

Outline

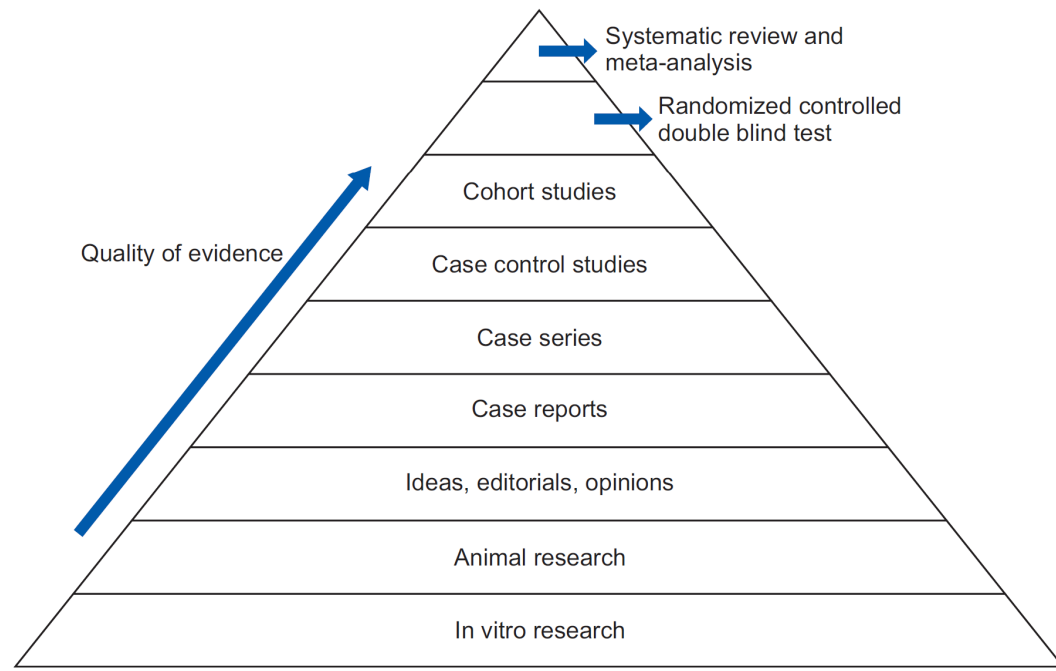
- Background on Systematic Review & Meta-Analysis
- Guidance on Meta-Analysis Process
- Data Extraction Process and Tips
- Common Statistical Methods for a Meta-Analysis
- Reporting Results for a Meta-Analysis
- Summary
- Biostatistics Resources at Northwestern University

Background

Systematic Review & Meta-Analysis

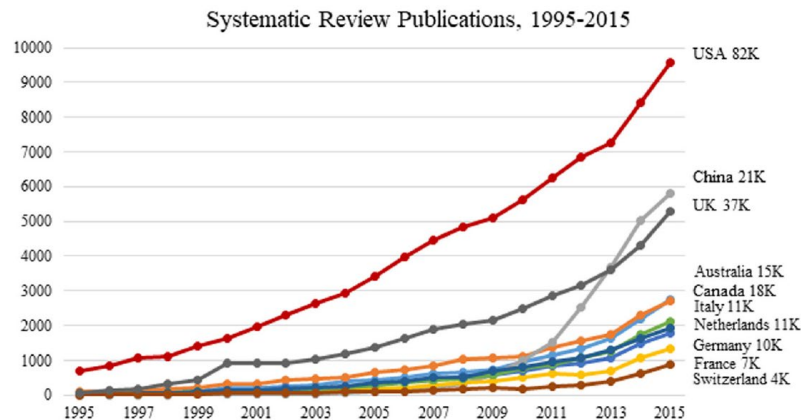
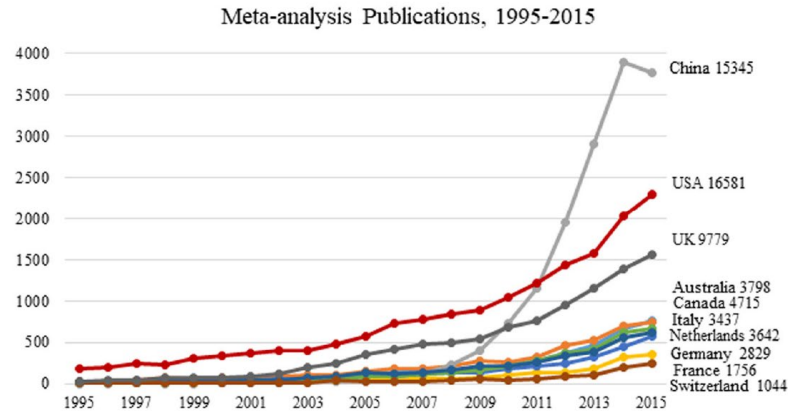
- Systematic Review – a reproducible process that reviews and synthesizes information obtained from a collection of available research studies that answer a specific research question
- Meta-Analysis – a statistical approach to summarize results from a systematic review
 - A subset of a systematic review
- Many systematic reviews include a meta-analysis, but a meta-analysis is not required for a systematic review
 - Guideline: Synthesis Without Meta-analysis (SWiM)

Pyramid of Levels of Evidence in Biomedical Research



Ahn E, Kang H. Introduction to systematic review and meta-analysis. *Korean J Anesthesiol.* 2018;71(2):103-112.

Meta-Analyses & Systematic Reviews from the Top Publishing Countries, 1995 – 2015



Fontelo P, Liu F. A review of recent publication trends from top publishing countries. *Systematic Reviews*. 2018;7(1):147.

Guidance on Meta-Analysis Process

Guidance on Meta-Analysis Process

- Descriptions of meta-analysis steps can be found through guidelines and tools
- PRISMA- Preferred Reporting Items for Systematic Reviews and Meta-Analyses (Page et al., 2021)
- Tools/Step by Step Guide for biomedical research with/without human participants (Haidich, 2010; Nakagawa, Noble, Senior, & Lagisz, 2017; Tawfik et al., 2019)

Framing Meta-Analysis Research Question/Objective

- Meta-analysis research question and/or objectives should be well-defined and answerable
- It is important that the question and objectives are very specific
 - This helps to ensure that the data from the different studies can be combined
- PICOT - Guidance for developing a research question (Riva, Malik, Burnie, Endicott, & Busse, 2012)
 - **P**opulation, **I**ntervention, **C**omparison, **O**utcome, and **T**ime
- It may be more plausible to use only **P**opulation, **O**utcome, and **T**ime
 - Observational study without an intervention and no comparison groups
- When selecting the **T**ime, take into consideration if there were any health or scientific guideline changes that could impact the methodology used in studies

Example of Research Question/Objective



Systematic Review and Meta-Analysis: Treatment of Substance Use Disorder in Attention Deficit Hyperactivity Disorder

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Background and Objectives: Treating substance use disorder (SUD) in patients with co-occurring attention deficit hyperactivity disorder (ADHD) and SUD may lower medical, psychiatric, and social complications. We conducted a systematic review with meta-analysis to investigate the clinical benefits of pharmacological interventions to treat SUD in patients with ADHD.

Methods: Articles were searched on Cochrane Central Register of Controlled Trials, PubMed, EBSCO, Google Scholar, Embase, Web of Science, and Ovid MEDLINE from 1971 to 2020. Data for SUD treatment as primary study endpoints and ADHD symptoms management as secondary outcomes were synthesized using random-effects model meta-analysis. Studies ($N = 17$) were included. The principal measure of effect size was the standardized mean difference (SMD). PROSPERO registration: CRD42020171646.





INTRODUCTION

The presence of attention deficit hyperactivity disorder (ADHD) not only increases vulnerability to substance use disorder (SUD) but also influences the long-term prognosis and treatment of SUD itself. ADHD is a chronic mental disorder that impacts an individual's biological, psychological, and social aspects. Encountered during childhood, ADHD can also carry onto adulthood.¹ ADHD often co-occurs with other psychiatric disorders and is associated with significant psychosocial complications.² A meta-analysis estimated that the overall prevalence of ADHD in SUD patients was approximately 23%, irrespective of age

Fluyau D, Revadigar N, Pierre CG. Systematic Review and Meta-Analysis: Treatment of Substance Use Disorder in Attention Deficit Hyperactivity Disorder. *The American Journal on Addictions*. 2021;30(2):110-121.

Example of Research Question/Objective

Prevalence of co-morbidities and their association with mortality in patients with COVID-19: A systematic review and meta-analysis

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Sam Seidu MBChB^{2,3}  | Francesco Zaccardi PhD^{2,3} | Melanie J. Davies FRCP³  |
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Abstract

Aim: To estimate the prevalence of both cardiometabolic and other co-morbidities in patients with COVID-19, and to estimate the increased risk of severity of disease and mortality in people with co-morbidities.

Materials and Methods: Medline, Scopus and the World Health Organization website were searched for global research on COVID-19 conducted from January 2019 up to 23 April 2020. Study inclusion was restricted to English language publications, original articles that reported the prevalence of co-morbidities in individuals with COVID-19, and case series including more than 10 patients. Eighteen studies were selected for inclusion. Data were analysed using random effects meta-analysis models.

Singh AK, Gillies CL, Singh R, et al. Prevalence of co-morbidities and their association with mortality in patients with COVID-19: A systematic review and meta-analysis. *Diabetes Obes Metab.* 2020;22(10):1915-1924. doi:10.1111/dom.14124

Inclusion/Exclusion Criteria

- PRISMA checklist states, “Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.”(Page et al., 2021)
 - A meta-analysis of a subset of the collected articles may be appropriate for the research area of interest
- The criteria and plan for grouping the studies should be determined prior extracting data during the systematic review process
 - Screen articles to assist with determining the inclusion and exclusion criteria (Mikolajewicz & Komarova, 2019)
 - Check registered protocols of systematic reviews with a meta-analysis
 - Search the Cochrane Database of Systematic Reviews (CDSR)
- There should be separate set of inclusion/exclusion criteria for each meta-analysis objective

Protocol Registration for a Systematic Review with Meta-Analysis

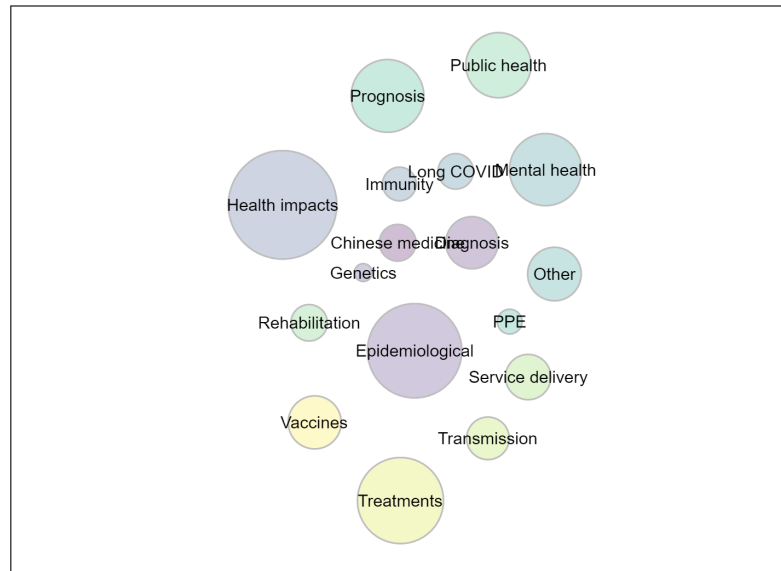
- It is not required to register the protocol for a systematic review with a meta-analysis
- Registration of the study must occur at the inception/protocol stage of the project
- PROSPERO is a common database for registering a systematic review with a meta-analysis protocol (Tawfik et al., 2020)
 - PROSPERO - International Prospective Register of Systematic Reviews
 - For systematic reviews of human and animal studies
- Can search through PROSPERO for overlapping studies
 - Help with deciding to conduct a systematic review/meta-analysis
 - Help with determining inclusion/exclusion criteria

PROSPERO - Registered COVID-19 Systematic Reviews

PROSPERO Covid-19 filters

Click any of the keywords below to search PROSPERO for Covid-19 registrations or click [here](#) to see all Covid-19 human studies or [here](#) to see all Covid-19 animal studies.

Click to [hide the Covid-19 filters and go back to standard PROSPERO searching](#)



Tag	Count
Chinese medicine	196
Diagnosis	396
Epidemiological	1292
Genetics	46
Health impacts	1708
Immunity	165
Long COVID	183
Mental health	755
Other	416
PPE	89
Prognosis	769
Public health intervention	617
Rehabilitation	193
Service delivery	298
Transmission	263
Treatments	1075
Vaccines	408

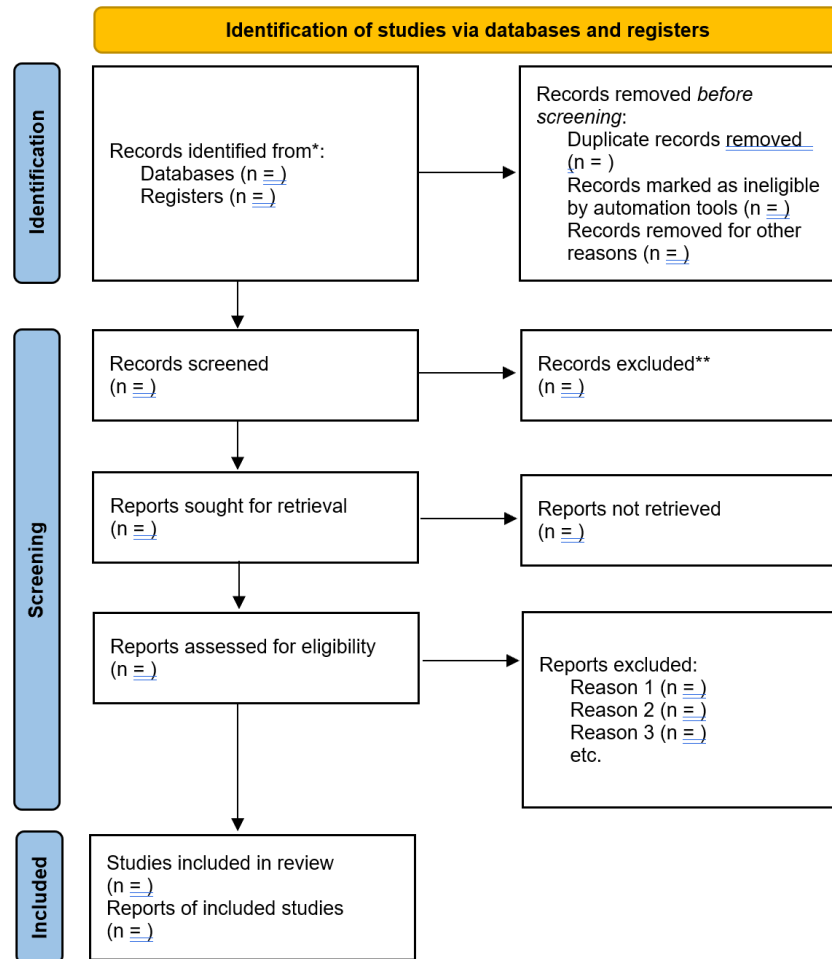
PROSPERO. National Institute of for Health Research.

<https://www.crd.york.ac.uk/PROSPERO/#searchadvanced>. Accessed January 6, 2022.

Tips for a Comprehensive Database Search

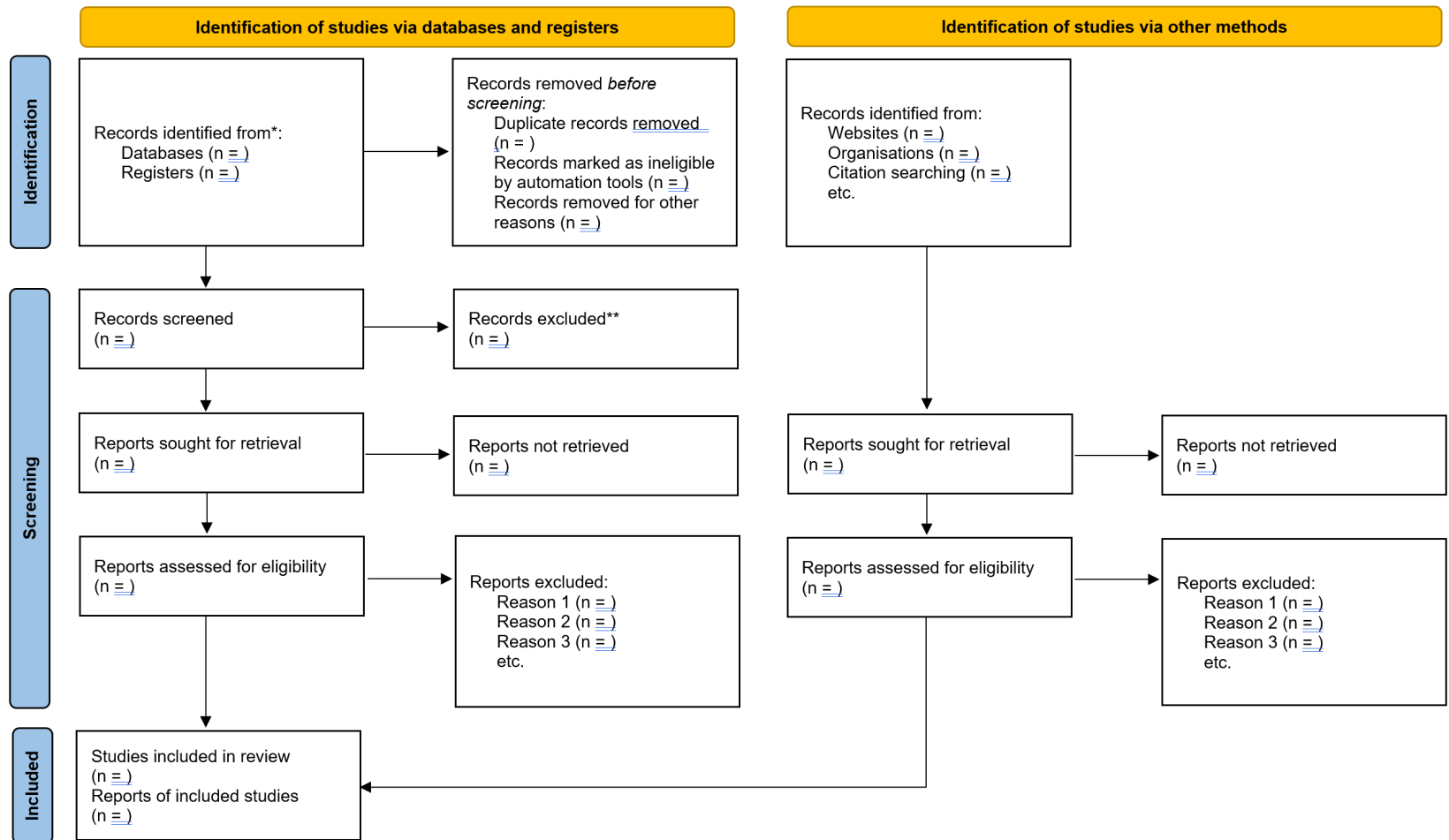
- Decide which dissemination sources are included in your meta-analysis
- Multiple databases should be used to conduct the search
 - Medline, Scopus, Web of Science, etc.
- A comprehensive search includes identifying relevant studies through popular and lesser-known databases
- Consult with an information specialist or librarian while conducting the search
 - They can aid with specific keywords and strings for database searches
- Make sure studies are selected for the appropriate timeframe
- Detailed documentation of the search methodology is required to ensure reproducibility

PRISMA Flow Diagram – Studies via Databases & Registers



Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71.

PRISMA Flow Diagram – Studies via Multiple Sources



Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71.



PRISMA Flow Diagram Creation

- Create your own without a template via word document
- Word document templates via PRISMA website
- PRISMA R package and ShinyApp (PRISMA2020)

PRISMA ShinyApp

PRISMA Flow Diagram x +

estech.shinyapps.io/prisma_flowdiagram/

PRISMA Flow Diagram Home Create flow diagram

Main options

Previous studies: Not included (v) Included (v)

Other searches for studies

Click to reset

Identification

Databases	Registers
0	0
Websites	Organisations
0	0
Citations	
0	
Duplicates removed	
0	
Automatically excluded	Other exclusions
0	0

```
graph TD; subgraph Identification; direction TB; I1[Records identified from:  
Databases (n = 0)  
Registers (n = 0)] --> I2[Records screened  
(n = 0)]; I1 --> I1_ex[Records removed before screening:  
Duplicate records (n = 0)  
Records marked as ineligible by automation  
tools (n = 0)  
Records removed for other reasons (n = 0)]; I2 --> I3[Reports sought for retrieval  
(n = 0)]; I2 --> I2_ex[Records excluded  
(n = 0)]; I3 --> I4[Reports assessed for eligibility  
(n = 0)]; I3 --> I3_ex[Reports not retrieved  
(n = 0)]; I4 --> I5[New studies included in review  
(n = 0)  
Reports of new included studies  
(n = 0)]; I4 --> I4_ex[Reports excluded:  
Reason1 (n = xxx)  
Reason2 (n = xxx)  
Reason3 (n = xxx)]; end; subgraph Screening; direction TB; S1[Records identified from:  
Websites (n = 0)  
Organisations (n = 0)  
Citation searching (n = 0)] --> S2[Reports sought for retrieval  
(n = 0)]; S1 --> S1_ex[Reports not retrieved  
(n = 0)]; S2 --> S3[Reports assessed for eligibility  
(n = 0)]; S2 --> S2_ex[Reports excluded:  
Reason1 (n = xxx)  
Reason2 (n = xxx)  
Reason3 (n = xxx)]; S3 --> I5; end; subgraph Included; direction TB; I5; end;
```

PRISMA - Literature Search for Studies



PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	
Selection process	8	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 Extraction Process and Tips

Data Extraction Process

- More than one reviewer should be extracting data
 - Make sure the reviewers are familiar with the inclusion/exclusion criteria and the database for the data extraction
- Assess the quality and validity of each study
- Compare reviewer agreement on the validity of each study
 - Detailed documentation on how disagreements were resolved
- Document any missing information that is related to the meta-analysis objectives
- Report details on any use of data extraction automation/scraping tools

Data Extraction Tips – Database

- Create a database for the data extraction prior to collecting the data
 - Create a test database
- Explore the options for creating a database
 - Excel
 - Google Spreadsheets
 - REDCap
 - Systematic Review Data Repository (SRDR)
 - Covidence
 - DistillerSR
 - Joanna Briggs Institute System for the United Management, Assessment and Review of Information (JBI Sumari)

Data Extraction Tips – Database

- At minimum, your database for data extraction will include:
 - Author Names
 - Year of Publication
 - Inclusion/Exclusion Criteria
 - Sample Size
 - Several ways to report sample size – Randomized, recruited, by group/arm
 - Be consistent throughout the database
 - Type of study
 - Number of intervention groups, if applicable
 - Quantitative data of the effect size
 - Collected in a uniform format
 - Follow-up data has the same follow-up period
 - Timing of the measurement (Baseline or post intervention/medical procedure)
 - **Only include data related to your meta-analysis objectives**

Data Extraction Tips – Common Effect Sizes

- Quantitative data of the effect size
 - Means (SDs)
 - Risk Ratios (SEs)
 - Odds Ratios (SEs)
 - Risk Difference (SEs)
 - Hazard Ratios (SEs)
 - Proportions
 - Difference of Proportions
 - Correlations

Common Statistical Methods for a Meta-Analysis

Common Statistical Methods for a Meta-Analysis

Statistical Method	Description
Fixed Effect Model	Statistical approach that obtains a weighted average of study estimates. There is an assumption that each study has the same underlying true effect. Larger studies receive a larger weight than smaller studies.
Random Effects Model	Statistical approach that obtains a weighted average of study estimates that assumes each study has varying underlying true effects. This approach takes into consideration the variability between each study.
Meta-Regression	Statistical method that determines the association between explanatory variables and effect estimates.
Subgroup Analysis	A meta-analysis conducted using only a subset of the studies based on a similar characteristic.

Dekkers OM. Meta-analysis: Key features, potentials and misunderstandings. Res Pract Thromb Haemost. 2018;2(4):658-663.

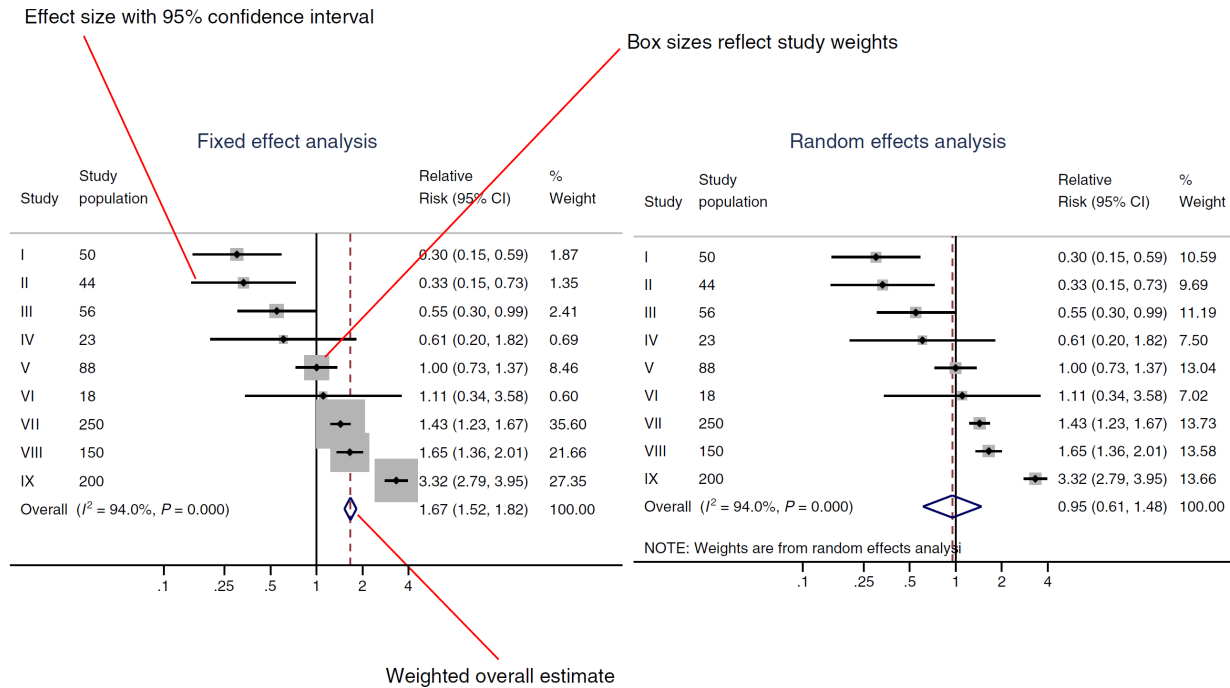
Common Statistical Methods for a Meta-Analysis

Statistical Method	Description
Network Meta-Analysis	Analysis approach for comparing studies with more than two groups.
Cochrane's Q Test	A test that has a null hypothesis that all studies have the same underlying true effect. Rejecting the null hypothesis means that there is evidence of statistical heterogeneity.
I^2 Statistic	A measure that captures the degree of heterogeneity among studies that is not due to random chance. I^2 is reported as a percentage.

Dekkers OM. Meta-analysis: Key features, potentials and misunderstandings. Res Pract Thromb Haemost. 2018;2(4):658-663.

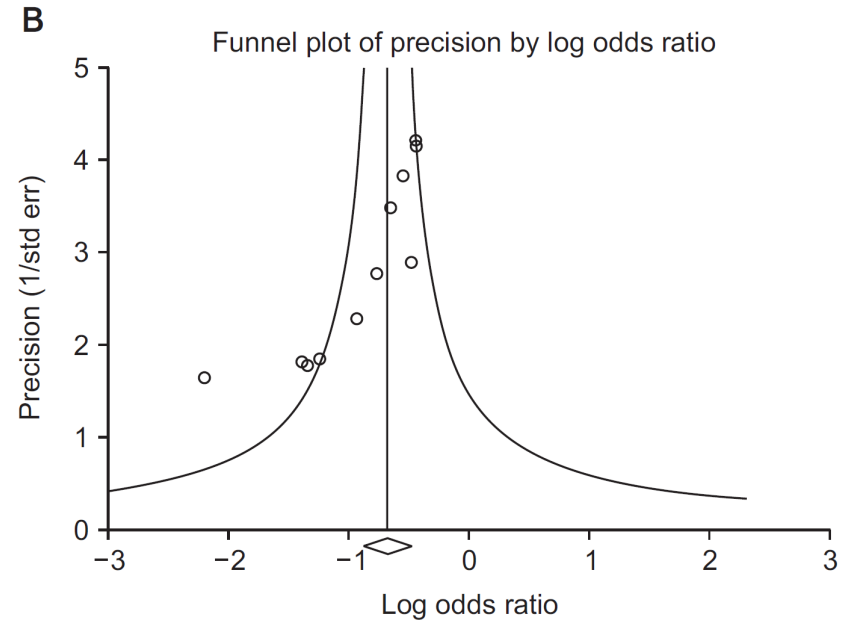
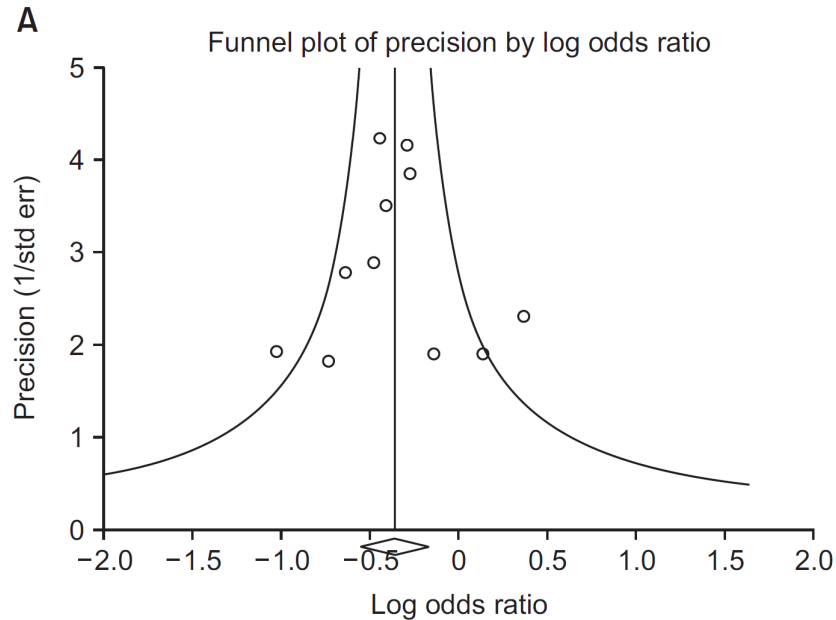
Reporting Results for a Meta-Analysis

Reporting Results – Forest Plot



Dekkers OM. Meta-analysis: Key features, potentials and misunderstandings. *Res Pract Thromb Haemost.* 2018;2(4):658-663.

Reporting Results – Funnel Plot



Ahn E, Kang H. Introduction to systematic review and meta-analysis. Korean J Anesthesiol. 2018;71(2):103-112.

Summary

Summary

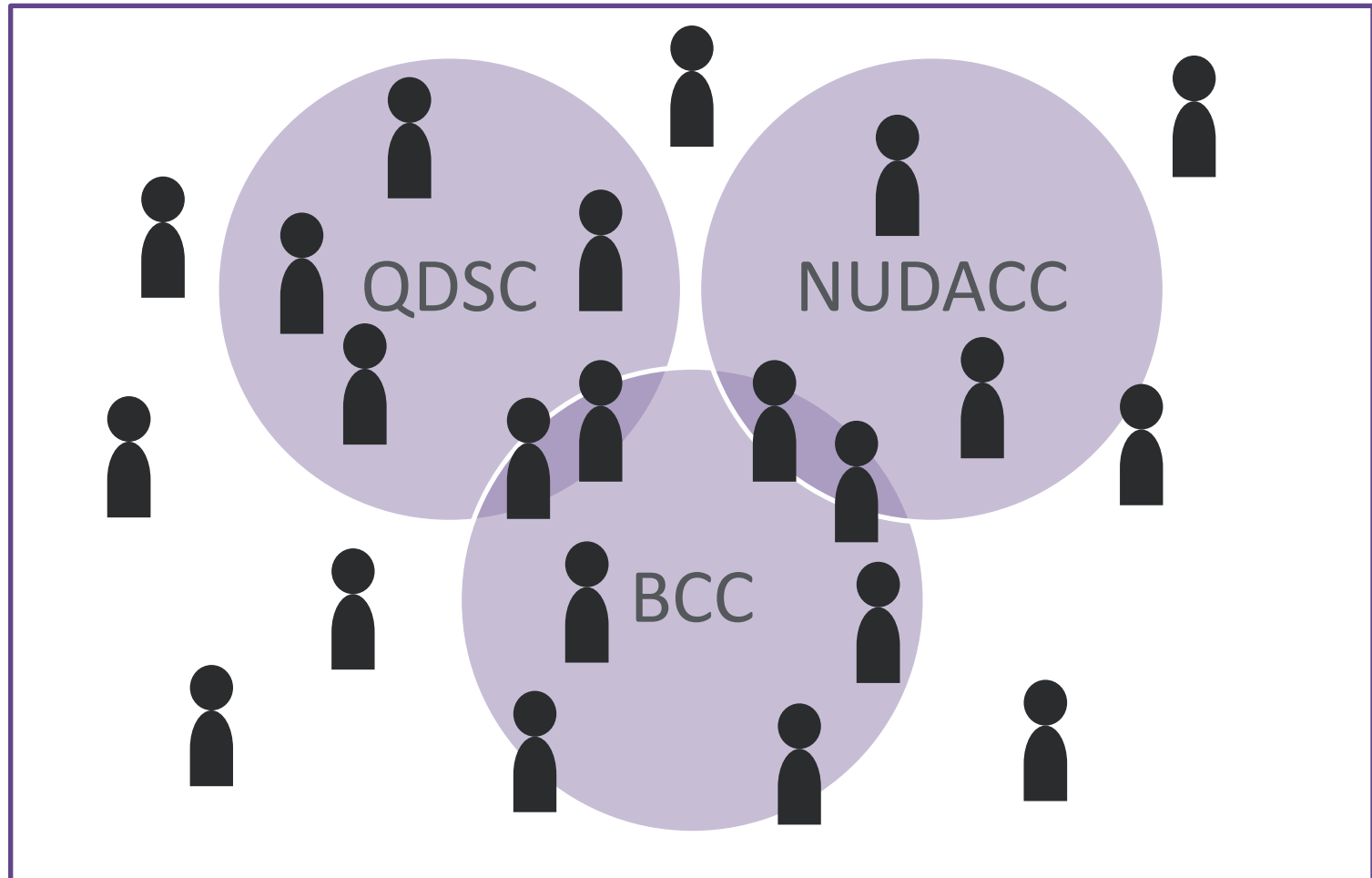
- A meta-analysis is a statistical approach to combine and summarize effects obtained from multiple studies
- **The validity of a meta-analysis heavily depends on the validity of the included studies**
- Studies included in a meta-analysis must meet the same inclusion and exclusion criteria
- Databases created to extract data collected from studies should be well documented in a uniform way
- There are different statistical methods for a meta-analysis based on if the underlying true effect is the same or not the same across all studies

NU Biostatistics Resources

Biostatistics at NU

- Overview

Division of Biostatistics (Chief: Denise Scholtens),
Department of Preventive Medicine (Chair: Donald Lloyd-Jones)



Biostatistics Centers and Cores

- Overview



Biostatistics Collaboration Center (BCC)

- Supports **non-cancer** research at NU
- Initial 1-2 hour consultation subsidized by FSM Research Office
- Grant, Hourly
- <https://www.feinberg.northwestern.edu/sites/bcc/>

Quantitative Data Sciences Core (QDSC)

- Supports **cancer-related** research at NU
- Free to Lurie Cancer Center (LCC) members
- Grant
- <https://www.cancer.northwestern.edu/research/shared-resources/quantitative-data-sciences.html>

Northwestern University Data Analysis and Coordinating Center (NUACC)

- Prospective, large **multicenter research**
- Comprehensive support (e.g., clinical monitoring, data analysis, project management)
- Grant
- <https://www.feinberg.northwestern.edu/sites/nudacc/>

References

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<https://www.crd.york.ac.uk/PROSPERO/#searchadvanced>. Accessed January 6, 2022.

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Singh AK, Gillies CL, Singh R, et al. Prevalence of co-morbidities and their association with mortality in patients with COVID-19: A systematic review and meta-analysis. *Diabetes Obes Metab*. 2020;22(10):1915-1924.
doi:10.1111/dom.14124

Tawfik GM, Dila KAS, Mohamed MYF, et al. A step by step guide for conducting a systematic review and meta-analysis with simulation data. *Tropical Medicine and Health*. 2019;47(1):46.

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