
بسم الله الرحمن الرحيم

Systematic Review & Meta-analysis

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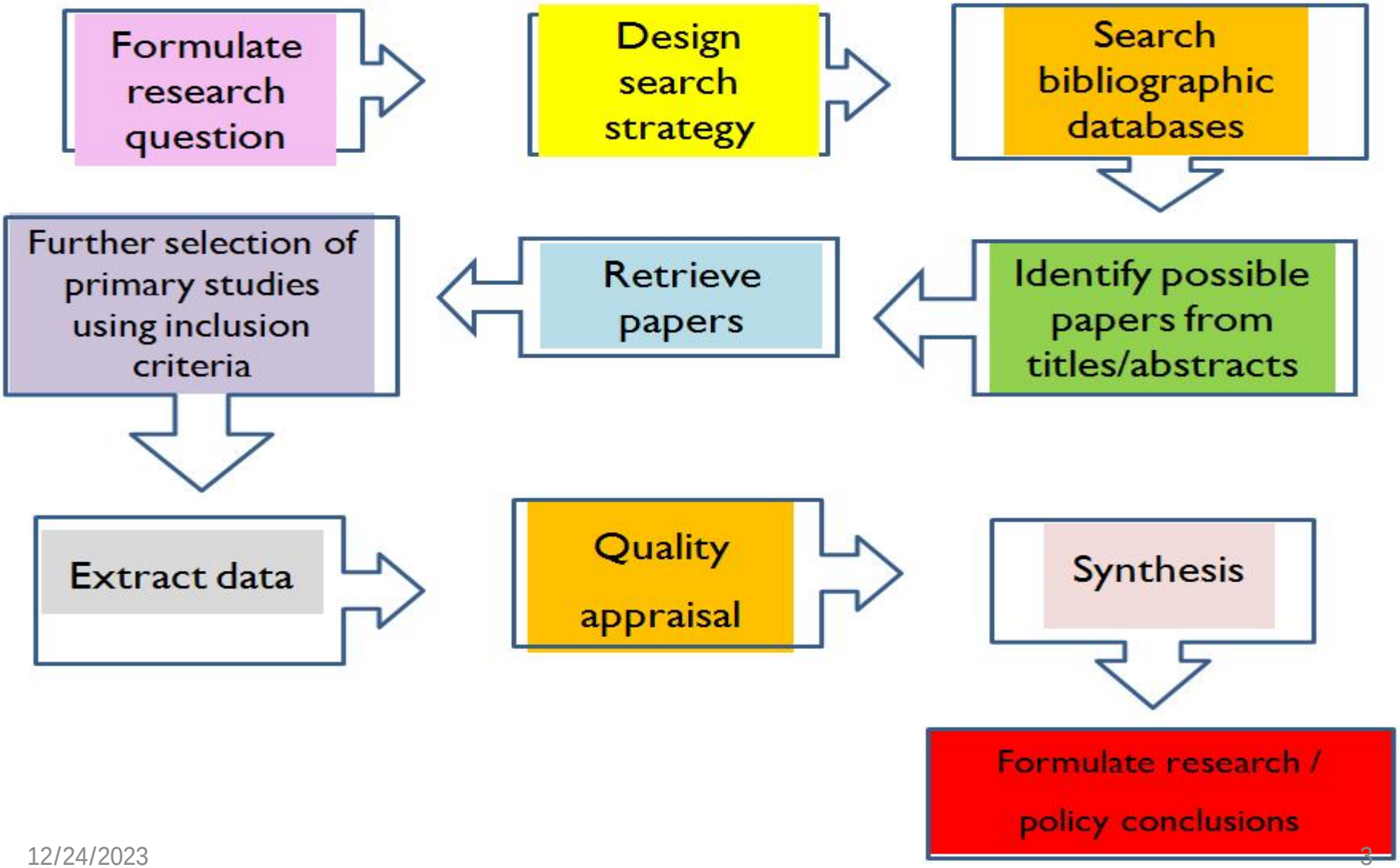
Outline


Formulate research question
Design search strategy
Search bibliographic databases
Identify possible papers from titles/abstracts
Retrieve papers
Further selection of primary studies using inclusion criteria
Extract data
Quality appraisal
Synthesis
Formulate research / policy conclusions

Different type of studies

Primary vs Secondary studies

Primary studies

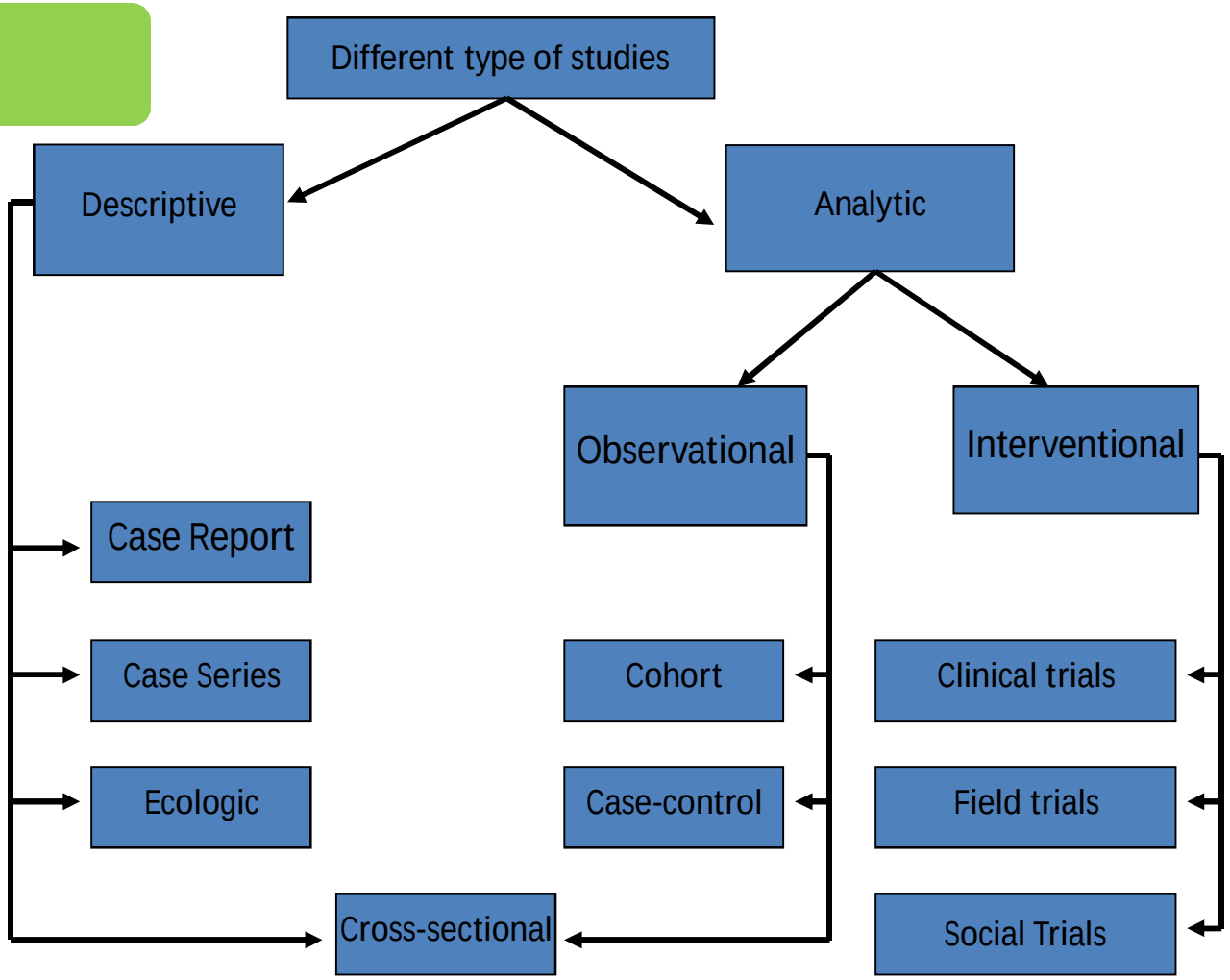
Experiment, clinical trail, survey

Secondary studies

Review, narrative review, & Meta-analysis ,guidelines , decision analysis, Economics analysis

Different type of studies

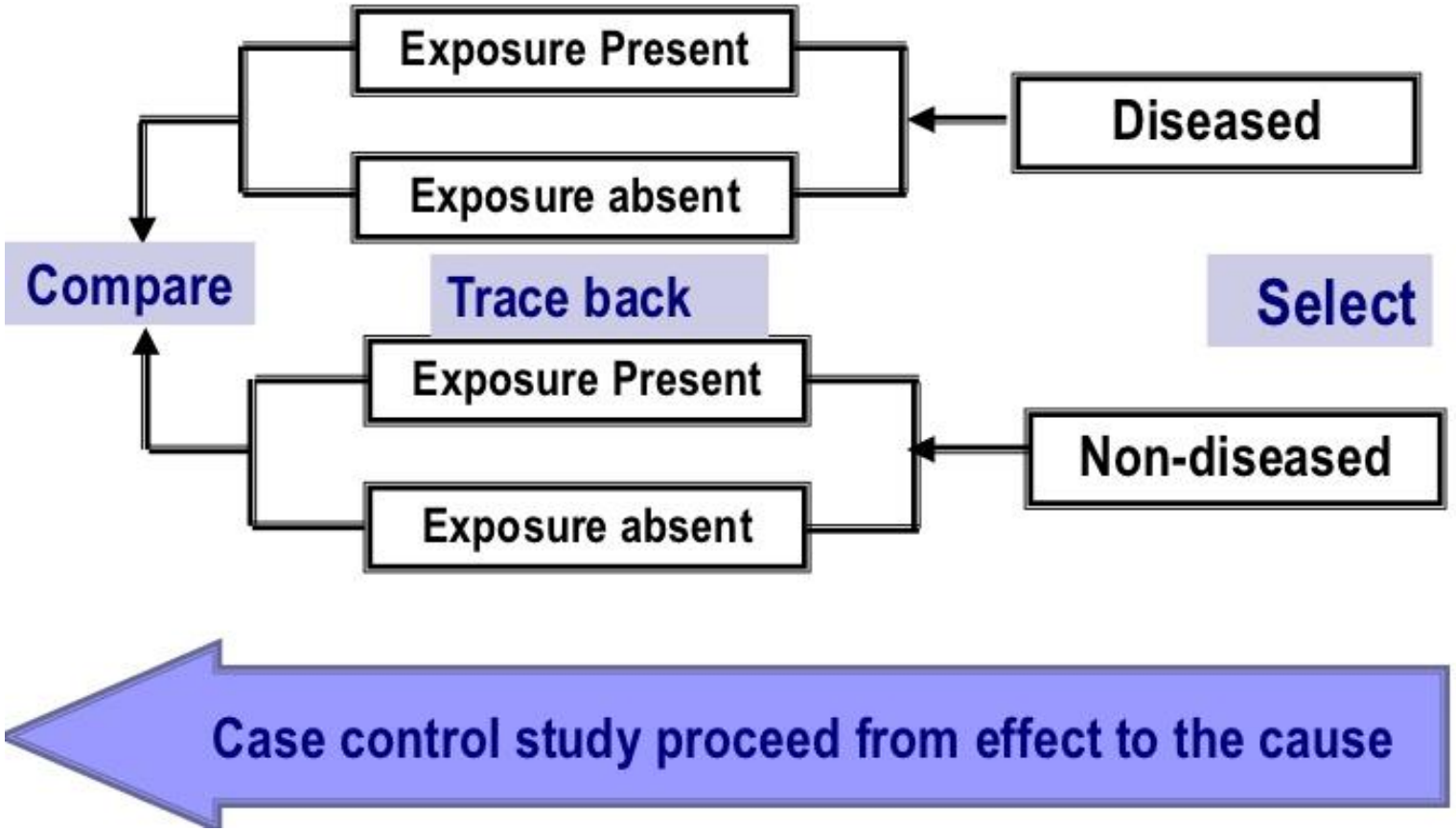
Different type of studies



Case-control study

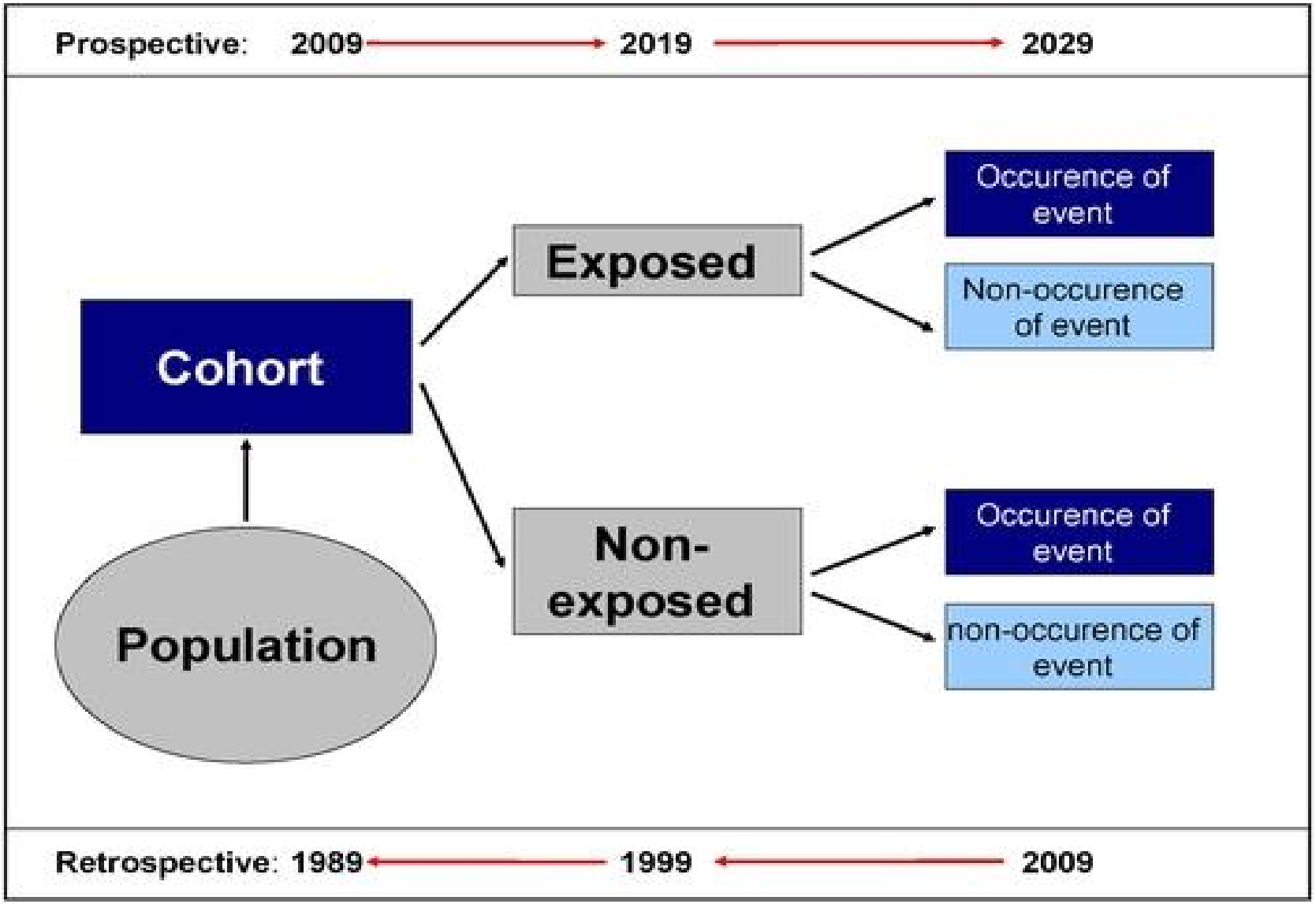
A case-control study belongs to the observational group of studies. It begins by choosing individuals who have a health outcome or disease whose cause you want to investigate. These are the cases. Controls without the health outcome are then chosen. You then determine the proportion of cases who were exposed to any risk factor of interest in the past, and compare this with the proportion exposed in the control group. The study is generally retrospective because it looks backwards in time to the earlier exposures of individuals.

Case Control Study design



Cohort study

A cohort study, also known as a follow-up or longitudinal study, is another observational study design. In this study a population who do not have the health outcome or disease of interest are first divided into those who are exposed to a risk factor and those who are not. Alternatively exposed and unexposed populations may be chosen separately. At the end of the period of observation the incidence of disease or frequency of health outcome in the exposed group is compared to that in the unexposed group. The study is generally prospective as it looks forward from potential cause to consequence.


Prospective: 2009
2019
2029
Cohort
Population
Exposed
Non-exposed
Occurence of event
Non-occurence of event
Occurence of event
non-occurence of event
Retrospective: 1989
1999
2009

RCT

An RCT is a type of interventional or experimental study design. Participants (individuals or groups) are randomly allocated to receive either the new intervention being tested or a control treatment (usually the standard treatment or a placebo). Each arm of the study is then followed up and the amount or severity of the disease measured in the intervention group and compared with the control group. RCTs are by definition prospective.

RCT Study Design

Point

❖ Frequently more than one study addressing a particular health question. In such circumstances it is logical to collect all these studies together and base conclusions on the cumulated results.

❖ However the same scientific principles as would be expected in the original studies need to be applied to the identification, sorting and analysis of potentially relevant studies.

❖ The most obvious sign that a review is systematic will be the presence of a methods section. Meta-analysis is the statistical process of combining the results from several studies that is often part of a systematic review.

Key elements of a systematic review

Structured, systematic process involving several steps :

1. **Formulate the question**
2. **Plan the review**
3. **Comprehensive search**
4. **Unbiased selection and abstraction process**
5. **Critical appraisal of data**
6. **Synthesis of data (may include meta-analysis)**
7. **Interpretation of results**

What is a systematic review?

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

What is a systematic review?

SYSTEMATIC: Done or acting according to a fixed plan or system: methodical

REVIEW: A critical appraisal of a book, play or other work

Systematic Review defined as:

"A review that is conducted according to clearly stated, scientific research methods, and is designed to minimize biases and errors inherent to traditional, narrative reviews."

Margaliot, Zvi, Kevin C. Chung. Systematic Reviews: A Primer for Plastic Surgery Research. PRS Journal. 120/7 (2007)

Types of papers

- Original Research Articles
- Letter to Editor
- Rapid Communication/Research Communication
- Brief Report
- Review Articles
  - Narrative Review Article
  - Systematic Review

Too much information, too little time

- There is simply too much information around for people to keep up to date.
- On top of this, high quality information is often not easy to find.

What’s the problem with

“**Expert Opinion**”?

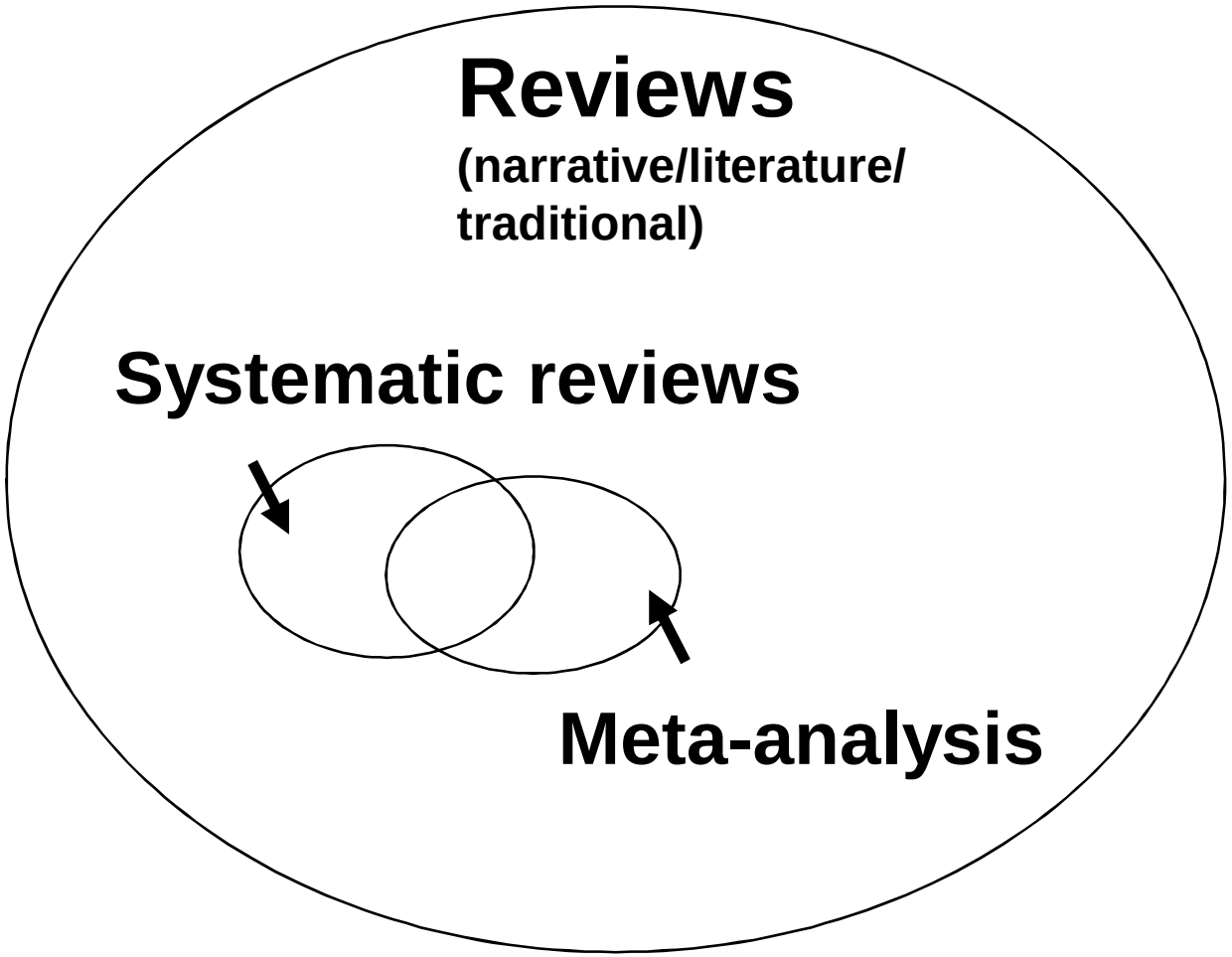
Unfortunately, expert reviewers often :

- Make conflicting recommendations
- Their advice frequently lags behind
- Inconsistent with the best available evidence.

Types of Reviews

- Systematic Review: literature review focused on a single question which tries to identify, appraise, select and synthesize all high quality research evidence relevant to that question
- Meta-analysis: a statistical technique often used in systematic reviews that enables the results from a number of studies to be combined into a common metric to determine the average effect of a given technique. Comparisons can then be made about the relative effectiveness of various techniques
- Integrative Review: literature review that attempts to combine experimental and non-experimental studies, or from experimental and theoretical work. Can be used to review theories, evidence, or to analyze methodological issues
- Qualitative Review: methods for combining qualitative research studies. Techniques include meta-synthesis, formal grounded theory, and meta-ethnography

Types of reviews



Narrative reviews

- Usually written by experts in the field
- Use informal and subjective methods to collect and interpret information
- Usually narrative summaries of the evidence

Read: Klassen et al. Guides for Reading and Interpreting Systematic Reviews. Arch Pediatr Adolesc Med 1998;152:700-704.

What is a systematic review?

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Systematic vs. Narrative reviews

- Scientific approach to a review article
- Criteria determined at outset
- Comprehensive search for relevant articles
- Explicit methods of appraisal and synthesis
- Meta-analysis may be used to combine data

- Depend on authors' inclination (bias)
- Author gets to pick any criteria
- Search any databases
- Methods not usually specified
- Vote count or narrative summary
- Can't replicate review

Bias means something that will cause a consistent deviation from the truth.

This is different from the play of chance.

There are three possible sources of bias in reviews:

- bias arising from the studies included in the review
- bias arising from the studies not included in the review
- Bias arising from the way the review is done.

- The principal findings should be related to the main question formulated in step1.
- Other finding should be considered secondary.

Validity of the main finding

- Are the searches adequate?
- Is there a risk of publication and related biases?
- Is the quality of the included studies high enough?

Point

- Reporting bias and the inadequate quality of primary research are potentially serious problems for systematic reviews.
- The dissemination of research findings is not a random process; rather it is strongly influenced by the nature and direction of results.

Type of reporting bias

Publication bias

The publication or non-publication of research findings, depending on the nature and direction of the results

Publication bias

- 1-Arising from the researchers deciding whether or not to submit result
- 2- Arising from the tendency of journals to reject negative studies
- 3-sponsorship
- ….

Methods of preventing publication bias

1-Registeries

2-Editorial policy

Time lag bias

The rapid or delayed publication of research finding, depending on the nature and direction of the results

Multiple (duplicate) publication bias

The multiple or singular publication of research finding, depending on the nature and direction of the results

Language bias

The publication of research finding in a particular language, depending on the nature and direction of the results

Outcome reporting bias

The selective reporting outcomes but not of others , depending on the nature and direction of the results

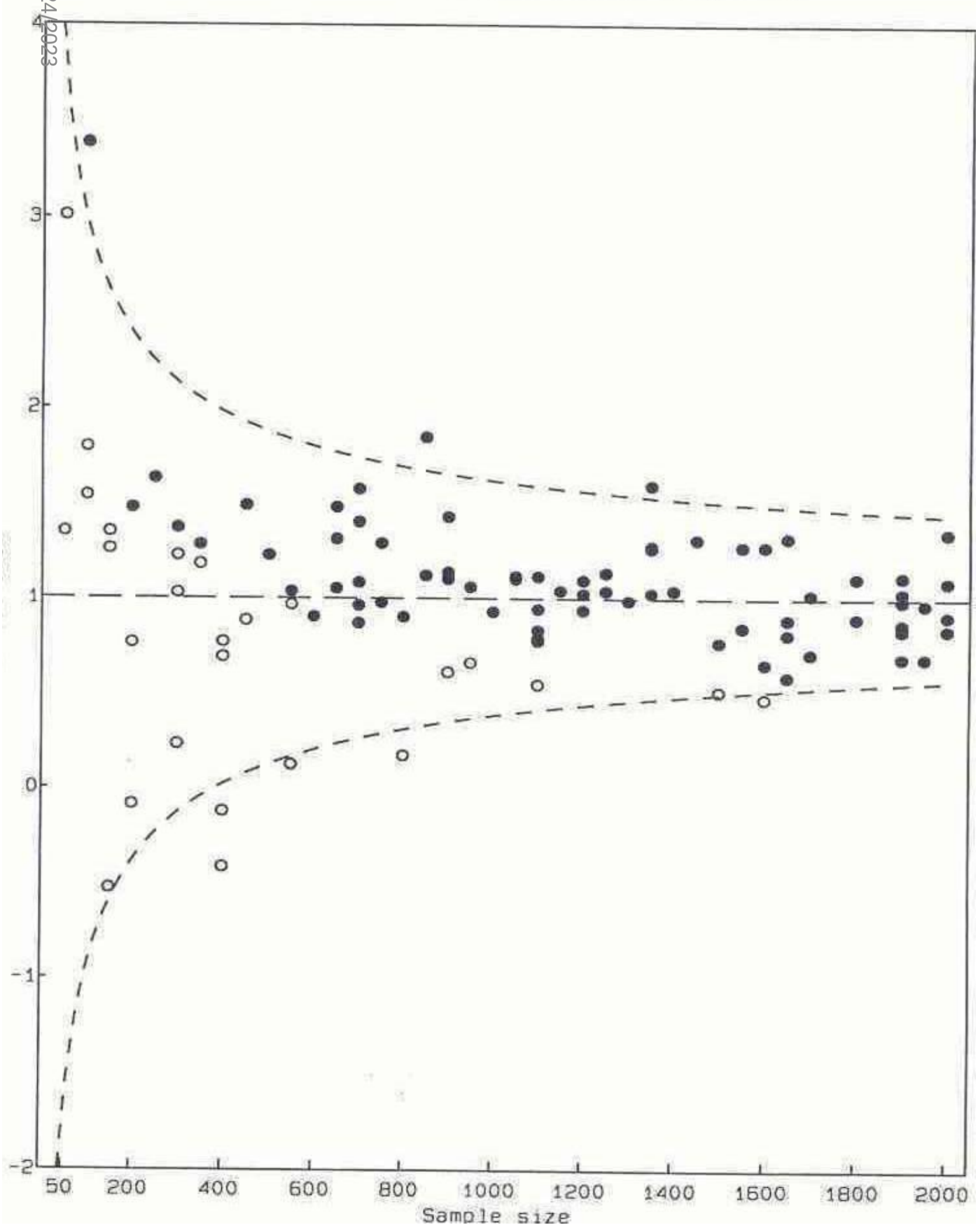
Citation bias

✓The citation or non-citation of research finding, depending on the nature and direction of the results.

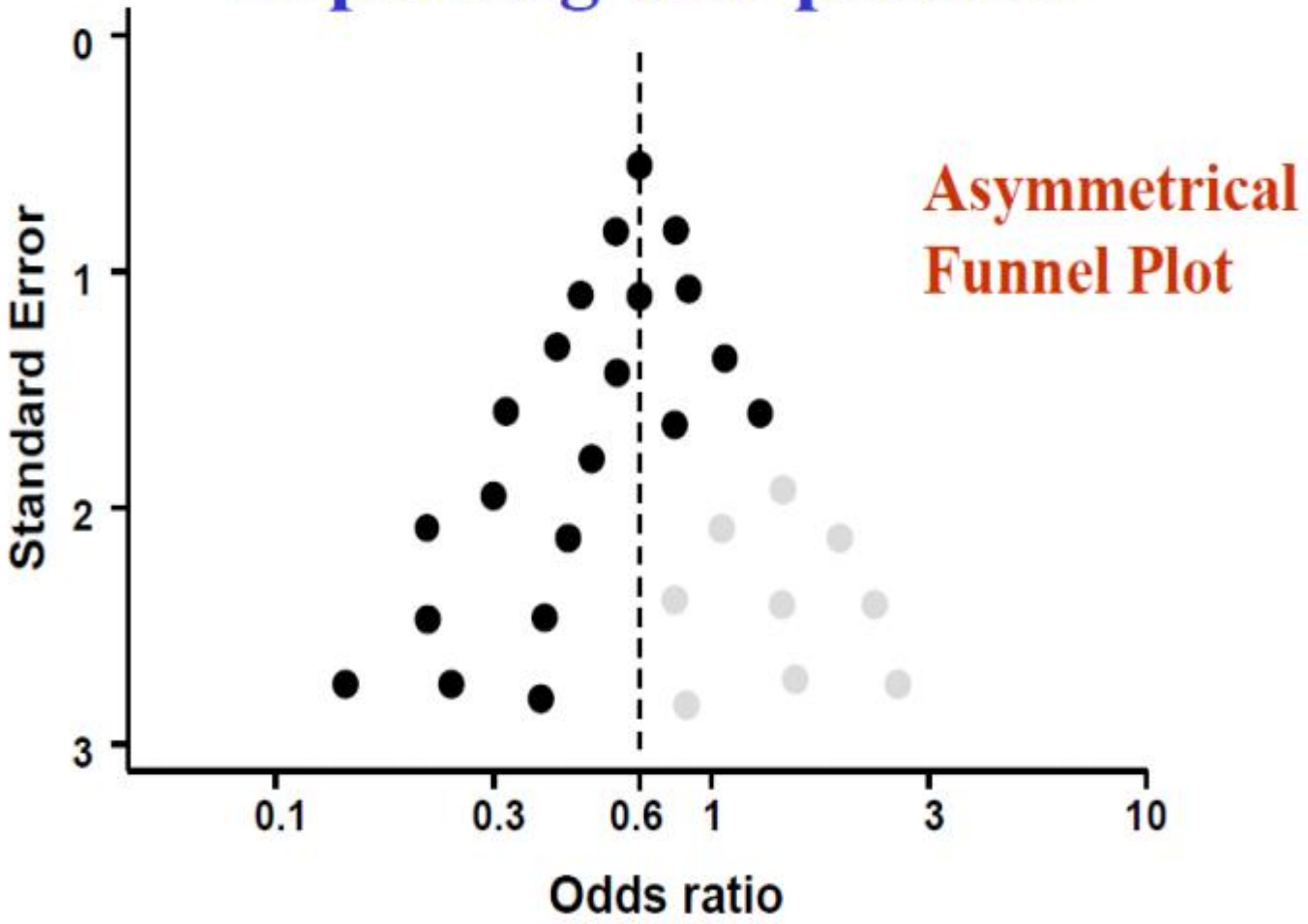
✓occurs when studies with significant or positive results are referenced in other publications, compared with studies with inconclusive or negative findings

Funnel Plot

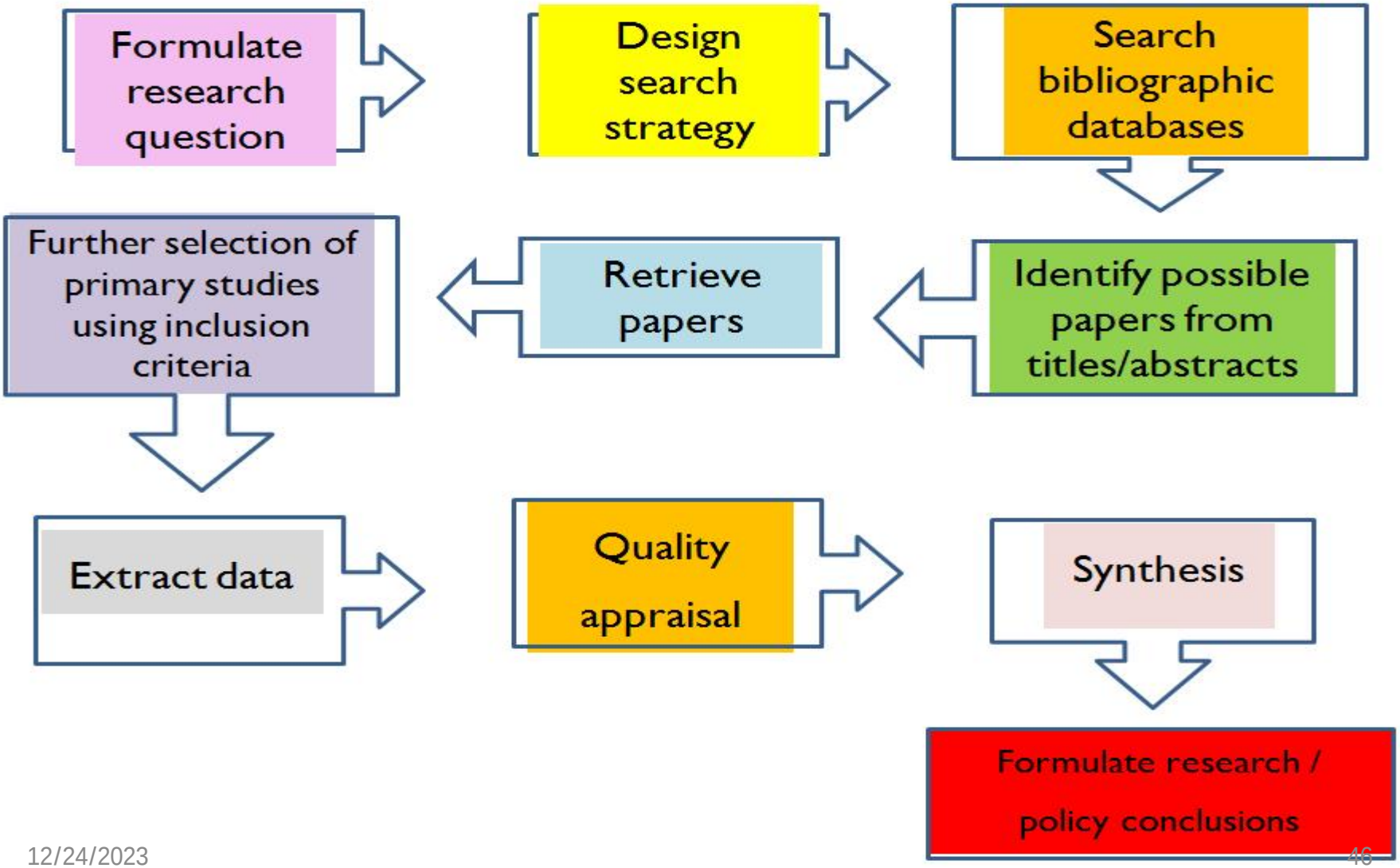
- Plots of the trials' effect estimates against sample size, may be useful to assess the validity of meta-analyses
- A symmetrical shape is expected, since greater scatter in estimate is expected for smaller study.
- The cardinal sign of publication bias is a **hole** in the middle or one side of the plot, that is an area where we would expect to see study result but where there are apparently none.


4
3
2
1
0
-1
-2
50
200
400
600
800
1000
1200
1400
1600
1800
2000
Sample size

Reporting bias present



Processes of systematic review



Formulating review questions

Define a four part clinical question

breaking the question down
into its component parts

Focus of the Question

- The structured question will determine the inclusion and exclusion criteria:
  - What is the population of interest?
  - What are the interventions?
  - What are the outcomes of interest?
  - What study designs are appropriate?

Inclusion/Exclusion Criteria

- “Once the study question is formalized, the authors must compose a comprehensive list of inclusion and exclusion criteria.”
- “To avoid selection bias, inclusion and exclusion criteria should be agreed upon and formalized before data extraction and analysis.”

Margaliot, Zvi, Kevin C. Chung. “Systematic Reviews: A Primer for Plastic Surgery Research.” PRS Journal. 120/7 (2007) p.1836

PICO

- The **PICO process** is a technique used in Evidence Base Practice to frame and answer a clinical or health care related question.
- The PICO framework is also used to develop literature search strategies.
- The PICO acronym stands for
  - P - patient, problem or population
  - I - intervention, indicator
  - C - comparison, control or comparator
  - O - outcomes

Classify the type of the question

- What is the treatment?
  Question of INTERVENTION/PREVENTION
- What causes the problem?
  Question of ETIOLOGY, RISK
- Does this person have the problem?
  Question of DIAGNOSIS
- Who (and how likely) will get the problem?
  Question of PROGNOSIS

Formulate the Clinical Question

- PICO

  P - 54 year old male with intermediate grade prostate cancer

  I - radical prostatectomy

  C- radiation treatment

  O- reduce risk of mortality, impotence, and incontinence

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- Focused clinical question

  In 54 year old male patients with intermediate grade prostate cancer is radical prostatectomy more effective compared to radiation treatment in reducing the risk of mortality, impotence, and incontinence?

How are these questions different?

- Does aspirin improve survival after acute myocardial infarction?

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- Does aspirin improve survival after acute myocardial infarction?

- In patients with acute myocardial infarction, does daily, low-dose, oral aspirin lead to higher survival rates as compared to placebo?

Formulation of a therapy question

Intervention

Outcome

Is Zinc effective in treating cold?

Patient/problem

Intervention

In children with common cold, is oral Zinc effective in reducing the duration of symptoms, as compared to placebo?

Outcome

+ RCTs

Comparison

Questions of interest

Effectiveness:

- Does the intervention work/not work?
- Who does it work/not work for?

Other important questions:

- How does the intervention work?
- Is the intervention appropriate?
- Is the intervention feasible?
- Is the intervention and comparison relevant?

Answerable questions

EFFECTIVENESS

A description of the populations **P**

An identified intervention **I**

An explicit comparison **C**

Relevant outcomes **O**

The PICO(T) chart

Problem, population	Intervention	Comparison	Outcome	Types of studies
Young people under 25 years of age	a) Television b) Radio c) Newspapers d) Bill boards e) Posters f) Leaflets g) Booklets	a) School-based interventions b) No intervention	a) objective measures of smoking (saliva thiocyanate levels, alveolar CO) b) self-reported smoking behaviour c) Intermediate measures (intentions, attitude, knowledge, skills) d) Media reach	a) RCT b) Controlled before and after studies c) Time series designs

Example PICO Questions

In school-age children (P),
what is the effect of a school-based physical activity program (I)
on a reduction in the incidence of childhood obesity (O)
compared with no intervention (C)
within a 1 year period (T)?

PICO elements according to question type (Domain)

Question Type	*Patient Problem or Population*	*Intervention or Exposure*	*Comparison or Control*	*Example Outcome Measures*
Therapy (Treatment)				
Prevention				
Diagnosis				
Prognosis (Forecast)				
Etiology (Causation)				

Question Type	Patient Problem or Population	Intervention or Exposure	Comparison or Control	Example Outcome Measures
Therapy (Treatment)	*Patient's disease or condition.*	*A therapeutic measure, eg., medication, surgical intervention, or life style change.*	*Standard care, another intervention, or a placebo.*	*Mortality rate, number of days off work, pain, disability.*
Prevention	*Patient's risk factors and general health condition.*	*A preventive measure, e.g., A lifestyle change or medication.*	*Another preventative measure OR maybe not applicable.*	*Mortality rate, number of days off work, disease incidence.*
Diagnosis	*Specific disease or condition.*	*A diagnostic test or procedure.*	*Current "reference standard" or "gold standard" test for that disease or condition.*	*Measures of the test utility, i.e. sensitivity, specificity, odds ratio.*
Prognosis (Forecast)	*Duration and severity of main prognostic factor or clinical problem.*	*Usually time or "watchful waiting".*	*Usually not applicable.*	*Survival rates, mortality rates, rates of disease progression.*
Etiology (Causation)	*Patient's risk factors, current health disorders, or general health condition.*	*The intervention or exposure of interest. Includes an indication of the strength/dose of the risk factor and the duration of the exposure.*	*Usually not applicable.*	*Survival rates, mortality rates, rates of disease progression.*