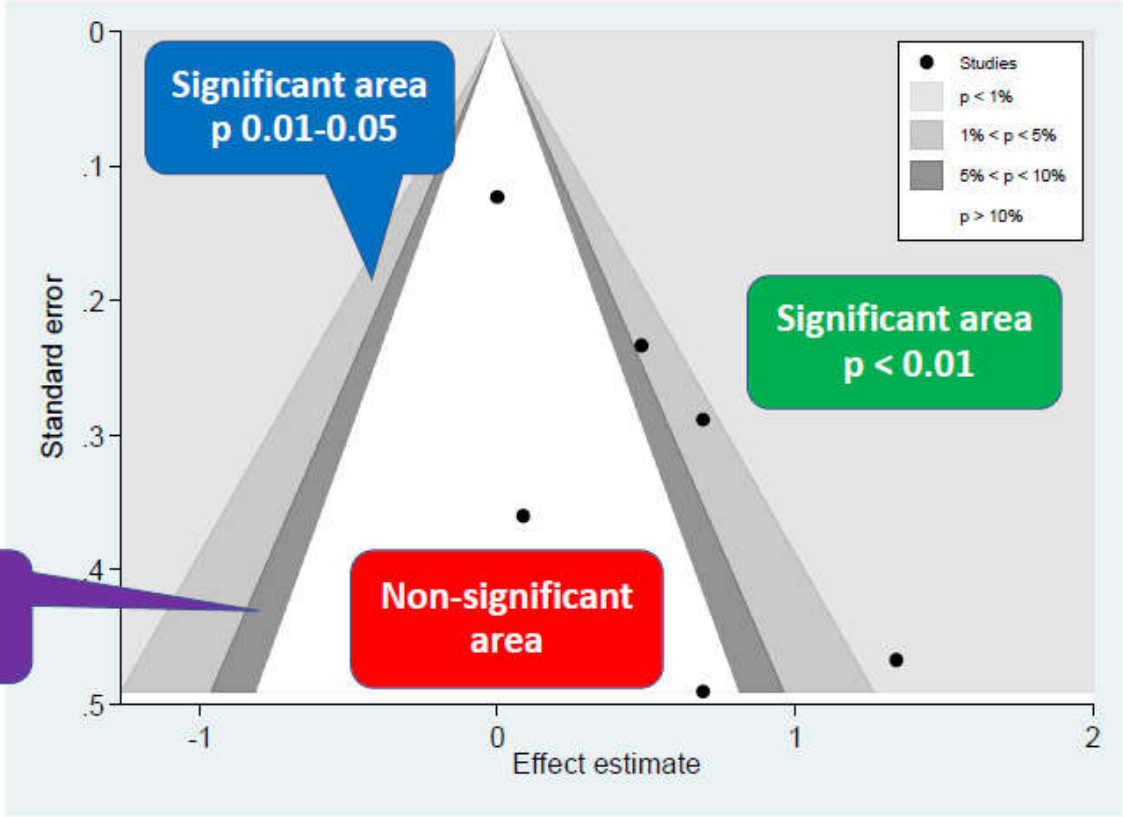


Systematic review &Meta-analyses

Steps of MA: Assess publication bias

Contour enhanced-funnel plot

Assessing publication bias: Contour enhanced-funnel plot



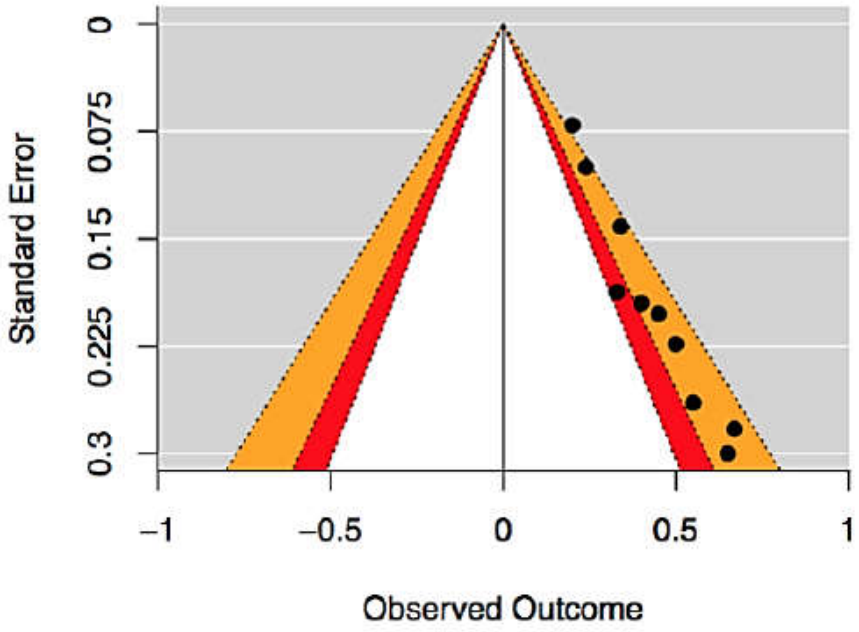
Systematic review &Meta-analyses

Steps of MA: Assess publication bias

Assessing publication bias: Contour enhanced-funnel plot

- Missing studies in non-sig. areas → asymmetry may be due to publication bias

Contour enhanced-funnel plot



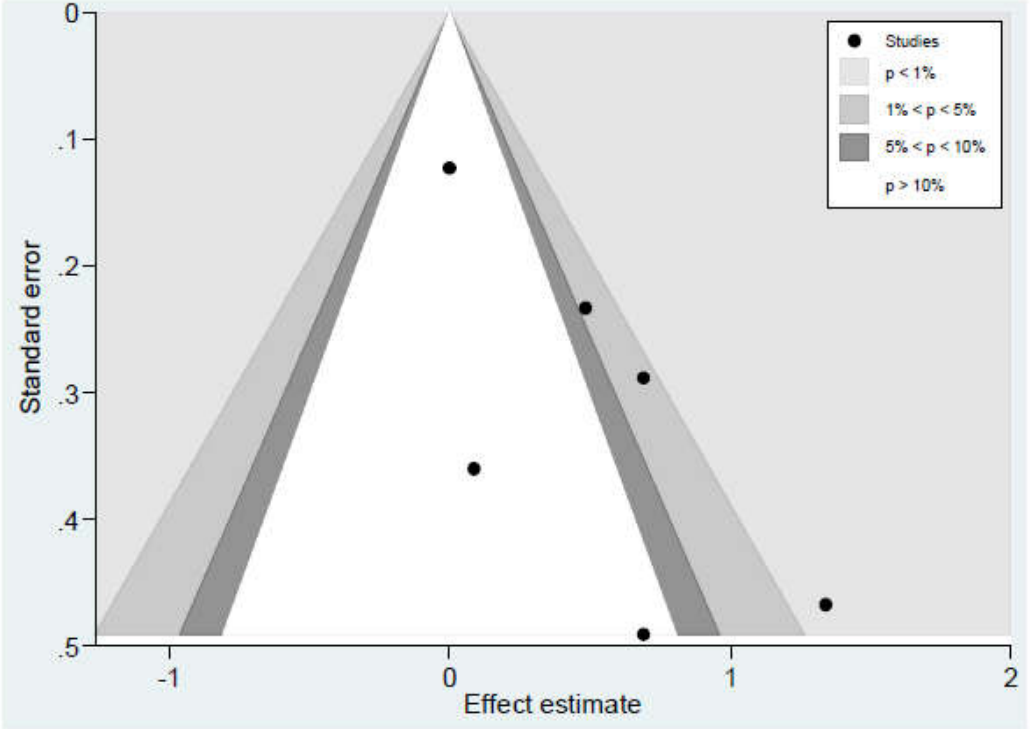
Systematic review &Meta-analyses

Steps of MA: Assess publication bias

Assessing publication bias: Contour enhanced-funnel plot

- Cause of asymmetry by heterogeneity not publication bias

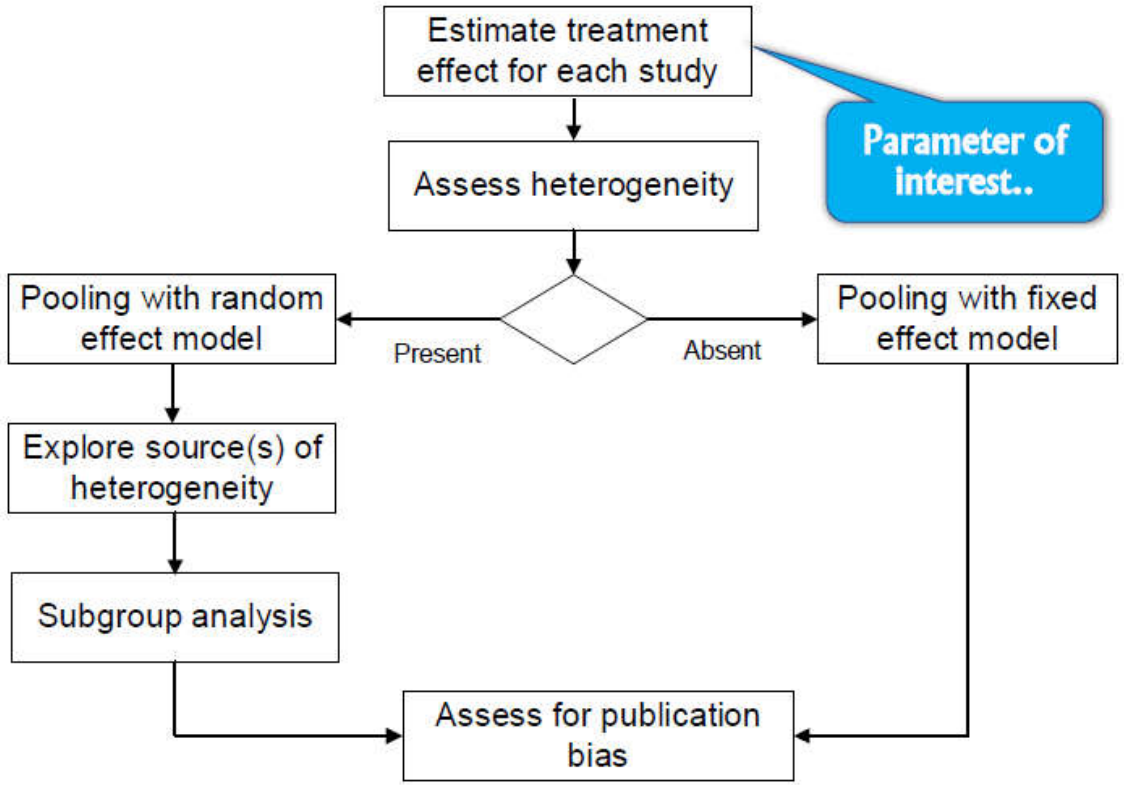
Contour enhanced-funnel plot



Systematic review &Meta-analyses

Steps of MA

- Estimate parameter of interest
- Assess heterogeneity
- Select appropriate model for pooling
- Explore sources of heterogeneity
- Assess publication bias

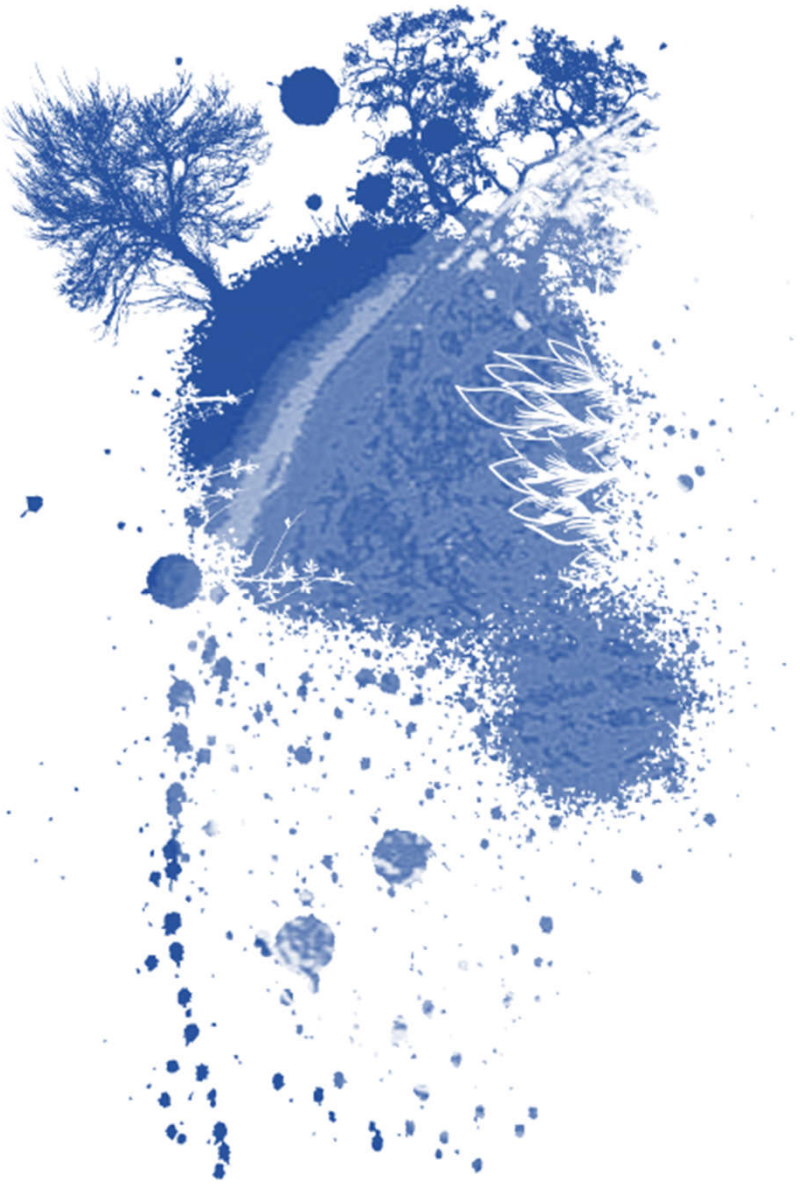


Critical Appraisal
SM&MA

Are the results of the study valid?

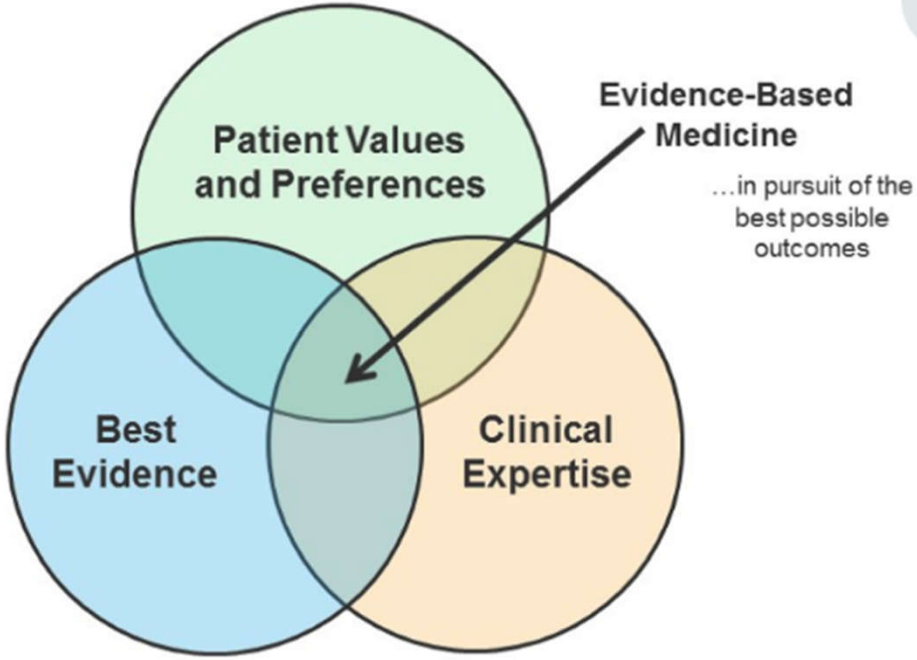
What are the results?

Will the results help locally?



Evidence-based medicine

EBM



"Expertise in integrating

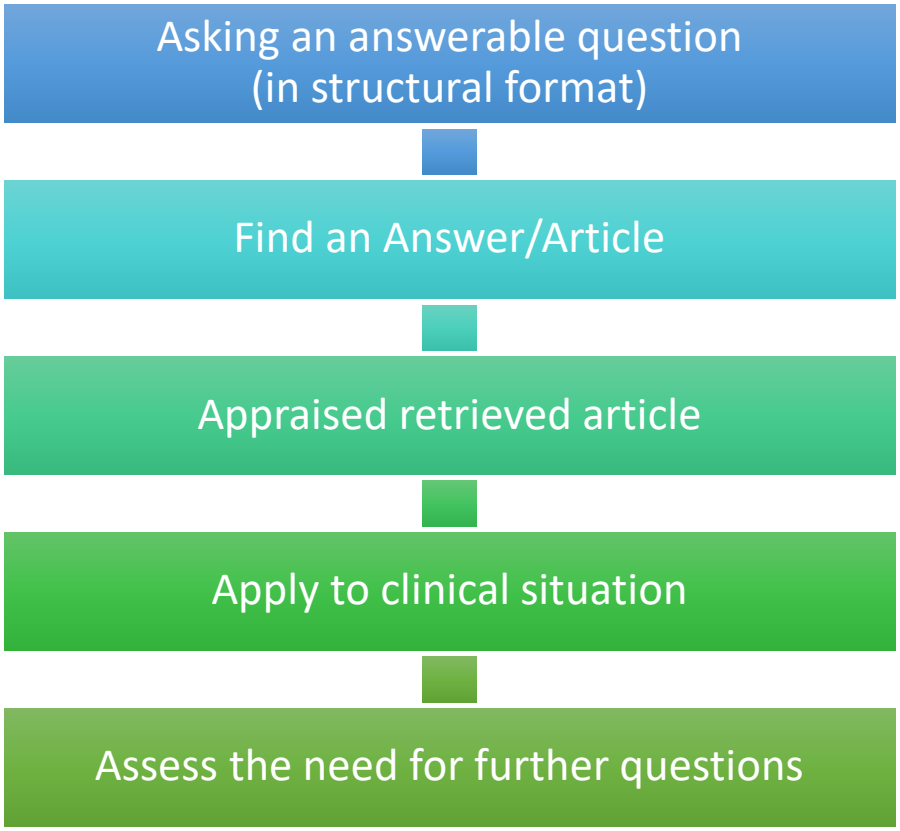
1. Best research evidence
2. Clinical Circumstance
3. Patient values

in clinical decisions"

(Haynes, Devereaux, & Guyatt, 2002)

Evidence-based medicine

EBM



Step 3: Critical appraisal

- Are the results of the study valid?
- What are the results?
- How can you apply the results to patient care?

Critical appraisal

Are the results of the study valid?

1.1 Did the Review Explicitly Address a Sensible Clinical Question?

1.2 Was the Search for Relevant Studies Detailed and Exhaustive?

1.3 Was the Risk of Bias of the Primary Studies Assessed?

1.4 Did the Review Address Possible Explanations of Between-Study Differences in Results?

1.5 Did the Review Present Results That Are Ready for Clinical Application?

1.6 Were Selection and Assessments of Studies Reproducible?

1.7 Did the Review Address Confidence in Effect Estimates?

Critical appraisal

Are the results of the study valid?

1.1 Did the Review Explicitly Address a Sensible Clinical Question?

1) Too broad or too narrow review?

2) Did it turn out that results were indeed similar across the range of PICOM?

3) Were inclusion/exclusion/eligibility criteria appropriate?

Results likely to be similar across range of patients? (older/younger, sicker/less sick)
Results likely to be similar across range of intervention? (higher/lower dose, expert/non expert use)
Results likely to be similar across range of outcome measured? (shorter/longer follow-up)

Critical appraisal

Are the results of the study valid?

1.1 Did the Review Explicitly Address a Sensible Clinical Question?

Too broad or too narrow review?

Consider these systematic review questions:

- All treatment modalities for all types of cancer to look for mortality
- All antiplatelet effect on all CV events
- Aspirin dose to prevent thrombotic stroke in patients who had TIA

Critical appraisal

Are the results of the study valid?

1.1 Did the Review Explicitly Address a Sensible Clinical Question?

Selecting articles that are most likely to provide valid results

Therapy	- Were patients randomized? - Was follow-up complete?
Diagnosis	- Was the patient sample representative of those with the disorder? - Was the diagnosis verified using credible criteria that were independent of the items of the medical history, physical examination, lab tests, or imaging procedures under study?
Harm	- Did the investigators demonstrate similarity in all known determinants of outcome or adjust for differences in the analysis? - Was follow-up sufficiently complete?
Prognosis	- Was there a representative sample of patients? - Was follow-up sufficiently complete?

Critical appraisal

Are the results of the study valid?

1.2 Was the Search for Relevant Studies Detailed and Exhaustive?

1) Appropriate databases and At least 2 databases?
   (MEDLINE, EMBASE, CINAHL, Cochrane Central Register of Controlled Trials)

2) Did unpublished studies are need?
   (Scientific meeting, doctoral thesis, ongoing trials by pharmaceutical companies)

3) Has Reporting bias been assessed?

4) Did the reviewer try to contact the primary-study's author for data retrieval?

Critical appraisal

Are the results of the study valid?

1.3 Was the Risk of Bias of the Primary Studies Assessed?

- Methodology
  - Study design
- Appraisal of quality
  - Quality scale: ex. JADAD scale
  - Quality table (Cochrane's risk of bias assessment)
- Quality of primary study is assessed using similar tool as you appraised primary study

Critical appraisal

Are the results of the study valid?

1.3 Was the Risk of Bias of the Primary Studies Assessed?

Table A1 Jadad scale for reporting randomized controlled trials.

Item	Maximum points	Description	Examples
Randomization	2	1 point if randomization is mentioned	"The patients were randomly assigned into two groups"
		1 additional point if the method of randomization is appropriate	The randomization was accomplished using a computer-generated random number list, coin toss or well-shuffled envelopes
		Deduct 1 point if the method of randomization is inappropriate (minimum 0)	The group assignment was accomplished by alternate assignment, by birthday, hospital number or day of the week
Blinding	2	1 point if blinding is mentioned	"The trial was conducted in a double-blind fashion"
		1 additional point if the method of blinding is appropriate	Use of identical tablets or injectables, identical vials Use of tablets with similar looks but different taste
		Deduct 1 point if the method of blinding is inappropriate (minimum 0)	Incomplete masking
An account of all patients	1	The fate of all patients in the trial is known. If there are no data the reason is stated	"There were 40 patients randomized but the data from 1 patient in the treatment group and 2 in the control were eliminated because of a break in protocol"

Critical appraisal

Are the results of the study valid?

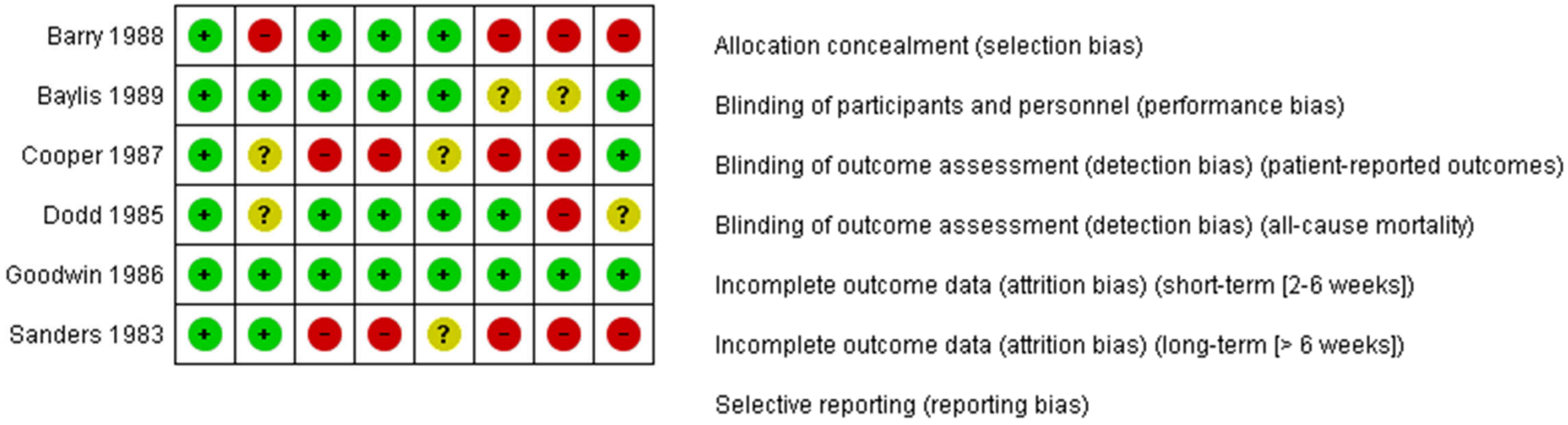
1.3 Was the Risk of Bias of the Primary Studies Assessed?

Type of bias	Description	Relevant domains in the Collaboration's 'Risk of bias' tool
Selection bias.	Systematic differences between baseline characteristics of the groups that are compared.	•Sequence generation. •Allocation concealment.
Performance bias.	Systematic differences between groups in the care that is provided, or in exposure to factors other than the interventions of interest.	•Blinding of participants and personnel. •Other potential threats to validity.
Detection bias.	Systematic differences between groups in how outcomes are determined.	•Blinding of outcome assessment. •Other potential threats to validity.
Attrition bias.	Systematic differences between groups in withdrawals from a study.	•Incomplete outcome data
Reporting bias.	Systematic differences between reported and unreported findings.	•Selective outcome reporting

Critical appraisal

Are the results of the study valid?

1.3 Was the Risk of Bias of the Primary Studies Assessed?



Critical appraisal

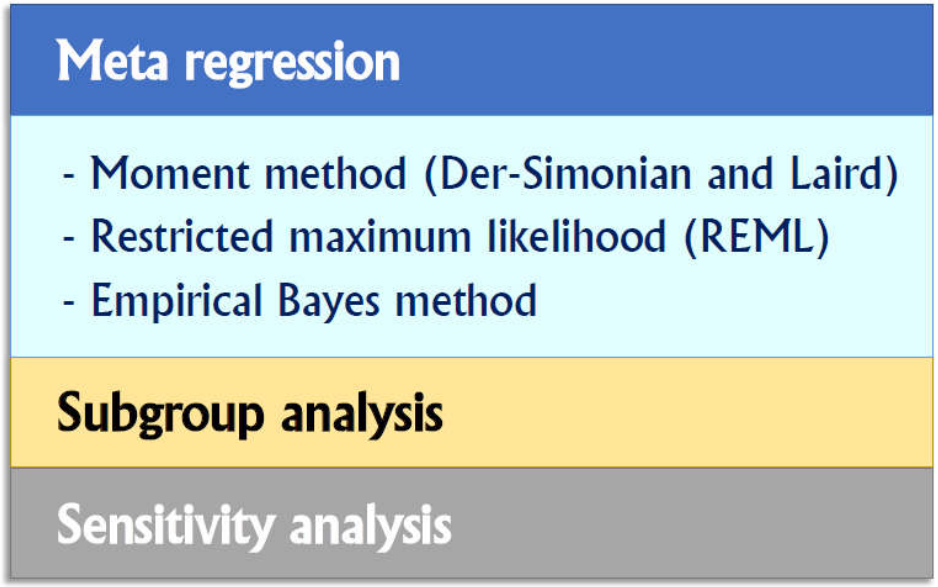
Are the results of the study valid?

1.4 Did the Review Address Possible Explanations of Between-Study Differences in Results?

Hypothesis about heterogeneity

Plan to assess source of heterogeneity

- Clinical variation
  - Population Characteristic
- Methodological variation
  - Type of study design
  - Type of outcome
  - Type of outcome measurement
  - Type of treatment



Critical appraisal

Are the results of the study valid?

1.5 Did the Review Present Results That Are Ready for Clinical Application?

1) Results That Are Ready for Clinical Application?
   - Solve routine pain point, need cost to make a decision
2) Appropriate measurement?
   - Ex. Report patient's risk difference

New treatment decreased risk of MI of 50% (RR=0.5)
But it depends on the baseline risk of MI

Cost?

Critical appraisal

Are the results of the study valid?

1.6 Were Selection and Assessments of Studies Reproducible?

- Explicit criteria
- At least 2 reviewers
- Report agreement analysis

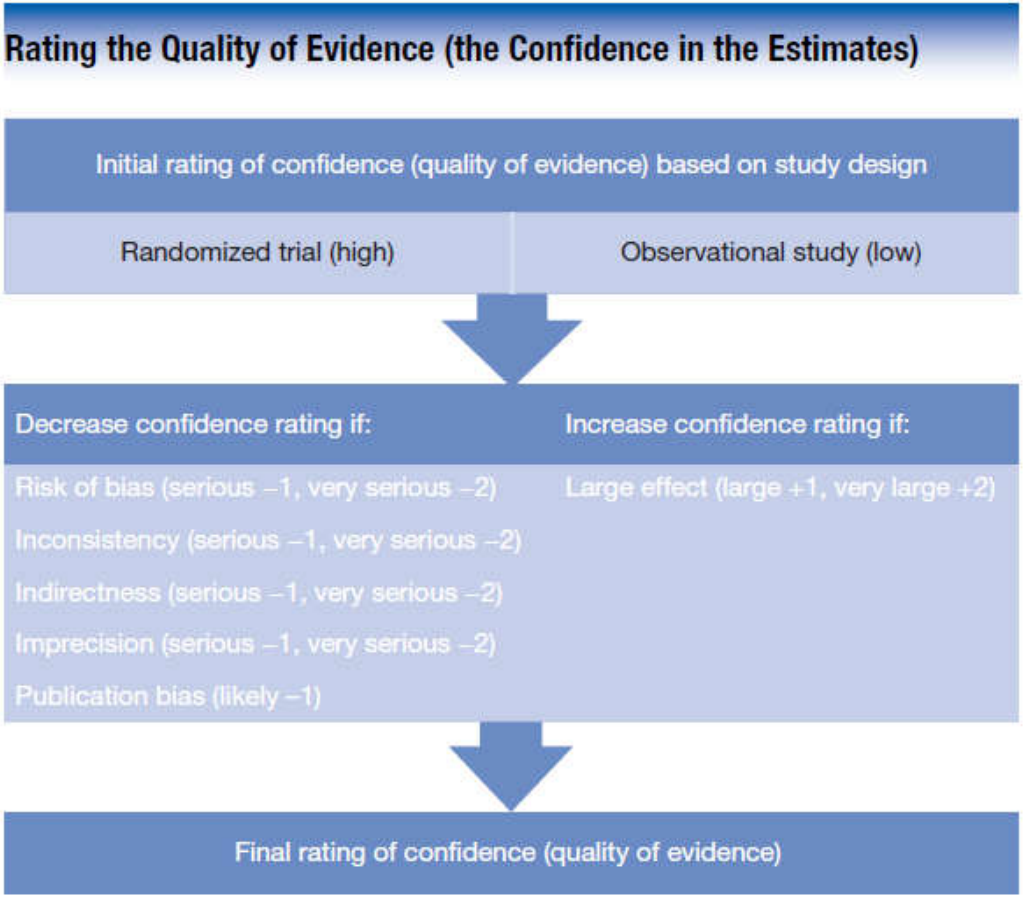
Critical appraisal

Are the results of the study valid?

1.7 Did the Review Address Confidence in Effect Estimates?

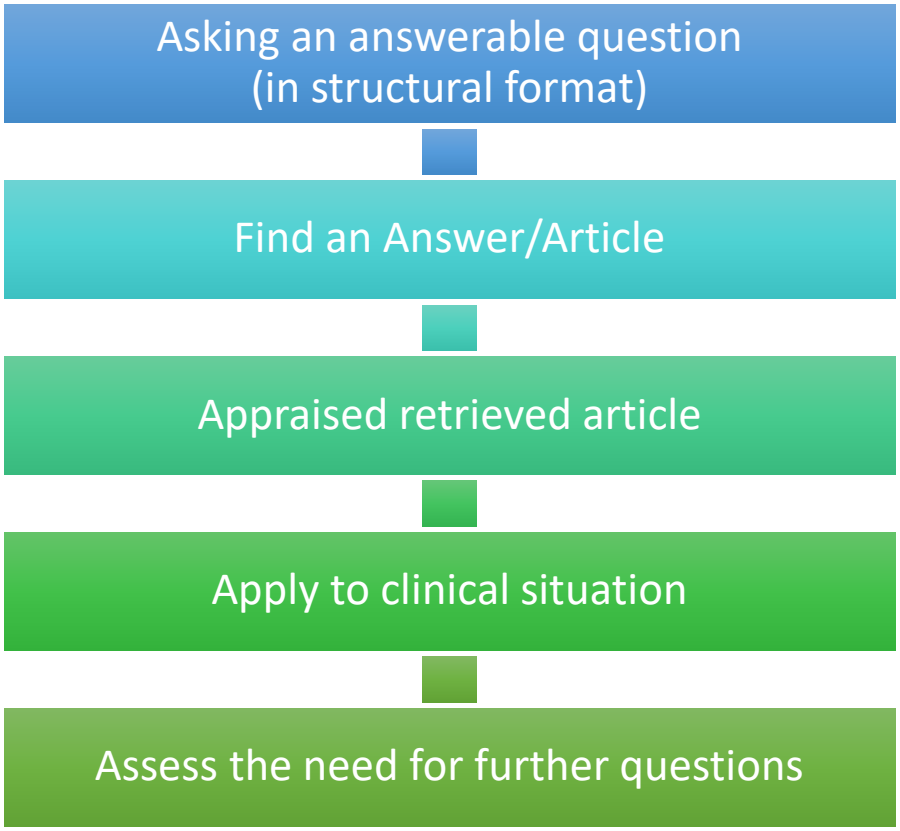
- Risk of bias ≠ confidence in effect estimate
- Explicitly address the risk of bias that can diminish confidence in estimates, imprecision, inconsistency
- GRADE → Rating confidence of estimate
  - High
  - Moderate
  - Low
  - Very low

Observed effect differs from the true effect



Evidence-based medicine

EBM



Step 3: Critical appraisal

- Are the results of the study valid?

Is it good enough to go to the next step?

- What are the results?
- How can you apply the results to patient care?

Critical appraisal

What are the results?

2.1 Were the results similar from study to study?

2.2 What are the overall results of the review?

2.3 How precise were the results?

Critical appraisal

Are the results of the study valid?

2.1 Were the results similar from study to study?

- Visual evaluation of variability
  - How similar are the point estimates
  - To what extent do confidence intervals overlap
- Statistical tests evaluating variability
  - Yes-or-no test for heterogeneity (p value)
  - I2 test that quantifies the variability explained by between-study differences in results

Critical appraisal

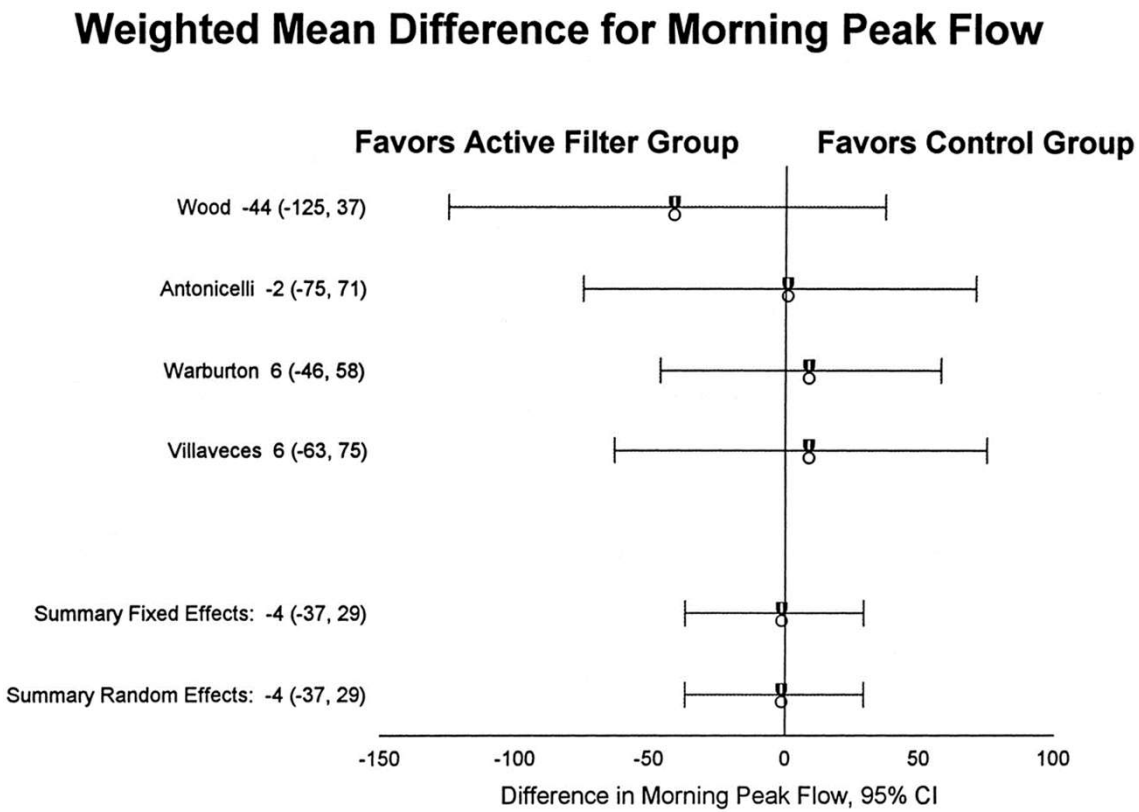
Are the results of the study valid?

2.1 Were the results similar from study to study?

Visual evaluation of variability

Statistical tests

- Cochrane Q
- I^2 test



Critical appraisal

Are the results of the study valid?

2.2 What are the overall results of the review?

- Dichotomous outcome
  - Relative risk
  - Odds ratio
- Continuous outcome
  - Mean different

Critical appraisal

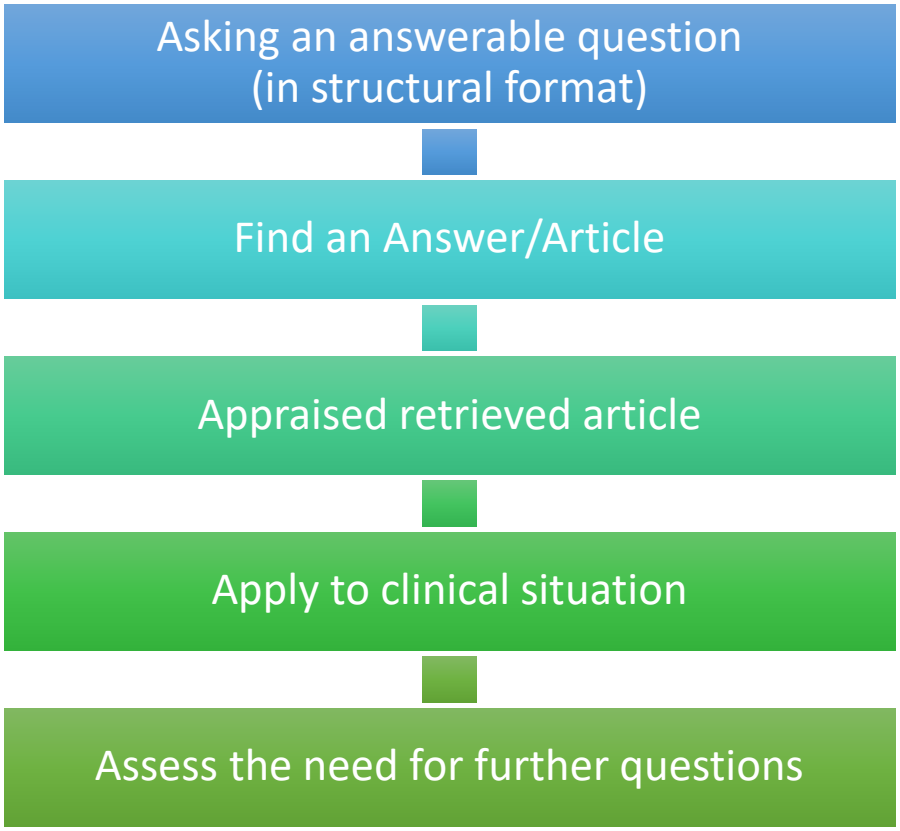
Are the results of the study valid?

2.3 How precise were the results?

- Confidence interval around that estimate

Evidence-based medicine

EBM



Step 3: Critical appraisal

- Are the results of the study valid?
- What are the results?
- How can you apply the results to patient care?

Critical appraisal

How can you apply the results to patient care?

3.1 Were all patient-important outcomes considered?

3.2 Are any postulated subgroup effects credible?

3.3 What is the overall quality of the evidence?

3.4 Are the benefits worth the costs and potential risks?

EBM SERIES

Thank You

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