How to Conduct a Systematic Review and Meta-analysis

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Systematic reviews and meta-analysis combine results and analysis of data from different primary studies (e.g. cross-sectional studies, case-control studies, cohort studies) conducted on similar or related research topics. They are secondary studies that guide clinical decision-making, delivery of care and policy development. This article aims to discuss how to conduct a systematic review and meta-analysis. The steps in conducting a systematic review and meta-analysis include: 1) Identify the purpose including formulating the research question and validating the purpose of the literature scan, 2) Formulate the objectives, 3) Literature search including selection of studies based on population, intervention, comparison and outcome, 4) Retrieval of full text articles, 5) Critical appraisal of articles, 6) Data extraction, 7) Data analysis and 8) Writing the final report. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) is a useful guide in conducting and write systematic review and meta-analysis. While ethics approval is not usually required for systematic review and meta-analysis, authors of such study should still observe good practices including avoiding plagiarism, maintaining transparency and ensuring data accuracy.

Key words: Systematic review, meta-analysis

Introduction

Systematic reviews and meta-analysis are research methods that combine and analyze data from different studies conducted on similar or related research topics. These are powerful tools that have been actively performed in various fields as they overcome difficulties in performing large-scale studies.[1] Systematic reviews involve a detailed and comprehensive plan and search strategy aimed at reducing bias through the identification, appraisal, and synthesis of all relevant studies on a particular topic. They differ from narrative reviews which are mainly descriptive and often only focus on a subset of studies in an area chosen based on availability or author selection.[2]

Systematic reviews may or may not include a statistical synthesis called meta-analysis, which involve techniques to synthesize the data from several into a single quantitative estimate or summary effect size. The type of effect size calculated depends on the type of outcome and intervention being examined as well as the data available from published trials.[3] Thus, a meta-analysis is the combination of data from several independent primary studies that address the same question to produce a single estimate like the effect of treatment or risk factor. Meta-analysis reduces the quantity of data by summarizing data from multiple resources, helps to make efficient use of existing data, ensuring generalizability, helping to check consistency of relationships, explaining data inconsistency, and quantifies the data and helps to improve the precision in estimating the risk by using explicit methods.[4] Although systematic reviews are published in academic forums, there are also organizations and databases specifically developed to promote and disseminate them. For example, the Cochrane Collaboration (www.cochrane.org) is a widely recognized and respected international and not-for-profit organization that promotes, supports, and disseminates systematic reviews and meta-analyses on the efficacy of interventions in the health care field.

Why Conduct a Systematic Review and Meta-analysis

Systematic reviews and meta-analyses can be used to produce statements to guide clinical decision-making, the delivery of care, as well as policy development. Systematic reviews and meta-analyses may be conducted to: 1) Investigate conflicting results of studies; 2) Address variations to clinical practice; 3) Inform areas for future research; and 4) Produce statements to guide decision-making and policy-making. A systematic review and meta-analysis may be conducted to determine whether or not current practice is based on relevant evidence and to

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address any variation in practice that may be occurring. Conducting a systematic review and meta-analysis may also identify gaps, deficiencies, and trends in the current evidence and can help underpin and inform future research in the area.[5]

An example of published systematic review and meta-analysis in family and community practice is "The effectiveness of community-based interventions in the control of hypertension: A systematic review and meta-analysis, published in the Filipino Family Physician and may be accessed in this link. https://thepafp.org/journal/abstract/the-effectiveness-of-community-based-interventions-in-the-control-of-hypertension-a-systematic-review-and-meta-analysis/[6]

Authorship in Meta-analysis: Team Size and Dynamics

While Cochrane recommends a team of two review authors for systematic reviews and meta-analyses, the Philippine Academy of Family Physicians (PAFP) advocates for a team of three review authors, consisting of two residents and one consultant who serves as the group's adviser.[7,8] In instances where the initial two reviewers encounter differing viewpoints or disagreements during the review process, it is important to resolve these through thorough discussion or consultation with the third reviewer, who serves as an impartial arbiter.[1] This collaborative approach promotes consensus and ensures that the final extracted data represent a collective agreement which reduces subjectivity and strengthens the overall validity of the review.

Steps in Conducting a Systematic Review and Meta-analysis

1. Identify the Purpose

There are two main goals in mind when making a systematic review and meta-analysis. First is the assessment of the evidence for the effectiveness of specific interventions for a certain condition or causal associations attributed to this specific condition. Second is to paint the big picture using broad generalizations across larger numbers of study outcomes. These two are often contrasting in their overarching purposes and must be clarified early in the study.[9]

When the goal is determining effectiveness of specific interventions or determining causal associations, PICO (population, intervention, comparator, outcome) is usually the framework being used in meta-analysis research in primary care practice in the Philippines. The approach is different when attempting to do broad generalizations. Here, the focus is mainly in identifying sources of heterogeneity in large swathes of knowledge, with deliberate incorporation of heterogeneous populations so that factors that modify their outcomes can be examined. This is usually done in social sciences and EEC (ecology, evolutionary biology, and conservation). For this text, the focus will be on the first type which is more relevant in family medicine practice in primary care settings.

Formulating the Research Question

Formulating the topic is an important step and is anchored by the formulation of the research question. The parameters of the study will be defined by the research question. The FINER criteria (Feasible, Interesting, Novel, Ethical, and Relevant) (Refer to Table 1 & Figure 1) are used to capture the engaging issues a systematic review should cover.[10]

Table 1. FINER criteria in formulating a research question.

Feasible	The study must be doable in terms of the breadth of the review being planned.
Interesting	There is commitment from the authors to see a study to its conclusion.
Novel	Made to address a genuine gap in knowledge.
Ethical	The opportunity costs must be considered, especially research that can have political implications that can widen health inequalities
Relevant	Involve stakeholders in defining the focus and questions it will address and to translate the writing to inform clinical decisions

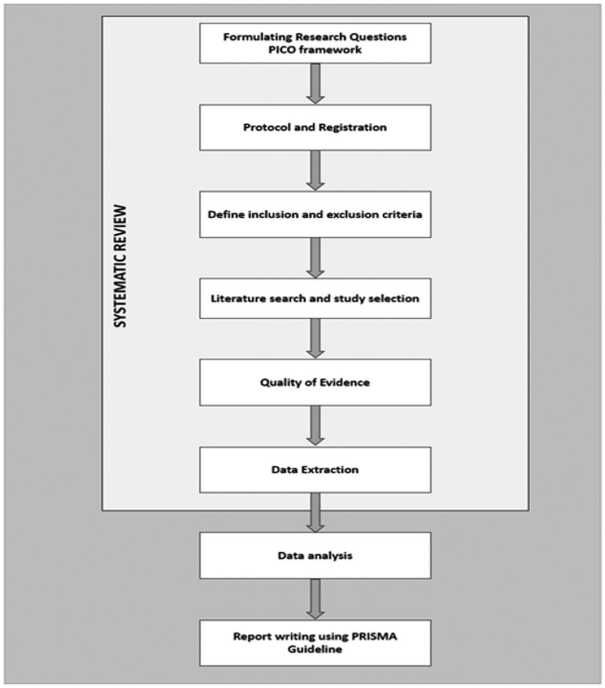


Figure 1. Overview of the steps in conducting a systematic review and meta-analysis.

Validating the Purpose with Literature Scan

Doing a literature scan gives the investigator a rough picture of the current available knowledge for their review. This is a continuous and overlapping process involving the desire of the reviewer to do broad or narrow topics. Broader topics allow better, and more accurate generalizations based on the available data, but this may involve a wider breadth of literature that needs to be processed. Narrower topics are

generally more feasible, but due to its more specific nature, literature availability and generalizability are an issue.[10] Thus, a literature scan allows investigators to gain methodological ground by identifying important issues to answer in their chosen topic and balance feasibility of a research question without sacrificing a meaningful output.[11]

2. Formulate the Objectives

The primary objective is ideally stated in one sentence and in the form of "To assess the effects of [intervention or comparison] for [health problem] in [types of people, disease, or problem and setting if specified]." This may be followed by secondary objectives. The PICO (Population, Intervention, Comparator, Outcome) pneumonic is usually the format followed. Different PICO constructs are used at different stages of the review:

- Review PICO – basis of study eligibility to be included.
- Synthesis PICO – determining how each synthesis will be structured.
- Studies PICO – what was actually investigated in the studies included.

3. Literature Search

Search strategies for meta-analysis should be systematic, transparent, and reproducible. This must include as many relevant studies as possible, including, possibly, unpublished studies. The most common search strategy being deployed in research practice is the use of keywords in electronic databases. The use of Boolean operators is advisable to narrow down search results and make the load more manageable. Databases used for clinical Systematic Review and Meta-analysis research include the following as principal search systems: ACM Digital Library, BASE, ClinicalTrials.gov, Cochrane Library, EbscoHost (tested for ERIC, Medline, EconLit, CINHAL Plus, SportsDiscus), OVID (tested for Embase, Embase Classic, PsychINFO), ProQuest (tested for Nursing & Allied Health Database, Public Health Database), PubMed, ScienceDirect, Scopus, TRID, Virtual Health Library, Web of Science (tested for Web of Science Core Collection, Medline), and Wiley Online Library.

Other search systems, like Google scholar, are not recommended as a principal search system due to various performance limitations.[12]

Selection of Studies

Studies should include all available literature, including gray literature, in order to prevent selection biases or "Matthew effect," or the bias towards highly cited articles.[13] Methodological peculiarities and appropriateness of the study in answering the research question can serve as reasons for study exclusion. This is conducted in a stepwise manner: 1) Removal of duplicate citations from different databases; 2) Abstract screening and 3) Full text screening

For in-depth criteria eligibility, the population, intervention, and comparison serve as the primary basis in the eligibility criteria for study inclusion. Outcomes are rarely used as an eligibility criterion. Hence studies should be included irrespective of their outcomes. Meaningful outcomes, such as outcomes of interest, may result in a study being included, while those that prevent certain outcomes may be excluded. Outcomes that are likely to be meaningful to all stakeholders involved should be included. Trivial outcomes should not be included.

Population

Disease or conditions of interest should be defined using explicit criteria that establishes their presence or absence. Broad population and setting of interest should be defined. Factors such as age, sex, race, educational status, or the presence of a particular condition such as pain or dyspnea. Settings may include primary care outpatient settings in low-middle income countries.

The following are useful criteria from Cochrane[14]

- How is the disease/condition defined?
- What are the most important characteristics that describe these people (participants)?
- Are there any relevant demographic factors (e.g. age, sex ethnicity)?
- What is the setting (e.g. outpatient, community, etc)?
- Who should make the diagnosis?
- Are there other types of people who should be excluded from the review (because they are likely to react to the intervention in a different way)?
- How will studies involving only a subset of relevant participants be handled?

Consider characteristics that might be expected to modify the size of the intervention effects. This means identifying subpopulations important for the implementation of the intervention which may modify its applicability or its expected effects. Once subpopulations are identified, the researcher may either maintain the breadth of the review or exclude these subpopulations.

Intervention

Interventions should be predefined and unambiguous in the studies to be included. Experimental interventions should be defined by specific comparators such as placebo, no treatment, standard of care, or if there is an active control such as a different type of intervention.

General considerations should include:

- What is delivered?
- Who delivered it?
- How is it delivered?
- Where is it delivered?
- Can the intervention be adapted or tailored?

Factors to consider when developing criteria for types of interventions:[14]

- What are the experimental and control (comparator) interventions of interest?
- Does the intervention have variations (e.g. dosage/intensity, mode of delivery, personnel who deliver it, frequency, duration or timing of delivery)?

- Are all variations to be included (for example, is there a dose below which the intervention may not be clinically appropriate, will all providers be included)?
- Will studies including only part of the intervention be included?
- Will studies including the intervention of interest combined with another?
- Have the different meanings of phrases such as 'control', 'placebo', 'no intervention' or 'usual care' been considered?

Minor differences can occur across different types of studies and should not hinder overall synthesis. However, what constitutes an important difference requires judgment from the reviewer. Generally, differences that alter decisions how an intervention is implemented or whether an intervention is used are important.

Comparison

Comparisons such as intervention versus placebo, intervention versus control, or intervention A versus intervention B must be considered. In some studies, multiple comparisons may result from multiple interventions. In these cases, a limited subset can be selected. The comparisons from these subsets can then be used for the review.

Retrieval of Full Text Articles

Retrieval of full text articles can be done via OpenAccess articles, Institutional subscriptions, or personal contact to the author.

Critical Appraisal of Studies

After retrieving the full text of selected articles, the next step in conducting a systematic review and meta-analysis involves critically appraising the individual studies. The caliber of the individual studies determines how reliable the systematic review and meta-analysis are. Meta-analyses can produce false conclusions if the findings of the initial studies are skewed.

Critical appraisal encompasses systematically assessing the risk of bias using predefined criteria, evaluating the relevance of the study populations, interventions, and outcome measures, and assessing the fidelity of intervention implementation. This process ensures the synthesis of credible and reliable evidence, enhancing the validity and impact of the review's findings.

Assessment of Bias

Bias is defined as a systematic error or deviation from the truth in the results obtained.[15] The presence of bias might cause the actual intervention effect to be underestimated or overestimated. To evaluate the reliability of the studies, review authors may include a section on Assessment of Bias in the data extraction form, as shown in Figure 2.

The study limitations are evaluated by review authors using the "Risk of Bias" method proposed by Cochrane 2022 (Table 2). Risk of bias is classified in randomized studies as "low", "unclear", or "high" based on the judgment of the review authors about the presence or absence of six domains: 1) Random sequence generation; 2) Allocation concealment; 3) Blinding participants or investigators; 4) Incomplete outcome data; 5) Selective reporting; 6) Other biases.

PRISMA Flow Diagram

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram is a crucial element in documenting and reporting the retrieval, inclusion, and exclusion process of studies in a systematic review. It provides a concise visual summary of the screening process, ensuring transparency by documenting decisions made at each stage.[16] Initially, the diagram reports the number of articles identified during the search. As the review progresses, it tracks the flow of articles, highlighting the number of included and excluded studies at each stage. It is essential to document the reasons for exclusion when excluding articles during the full-text assessment. By presenting this information in a clear and structured manner, the flow diagram enhances the reproducibility of the systematic review. Figure 3 shows the recommended format of the PRISMA 2020 flow diagram, depicting the selection process, the corresponding numbers of included and excluded reports, and the reasons for exclusions. This diagram should be included in the Results section of the final write-up of a Systematic Review and/or Meta-analysis

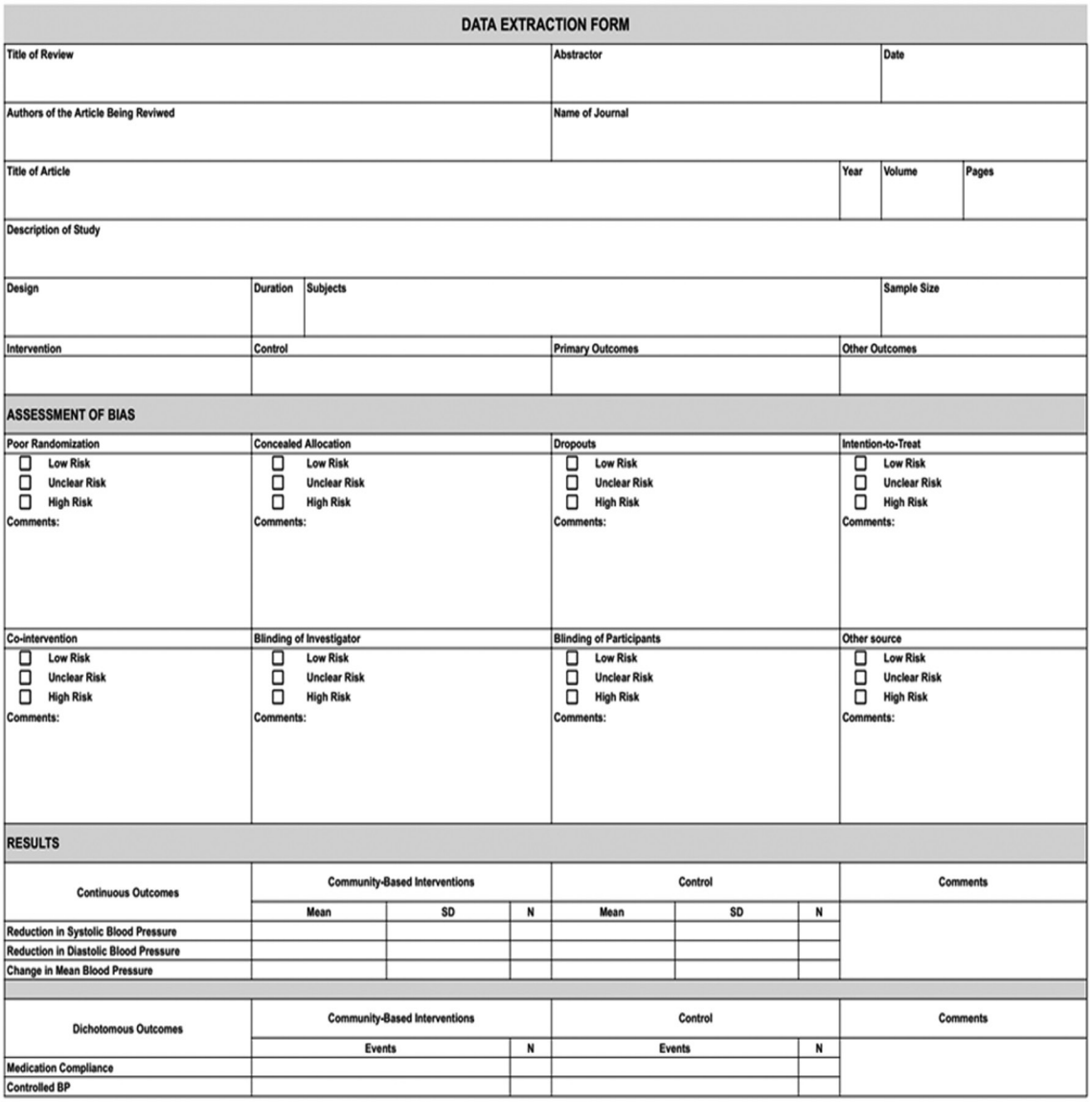
Data Extraction

The extraction of data involves systematically gathering pertinent information from a selected set of articles to establish a comprehensive understanding of the research topic. This process ensures that the review is founded on meticulous and accurate data, thereby minimizing potential biases. Currently, there are a number of online software that manage articles for systematic review including functions for data extraction. Some of these are Covidence, Rayyan, and Cachii.

When performing data extraction manually, a standardized Data Extraction Form for each study should be used by all review authors as seen in Figure 2. The reviewers should plan and discuss what data are to be extracted from the studies and independently extract data from each study.[7,8] In situations where initial reviewers encounter differing viewpoints or disagreements during the review and extraction process (e.g., whether a study should be included or excluded), a consultation with the third reviewer can be done to settle the decision. Table 3 presents the essential information that must be obtained at a minimum.

Data Analysis

As previously discussed, a meta-analysis synthesizes results from different studies in order to derive a conclusion that has greater accuracy and precision than may be possible when looking at individual studies. To do this, it is important to assess the direction of the effect, size of the effect, homogeneity of effects among studies, and strength of evidence.[1] This evaluation sets the foundation for a comprehensive review of the data, both qualitatively and quantitatively.



DATA EXTRACTION FORM

Title of Review		Abstractor	Date
Authors of the Article Being Reviwed		Name of Journal	
Title of Article		Year / Volume / Pages	
Description of Study			
Design	Duration / Subjects		Sample Size
Intervention	Control	Primary Outcomes	Other Outcomes

ASSESSMENT OF BIAS

Poor Randomization	Concealed Allocation	Dropouts	Intention-to-Treat
☐ Low Risk ☐ Unclear Risk ☐ High Risk Comments:	☐ Low Risk ☐ Unclear Risk ☐ High Risk Comments:	☐ Low Risk ☐ Unclear Risk ☐ High Risk Comments:	☐ Low Risk ☐ Unclear Risk ☐ High Risk Comments:
Co-intervention	**Blinding of Investigator**	**Blinding of Participants**	**Other source**
☐ Low Risk ☐ Unclear Risk ☐ High Risk Comments:	☐ Low Risk ☐ Unclear Risk ☐ High Risk Comments:	☐ Low Risk ☐ Unclear Risk ☐ High Risk Comments:	☐ Low Risk ☐ Unclear Risk ☐ High Risk Comments:

RESULTS

Continuous Outcomes	Community-Based Interventions			Control			Comments
	Mean	SD	N	Mean	SD	N	
Reduction in Systolic Blood Pressure							
Reduction in Diastolic Blood Pressure							
Change in Mean Blood Pressure							

Dichotomous Outcomes	Community-Based Interventions		Control		Comments
	Events	N	Events	N	
Medication Compliance					
Controlled BP					

Figure 2. Sample Data Extraction Form, adapted from the study "The Effectiveness of Community-based Interventions in the Control of Hypertension - A Systematic Review and Meta-analysis" by Arteza, Yayen, and Mendoza (2022) published in The Filipino Physician Journal (Arteza, et al, 2022)

Table 2. Cochrane Risk of Bias Assessment Tool adapted from Cochrane 2022.

Domain	Description	Review authors' judgment
1. Sequence generation.	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.	Was the allocation sequence adequately generated?
2. Allocation concealment	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment.	Was allocation adequately concealed?

3. Blinding of participants, personnel, and outcome assessors	Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	Was knowledge of the allocated intervention adequately prevented during the study?
4. Incomplete outcome data	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions were reported, and any re-inclusions in analyses performed by the review authors.	Were incomplete outcome data adequately addressed?
5. Selective outcome reporting	State how the possibility of selective outcome reporting was examined by the review authors, and what was found.	Are reports of the study free of suggestion of selective outcome reporting?
6. Other sources of bias	State any important concerns about bias not addressed in the other domains in the tool. If particular questions/entries were pre-specified in the review's protocol, responses should be provided for each question/entry	Was the study apparently free of other problems that could put it at a high risk of bias?

Table 3. Essential information to be obtained from each study (Mendoza 2022; Espallardo 2023).

Information	Purpose
1. The title of the article / Name of the Journal	Provides the title of the study, aiding in the identification and referencing of the specific article
2. The name of the first author	Proper identification and citation of the study
3. The year the article was published	Provides temporal context and establishes the chronological timeline of research on the topic
4. The population on whom the study was conducted	Specifies the characteristics of the individuals or groups involved in the study
5. The type of research	Identifies the study design (e.g., randomized controlled trials, cohort studies, case-control studies)
6. Brief description of the intervention	Provides information on the intervention's dosage, form, administration method, and other relevant details

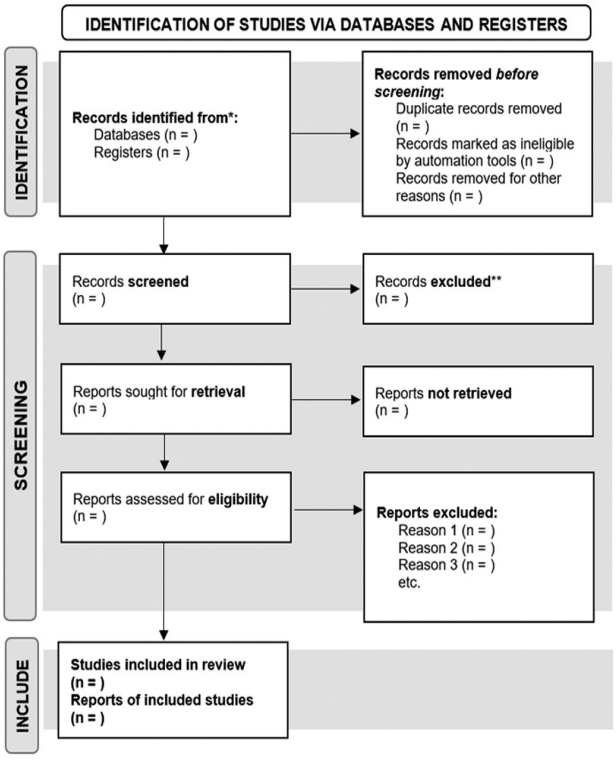


Figure 3. PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only (Figure recreated from PRISMA 2020 Flow Diagram template.)

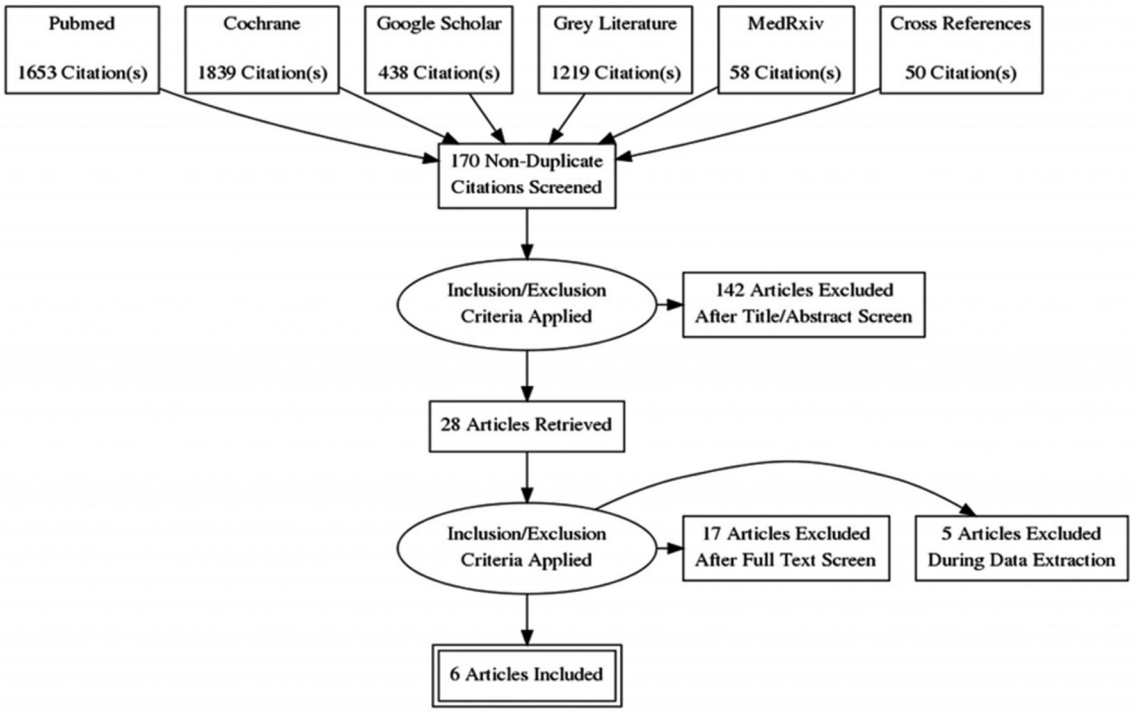


Figure 4. PRISMA flow diagram from The Effectiveness of Community-based Interventions in the Control of Hypertension: A Systematic Review and Meta-analysis by Arteza, Yayen, Mendoza (2022); The Filipino Family Physician Journal.

A qualitative review is done if the different research outcomes cannot be combined due to inherent differences.[1] This involves presenting the results and characteristics of the individual studies in a tabulated or a descriptive format allowing for a comprehensive understanding of each study's contribution to the topic at hand. Conversely, if the results are comparable and can be combined, then the review authors can proceed to create a quantitative review or a meta-analysis.

A meta-analysis typically involves two stages. In the first stage, a summary statistic or an effect measure is computed to effectively describe the observed intervention effect in the same manner across all studies. This summary statistic may take the form of a risk ratio for dichotomous data or a difference between means for continuous data, ensuring uniformity in reporting the effect size. In the second stage, the clinical effectiveness of the treatment is assessed by calculating a weighted pooled estimate based on individual studies.[15] This pooled estimate serves as the primary outcome of the meta-analysis and is often visually represented using a forest plot, providing a clear overview of the collective evidence. The calculations and generation of a forest plot are done using statistical software (e.g., Review Manager) that researchers can either download for free or access through a paid subscription. An example of a forest plot generated through the software Review Manager v 5.4 is illustrated in Figure 5.

For detailed instructions on how to use Review Manager, version 5.4, you can refer to the official user guide provided by Cochrane, which is available at https://training.cochrane.org/system/files/uploads/protected_file/RevMan5.4_user_guide.pdf. Additionally, online learning resources on using RevMan 5.4 can be found at https://training.cochrane.org/online-learning/core-software/revman.

Establish Types of Data and Effect Measures: Continuous and Dichotomous Variables

When evaluating data, there are two types of outcome variables: continuous variables and dichotomous variables. Continuous variables are measurements that can take any value within a specific range, such as blood pressure or cholesterol levels. (Table 3) In contrast, dichotomous variables are outcomes with only two possible categories, such as the presence or absence of disease. In studies, the outcomes of participants are summarized by an estimate of effect or association, these are referred to as Effect Measures or Measures of Association. The types of Effect Measures for each outcome data are enumerated in Table 4.

When combining data from continuous variables, the effect measures used are the mean difference (MD) and standardized mean difference (SMD). The mean difference represents the absolute difference in mean values between groups and is used when all studies utilize the same scale of measurement (e.g., blood pressure in mmHg).[1] Alternatively, the standardized mean difference is employed when studies assess the same outcome using different scales or instruments (e.g., WHO Quality of Life Measurement and the McGill Quality of Life Questionnaire).

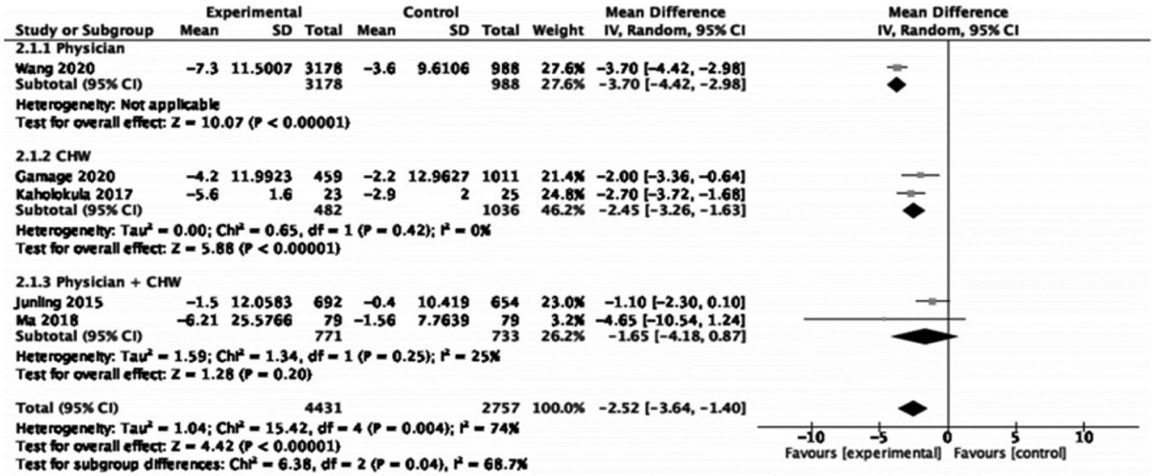


Figure 5. Example of a Forest plot illustrating the pooled estimate of community-based interventions in the control of hypertension,adapted from the study "The Effectiveness of Community-based Interventions in the Control of Hypertension - A Systematic Review and Meta-analysis" by Arteza, Yayen, and Mendoza (2022) published in The Filipino Family Physician (Arteza et al, 2022)

Table 4. Outcome Variables with corresponding definitions, examples, and effect measures.

Outcome Variables	Definition	Examples	Effect Measures/ Measures of Association
Continuous Variables	• Refers to data that can take any value within a range. • It is characterized by its ability to be measured on a continuous scale. • Typically obtained through instruments or measurements that can provide precise numerical values	• Blood Pressure • Quality of life • Fasting blood sugar • Hemoglobin A1c	1 . Mean Difference (MD) 2. Standard Mean Difference (SMD)
Dichotomous Variables	• Refers to data that has only two possible outcomes or responses. • It has a binary nature, where each observation or data can be classified into one of two mutually exclusive categories.	• BP control, • Medication compliance • Mortality	1. Risk Ratio (RR) 2. Odds Ratio (OR) 3. Risk Difference (RD) 4. Number Needed to Treat (NNT)

The effect measures used in dichotomous variables are enumerated in Table 4. For randomized controlled trials (RCTs), quasi-experimental studies, or cohort studies The Risk Ratio and Risk Difference can be used. On the other hand, in case-control studies or cross-sectional studies, the Odds Ratio is typically used.[1] It should be noted that the interpretation of the Odds Ratio can be challenging; hence, using the Risk Ratio or Risk Difference is recommended when possible.

When choosing an effect measure for a meta-analysis, it is important to consider whether it conveys the necessary clinically useful information, is appropriate for the study design, and is statistically suitable and convenient for analysis. By understanding the nature of continuous and dichotomous variables and selecting appropriate effect measures, review authors can effectively combine and analyze data in a systematic review and meta-analysis, ultimately providing valuable insights into the efficacy of interventions or the impact of risk factors.

Analyze the Effect Size: Fixed-effects and Random-effects Models

In a meta-analysis, each study is summarized by an estimate, and the overall measure of effect is calculated as a weighted average of these individual study results. 15 When analyzing the effect size, review authors can choose between two models: the Fixed Effects Model and the Random Effects Model. Before choosing the type of model to be used in the meta-analysis, researchers must consider assumptions intrinsic in each model as well as factors within each study and differences between studies. Refer to Table 5.

Table 5. Comparison of fixed effects model and random effects model.

	Fixed-Effects Model	Random-Effects Model
Assumption of Effect	Assumes a single true effect size across all studies	Allows for different true effect sizes across studies
Weighting of Studies	Assigns greater weight to larger studies	Assigns weights based on within-study and between-study variation
Interpretation	Estimated effect size represents the average effect across studies	Estimated effect size represents the average effect, accounting for heterogeneity
Heterogeneity	Does not account for heterogeneity between studies	Accounts for heterogeneity between studies
Study Selection	Assumes studies are drawn from the same population	Can accommodate studies with varying characteristics
Precision	Relatively more precise estimates due to emphasis on larger studies	Less precise estimates due to consideration of between-study variation
Sensitivity Analysis	Limited ability to explore and assess heterogeneity	Allows for exploration and assessment of heterogeneity
Statistical Testing	Typically uses fixed effects estimators and tests	Utilizes random effects estimators and tests

The Fixed Effects Model assumes that all studies in the meta-analysis share a common true effect size.[7] This means that the treatment's effect is consistent across all studies, and any apparent variation across studies is solely attributed to random errors inherent in each study. In essence, if it were not for random (sampling) error, all study results would be identical. Consequently, the Fixed Effects Model assigns greater weight to larger studies, as they provide more precise estimates.[1] This model is appropriate when the studies are homogeneous, meaning they are drawn from the same population, share similar characteristics, adopt the same design and methodology, or when there is minimal variability in results within each study and any remaining variance is thought to be caused by random error.

On the other hand, the Random Effects Model assumes that there is heterogeneity or variation in the true effect size across studies, in addition to sampling error. This model is used when the studies are considered different from each other.[1] It considers both within-study sampling error and between-study variation when estimating the overall effect size. Unlike the Fixed Effects Model, the Random Effects Model does not significantly decrease the weight assigned to studies with a small number of patients, as it acknowledges the potential heterogeneity among studies.

In summary, the choice between these models is determined by the underlying assumptions regarding the similarity of studies and the presence of heterogeneity. If the studies are assumed to be homogeneous, the Fixed-Effects Model is appropriate. However, if substantial heterogeneity is deemed present between studies, the Random Effects Model is preferred as it provides a more comprehensive estimate by incorporating both within-study and between-study variation.

Evaluate Heterogeneity

Heterogeneity arises from variations in experimental effects analyzed across studies included in the meta-analysis, which cannot be solely attributed to random error. It results from differences in clinical and methodological aspects across each study.[15] Clinical variations can lead to different intervention effects measured in different types of studies, while methodological differences reflect varying degrees of bias. However, methodological diversity does not necessarily imply variations in the true outcome across studies. Thus, a valid meta-analysis should include studies that are sufficiently homogeneous in terms of participants, interventions, and outcomes. Evaluating the heterogeneity of the included studies is therefore crucial for each assessed outcome.

Qualitatively, heterogeneity can be assessed by comparing the confidence intervals of individual studies in the forest plot. Poor overlap among confidence intervals suggests statistical heterogeneity. In Table 6, studies with smaller confidence intervals show limited overlap, indicating possible statistical heterogeneity.

Quantitatively, the chi-square (χ^2 or Chi^2) test is used to evaluate the presence of statistically significant heterogeneity across the included studies. A p-value below the threshold of statistical significance (commonly $p < 0.05$ or $p < 0.10$) indicates significant heterogeneity among the outcome estimates. For instance, in Figure 5, the p-value is $p = 0.004$, indicating a statistically significant degree of heterogeneity. Conversely, the Higgins I^2 test is employed to assess the degree of statistical heterogeneity. Interpretation of I^2 values varies across references, but the Cochrane Handbook suggests the following thresholds listed in Table 6. In Figure 5, the I^2 value is $I^2 = 74\%$,

indicative of moderate to substantial heterogeneity across the included studies which the researchers attributed to differences in the study population, study location, and intervention.[6]

Table 6. I^2 values with their corresponding degrees of heterogeneity according to Cochrane Handbook 2022.

I^2 Value	Degree of Heterogeneity
0%-40%	Might not be important
30%-60%	May represent moderate heterogeneity
50%-90%	May represent substantial heterogeneity
75%-100%	Considerable heterogeneity

Assess for Publication Bias

Publication Bias is the most common bias in meta-analyses (Ahn, 2018), it refers to the selective publication or non-publication of research results based on their nature and direction (Cochrane, 2022). It has been widely acknowledged that published trials tend to present results favoring the intervention and are more likely to show statistical significance compared to unpublished trials. Studies with positive findings are also more likely to receive funding and subsequent publication, while those with unfavorable results may be less likely to be published or may be published later. Additionally, smaller studies with inconclusive or negative findings face higher chances of non-publication or delayed publication compared to larger studies with favorable experimental results.[7,8] Therefore, a funnel plot is generated to assess publication bias among the included studies in the meta-analysis.

A funnel plot is a scatter plot that compares the intervention effect point estimates of each study against a measure of its size or precision. The plot is based on the understanding that the precision of the calculated outcome is directly proportional to the study's size. A funnel plot can be constructed when there are more than five studies included in the meta-analysis.[7,8]

Typically, this plot is generated using statistical software such as Review Manager, providing a graphical representation of potential bias by displaying the distribution of study results relative to their sample size or precision. In the funnel plot, the intervention effect estimates are plotted on the vertical axis, while the sample size or precision is plotted on the horizontal axis for each study. Consequently, smaller studies may be spread out at the bottom of the graph, with the spread narrowing as studies increase in size or precision. Interpreting the funnel plot is qualitative: the presence of a symmetric inverted funnel suggests the absence of publication bias (Figure 6-A), while an asymmetrical appearance indicates potential publication bias (Figure 6-B). The extent of asymmetry corresponds to the magnitude of bias.

Sensitivity Analysis

A Sensitivity Analysis examines the robustness of the conclusions with respect to the overall quality of the included studies.[15] It is a procedure used to determine how the values of an independent variable will influence the significance of a given dependent variable when one or more studies are removed from the meta-analysis.[17] Following the individual article appraisals, certain studies may be identified as having a high risk of bias, which could potentially impact or invalidate the overall result, particularly if it is statistically significant. In such cases, a sensitivity analysis can be conducted by reassessing the relevant outcome after excluding the studies with a high risk of bias from the analysis. If the sensitivity analysis demonstrates that the overall result and conclusions remain unchanged despite the removal of studies with

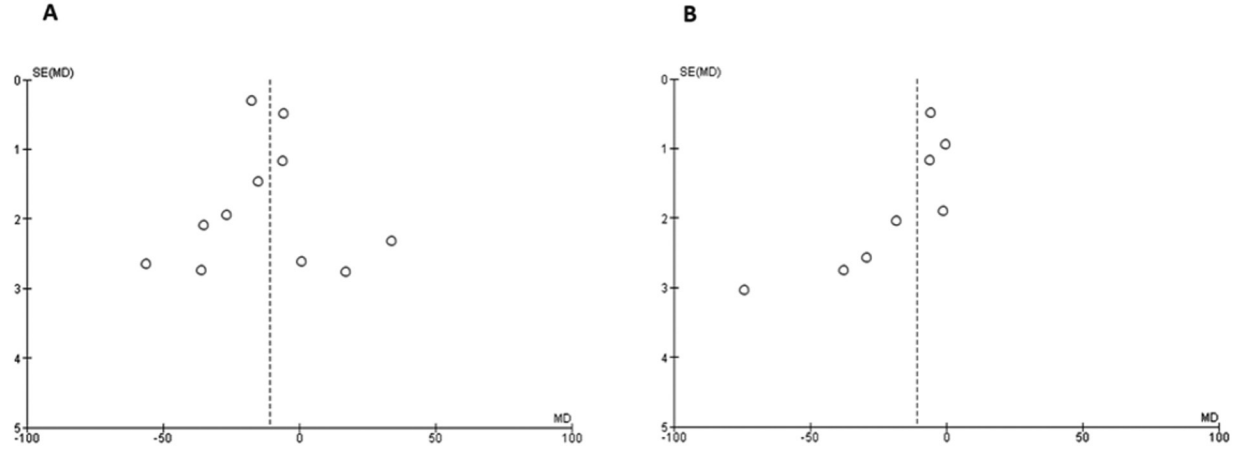


Figure 6. Theoretical Funnel Plots showing the effect size on the x-axis and sample size on the y-axis as a scatter plot. (A) Funnel plot without publication bias. The individual plots are broader at the bottom and narrower at the top. (B) Funnel plot with publication bias. The individual plots are located asymmetrically.

a higher risk of bias, the results are considered more robust, and their interpretation becomes more reliable.

Subgroup Analysis

Subgroup analysis involves classifying participant data into subsets for comparison based on criteria such as gender, geographical area, or other relevant parameters.[15] It addresses issues about specific patient groups, interventions, or study designs, particularly when faced with persisting heterogeneity despite a random-effects model. In such cases, subgroup analysis becomes critical, assisting in the exploration of potential causes of variability by determining whether the treatment impact varies across study subgroups.

In Figure 7, the forest plots illustrate the subgroup analysis conducted by Arteza et al in their study entitled 'The Effectiveness of Community-based Interventions in the Control of Hypertension: A Systematic Review and Meta-analysis.' The subgroup analyses were based on two key factors: (a) who is responsible for implementing the interventions and (b) the types of interventions employed. Identification and analysis of subgroups based on characteristics offer insights into factors contributing to observed heterogeneity, refining the precision and applicability of findings.

The plan for subgroup analysis should be explicitly stated in the research protocol. A priori decisions enable transparency, methodological rigor, and the mitigation of data-driven issues. Criteria, rationale, and anticipated differences in treatment effects based on chosen factors should be clearly outlined in the research protocol. This pre-specification reduces bias and increases the credibility of study results. If additional relevant subgroups emerge during the research, this should be documented as exploratory post hoc analyses.

Ethical Issues

A systematic review and meta-analysis study does not require ethics board approval as it involves analyzing data that has been previously published, assuming it was approved by respective review

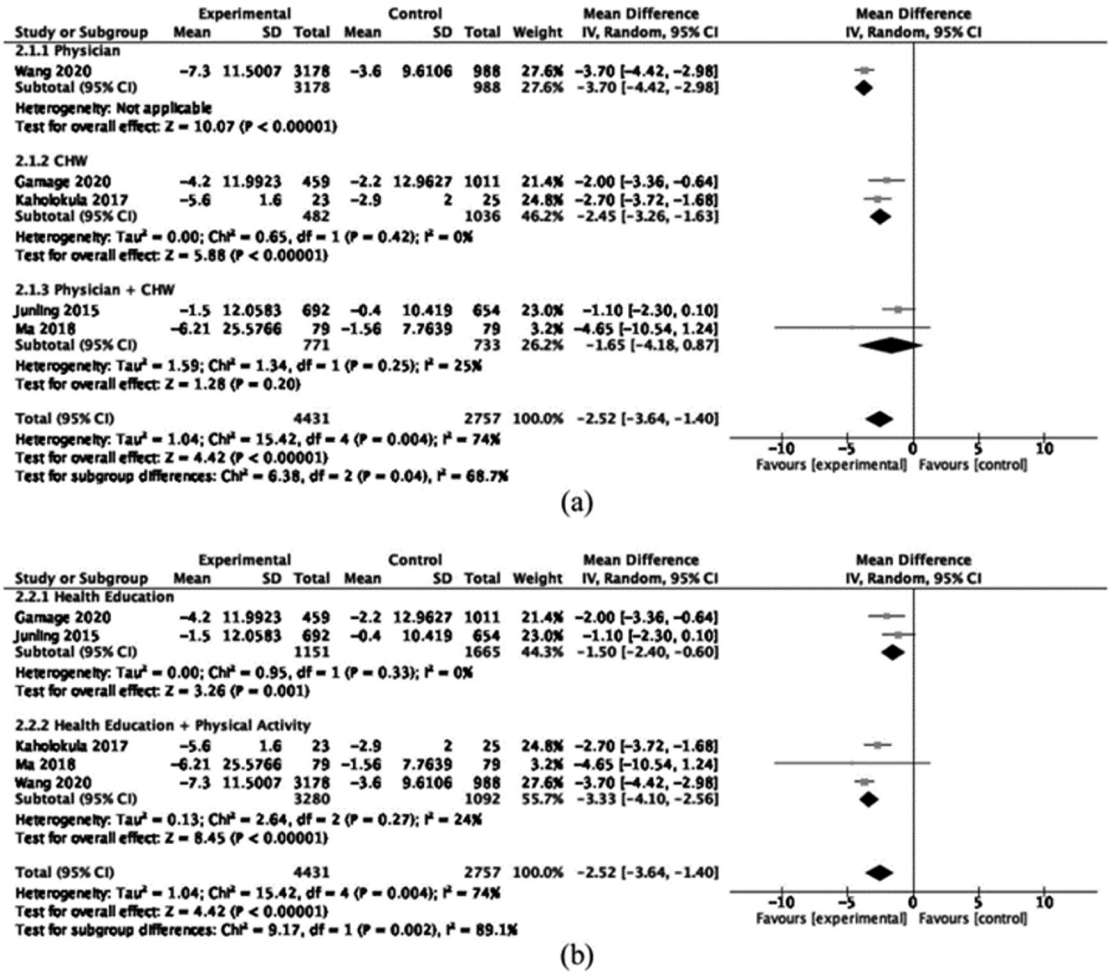


Figure 7. Forest plots illustrating the Reduction of DBP with subgroups based on (a) who is responsible for the interventions, (b) type of interventions, adapted from the study "The Effectiveness of Community-based Interventions in the Control of Hypertension - A Systematic Review and Meta-analysis" by Arteza, Yayen, and Mendoza (2022) published in The Filipino Family Physician (Arteza et al, 2022)

boards. Nevertheless, ethical considerations play a crucial role in conducting and writing the final report of a systematic review and meta-analysis to maintain the credibility of the research process. Maintaining academic honesty and intellectual integrity is paramount to ensure the accurate representation of ideas and findings. Good practices that research authors should observe include: 1) Avoiding plagiarism; 2) Maintaining transparency; and 3) Ensuring data accuracy.[18]

Plagiarism is defined as the act of using another person's original words, ideas, data, or other creations without proper credit or permission. Review authors must correctly cite and acknowledge prior work, giving credit to the original authors, in order to avoid plagiarism. It is acceptable to describe other works using the review author's own words, as long as proper citations are provided to attribute the information to its original source.[18] By adhering to rigorous citation practices, researchers demonstrate respect for the intellectual contributions of others and uphold the principles of academic integrity. Another ethical consideration that should be maintained throughout the research process is transparency. Transparent reporting ensures the accuracy and reliability of the review. Review authors should provide detailed descriptions of the methods used, including the criteria for study selection, data extraction, and analysis techniques. By openly disclosing the procedures and decision-making processes involved, readers can assess the reliability and validity of the review. Additionally, any potential conflicts of interest should be disclosed to ensure transparency and minimize bias.

Lastly, accurate data synthesis and analysis techniques are essential for maintaining the credibility of the review. Researchers should employ robust statistical methods and clearly report their findings. Misrepresentation or manipulation of data can significantly undermine the trustworthiness of the review and compromise its scientific value. By adhering to rigorous data synthesis and analysis practices, researchers demonstrate their commitment to producing reliable and unbiased results.

Write the Final Report using the PRISMA Guidelines

The final report of a systematic review and meta-analysis is vital in disseminating the findings to the scientific community and guiding evidence-based decision-making. This final report is done based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guideline.[16] The PRISMA 2020 guideline is a widely recognized and recommended framework for reporting systematic reviews and meta-analyses. By adhering to this guideline, researchers can ensure transparency and reproducibility in their final reports, facilitating the effective communication and interpretation of research findings. The checklists presented in Tables 7 and 8 summarize the key components of the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline. Each section of the guideline corresponds to specific items that are crucial for ensuring the transparency, thoroughness, and reproducibility of the review process.

Table 7. PRISMA 2020 item checklist.

Section and topic	Checklist item
Title	
Title	Identify the report as a systematic review and a meta-analysis or both
Abstract	
Abstract	*See the PRISMA 2020 for the Abstracts checklist (Table 8)*
Introduction	
Rationale	Describe the rationale for the review in the context of existing knowledge: - Describe the condition. - Describe the intervention being evaluated. - Describe how the intervention might provide benefits. - Elaborate on the reason why the meta-analysis was conducted.
Objectives	Provide an explicit statement of the objective(s) or question(s) the review addresses.
Methods	
Eligibility criteria	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.
Information sources	Specify all databases, registers, websites, organizations, reference lists, and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.

Search strategy	Present the full search strategies for all databases, registers, and websites, including any filters and limits used, such that it could be repeated.
Selection process	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.
Data collection process	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.
Data items	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.
	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.
Study risk of bias assessment	Specify the methods used to assess the risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.
Effect measures	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.
Synthesis methods	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis).
	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.
	Describe any methods used to tabulate or visually display results of individual studies and syntheses.
	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.
	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).
	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.
Reporting bias assessment	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).
Certainty assessment	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.
Results	
Study selection	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using the PRISMA flow diagram (See Figure 3)
	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.
Study characteristics	Cite each included study and present its characteristics.
Risk of bias in studies	Present assessments of risk of bias for each included study.

Search strategy	Present the full search strategies for all databases, registers, and websites, including any filters and limits used, such that it could be repeated.
Selection process	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.
Data collection process	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.
Data items	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.
	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.
Study risk of bias assessment	Specify the methods used to assess the risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.
Effect measures	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.
Synthesis methods	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis).
	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.
	Describe any methods used to tabulate or visually display results of individual studies and syntheses.
	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.
	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).
	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.
Reporting bias assessment	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).
Certainty assessment	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.

Table 8. PRISMA 2020 for abstracts checklist.

Section and topic	Checklist item
Title	
Title	Identify the report as a systematic review, a meta-analysis, or both.
Background	
Objectives	Provide an explicit statement of the main objective(s) or question(s) the review addresses.
Methods	
Eligibility criteria	Specify the inclusion and exclusion criteria for the review.
Information sources	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.
Risk of bias	Specify the methods used to assess risk of bias in the included studies.
Synthesis of results	Specify the methods used to present and synthesize results.
Results	
Included studies	Give the total number of included studies and participants and summarize relevant characteristics of studies.
Synthesis of results	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favored).
Discussion	
Limitations of evidence	Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision).
Interpretation	Provide a general interpretation of the results and important implications.
Other	
Funding	Specify the primary source of funding for the review.
Registration	Provide the register name and registration number.

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