Meta-analysis

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Meta analysis refers to a statistical step by step process of (1) framing of answerable questions, (2) identifying primary sources of data and literature, (3) selection of the sources, (4) assimilation and quality assessment, (5) integration and summarisation of the data in the literature, (6) presentation of summary findings, (7) assessment of biases, and (8) reporting of the subgroup analyses, sensitivity analyses, or meta-regressions.

Gene Glass (1975) first proposed meta analysis as he has outlined in this essay [1], and subsequently, meta-analysis has undergone major developments. The steps of meta-analysis are described are as follows:

Step 1: framing of an answerable question:

Framing an answerable question initiates with the setting up the question in the form of PICO (where "P" == patients in clinical setting or persons, "I" == interventions or exposure, "C" == comparator conditions, and "O" == health outcomes). Cooke et.al(2012) have advocated for the use of SPIDER ((Sample, Phenomenon of Interest, Design, Evaluation, Research type) statements [2].

Steps 2 and 3: Searching and identification of articles or primary studies for synthesis:

In this step, the meta-analyst first goes through the titles and abstracts of each article turn by turn and based on pre-specified criteria selects or reject a primary study on the basis of reading the title and the abstract of the study. Following this step, the meta-analyst then collects full texts of the retained studies and scans their reference lists and searches the names of other authors for additional studies. in this way, iteratively the meta-analyst puts together a database of primary studies that would form the data base of the analyses. In order to do so, the analyst uses a flow chart referred to as PRISMA (Preferred Reporting Items in Systematic Reviews and Meta Analysis). Moher et.al. (2009) has described the process of preferred reporting items in details [3]

Step 4: Quality assessment for systematic reviews and meta-analysis

Following search, identification, and selection of the studies for meta-analysis, the analyst conducts assessment of the study quality of each primary study under review. For each study, the analyst examines the effect size estimates, and evaluates the possibility of

biases in the study. Following the examination of study design, effect estimates and confidence intervals, the possibility of biases, and how the researchers of the original studies may have controlled for the effects of possible confounding variables, the analyst(s) assign each study a score that they then use for further analysis. Zeng et.al. (2015) have conducted a systematic review of the quality appraisal tools that can be used for meta analyses [4]. Another popularly used tool is GRADE tool put together by the GRADE working group [5].

Steps 5 and 6: Assimilation, summarisation and presentation of summary results

In this step the studies are summarised and a pooled estimate is presented for the body of studies evaluated for meta-analysis. Initially, the studies are evaluated for heterogeneity analysis where, on the basis of the results presented and the sample of the population studied, the studies are evaluated if the studies are very different or tested that they 'do not belong' to a 'group' from where an analyst can pool the estimates. Refer to Higgins et.al (2003) for a detailed discussion of how to measure inconsistency in the studies selected for meta-analysis [6]. In general, the Cochran's Q, defined as the weighted sum of squared differences between individual study effects and the pooled effect across studies, with the weights being those used in the pooling method, and distributed as a chi-square statistic with k (number of studies) minus 1 degrees of freedom. An alternative test is to use I-squared statistic given as $I^2 = 100\% \times (Q-df)/Q$ is used to assess heterogeneity in the studies. For more information, see the help page of StatsDirect on conducting meta-analysis [7]. If the studies are found to be heterogeneous, then the analyst should first explore the cause of such heterogeneity and either can report a systematic review or the narrative review of the key findings of the studies, or (2) the analyst can report 'fixed effects' estimate of the pooling of the results, as opposed to 'random effects estimate'. A 'fixed effects estimate' of the pooled result indicate that the pooled estimate was based on the assumption that the summary estimate came from the studies included in the analysis, as opposed to assuming that the studies belonged to a 'randomly distributed' sample of a wider population of studies. Hunter and Schmidt (2000) have discussed the implications and interpretations of fixed-effects versus random-effects in the context of social sciences studies [8]. For a discussion on the difference between fixed-effects and random-effects model, see Borenstein et.al. (2010) [9].

Meta-analysts present the pooled effect estimates in the form of a "Forest Plot" (Figure 1).

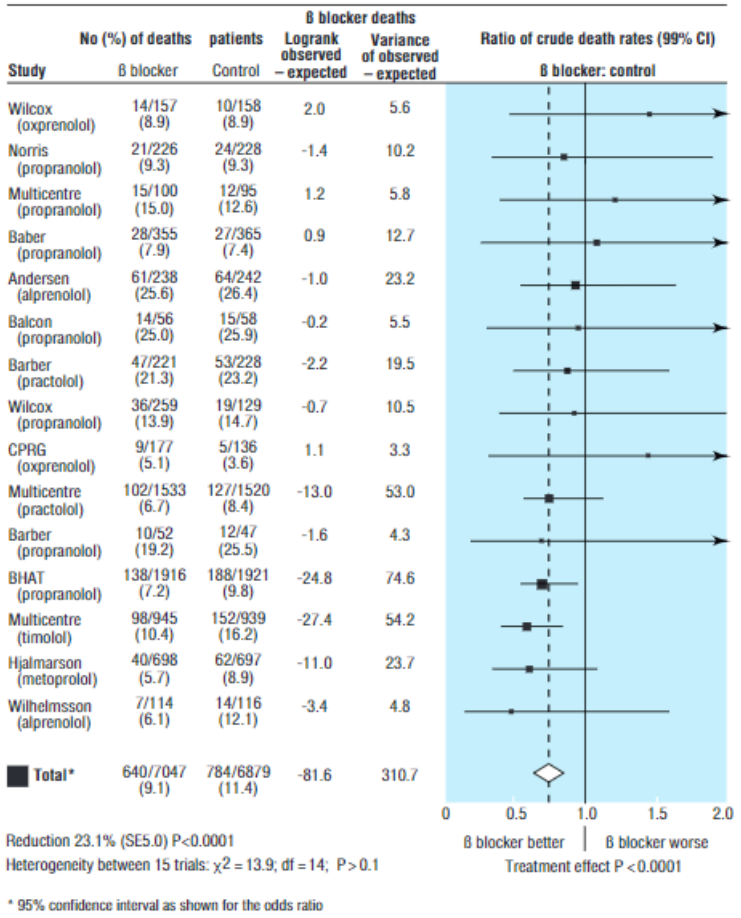

Fig 2 Updated version of Lewis and Ellis's original plot (fig 1) showing effect of β blockers on mortality

Figure 1. Forest Plot taken from the article by Lewis and Clarke (2001) [10]

As can be seen in the above figure, a Forest Plot consists of the following features:

- A set of squared boxes. The size of each squared box represents the "Weight" assigned to each individual study included in the meta-analysis, based on the variance of the effect estimate
- The position of each squared box corresponds to the the value of the effect size of each study. The effect size itself is located on the X axis of the plot
- The y-axis position of each 'box' corresponds to the order in which the studies are presented in the analyses. Usually this is a list of all studies with the names of the first author and the year the study was published in parentheses.
- Extending from each box is a "whisker'. The left side of the whisker ends at the lower of the 95% (or chosen) confidence interval of the effect size, and the right hand side of the whisker correponds to the upper end of the 95% (or chosen) confidence interval around the effect size.
- A dotted line runs top down. The dotted line corresponds to the pooled estimate of

the studies. The pooled estimate itself is presented in the shape of a diamond below the studies included in the meta-analysis. The size of the diamond corresponds to the pooled estimate itself and the confidence band (95% confidence interval or another chosen confidence interval)

- A solid line runs parallel to the dotted line. This solid line presents the null estimate (in this case 1.0 to indicate relative risk estimate for randomised controlled trials or cohort studies, or odds ratios in case of case control studies

The pooled effect estimate itself is presented in the form of an Odds Ratio and is estimated from as the summation of the weight adjusted effect size of the individual studies. The interpretaton of the Odds Ratio is based on the nature of the research question; and along with the Odds Ratio, the analyst also presents the 95% (or an appropriate band) of confidence interval. For studies that have met the criteria of homogeneity, the analyst presents Odds Ratios of both Random-effects model and the Fixed-effects models.

Step 7: Assessment of biases and presentation of results

The analyst must also present the results of the assessment of biases in meta-analysis. The main source of bias in any meta-analysis is publication bias, where it is possible that the meta-analysis was based only on the basis of published studies and the meta-analyst failed to take into consideration the studies that may have been conducted but the researchers did not report them to peer-reviewed journals or that they were not included in the databases that the analysts searched and hence the anaysts were unable to report them. A common cause of publication bias is that, smaller studies and studies that have equivocal findings or null findings are less likely to be represented in research reports that are indexed in scholarly literature databases, and hence likely that the analyst can miss such studies. In order to examine the possibility of publication bias, the analysts report such biases using a visual tool referred to as "funnel plot" (Figure 2). Egger (1997) proposed the Funnel Plot as a tool to assess publication biases in meta-analyses [11]

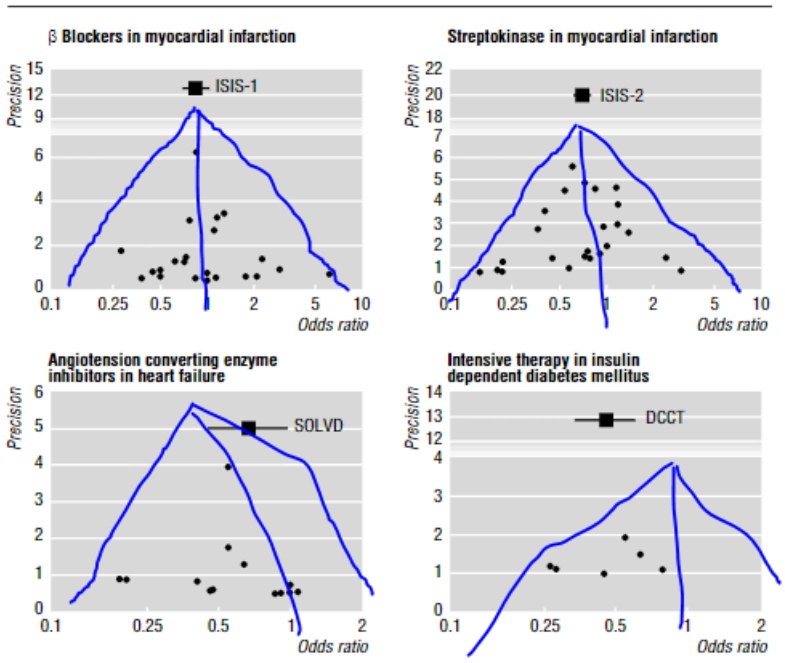

Figure 2. Funnel Plots, adapted and modified from the article by Egger et.al. (1997). Publication biases are detected by assessing assymetries in the funnel plot constructed.

The features of the funnel plot:

- The effect size of each study is plotted on the X axis
- An inverse of the variance measure is plotted on the y axis, so that a study with high precision and therefore "low variance" in the effect estimate will be on the top and a study with low precision (and therefore high variance of the effect size) will be located at the bottom of the chart.
- Each dot in the graph presents a study.

If the studies are evenly scattered, this indicates that the analyst has reported on the basis of small and large studies, imprecise and precise estimates about the null value and the effect estimate. But if any particular quadrant or the area within the funnel is blank or empty, it suggests publication bias. For a comprehensive discussion of different statistics and tests for publication bias in meta-analysis, read this paper by Sterne et.al. (2001) [12]

Step 8: Subgroup analyses and meta-regression

Analysts present a range of subgroup analyses in their meta-analysis. They do this to show how the effect estimates and effect sizes of the meta-analysis would vary based on the study characteristics or study quality. Meta-regression are statistical techniques used to regress effect sizes of the studies themselves on the study characteristics. For a discussion on the process and interpretation of the results of meta-regression on meta-analysis, review the paper by Thompson and Higgins (2002)[13]

Software and tools for meta-analysis

In general, these steps -- framing question, search and retrieval, quality assessment, assessment of heterogeneity, pooling of results, investigation of publication bias, and meta-regression or sensitivity analysis -- are the main components of meta-analysis. Several specialised free and open-source or free software and tools are available to enable a meta-analyst to conduct meta-analysis and publish results (Table 1)

Software or app	URL	Description
Cochrane Revman5	https://community.cochrane.org/help/tools-and-software/revman-5	End to end tool for authoring meta-analyses. A web version is in preparation but as of 2019, can be accessed only by registered authors
CRAN Task View for meta analysis	https://cran.r-project.org/web/views/MetaAnalysis.html	A list of different R packages for conducting meta analysis
Open Meta (analyst)	http://www.cebm.brown.edu/openmeta/index.html	Free meta analysis software for Windows and MacOS
Meta-essentials	http://www.erim.eur.nl/research-facilities/meta-essentials/download/	Excel add-on tool from Erasmus Institute, Netherlands

Table 1. A list of free and/or open-source tools and software or collections that one can use to conduct meta-analysis

References

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