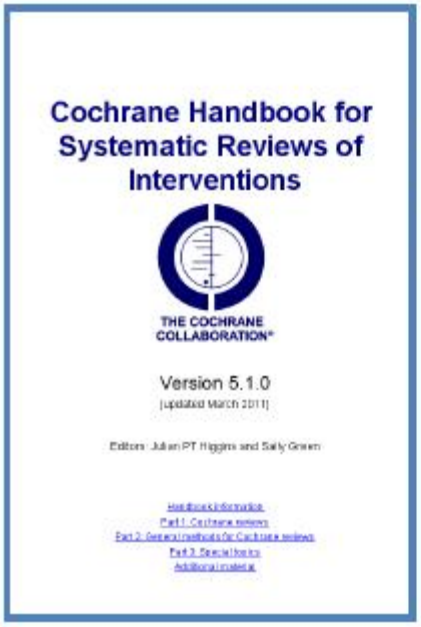
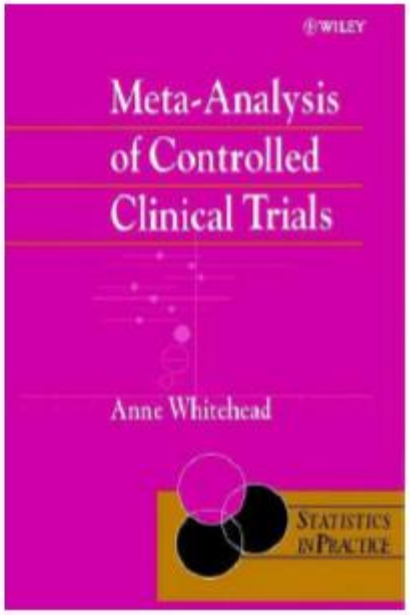

بسم الله الرحمن الرحيم

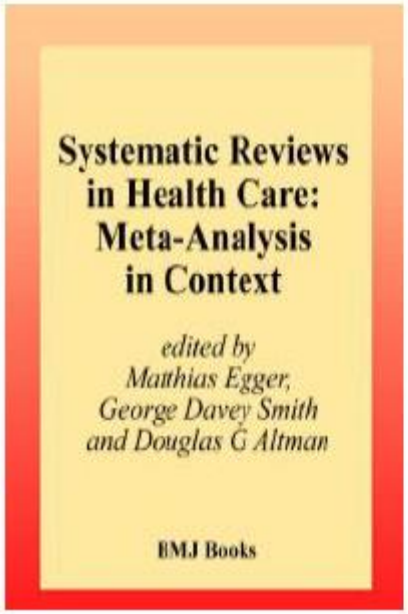
Systematic Reviews & Meta-analysis

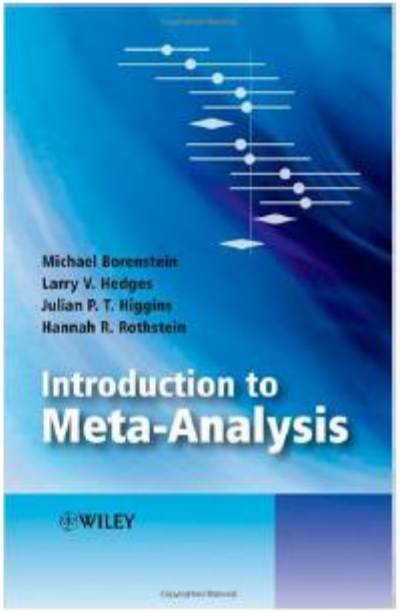
Dr. Reza Pakzad
MSc, Ph.D. of Epidemiology (TUMS)
Faculty Member of Ilam.UMS

References

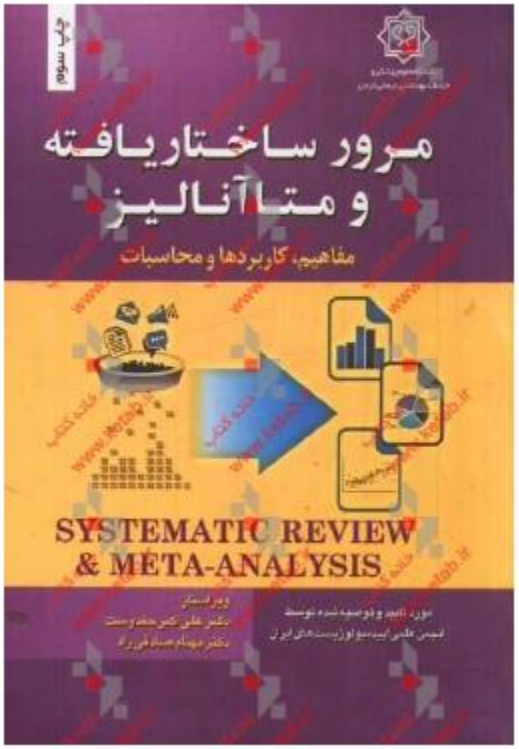

Cochrane Handbook for Systematic Reviews of Interventions
THE COCHRANE COLLABORATION®
Version 5.1.0
[updated March 2011]


WILEY
Meta-Analysis of Controlled Clinical Trials
Anne Whitehead
STATISTICS IN PRACTICE


Systematic Reviews in Health Care: Meta-Analysis in Context
edited by
Matthias Egger,
George Davey Smith
and Douglas G Altman
BMJ Books


Michael Borenstein
Larry V. Hedges
Julian P. T. Higgins
Hannah R. Rothstein
Introduction to Meta-Analysis
WILEY

References


چاپ سوم
مرور ساختاریافته و متاآنالیز
مفاهیم، کاربردها و محاسبات
SYSTEMATIC REVIEW
& META-ANALYSIS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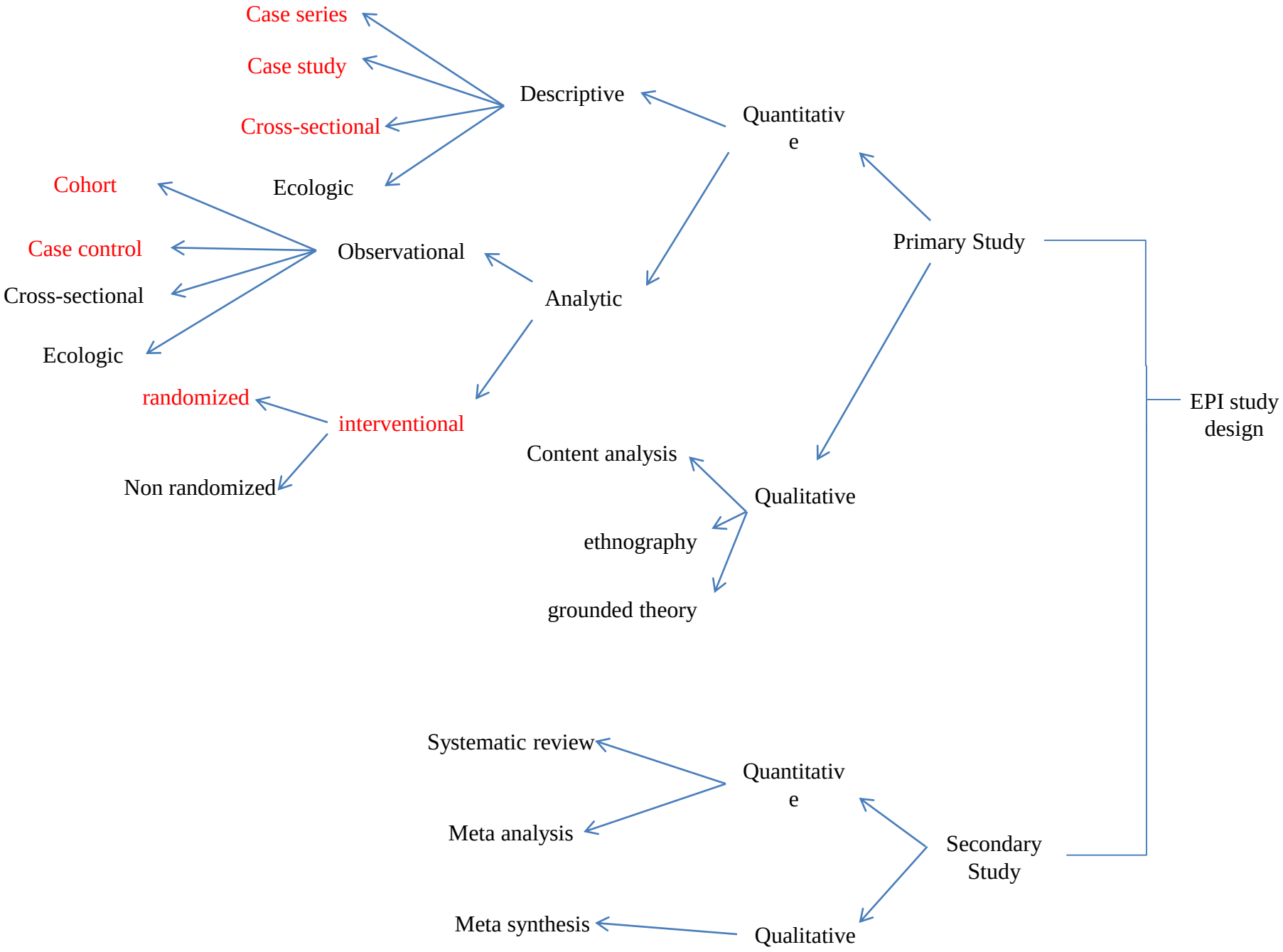
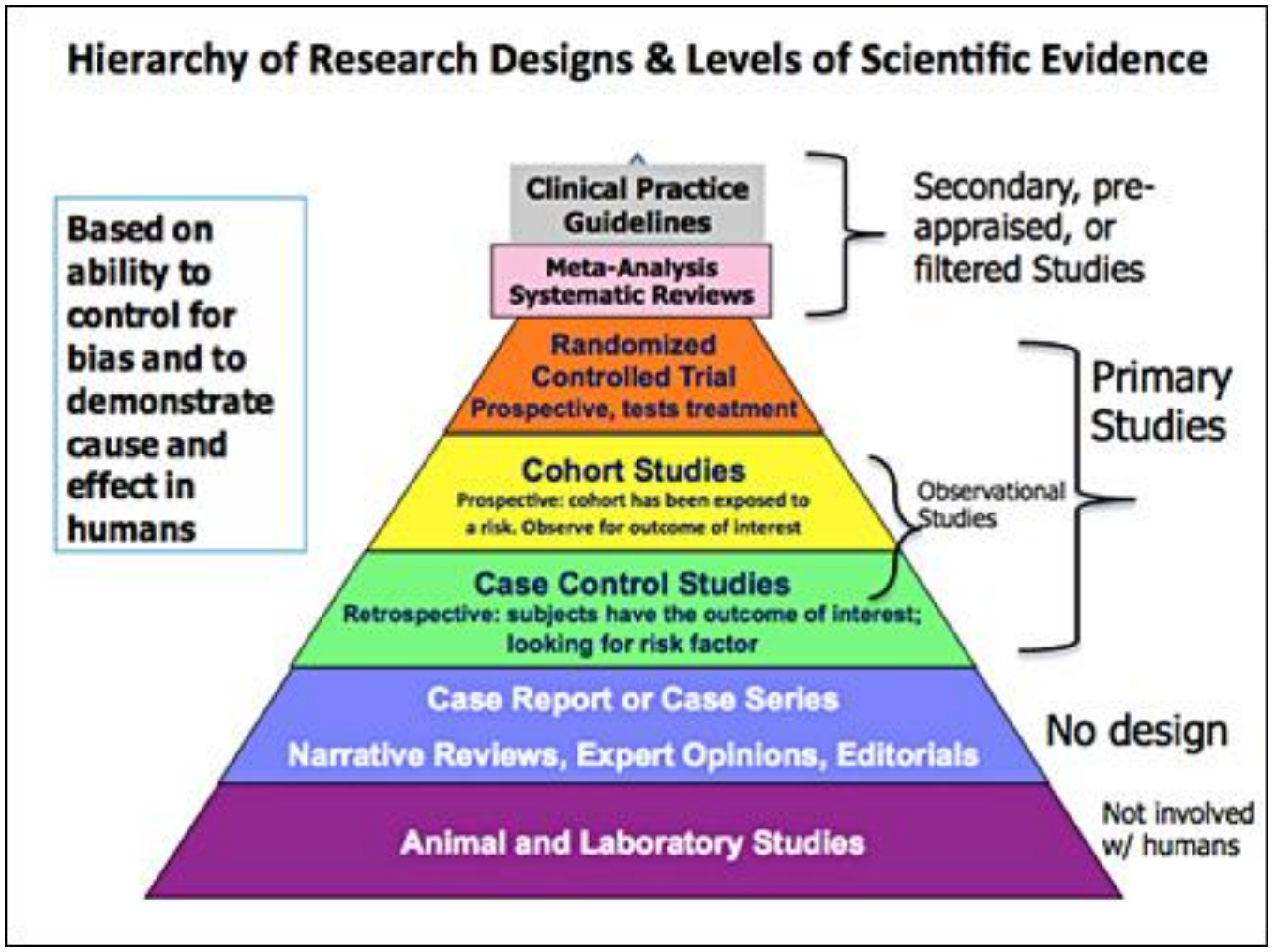

EPI study design
Primary Study
Quantitative
Descriptive
Case series
Case study
Cross-sectional
Ecologic
Analytic
Observational
Cohort
Case control
Cross-sectional
Ecologic
interventional
randomized
Non randomized
Qualitative
Content analysis
ethnography
grounded theory
Secondary Study
Quantitative
Systematic review
Meta analysis
Qualitative
Meta synthesis

Evidence-Based Medicine



Type of studies

- Primary study
- Secondary studies
- Review article (Narrative/Traditional review)
- Systematic review
- Meta-analysis

Narrative vs systematic review

Narrative

- Many questions
- No search methods
- No inclusion criteria
- No combining studies
- Prone to random and systematic error
- Provide conflicting summaries

Systematic

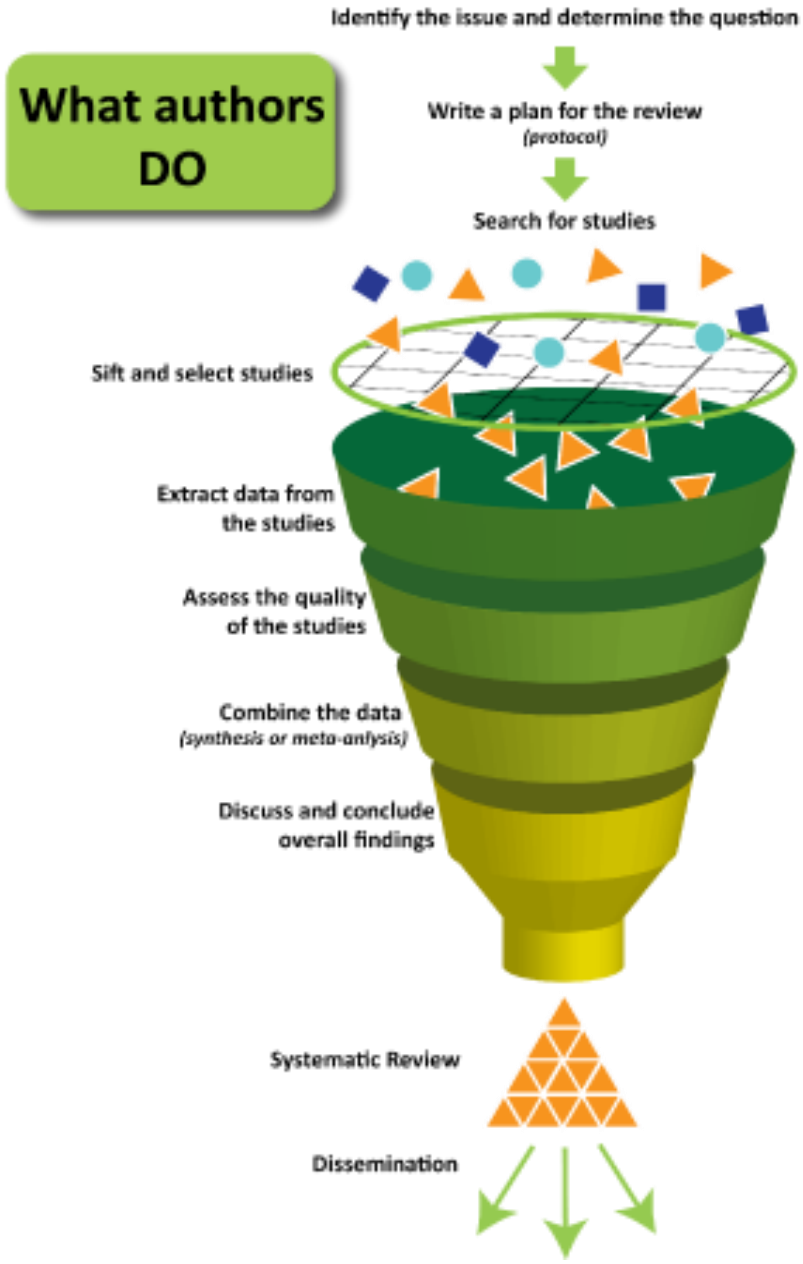
- One question
- Explicit search
- Explicit inclusion criteria
- Combine study results (meta-analysis)

Professor Paul Knipschild has described how Nobel prize winning biochemist **Linus Pauling** used selective quotes from the medical literature to "prove" his theory that

“vitamin C helps you live longer and feel better”

When Knipschild and his colleagues searched the literature systematically for evidence

“They found that”

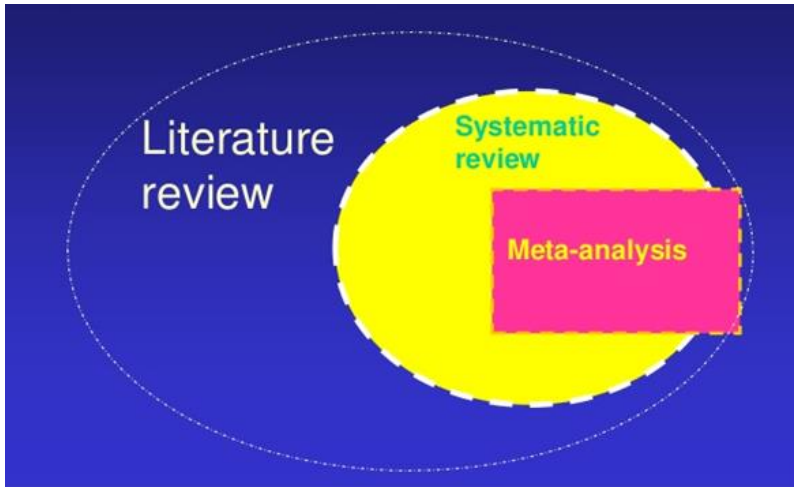

What authors DO
Identify the issue and determine the question
Write a plan for the review
(protocol)
Search for studies
Sift and select studies
Extract data from the studies
Assess the quality of the studies
Combine the data
(synthesis or meta-anlysis)
Discuss and conclude overall findings
Systematic Review
Dissemination

Key Characteristics of Systematic Reviews

- Features that distinguish a systematic review from a review article
  - Clearly stated title and **objectives**
  - Comprehensive **strategy to search** for relevant studies (unpublished and published)
  - Explicit and justified criteria for the **inclusion or exclusion** of any study
  - Clear presentation of characteristics of each study included and an **analysis of methodological quality**
  - Synthesis of findings

Meta-analysis

- “Meta-analysis is a statistical technique for combining the results of independent, but similar, studies to obtain an overall estimate of treatment effect.”
- “While all meta-analyses are based on systematic review of literature, not all systematic reviews necessarily include meta-analysis.”



Type of meta-analysis

- Meta-analysis of interventional studies
  - Randomized controlled trials
    - Estimate of a treatment effect
- Meta-analysis of observational studies
  - Cohort studies
    - Measure of an association (RD or RR or HR)
  - Case-control studies
    - Measure of an association (OR)
  - Cross-sectional studies
    - Estimate of a prevalence (P)

Information Resources for systematic review

Information Resources

- Print Materials

Book-, thesis, paper. J …

- Electronic Materials

Database, E. J …

- Journals & Papers
- Indexes
- Dissertations & Thesis
- Abstracts of Seminars
- Books & Booklets

Information Resources

• Local Data	www.civilica.com
	www.magiran.com
	www.barakatkns.com
	www.sid.ir
•International Data	www.pubmed.com
	www.scopus.com
	www.wos.org

Bibliographic database

A **bibliographic** or **library database** is a collection of bibliographic information.

May contain information about papers, books and other materials held in a library.

Databases

- General Databases
  (Comprehensive OR Core Databases)

- Specialized Databases
  (Subjects Specified Databases)

General Databases (Comprehensive OR Core Databases)

- Medical Sciences
  - Medline
  - Embase
  - Scopus
- All Sciences
  - Web of Sciences

Specialized Databases (Subjects Specified Databases)

- Biological Abstracts
- International Pharmaceutical Abstract
- PsychInfo
- CINAHL
- Chemical Abstracts
- Agricola
- Econlite

Citation Databases

- Web of Science
- Scopus
- Google Scholar
  - (http://scholar.google.com)

Electronic Journals & Collection

- Elsevier Science
- Ovid (LWW)
- Wiley InterScience (Included old Blackwell Science)
- Springer
- Oxford university Press
- Thieme
- Proquest
- Ebsco

Journal Access

Open Access

- Free access to reader
- Online accessibility
- Payment by Authors
- Short review process

Close Access

- Famous/rich history
- IF index
- Payment by readers/organization
- Long review process (payments)

Search Techniques

Star ads Question mark

? Wildcard: replaces a character anywhere in a word, except the first character.

- Wom?n finds woman and women
- except the first character

Truncation

- For singular, plural or word-roots findings.
- Examples:

  child* will retrieve **children, childhood, childlike**

  adolescen* will retrieve **adolescent, adolescence, adolescently**

  derm* will retrieve **dermal, dermatitis, dermatology, dermoid, dermatologist, dermatopathologist, …**

- Be very careful of small word roots when looking for plurals…

cat*	rat*
catastrophe	rational
cataract	ratify
category	ratio

Rather use: (cat OR cats) (rat OR rats)

Searching Technics (Elsevier & Scopus Only)

- There are two options for searching a phrase:
  - Loose phrase search – double quotes “ “
  - Exact phrase search – single quotes ‘ ‘ Or Curly Brackets { }

- Loose phrase search – enclose in double quotes
  - Will search for documents where the words are adjacent to each other
  - Does not insert the AND operator
  - Will ignore punctuation, e.g, hyphens or apostrophes,
    - e.g., “heart-attack” will find docs with and without the hyphen
    - “C++” or “C” will find the same results

- Exact phrase search – enclose in single quotes
  - Stop words, punctuation, special characters and wildcards are searched
  - ‘C++’ will only return docs with this exact character combination
  - ‘C’ will return different results
  - Searching for quotation marks requires a \ before the actual quotation mark \’best practice\’

Registrations

NIHR | National Institute for Health Research

PROSPERO
International prospective register of systematic reviews

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**.

Before registering a new systematic review, check **PROSPERO** and the resources on COVID-END to see whether a similar review already exists. If so, **please do not duplicate without good reason**. Your efforts may be much more useful if switched to a different topic. This will avoid research waste and contribute more effectively to tackling the pandemic.

NIHR | National Institute for Health Research

PROSPERO
International prospective register of systematic reviews

Home | About PROSPERO | How to register | Service information | Search | Log in | Join

Click to **show your search history and hide search results**. Open the **Filters** panel to find records with specific characteristics (e.g. all reviews about cancer or all diagnostic reviews etc)

Click to **hide the standard search and use the Covid-19 filters.**

amblyopia | Go | MeSH | Clear filters | Show filters

First | Previous | Next | Last (page 1 of 1)

39 records found for **amblyopia**

Show checked records only | Export

	Registered	Title	Type	Review status
☐	20/03/2018	A comparison of the effects of multifocal lenses and single focus lenses for myopia control in children: a meta-analysis [CRD42018087246]		Review Ongoing
☐	03/09/2018	A meta-analysis and systematic review on parental cigarette smoking and eye disease in children [CRD42018106371]		Review Ongoing
☐	16/12/2016	A protocol for causes determining visual impairment in Iran; a meta-analysis		Review

Materials and methods

Search strategy and study selection

The results of this meta-analysis are presented according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline.[18] The protocol of the study was registered in the International Prospective Register of Systematic Reviews with CRD42019119961 code. Four international electronic databases (Web of Science, PubMed, Scopus, and Embase) were searched extensively and systematically from inception to 29 September 2018 to retrieve articles related to the prevalence of any strabismus using its MeSH terms (Table 1). The PICO of the study was as follows:

Exclusion criteria

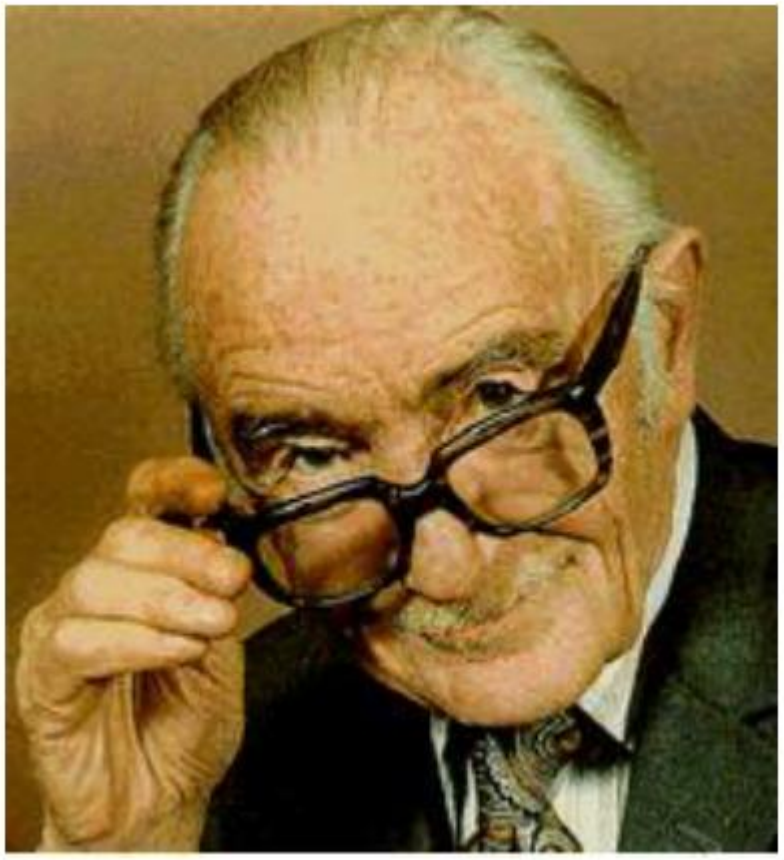
The inclusion criteria of this study were studies with a cross-sectional design (population based and) and surveys. Studies originating from the phase one of large cohort studies with a cross-sectional design were also included.

Since the aim of the study was to assess the prevalence of any strabismus in the general population, studies performed in certain groups like inpatients and patients suffering from ocular or certain systemic diseases (Down syndrome, etc.) were excluded from analysis. Moreover, cohort, follow-up and longitudinal, retrospective, and hospital and clinic based studies, conference reports, letters, editorials, commentaries, reviews and case series also excluded.

Cochrane collaboration

www.cochrane.org

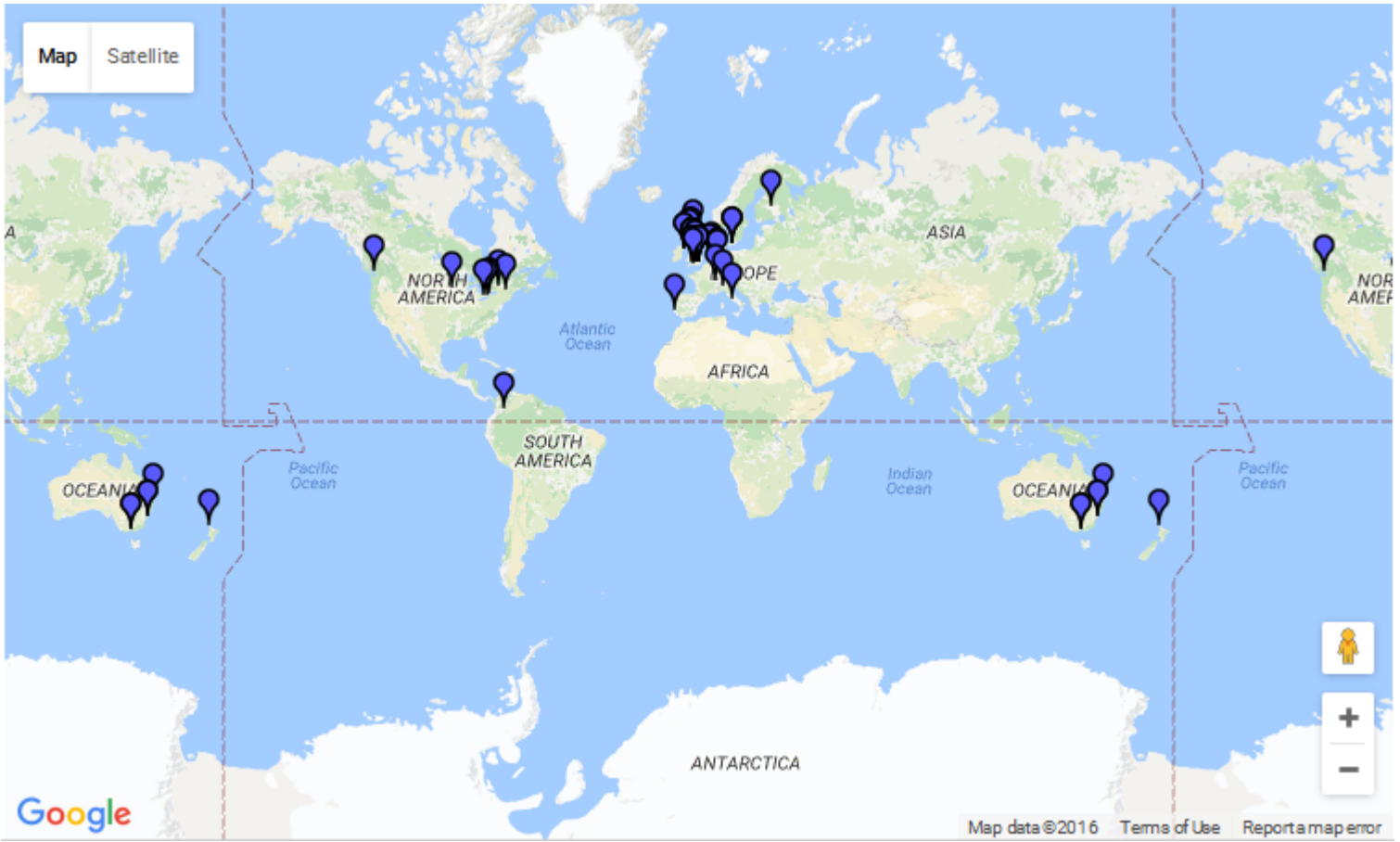
Archie Cochrane (1990-1988)
Scottish physician & epidemiologist



The Cochrane collaboration

- Non-profit, non-governmental organization
- Formation: 1993
- Headquarters: Oxford, England
- Region served: Worldwide
- Over 120 countries
- Volunteers: Over 31,000
- Over 5,000 published online reviews
- Website: www.cochrane.org

The Cochrane review groups
53 groups worldwide



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Find out more about who we are, what we do, and why it matters.

What is Cochrane evidence and how can it help you?

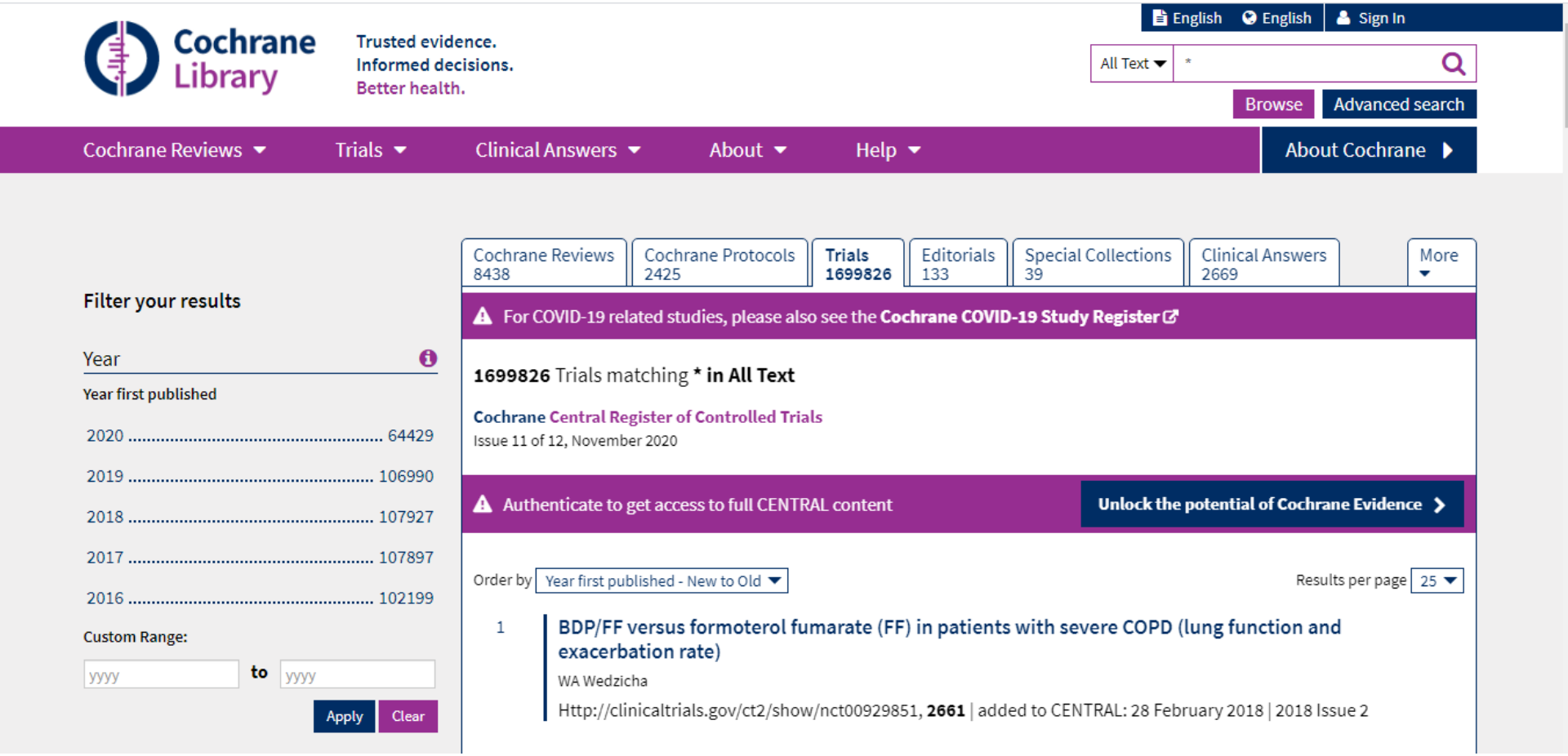
Latest Cochrane evidence | Top 10

- Does chewing gum after a caesarean section lead to quicker recovery of bowel function?
- Vaccines to prevent influenza in healthy adults
- Gabapentin for chronic neuropathic pain and fibromyalgia in adults
- Topical non-steroidal anti-inflammatory drugs for acute musculoskeletal pain in adults
- Vitamin E supplementation in pregnancy
- Replacing a peripheral venous catheter when

Latest News and Events

Cochrane seeks Web Application Developer - Western Europe location

Cochrane seeks members for its inaugural Scientific


Cochrane Library
Trusted evidence.
Informed decisions.
Better health.
English
English
Sign In
All Text
*
Browse
Advanced search
Cochrane Reviews
Trials
Clinical Answers
About
Help
About Cochrane
Cochrane Reviews 8438
Cochrane Protocols 2425
Trials 1699826
Editorials 133
Special Collections 39
Clinical Answers 2669
More
Filter your results
Year
Year first published
2020 64429
2019 106990
2018 107927
2017 107897
2016 102199
Custom Range:
yyyy
to
yyyy
Apply
Clear
For COVID-19 related studies, please also see the Cochrane COVID-19 Study Register
1699826 Trials matching * in All Text
Cochrane Central Register of Controlled Trials
Issue 11 of 12, November 2020
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Order by
Year first published - New to Old
Results per page
25
1
BDP/FF versus formoterol fumarate (FF) in patients with severe COPD (lung function and exacerbation rate)
WA Wedzicha
Http://clinicaltrials.gov/ct2/show/nct00929851, 2661 | added to CENTRAL: 28 February 2018 | 2018 Issue 2

2019 Journal Impact Factor for Cochrane Database of Systematic Reviews is 7.890

Print

The 2019 Journal Citation Report (JCR) has just been released by Clarivate Analytics, and we are delighted to announce that Cochrane Database of Systematic Reviews (CDSR) Journal Impact Factor is now **7.890.**

This is an **increase** on the 2018 Journal Impact Factor, which was 7.755.

The CDSR Journal Impact Factor is calculated by taking the total number of citations in a given year to all Cochrane Reviews published in the past 2 years and dividing that number by the total number of Reviews published in the past 2 years. It is a useful metric for measuring the strength of a journal by how often its publications are cited in scholarly articles.

Some highlights of the CDSR 2019 Journal Impact Factor include:

- The CDSR is ranked 10 of the 165 journals in the Medicine, General & Internal category
- The CDSR received 67,763 cites in the 2019 Journal Impact Factor period, compared with 67,607 in 2018
- The 5-Year Journal Impact Factor is 7.974 compared with 7.949 in 2018

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If you think the page existed in the past, please **send an email to support@cochrane.org** with details of the page you were trying to access.

Review production

Organizational info

Help

Review Manager (RevMan)

- **mandatory** software for writing and publishing your review
- available from http://ims.cochrane.org/revman
- free for Cochrane authors and academic use

cochrane training

Preparing a Systematic review

Steps in conducting a systematic review

1. Objective
2. Inclusion and exclusion criteria
3. Search methods
4. Study selection
5. Data extraction
6. Assessment of metrological quality
7. Measures of treatment/risk effect
8. Data synthesis
9. Assessment of heterogeneity
10. Assessment of reporting biases
11. Sensitivity analysis
12. Subgroup analysis

Step 1: objective

- **The topic should be**
  - Focus of special attention
  - Enough evidence
  - Controversial

Step 1: objective

- **Primary objective**
  - A precise statement of the primary objective of the review, ideally in a single sentence.
- **Specific objectives**
  - A series of specific objectives relating to different subgroups.
  - e.g. age, sex, dose, etc.

Step 1: objective

- **Structure**
  - To assess the effects of *intervention* for *health problem* for/in *types of people*.
- **Example 1**
  - To assess the effect of booster dose vaccination for preventing hepatitis B infection in previously vaccinated healthy individuals.
- **Example 2**
  - To assess the effect of vitamin D supplementation for treatment of essential hypertension
- **Example 3**
  - To estimate the prevalence of chronic hepatitis B infection in Iran

Step 2: inclusion & exclusion criteria

- P
  - Population, Patient, Problem
- I
  - Intervention/Indicator/Exposure
- C
  - Comparison
- O
  - Outcome
- S
  - Study design

Does hand washing among healthcare workers reduce hospital acquired infections?

- P (Problem or Patient or Population): **hospital acquired infection/ healthcare workers**
- I (intervention/indicator) : **hand washing**
- C (comparison): **no hand washing; other solution; masks**
- O (outcome of interest): **reduced infection**

Effect of Alcohol on Stroke

- **P:** both men and women in any age
- **I:** Alcohol
- **C:** no drinker
- **O:** Stroke
- **T:** without restriction
- **S:** observational studies (case-control and cohort)

Step 2: inclusion & exclusion criteria

1. **Types of participants**
   - Diagnoses, Age groups, Sex, Settings
- **Example**
   - We will include those patients with essential hypertension (i.e., diastolic BP equal to or greater than 90 mmHg and/or systolic BP equal to or greater than 140 mmHg).
   - We will exclude studies whose participants were not screened for ruling out the secondary hypertension.

Step 2: inclusion & exclusion criteria

2. Types of intervention or risk factor

- Dose, Interval, Duration

Example

- The intervention of interest is administering vitamin D supplementation with or without calcium versus placebo or no treatment to assess reduction in BP.
- We will assess vitamin D supplementation, irrespective of drug preparation, dosage, frequency, or duration.
- We excluded other types of intervention, including vitamin D supplementation in combination with other vitamins (i.e. multivitamin)

Step 2: inclusion & exclusion criteria

3. Types of comparison or control

- Placebo
- No intervention

Example

- The intervention of interest is administering vitamin D supplementation with or without calcium versus placebo or no treatment to assess reduction in BP.

Step 2: inclusion & exclusion criteria

4. Types of outcome measures

- Death, Disease, Recovery

❖ Example

- The primary outcome of interest is the reduction in diastolic and/or systolic BP in term of mmHg.
- The secondary outcome of interest is proportion with undesirable systemic adverse events developed after vitamin D supplementation including weakness, fatigue, sleepiness, headache, loss of appetite, dry mouth, metallic taste, nausea, vomiting and constipation.

Step 2: inclusion & exclusion criteria

5. Types of studies

- RCT, Cohort, Case-control, Cross-sectional

Example

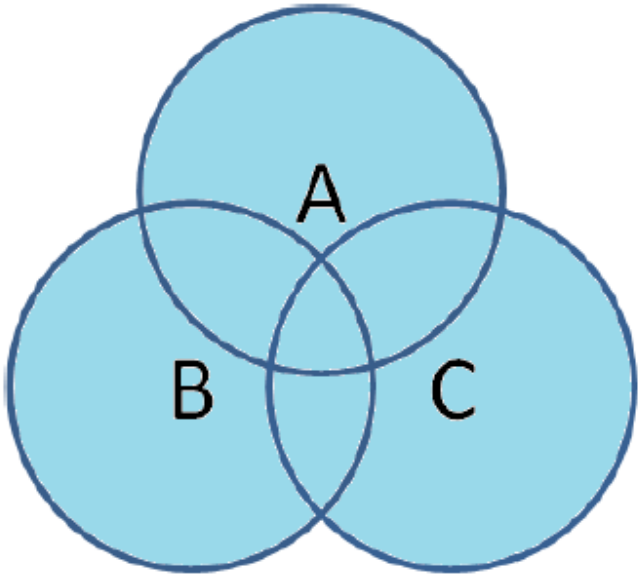
- We will include RCTs addressing response to vitamin D supplementation in patients with essential hypertension.
- We will include trials, irrespective of randomization method, blinding, period of follow-up, publication status, or language.
- We will exclude particular types of randomized studies such as crossover or factorial trials.

1) P: Term [title/abstract] OR Term [Mesh]
2) I: Term [title/abstract] OR Term [Mesh]
3) C: Term [title/abstract] OR Term [Mesh]
4) O: Term [title/abstract] OR Term [Mesh]

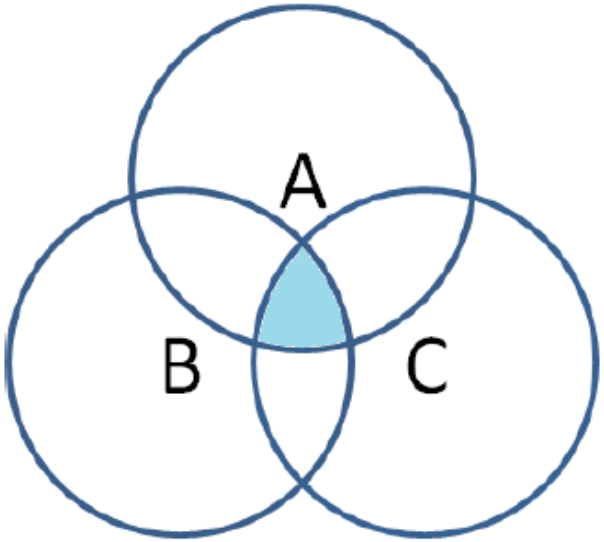
- 1 AND 2 AND 3 AND 4

Step 3: Search Methods

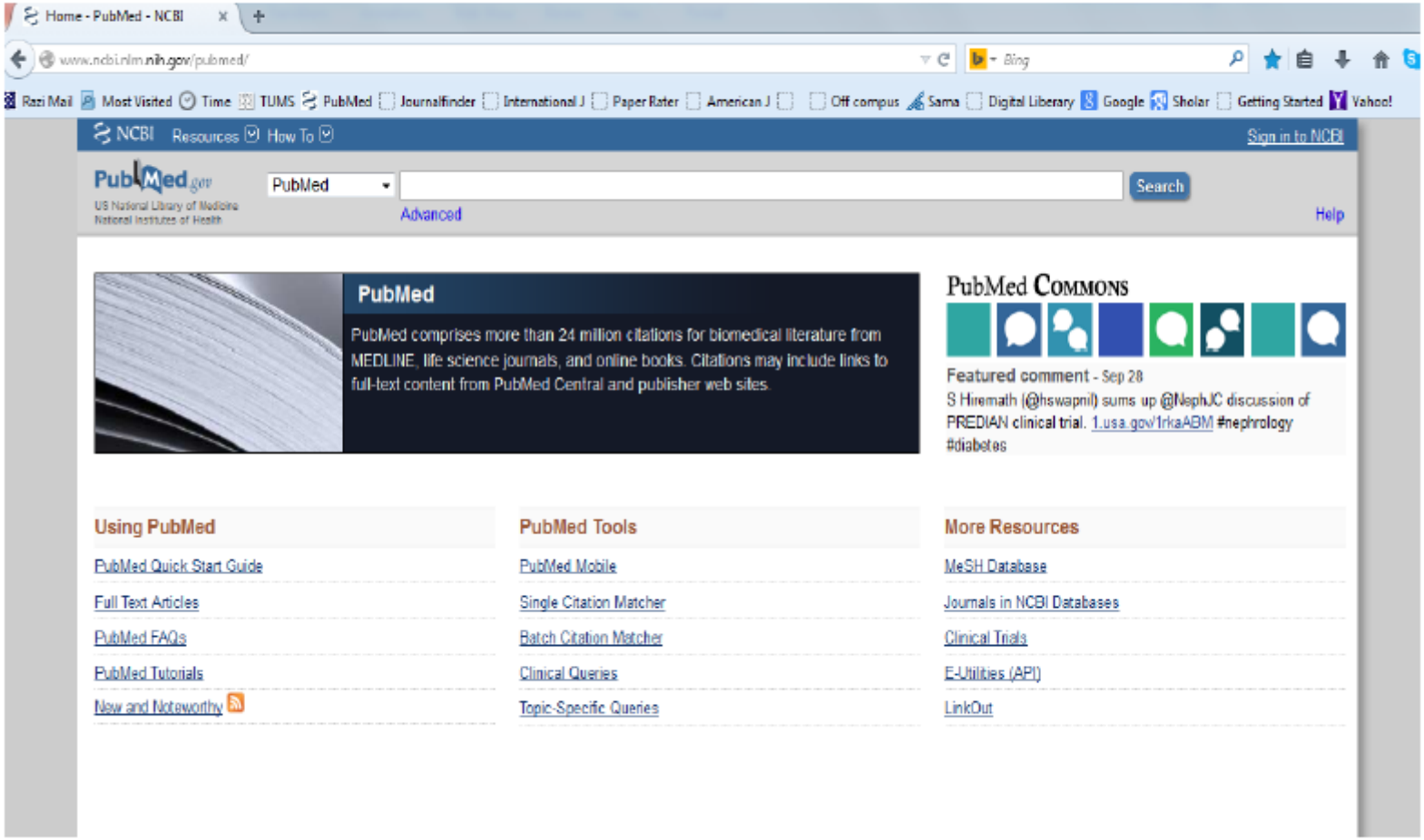
A OR B OR C = A U B U C



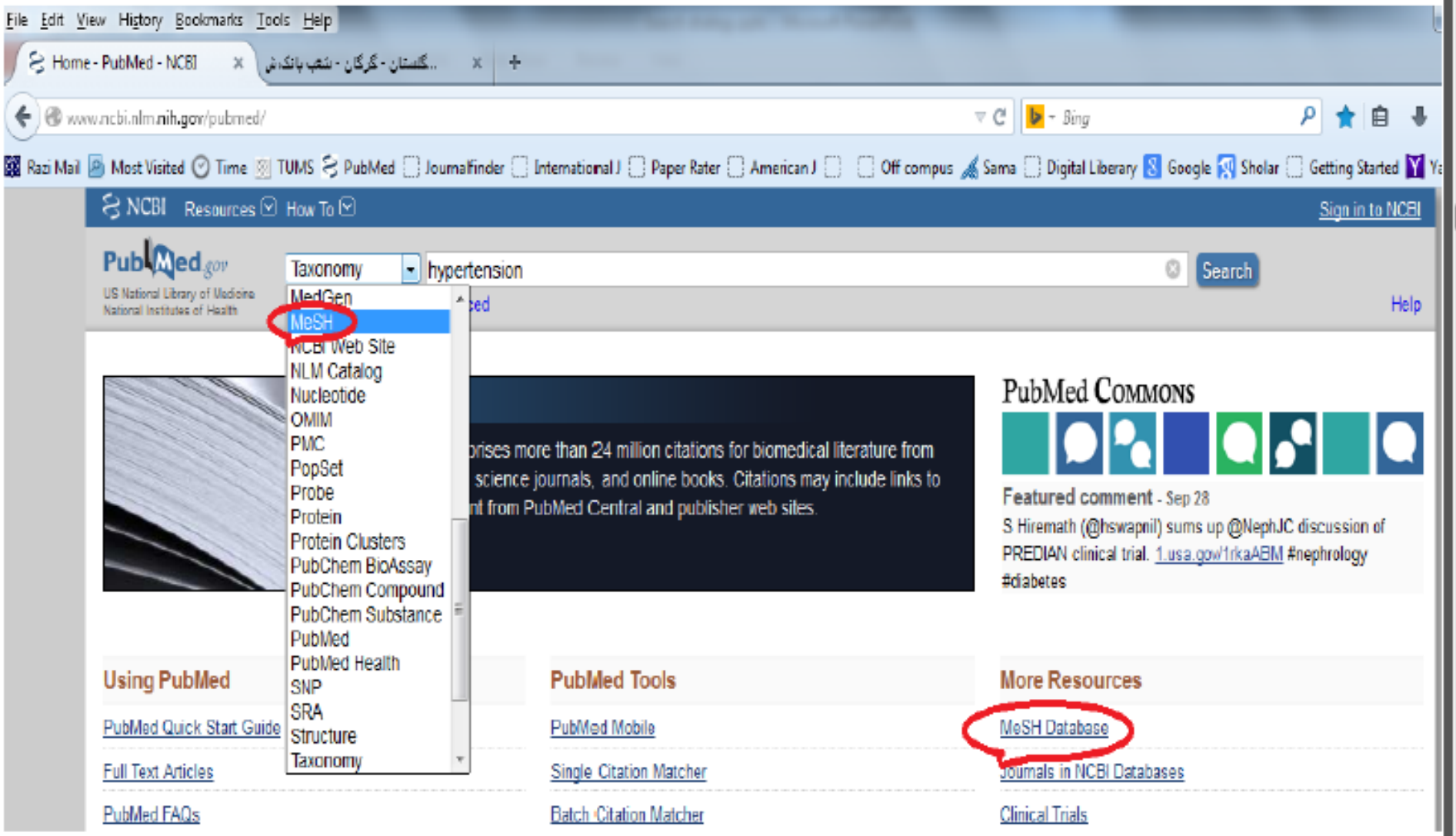
A AND B AND C = A ∩ B ∩ C

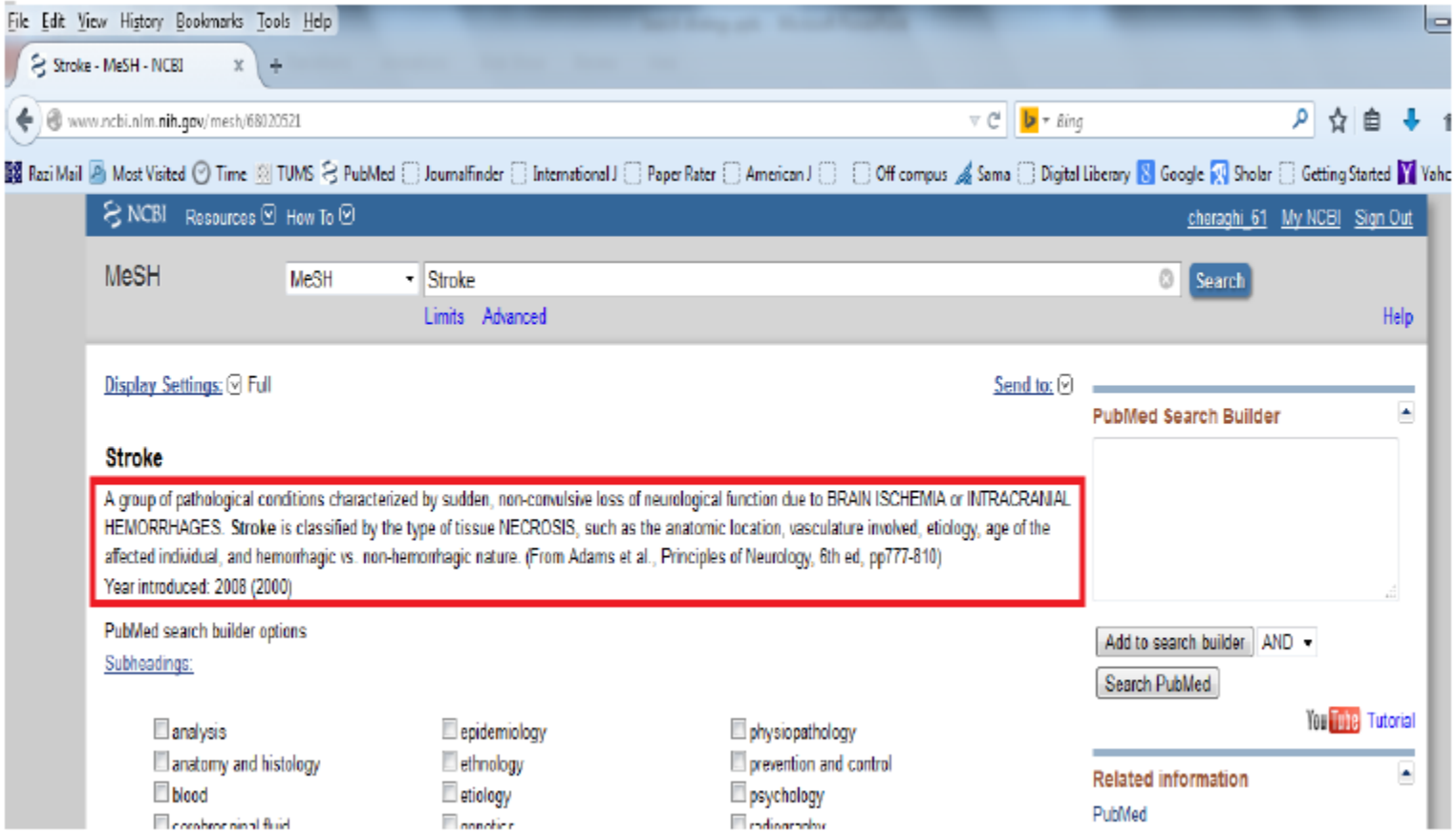


- Go to http://www.ncbi.nlm.nih.gov/pubmed/



- **Write each related term from previous box in the search PubMed box and choose MeSH from the other box**




File Edit View History Bookmarks Tools Help
Stroke - MeSH - NCBI
www.ncbi.nlm.nih.gov/mesh/68020521
Bing
Razi Mail Most Visited Time TUMS PubMed Journalfinder International J Paper Rater American J Off campus Sama Digital Library Google Scholar Getting Started
NCBI Resources How To
cheraghi_61 My NCBI Sign Out
MeSH
MeSH
Stroke
Search
Limits Advanced
Help
Display Settings: Full
Send to:
Stroke
A group of pathological conditions characterized by sudden, non-convulsive loss of neurological function due to BRAIN ISCHEMIA or INTRACRANIAL HEMORRHAGES. Stroke is classified by the type of tissue NECROSIS, such as the anatomic location, vasculature involved, etiology, age of the affected individual, and hemorrhagic vs. non-hemorrhagic nature. (From Adams et al., Principles of Neurology, 6th ed, pp777-810)
Year introduced: 2008 (2000)
PubMed search builder options
Subheadings:
analysis
anatomy and histology
blood
epidemiology
ethnology
etiology
physiopathology
prevention and control
psychology
PubMed Search Builder
Add to search builder
AND
Search PubMed
YouTube Tutorial
Related information
PubMed

Tree Number(s): C10.228.140.300.775, C14.907.253.855

Entry Terms:

- Strokes
- Apoplexy
- CVA (Cerebrovascular Accident)
- CVAs (Cerebrovascular Accident)
- Cerebrovascular Accident
- Cerebrovascular Accidents
- Cerebrovascular Apoplexy
- Apoplexy, Cerebrovascular
- Cerebrovascular **Stroke**
- Cerebrovascular Strokes
- **Stroke**, Cerebrovascular
- Strokes, Cerebrovascular
- Vascular Accident, Brain
- Brain Vascular Accident
- Brain Vascular Accidents
- Vascular Accidents, Brain
- Cerebral **Stroke**
- Cerebral Strokes
- **Stroke**, Cerebral
- Strokes, Cerebral
- **Stroke**, Acute
- Acute **Stroke**
- Acute Strokes
- Strokes, Acute
- Cerebrovascular Accident, Acute
- Acute Cerebrovascular Accident
- Acute Cerebrovascular Accidents

1. alcohol drinking [Title/Abstract] OR alcohol drinking [MeSH Terms] (6280)
2. alcohol drinking habit [Title/Abstract] OR alcohol drinking habit [MeSH Terms] (6010)
3. alcohol consumption [Title/Abstract] OR alcohol consumption [MeSH Terms] (8752)
4. 1 OR 2 OR 3 (8966)
5. Stroke [Title/Abstract] OR Stroke [MeSH Terms] (45277)
6. cerebrovascular accident [Title/Abstract] OR cerebrovascular accident [MeSH Terms] (20351)
7. Apoplexy [Title/Abstract] OR Apoplexy [MeSH Terms] (20299)
8. 5 OR 6 OR 7 (45734)
9. 4 AND 8 (287)

Use the builder below to create your search

Edit

Builder

All Fields

AND All Fields

Search or Add to history

History Dov

Search	Add to builder	Query
#11	Add	Search **(("Stroke"[Mesh]) AND (("Case-Control Studies"[Mesh] OR "Cohort Studies"[Mesh]) OR "Epidemiologic Studies"[Mesh])) AND ((("Alcohols"[Mesh]) OR "Beer"[Mesh]) OR "Wine"[Mesh])**
#10	Add	Search **(("Alcohols"[Mesh]) OR "Beer"[Mesh]) OR "Wine"[Mesh]**
#7	Add	Search **("Case-Control Studies"[Mesh] OR "Cohort Studies"[Mesh]) OR "Epidemiologic Studies"[Mesh]**
#3	Add	Search **"Stroke"[Mesh]**

TEXT AVAILABILITY

- [ ] Abstract
- [ ] Free full text
- [ ] Full text

ARTICLE ATTRIBUTE

- [ ] Associated data

ARTICLE TYPE

- [ ] Books and Documents
- [ ] Clinical Trial
- [ ] Meta-Analysis
- [x] Randomized Controlled Trial
- [ ] Review
- [ ] Systematic Review

PUBLICATION DATE

- ( ) 1 year
- ( ) 5 years
- ( ) 10 years

died compared with 82 participants in the placebo group (094, 069-128; p=068). 65 participants in the ginkgo group had a **stroke** compared with 60 participants in the placebo gr ...

2 Cite Share

Results of the CAPRIE trial: efficacy and safety of clopidogrel. Clopidogrel versus aspirin in patients at risk of ischaemic events.

Creager MA.

Vasc Med. 1998;3(3):257-60. doi: 10.1177/1358836X9800300314.

PMID: 9892520 Review.

The primary outcome measurement was an aggregate of myocardial infarction, ischemic **stroke** and vascular death. Event rates of 5.32% and 5.83% were associated with clopidogrel and aspirin therapy, respectively. ...

3 Cite Share

The VITATOPS (Vitamins to Prevent **Stroke**) Trial: rationale and design of an international, large, simple, randomised trial of homocysteine-lowering multivitamin therapy in patients with recent transient ischaemic attack or **stroke**.

VITATOPS Trial Study Group.

Cerebrovasc Dis. 2002;13(2):120-6. doi: 10.1159/000047761.

PMID: 11867886 Review.

BACKGROUND: Epidemiological studies suggest that raised plasma concentrations of total homocysteine (tHcy) may be a common, causal and treatable risk factor for atherothromboembolic ischaemic **stroke**. Although tHcy can be lowered effectively with small doses of folic acid, ...

4

2013 SYR Accepted Poster Abstracts.

[No authors listed]

Int J Yoga Therap. 2013;23 Suppl:32-53

Time and Language

Step 3: Search Methods

1. **Electronic searches**
   - Bibliographic databases
     - CENTRAL
     - MEDLINE
     - ISI Web of Knowledge
     - Scopus
     - EMBASE
   - Dates and periods of search
   - Language
   - Full search strategies for each database

Step 3: Search Methods

Example

Effect of vitamin D supplement on hypertension

- #1 Vitamin D
- #2 Ergocalciferol
- #3 Cholecalciferol
- #4 Calciferol
- #5 (#1 OR #2 OR #3 OR #4)
- #6 Hypertension
- #7 Hypertensive
- #8 Blood Pressure
- #9 (#6 OR #7 OR #8)
- #10 Randomized Controlled Trial
- #11 Randomised Controlled Trial
- #12 Randomized Clinical Trial
- #13 Randomised Clinical Trial
- #14 Controlled Clinical Trial
- #15 Placebo
- #16 (#10 Or #11 Or #12 Or #13 Or #14 Or #15)
- #17 Animals
- #18 (#5 AND #9 AND #16)
- #19 (#18 NOT #17)

Use the builder below to create your search

Edit Clear

Builder

All Fields Show index list

AND All Fields Show index list

Search or Add to history

History Download history Clear history

Search	Add to builder	Query	Items found	Time
#17	Add	Search **#7 AND #13 AND #16**	108	21:56:48
#16	Add	Search **#14 OR #15**	462483	21:54:15
#15	Add	Search **Controlled Clinical Trial[Publication Type]**	88298	21:53:57
#14	Add	Search **Randomized Controlled Trial[Publication Type]**	378972	21:50:58
#13	Add	Search **#8 OR #9 OR #10 OR #11 OR #12**	507164	21:49:51
#12	Add	Search **Blood Pressure[Title/Abstract]**	227307	21:48:48
#11	Add	Search **Blood Pressure[MeSH Major Topic]**	77904	21:48:38
#10	Add	Search **Hypertensive[Title/Abstract]**	90581	21:48:09
#9	Add	Search **Hypertension[Title/Abstract]**	286426	21:47:32
#8	Add	Search **Hypertension[MeSH Major Topic]**	152500	21:47:20
#7	Add	Search **#1 OR #2 OR #3 OR #4 OR #5 OR #6**	51530	21:46:42
#6	Add	Search **Cholecalciferol[Title/Abstract]**	1622	21:44:13
#5	Add	Search **Cholecalciferol[MeSH Major Topic]**	14610	21:44:04
#4	Add	Search **Ergocalciferols[Title/Abstract]**	3	21:42:28
#3	Add	Search **Ergocalciferols[MeSH Major Topic]**	2015	21:42:16
#2	Add	Search **vitamin D[Title/Abstract]**	40428	21:41:24
#1	Add	Search **vitamin D[MeSH Major Topic]**	29333	21:41:10

PubMed.gov

(((Stroke[Title/Abstract]) OR (Strokes[MeSH Terms]) AND (review[Filter] OR sy

Search

Advanced Create alert Create RSS User Guide

Save Email Send to Sorted by: Best match Display options

Create a file for external citation management software

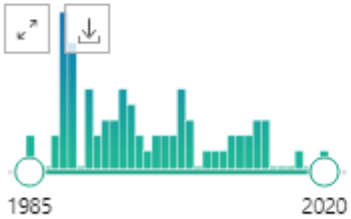
Selection: **All results**

Create file Cancel

MY NCBI FILTERS

76 results

RESULTS BY YEAR



Filters applied: Randomized Controlled Trial. Clear all

1 Cite Share

Long-term use of standardised Ginkgo biloba extract for the prevention of Alzheimer's disease (GuidAge): a randomised placebo-controlled trial.

Vellas B, Coley N, Ousset PJ, Berrut G, Dartigues JF, Dubois B, Grandjean H, Pasquier F, Piette F, Robert P, Touchon J, Garnier P, Mathiex-Fortunet H, Andrieu S; GuidAge Study Group.

Lancet Neurol. 2012 Oct;11(10):851-9. doi: 10.1016/S1474-4422(12)70206-5. Epub 2012 Sep 6.

PMID: 22959217 Review.

Incidence of adverse events was much the same between groups. 76 participants in the ginkgo group died compared with 82 participants in the placebo group (094, 069-128; p=068). 65 participants in the ginkgo group had a **stroke** compared with 60 participants in the placebo gr ...

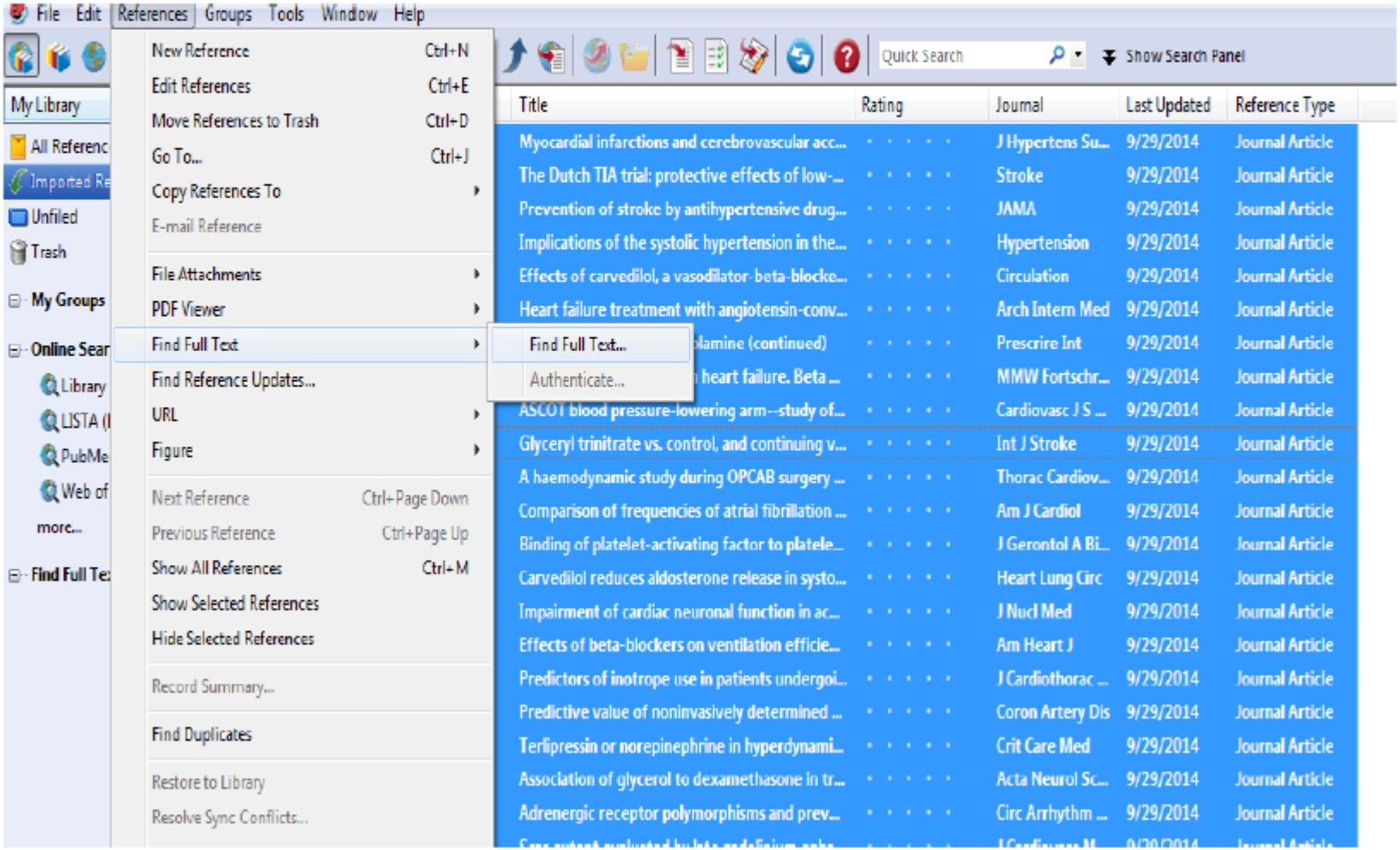
TEXT AVAILABILITY

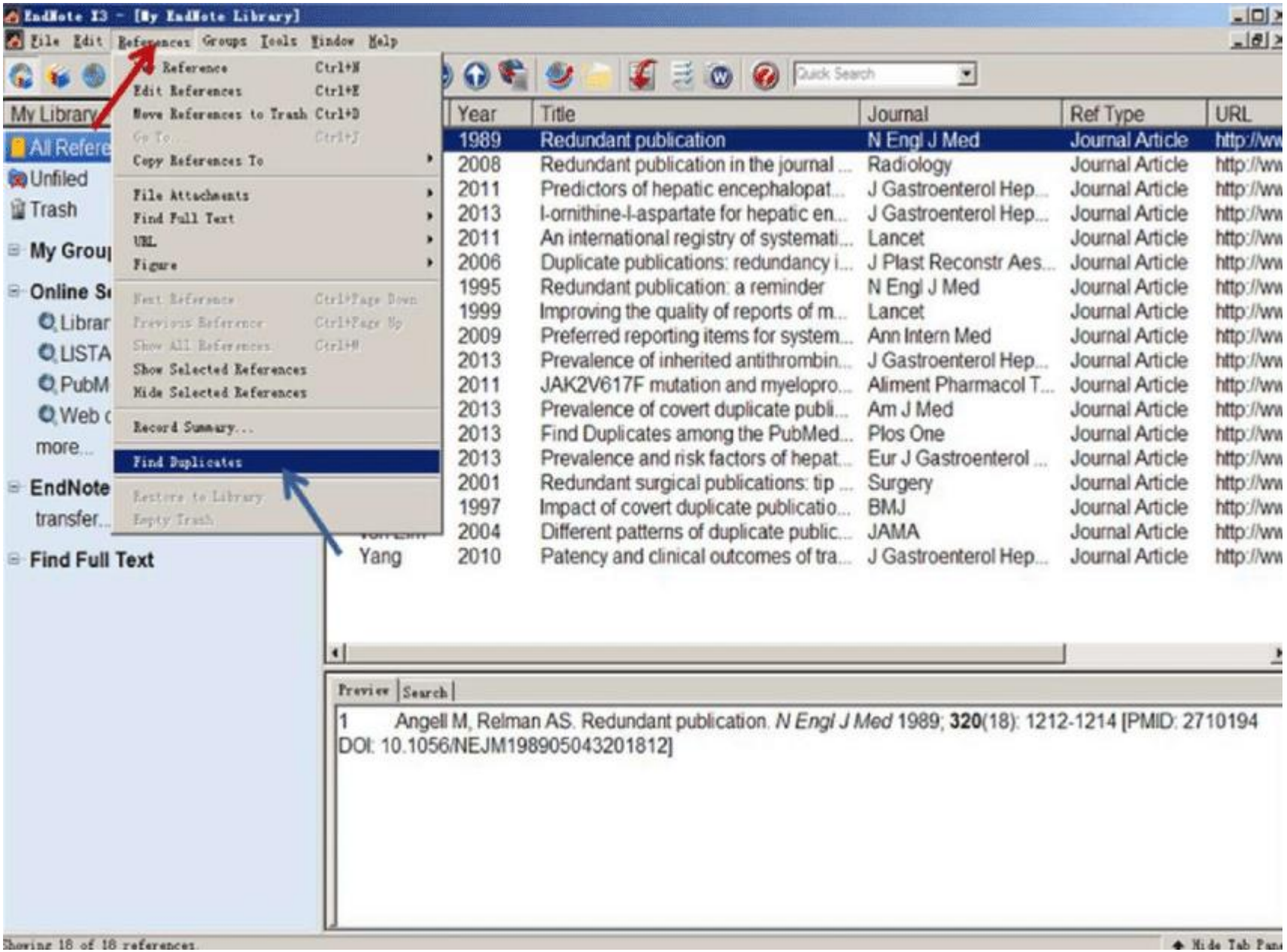
- Abstract
- Free full text

Results of the CAPRIE trial: efficacy and safety of clopidogrel. Clopidogrel versus

Import your search result in *EndNote*

➢ Find all full text in Endnote




EndNote X3 - [My EndNote Library]
File Edit References Groups Tools Window Help
New Reference Ctrl+N
Edit References Ctrl+E
Move References to Trash Ctrl+D
Go To... Ctrl+J
Copy References To
File Attachments
Find Full Text
URL
Figure
Next Reference Ctrl+Page Down
Previous Reference Ctrl+Page Up
Show All References Ctrl+M
Show Selected References
Hide Selected References
Record Summary...
Find Duplicates
Restore to Library
Empty Trash
My Library
All Refere
Unfiled
Trash
My Grou
Online S
Librar
LISTA
PubM
Web
more...
EndNote
transfer...
Find Full Text
Quick Search
Year
Title
Journal
Ref Type
URL
1989 Redundant publication N Engl J Med Journal Article
2008 Redundant publication in the journal ... Radiology Journal Article
2011 Predictors of hepatic encephalopat... J Gastroenterol Hep... Journal Article
2013 l-ornithine-l-aspartate for hepatic en... J Gastroenterol Hep... Journal Article
2011 An international registry of systemati... Lancet Journal Article
2006 Duplicate publications: redundancy i... J Plast Reconstr Aes... Journal Article
1995 Redundant publication: a reminder N Engl J Med Journal Article
1999 Improving the quality of reports of m... Lancet Journal Article
2009 Preferred reporting items for system... Ann Intern Med Journal Article
2013 Prevalence of inherited antithrombin... J Gastroenterol Hep... Journal Article
2011 JAK2V617F mutation and myelopro... Aliment Pharmacol T... Journal Article
2013 Prevalence of covert duplicate publi... Am J Med Journal Article
2013 Find Duplicates among the PubMed... Plos One Journal Article
2013 Prevalence and risk factors of hepat... Eur J Gastroenterol ... Journal Article
2001 Redundant surgical publications: tip ... Surgery Journal Article
1997 Impact of covert duplicate publicatio... BMJ Journal Article
2004 Different patterns of duplicate public... JAMA Journal Article
Yang 2010 Patency and clinical outcomes of tra... J Gastroenterol Hep... Journal Article
Preview Search
1 Angell M, Relman AS. Redundant publication. N Engl J Med 1989; 320(18): 1212-1214 [PMID: 2710194
DOI: 10.1056/NEJM198905043201812]
Showing 18 of 18 references.

Step 3: Search Methods

2. **Searching other resources**
   - Reference lists
   - Hand searching
   - Conference proceedings
   - Authors of the included articles

Step 3: Search Methods

- **Example**
  - We will scan the reference lists of all included studies and pertinent reviews for additional relevant reports.
  - We will contact the trials' authors of included studies for additional unpublished trials.
  - The following conference databases will be searched for unpublished data:
    - American Society of Hypertension; available form: http://www.ash-us.org
    - American Heart Association; available from: http://www.ish-world.com
    - British Hypertension society; available from: http://www.bhsoc.org
    - Europeant Society of Hypertension; available form: http://www.eshonline.org
    - International Society of Hypertension; available from: http://www.ish-world.com

Step 4: Study Selection

- **Examine identified studies**
  1. Titles and abstracts
  2. Full text reports
- Studies have to meet pre-specified criteria for inclusion in the review
  - A single failed eligibility criterion is sufficient for a study to be excluded from a review.

Step 4: Study Selection

- Assessment of eligibility of studies should be done by at least two people, ideally independently.
  - Any disagreements should be resolved either via discussion or by 3rd author.
- Classification of the studies
  - Include
  - Exclude
  - Unsure

Step 4: Study Selection

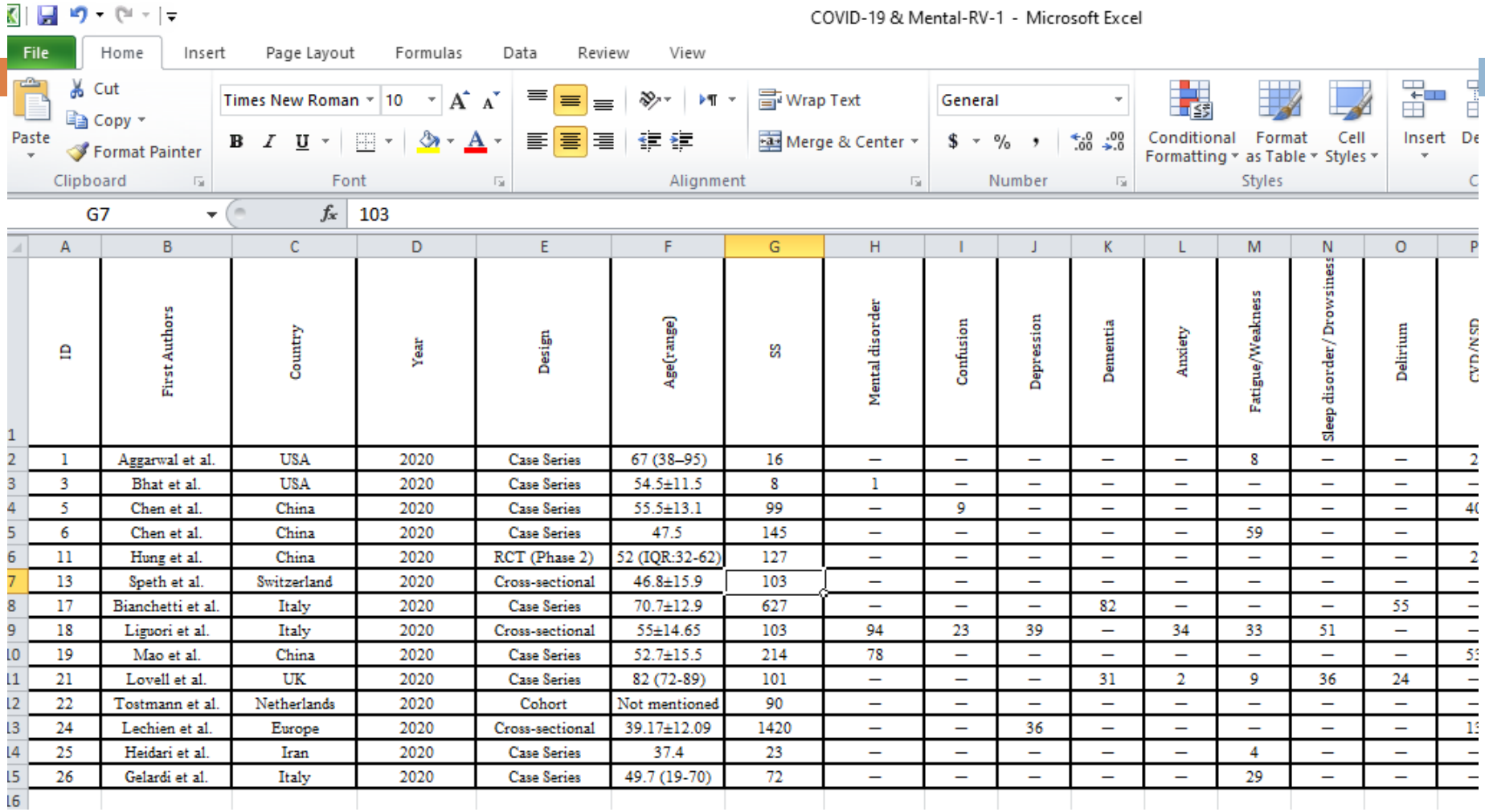
- **Example**
  - Two authors independently will make the decision on which studies meet the inclusion criteria to objective of this meta-analysis.
  - The authors will not be blinded to the names of the studies authors, journals, and results.
  - Any disagreements will resolve through discussion among the authors until consensus is reached.

Step 5: Data extraction

- **Data collection form**
  - Electronic forms
  - Paper forms
- Extraction of data from study reports should be done by at least two people, ideally independently.
  - Any disagreements should be resolved either via discussion or by 3rd author.

Step 5: Data extraction

- **Example**
  - Extraction of data from study reports, will be done by at least two authors independently using the 'Data Collection Form‘.
  - Any disagreements will be resolved through discussion among the authors until consensus is reached.
  - In cases of missing data or need for clarification, trial authors will be contacted.



	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P
1	ID	First Authors	Country	Year	Design	Age(range)	SS	Mental disorder	Confusion	Depression	Dementia	Anxiety	Fatigue/Weakness	Sleep disorder/ Drowsiness	Delirium	CVD/NSD
2	1	Aggarwal et al.	USA	2020	Case Series	67 (38–95)	16	—	—	—	—	—	8	—	—	2
3	3	Bhat et al.	USA	2020	Case Series	54.5±11.5	8	1	—	—	—	—	—	—	—	—
4	5	Chen et al.	China	2020	Case Series	55.5±13.1	99	—	9	—	—	—	—	—	—	40
5	6	Chen et al.	China	2020	Case Series	47.5	145	—	—	—	—	—	59	—	—	
6	11	Hung et al.	China	2020	RCT (Phase 2)	52 (IQR:32-62)	127	—	—	—	—	—	—	—	—	2
7	13	Speth et al.	Switzerland	2020	Cross-sectional	46.8±15.9	103	—	—	—	—	—	—	—	—	—
8	17	Bianchetti et al.	Italy	2020	Case Series	70.7±12.9	627	—	—	—	82	—	—	—	55	—
9	18	Liguori et al.	Italy	2020	Cross-sectional	55±14.65	103	94	23	39	—	34	33	51	—	—
10	19	Mao et al.	China	2020	Case Series	52.7±15.5	214	78	—	—	—	—	—	—	—	53
11	21	Lovell et al.	UK	2020	Case Series	82 (72-89)	101	—	—	—	31	2	9	36	24	—
12	22	Tostmann et al.	Netherlands	2020	Cohort	Not mentioned	90	—	—	—	—	—	—	—	—	—
13	24	Lechien et al.	Europe	2020	Cross-sectional	39.17±12.09	1420	—	—	36	—	—	—	—	—	13
14	25	Heidari et al.	Iran	2020	Case Series	37.4	23	—	—	—	—	—	4	—	—	—
15	26	Gelardi et al.	Italy	2020	Case Series	49.7 (19-70)	72	—	—	—	—	—	29	—	—	—
16																

Step 6: Assessment of Methodological Quality

- The methodological quality should be assessed by at least two people independently.
- Many tools have been proposed for assessing the quality of studies, including:
  - **Scales**
    - in which various components of quality are scored and combined to give a summary score;
  - **Checklists**
    - in which specific questions are asked

- Critical Appraisal Skills Program (CASP) checklist

1. Observational study
2. RCT
3. Systematic reviews

- Quality assessment checklist

1. Cross sectional: newcastle-ottawa scale (nos)
2. Observational: STROBE
3. RCT: Cochrane Risk of Bias Tool
4. SR: ROBIS tools

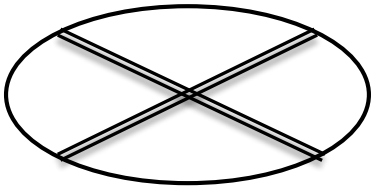
PRISMA

- PRISMA is an evidence-based minimum set of items for reporting in systematic reviews and meta-analyses. PRISMA focuses on the reporting of reviews evaluating randomized trials, but can also be used as a basis for reporting systematic reviews of other types of research, particularly evaluations of interventions.

TITLE
Title
ABSTRACT
Structured summary
INTRODUCTION
Rationale
Objectives
METHODS
Protocol and registration
Eligibility criteria
Information sources
Search
Study selection
Data collection process
Data items
Risk of bias in individual studies
Summary measures
Synthesis of results
Risk of bias across studies
Additional analyses

RESULTS
Study selection
Study characteristics
Risk of bias within studies
Results of individual studies
Synthesis of results
Risk of bias across studies
Additional analysis
DISCUSSION
Summary of evidence
Limitations
Conclusions
FUNDING
Funding

The present meta-analysis was conducted according to the Preferred Reporting Item for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.[9]



In this study, the results were reported based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA guideline).[22] For this purpose,

The results of this meta-analysis are presented according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline.[18] The protocol of the study was registered in the

Step 6: Assessment of Methodological Quality

- **PRISMA Statement (2009)**
  - **P**referred **R**eporting **I**tems for **S**ystematic Reviews and **M**eta-**A**nalyses.
- **QUOROM Statement (1999)**
  - Improving the **Qu**ality **o**f **R**eports **o**f **M**eta-analyses of Randomized Controlled Trials
- **Moose Statement (2000)**
  - **M**eta-analysis **o**f **O**bservational **S**tudies in **E**pidemiology

Step 6: Assessment of Methodological Quality

- Cochrane criteria for judging risk of bias in RCTs
  - Sequence generation
  - Allocation concealment
  - Blinding of participants and personnel
  - Incomplete outcome data
  - Selective outcome reporting
- Judgment

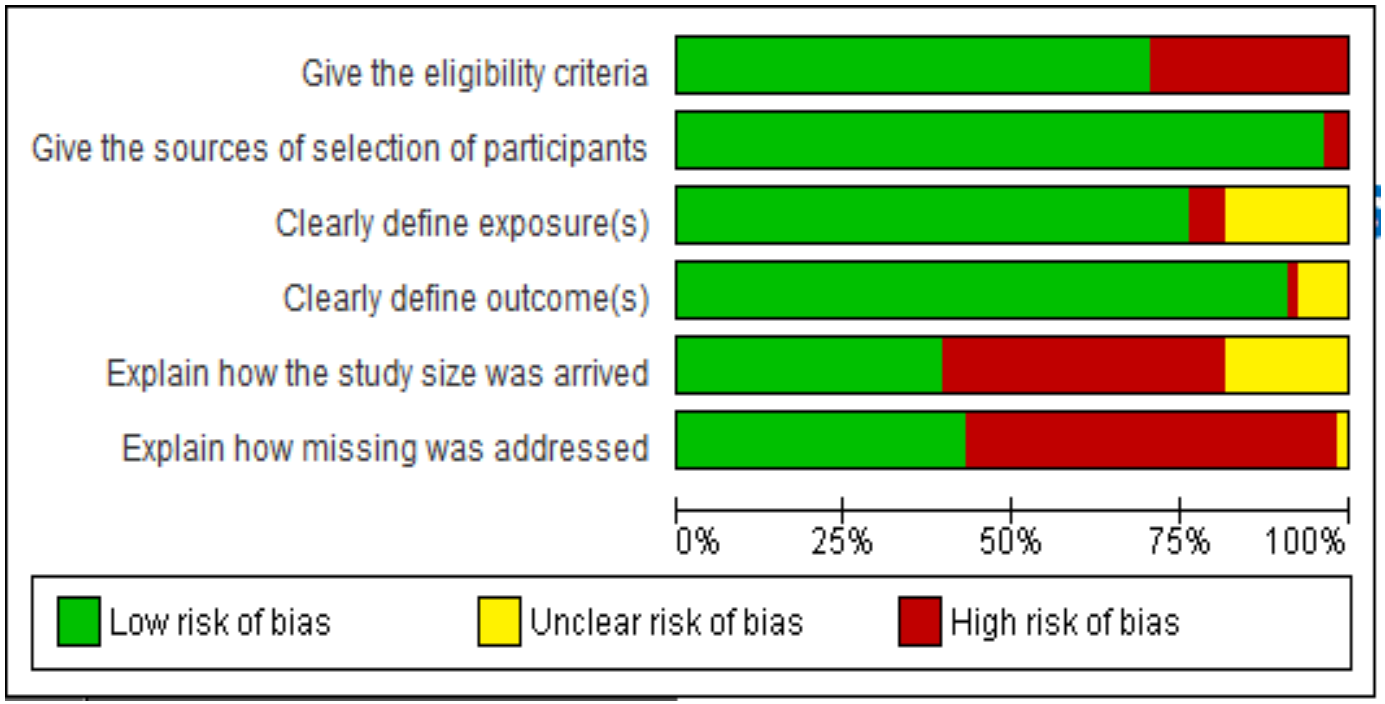
Low Risk
High Risk
Unknown

Step 6: Assessment of Methodological Quality

- **Example**
  - The risk of bias in included studies will be assessed by two authors independently using the risk of bias tool.
  - Any disagreements will be resolved through discussion among the authors until consensus is reached.

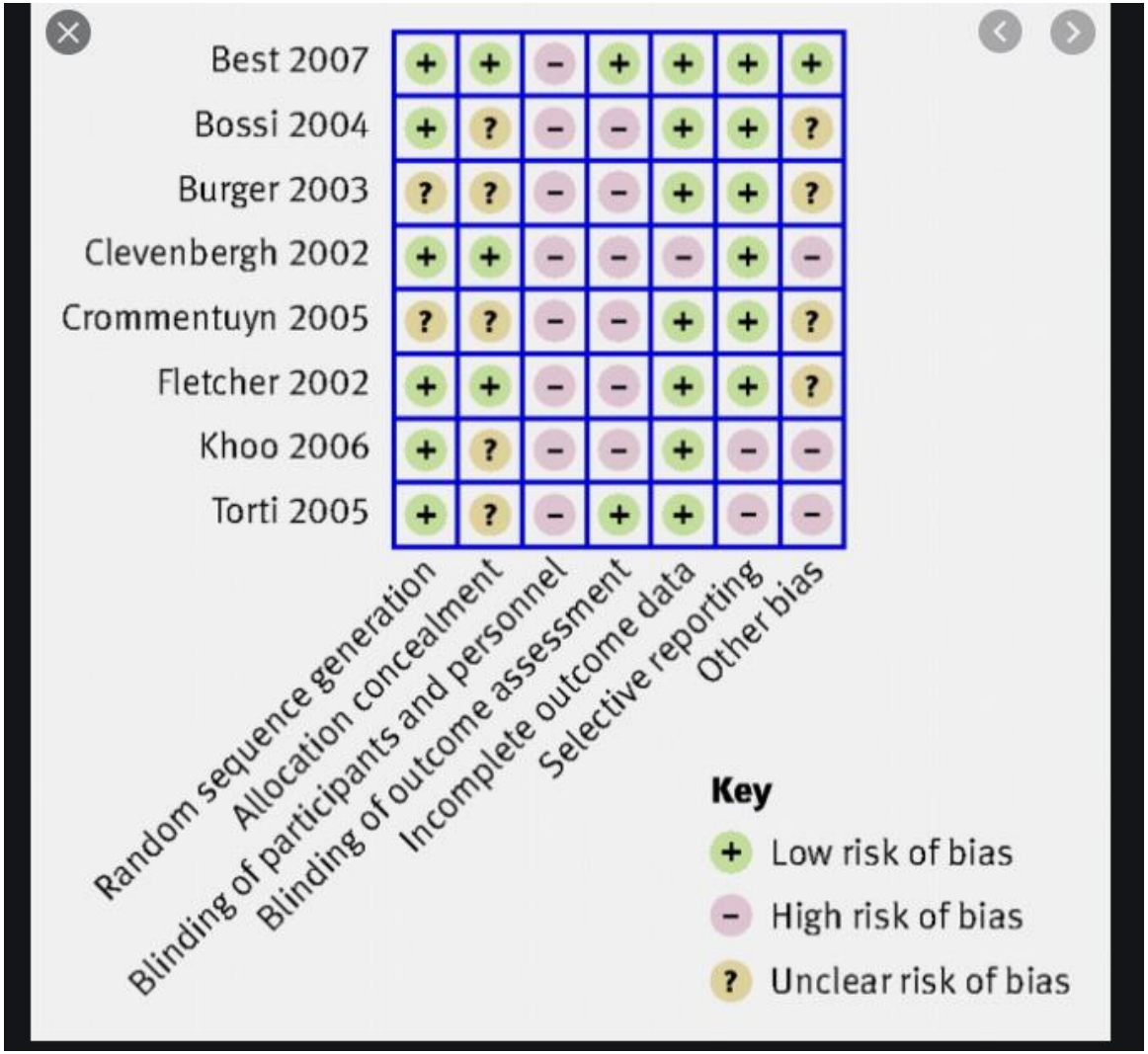
Step 6: Assessment of Methodological Quality

Risk of bias graph



Step 6: Assessment of Methodological Quality

Risk of bias summary



Step 7: Measure of Treatment/ Risk Effect

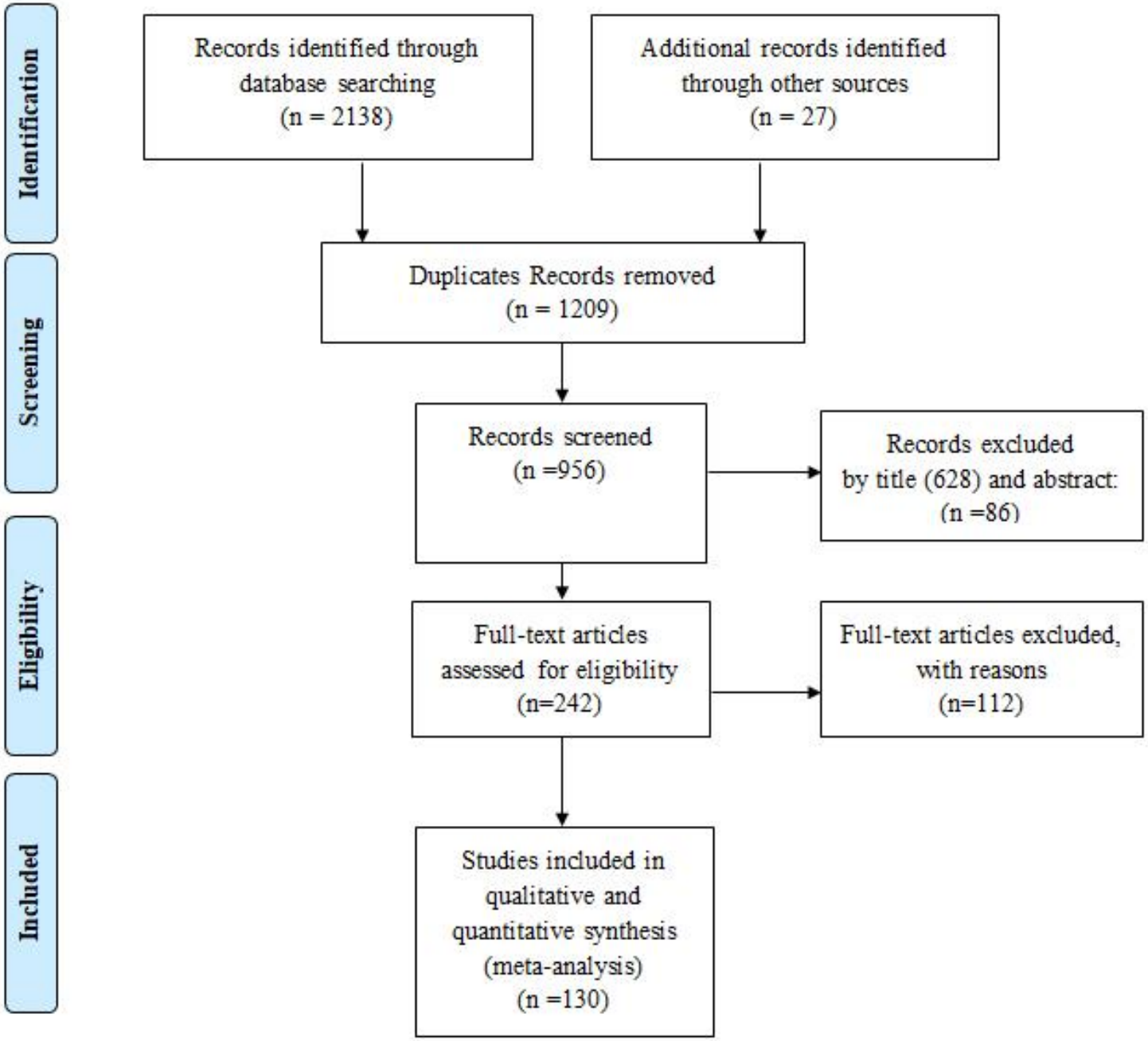
- The effect measures of choice should be stated.
  - Dichotomous data
    - Risk Ratio (RR)
    - Odds Ratio (OR)
    - Risk Difference (RD)
  - Continuous data
    - Mean Difference (MD)
    - Standardized Mean Difference (SMD)
  - Count data
    - Rate Ratio (RR)
  - Time-to-event data
    - Hazard Ratio

Step 7: Measure of Treatment/ Risk Effect

- **Example**
  - The effect measure of choice for dichotomous outcome was risk ratio (RR).
  - The effect measure of choice for continuous outcome was mean difference (MD).
  - All estimates were reported with 95% confidence interval (CI)

Step 8: Data Synthesis

- One goal of a meta-analysis will often be to estimate the overall, or combined effect.
- If all studies in the analysis were equally precise we could simply compute the mean of the effect sizes.
- However, some studies were more precise than others.
- Therefore, in meta-analysis, we compute a weighted mean, with more weight given to the studies that carried more information and less weight given to others.


Identification
Screening
Eligibility
Included
Records identified through database searching (n = 2138)
Additional records identified through other sources (n = 27)
Duplicates Records removed (n = 1209)
Records screened (n =956)
Records excluded by title (628) and abstract: (n =86)
Full-text articles assessed for eligibility (n=242)
Full-text articles excluded, with reasons (n=112)
Studies included in qualitative and quantitative synthesis (meta-analysis) (n =130)

Also Note Biases

- Publication Bias
- Fulltext Bias
- Language Bias
- Database Bias
- …
- …

Publication Bias

- "Publication bias refers to the greater likelihood that studies with positive results will be published"

- *JAMA* 2002;287:2825-2828

Publication Bias

- Positive trials are more likely to be submitted for publication
- Positive trials are more likely to be published
- Positive trials are more likely to be published quickly

- Stern and Simes *BMJ 1997;*315:640-645

Publication Bias

- Sterling study: 97% of papers published in 4 psychology journals showed statistically significant results at alpha level 5% !
- Dickersin study: compared published RCTs with unpublished ones .results:55%pub,15% unpub, favoring new therapy!
- Mahoney stuD:75 reviewers asked to review different versions of a fictitious manuscript. ”introduction” & ”methods” : identical, ”results” & “discussion” : different (+/ambiguous /-). results of reviewers evaluation : manuscripts with “positive” results received higher average scores!

Publication Bias

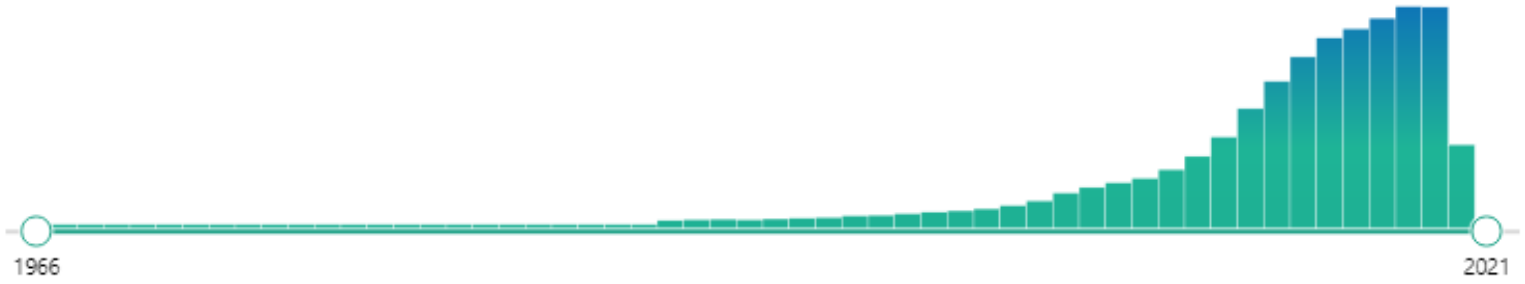
- 1)…if they had reached sig.
- 2) positive result
- 3) interesting results for both reviewers & authors!
- 4) language bias (ENG) in being included in a meta-analysis.

How to Bypass Publication Bias

- Searching Libraries for Thesis & Research Reports
- Searching Registries
- Searching Grey Literature
- Searching especial Journals like:

"*Journal of Negative results in Biomedicine*"

Meta Analysis



Software

- Review Manager 5
- Stata
- Comprehensive Meta-analysis
- Metanalysis
- Metawin

What is Meta Analysis?

- Meta-analysis is a statistical technique for combining the results of independent, but similar, studies to obtain an overall estimate of treatment effect.
- While all meta-analyses are based on systematic review of literature, not all systematic reviews necessarily include meta-analysis.
- Meta-analysis is a weighted mean. More weighting given to precise studies.

Blood Pressure

- BP mean in Tehran: 120
- BP mean in Shiraz: 130

Simple mean: 120 + 130 / 2 = 125

- Is it true??

- Mathematic score = 10

weight : 2

- Chemistry = 15

weight : 2

- Physic = 20

weight : 4

Simple mean: 10+15+20 / 3 = 15

Weighted mean: ((10*2) + (15*2) + (20*4))/8 = 16.25

	Study1	Study2	Study 3	Total
Sample	20	10	10	40
Mean	120	125	127	-
Weight	50%	25%	25%	100

Weighted Mean: $\sum$ (wi * mean) / $\sum$wi

Wi = 1/ Variance

Variance = 1/ sample size

- Population: 1000; LC: 100 ➔ Prevalence: 10%; variance: 0.009
- Population: 10000; LC: 1000 ➔ Prevalence: 10%; variance: 0.003
- Population: 100000; LC: 10000 ➔ Prevalence: 10%; variance: 0.0009

Large sample size ➔ get more weight

Point Estimation and Precision

Census VS Sampling

Parameter = Population

Statistics = Sample

شاخص	تعداد	میانگین	واریانس	انحراف معیار	نسبت	همبستگی
آماره	n	$\overline{X}$	S^2	s	$\frac{x}{n}$	r
پارامتر	N	μ	σ^2	σ	P	ρ

Statistics Precision: CI; SE

The age- and sex-standardized prevalence of any type cataract was 57.64% (95% CI: 54.57 to 60.66).

Mean (SE) of BP in woman was 135 (0.0124)

Odds Ratio and Risk Ratio

- 1000 smoker ➔ 500 lung cancer
- 1000 non-smoker ➔ 200 lung cancer

exposure	Lung cancer	
	Yes	No
Smoker	500 (a)	500 (b)
Non-smoker	200 (c)	800 (d)

- a = exposure+ & outcome+
- b = exposure+ & outcome-
- c = exposure- & outcome+
- d = exposure- & outcome-
- Odds in smoker = (number of event/ number of no-event) OR (a/b) = 500/500 = 1
- Odds in non-smoker = (number of event/ number of no-event) OR (c/d) = 200/800 = 0.25
- Odds ratio = Odds in smoker / Odds in non-smoker OR (a/b)/ (c/d) = 1/0.25= 4
- OR = (a/b)/ (c/d) = (a*d) / (b*c) = (500 * 800) / (200*500) = 4

Odds Ratio and Risk Ratio

- 1000 smoker ➔ 500 lung cancer
- 1000 non-smoker ➔ 200 lung cancer

exposure	Lung cancer	
	Yes	No
Smoker	500 (a)	500 (b)
Non-smoker	200 (c)	800 (d)

- a = exposure+ & outcome+
- b = exposure+ & outcome-
- c = exposure- & outcome+
- d = exposure- & outcome-
- risk in smoker = (number of event/ total number of smoker) OR (a/a+b) = 500/1000 = 0.5
- risk in non-smoker = (number of event/ total number of non-smoker) OR (c/c+d) = 200/1000 = 0.2
- risk ratio = risk in smoker / risk in non-smoker OR (a/a+b) / (c/c+d) = 0.5/0.2= 2.5

- OR & RR > 1 ➔ exposure is risk factor
- OR & RR = 1 ➔ exposure have no effect
- OR & RR < 1 ➔ exposure is protective factor

- the odds of lung cancer were 4 times higher in smoker compared non-smoker

the odds ratio between the smoking and lung cancer was 4

- the risk of lung cancer were 2.5 times higher in smoker compared non-smoker

the risk ratio between the smoking and lung cancer was 4

Standard error and CI

- SE of Prevalence ➔ $\sqrt{\frac{pq}{n}}$
- 95% CI: prevalence ± (1.96 * $\sqrt{\frac{pq}{n}}$)

- SE of Mean ➔ $\frac{s}{\sqrt{n}}$
- 95% CI: Mean ± (1.96 * $\frac{s}{\sqrt{n}}$)

- SE of Mean difference➔ $\sqrt{\frac{s2}{n} + \frac{s2}{n}}$
- 95% CI: Mean difference ± (1.96 * $\sqrt{\frac{s2}{n} + \frac{s2}{n}}$)

Standard error and CI

$$SE(\log(OR)) = \sqrt{\frac{1}{a} + \frac{1}{b} + \frac{1}{c} + \frac{1}{d}}$$

$$e^{(\log(OR) \pm [1.96 \times SE(\log(OR))])}$$

$$\text{SE } (\log(RR)) = \sqrt{\left(\frac{1}{a}\right) - \left(\frac{1}{a+b}\right) + \left(\frac{1}{c}\right) - \left(\frac{1}{c+d}\right)}$$

$$e^{\{\log(RR) \pm [1.96 \times SE(\log(RR))]\}}$$

$$95\%\ \text{conf. int.} = \log(OR) \pm 1.96 \times SE(\log(OR))$$

$$SE(\log(OR)) = \sqrt{\frac{1}{992} + \frac{1}{165} + \frac{1}{2260} + \frac{1}{1017}} = \sqrt{0.008494} = 0.092165$$

```
> exp(0.816)
[1] 2.261436
> exp(1.178)
[1] 3.247872
```

$$95\%\ \text{conf. int. for } \log(RR) = \log(RR) \pm 1.96\sqrt{\frac{1-p_1}{n_1 p_1} + \frac{1-p_2}{n_2 p_2}}$$

$$95\%\ \text{confid. int.} = 0.779 \pm 1.96\sqrt{\frac{1-0.305}{3252(0.305)} + \frac{1-0.140}{1182(0.14)}}$$

$$= 0.779 \pm 1.96\sqrt{\frac{0.695}{992} + \frac{0.86}{165}} = (0.628,\ 0.930)$$

```
> exp(0.628)
[1] 1.873859
> exp(0.930)
[1] 2.534509
```

- Prevalence of diabetic in participants was 15% (95% CI: 12 to 17)

- Mean of BP woman was 129 mmHg (95% CI: 121 to 135)

Zero and Alternative hypothesis

Association between gender and BP Iran

H0 ➔ mean of BP in women = mean of BP in men

H1➔ mean of BP in women ≠ mean of BP in men

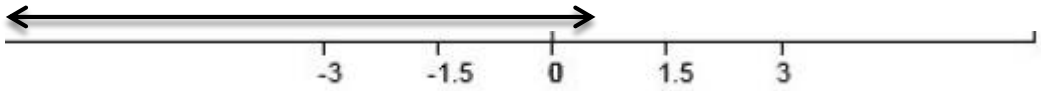
Mean of BP in 100 woman was 110 ± 16

Mean of BP in 100 man was 113 ± 11

$$z = \frac{(\overline{x_1} - \overline{x_2})}{\sqrt{\frac{\sigma_1^2}{n_1} + \frac{\sigma_2^2}{n_2}}}$$

➔ p>0.05

Mean Difference (SE): -3 ± 1.94 (-6.88 to 0.88)



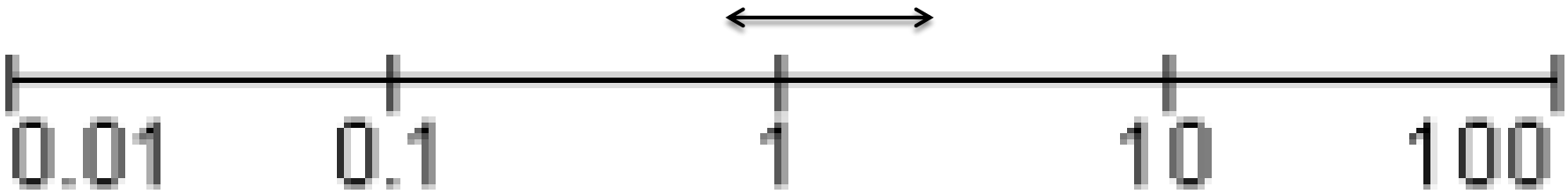
Zero and Alternative hypothesis

Association between smoking and LC Iran

H0 ➔ Odds/Risk in smoking = Odds/Risk in non-smoking

H1➔ Odds/Risk in smoking ≠ Odds/Risk in non-smoking

OR/RR = 1.6 (95% CI: 0.9 to 2.2)



- What is need to extract in studies?

- For main pooling
  - Point estimation (mean, prevalence, OR, RR, HR) and its dispersion (SE & CI)

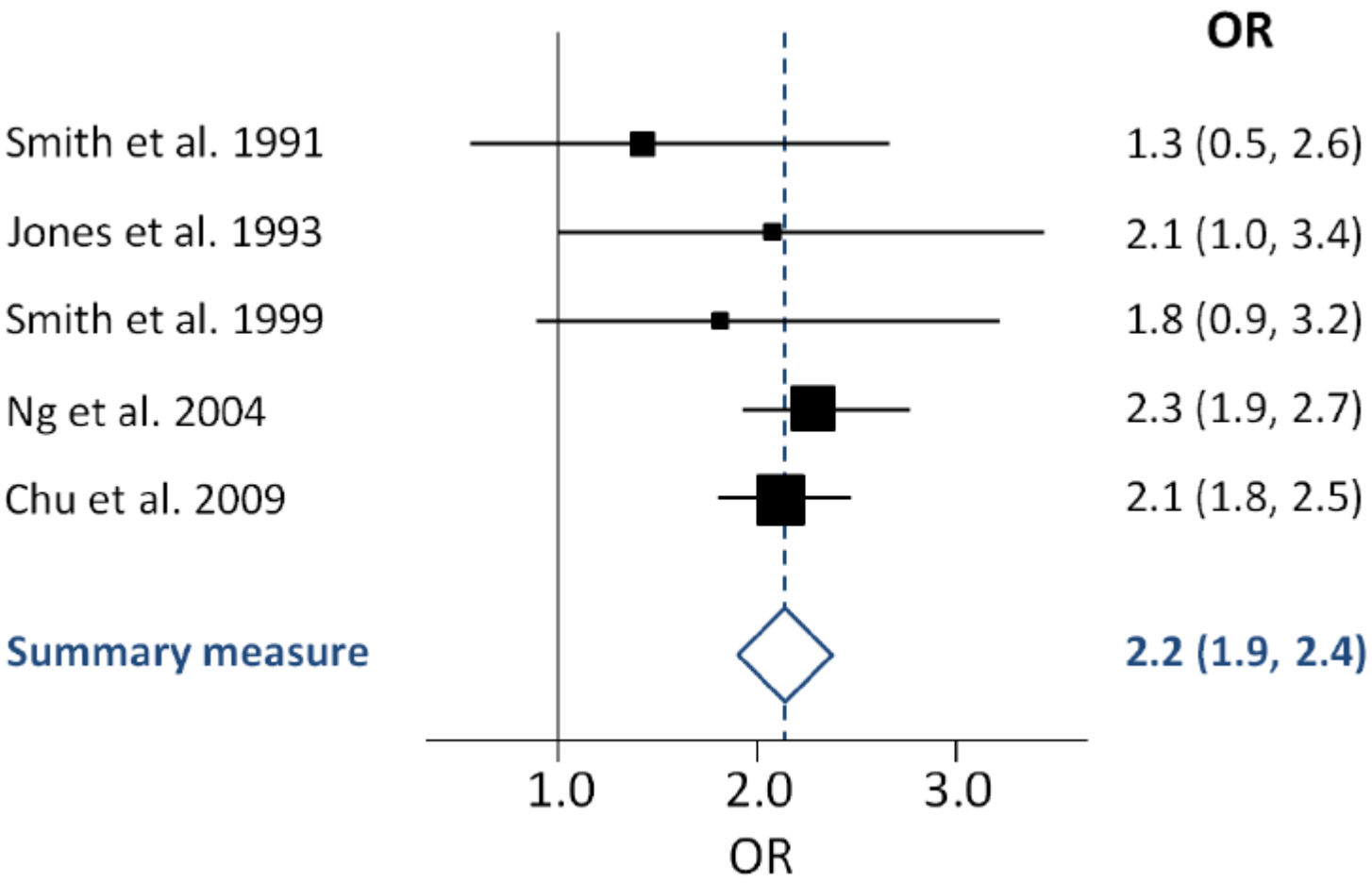
- For complementary analysis
  - Age, sex, year and etc…

Data Synthesis- Forest Plot

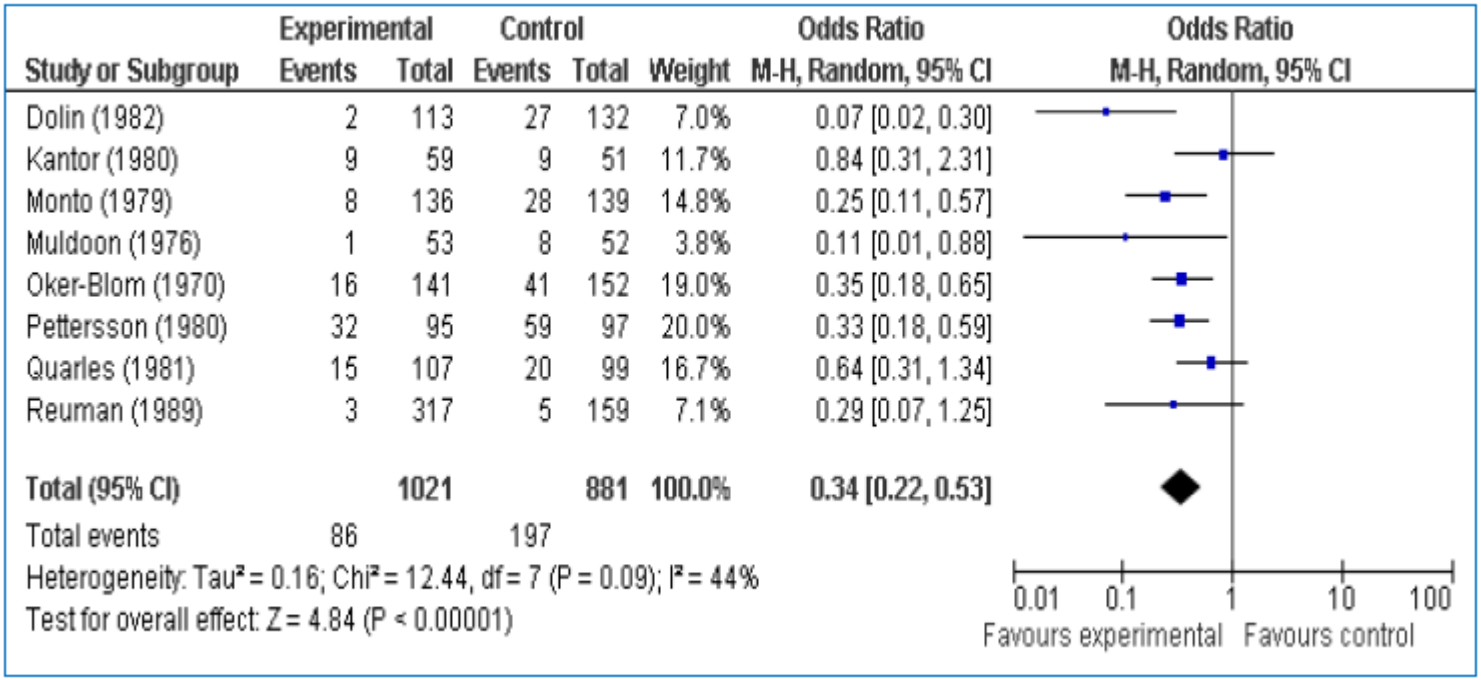
- Square: Point estimate
- Horizontal line: Confidence interval
- Square area: Sample size
- Vertical line: No effect
- Diamond: Summary measure

- If confidence intervals include vertical line, then the difference in the effect of experimental and control groups is not statistically significant at conventional levels.

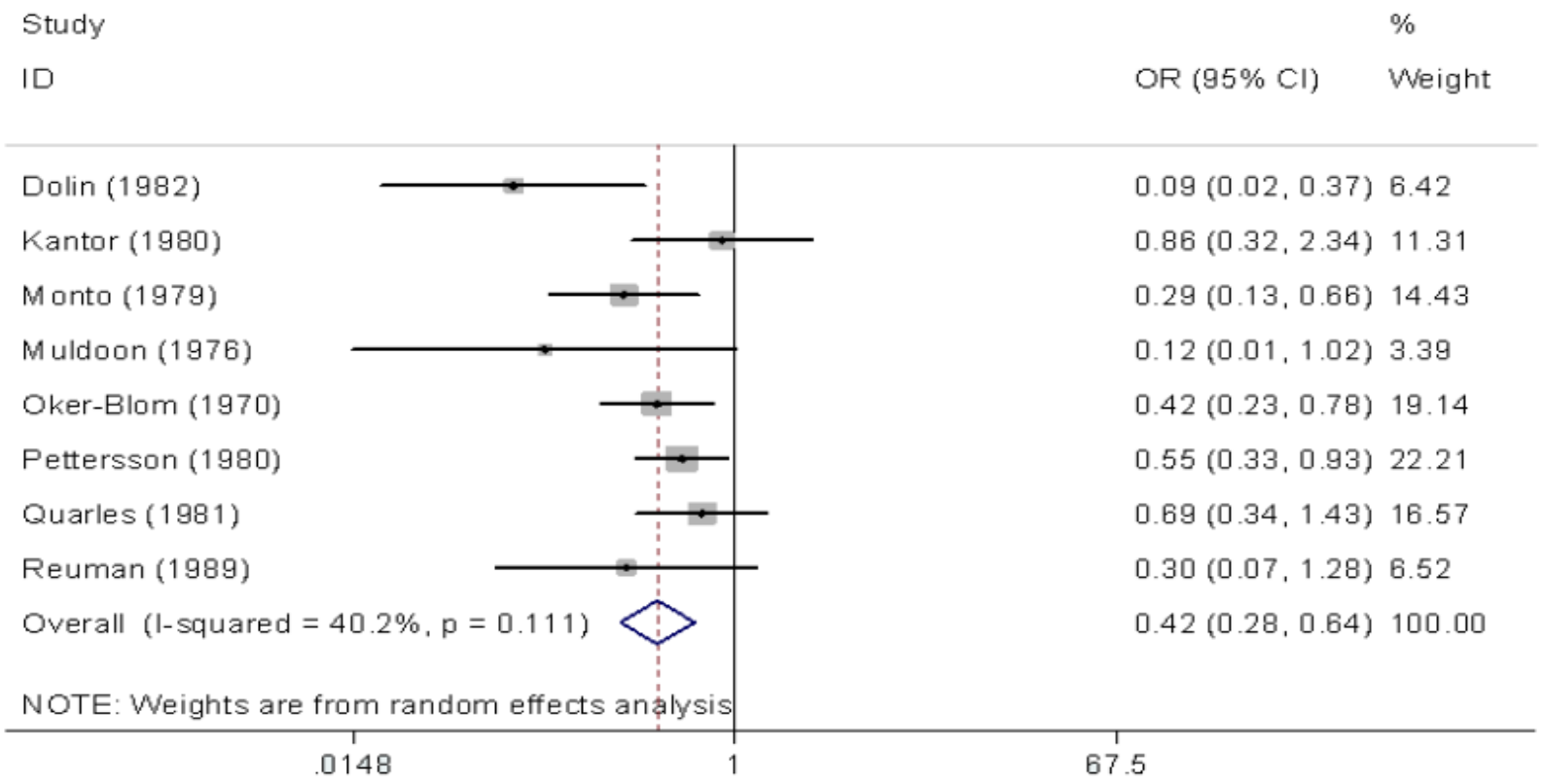
Data Synthesis- Forest Plot



Step 8: Data Synthesis- Forest Plot

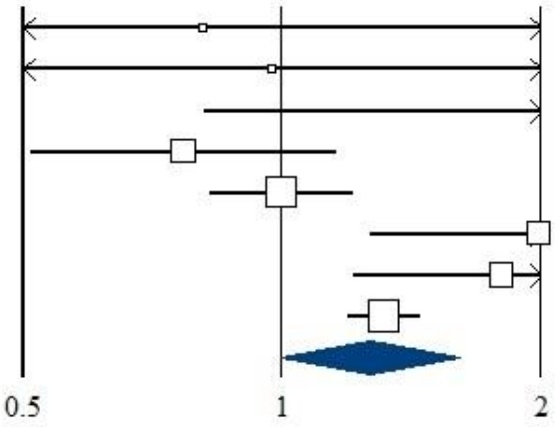


Step 8: Data Synthesis- Forest Plot



Step 8: Data Synthesis- Forest Plot

Study name	Odds ratio	Lower limit	Upper limit	p-Value	Relative weight
Anastasovska 2014	0.81	0.19	3.39	0.772	2.53
Golbahar 2010	0.97	0.20	4.82	0.972	2.06
Mikelsaar 1998	6.74	0.81	56.02	0.077	1.22
Zeinalzadeh 2012	0.77	0.51	1.16	0.207	15.18
Dorreh 2014	1.00	0.82	1.21	1.000	23.33
Mirjana 2015	1.99	1.27	3.12	0.003	13.89
Law 1998	1.80	1.21	2.69	0.004	15.53
Gu 2007	1.31	1.19	1.45	0.000	26.27
	1.27	1.00	1.61	0.053	



Heterogeneity: Q-value = 21.7, df = 7 (*P*=0.003);
I^2 = 67.7%; Tau^2 = 0.05

Data Synthesis

- The choice of meta-analysis method should be stated:
  1. Fixed-effect model
  2. Random-effects model

HIV knowledge

- Fist study: 44%
- Second study: 4.13%
- Third study: 16.2%

What is Pooled Estimate?

- Are the observed estimations are consistent among the included studies? (if not, why?)
- Is a statistical combination of individual effects is feasible?

Fist study was done in addict
Second study was done in primary student
Third study was done in housekeeper woman

fixed-effect model

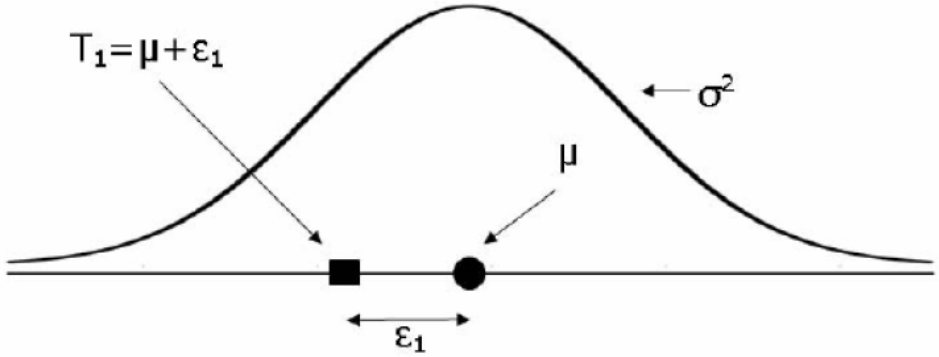
- Under the fixed-effect model we assume that there is **one** true effect size (hence the term fixed effect) which underlies all the studies in the analysis, and that all differences in observed effects are due to sampling error.

- While we follow the practice of calling this a fixed-effect model, a more descriptive term would be a **common-effect model**.

- In either case, we use the singular (effect) since there is only one true effect.

Data Synthesis

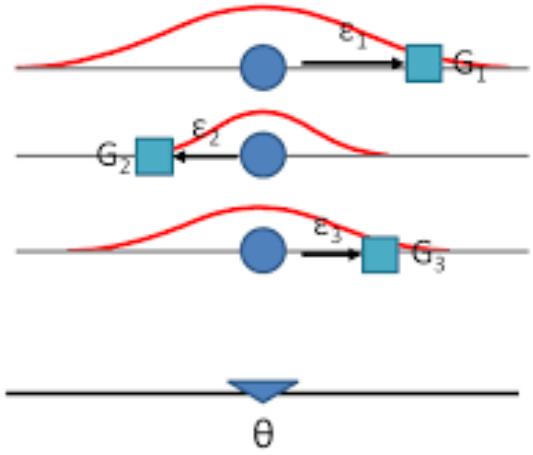
Fixed effect model



Fixed effect model. The observed effects are sampled from a distribution with true effect μ, and variance σ^2. The observed effect T_1 is equal to $\mu+\varepsilon_i$.

$$T_1=\mu+\varepsilon_1$$

The Fixed-Effect Model



Variation Source: Sampling Error

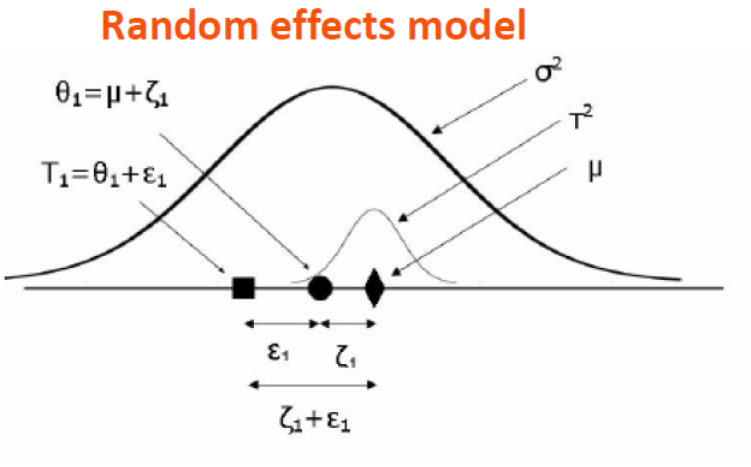
random-effects model

- By contrast, under the random-effects model we allow that the true effect could vary from study to study. Because studies will differ in the mixes of participants and in the implementations of interventions, among other reasons, there may be different effect sizes underlying different studies.

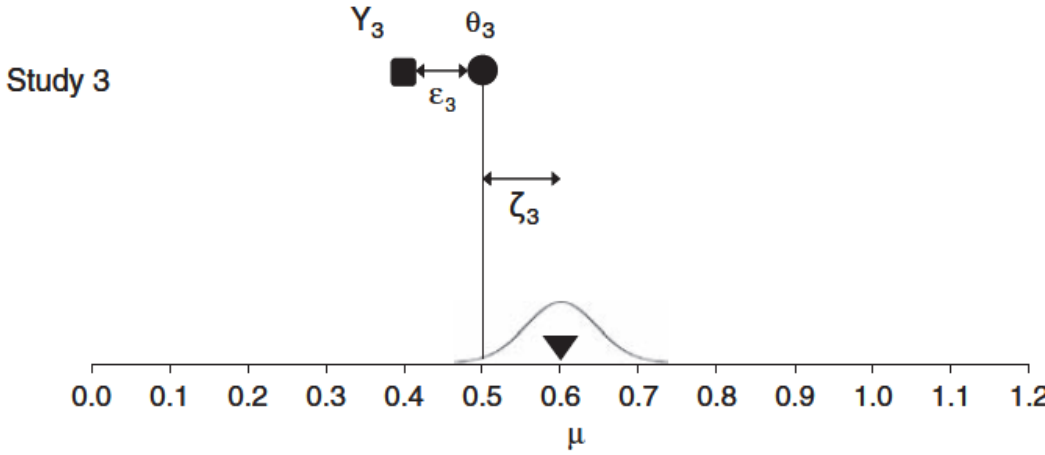
- If it were possible to perform an infinite number of studies (based on the inclusion criteria for our analysis), the true effect sizes for these studies would be distributed about some mean. **The effect sizes in the studies that actually were performed are assumed to represent a random sample of these effect sizes** (hence the term random effects).

- Here, we use the plural (effects) since there is an array of true effects.

Data Synthesis



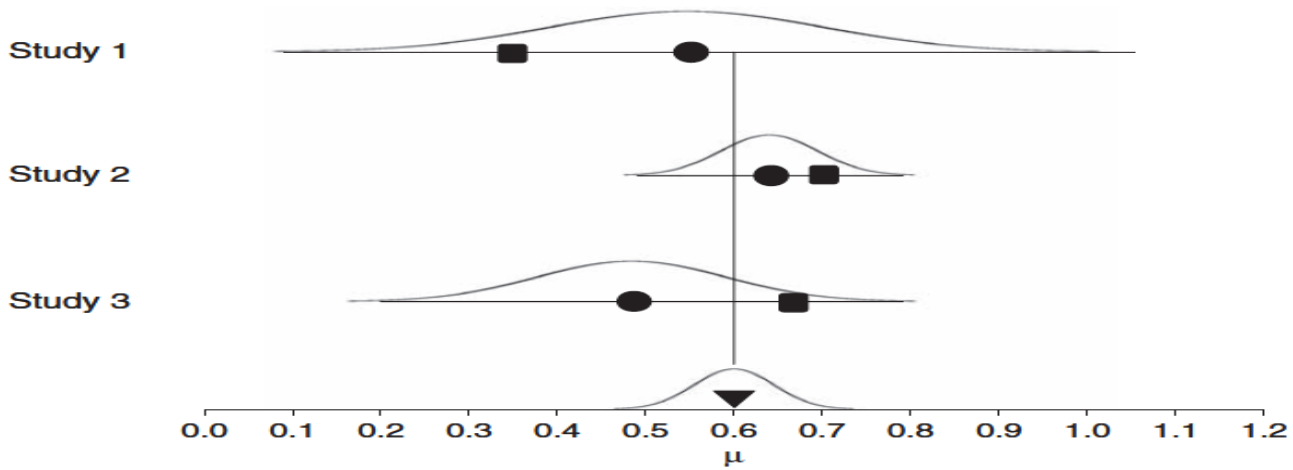
Random effects model. The observed effect T_1 (box) is sampled from a distribution with true effect θ_1, and variance σ^2. This true effect θ_1, in turn, is sampled from a distribution with mean μ and variance τ^2.



$$Y_i = \mu + \zeta_i + \varepsilon_i.$$

Variation Source: Sampling Error + between difference variation

Random-effects model – between-study and within-study variance



- The parameter τ^2 (tau-squared) is the between-studies variance (the variance of the effect size parameters across the population of studies).
- In other words, if we somehow knew the true effect size for each study, and computed the variance of these effect sizes (across an infinite number of studies), this variance would be τ^2.

Data Synthesis

Fixed-effect model

- Under the fixed effect model the only source of error in our estimate of the combined effect is the random error (within studies variance).
- Therefore, with a large enough sample size, the error will tend toward zero.

$$w_i = \frac{1}{v_i}$$

τ^2 (tau-squared) estimation

$$Q = \sum_{i=1}^{k} W_i Y_i^2 - \frac{\left(\sum_{i=1}^{k} W_i Y_i\right)^2}{\sum_{i=1}^{k} W_i},$$

$$df = k - 1,$$

where k is the number of studies, and

$$C = \sum W_i - \frac{\sum W_i^2}{\sum W_i}.$$

One method for estimating τ^2 is the method of moments (or the DerSimonian and Laird) method, as follows. We compute

$$T^2 = \frac{Q - df}{C}, \qquad (12.2)$$

Data Synthesis

Random-effects model

- Under the random effects model there are two levels of sampling and two levels of error and our combined effect depends on both:
  1. the number of subjects within studies (within studies variance)
  2. the total number of studies (between studies variance)

$$w_i^* = \frac{1}{v_i^*} \qquad v_i^* = v_i + T^2$$

Data Synthesis

- **Example**
  - Data were analyzed and the results were reported using a fixed effect model with 95% CI when the results of fixed and random effects models are the same.
  - Otherwise, the random effects models are reported.

Fixed E VS random Es

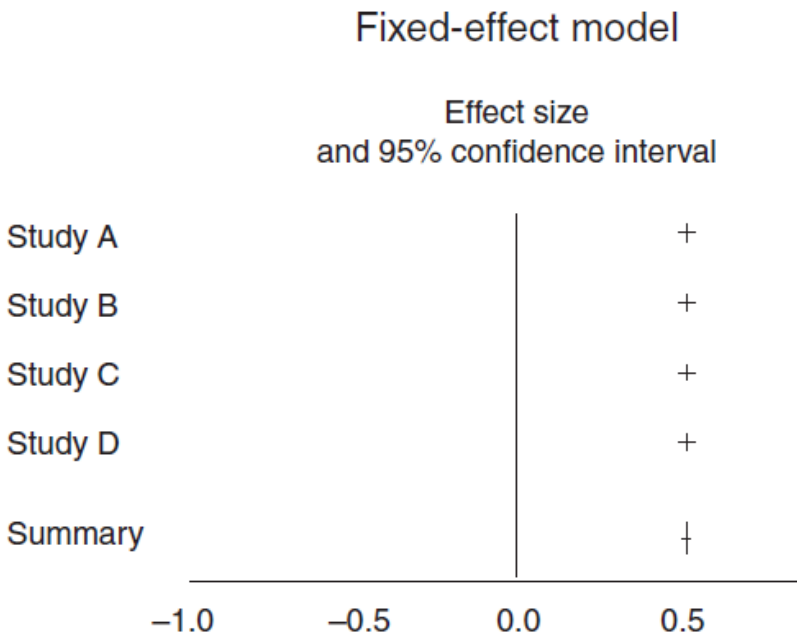
- Under the fixed-effect model there is a wide range of weights (as reflected in the size of the boxes) whereas under the random-effects model the weights fall in a relatively narrow range.
  - ✓ Under the fixed-effect model Donat is given about five times as much weight as Peck. Under the random-effects model Donat is given only 1.8 times as much weight as Peck.

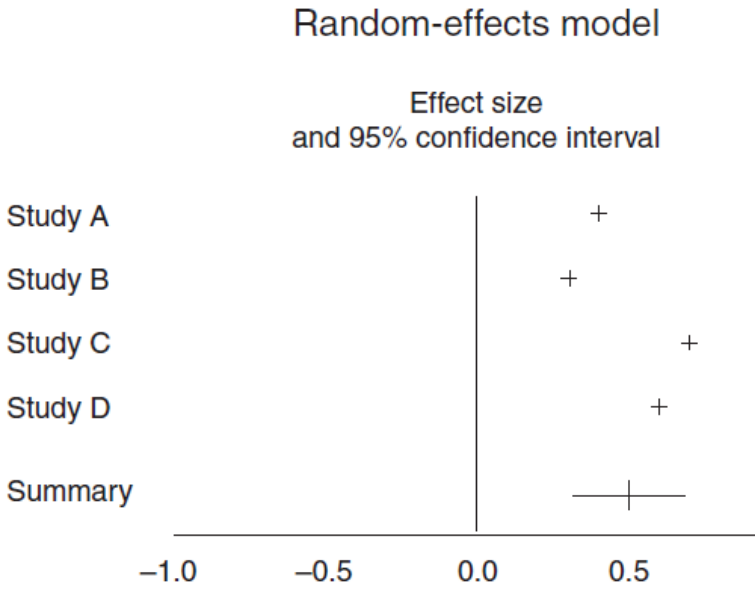
- The operating premise, as illustrated in these examples, is that whenever τ^2 is nonzero, the relative weights assigned under random effects will be more balanced than those assigned under fixed effects.

✓ As we move from fixed effect to random effects, extreme studies will lose influence if they are large, and will gain influence if they are small.

- It follows that the variance, standard error, and confidence interval for the summary effect will always be larger (or wider) under the random-effects model than under the fixed-effect model (unless T2 is zero, in which case the two models are the same).

Very large studies under fixed-effect model





Under the fixed-effect model the standard error of the summary effect is given by

$$SE_M = \sqrt{\frac{\sigma^2}{k \times n}}. \tag{13.1}$$

It follows that with a large enough sample size the standard error will approach zero, and this is true whether the sample size is concentrated on one or two studies, or dispersed across any number of studies.

Under the random-effects model the standard error of the summary effect is given by

$$SE_M = \sqrt{\frac{\sigma^2}{k \times n} + \frac{\tau^2}{k}}. \qquad (13.2)$$

- The first term is identical to that for the fixed-effect model and, again, with a large enough sample size, this term will approach zero. By contrast, the second term (which reflects the between-studies variance) will only approach zero as the number of studies approaches infinity.
- Namely, increasing the sample size within studies is not sufficient to reduce the standard error beyond a certain point. If there is only a small number of studies, then the standard error could still be substantial even if the total n is in the tens of thousands or higher.

Fixed: 1000 = 100 k * 10 n is same 1000 = 10 k * 100 n

random: 1000 = 100 k * 10 n isn't same 1000 = 10 k * 100 n

Random effects

- When the researcher is accumulating data from a series of studies that had been performed by researchers operating independently, it would be unlikely that all the studies were functionally equivalent. Typically, the subjects or interventions in these studies would have differed in ways that would have impacted on the results.

When studies are gathered from the published literature, the random effects model is generally a more plausible match.

Pooling the Data

1: Inverse variance weighting

- ✓ All estimate ➔ P;OR/RR/MD
- ✓ zero event/rare event

$$\overline{X} = \frac{\sum W_i X_i}{\sum W_i}$$

SE of Prevalence ➔ $\frac{pq}{n}$

$$W = 1/\text{var}(OR) = \left[\frac{1}{\frac{1}{a} + \frac{1}{b} + \frac{1}{c} + \frac{1}{d}} \right]$$

CI for rare event ➔

$$\frac{2n\hat{p} + z^2_{1-\frac{\alpha}{2}} - z_{1-\frac{\alpha}{2}}\sqrt{z^2_{1-\frac{\alpha}{2}} + 4n\hat{p}(1-\hat{p})}}{2\left(n + z^2_{1-\frac{\alpha}{2}}\right)} \leq p \leq \frac{2n\hat{p} + z^2_{1-\frac{\alpha}{2}} + z_{1-\frac{\alpha}{2}}\sqrt{z^2_{1-\frac{\alpha}{2}} + 4n\hat{p}(1-\hat{p})}}{2\left(n + z^2_{1-\frac{\alpha}{2}}\right)}.$$

Odds Ratio

1000 smoker ➔ 500 lung cancer

1000 non-smoker ➔ 0 lung cancer

exposure	Lung cancer	
	Yes	No
Smoker	500 (a)	500 (b)
Non-smoker	0 (c)	1000 (d)

OR = (a*d) / (b*c) = (500 * 1000) / (0*500) = ???

exposure	Lung cancer	
	Yes	No
Smoker	500.5 (a)	500.5 (b)
Non-smoker	0.5 (c)	1000.5 (d)

Pooling the Data

2: Mantel – Haenzel Weighting

- Dichotomous
- For small/zero sample size

$$w_i = \frac{b_i c_i}{N_i}$$

$$OR = \frac{\sum (w_i \times OR_i)}{\sum w_i} \rightarrow OR = \frac{\sum (a_i d_i / N_i)}{\sum (b_i c_i / N_i)}$$

Pooling the Data

3. Peto

- Dichotomous
- For small/Zero sample size

$$\exp(a_i) = \frac{(a_i + b_i)(a_i + c_i)}{N_i} \rightarrow \log(OR_i) = \frac{a_i - \exp(a_i)}{Var(a_i)} \rightarrow Var(a_i) = \frac{(a_i + b_i)(a_i + c_i)(d_i + b_i)(d_i + c_i)}{N_i}$$

$$\log(OR) = \frac{\sum\left(w_i \times \log(OR_i)\right)}{\sum w_i} \quad and \quad Var(\log(OR)) = \frac{1}{\sum w_i}$$

نوع داده	شاخص آماری	روش آماری	نوع
دوحالته	نسبت شانس (Odds Ratio)	Woolf	ثابت
		Mantel-Haenzel	ثابت
		Peto	ثابت
		Der simonian-Laird	تصادفی
		Meta-Regression	تصادفی
	خطر نسبی (Risk Ratio)	Mantel-Haenzel	ثابت
		Inverse Variance	ثابت
		Der Simonian-laird	تصادفی
		Meta-Regression	تصادفی
	تفاضل خطر (Risk Difference)	Mantel-Haenzel	ثابت
		Inverse Variance	ثابت
		Der Simonian-laird	تصادفی
		Meta-Regression	تصادفی
عددی	تفاضل میانگین‌ها و یا تفاضل میانگین‌های استاندارد	Inverse Variance	ثابت
		Der Simonian-laird	تصادفی
		Meta-Regression	تصادفی

Assessment of Heterogeneity

1. Chi-squared test
2. I^2 statistic
3. Tau-squared statistic (τ^2 or Tau^2)
4. Galbraith plot (Radial plot)
5. L'Abbe plot
6. Meta-regression

Assessment of Heterogeneity

- **Chi-squared test (χ^2 or Chi^2)**
  - Chi-squared test has low power in the common situation of a meta-analysis when studies have small sample size or are few in number.
    - A statistically significant result may indicate a problem with heterogeneity
    - A non-significant result must not be taken as evidence of no heterogeneity.
  - This is also why a P value of 0.10, rather than the conventional level of 0.05, is sometimes used to determine statistical significance.

$$Q = \sum_{i=1}^{k} W_i Y_i^2 - \frac{\left(\sum_{i=1}^{k} W_i Y_i\right)^2}{\sum_{i=1}^{k} W_i},$$

$$df = k - 1,$$

Assessment of Heterogeneity

I^2 statistic

$$I^2 = \left(\frac{Q - df}{Q} \right) \times 100\%$$

$$T^2 = \frac{Q - df}{C},$$

Cochrane categorization

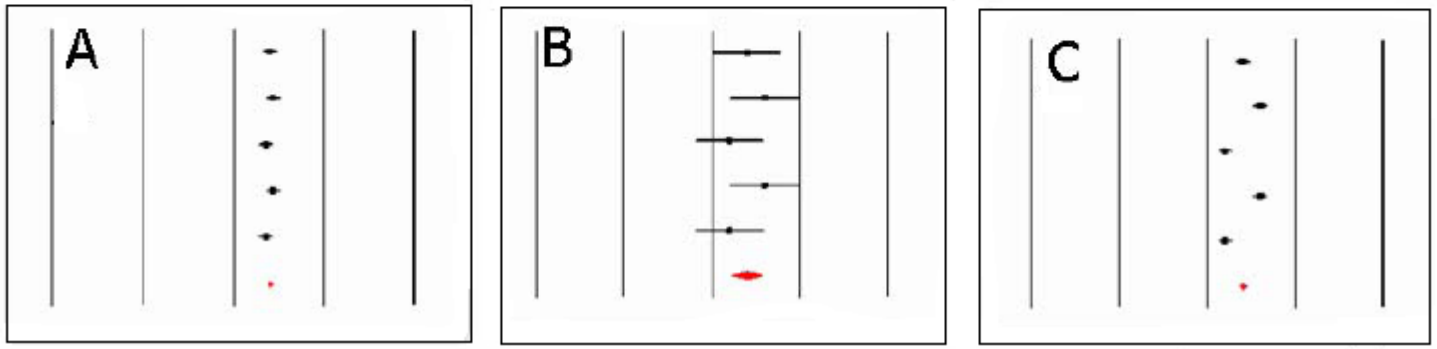
- 0% to 40%: Unimportant
- 30% to 60%: Moderate heterogeneity
- 50% to 90%: Substantial heterogeneity
- 75% to 100%: Considerable heterogeneity

Higgins categorization

- 25%: Low heterogeneity
- 50%: Moderate heterogeneity
- 75%: High heterogeneity

Assessment of Heterogeneity

- **Tau-squared (τ^2 or Tau^2)**
  - between-study variance in a random-effects model
    - A: between-studies variance is low, because total variance is low.
    - B: Between-studies variance is low, because within-studies variance is high.
    - C: between-studies variance is high, because total variance is high and within-studies variance is low.



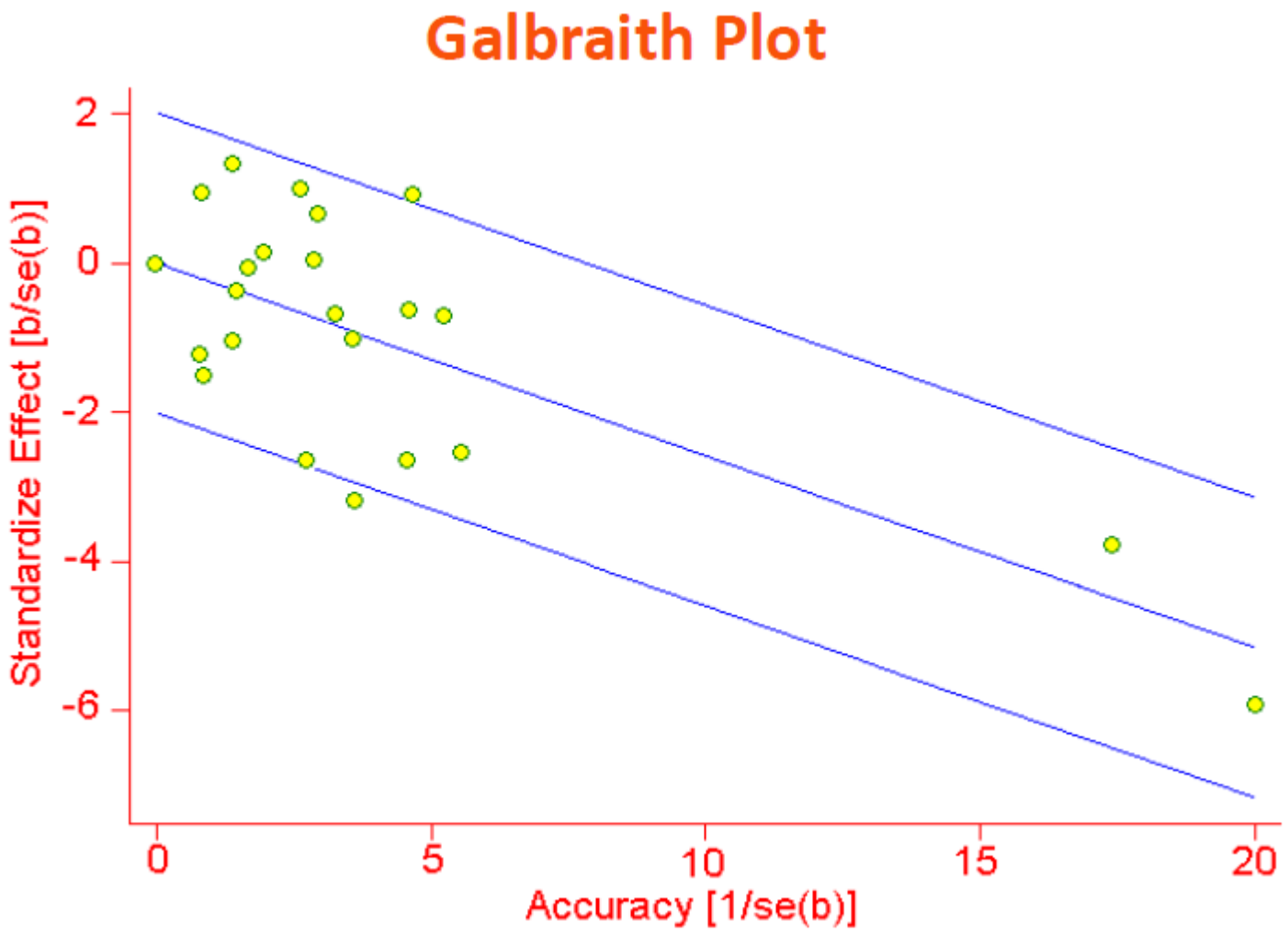
Assessment of Heterogeneity

- **Example**
  - The statistical heterogeneity was explored using the chi-squared test at the 10% significance level ($P<0.10$).
  - The inconsistency across studies results was quantified using I^2 statistic.
  - In addition, the between-study variance was estimated using tau-squared.

Assessment of Heterogeneity

- **Galbraith plot (Radial plot)**
  - Regression line constrained through the origin, with its 95% CI.
    - Y axis: θ/se (z statistic)
    - X axis: 1/se
    - Slope: log OR, RR or HR in a fixed effect model.
    - The position of each trial on the horizontal axis indicates its allocated weight (small trials on the left and large trials on the right)
  - In the absence of heterogeneity we could expect all the points to lie within the confidence bounds.

Assessment of Heterogeneity



Assessment of Heterogeneity
Meta-regression

- Meta-regression is used to explore
  - sources of heterogeneity
  - associations between treatment effects and other covariates

Assessment of Heterogeneity

BCG vaccination for preventing tuberculosis

trial	author	year	latitude	a	b	c	d	logrr	selogrr
1	Ferguson	1933	55	6	300	29	274	-1.59	0.44
2	Aronson	1935	52	4	119	11	128	-0.89	0.57
3	Stein	1935	52	180	1361	372	1079	-0.79	0.08
4	Rosenthal	1937	42	17	1699	65	1600	-1.37	0.27
5	Rosenthal	1941	42	3	228	11	209	-1.35	0.64
6	Comstock	1947	33	5	2493	3	2338	0.45	0.73
7	Comstock	1949	18	186	50448	141	27197	-0.34	0.11
8	Hart	1950	53	62	13536	248	12619	-1.44	0.14
9	Frimont-Moller	1950	13	33	5036	47	5761	-0.22	0.23
10	Comstock	1950	33	27	16886	29	17825	-0.02	0.27
11	Vandeviere	1965	18	8	2537	10	619	-1.62	0.47
12	Coetzee	1965	27	29	7470	45	7232	-0.47	0.24
13	TB prevention trial	1968	13	505	87886	499	87892	0.01	0.06

Assessment of Heterogeneity

Meta-Analysis & Meta-Regression

Meta-analysis (exponential form)

Method	Pooled Est	95% CI Lower	95% CI Upper	Asymptotic z_value	Asymptotic p_value	No. of studies
Fixed	0.647	0.595	0.702	-10.319	0.000	13
Random	0.474	0.325	0.690	-3.887	0.000	

Method	Pooled Est	95% CI Lower	95% CI Upper	Asymptotic z_value	Asymptotic p_value	No. of studies
Fixed	-0.436	-0.519	-0.353	-10.319	0.000	13
Random	-0.747	-1.124	-0.371	-3.887	0.000	

Test for heterogeneity: Q= 163.165 on 12 degrees of freedom (p= 0.000)
Moment-based estimate of between studies variance = 0.366

Meta-regression
REML estimate of between-study variance
% residual variation due to heterogeneity
With Knapp-Hartung modification

Number of obs = 13
tau2 = .3378
I-squared_res = 92.65%

logor	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
_cons	-.7451778	.1867262	-3.99	0.002	-1.152019	-.3383363

Assessment of Heterogeneity

Meta-Regression

Meta-regression
REML estimate of between-study variance
% residual variation due to heterogeneity
Proportion of between-study variance explained
Joint test for all covariates
With Knapp-Hartung modification

Number of obs	= 13
tau2	= .1357
I-squared_res	= 69.20%
Adj R-squared	= 59.82%
Model F(2,10)	= 4.46
Prob > F	= 0.0413

logor	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
year	-.0030306	.0178584	-0.17	0.869	-.0428217	.0367605
latitude	-.0282374	.0129503	-2.18	0.054	-.0570925	.0006177
_cons	6.125588	35.12686	0.17	0.865	-72.14193	84.3931

- In 1950 and Latitude 50°
- Log OR = 6.125588 – (1950×0.0030306) – (50×0.0282374) = -1.1959521
- OR = exp(-1.1959521) = 0.30

Assessment of Reporting Biases

1. Funnel plot
2. Begg adjusted rank correlation
3. Egger regression asymmetry test
4. Trim & Fill

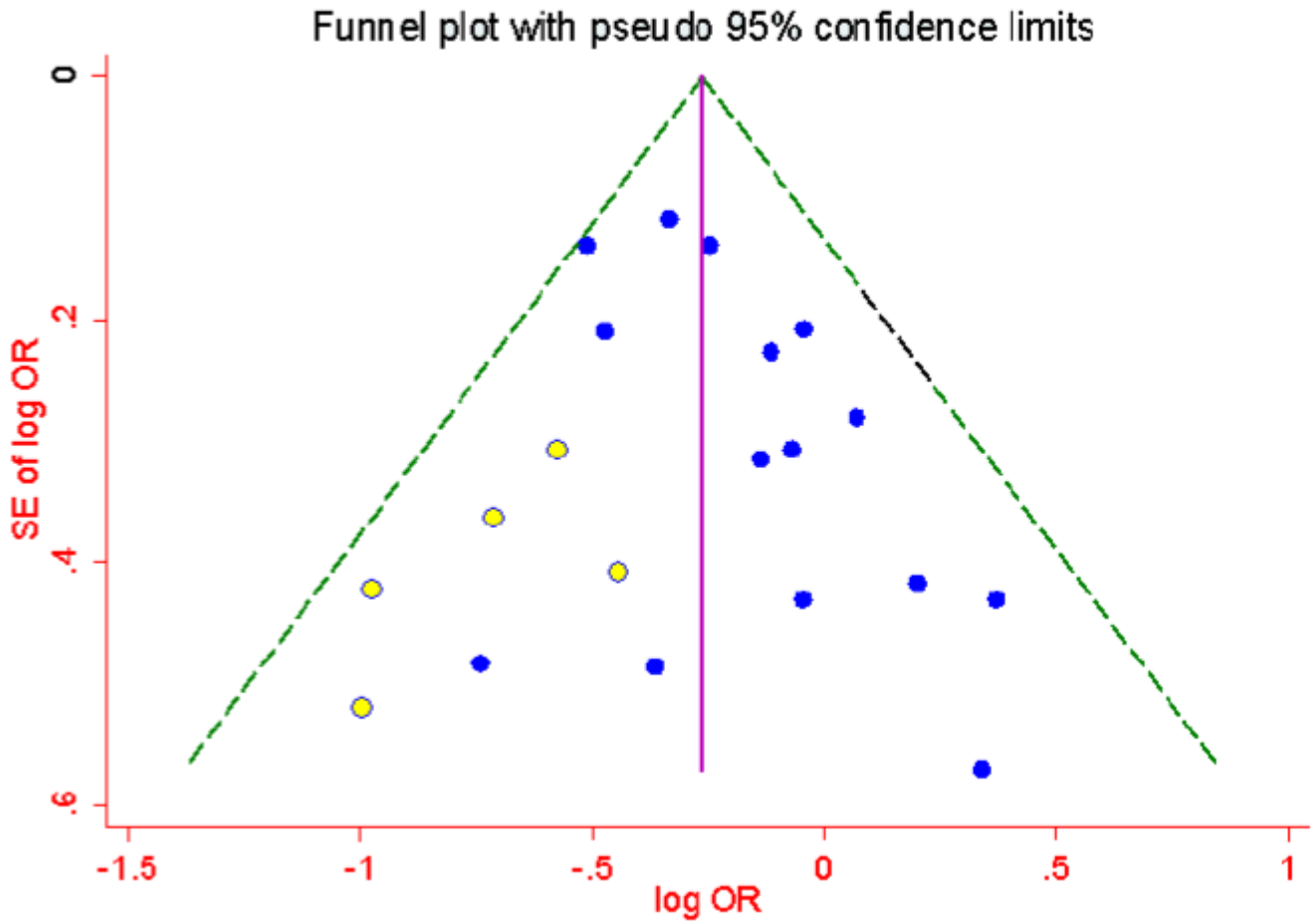
Assessment of Reporting Biases

Funnel plot

- A funnel plot is a simple scatter plot of the intervention effect estimates against study's size or precision.
  - X axis: the effect estimates
  - Y axis: the measure of study size
- Effect estimates from small studies scatter more widely at the bottom of the graph, with the spread narrowing among larger studies.
- In the absence of bias the plot should resemble a symmetrical (inverted) funnel.

Assessment of Reporting Biases

Funnel plot



Assessment of Reporting Biases

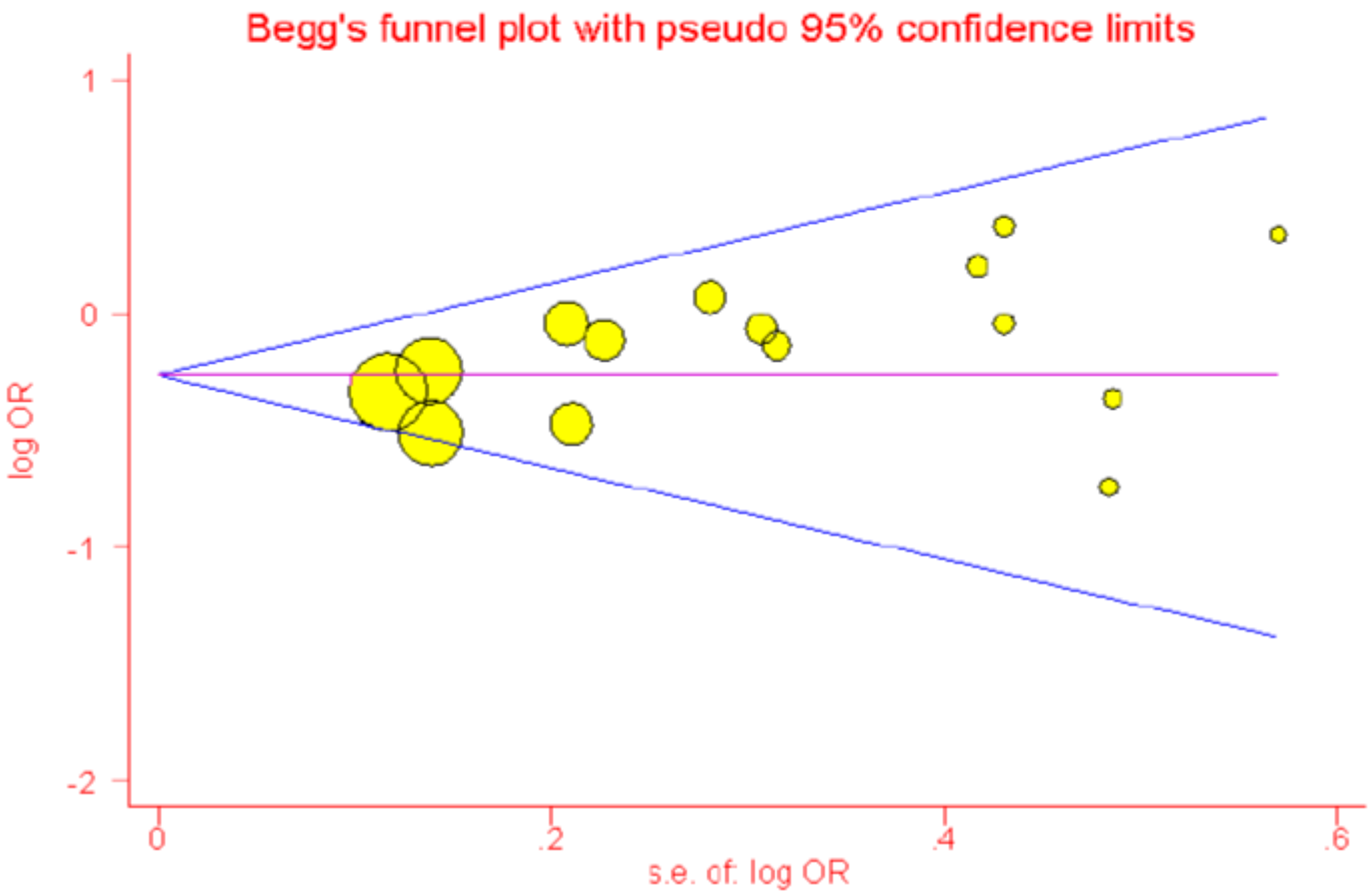
Begg adjusted rank correlation

- It is a direct statistical analogue of the funnel plot performing an adjusted rank correlation test based on Kendall's tau (ρ).
  - *P*>0.05: no publication bias
  - *P*<0.05: publication bias

```
Begg's Test

  adj. Kendall's Score (P-Q) =      21
         Std. Dev. of Score =   20.21
          Number of Studies =      15
                          z  =    1.04
                    Pr > |z| =   0.299
                          z  =    0.99 (continuity corrected)
                    Pr > |z| =   0.322 (continuity corrected)
```

Assessment of Reporting Biases

Begg's plot



Assessment of Reporting Biases

Egger regression asymmetry test

- This test regresses the standardized effect estimates against their precision.
- If intercept deviates significantly from zero and confidence interval about the intercept fails to include zero indicates asymmetry in the funnel plot.

Egger's test

Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	-.4823081	.1086472	-4.44	0.001	-.7170261	-.2475902
bias	1.114582	.4891211	2.28	0.040	.0579	2.171264

Assessment of Reporting Biases

Metatrim

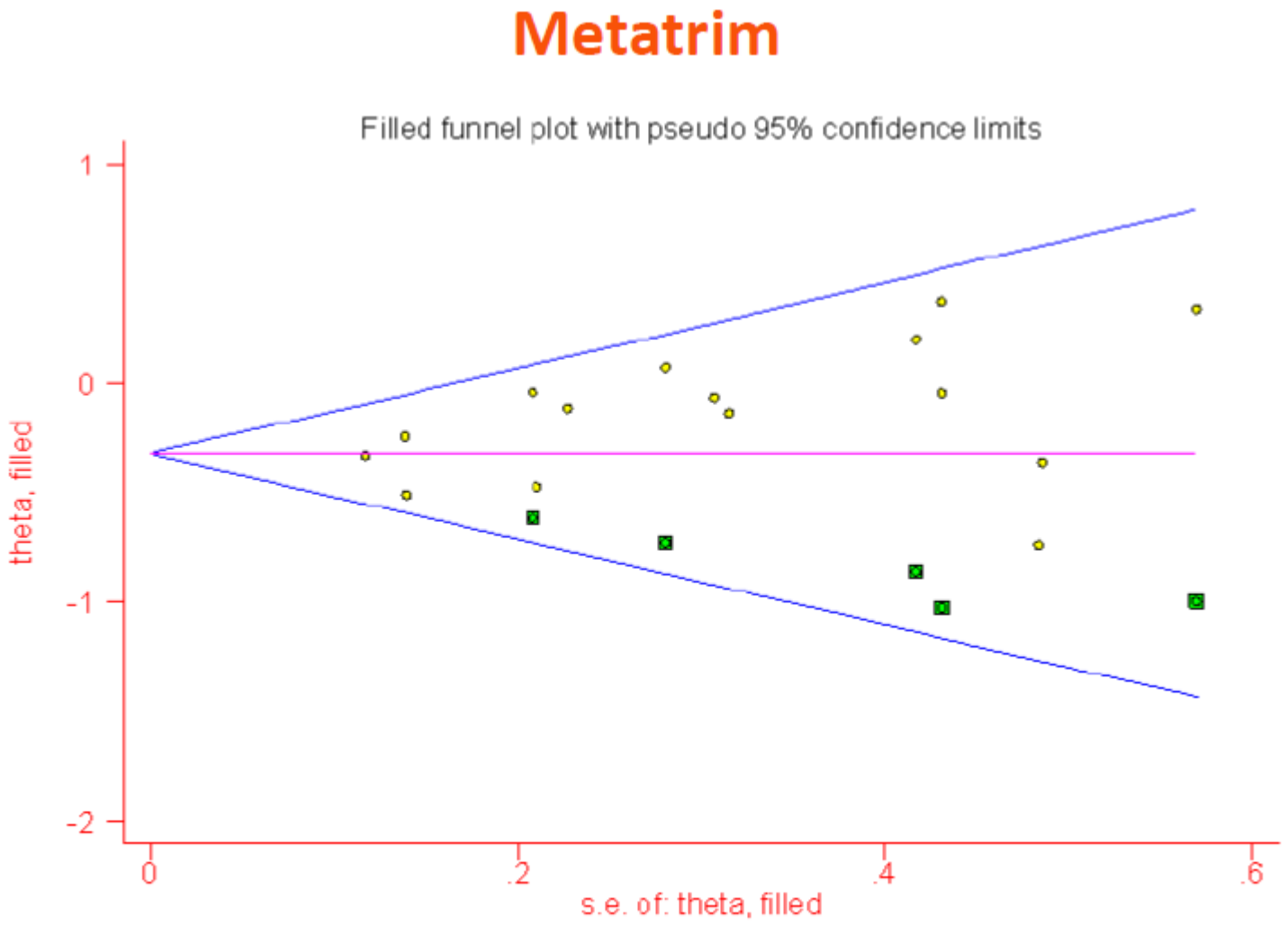
- The method estimates the number and outcomes of missing studies and adjusts the meta-analysis to incorporate the theoretical missing studies.
- As an option, metatrim provides a funnel graph of the filled data.

Assessment of Reporting Biases

Metatrim

```
Meta-analysis

        |  Pooled       95% CI          Asymptotic       No. of
Method  |     Est    Lower    Upper   z_value  p_value   studies
--------+-------------------------------------------------------
Fixed   |  -0.263   -0.375   -0.150    -4.581    0.000      15
Random  |  -0.263   -0.375   -0.150    -4.581    0.000

Test for heterogeneity: Q= 13.942 on 14 degrees of freedom (p= 0.454)
Moment-based estimate of between studies variance =  0.000

Trimming estimator: Linear
Meta-analysis type: Random-effects model

iteration |  estimate    Tn    # to trim     diff
----------+-----------------------------------
    1     |   -0.263     85         3         120
    2     |   -0.290     90         4          10
    3     |   -0.307     94         5           8
    4     |   -0.331     96         5           4
    5     |   -0.331     96         5           0

Filled
Meta-analysis

        |  Pooled       95% CI          Asymptotic       No. of
Method  |     Est    Lower    Upper   z_value  p_value   studies
--------+-------------------------------------------------------
Fixed   |  -0.331   -0.435   -0.226    -6.221    0.000      20
Random  |  -0.323   -0.454   -0.191    -4.814    0.000

Test for heterogeneity: Q= 24.949 on 19 degrees of freedom (p= 0.162)
Moment-based estimate of between studies variance =  0.019
```

Assessment of Reporting Biases



Sensitivity Analysis

- The potential impact of the missing data on the results should be considered in the interpretation of the results of the review.
- Sensitivity analysis for dichotomous outcomes
  - Best-case scenarios
  - Worst-case scenarios

Sensitivity Analysis

- **Metainf**
  - This method investigates the influence of a single study on the overall meta-analysis estimate.
  - This command shows the results of an influence analysis, in which the meta-analysis estimates are computed omitting one study in each turn.

Sensitivity Analysis

Metainf Analysis

Study ommited	e^coef.	[95% Conf.	Interval]
Fletcher 1959	.78536546	.69640136	.88569456
Dewar 1963	.78565162	.69409162	.88928962
1st European 1969	.77083343	.6846385	.86788017
Heikinheimo 1971	.7714709	.68329889	.87102062
Italian 1971	.77686858	.68536782	.88058531
2nd European1971	.79687357	.70091492	.90596944
2nd Frankfurt1973	.79471207	.70822829	.89175659
1st Australian 1973	.78423995	.68998003	.89137697
NHLBI SMIT 1974	.77551377	.68975067	.87194061
Valere 1975	.77927077	.68790686	.88276905
Frank 1975	.78119284	.68936247	.88525605
UK Collaborative 1976	.77725375	.68318355	.88427681
Klein 1976	.77954084	.69061023	.87992311
Austrian 1977	.79831713	.70553684	.90329832
Lasierra 1977	.7849502	.69472808	.88688916
N German 1977	.76074833	.67770356	.85396922
Witchitz 1977	.78291738	.69078761	.88733441
2nd Australian 1977	.78208435	.68848521	.8884083
3rd European 1977	.79927272	.71484172	.89367604
ISAM 1986	.77630609	.68161374	.88415349
GISSI-1 1986	.78178149	.66964346	.91269809
ISIS-2 1988	.79287457	.67843443	.92661875
Combined	.78249226	.69266409	.88396979

Subgroup Analysis

- Subgroup analyses may be done often so as to make comparisons between:
  - subsets of participants (sex, age groups)
  - types of studies
  - types of interventions
  - different geographical locations
- Subgroup analyses may be done:
  - to investigate heterogeneous results
  - to answer specific questions about particular patient groups

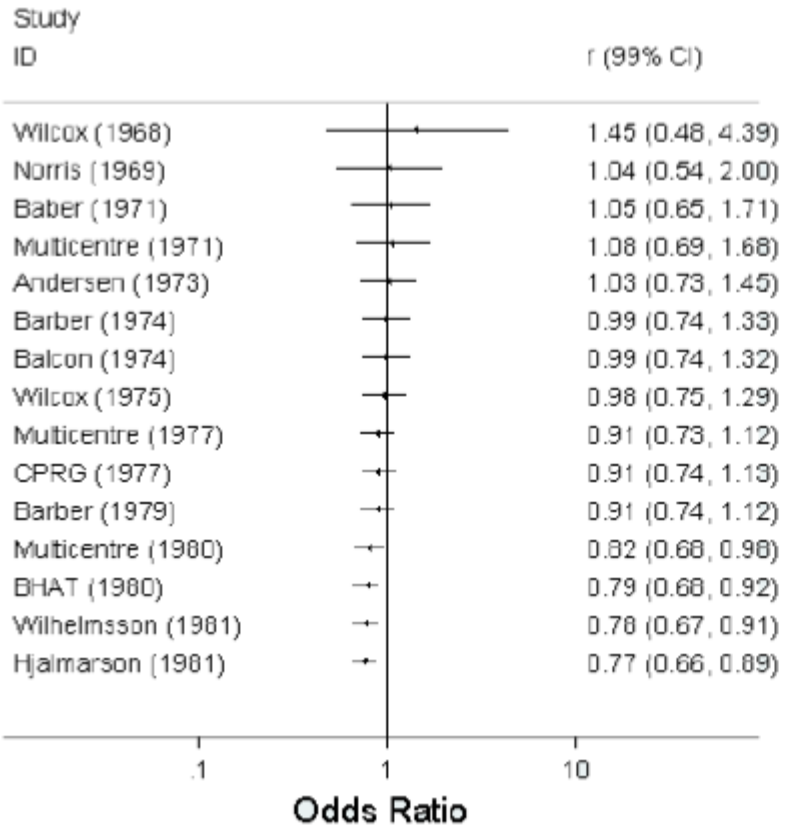
Subgroup Analysis

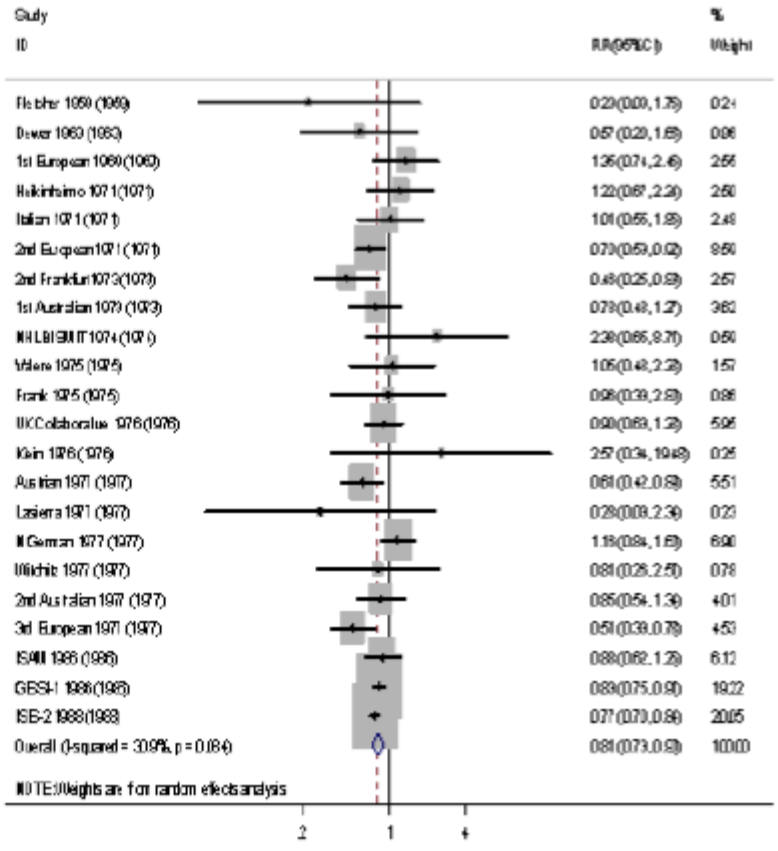
- **Example**
  - To assess the effect of various variables on cumulative incidence of HBV infection at maximum follow-up, we performed subgroup analysis across different levels of variables.
  - The variables under investigation included: studies design, types of vaccine, various endemic regions, types of participants, and age groups.

Cumulative Meta-analysis

- Cumulative meta-analysis is defined as the repeated performance of meta-analysis whenever a new relevant trial becomes available for inclusion.
- This allows the retrospective identification of the point in time when a treatment effect first reached conventional levels of statistical significance.

Cumulative Meta-analysis





- heterogi Q df, level(1-a)
- confunnel logθ selogθ, contours(# # #) contcolor(colorname) shadedcontours solidcontours metric(se|invse|var|invvar) onesided(lower|upper)

- Metannt

Number Needed to Treat

- meta_lr

likelihood ratio

- Metandi

sen spe

Metandiplot

- Metap

P-value