Yarmouk University

Community Medicine

Lec. 17 - Introduction to Systematic Reviews

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INTRODUCTION TO SYSTEMATIC REVIEWS

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MED 410

PRIMARY AND SECONDARY RESEARCH

- **Medicine and health sciences**
  - **Primary sources:** are clinical trials, research notes, original research papers, case reports…
  - **Secondary sources:** are works that interpret or analyze the content of the primary sources.
    - Literature reviews,
    - Systematic reviews,
    - Meta-analyses,
    - Textbooks,
    - Newspapers

Systemic review is one of the secondary researches.

SYSTEMATIC REVIEWS

- **Systematic review**: A systematic review attempts to collate all empirical evidence that fits pre-specified eligibility criteria to answer a specific research question.
  - It uses explicit, systematic methods
  - Minimizes bias
  - Providing reliable findings from which conclusions can be drawn and decisions made.

- Systematic reviews provide the best available evidence to support evidence-based medicine

Sheet# 1

- We use specific methods here to minimize bias in systematic review.
- Systematic review has a conclusion that can be used as guidelines for a specific disease. So, the research must be unbiased and reliable to form disease guidelines/recommend.

LEVELS OF EVIDENCE PYRAMID

Highest

Lowest

SYSTEMATIC REVIEWS DEFINITION

- **The key characteristics of a systematic review are:**
  a) a clearly stated set of objectives with an explicit, reproducible methodology;
  b) a systematic search that attempts to identify all studies that would meet the eligibility criteria;
  c) an assessment of the validity of the findings of the included studies, for example through the assessment of risk of bias; and
  d) systematic presentation, and synthesis, of the characteristics and findings of the included studies.
- You have a specific questions and you need to have a specific reproducible approach to get the same results.
- If the study is well done but there is a different in time periods and literature, you might get different results.
- All included studies need to be listed with their individual characteristics.

META-ANALYSIS

- **Meta-analysis:** Meta-analysis is the use of statistical techniques to integrate and summarize the results of included studies.

- **RELATIONSHIP WITH SYSTEMATIC REVIEWS:** Many systematic reviews contain meta-analyses, but not all.

- By combining information from all relevant studies, meta-analyses can provide more precise estimates of the effects of health care than those derived from the individual studies included within a systematic review.

- To obtain more reliable results, a meta-analysis is mainly conducted on randomized controlled trials (RCTs), which have a high level of evidence

- Meta analysis: after finishing the systematic review and compiling the literature you get risk estimate (example: association between A and B). Meta analysis is the summary.

PRISMA Guidelines

- Since 1999, various papers have presented guidelines for reporting meta-analyses of RCTs.
- Following the Quality of Reporting of Meta-analyses (QUORUM) statement, and the appearance of registers such as Cochrane Library's Methodology Register, a large number of systematic literature reviews have been registered.
- In 2009, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement was published, and it greatly helped standardize and improve the quality of systematic reviews and meta-analyses

- You need guidelines and steps for comparability and reliable evidence. Registration with the RCT is to avoid publication bias. Registry means all the results are listed negative and positive.

The PRISMA 2020 statement: an updated guideline for reporting systematic reviews

- **Many innovations in the conduct of systematic reviews have occurred since publication of the PRISMA 2009 statement.**
  - Technological advances have enabled the use of natural language processing and machine learning to identify relevant evidence
  - Methods have been proposed to synthesize and present findings when meta-analysis is not possible or appropriate
  - New methods have been developed to assess the risk of bias in results of included studies
  - Evidence on sources of bias in systematic reviews has accrued, culminating in the development of new tools to appraise the conduct of systematic reviews.
  - Terminology used to describe particular review processes has also evolved, as in the shift from assessing "quality" to assessing "certainty" in the body of evidence
  - The publishing landscape has transformed, with multiple avenues now available for registering and disseminating systematic review protocols disseminating reports of systematic reviews, and sharing data and materials, such as preprint servers and publicly accessible repositories

Sheet# 2

- The Prisma checklist was updated from 2009 to 2020 because of technology
- The updating also helped find room for new researches and allowed us to read those researches online to review them later

PRISMA 2020 checklist

- includes seven sections with 27 items, some of which include sub-items (table 1).

- Table 1: before you submit a systemic review, you must use the checklist table to make sure you do not miss anything.

Glossary of terms

- **Outcome—**An event or measurement collected for participants in a study (such as quality of life, mortality)

- **Result—**The combination of a point estimate (such as a mean difference, risk ratio, or proportion) and a measure of its precision (such as a confidence/credible interval) for a particular outcome

- **Report**—A document (paper or electronic) supplying information about a particular study. It could be a journal article, preprint, conference abstract, study register entry, clinical study report, dissertation, unpublished manuscript, government report, or any other document providing relevant information

Glossary of terms-cont.

- **Record**—The title or abstract (or both) of a report indexed in a database or website (such as a title or abstract for an article indexed in Medline). Records that refer to the same report (such as the same journal article) are "**duplicates**";

- **Study**—An investigation, such as a clinical trial, that includes a defined group of participants and one or more interventions and outcomes. A "**study**" might have multiple reports. For example, reports could include the protocol, statistical analysis plan, baseline characteristics, results for the primary outcome, results for harms, results for secondary outcomes, and results for additional mediator and moderator analyses
- Records and studies may sound similar, but study might have multiple reports for more than one outcome.

The PRISMA 2020 statement: an updated guideline for reporting systematic reviews

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http://dx.doi.org/10.1136/bmj.n71

- Table 1 | PRISMA 2020 item checklist
- Table 2 | PRISMA 2020 for Abstracts checklist*

In 2020 the Prisma guidelines were updated.

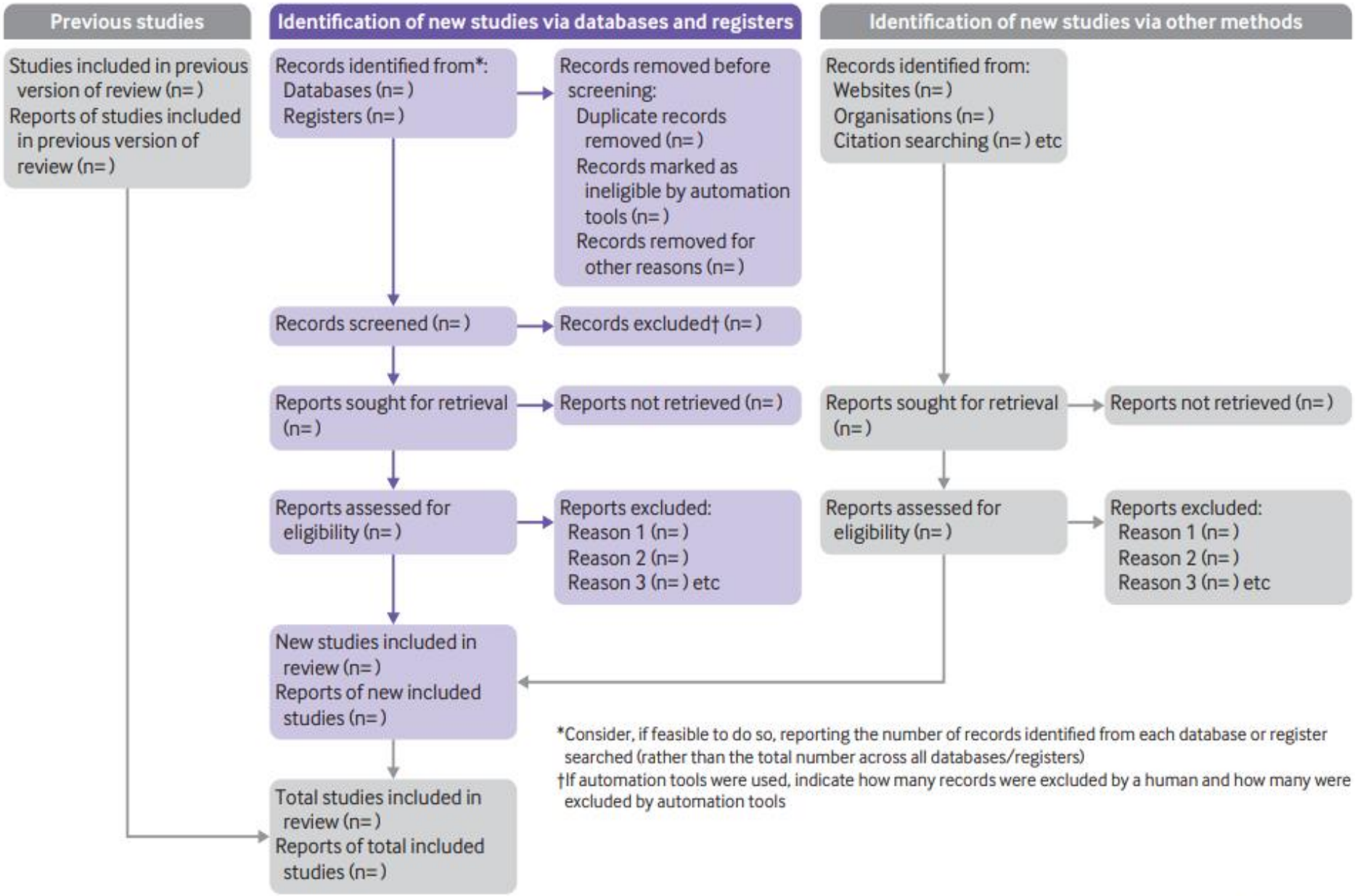
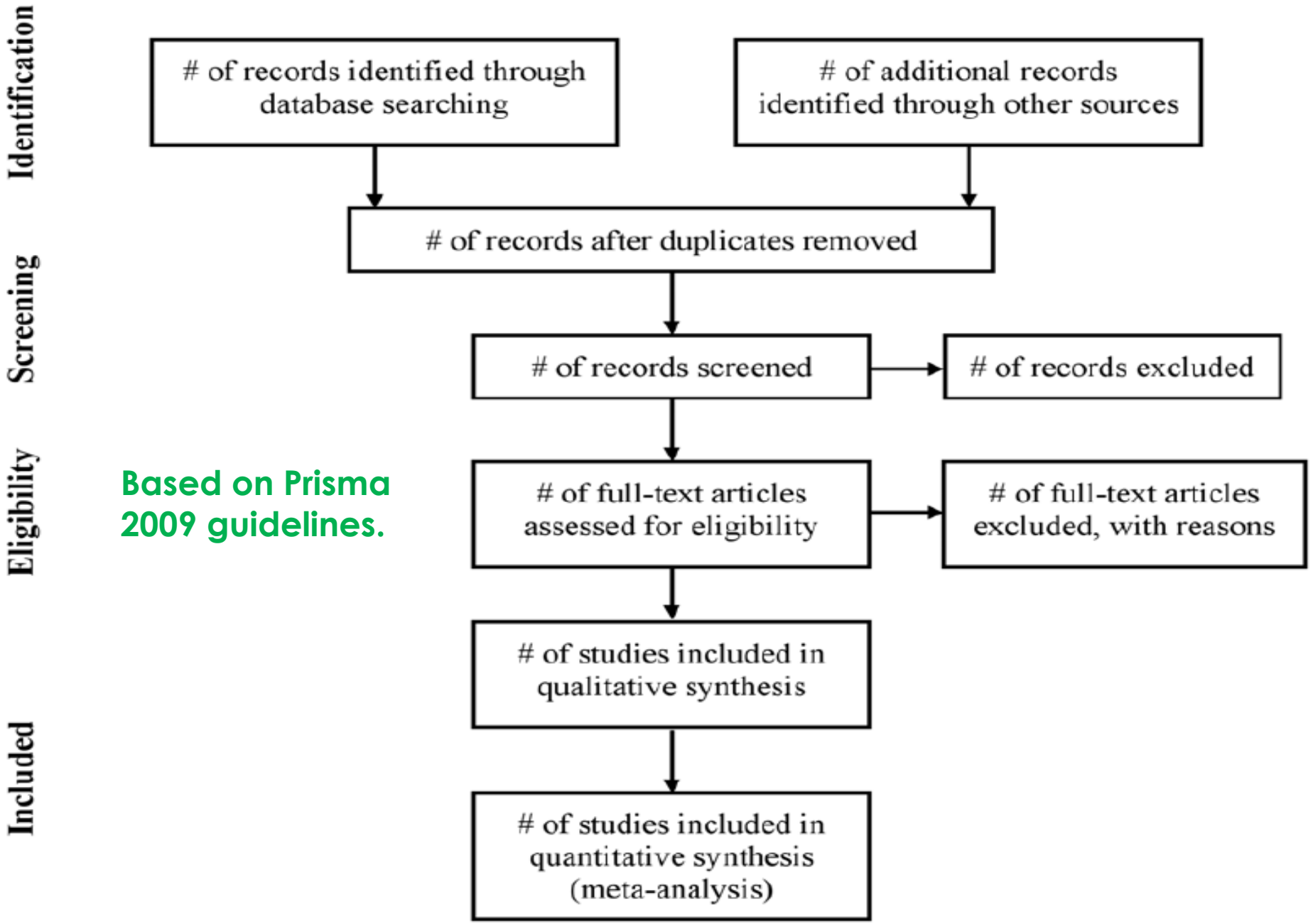


Fig 1 | PRISMA 2020 flow diagram template for systematic reviews. The new design is adapted from flow diagrams proposed by Boers,[55] Mayo-Wilson et al.[56] and Stovold et al.[57] The boxes in grey should only be completed if applicable; otherwise they should be removed from the flow diagram. Note that a "report" could be a journal article, preprint, conference abstract, study register entry, clinical study report, dissertation, unpublished manuscript, government report or any other document providing relevant information.



Based on Prisma 2009 guidelines.

Figure 1. Flow of information through the different phases of a systematic review.
doi:10.1371/journal.pmed.1000100.g001

literature reviews and meta-analyses are being conducted in diverse medical fields

- Systematic reviews and meta-analyses include various topics
- For example:
  - comparing various treatments of postoperative nausea and vomiting
  - comparing general anesthesia and regional anesthesia
  - comparing airway maintenance devices
  - comparing various methods of postoperative pain control (e.g., patient-controlled analgesia pumps, nerve block, or analgesics),
  - comparing the precision of various monitoring instruments,
  - meta-analysis of dose-response in various drugs
- What is the relationship between meta-analysis and literature review?
  - It is a statistical method from 2 or more different studies to form estimates.

Study Planning

- It is easy to confuse systematic reviews and meta-analyses.
- **A systematic review** is an objective, reproducible method to find answers to a certain research question, by collecting all available studies related to that question and reviewing and analyzing their results.

- **A meta-analysis** differs from a systematic review in that it uses statistical methods on estimates from two or more different studies to form a **pooled estimate**.

- Following a systematic review, if it is not possible to form a pooled estimate, it can be published as is without progressing to a meta-analysis; however, if it is possible to form a pooled estimate from the extracted data, a meta-analysis can be attempted.

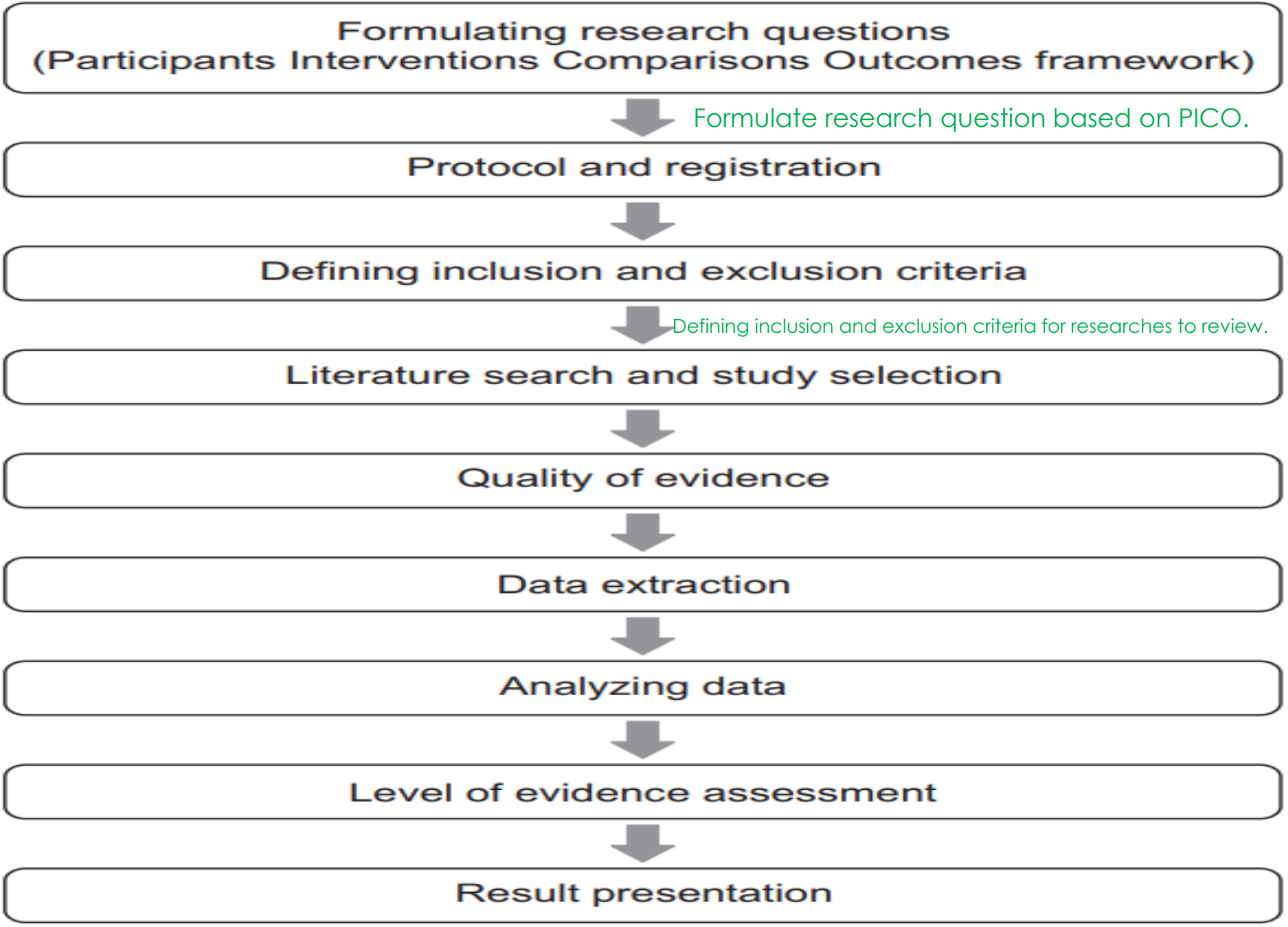


Fig. 2. Flowchart illustrating a systematic review.

Formulating research questions

- A systematic review attempts to gather all available empirical research by using clearly defined, systematic methods to obtain answers to a specific question.
- A meta-analysis is the statistical process of analyzing and combining results from several similar studies.
- Here, the definition of the word "similar" is not made clear, but when selecting a topic for the meta-analysis, it is essential to ensure that the different studies present data that can be combined.
- If the studies contain data on the same topic that can be combined, a meta-analysis can even be performed using data from only two studies

- Study selection via a systematic review is a precondition for performing a meta-analysis, and it is important to clearly define the Population, Intervention, Comparison, Outcomes (PICO) parameters that are central to evidence-based research.

- Selection of the research topic is based on logical evidence, and it is important to select a topic that is familiar to readers without clearly confirmed the evidence

Protocols and registration

- In systematic reviews, prior registration of a detailed research plan is very important.

- In order to make the research process transparent, primary/secondary outcomes and methods are set in advance, and in the event of changes to the method, other researchers and readers are informed when, how, and why.

- Many studies are registered with an organization like **PROSPERO (http://www.crd.york.ac.uk/PROSPERO/),** and the registration number is recorded when reporting the study, in order to share the protocol at the time of planning.

Defining inclusion and exclusion criteria

- Information is included on
  - The study design
  - Patient characteristics
  - Publication status (published or unpublished)
  - Language used
  - And research period.

Literature search and study selection

- In order to secure proper basis for evidence-based research, it is essential to perform a broad search that includes as many studies as possible that meet the inclusion and exclusion criteria.

- Typically, the three bibliographic databases **Medline**, **Embase**, and **Cochrane Central Register of Controlled Trials (CENTRAL)** are used.

- Effort is required to identify not only published studies but also abstracts, ongoing studies, and studies awaiting publication.

- Among the studies retrieved in the search, the researchers remove duplicate studies, select studies that meet the inclusion/exclusion criteria based on the abstracts, and then make the final selection of studies based on their full text.

- In order to maintain transparency and objectivity throughout this process, study selection is conducted independently by at least two investigators.

- When there is an inconsistency in opinions, intervention is required via debate or by a third reviewer.

- The methods for this process also need to be planned in advance. It is essential to ensure the reproducibility of the literature selection process

Sheet# 3

- At least two independent researchers need to work separately to make sure they get the same results in literature review. If there is a difference, the differing articles need to be either excluded or included in the systematic review. If they cannot decide, they must ask a third party whether to include or exclude the article. This is done to maintain transparency of the project.

Quality of evidence

- Well planned the systematic review or meta-analysis is, if the quality of evidence in the studies is low, the quality of the meta-analysis decreases, and incorrect results can be obtained

- Even when using randomized studies with a high quality of evidence, evaluating the quality of evidence precisely helps determine the strength of recommendations in the meta-analysis.

- One method of evaluating the quality of evidence in non-randomized studies is the **Newcastle-Ottawa Scale**, provided by the Ottawa Hospital Research Institute.

Sheet# 4

- Every article included needs to be documented in a form using tools. For example, Newcastle-Ottawa Scale. This form asks like a checklist for every article. The total marks gathered in the checklist = quality control for the article.

- The quality of evidence is evaluated on the basis of:
  - The study limitations
  - Inaccuracies
  - Incompleteness of outcome data
  - Indirectness of evidence
  - Risk of publication bias

- This is used to determine the strength of recommendations
- For the quality control, all study limitations must be noted.

- The study limitations are evaluated using the "risk of bias" method proposed by Cochrane.

- This method classifies bias in randomized studies as "low," "high," or "unclear" on the basis of the presence or absence of six processes:
  - Random sequence generation
  - Allocation concealment
  - Blinding participants or investigators
  - Incomplete outcome data
  - Selective reporting and other biases
- All the following points effect the quality of the data.

Table 1. The Cochrane Collaboration's Tool for Assessing the Risk of Bias [28]

Domain	Support of judgement	Review author's judgement
Sequence generation	Describe the method used to generate the allocation sequence in sufficient detail to allow for an assessment of whether it should produce comparable groups.	Selection bias (biased allocation to interventions) due to inadequate generation of a randomized sequence.
Allocation concealment	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrollment.	Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment.
Blinding	Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received.	Performance bias due to knowledge of the allocated interventions by participants and personnel during the study.
	Describe all measures used, if any, to blind study outcome assessors from knowledge of which intervention a participant received.	Detection bias due to knowledge of the allocated interventions by outcome assessors.
Incomplete outcome data	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group, reasons for attrition/exclusions where reported, and any re-inclusions in analyses performed by the review authors.	Attrition bias due to amount, nature, or handling of incomplete outcome data.
Selective reporting	State how the possibility of selective outcome reporting was examined by the review authors, and what was found.	Reporting bias due to selective outcome reporting.
Other bias	State any important concerns about bias not addressed in the other domains in the tool. If particular questions/entries were prespecified in the review's protocol, responses should be provided for each question/entry.	Bias due to problems not covered elsewhere in the table.

Data extraction

- Two different investigators extract data based on the objectives and form of the study; thereafter, the extracted data are reviewed.
- Since the size and format of each variable are different, the size and format of the outcomes are also different, and slight changes may be required when combining the data.
- If there are differences in the size and format of the outcome variables that cause difficulties combining the data, such as the use of different evaluation instruments or different evaluation timepoints, the analysis may be limited to a systematic review.
- The investigators resolve differences of opinion by debate, and if they fail to reach a consensus, a third-reviewer is consulted

Data Analysis

- The aim of a meta-analysis is to derive a conclusion with increased power and accuracy than what could not be able to achieve in individual studies.

- Therefore, before analysis, it is crucial to evaluate the direction of effect, size of effect, homogeneity of effects among studies, and strength of evidence.

- Thereafter, the data are reviewed qualitatively and quantitatively.

- If it is determined that the different research outcomes cannot be combined, all the results and characteristics of the individual studies are displayed in a table or in a **descriptive form**; this is referred to as a **qualitative review**.

- A meta-analysis is a **quantitative review**, in which the clinical effectiveness is evaluated by calculating the weighted pooled estimate for the interventions in at least two separate studies.

- The pooled estimate is the outcome of the meta-analysis and is typically explained using a forest plot (Figs. 3 and 4).
- The black squares in the forest plot are the odds ratios (ORs) and 95% confidence intervals in each study.
- The area of the squares represents the weight reflected in the meta-analysis.
- The black diamond represents the OR and 95% confidence interval calculated across all the included studies.
- The bold vertical line represents a lack of therapeutic effect (OR = 1); if the confidence interval includes OR = 1, it means no significant difference was found between the treatment and control groups.

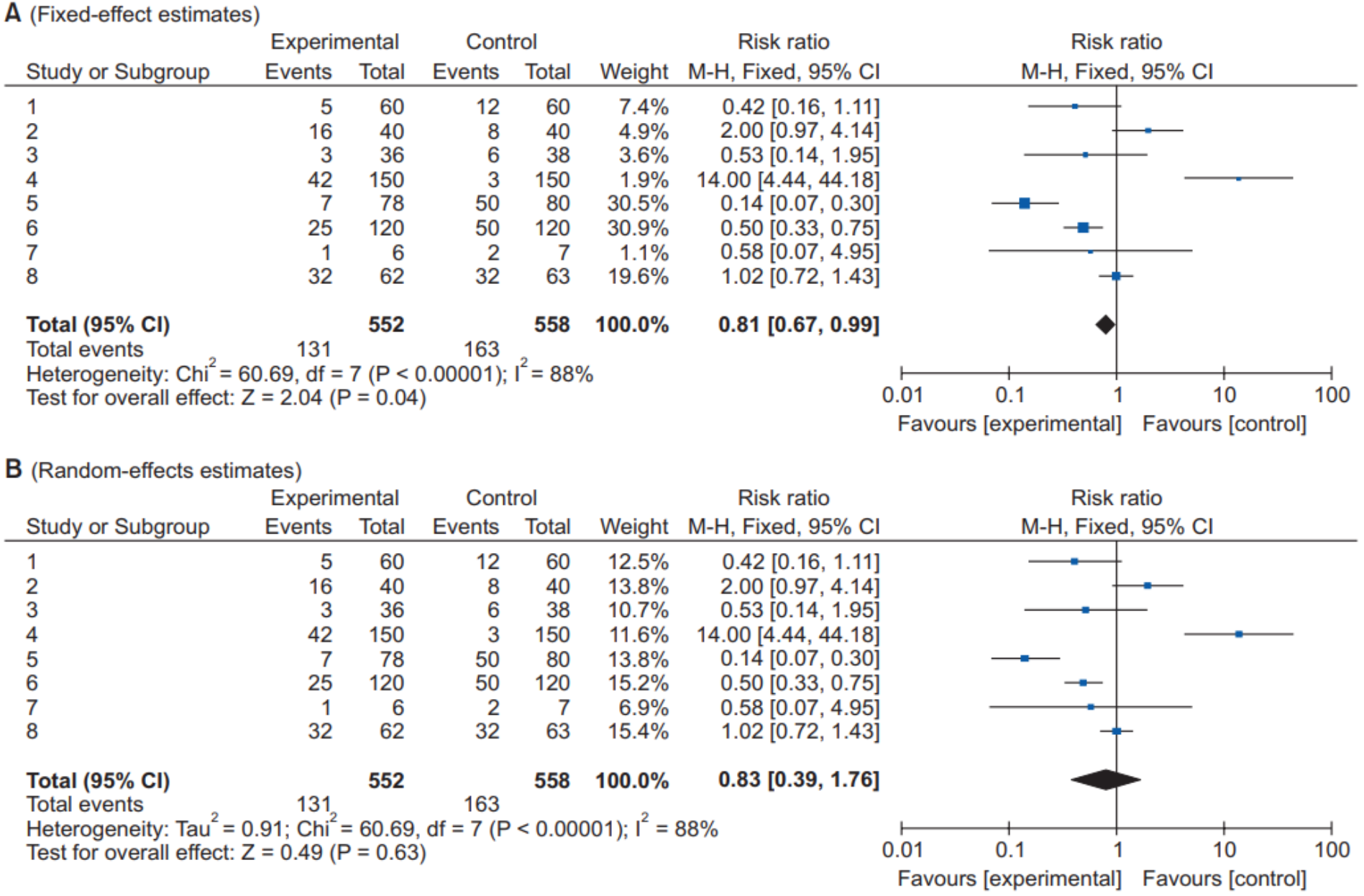


Fig. 3. Forest plot analyzed by two different models using the same data. (A) Fixed-effect model. (B) Random-effect model. The figure depicts individual trials as filled squares with the relative sample size and the solid line as the 95% confidence interval of the difference. The diamond shape indicates the pooled estimate and uncertainty for the combined effect. The vertical line indicates the treatment group shows no effect (OR = 1). Moreover, if the confidence interval includes 1, then the result shows no evidence of difference between the treatment and control groups.

Sheet# 5

- The figure is the result of meta-analysis. It will produce a forest plot.
- Each square is a value for risk ratio. The lines through the squares are confidence intervals. The thicker the square is, the more powerful a study is. The longer the line is, the less the confidence because there is a wider range. 1= no association. If the confidence interval cuts through "1" that means, there is no association, and the finding is insignificant. You should know which studies are significant.

This plot shows homogenous data.

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk ratio M-H, Fixed, 95% CI
1	3	37	6	24	7.4%	0.32 [0.09, 1.17]
2	7	106	15	104	15.4%	0.46 [0.19, 1.08]
3	17	52	36	36	43.7%	0.33 [0.23, 0.49]
4	3	30	7	48	5.5%	0.69 [0.19, 2.45]
5	6	36	5	28	5.7%	0.93 [0.32, 2.75]
6	16	96	17	95	17.4%	0.93 [0.50, 1.73]
7	3	66	5	68	5.0%	0.62 [0.15, 2.48]
Total (95% CI)		**423**		**403**	**100.0%**	**0.52 [0.40, 0.69]**
Total events	55		91			

Heterogeneity: $Chi^2 = 10.45$, df = 6 (P = 0.11); $I^2 = 43\%$

Test for overall effect: Z = 4.53 (P < 0.00001)

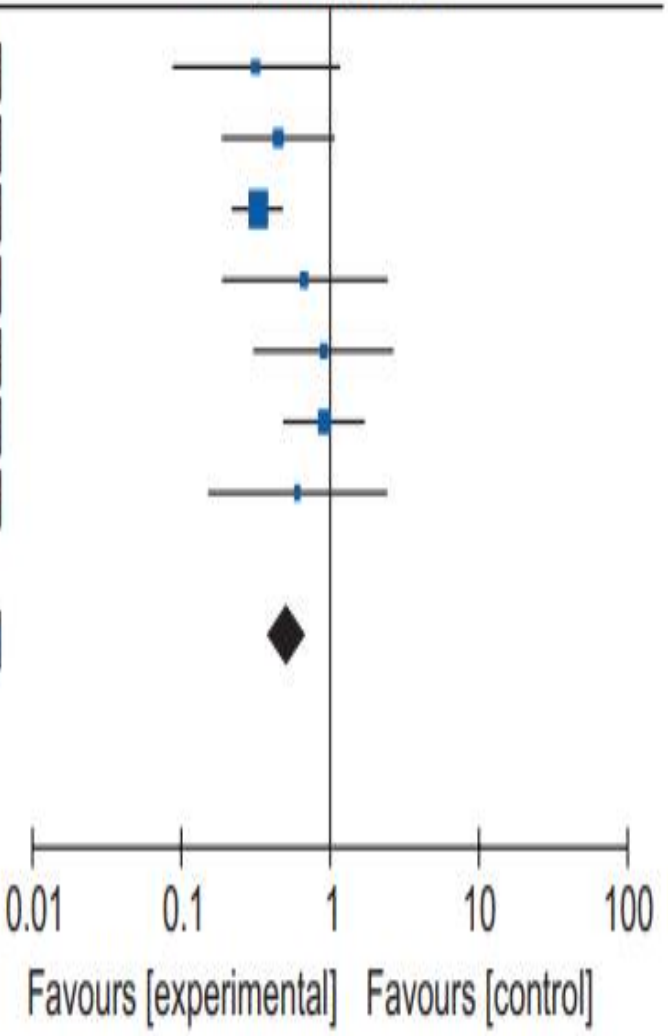


Fig. 4. Forest plot representing homogeneous data.

Dichotomous variables and continuous variables

- In data analysis, outcome variables can be considered broadly in terms of dichotomous variables and continuous variables.

- **When combining data from continuous variables**
  - the mean difference (MD) and standardized mean difference (SMD) are used
  - When results are presented in the same units, the MD can be used, but when results are presented in different units, the SMD should be used

- **When combining data for dichotomous variables**
  - the OR, risk ratio (RR), or risk difference (RD) can be used.
  - The RR and RD can be used for RCTs, quasi-experimental studies, or cohort studies
  - the OR can be used for other case-control studies or cross-sectional studies.
    - However, because the OR is difficult to interpret, using the RR and RD, if possible, is recommended
- We prefer using RR and RD instead of OR.

Fixed-effect models and random-effect models

- In order to analyze effect size, two types of models can be used:
  - **a fixed-effect model**
    - Assumes that the effect of treatment is the same, and that variation between results in different studies is due to random error.
    - Can be used when the studies are considered to have the same design and methodology, or when the variability in results within a study is small, and the variance is thought to be due to random error.
  - **a random-effect model**.
    - Assumes heterogeneity between the studies being combined
    - Can be used when the studies are assumed different
    - Differences in variation among studies are thought to be due to not only random error but alsobetween-study variability in results

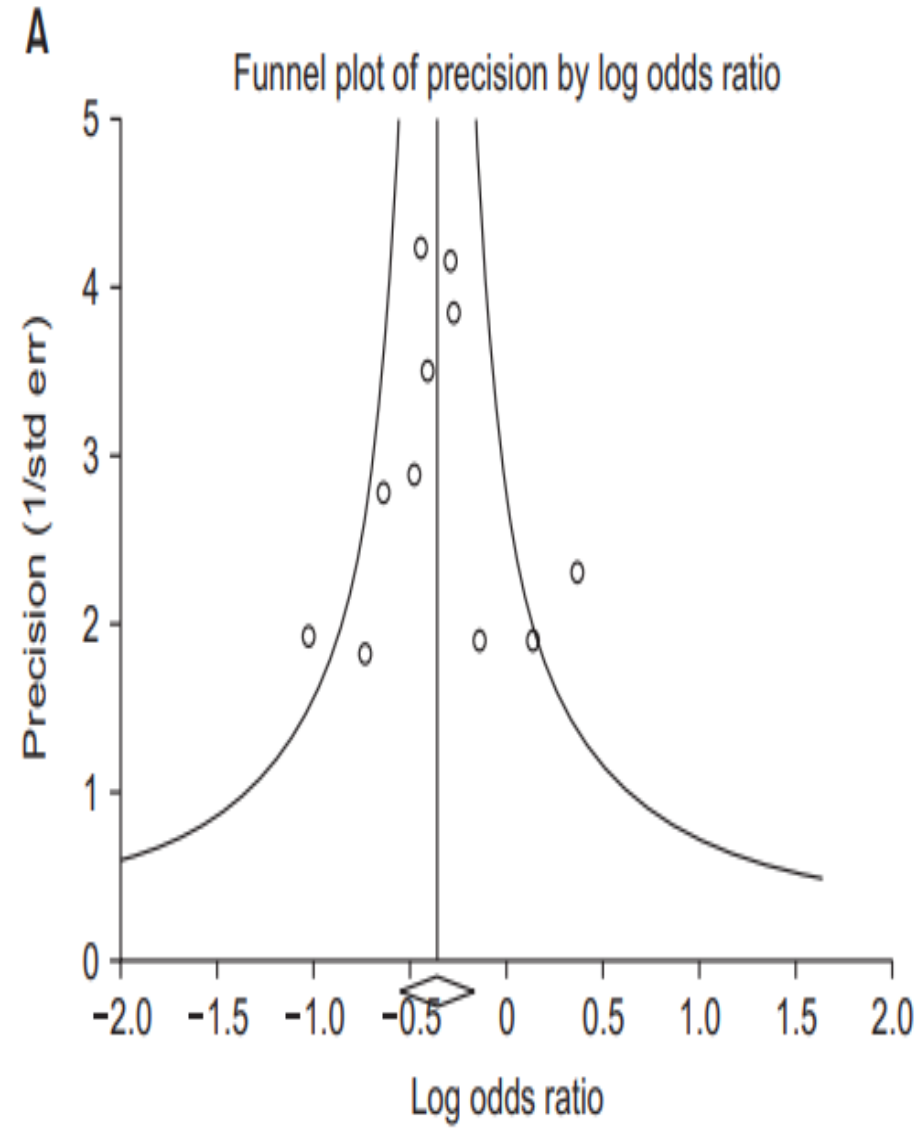
Heterogeneity

- Homogeneity test is a method whether the degree of heterogeneity is greater than would be expected to occur naturally

- **Three types of homogeneity tests can be used:**
  - 1) forest plot,
  - 2) Cochrane's Q test (chi-squared)
  - 3) Higgins I^2 statistics.
- Do not learn how to calculate the homogeneity tests. Just know there are 3 and their names.

Publication bias

- Publication bias is the most common type of reporting bias in meta-analyses.
- This refers to the distortion of meta-analysis outcomes due to the higher likelihood of publication of statistically significant studies rather than non-significant studies.
- In order to test the presence or absence of publication bias, first, a funnel plot can be used (Fig. 5).
- Publication bias happens because studies with strong association get published while others do not.



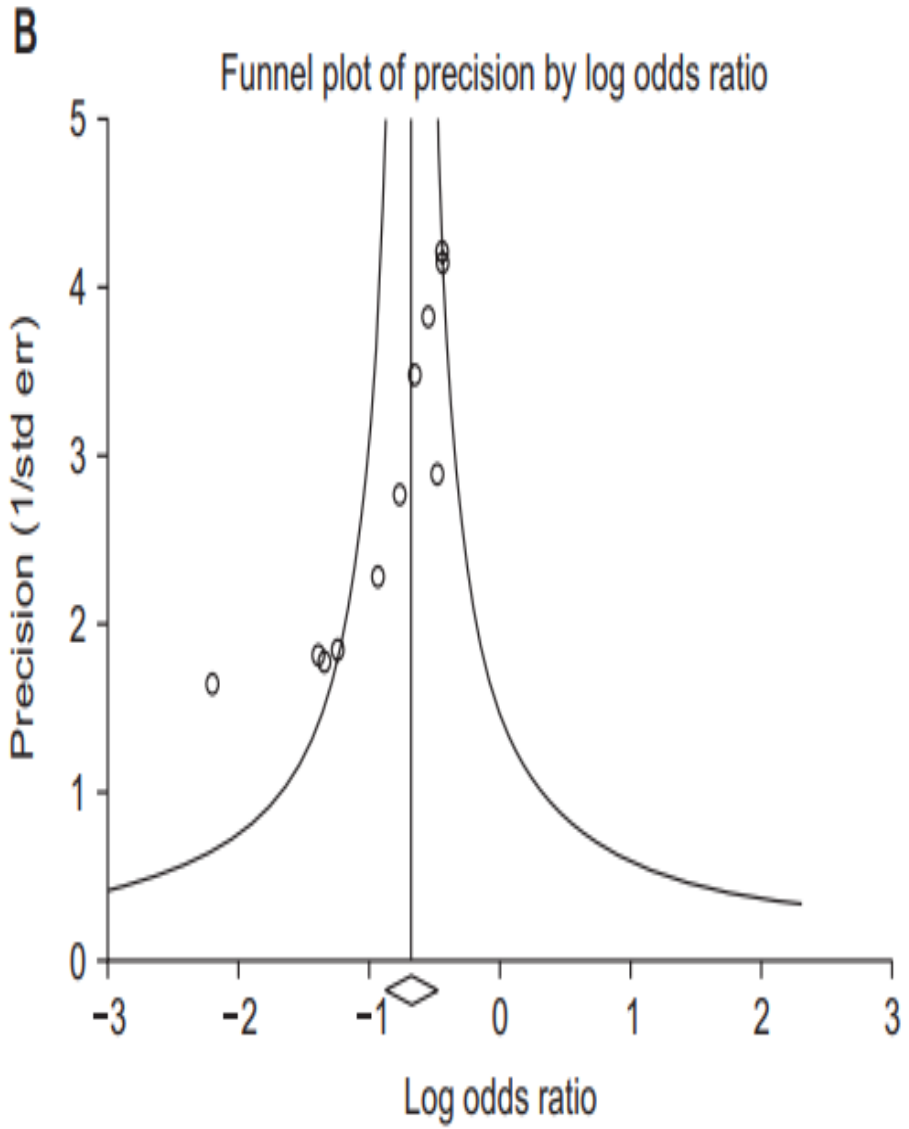


Fig. 5. Funnel plot showing the effect size on the x-axis and sample size on the y-axis as a scatter plot. (A) Funnel plot without publication bias. The individual plots are broader at the bottom and narrower at the top. (B) Funnel plot with publication bias. The individual plots are located asymmetrically.

Funnel plot

- Studies are plotted on a scatter plot with effect size on the x-axis and precision or total sample size on the y-axis.
- If the points form an upside-down funnel shape, with a broad base that narrows towards the top of the plot, this indicates the absence of a publication bias (Fig. 5A).
- if the plot shows an asymmetric shape, with no points on one side of the graph, then publication bias can be suspected (Fig. 5B)

Result Presentation

- When reporting the results of a systematic review or meta-analysis, the analytical content and methods should be described in detail.
  1. A flowchart is displayed with the literature search and selection process according to the inclusion/exclusion criteria.
  2. A table is shown with the characteristics of the included studies.
  3. A table should also be included with information related to the quality of evidence
  4. The results of data analysis are shown in a forest plot and funnel plot.

Conclusion

- When performing a systematic literature review or meta-analysis, if the quality of studies is not properly evaluated or if proper methodology is not strictly applied, the results can be biased and the outcomes can be incorrect.
- However, when systematic reviews and meta-analyses are properly implemented, they can yield powerful results that could usually only be achieved using large-scale RCTs, which are difficult to perform in individual studies.
- As our understanding of evidence-based medicine increases and its importance is better appreciated, the number of systematic reviews and meta-analyses will keep increasing.
- However, indiscriminate acceptance of the results of all these meta-analyses can be dangerous, and hence, we recommend that their results be received critically on the basis of a more accurate understanding