SYSTEMATIC REVIEW and **META-ANALYSIS**

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Primary vs. Secondary Research



Secondary

Definitions

First-hand report of a study, Analyzes experiment, procedure or event studies, eve

Analyzes and interprets studies, events or procedures

Elements

Examples

Population, intervention, instruments, results, methods, implications and conclusion

Clinical Trials,

Cohort, RCT, CCT

Randomized Control

Trial, Study

Review, analyzes, parameters of included studies, table list of studies, procedures, interventions

Systematic Review, Meta analysis, meta-synthesis, reviews, opinion



Observing the source of information directly

Secondary Research

Gathering information from research that has already been conducted







Importance of Systematic Reviews

✓ Summarizing Large Volumes of Data

✓ Evidence-Based Decision-Making

✓ Minimizing Bias

✓ Identifying Knowledge Gaps

✓ Impact in Medicine and Public Health



Systematic Reviews?

- A systematic review is a **rigorous** approach to identifying, appraising, and synthesizing all empirical evidence that meets pre-defined eligibility criteria to specific research answer a question.

- High Reliability and Sensitivity



And Meta-analysis?

A meta-analysis is a valid, objective, and scientific method of analyzing and combining different results. Usually, in order to obtain more reliable results, a meta-analysis is mainly conducted on randomized controlled trials (RCTs), which have a high level of evidence.











Research Question

Formulating the Research Question

- For Intervention Reviews, Define the question using
 PICO (Population, Intervention, Comparison, Outcome).
- PICOT adds Time / PICOS adds Study design
- Ensure the question is specific, measurable, and relevant.

| | Р | | С | 0 |
|---------|--|---|--|---|
| | Population Patient Problem | Inter∨ention Or Exposure | Comparison | Outcome |
| 12/14/2 | Who are the patients? What is the o24 | What do we do to them? What are they exposed to? | What do we compare the intervention with? | What happens? What is the outcome? |



Azathioprine for people with multiple sclerosis

PICOs

| Population (6) | Intervention (1) | |
|----------------------------|------------------|--|
| Aged 80 and over 80+ years | Azathioprine | |
| Multiple Sclerosis | | |
| Adult 19-44 years | | |
| Middle Aged 45-64 years | | |
| Young Adult 19-24 years | | |
| Aged 65-79 years | | |

Comparison (2) Disease Modifying Drugs for Multiple Sclerosis Placebo

Outcome (4)

Multiple Sclerosis Disability Relapse Serious Adverse Event

Exercise for osteoarthritis of the knee

PICOs[®]

Population (6)

Aged 80 and over 80+ years Adult 19-44 years Middle Aged 45-64 years Young Adult 19-24 years Aged 65-79 years Knee osteoarthritis 12/14/2024

Intervention (1)

Therapeutic Exercise

Comparison (2)

Usual Care Waiting list control

Outcome (5)

rol Withdrawn From Research Study Knee Pain Quality of Life Functional ability Adverse Event



Question about etiology or risk?



Register a Protocol!



International prospective register of systematic reviews

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PROSPERO

Welcome to PROSPERO International prospective register of systematic reviews

PROSPERO is fast-tracking registration of protocols related to COVID-19

PROSPERO accepts registrations for systematic reviews, **rapid reviews** and umbrella reviews. PROSPERO **does not accept scoping reviews** or **literature scans**. Sibling PROSPERO sites registers systematic reviews of **human studies** and systematic reviews of **animal studies**.

Defining Inclusion/Exclusion Criteria

Example: Epidemiology of GERD in Iran?

Inclusion criteria:

- Exclusion criteria:
- (1) Observational studies (case-control, (1) cross-sectional, or cohort studies) con
- (2) studies with available full texts
- (3) studies examined GERD
- (4) Done in Iran
- (5) adult patients (>18 y/o)
- (6) studies that evaluate prevalence risk factor or any related content

- (1) reviews, case report, case series, commentary
- (2) Gray literature (conferences papers, thesis, short communications, etc), or any non-clinical study related to our topic will be included.
- (3) studies were not related to the topic of the interest (e.g., when the studies investigated other diseases)
- (4) in vitro and in vivo studies
- (5) studies with a lack of sufficient and useful data.
- (6) Before 2000

Search Strategy

Before going to Search Strategy!!!

Boolean Operators:

- **AND:** Narrows the search by including all terms
- OR: Broadens the search by including any of the terms
- **NOT:** Excludes specific terms

Truncation Symbols:

| Symbols | Aim | |
|-------------------|--|--|
| Asterisk (*) | Finds all words with the same root or prefix. "cancer*" \rightarrow "cancer" / "cancers" / "cancerous" / etc. | |
| Question Mark (?) | Replaces a single character within a word "colo?r" \rightarrow "color"/ "colour" | |
| Dollar Sign (\$) | Used in some databases as a truncation or wildcard symbol. "neoplasm\$"→"neoplasm" / "neoplasms" / etc. | |



Search Strategy

Steps:

- Identify key concepts (based on research question)
- identifying search terms
- selecting data-bases

PubMed, Scopus, Embase, Web of science, Clinical trial registries (e.g., ClinicalTrials.gov), Cochrane library, National Data bases (SID, Magiran)

• staying up to date with search results





- 1. Gastroesophageal Reflux Disease (GERD)
- 2. Epidemiology
- 3. Iran

Identifying search terms

| Key Concept | Synonyms/Controlled Vocabulary/Free text words |
|------------------------------------|--|
| Gastroesophageal Reflux Disease | "Gastroesophageal Reflux" OR "gastroesophageal reflux disease" OR "acid reflux"OR "heartburn" OR "Gastric Acid Reflux" OR "Gastric Acid Reflux Disease" OR "Gastro Esophageal Reflux Disease" OR "Gastro oesophageal Reflux" OR "GERD" OR "Esophageal Reflux" OR "Gastro Esophageal Reflux" |
| Epidemiology | "Epidemiology" OR "Prevalence " OR "Incidence " OR "Risk factor*" OR "Health Correlate*" OR "Related factor*" OR "Relate factor*" OR "Associated factor*" OR "Associated factor*" OR "Odds ratio" OR "Relative Odds" OR "Risk Ratio*" |
| Iran | "Iran" OR "Iranian population" |

Let's proceed and try it on PubMed! An official website of the United States government Here's how you know V National Library of Medicine National Center for Biotechnology Information Log in Pub Med[®] PubMed Advanced Search Builder User Guide Add terms to the query box All Fields ٠ Enter a search term ADD 🗸 Show Index Query box Enter / edit your search query here Search 12/14/2024 Fateme Sheida, MD

Screening



Double Screening!

Potentially relevant citations identified searching online medical databases.



Screen titles and abstracts in pairs then collect and compare. In case of disagreement consult senior third reviewer.

The full texts of overllaping references included in review based on titles and abstracts are further retrieved in pairs.

Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA)

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only









When to Perform a Meta-Analysis?

Minimum Number of Studies: A meta-analysis typically requires at least *two-three similar studies* that measure the same outcome or effect. This allows for a meaningful synthesis of results.

Homogeneity of Studies: The included studies should be sufficiently similar in terms of:

- Population: Characteristics of participants (age, gender, health status).
- Intervention: Types of interventions being compared.
- *Outcomes:* The outcomes measured must be comparable across studies.
- *Study Design:* Ideally, studies should have similar methodologies (e.g., randomized controlled trials) to reduce variability.

Note: Assessing heterogeneity among studies is crucial. If there is significant variability (often measured using I² statistics), it may not be appropriate to combine results.





Forrest Plot

Prophylactic prenatal corticosteroid to prevent neonatal mortality



Meta-analysis: Prenatal corticosteroid reduces early neonatal death by between 30 and 50 per cent.



Key concepts in Meta-Analysis

-1.00

• Forest plot: Graphical display of *studies' effect estimates* and *95% confidence intervals*.

| <u>Study name</u> | Statistics for each study | | |
|--------------------|----------------------------------|----------------|----------------|
| | Event rate | Lower limit | Upper limit |
| Emadian, 2011 | 0.125 | 0.053 | 0.267 |
| Farhadi, 2005 | 0.132 | 0.056 | 0.280 |
| Haeri, 2013 | 0.016 | 0.001 | 0.211 |
| Milani, 2024 | 0.019 | 0.001 | 0.244 |
| Mohammadpour, 2019 | 0.186 | 0.096 | 0.330 |
| Moradi, 2006 | 0.581 | 0.404 | 0.739 |
| Sadeghian, 2022 | 0.007 | 0.000 | 0.103 |
| Yahyapour, 2016 | 0.444 | 0.308 | 0.590 |
| Yahyapour, 2018 | 0.412 | 0.302 | 0.532 |
| | 0.193 | 0.099 | 0.343 |
| | | | |



Event rate and 95% CI



Key concepts in Meta-Analysis

• Heterogeneity: Included papers should "tell a similar story".









Heterogeneity (Identifying and measuring)





Heterogeneity (Strategies for addressing)

- 1. Check again that the data are correct
- 2. Do not do a meta-analysis
- 3. Perform a random-effects meta-analysis
- 4. Change the effect measure
- 5. Exclude studies by sensitivity analysis
- 6. Do Subgroup-analysis
- 7. Run Meta-regression



Fixed vs. Random-effects Model

Impact of Intervention (Fixed effect)



Fixed-effect model - forest plot showing relative weights.

Impact of Intervention (Random effects)





Random-effects model – forest plot showing relative weights.

Fixed vs. Random-effects Model

| Feature | Fixed-Effect Model | Random-Effects Model | |
|----------------------|--|--|--|
| | | | |
| Assumptions | Common effect size across all studies | Varying effect sizes across studies | |
| Weighting | Inverse variance | Inverse variance plus between-study variance | |
| Confidence Intervals | Narrower, reflecting only sampling error | Wider, accounting for both types of variance | |
| Applicability | Homogeneous study designs | Heterogeneous study designs | |



Sources of Bias in Meta-Analyses

Publication Bias

non-significant, low sample size,... \rightarrow Reporting Bias (better to be said non-reporting bias)

- Multiple (duplicate) Publication Bias
- Selection Bias
- Language Bias
- citation bias

Addressing Publication Bias

Funnel plots

- A funnel plot is a graphical tool used in meta-analysis to assess the presence of publication bias and other biases.

- Structure of a Funnel Plot

- Horizontal Axis: Represents the effect sizes (e.g., odds ratios, mean differences) from individual studies.
- Vertical Axis: Represents a measure of precision, such as the standard error or inverse of the standard error. Higher precision (larger sample sizes) is represented towards the top of the plot.
- In the absence of bias, the plot should resemble an inverted funnel shape, where smaller studies scatter widely at the bottom and larger studies cluster near the top.
- Should be more than 10 studies



Funnel plot



Begg's and Egger's tests are statistical methods used to assess publication bias in meta-analyses through the examination of funnel plots. A low p-value (typically <0.05) indicates potential publication bias due to asymmetry, while a high p-value suggests no 12/14/2024 Fateme Sheida, MD

Quality Assessment



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CRITICAL APPRAISAL TOOLS

JBI's critical appraisal tools assist in assessing the trustworthiness, relevance and results of published papers.



riskofbias.info

Welcome to our pages for risk of bias tools for use in systematic reviews.

- RoB 2 tool (revised tool for Risk of Bias in randomized trials)
- ROBINS-E tool (Risk Of Bias in non-randomized Studies of Exposures)
- ROB ME (Risk Of Bias due to Missing Evidence in a synthesis)
- ROBINS-I tool (Risk Of Bias in Non-randomized Studies of Interventions)
- robvis (visualization tool for risk of bias assessments in a systematic review)

Finally, performing a Meta-Analysis!

COMPREHENSIVE META-ANALYSIS









