BIOL 501: Meta-Analysis

Peer-Feedback Survey

28 March. 2023 Dr. Beth Volpov, b.volpov@oceans.ubc.ca; UBC 2022 Term 2

Outline

- Meta analysis compared with traditional review article

- Vote-counting (cautious)

- What is meta-analysis?

- Effect size

- Fixed and mixed-effects

- Associating effect sizes with relevant variables

- Make your results accessible to meta-analysis

- Workshop

The problem: need to summarize multiple studies

- Scientific studies on a topic are often repeated on different study system or with different methods

- New studies improve, expand, refine

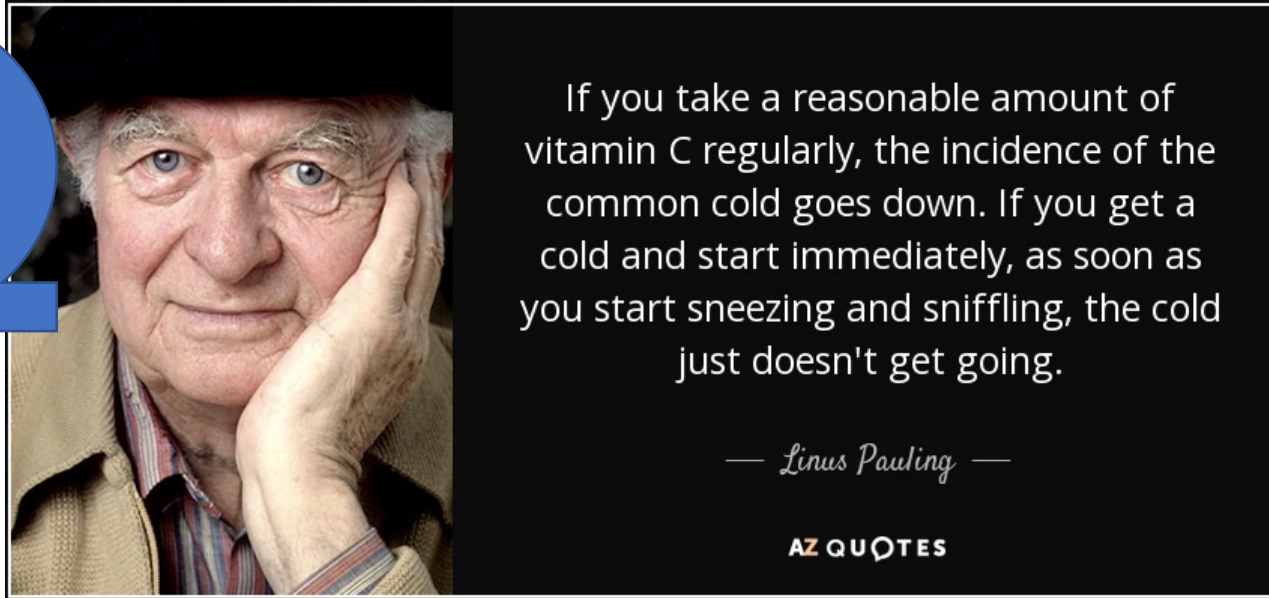- **Problem:** A method is needed to summarize results from multiple studies

Traditional Approach: Review Article

- An expert in the field assembles studies published on a topic, thinks about them carefully and (hopefully) fairly, and then writes a review article summarizing the overall conclusions reached.

- Reviews and comments on the current state of thought and knowledge about a particular topic.

- **What's new?** Propose new hypotheses, uncover previously unnoticed relationships, and point to new paths of research. If done right, advances field far beyond a mere summary.

But, review articles often have bias and lack a quantitative method

Review Article Problems: Bias

Bias in who is accepted or invited to do reviews also? Only those at "the top"?

If you take a reasonable amount of vitamin C regularly, the incidence of the common cold goes down. If you get a cold and start immediately, as soon as you start sneezing and sniffling, the cold just doesn't get going.

— Linus Pauling —

AZ QUOTES

- Hypothesized > daily doses vitamin C reduces risk of contracting common cold

- Cited 30 studies in support, but **no studies opposing** (even though many had been published)

- Not all reviews are **so** biased, but there are few rules regarding selection of studies for review.

1986 book *How to Live Longer and Feel Better*, Linus Pauling (the only person to be awarded two unshared Nobel Prizes)

File-Drawer Problem and Publication Bias

- **Definition:** possible bias in estimates and tests caused by publication bias

- Statistically non-significant results are less likely to be published (and thus included in meta-analysis)

- If they are published less likely in "top-tier" journals, so possibly referened less

Refers to the unknown studies sitting unavailable in scientists' file drawers or hidden in obscure journals

Funnel plots: visual tool to examine bias

- Indication of the bias resulting from small studies.
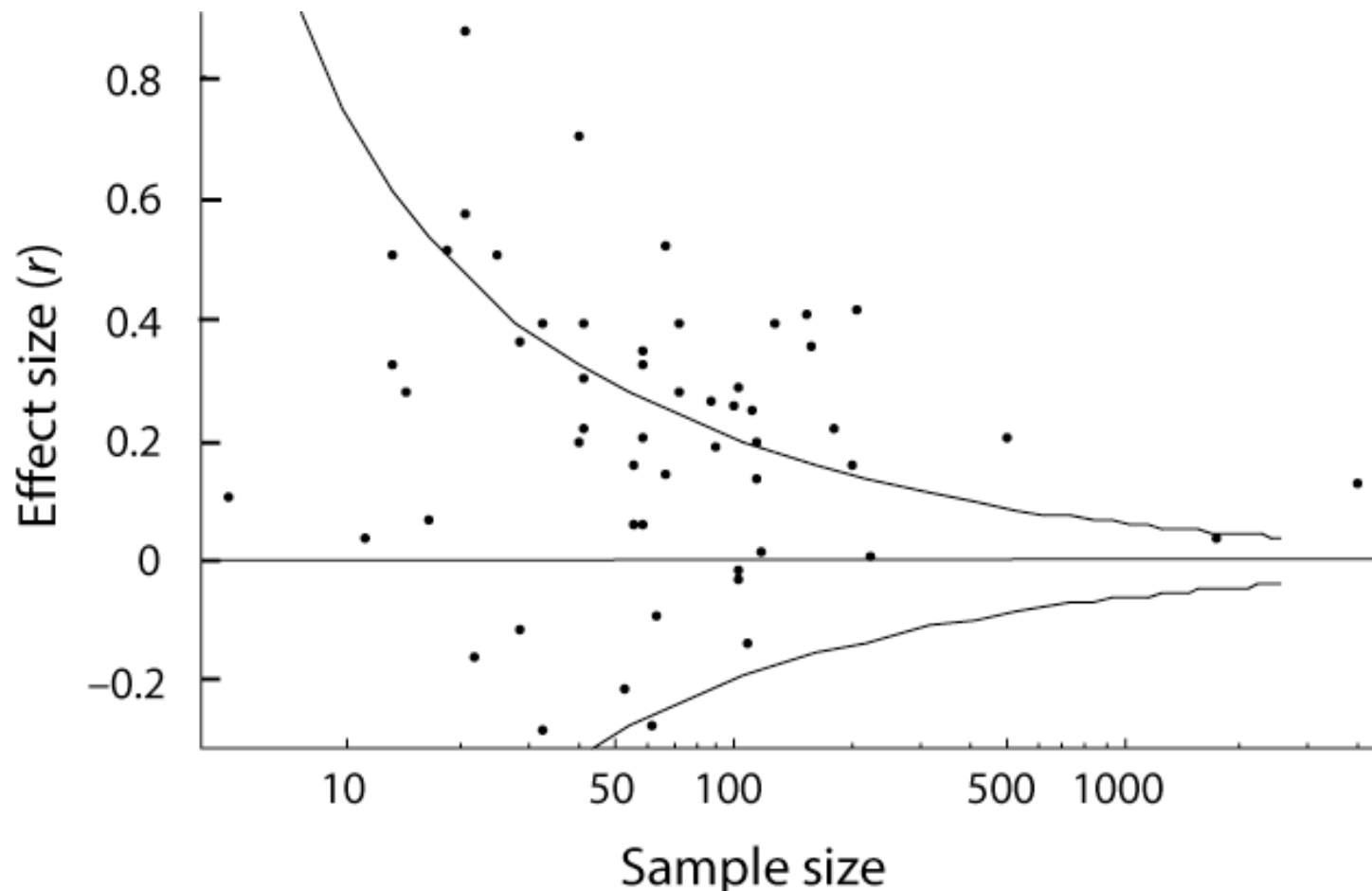
- **A type of scatterplot**
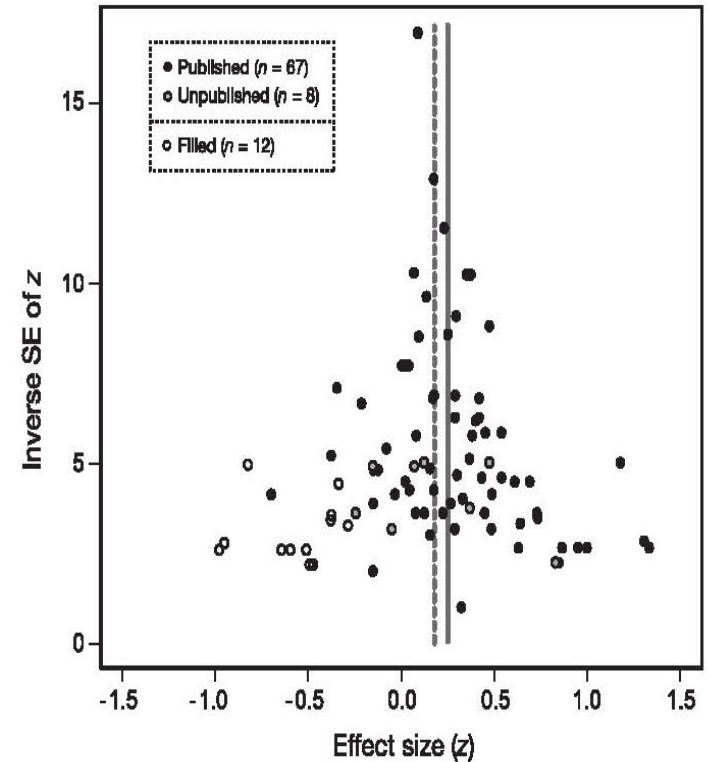
Figure 1

Funnel plot of effect sizes for the relationship between song complexity and reproductive success when using the multiple effect size data set (data set A). Black and gray circles show published and unpublished effect sizes, respectively. Solid and dotted lines show mean effect sizes before and after controlling for publication bias, in which theoretical missing data points (open circles, $n = 12$) were added to adjust funnel plot asymmetry.

Soma and Garamszegi (2011) used the Trimfill algorithm to fill in hypothetical missing studies in the funnel plot to achieve theoretical symmetry.

Conventional to plot treatment effects on X and measure of study size on Y, but it's ok to flip them (you just get a funnel on the side)
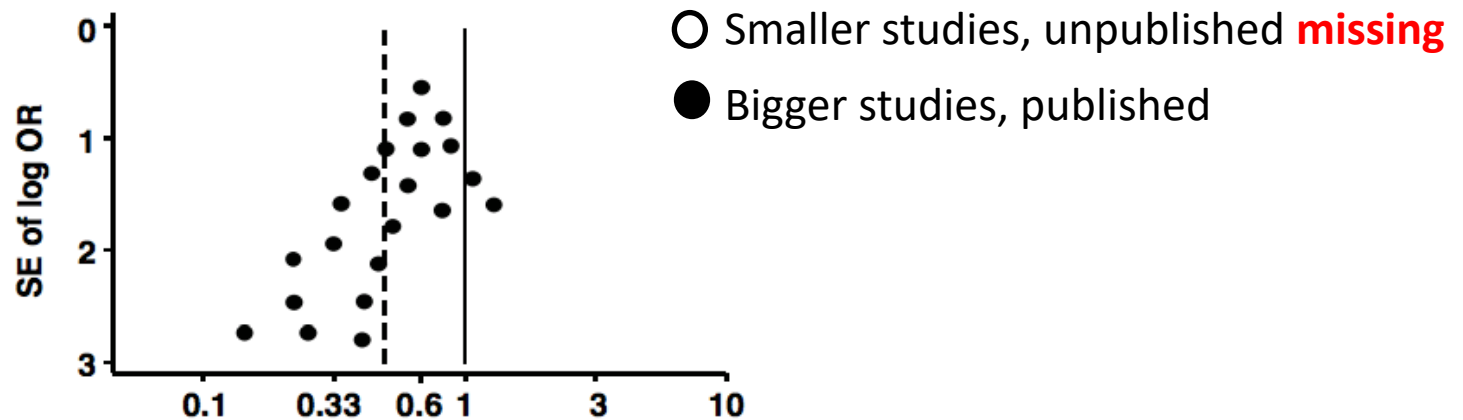

plot(effect sizes ~ sample size, data=mydata)

Funnel plots: visual tool to examine bias

○ Smaller studies, unpublished are present

● Bigger studies, published
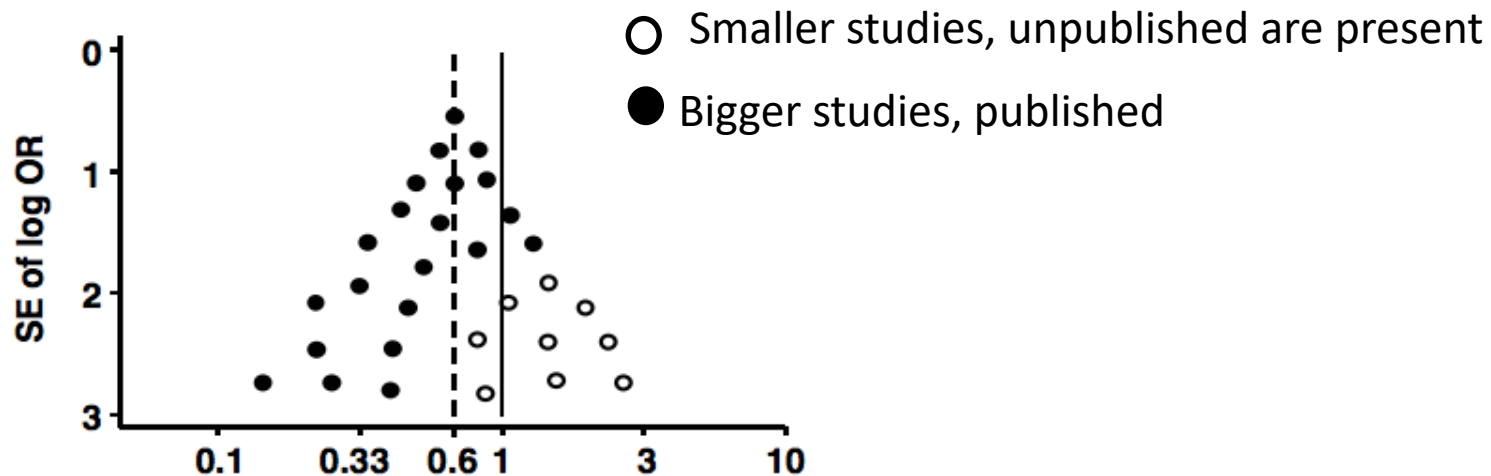
- A type of scatterplot that shows relationship between treatment effects estimated from individual studies vs. a measure of study size (sometimes N, sometimes other measures)

- **No bias=symmetrical, inverted funnel**

- If no bias, results from small studies should scatter widely the bottom with spread narrowing among larger studies (creating a funnel)

Sterne, Jonathan AC, and Roger M. Harbord. "Funnel plots in meta-analysis." *The stata journal* 4.2 (2004): 127-141.

Funnel plots: visual tool to examine bias

○ Smaller studies, unpublished **missing**

● Bigger studies, published

- The smaller studies are missing from meta-analysis

- **Yes bias=asymmetrical funnel**

- The more pronounced the asymmetry, the more likely it is that bias is substantial

Sterne, Jonathan AC, and Roger M. Harbord. "Funnel plots in meta-analysis." *The stata journal* 4.2 (2004): 127-141.

Publication Bias and Fail-Safe Number

- Assess publication bias by trying to estimate number of "missing" studies needed to change results

- Calculates how many missing studies (e.g. unpublished or unavailable) would be needed to change the overall result of the meta-analysis

  - Large fail-safe #: suggests conclusion of meta-analysis is reliable

  - Small fail-safe #: suggest conclusion of meta-analysis is <u>less reliable</u>

Fail-safe number & publication bias

Fail-safe number

The *fail-safe number* calculates how many missing studies would be needed to change the overall result of the meta-analysis.

Vilà et al (2011) estimated the number of studies that would have to be added to change the results of their invasive plant meta-analysis from significant to non-significant as 37,689. This was too implausible, so they concluded that their estimates were reliable.

(Fig 1a: top line refers to total plant production; other lines are effects on native plants and animals (1b))
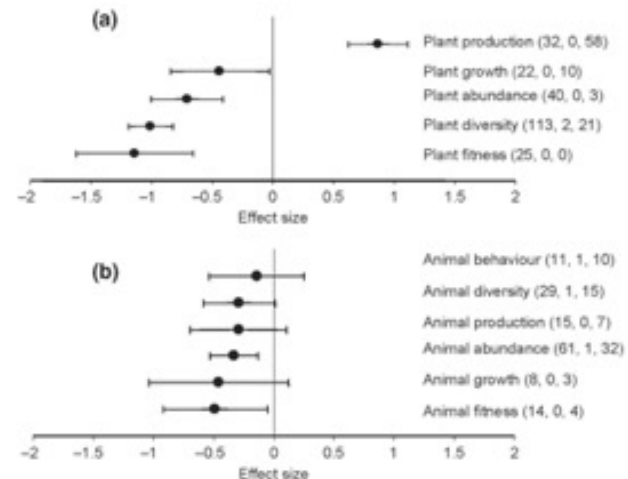
Figure 1 Mean effect size (Hedges' *d*) of differences between alien plant species impacts to (a) plant species and communities and (b) animal species and communities. The bars around the means denote bias-corrected 95%-bootstrap confidence intervals. A mean effect size is significantly different from zero when its 95% confidence interval do not bracket zero. Positive mean effect sizes indicate that the invaded plots had on average greater values for variables describing a particular impact type. The sample sizes with Hedges' $d < 0$, Hedges' $d = 0$ and Hedges' $d > 0$ are given next to the bars.

Review Article Problems

- Lacks a quantitative method
- Lack of a quantitative summary of research findings.
- Reviews don't tell us about how large the effect is.

Outline

- Meta analysis compared with traditional review article

- **Vote-counting**

- What is meta-analysis

- Effect size

- Fixed and mixed-effects

- Associating effect sizes with relevant variables

- Make your results accessible to meta-analysis

Vote Counting

- Meta-analysis is valuable because it is more reliable than one alternative called "vote counting"
- **How it works:**
  - Divide studies into 2 categories based on if they do or do not statistically support a given hypothesis
  - Count the proportions of studies "voting" for or against hypothesis
- E.g."4 out of the 5 studies show….."
- What if those 4 studies are all small with low power and bad experimental design and the 5th is the only well-designed study with power?

Limitations with vote counting

- Counting only statistically significant studies ignores all the quantitative information about the magnitudes of effects.

- Too conservative. "Votes" are affected by the power of individual studies, which may be weak.

- Significance level by itself doesn't indicate whether two or more studies obtained the same outcome.

- Magnitude of the effect is downplayed.

- Difficult to quantify effects of publication bias.

- Unable to weigh effect of studies differing in sample size, and therefore power.

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What is meta-analysis?

- **The "analysis of analyses"**

- Statistical synthesis of results from a series of studies (Borenstein et al 2009).

- Data from more than 1 study to be combined and analyzed as a new dataset

What is meta-analysis?

- Compiling all known scientific studies estimating an effect ("systematic review") and **quantitatively combining** them to give an overall estimate of the effect.

- Allows us to **generalize**. It lets us determine how frequent, how important, and how consistent effects are across a variety of systems.

- Gets past occasional sensational result (the one you read about in the newspaper) to an objective assessment of all the evidence.

Forest Plot
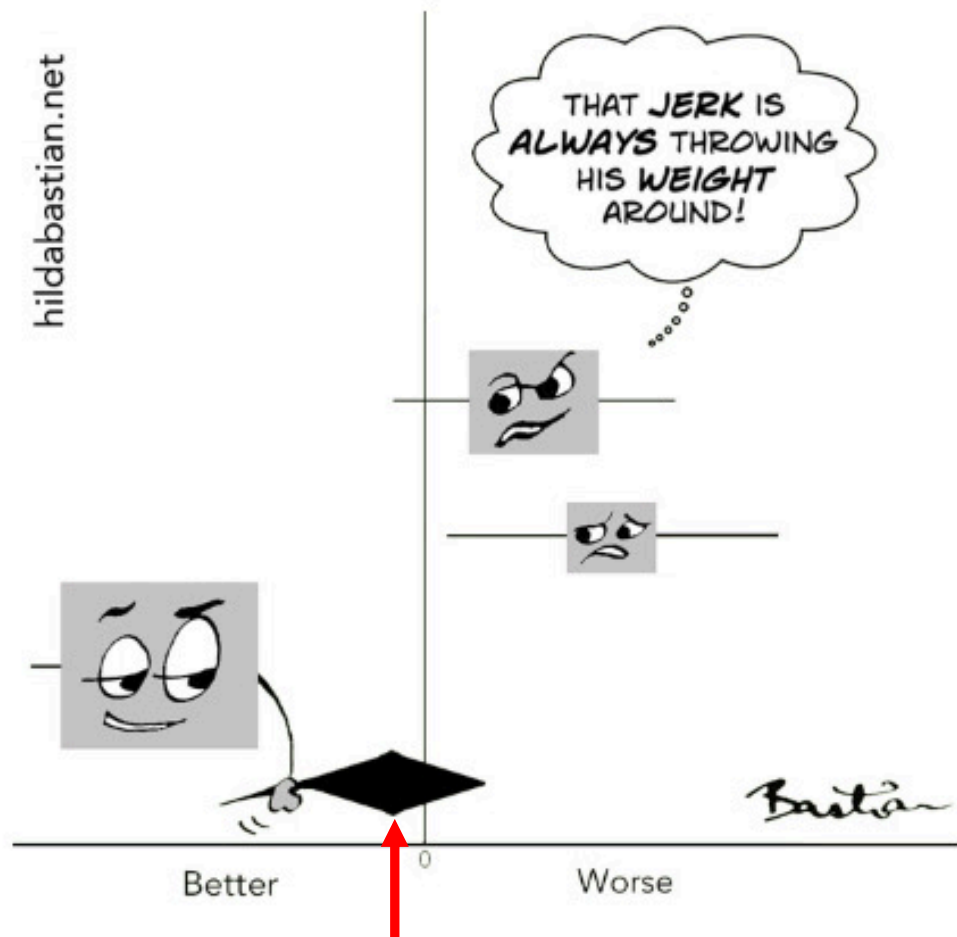
Diamond represents the most important part of the plot. The point estimate and CI when combine and average **all the individual studies** together

Forest Plot

- Originated in medical research, all studies on same species (humans).

- Ecologists and evolutionary biologists attempt to generalize across a much wider range of species and systems.

- More challenging than studies carried out on a single species (e.g., humans).

Forest Plot

- Tutorial on how to read a forest plot
    - https://s4be.cochrane.org/blog/2016/07/11/tutorial-read-forest-plot/
- YouTube
- https://www.youtube.com/watch?v=Pxs0gl3hRKE

Forest Plot

Wider CI=less precision compared to others in this meta-analysis

Fixed or random model
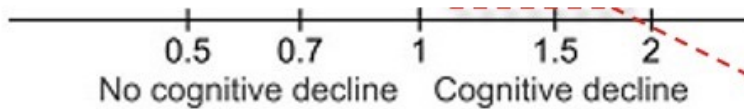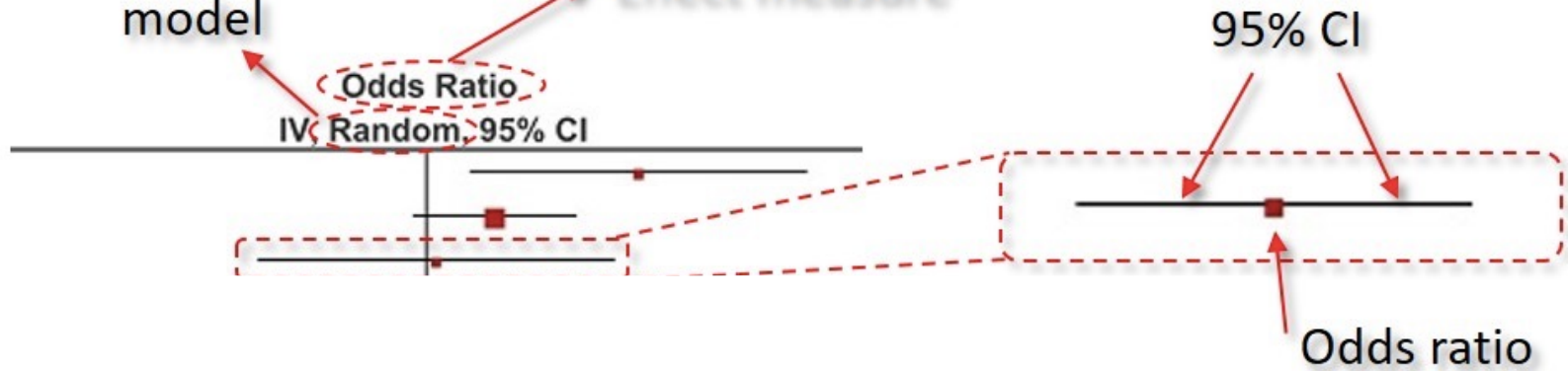
Effect measure

Odds Ratio
IV, Random, 95% CI

95% CI

Odds ratio

0.5   0.7   1   1.5   2
No cognitive decline   Cognitive decline

https://toptipbio.com/forest-plot/

Why are some squares big vs small size?
Size of point representing the effect measure is proportional to the study weight in the meta-analysis

Fixed or random model

Effect measure

Odds Ratio

IV, Random, 95% CI

95% CI

Odds ratio

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Why are some squares big vs small size?
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Fixed or random model

Effect measure

Odds Ratio
IV, Random, 95% CI

95% CI

Odds ratio

Overall 95% CI

Overall odds ratio

0.5 0.7 1 1.5 2
No cognitive decline Cognitive decline
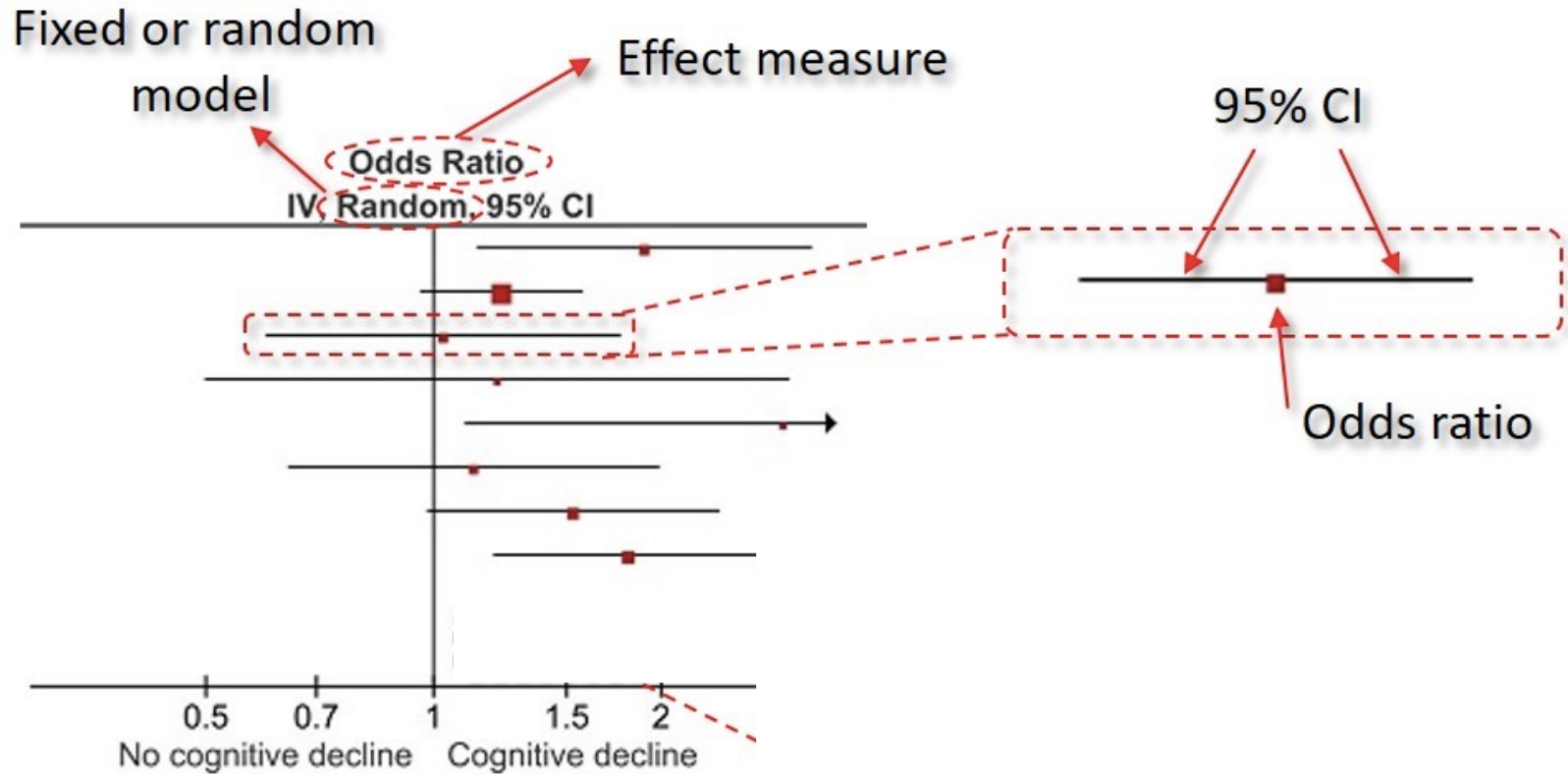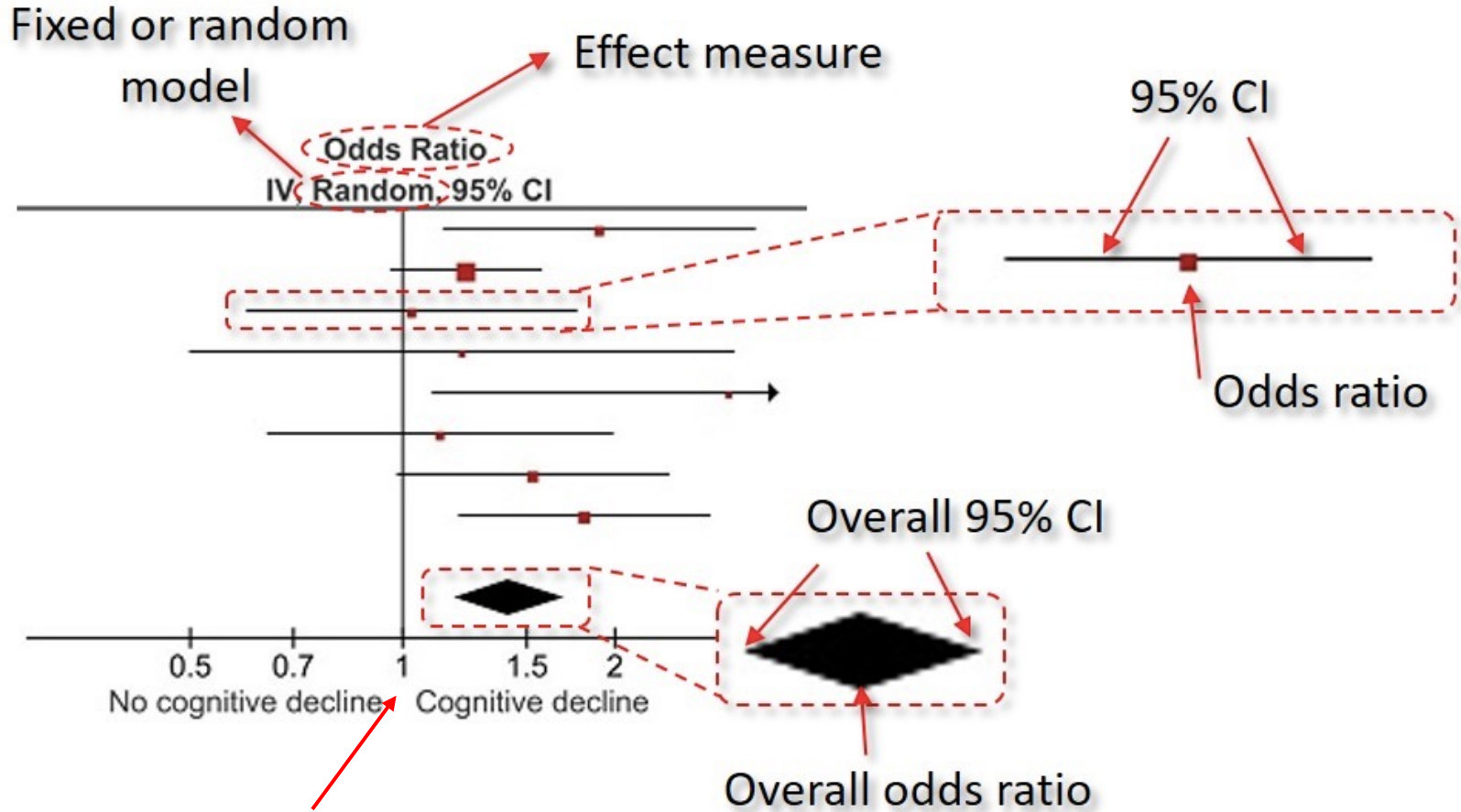
Line of no effect (often 0 or 1)
If each individual study's CI **don't cross this line**, then the results are significant
If diamond **doesn't cross this** line, yes results are significant overall

Forest Plot
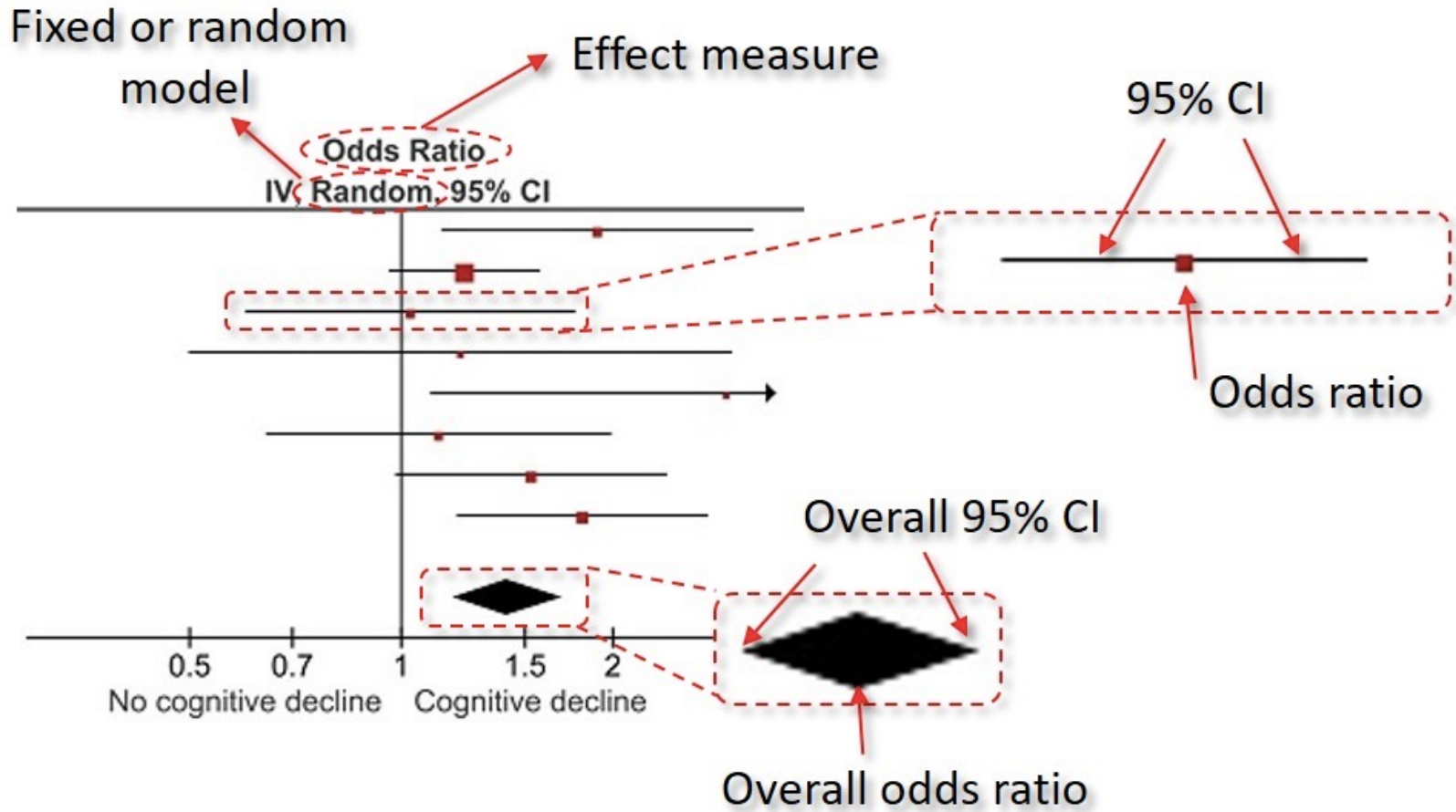
Steps of a meta-analysis

Overview

1. Define the question and scope
2. Literature search, systematic review, gather data
3. Calculate an effect size that can be combined across studies to produce a quantitative summary of the findings.
4. Statistical inference on average effect size
5. Look for effects of study quality.
6. Look for associations with variables that might explain heterogeneity of effect sizes among studies.

Step 1: Define the question and scope

Question

- A narrow question applied to a homogeneous group?
  "Does aspirin reduce incidence of myocardial infarction?"

- Or a heterogeneous set of studies or variables?
  "How much genetic variation exists in populations for behavioral traits?"

Scope

- What to include?
  - Only experiments with controls and randomization?
  - Only replicated experiments?
  - Only experiments with blinding?

- It may be best to adopt a reasonably wide scope and investigate later whether differences between methods lead to different effects overall.

Step 2: Literature search gather data

- Make it exhaustive to reduce bias.
- Easily-found studies are *different* from those that we cannot find easily.
  - Studies finding large, statistically significant effects are more likely to be published, more likely to be in "first-rate" journals, and more likely to be referenced in other articles.
- Statistical techniques exist to account partially for publication bias (funnel plots) but they do not replace an exhaustive survey.
- Decide whether to (hold your nose and) include studies of apparently poor quality.
  - **Caution:** Failure to have well-defined criteria can lead to bias (we are more likely to discard a poor study if it disagrees with our pet hypothesis).

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Step 3: Calculate Effect Size

- Calculate an effect size that can be combined across studies to produce a quantitative summary of the findings

- **Correlation coefficient *r*:** commonly used though not always ideal, because effect size depends on the range of the data.

- **Odds ratio:** used in highly homogeneous studies (e.g., in tests of aspirin and myocardial infarctions).

- **Response ratio**: $R = \bar{Y}_E / \bar{Y}_C$ or log of response ratio: $\ln(R)$

- Standardized mean difference, Cohen's *d*, or Hedges' *g*

3. Continued

- Standardized mean difference, Cohen's *d* or Hedges' *g*:

$$g = \frac{\bar{Y}_E - \bar{Y}_C}{s_{\text{pooled}}} J(m)$$

s is the pooled sample variance and *J*(*m*) is a small-sample bias correction.

Outline

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- Quantitative summaries vs. vote-counting (SKIP)

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Step 4: Statistical Inference on average effect size

- Fixed-effect models*
  - Assume one true effect size that underlies **all** studies

- Random-effect**s** (mixed) models
  - Effect size varies among studies

*Common in mostly only medical studies

Fixed effect models

- Assumes
  - **1 true effect size that underlies all the studies** in the analysis
  - Sometimes called the "common-effect" model (*not plural effects*)
  - Multiple studies have the same mean, differing only because of sampling error.
  - If every study were infinitely large, every study would yield an identical result.
  - No heterogeneity among the studies.

  When to use it? Most common in medical studies. Perhaps never justified unless all studies conducted similarly and on the same species. This is rarely the case in ecology and evolution.

Random (mixed) effects models

- Random variation is present among means of studies in addition to sampling error.
- Individual studies are therefore estimating <u>different</u> treatment effects.
- Most interest is focused on the central value, or mean, of the distribution of effects.
- The idea of a random effects meta-analysis is also to understand the distribution of effects across different studies.

Random vs Fixed in Meta-Analysis

- Difference between random vs. fixed effects in meta-analysis affects how each study is **weighted** when calculating the average effect size over all studies
- We will do this in the workshop

If you want more information…

A basic introduction to fixed-effect and random-effects models for meta-analysis

Michael Borenstein[a*†], **Larry V. Hedges**[b], **Julian P.T. Higgins**[c] and **Hannah R. Rothstein**[d]

There are two popular statistical models for meta-analysis, the fixed-effect model and the random-effects model. The fact that these two models employ similar sets of formulas to compute statistics, and sometimes yield similar estimates for the various parameters, may lead people to believe that the models are interchangeable. In fact, though, the models represent fundamentally different assumptions about the data. The selection of the appropriate model is important to ensure that the various statistics are estimated correctly. Additionally, and more fundamentally, the model serves to place the analysis in context. It provides a framework for the goals of the analysis as well as for the interpretation of the statistics.

In this paper we explain the key assumptions of each model, and then outline the differences between the models. We conclude with a discussion of factors to consider when choosing between the two models. Copyright © 2010 John Wiley & Sons, Ltd.

Keywords: meta-analysis; fixed-effect; random-effects; statistical models; research synthesis; systematic reviews

https://www.meta-analysis.com/downloads/Intro_Models.pdf

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Step 5: Look for effects of study quality

- For example, are effect sizes different on average between studies that included blinding and those that did not?

Step 6: Look for associations with variables

- Look for associations with variables that might explain heterogeneity of effect sizes among studies.

- For example, does the average effect size differ between studies carried out on women subjects and those on male subjects?

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- **Make your results accessible to meta-analysis**

Availability of Data

- Many published papers do not report enough information for meta-analysts to extract the numbers that they need.

- As a result, many otherwise relevant papers have to be discarded.

- Don't let this happen to your work.

Be the change you wish to see in the world.

– Mahatma Gandhi

Availability of Data

- Always give sizes of effects and their standard errors. A *P*-value by itself is useless.

- Give estimates of the means and standard deviations of the important variables.

- Always indicate your sample sizes and/or degrees of freedom.

- **Make the data accessible.** Publish the *__raw__* data in the paper or deposit to an online archive such as Dryad.

Availability of Data

- **Consider a meta-analysis for your first thesis chapter.** Often, the first chapter of a thesis is a review of the literature. If your review is a systematic review, and you kept track of the important quantities and feature of each study, you may have enough for a quantitative component – a meta-analysis.

Optional Extra Sides on Useful Blog:5 Tips for Understanding Data in Meta-Analysis

5 Tips for Understanding Data in Meta-Analysis

1. Don't jump to conclusions without looking at context and perspective

2. Don't loose sight of what data is *not* included

3. Check for heterogeneity (studies are too different)

4. See if a few results have extra leverage

5. Be careful of "vote counting"

Optional Extra Details and Slides on best practices for meta-analysis

Guidelines and Guidance

Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement

David Moher[1,2]*, Alessandro Liberati[3,4], Jennifer Tetzlaff[1], Douglas G. Altman[5], The PRISMA Group[¶]

1 Ottawa Methods Centre, Ottawa Hospital Research Institute, Ottawa, Ontario, Canada, 2 Department of Epidemiology and Community Medicine, Faculty of Medicine, University of Ottawa, Ottawa, Ontario, Canada, 3 Università di Modena e Reggio Emilia, Modena, Italy, 4 Centro Cochrane Italiano, Istituto Ricerche Farmacologiche Mario Negri, Milan, Italy, 5 Centre for Statistics in Medicine, University of Oxford, Oxford, United Kingdom

Introduction

Systematic reviews and meta-analyses have become increasingly important in health care. Clinicians read them to keep up to date with their field [1,2], and they are often used as a starting point for developing clinical practice guidelines. Granting agencies may require a systematic review to ensure there is justification for further research [3], and some health care journals are moving in this direction [4]. As with all research, the value of a systematic review depends on what was done, what was found, and the clarity of reporting. As with other publications, the reporting quality of systematic reviews varies, limiting readers' ability to assess the strengths and weaknesses of those reviews.

Several early studies evaluated the quality of review reports. In 1987, Mulrow examined 50 review articles published in four leading medical journals in 1985 and 1986 and found that none met all eight explicit scientific criteria, such as a quality assessment of included studies [5]. In 1987, Sacks and colleagues [6] evaluated the adequacy of reporting of 83 meta-analyses on 23 characteristics in six domains. Reporting was generally poor; between one and 14 characteristics were adequately reported (mean = 7.7; standard deviation = 2.7). A 1996 update of this study found little improvement [7].

In 1996, to address the suboptimal reporting of meta-analyses, an international group developed a guidance called the QUOROM Statement (QUality Of Reporting Of Meta-analyses), which focused on the reporting of meta-analyses of randomized controlled trials [8]. In this article, we summarize a revision of these guidelines, renamed PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses), which have been updated to address several conceptual and practical advances in the science of systematic reviews (Box 1).

clinicians, medical editors, and a consumer. The objective of the Ottawa meeting was to revise and expand the QUOROM checklist and flow diagram, as needed.

The executive committee completed the following tasks, prior to the meeting: a systematic review of studies examining the quality of reporting of systematic reviews, and a comprehensive literature search to identify methodological and other articles that might inform the meeting, especially in relation to modifying checklist items. An international survey of review authors, consumers, and groups commissioning or using systematic reviews and meta-analyses was completed, including the International Network of Agencies for Health Technology Assessment (INAHTA) and the Guidelines International Network (GIN). The survey aimed to ascertain views of QUOROM, including the merits of the existing checklist items. The results of these activities were presented during the meeting and are summarized on the PRISMA Web site (http://www.prisma-statement.org/).

Only items deemed essential were retained or added to the checklist. Some additional items are nevertheless desirable, and review authors should include these, if relevant [10]. For example, it is useful to indicate whether the systematic review is an update [11] of a previous review, and to describe any changes in procedures from those described in the original protocol.

http://www.prisma-statement.org/

Check out this webpage

- PRISMA: **P**referred **R**eporting **I**tems for **S**ystematic Reviews and **M**eta-**A**nalysis

- Different **flow-charts on systematic review process** are available depending on the type of review (new or updated) and sources used to ID studies

http://prisma-statement.org/PRISMAStatement/FlowDiagram.aspx?AspxAutoDetectCookieSupport=1#:~:text=The%20flow%20diagram%20depicts%20the,and%20the%20reasons%20for%20exclusions.

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only
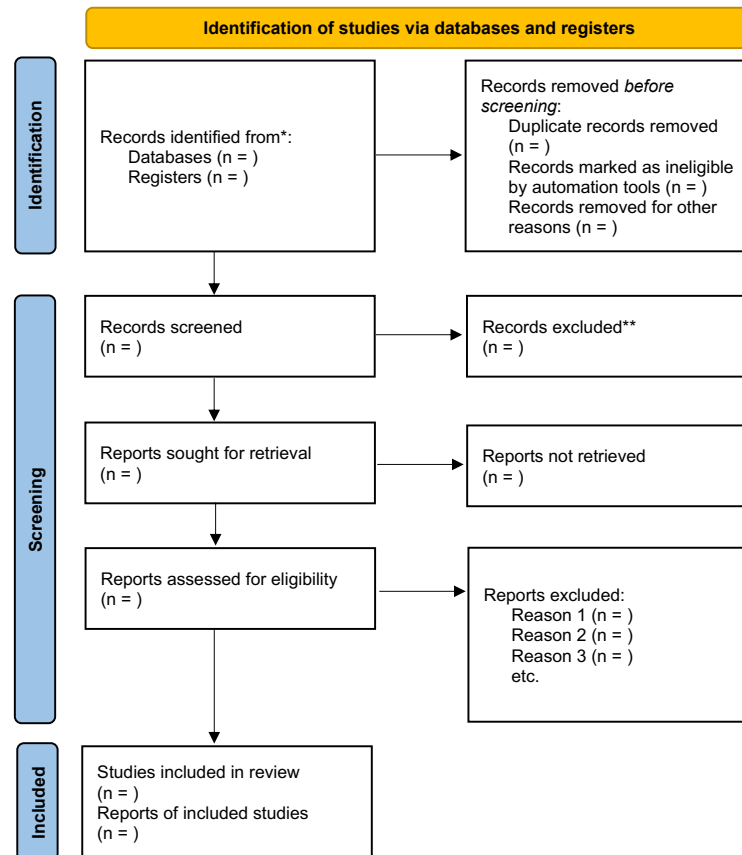
This is the first flow diagram in the list

*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).

**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

PRISMA Checklists

- 27-item checklist addressing the intro,methods,results, and discussion sections of what to include in a meta-analysis paper

- http://prisma-statement.org/PRISMAStatement/Checklist

Meta-analysis of open datasets

Culina, Antica, et al. "How to do meta-analysis of open datasets." *Nature Ecology & Evolution* 2.7 (2018): 1053-1056.

Workshop

Workshop Thurs

See the "Meta-analysis" tab in R Tips page for help getting started *prior*

https://www.zoology.ubc.ca/~schluter/R/Meta.html

Doing Meta-Analysis in R Blog
https://bookdown.org/MathiasHarrer/Doing_Meta_Analysis_in_R/pub-bias.html

Workshop Thurs

- Use **dedicated packages for meta-analysis** available in R (e.g., metafor).
- lmer() in lme4 package can't be used for random effects meta-analysis in R, because it won't calculate the necessary weights.

Aggressive bibs in sparrows:

- Data: Investigates relationship between male sparrow bib (black throat patch) and male size, behaviour, and reproductive success
    1. Do as a fixed-effect meta-analysis
    2. Do as a random-effects meta-analysis
    3. Use metafor() package to compare published vs. un published studies
        - Funnel plot
        - Forest plot

Workshop Thurs

Latitudinal diversity gradient

- Data:There are > species in tropics than temperate zone, but how strong and general is this pattern? Meta-analysis to examine relationship between diversity and latitude.
- Uses metafor() package to compare latitudinal gradients

R toolkit for meta-analysis?

APPLICATION

Facilitating systematic reviews, data extraction and meta-analysis with the METAGEAR package for R

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Summary

1. The R package ecosystem is rich in tools for the statistics of meta-analysis. However, there are few resources available to facilitate research synthesis as a whole.

2. Here, I present the METAGEAR package for R. It is a comprehensive, multifunctional toolbox with capabilities aimed to cover much of the research synthesis taxonomy: from applying a systematic review approach to objectively assemble and screen the literature, to extracting data from studies, and to finally summarize and analyse these data with the statistics of meta-analysis.

3. Current functionalities of METAGEAR include the following: an abstract screener GUI to efficiently sieve bibliographic information from large numbers of candidate studies; tools to assign screening effort across multiple collaborators/reviewers and to assess inter-reviewer reliability using kappa statistics; PDF downloader to automate the retrieval of journal articles from online data bases; automated data extractions from scatter-plots, box-plots and bar-plots; PRISMA flow diagrams; simple imputation tools to fill gaps in incomplete or missing study parameters; generation of random-effects sizes for Hedges' d, log response ratio, odds ratio and correlation coefficients for Monte Carlo experiments; covariance equations for modelling dependencies among multiple effect