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Department of Internal Diseases**

Gamil U. M., Oleynik A.F., Abdulkhakov S.R.

**Evidence Synthesis in Medicine
Systematic Review & Meta-Analysis**

Practical handbook



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Reviewers:

PhD, Associate professor **Khaziakhmetova V.N.**

PhD, Associate professor **Marapov D.I.**

Gamil U. M., Oleynik A.F., Abdulkhakov S.R.

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This educational and methodological handbook was created to guide readers through the complex and intellectually engaging process of conducting systematic reviews and meta-analyses. It presents a coherent and practice-oriented overview of contemporary standards in evidence-based medical research, combining methodological rigor with clarity and accessibility. The handbook presents general principles of systematic evidence synthesis and demonstrates their application through examples drawn from clinical medical research. It offers a step-by-step approach, from the formulation of a research question to the transparent reporting of results. Designed for independent self-study, the handbook targets medical students, clinicians, and researchers.

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LIST OF ABBREVIATIONS

CDC	Centers for Disease Control and Prevention
CENTRAL	Cochrane Central Register of Controlled Trials
CI	Confidence Interval
DOI	Digital Object Identifier
FN	False Negative
FP	False Positive
HR	Hazard Ratio
IPD	Individual Participant Data
IQR	Interquartile Range
MA	Meta-Analysis
MD	Mean Difference
Me	Median
NMA	Network Meta-Analysis
OR	Odds Ratio
OSF	Open Science Framework
PRISMA	Preffered Reporting Items for Systematic reviews and Meta-Analyses
PROSPERO	International Prospective Register of Systematic Reviews
RCT	Randomized Controlled Trial
ROB	Risk of Bias
RR	Risk Ratio
SD	Standard Deviation
SE	Standard Error
SMD	Standardized Mean Difference
SR	Systematic Review
TN	True Negative
TP	True Positive
WHO	World Health Organization



TERMS & DEFINITIONS

1. Core concepts

- **Systematic review (SR):** A comprehensive and structured approach to synthesizing existing research on a specific question. It uses explicit, reproducible methods to identify, select, assess, and synthesize all relevant evidence, minimizing bias and enhancing the reliability of findings.

Let's breakdown the definition:

- Systematic = Following a fixed, organised plan w/o skipping steps.
- Review = summarizing and analysing information from other studies.

A comprehensive and structured (following clear, predefined steps) approach to synthesizing existing research on a specific question.

It uses:

- *Explicit methods* (clearly stated that everyone can understand exactly what was done and why),
- *reproducible methods* (Someone else could repeat the review in the exact same way and get *the same results*)

to:

- *Identify* (Find all relevant studies by searching scientific databases and other sources)
- *Select* (following the pre-defined eligibility criteria)
- *Appraise/assess* (check the quality of the studies, looking for bias, poor design, or small sample sizes)
- *Synthesize* (Bring together the results from the chosen studies into single, organised conclusion)
- *Enhancing the reliability of findings* (Making sure the conclusions are trustworthy because they're based on all the available high-quality evidence)

- **Meta-Analysis (MA):** An advanced type of SR that uses a *quantitative*, statistical method that integrates the results of multiple independent studies addressing the same research question, producing *a single pooled estimate* of effect or association.

Let's breakdown the definition:

- Meta: beyond



- Meta analysis: An analysis of analyses.
- Quantitative (uses numbers, not just words as in systematic review)
- Results integration (combining data from different studies)
- Pooled estimate (one overall number that represents the combined evidence)

- **Individual participant data (IPD) Meta-Analysis:** A type of MA when researchers collect raw, individual-level data from each study rather than relying on summary statistics.

- **Narrative review:** A type of literature review that synthesizes and summarizes existing research on a focused topic, often without strict adherence to SR protocols. Overall, this can lead to biases favouring the opinion of the author

2. Search and selection:

- **Research question:** Framed using PICO (Population, Intervention, Comparison, Outcome); PECO (Population, Exposure, Comparison, Outcome) and others.
- **Eligibility criteria:** Inclusion/Exclusion criteria based on PICO and some other factors.
- **Databases:** e.g. PubMed, Cochrane Library, Embase, Scopus, etc.
- **Grey literature:** Research not published in standard journals (e.g. theses, conference papers)
- **Handsearching:** Reviewing reference lists or specific journals *manually* to find additional studies

3. Screening & Data Extraction:

- Screening is preceded by deduplication (removing duplicates from multiple sources)
- **Screening:** The process of reviewing identified studies to determine whether they meet the preset eligibility criteria. This includes



Title & Abstract screening, followed by a Full-text screening. Use PRISMA Flow diagram to document the number of records identified, screened, excluded, and included.

- **Data Extraction:** The systematic process of collecting relevant information from *included studies* for analysis. This includes study ID (Author et al., year of publication), study design, sample size, population baseline characteristics, inclusion/exclusion criteria, Intervention/Exposure, Comparator, Outcomes, Effect measures, funding and conflicts of interest

4. Assessing quality:

- **Risk of bias:** Systematic errors in study design, execution, or reporting that can *distort* results. This includes selection, performance, detection, reporting, publication biases.

- **Critical appraisal:** Systematic evaluation of study quality

- **Quality assessment tools:** e.g. Cochrane Risk of Bias tool, Newcastle-Ottawa Scale

5. Meta-Analysis statistics:

- **Effect size:** numerical measure of the strength of an effect (e.g. odds ratio (OR), relative risk (RR), Hazard ratio (HR), mean difference (MD), standardized mean difference (SMD))

- **Fixed-effect model:** A modelling assumption in MA that all studies estimate the same underlying true effect, with differences attributed solely to *chance*

- **Random-effect model:** Assumes true effects differ across studies following a distribution, accounts for between-study heterogeneity

- **Heterogeneity:** Variation in study results beyond chance. Assessed by using tools (e.g. Cochran's Q test (p-value), I² Statistic)

Addressed by:

- **Subgroup Analysis:** Examine effect sizes in subsets of studies (e.g. age, gender, dosage)

- **Meta-Regression:** Explore study-level factors that explain variability



- **Sensitivity Analysis:** Re-Analysis to test robustness of results by changing assumptions or excluding some studies
- **Weighting:** Assigning relative importance to each study based on its precision (large sample sizes, small variance). It ensures that more reliable studies contribute more to the pooled estimate
- **Funnel plot:** A scatter plot used to assess *visually* the publication bias (whether small studies with negative results are missing)
- **Forest plot:** A graphical display of the results of individual studies included in MA and the overall pooled estimate

6. Network Meta-Analysis (NMA): A statistical method that allows comparison of multiple interventions simultaneously, even if some have not been directly compared in head-to-head trials. It allows us to combine direct evidence (e.g. Drug A vs Drug B) and Indirect evidence (e.g. if Drug A vs placebo and Drug B vs placebo are known, we can estimate Drug A vs Drug B indirectly)

BEFORE WE START

Think of a systematic review and meta-analysis as cooking a scientific dish:

- The **question** is your recipe idea.
- The **protocol** is your recipe written down.
- The **search** is getting ingredients.
- The **data extraction** is chopping and prepping.
- The **analysis** is cooking.
- The **reporting** is plating and serving.

If you skip steps or change the plan halfway, the dish won't turn out right, and in science, that means bias and unreliability.



PERFORMING SYSTEMATIC REVIEW AND META-ANALYSIS

STEP 1 – FORMULATING YOUR RESEARCH QUESTION

Why we do this: Without a clear question, your review will be messy. A precise question guides every single decision later (what studies to include, what data to extract, and which analysis to run).

What it is: A research question written in a structured way so you can answer it with evidence.

When to do it: Always first, before any searching or reading.

How to do it: Use frameworks:

- **PICO:** for clinical questions (Population, Intervention, Comparator, Outcome)
- **PEO:** for observational studies (Population, Exposure, Outcome)
- **SPIDER:** for qualitative research (Sample, Phenomenon of Interest, Design, Evaluation, Research type). Example: [SPIDER](#)

Example (PICO): (Table 1)

In adults with hypertension, does the new antihypertensive drug (Drug A) compared to standard treatment (Drug B) lead to a greater reduction in blood pressure?

Table 1

Formulating PICO

P (Population/Patient)	Adults with hypertension
I (Intervention)	Drug A
C (Comparison)	Drug B
O (Outcome)	Greater reduction in BP

Check the validity of your PICO by ensuring:

- You have identified ≥ 2 -4 studies addressing the same PICO question and no SR.
- There are at least 2 Randomized Controlled Trials (RCTs) on the same topic published after the latest SR, and together they contribute to at least 20 % of the total sample size of that published SR.



STEP 2 – DEFINE YOUR ELIGIBILITY CRITERIA

Rules to consider:

- Define exactly who, what, and which outcomes are included
- Avoid vague terms (e.g. adult patient without specifying age range; effective treatment without specifying outcomes)
 - Example: Include adults ≥ 18 years with primary hypertension, exclude secondary hypertension
- Base criteria on your PICO
- Consider study characteristics
 - Language: include or exclude non-English studies
 - Publication status: peer-reviewed, grey literature, conference abstracts
 - Time frame: Publication dates to ensure relevance
- Avoid Bias
 - Make criteria pre-specified, not decided after seeing the results
 - Include all studies that meet criteria, *regardless of outcome direction or significance*
- Be reproducible
 - Anyone reading your SR protocol should be able to apply your eligibility criteria and get the same set of included studies
- Align with Guidelines
 - Follow PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) or Cochrane guidance for SRs

See table 2 for eligibility criteria based on our previously mentioned PICO:



Table 2

Eligibility criteria

Domain	Inclusion Criteria	Exclusion Criteria
P	Adults \geq 18 years, diagnosed with primary hypertension: any sex or ethnicity.	< 18 years, patients with secondary hypertension.
I	Any study evaluating the new antihypertensive drug (Drug A), alone or in combination with standard therapy.	Experimental drugs not widely available; studies combining with non-standard therapies.
C	Standard antihypertensive treatment (ACEIs, ARBs, BBs, CCBs, Diuretics).	Unclear/No comparator.
O	Primary: Reduction in SBP and DBP (mmHg). Secondary: Adverse effects, treatment adherence, cardiovascular events.	Studies not reporting BP outcomes.
Study Design (S)	RCTs, controlled clinical trials.	Other study designs (cohort, cross sectional, case-control)
Language	English.	Non-English publications without translations.
Publication status	Peer-reviewed full text articles.	Abstracts without full text.
Time frame	Published between 2010-2025.	Outside the specified date range.



STEP 3 – ANALYSIS PLAN AND PREREGISTRATION

After your research question and eligibility criteria are set, it is sensible to also write an analysis plan. In statistics, there is an important distinction between a priori and post hoc analyses. A priori analyses are specified before seeing the data. Post hoc, or exploratory, analyses are conducted after seeing the data or based on the results implicated by the data.

Results of a priori analyses can be regarded as much more valid and trustworthy than post hoc analyses.

This serves two purposes:

First, it allows others to verify that the analyses we made were indeed planned and are not the mere result of us playing around with the data until something desirable came out. Second, a detailed analysis plan also makes our meta-analysis reproducible, meaning that others can understand what we did at each step of our meta-analysis, and try to replicate them.

An analysis plan should clearly state:

- The information to extract from each study and the effect size metric to calculate.
- Whether a fixed- or random-effects model will be used, based on expected between-study variation.
- If an a priori power analysis will determine the number of studies needed for statistical significance.
- Plans for subgroup analyses or meta-regression, including exact criteria for subgroup classification.
- All statistical techniques intended for use in the meta-analysis.

Once written, make the plan public via platforms like OSF or preprint servers and consider registering the meta-analysis in PROSPERO.

A full meta-analysis protocol can include the analysis plan, study background, detailed methodology, and potential impact. Guidelines such as PRISMA-P can guide protocol preparation.

Preregistration and a priori analysis plans enhance credibility. *Changes to the plan are acceptable if transparently reported.*



STEP 4 – WRITING AND REGISTERING YOUR PROTOCOL

Before starting the search, write your full step-by-step plan for the review to prevent bias. Writing it down means you stick to your plan and don't change outcomes after seeing results.

How:

- Write your protocol (introduction, objectives, methods, criteria, search plan, data handling, bias assessment, analysis plan), and save it in pdf format.
 - Example of a registered protocol: [Clinical Outcomes of Individuals with COVID-19 and Tuberculosis Disease: a Living Systematic Review](#)
- Register it on **PROSPERO** (See figure 1)
- **Links:**
 - [PROSPERO](#)
 - Follow the Protocol checklist to ensure accuracy and completeness: [PRISMA P](#)

NIHR | National Institute for Health and Care Research

PROSPERO
International prospective register of systematic reviews

Home | FAQs | About PROSPERO ▾

Search Logout: Usama Gamil

My PROSPERO

2 Create a new PROSPERO record...

What are you registering?

*PROSPERO uses different templates for different types of review.
Use this page to select the correct template. This page will determine the information you need to provide in your registration record. Answer correctly here to avoid having to restart the process later.*

Review of human or animal studies?

PROSPERO comprises two complementary registries - one of reviews of human health and wellbeing and one of animal pre-clinical studies that have a clear and direct link to human health and wellbeing

I am registering

A systematic review of studies with people/humans as participants

A systematic review of studies with animals as participants that is directly relevant to human health



Is this registration record being created by a student as part of a course or module?
(Help me decide)

This record is NOT being created as part of a student project or training course
All of the registration process will be available to you and your record will be published on the public PROSPERO site

This record is being created as part of a training course. It will NOT be published on the public site.
All of the registration process will be available to you but your record will not be published on the public PROSPERO site. You will be able to give access to your record to your supervisor. It is not possible to change this status at a later date - if you decide you want the record to be published you will have to create a new record.

What type of review are you planning?

Intervention review
Assessing the benefits, harms or experience of a health intervention (medicine, treatment, vaccine, device, preventative measure, procedure or policy).

Coming soon: Review of incidence or prevalence
Assessing the prevalence or incidence of a disease or condition.

Coming soon: Methodology
Examining the evidence on methodological aspects of systematic reviews, trials and other evaluations of health and social care.

3 [Register your review now](#)

Fig. 1. PROSPERO registration steps

After completing these steps, enter all required information and save your changes.

STEP 5 – LITERATURE SEARCH

We aim to find *all* available evidence on a research question to get an unbiased, comprehensive view of the facts.

Commonly used sources:

➤ Review articles: It can be very helpful to screen previous reviews on the same or similar topics for relevant references.

➤ Databases: at least the following: PubMed, Embase, CENTRAL, SCOPUS, (*see links below*).

➤ References in studies: If you find a study that is relevant for your meta-analysis, it is sensible to also screen the articles that this study references.

➤ Forward search: The opposite of screening the references of previous primary studies and reviews. It means to take a study that is relevant for the



meta-analysis as basis and then search for other articles that have cited this study since it has been published.

➤ Relevant journals: Specialised in the type of research question you are focused on.

➤ Grey literature: conference materials, theses, government and official reports (CDC, WHO), Clinical trial registries, etc.

Useful links:

- [PubMed](#)
- [Cochrane](#)
- [Embase](#)
- [SCOPUS](#)
- [Google Scholar](#)
- [ClinicalTrials.gov](#)
- [CENTRAL](#)
- [CDC](#)
- [WHO](#)

Rules:

- Pick at least 3 main databases + 1 grey literature source.
- Search by using the pre-set keywords
 - Keywords are set based on your PICO. Let's come back to our PICO: In adults with primary hypertension, does the new anti-hypertensive drug (Drug A) compared to standard treatment (Drug B) lead to a greater reduction in blood pressure?

➤ Population/Patients: adults, primary hypertension, essential hypertension

➤ Intervention: Drug A, new antihypertensive

➤ Comparison: Drug B, standard treatment, conventional antihypertensive

➤ Outcome: blood pressure reduction, BP reduction

Boolean Operators:

("adult") AND ("primary hypertension" OR "essential hypertension") AND NOT ("secondary hypertension") AND ("Drug A" OR "new antihypertensive") AND ("Drug B" OR "standard treatment" OR "conventional antihypertensive") AND ("blood pressure reduction" OR "BP reduction")



With MeSH (Medical Subject Heading), you don't need to guess every synonym, it will do it for you:

“Adult”[MeSH] AND “hypertension, primary”[MeSH] AND NOT “Hypertension, secondary”[MeSH] AND “Drug A”[MeSH] AND “antihypertensive agents”[MeSH] AND “Blood Pressure”[MeSH]

Mixed:

("Adult"[MeSH]) AND ("Hypertension, Primary"[MeSH] OR "primary hypertension" OR "essential hypertension") AND NOT ("Secondary Hypertension"[MeSH] OR "secondary hypertension") AND ("Drug A" OR "new antihypertensive") AND ("Drug B" OR "standard treatment" OR "conventional antihypertensive") AND ("Blood Pressure"[MeSH] OR "blood pressure reduction" OR "BP reduction")

You can use asterisk (*) for truncation. For instance: (antihypertens*) finds antihypertensive, antihypertensives.

NB: Don't use it with MeSH

NB: MeSH: PubMed and CENTRAL

Boolean logic + free-text keywords: all

- Save you search strings in protocol.
- Search the databases using the search string, as shown in figure 2.
- Export results from each database (usually **.ris** or **.nbib** format).
- Import the exported results into reference manager (e.g. Zotero).

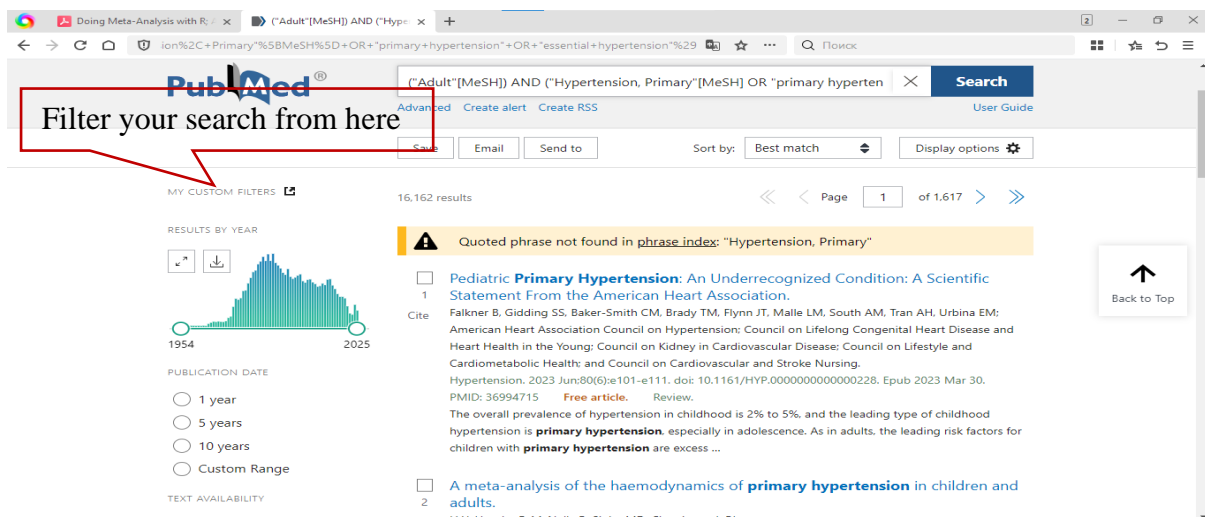


Fig. 2. Searching the database

NB! You can find all keywords related to your PICO question using PubMed (with Mesh) and Google.



Export the findings and import them into a reference manager (preferably Zotero or Mendeley), as illustrated in figure 3 and 4.

The image shows the PubMed interface for a search query: "(adults) AND ((primary hypertension) OR (essential hypertension))". The search results page displays 1,760 results. A red box labeled '1' highlights the 'Send to' button. A dropdown menu is open, showing options: Clipboard, My Bibliography, Collections, and Citation manager. The 'Citation manager' option is highlighted with a red box and a '2'. A dialog box titled 'Create a file for external citation management' is shown, with a dropdown menu set to 'All results'. The 'All results' option in the dropdown is highlighted with a red box and a '3'. The 'Create file' button at the bottom of the dialog is highlighted with a red box and a '4'.

Fig. 3. Exporting the results from PubMed



The screenshot displays the Zotero application interface. At the top, the menu bar includes 'File', 'Edit', 'View', 'Tools', and 'Help'. The 'File' menu is open, showing options like 'New Collection...', 'New Library', 'Close', 'Show File', 'Import...', 'Import from Clipboard', 'Export Library...', and 'Exit'. The 'Import...' option is highlighted with a red box and the number '2'. An 'Import' dialog box is open, asking 'Where do you want to import from?'. The 'A file (BibTeX, RIS, Zotero RDF, etc.)' option is selected with a red box and the number '3'. The 'Next >' button is highlighted with a red box and the number '4'. Below the dialog, a file explorer shows a list of files, with 'pubmed-adultsANDp-set.nbib' highlighted with a red box and the number '5'. At the bottom, the 'Открыть' (Open) button is highlighted with a red box and the number '6'.

1 File Edit View Tools Help

pubmed-adultsANDp-set

Back up your library with Zotero syncing. [Set Up Syncing](#) [Learn More](#)

My Library

- PI on CVS
 - cardiovascular
- prelim. UFA article
- pubmed-adultsAND...
- My Publications
- Duplicate Items
- Unfiled Items
- Trash

Title

- > Atherosclerosis in HIV Patients: What Do We Know so
- > Cardiovascular Disease Among Persons Living With H
- > Cardiovascular disease and antiretroviral therapy
- Cardiovascular disease and risk assessment in people
- Cardiovascular diseases in HIV patients
- > Cardiovascular risk and D-dimer levels in HIV-infected
- > Cardiovascular risk factors among patients with huma
- Cardiovascular toxicity of contemporary antiretroviral

New Collection...
New Library >
Close Ctrl+W
Show File
2 Import... Ctrl+Shift+I
Import from Clipboard Ctrl+Shift+Alt+I
Export Library...
Exit

Import

Where do you want to import from?

3 A file (BibTeX, RIS, Zotero RDF, etc.)
 Mendeley Reference Manager online import

< Back **4** Next > Cancel

5 pubmed-adultsANDp-set.nbib 16/08/2025 01:22 Файл "NBIB"
Telegram 03/05/2021 02:43 Ярлык
Word 30/09/2024 13:51 Ярлык
Zoom Workplace 19/07/2025 18:28 Ярлык
Zotero 12/09/2024 10:59 Ярлык
Установить Kaspersky Internet Security в... 13/06/2024 04:20 Ярлык

Файла: | All Files

6 Открыть Отмена

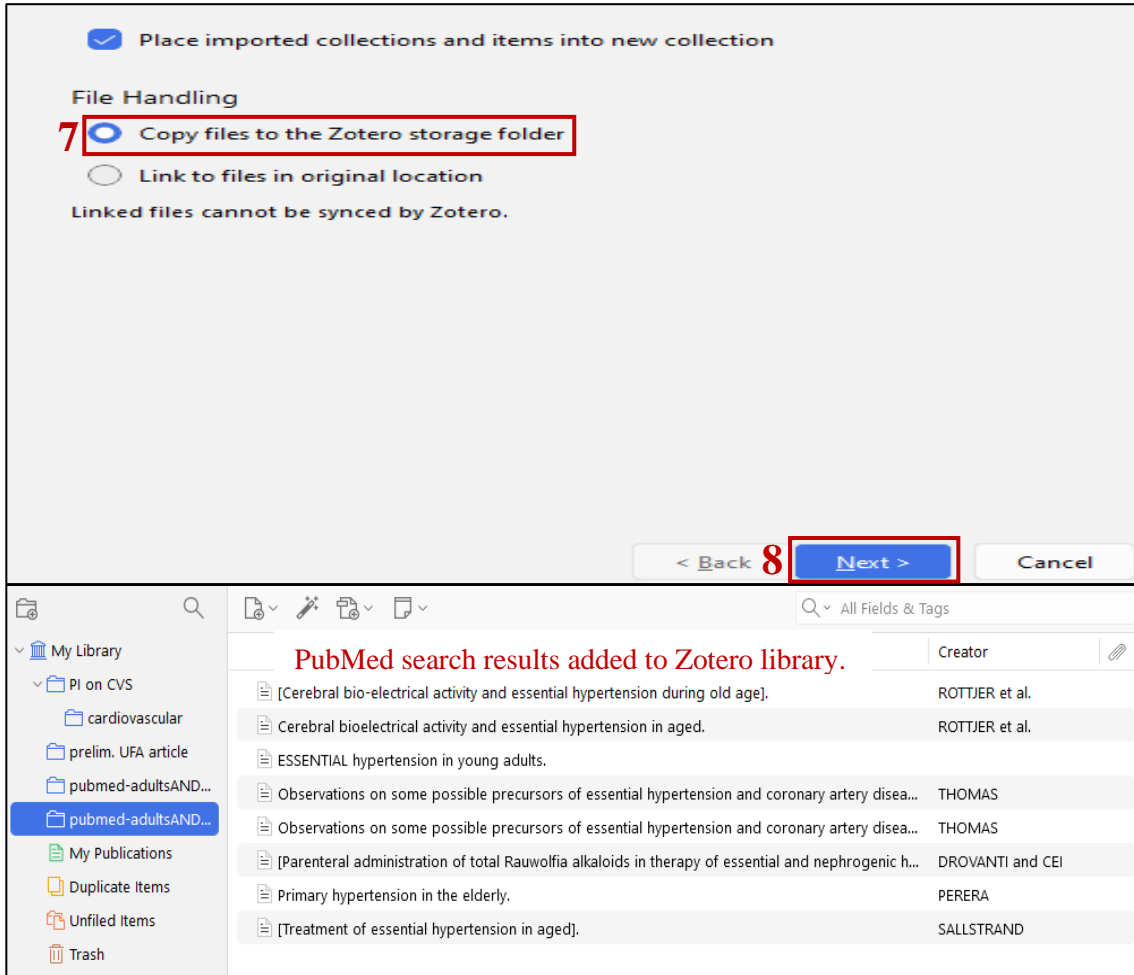


Fig. 4. Importing the exported results into Zotero

Citation Manager Links:

- [ZOTERO](#)
- [MENDELEY](#)



STEP 6 – STUDY SELECTION (SCREENING)

i.e. Filter out irrelevant studies.

You may use either Zotero or Mendeley (both can be downloaded from the links provided on the previous page)

Steps:

1. Deduplicate the studies: (figure 5)
 - a. In the left panel, click on *Duplicate Items*
 - b. Click on *Merge items*

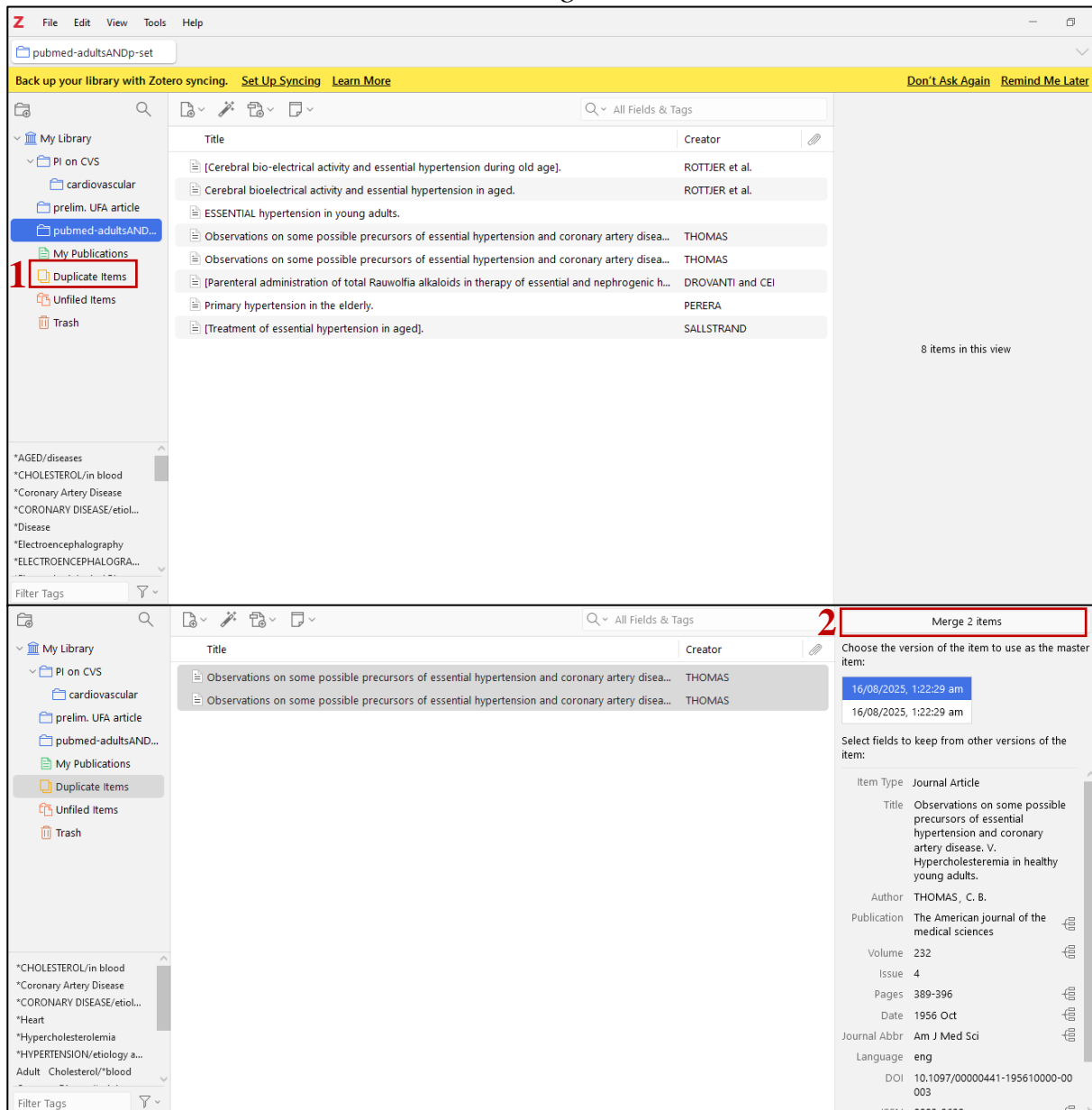


Fig. 5. Deduplication on Zotero



2. Export as .ris or .csv and import into [Rayyan](#) (as illustrated in figure 6) or Excel.
 - a. Go to Files (left upper corner) and click *Export library*
 - b. Sign up and create a new review in Rayyan
 - c. Add your team members

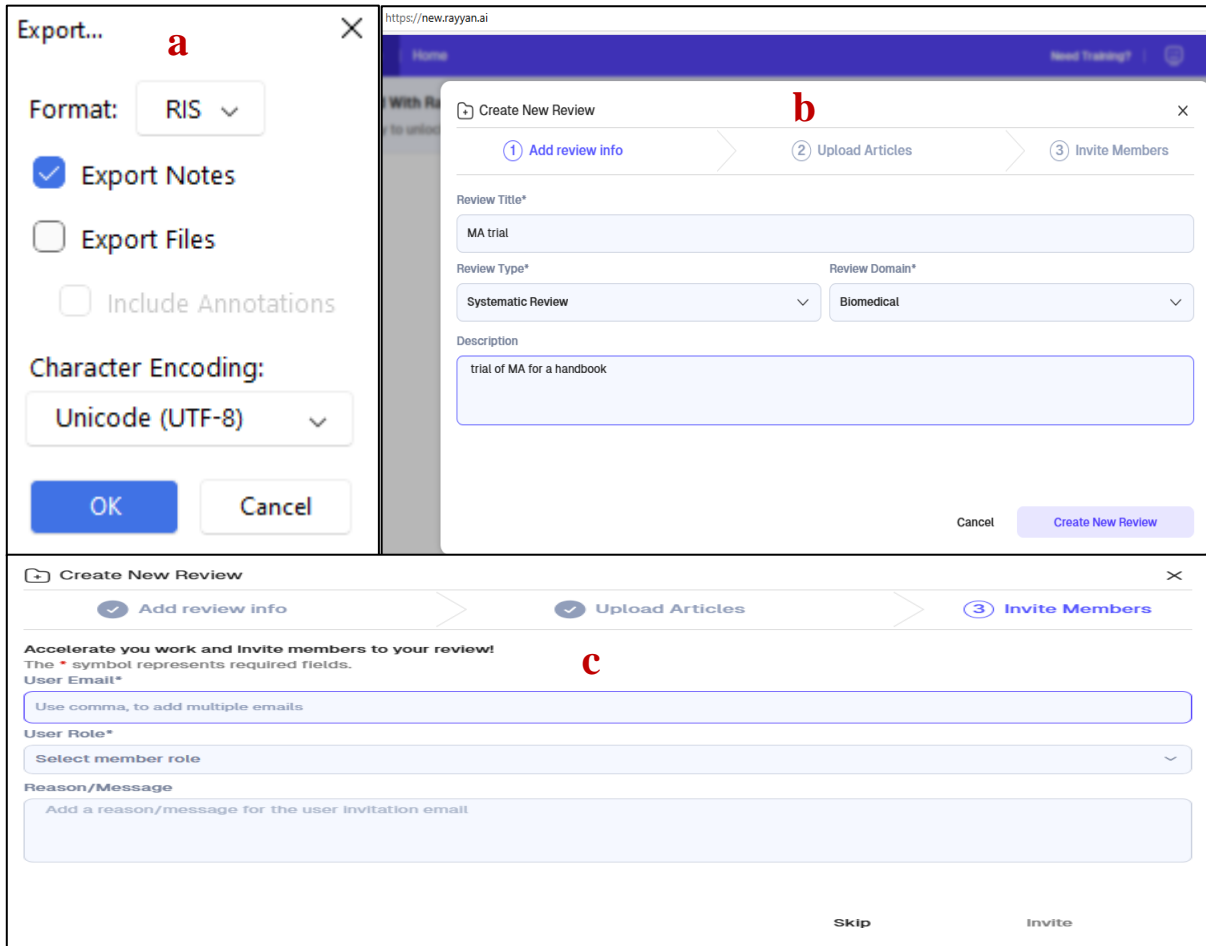


Fig. 6. Creating a new review in Rayyan



3. Title/Abstract screening: Click on “Screening” panel. (Figure 7).
 - a. Start “Title and Abstract Screening”. For each article, choose: Include, Exclude, or Maybe.
 - b. NB: In Title/Abstract screening: Reasons are optional (not required).
 - c. Use “Blind On” so reviewers don’t see each other’s decision until later.

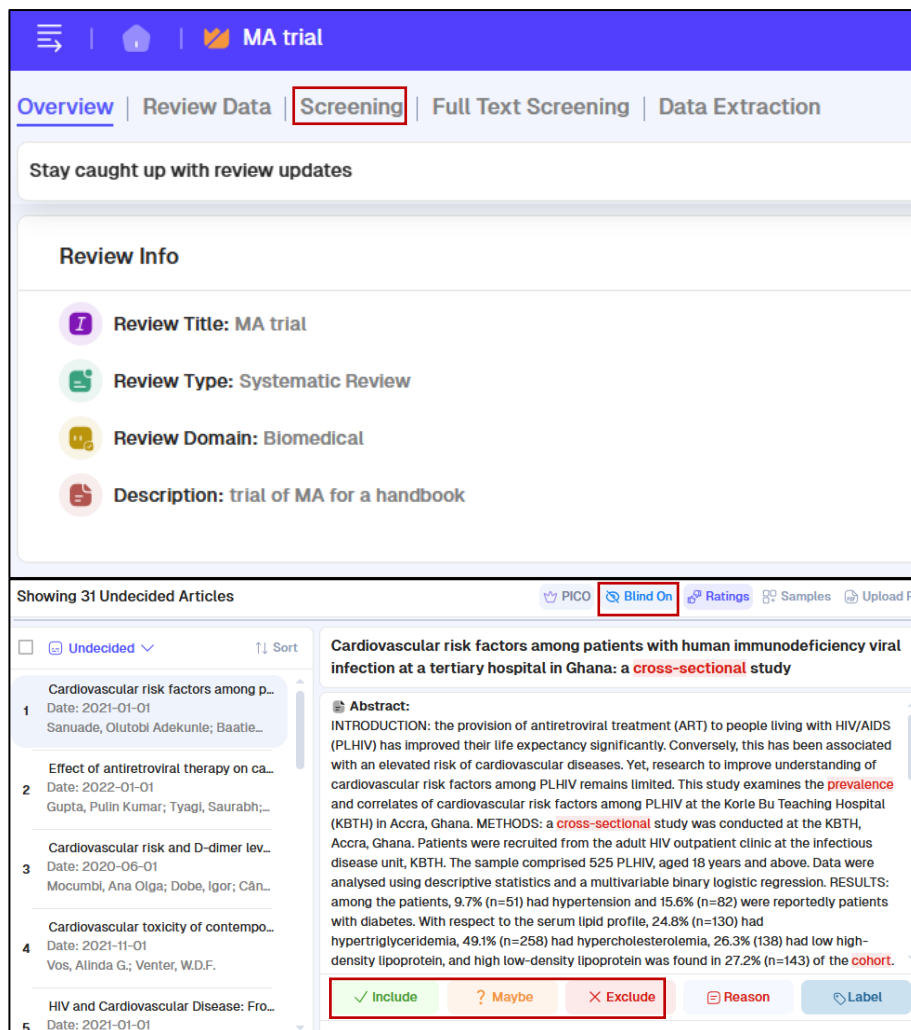


Fig. 7. Title/abstract screening



4. Full-text screening: Click on “Full text screening”
 - a. Select “Included Articles” (figure 8)
 - b. Double click on each study and download its file (.pdf)

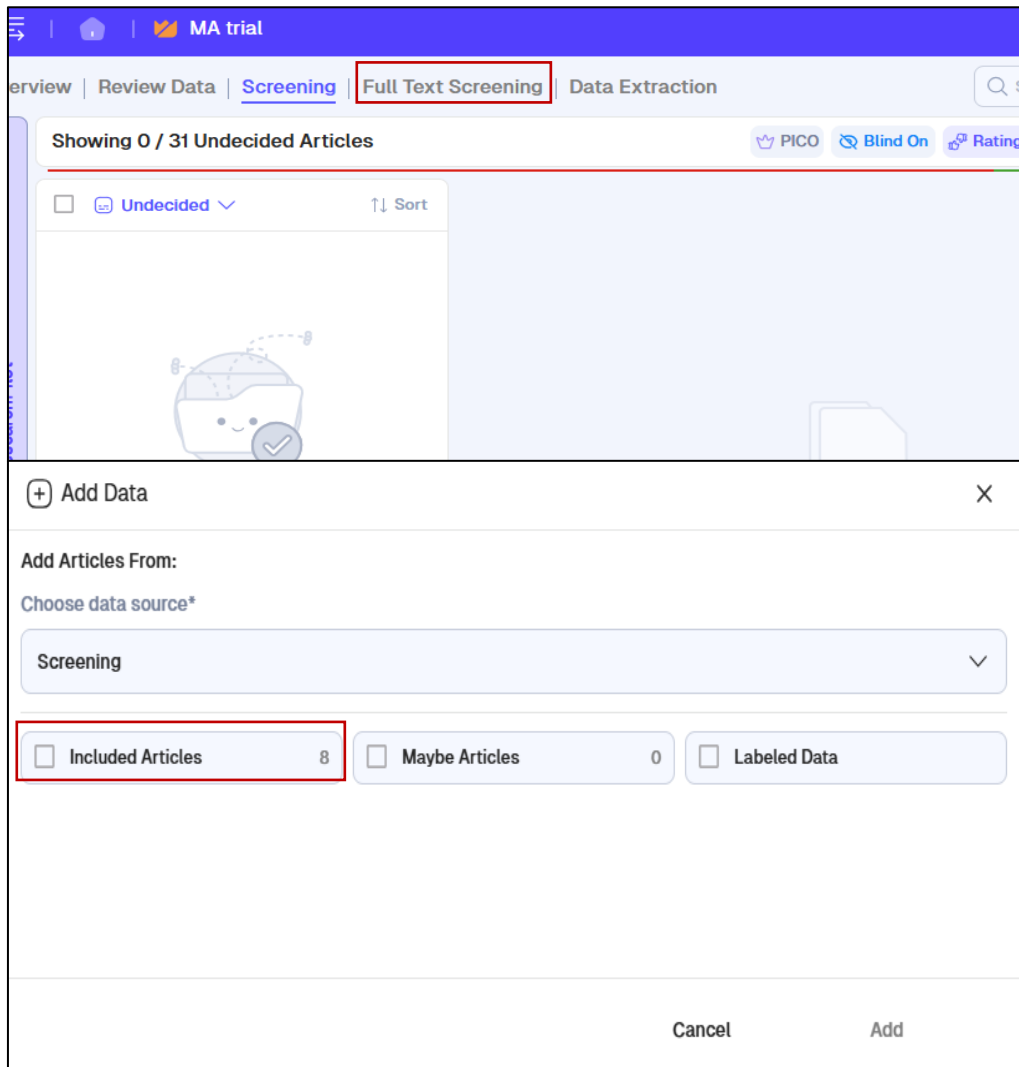


Fig. 8. Initiating full-text screening

- c. Find the article by:
 - i. Scrolling down and clicking the link of the selected study
 - ii. By DOI (if a database doesn't find it, try searching on <https://doi.org/> place your DOI here)
 - ✓ Example:
<https://doi.org/10.1097/COH.0000000000000702>
 - iii. Manually: Title and Authors' search

- d. Download the file in .pdf format
- e. Upload it to Rayyan, as illustrated in figure 9.

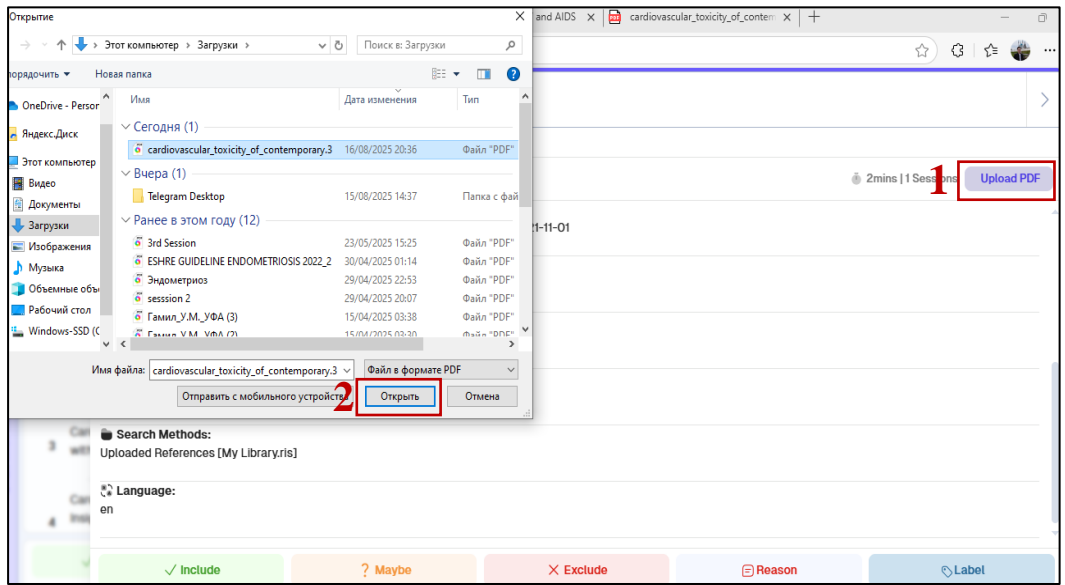


Fig. 9. Uploading files of the included studies into Rayyan

- f. Click on the PDF and start the Full-Text Screening based on your eligibility criteria, as shown in figure 10)
- NB! Don't forget to mention the reason of EXCLUSION.

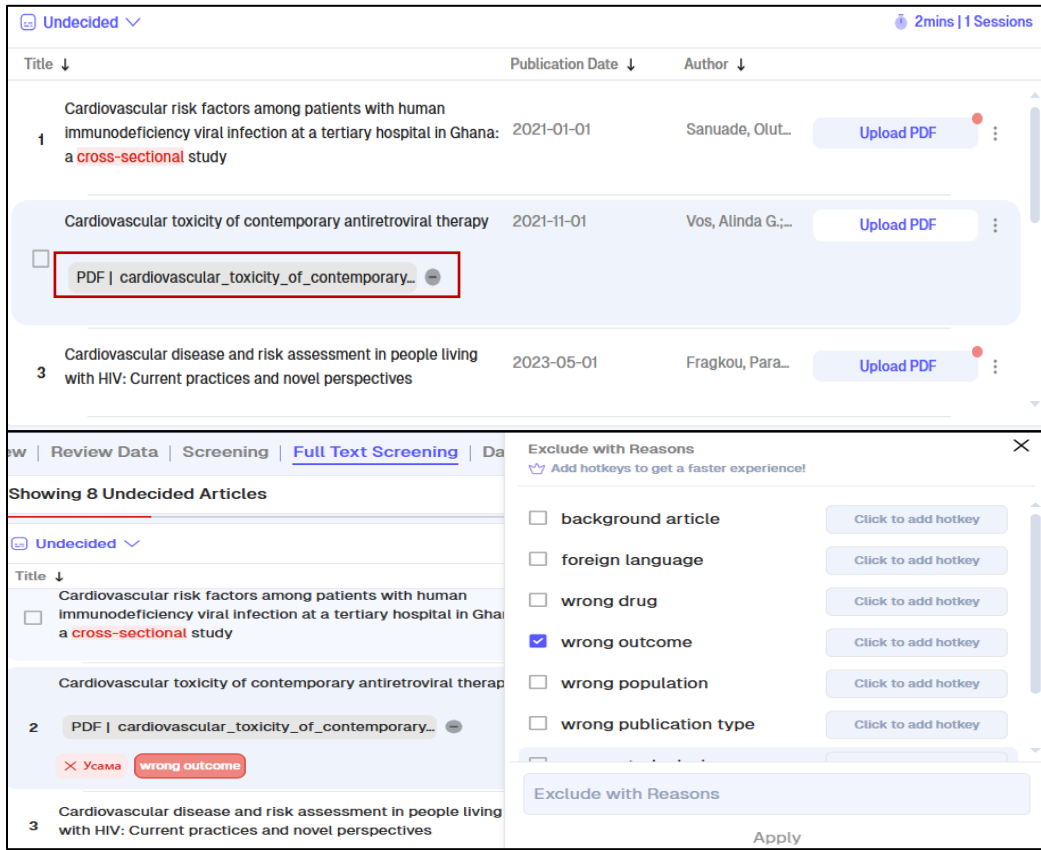


Fig. 10. Full-text screening



Important notes:

- ✓ At least 2 reviewers should screen the studies *independently*.
- ✓ In case of conflict (disagreement), both reviewers need to re-evaluate the study and try to reach *consensus*.
- ✓ If consensus cannot be reached, a third independent reviewer makes the final decision.
- ✓ Keep a record of:
 - which studies had conflicts.
 - Reason of disagreement.
 - Final decision and who resolved it.
- ✓ Keep track of included and excluded studies and follow the PRISMA flowchart to ensure transparency and reproducibility of the review process.

[PRISMA flow diagram](#)

STEP 7 – DATA EXTRACTION

i.e. Turn text from studies into analysable numbers. Data are generally classified into two categories: qualitative and quantitative, as illustrated in figure 11.

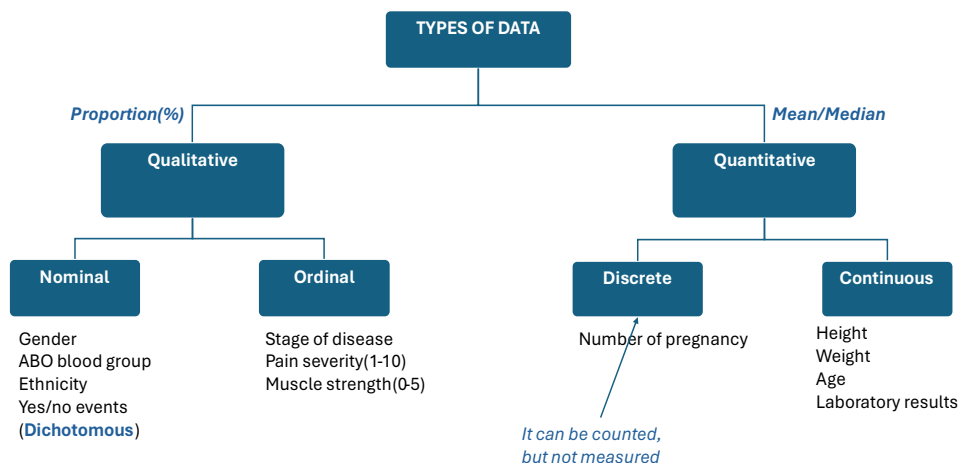


Fig. 11. Classification of data

Quantitative data may exhibit either normal or abnormal distributions. Data with a normal distribution are summarized using Mean \pm Standard Deviation, while data with an



abnormal distribution are described using Median + range. Qualitative data are expressed as frequencies (percentages), as illustrated in figure 12.

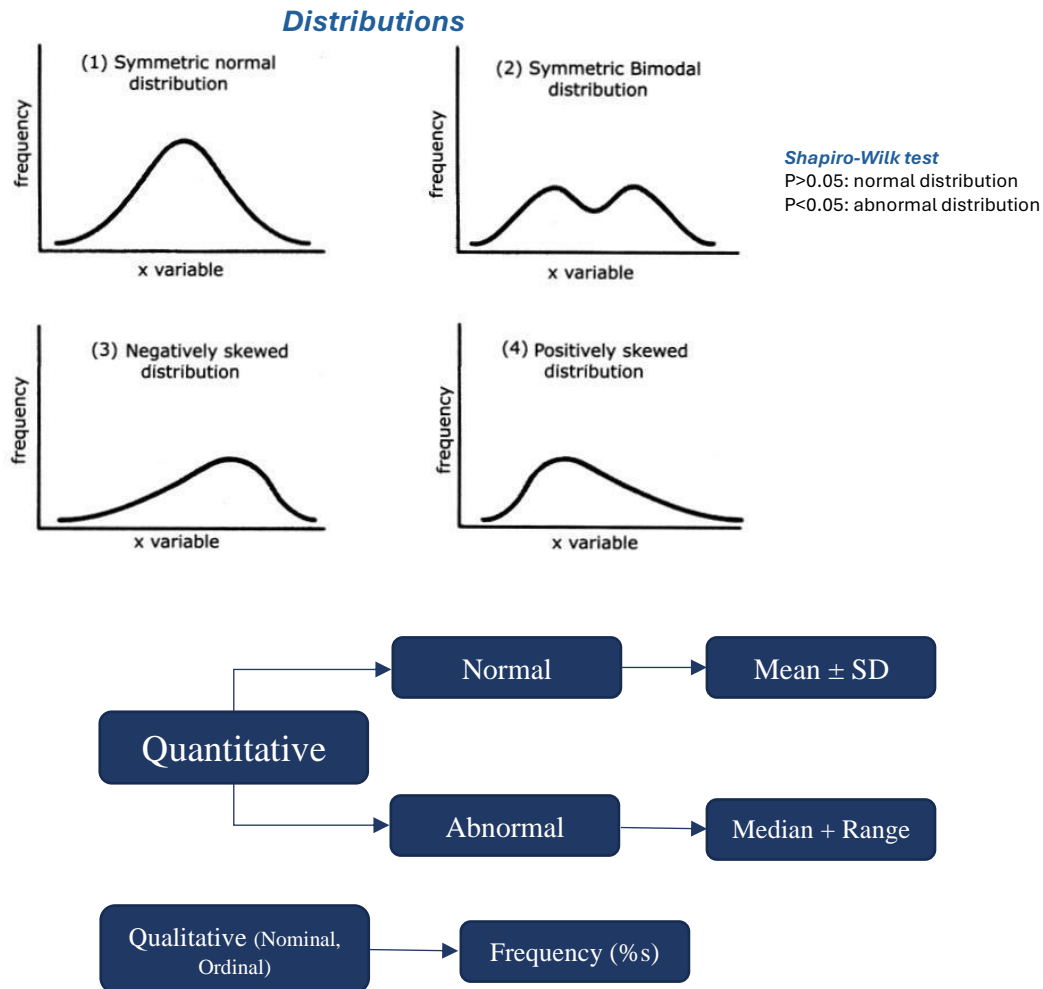


Fig. 12. Data distribution

We should extract three major types of information from the selected articles:

1. Characteristics of the studies:
 - a. Study ID (Author(s), year of publication, country)
 - b. Study Design (e.g. RCT, cohort, case-control, etc.)
 - c. Sample size (n)
 - d. Population baseline characteristics (Inclusion/Exclusion criteria, Age, sex, ethnicity, comorbidities, disease severity, etc.)
 - e. Intervention (Type of intervention (e.g. drug, surgery); Dose, frequency, and duration)
 - f. Comparator (placebo, standard care, another intervention)



- g. Outcome(s) (primary and secondary outcomes, measurement tools, timing of outcome assessment)

2. Data needed to calculate effect sizes: for pooling across studies, we need *numerical results* that can be standardized into a common effect. Depending on outcome type:

- a. Continuous outcome (e.g. Blood pressure, lipid levels):
 - i. Mean and Standard deviation (SD) in each group,
 - ii. sample size (n) in each group.
 - iii. To find the effect size, use Mean difference (MD) or Standardized mean difference (SMD) (both with 95 % Confidence Interval)
- b. Dichotomous outcomes (yes/no events):
 - i. Number of events (e.g. Death, responders) in each group.
 - ii. Total number of participants per group.
 - iii. To find the effect size, use Risk Ratio (RR), Odds Ratio (OR), or Risk Difference (RD) (all with 95 % CI).
- c. Time-to-event outcomes (e.g. survival, time to relapse):
 - i. Hazard Ratio (HR) with 95 % CI.
- d. Correlation (r):
 - i. Pearson (normally distributed data), Spearman (Skewed data) with Standard of Error (SE) or 95 % CI.
 - ii. Correlations are restricted in their range, and it can introduce bias when we estimate the standard error for studies with a small sample size. In meta-analyses, correlations are therefore usually transformed into Fisher's z scores.
 - iii. We don't use r in MA because its variance depends on r itself. Fisher's Z stabilizes the variance, making pooling more accurate.
- e. For diagnostic test papers: True Positive (TP), False Positive (FP), True Negative (TN), and False Negative (FN) to find specificity and sensitivity.

3. Study quality or risk of bias characteristics: Will be discussed in the following step.

Save as:

- .csv for R



- Excel for RevMan

This form can be used to enter the extracted data from the selected studies:

- [RCT only](#)
- [RCT and nRCT](#)

Essential rules to follow:

- ✓ Use a standardized form (from the links above).
- ✓ At least two reviewers should extract the data *independently*.
- ✓ Conflicts are resolved by discussion or a third reviewer.
- ✓ Try to contact study authors for missing information. If not possible, clearly report missing data.
- ✓ Cross-check for consistency and accuracy.
- ✓ Record all decisions and any changes made during extraction.
- ✓ Piloting a data extraction form (Testing your table/form on a small sample of studies (2-3 articles) before you extract from all studies.

- Why doing it?

- To check if the form captures all the important data for your review.
- To see if any fields are unclear or missing.

- How to do it?

- Select 2-3 articles from your included studies.
- Both reviewers extract independently.
- Check whether both reviewers interpret the questions in the same way, and whether some fields are confusing or unnecessary.
- Revise the form (add/remove fields, clarify wording)
- Start full data extraction for all included studies

- ✓ Always think “Could someone else reproduce this review using only my extraction sheet?”

Data extraction can be challenging, so we have compiled some tips and strategies to help you avoid common pitfalls:



- To extract baseline characteristics, always check the *first table or section in results*

- To extract summary of study (e.g. Study design, sample size, Inclusion/Exclusion criteria, main findings), always check *methods* section

- To extract outcome(s), always check the *results* section

- If dichotomous data are reported as percentages, convert them to the number of events per group by multiplying the percentage (as a decimal) by the total number of participants in each group

- Example: If 40% of 50 participants had an event

- $0.4 \times 50 = 20$ events in 50 participants

- As discussed previously, continuous data should be extracted as Mean \pm SD. If the data are reported in other format (e.g., mean \pm SE, mean with CI, Me [IQR], or individual-level data), they should be converted to Mean \pm SD. Additionally, the *Mean change \pm SD* (i.e., the difference between the pre-treatment and post-treatment means) should be extracted or calculated.

- $\text{Mean}_{\text{change}} = \text{Mean}_{\text{post}} - \text{Mean}_{\text{pre}}$

- Example: BP_{before tx} = 180 mmHg; BP_{post tx} = 140 mmHg

- $\text{Mean}_{\text{change}} = 140 - 180$

- $= -40$ mmHg

- If the SD_{change} is not reported, you need to calculate it using the following formula:

$$SD_{\text{change}} = \sqrt{SD_{\text{pre}}^2 + SD_{\text{post}}^2 - 2 \times \text{Corr} \times SD_{\text{pre}} \times SD_{\text{post}}}$$

- SD_{pre} = standard deviation at baseline (pre-tx)

- SD_{post} = standard deviation post follow-up

- Corr = correlation coefficient between baseline and final measurements, can be calculated using the following formula:

$$\text{Corr} = \frac{SD_{\text{pre}}^2 + SD_{\text{post}}^2 - SD_{\text{change}}^2}{2 \times SD_{\text{pre}} \times SD_{\text{post}}}$$

- If the correlation is not provided, use the correlation reported in another study. If no studies report it, assume the correlation is 0.5, as its impact is minimum.

- Fortunately, there is no need for you to perform any calculations, as we have already prepared a sheet for your convenience. [Conversion sheet](#)

- If the outcome data are not reported in the results section:



- Identify the trial registration number (NCT#####) and search for the study on ClinicalTrials.gov (or another trial registry).
- If the data are still not available, check the supplementary materials.
- Always check the legends of labels and figures to define the units used in the selected studies.
- If data are reported only in graphical form, extract them using [WebPlotDigitizer](#).

Three different sheets are needed for data extraction:

1. Summary sheet:

- a. Study ID (the last name of the first author and the year of publication)
- b. Study design, location, and time
- c. Total sample size
- d. Eligibility criteria and population definition
- e. Intervention group (Intervention, any add-on therapy, regimen, route of administration, n of patients in the group)
- f. Control group (materials given, n of patients in the group)
- g. Duration of follow up
- h. Any additional medication given to the population
- i. Results in brief (2-3 lines)

2. Baseline characteristics of included patients' sheet:

- a. Examples: Age, Gender, ethnicity, weight, height, BMI, disease, Disease duration, comorbidities, etc.
- b. Extracted as numbers only (Mean \pm SD, %s)
- c. Using the included articles, design your sheet and decide which characteristics need to be recorded.

3. Outcomes' sheet:

- a. Using the included articles, design your sheet and decide which outcomes' characteristics need to be recorded.
- b. Extract all the outcomes reported in the included studies
- c. Delete outcomes that appear only once



STEP 8 – QUALITY AND RISK OF BIAS ASSESSMENT

Evaluating how much the design, conduct, or reporting of research study may have introduced some systematic errors (biases) that could affect the validity or reliability of findings.

i.e. It helps you judge whether you can trust the study's results.

It allows reviewers, researchers, and clinicians to interpret findings more carefully. Table 3 shows the most common biases to be assessed

Table 3

Common types of biases and their prevention

Type of bias	Prevention of bias
<i>Selection bias</i>	Proper randomization.
<i>Performance bias</i>	Blinding of participants and personnel.
<i>Detection bias</i>	Blinding of outcome assessors/analysers.
<i>Attrition bias</i>	Intention to treat analysis. *
<i>Reporting bias</i>	Trial registration, no selective reporting.
<i>Other bias</i>	e.g. conflicts of interests, inappropriate statistical methods.

* A strategy in clinical trials where all randomized participants are included in the statistical analysis according to their assigned groups, preserving the benefits of randomisation.

Tools:

- Randomized controlled trials:
 - Crib sheet: [ROB2](#) (2019)
 - Excel sheet: [ROB2 sheet](#) (2019)
 - [ROB2 Manual](#)
 - [Simplified ROB2 manual](#)
- Observational studies: [NewCastle-Ottawa Scale](#)
- Diagnostic studies:
 - [QUADAS 2](#) (2011)
 - [QUADAS 3](#) (2025) Still in piloting stage

Using these tools, answer the corresponding questions to assess the quality of each study.



Instructions to use ROB2 sheet: (See figures 13-16)

- Download the sheet
- Right-click, click on “Properties”, and then select “Unblock”
- Click on “ROB2 assessment tool”

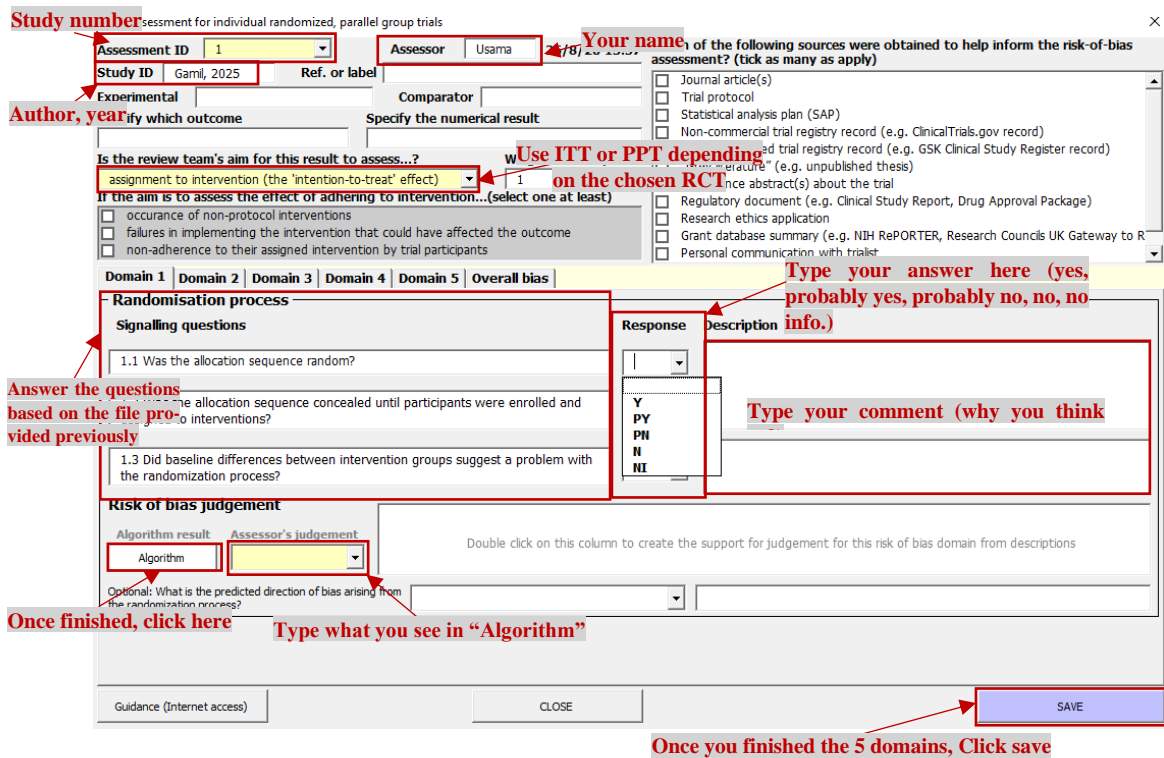
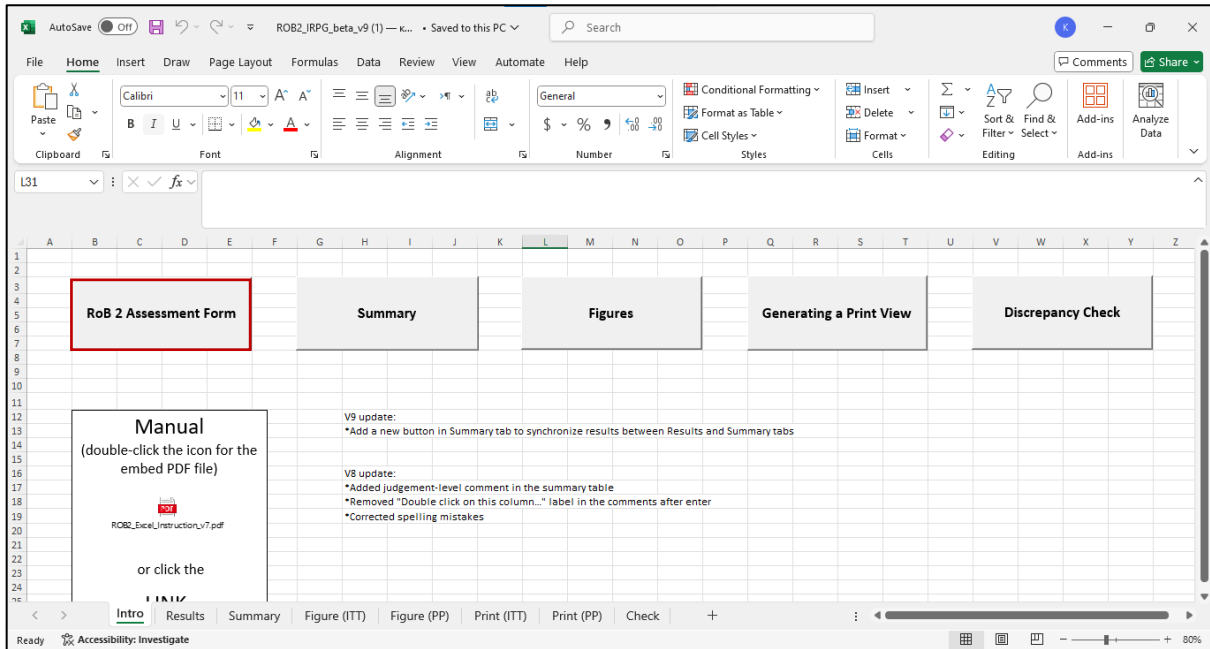


Fig. 13. Instructions of ROB2 tool



- Click on “Summary”
- Go to “summary sheet” and use the horizontal scrollbar to move to the far right of the sheet
- Scroll down to the summary chart
- Click on “Figures”

The screenshot shows an Excel spreadsheet with three tabs: "RoB 2 Assessment Form", "Summary", and "Figures". The "Summary" tab is selected and highlighted with a red box labeled "1". Below the tabs, there is a "Manual" icon with the text "(double-click the icon for the embed PDF file)" and "or click the". To the right, there are update notes for V9 and V8. The spreadsheet is scrolled to the right, with a red arrow labeled "2" pointing to the right edge of the sheet. Below the spreadsheet, the "Summary" tab is active, showing a risk of bias summary chart. The chart is titled "As percentage (intention-to-treat)" and shows the following data:

Domain	Risk Level
Overall Bias	High risk
Selection of the reported result	High risk
Measurement of the outcome	High risk
Missing outcome data	Low risk
Deviations from intended interventions	High risk
Randomization process	Some concerns

The chart includes a legend: Low risk (green), Some concerns (yellow), High risk (red). A red box labeled "3" is placed to the left of the chart.

Fig. 14. Risk of bias summary chart

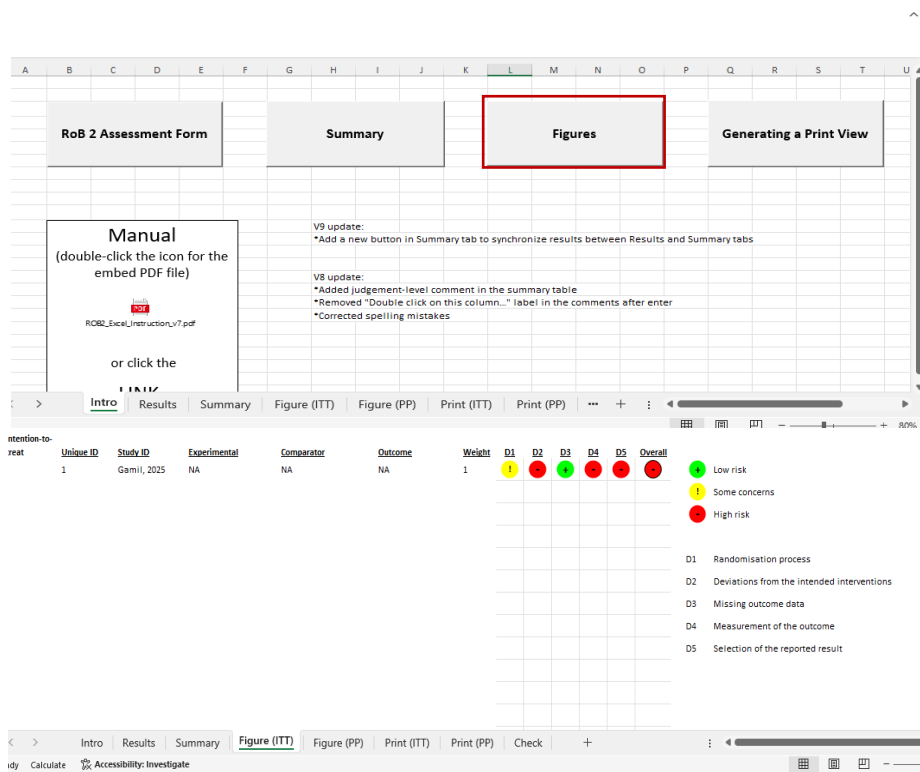


Fig. 15. Risk of bias summary table

In the “Check” sheet, you can paste the second assessor’s/reviewer’s results and check for discrepancies. If conflicts are found, resolve accordingly.

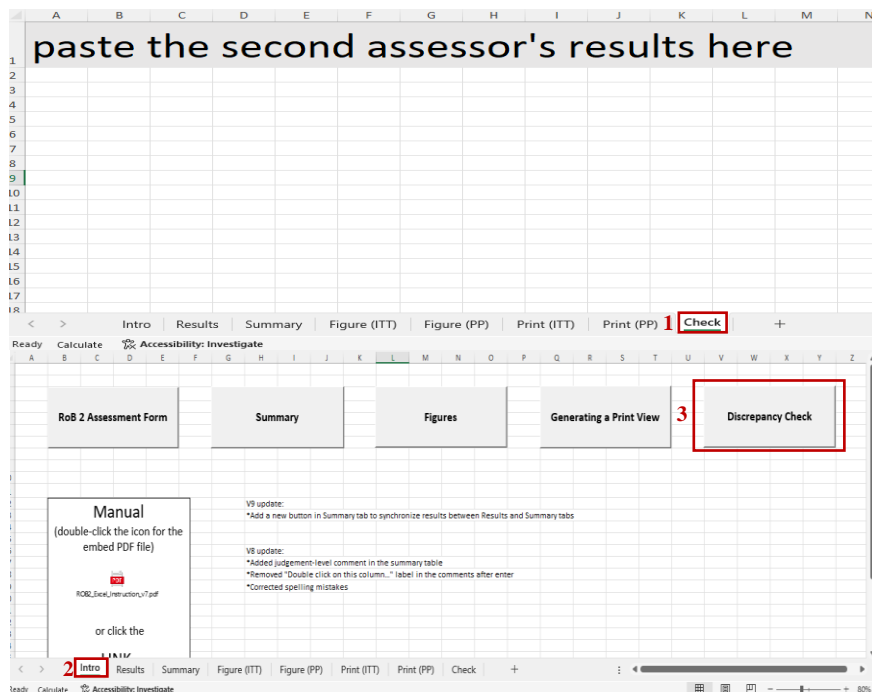


Fig. 16. Checking for discrepancies

As with other previously mentioned steps in MA and SR, the ROB assessment should be conducted independently by at least 2 reviewers.



STEP 9 – META-ANALYSIS

Combining results from multiple studies to produce a pooled estimate of effect size, thereby increasing statistical power and providing a more precise measure of the intervention or exposure effect.

Steps:

- Define your effect measures: Dichotomous (RR, OR), Continuous (MD, SMD)
- Follow the instructions illustrated in figures 17-23 to generate forest plot (to visualize pooled effect).

We will use [RevMan](#) , as it is the software recommended by Cochrane.

The image shows two screenshots of the Cochrane RevMan software interface. The top screenshot displays the 'Portfolio' page for a user named 'Usama Gamil'. It features a navigation sidebar on the left with options like 'Portfolio', 'Tasks', 'Subscription details', and 'Find reviews'. The main content area shows a progress bar with 'In progress' and 'Complete' sections, and a 'New review' button highlighted with a red box. The bottom screenshot shows the 'New review' form, also for 'Usama Gamil'. It includes three radio buttons for 'Create new review' (selected), 'Create review from file', and 'Create review using copying key'. Under 'Key fields', there are input boxes for 'Title' (containing 'Title of review'), 'Code', and 'Type' (set to 'Intervention review'). There are also dropdown menus for 'Template' (set to 'Organization') and another 'Template' field. At the bottom, there are 'Cancel' and 'Add review' buttons.

Fig. 17. Signing up and creating a new review

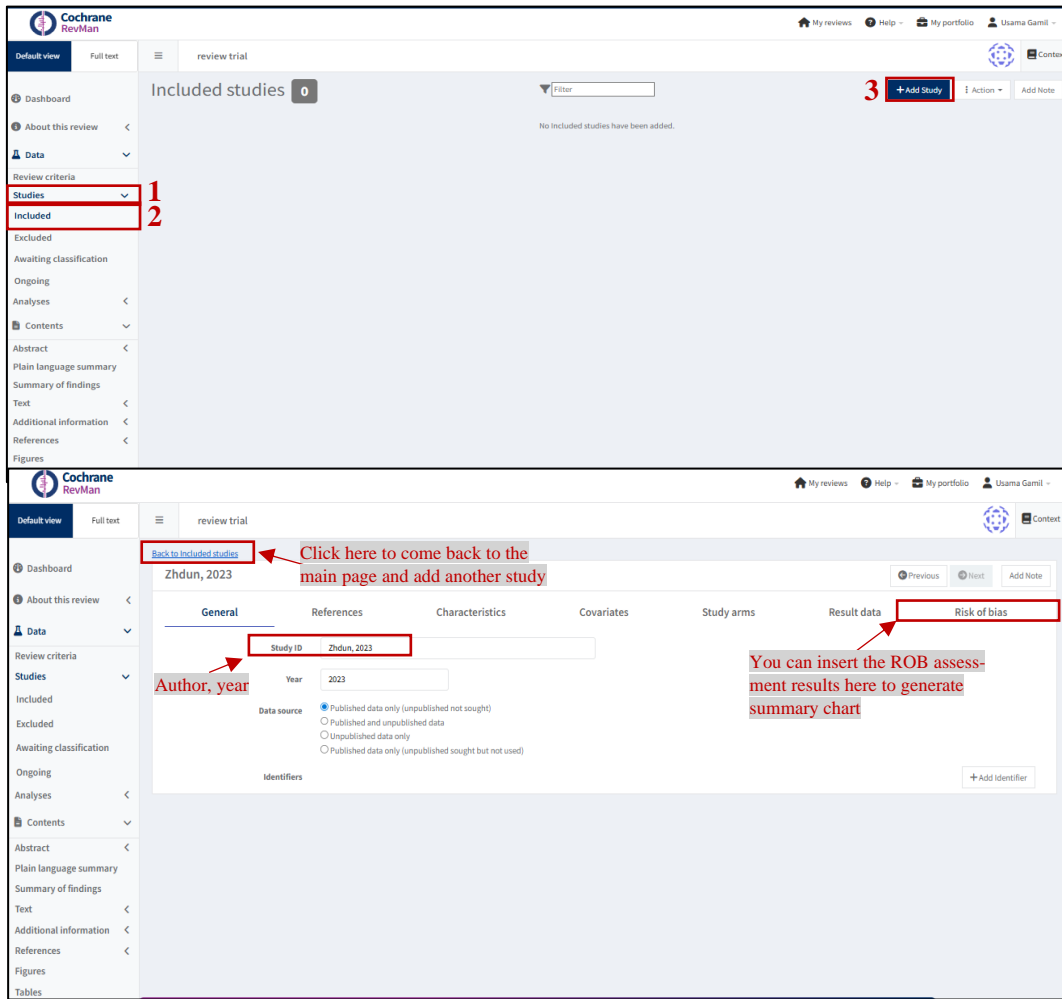
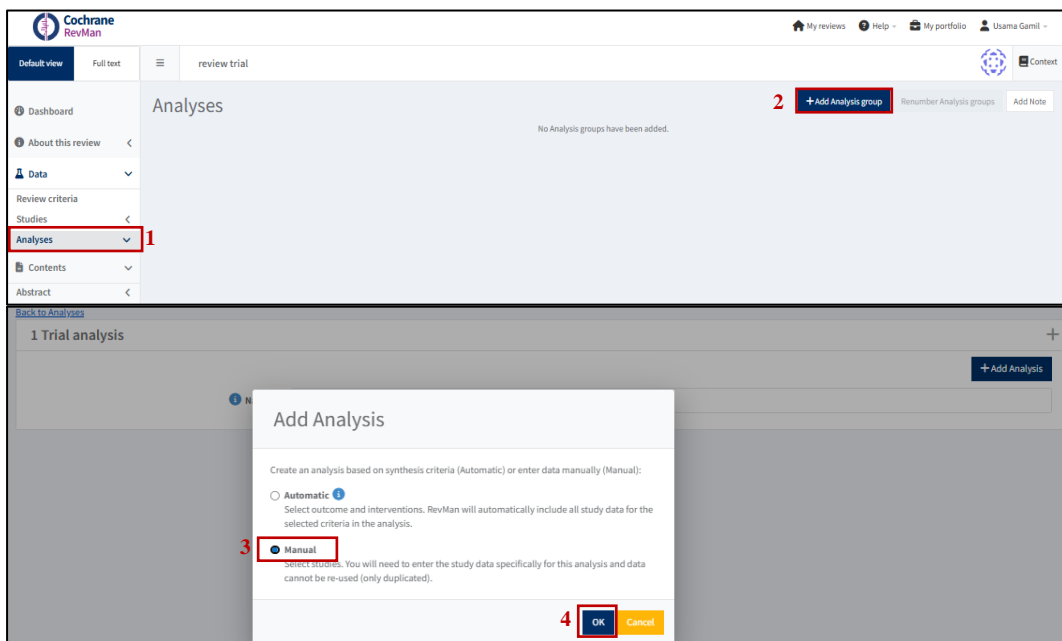


Fig. 18. Adding the included studies





1.1 New Analysis

Once finished, click here

Data

Options

Graphs

Name: New Analysis

Data source: Manual

Data type: Choose your data type (dichotomous or continuous)

Intervention group 1: Name your experimental and control groups (Drug A vs placebo)

Intervention group 2:

Statistical settings

Statistical method: Dichotomous: Mantel Haenszel, Continuous: Inverse variance

Effect measure: Dichotomous: OR, RR, RD, Continuous: MD, SMD

Analysis model: Fixed effect: studies are very similar, Random effect: Studies differ

Based on between-study heterogeneity (I²)

Test for overall effect: Not applicable
Heterogeneity: Not applicable

Study	Drug A			Placebo			Weight	Mean difference IV, Fixed, 95% CI	Action
	Mean	SD	Total	Mean	SD	Total			
No Rows To Show									

1

Study ID	Already added
Alex, 2024	No
Author, 2023	No
Zhdun, 2023	No

2

OK Cancel

Fig. 20. Defining analysis options

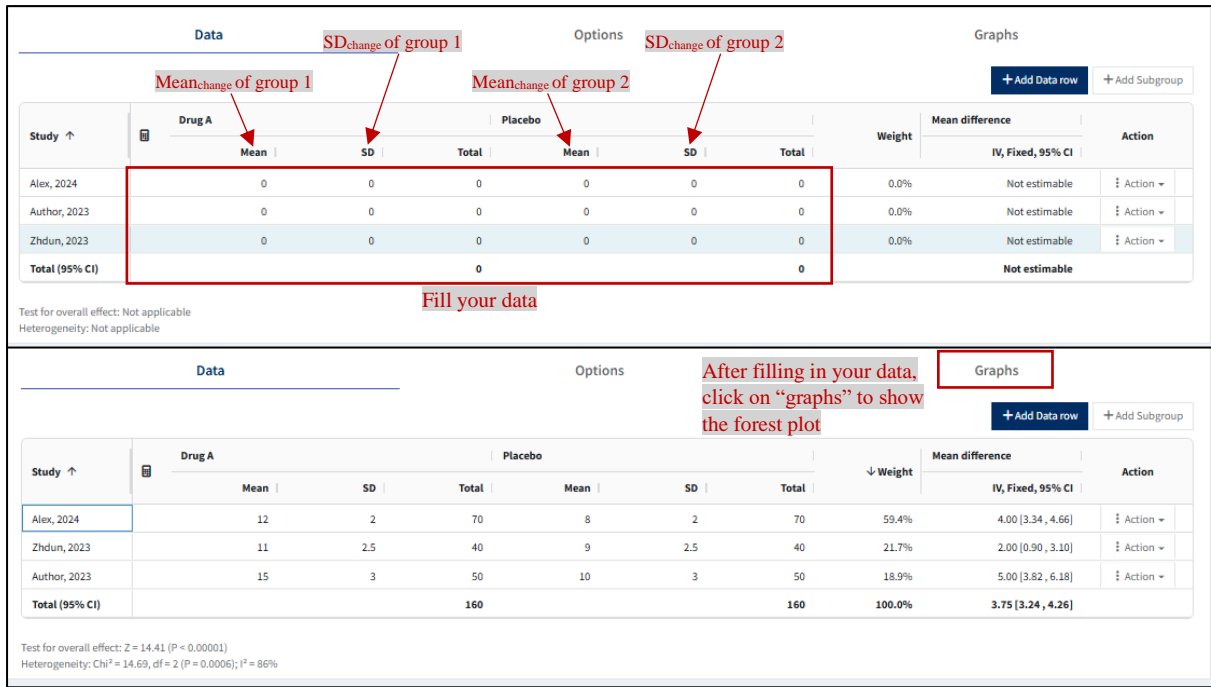


Fig. 21. Filling data of each study

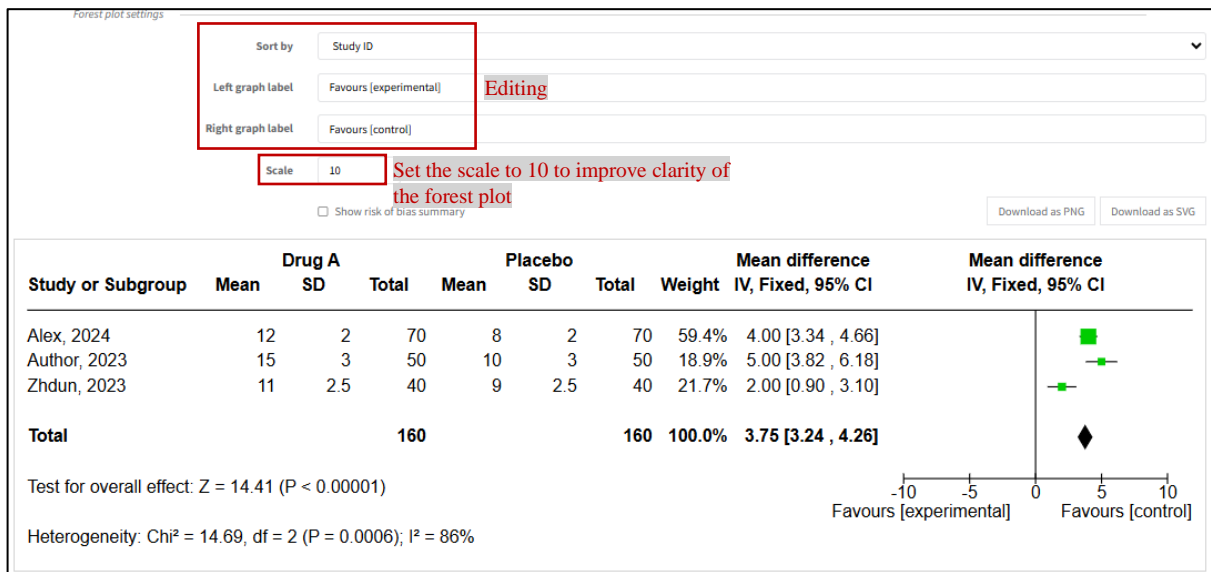


Fig. 22. Generated forest plot

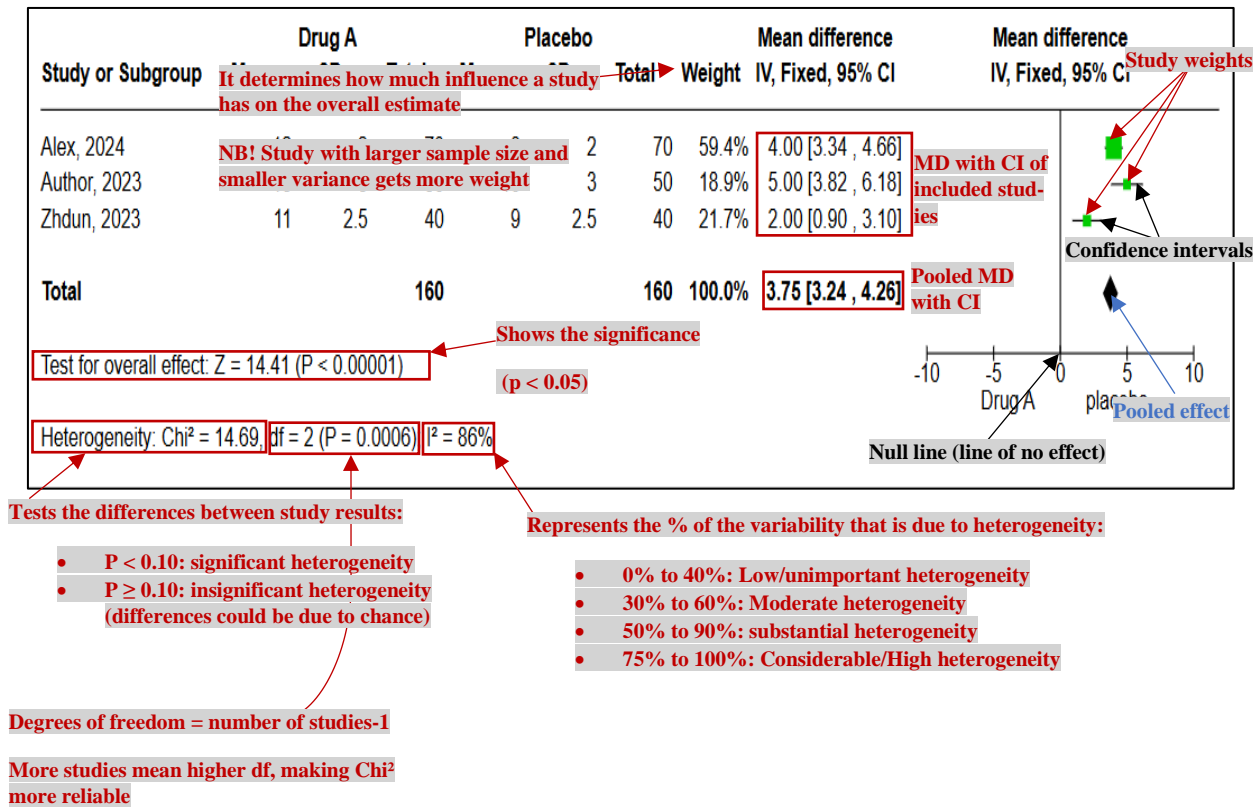


Fig. 23. Forest plot interpretation

Generating funnel plot to visualize publication bias (studies with negative or non-significant results are less likely to be published), as shown in figures 24-25.

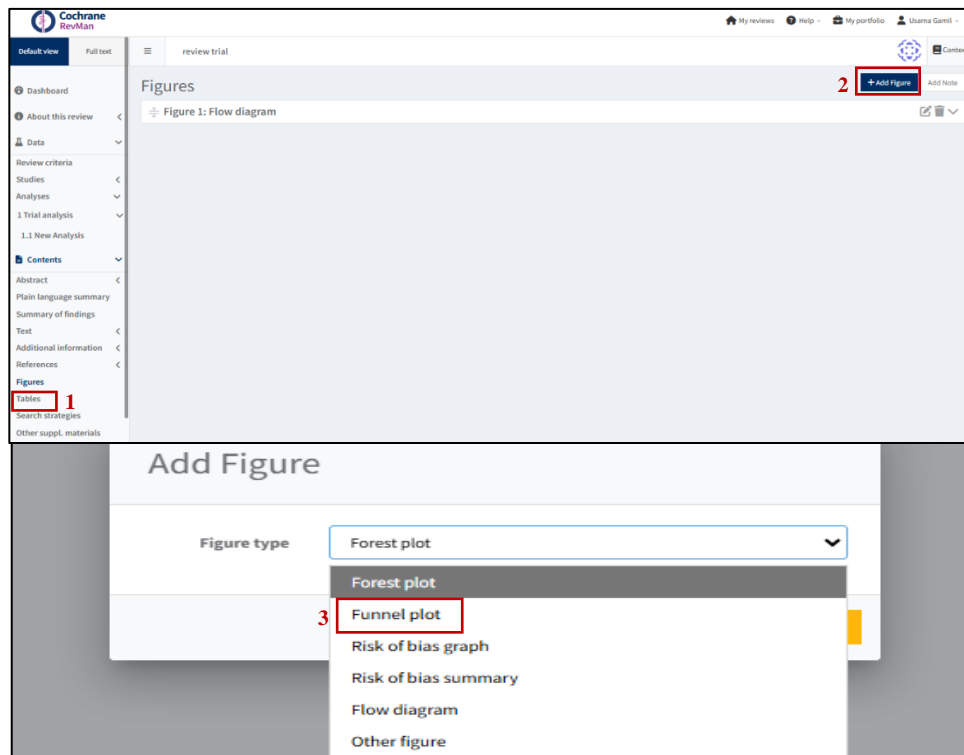


Fig. 24. Funnel plot generation

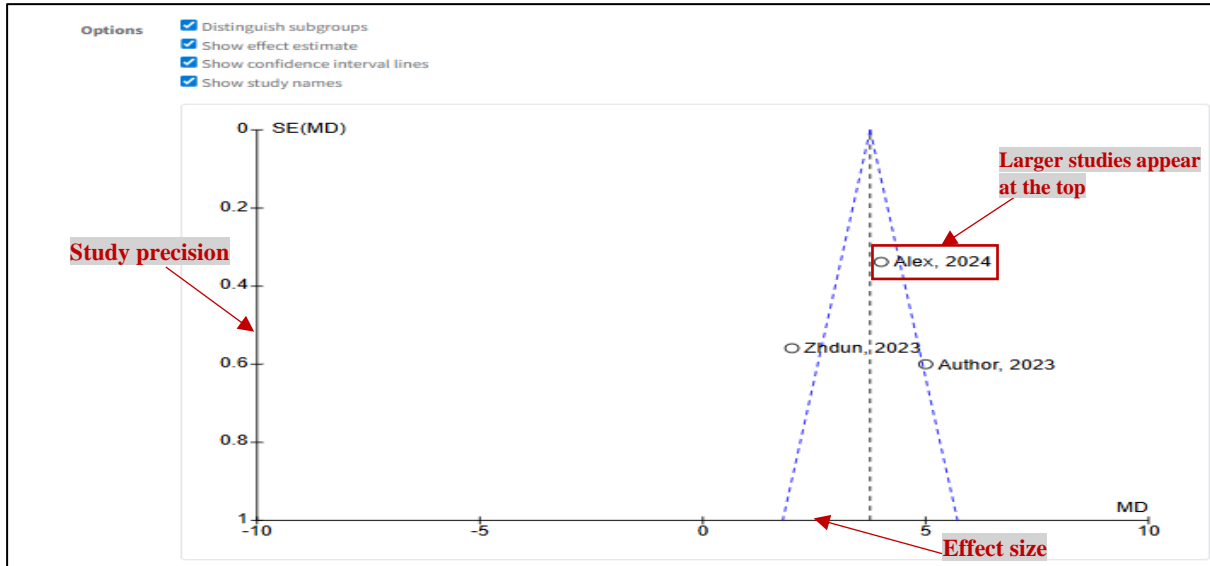


Fig. 25. Interpretation of generated funnel plot

Characteristics of funnel plot:

1. Ideal (no bias, symmetrical funnel):

- Points are spread evenly on both sides of the pooled effect line.
- Suggests results are not symmetrically missing.

2. Signs of publication bias (asymmetry in the funnel plot):

- Missing small negative studies.
- One sided scatter.

NB. Funnel plots are not reliable if fewer than 10 studies are included in MA.

Other way of assessing publication bias is by performing Egger's test (using Jamovi or R (figure 26)).

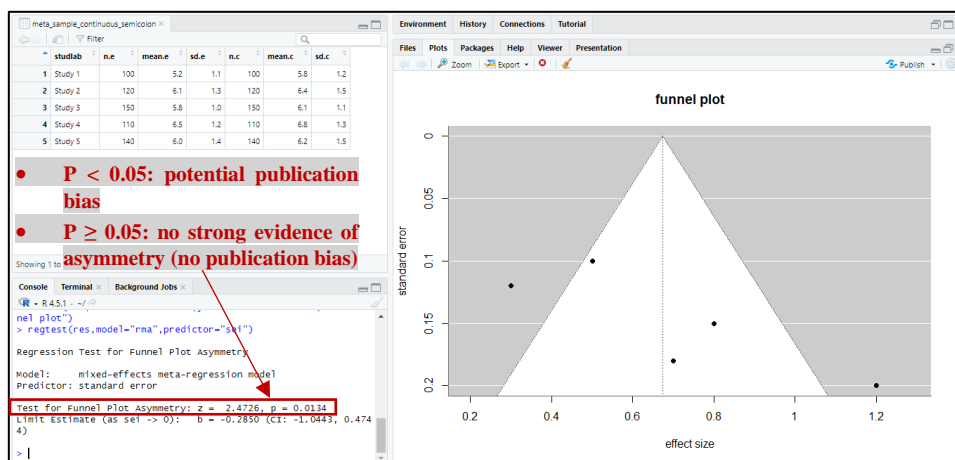


Fig. 26. Generated Egger's test for publication bias using R



Additional notes:

Table 4 summarizes when a meta-analysis should and should not be conducted.

Table 4

Situations favoring and discouraging meta-analysis

MA applicable	MA not applicable
The studies are similar enough	Combining oranges and apples
The outcome has been measured in a similar way	Outcomes are too different to be pooled
Ideally ≥ 2 studies (but meaningful synthesis requires $\geq 5-10$)	≤ 2 studies (better to do a narrative synthesis*)
Sufficient data: effect sizes, sample sizes, CIs, SDs)	Insufficient data
Acceptable heterogeneity (studies shouldn't be too different)	If all available studies are of very poor quality (High ROB)

* A *qualitative* summary of the results

The following software programs can be used to conduct MA:

- [RevMan](#)
- R:
 - Windows: [R](#) and [RStudio](#)
 - Mac: [R](#) and [RStudio](#)
- [JASP](#)



STEP 10 – WRITING AND REPORTING

1. Download [PRISMA 2020 checklist](#)
2. Write your review section-by-section:
 - Divide it into 3 stages: Pre-writing, first draft, and revision
 - Abstract, introduction (what we know? what we don't know? aim and objectives), methods, results, discussion, and conclusion.
3. Include:
 - Summary sheet, Baseline characteristics sheet, Outcomes sheet
 - PRISMA flow diagram
 - Forest plots
 - Funnel plot
 - Risk of bias summary
4. Save all datasets & code for reproducibility.
5. Plagiarism check

Structure:

1. Title

- a. Clear and descriptive, avoid abbreviations.
- b. Ex: The efficacy and safety of metformin in patients with type 2 diabetes: A systematic review and meta-analysis

2. Abstract

- a. Introduction
- b. Aim
- c. Methods
- d. Results
- e. Conclusion

3. Introduction

- a. Background: Burden of disease, role of treatment, importance of evaluating both efficacy and safety (What we know).
- b. Problem statement: Conflicting evidence exists; no comprehensive analysis (what we don't know yet).
- c. Aim and objectives (to discover what we don't know).

4. Methods



- a. Protocol & registration: PROSPERO registration number.
- b. Eligibility criteria: Define your PICO precisely, which study designs will be included?
- c. Search strategy: What you searched in different databases? what databases were included? which search terms did you use? any filters added?
- d. Study selection: How you screened your included studies? which software did you use?
- e. Data extraction: What data were extracted?
- f. Risk of Bias assessment: Which tool did you use?
- g. Data synthesis (meta-analysis): which effects did you use? Random or fixed? how the heterogeneity was assessed? any subgroup analysis?

5. Results

- a. Study selection: presented by PRISMA flowchart.
- b. Study characteristics: Summary table, baseline characteristics table, and outcomes table
- c. Risk of Bias: Summary table of quality assessment.
- d. Synthesized results: presented by forest plots.

6. Discussion

- a. Summary of main findings
- b. Comparison with literature: Discuss consistencies and differences.
- c. Strengths and limitations: e.g. comprehensive search, standardized data extraction, but heterogeneity across studies.
- d. Clinical implications

7. Conclusion

8. *References*: Include all included studies and relevant background literature.

9. *Supplementary materials* (optional): Full search strategies, data extraction sheets, additional forest plots.



REFERENCES

1. Harrer, M., Cuijpers, P., Furukawa, T. A., & Ebert, D. D. (2022). Doing meta-analysis with R: A hands-on guide. CRC Press. <https://doi.org/10.1201/9781003107347>
2. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.5 (updated August 2024). Cochrane, 2024. Available from www.cochrane.org/handbook.