Meta-analysis and the science of research synthesis

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Preface

Meta-analysis is the quantitative, scientific synthesis of research results. Since the term and modern approaches were first introduced in the 1970s, meta-analysis has had a revolutionary impact on many scientific fields, and helped to establish evidence-based practice and resolve seemingly contradictory results. At the same time, its implementation has engendered criticisms and controversies, some general and some specific to particular disciplines. The recent 40th anniversary of meta-analysis provides a timely opportunity to reflect on the accomplishments, limitations, recent advances, and the direction of future developments in the field of research synthesis.

(Introduction)

Synthesizing results across studies to reach an overall understanding of a problem and identify sources of variation in outcomes is an essential part of the scientific process. Until recently, the results of scientific studies have been summarized in narrative reviews. However, this approach becomes inadequate when there may be hundreds of studies on a given research question[1,2], and the difficulties of carrying out narrative reviews to identify and summarize evidence in a transparent and objective manner have become increasingly apparent as research results have mushroomed across scientific fields[3].

During the last few decades, more scientifically rigorous systematic reviews and meta-analyses, carried out following formal protocols to ensure reproducibility and reduce bias, have become more prevalent in a range of fields[1] (Box 1). Systematic reviews aim to provide a robust overview of the efficacy of an intervention, or of a problem or field of research, and can be combined with quantitative meta-analysis to assess the magnitude of the outcomes (effect sizes) across studies and investigate the causes of their variation. Narrative reviews remain useful for exploring the development of particular ideas (as we do here) or to advance conceptual frameworks, but they cannot accurately summarize results across studies[4].

Four decades after its introduction, we are seeing both widespread mainstream acceptance of meta-analysis as a research synthesis tool, and also the signs of what may be considered a 'meta-analytic midlife crisis.' While the number of published meta-analyses has continued to increase rapidly, too many meta-analyses and systematic reviews are of low quality[5-7]. The publication of methodologically flawed meta-analyses indicates that peer reviewers, editors, and authors are not fully aware of or are indifferent to the large body of well-developed meta-analysis methodology, or feel unqualified to address methodological issues. Low quality meta-analyses have attracted strong criticism[5,8] and even calls for a halt in publication of all meta-analyses[9]. While it is certainly both valid and valuable to criticise poor methodology and reporting, this should result in a call for improved standards (as for pre-clinical trials[10]) rather than abandonment of the field[11]. We believe that the solution lies in rigorous application of stricter methodological and reporting quality criteria for published meta-analyses (e.g., Tools for Transparency in Ecology and Evolution, TTEE: osf.io/g65cb), and in better practitioner and reviewer training in meta-analysis and systematic review rationale and methodology.

We highlight some of the main principles and characteristics of high quality meta-analytic methodology in this review and briefly summarize the development of the field. We also discuss the limitations, utility and achievements made by applications of meta-analysis in several fields, and its role in advances in ecology, evolutionary biology and conservation (EEC) as a case study. Finally, we address several recent criticisms of the meta-analytic approach and suggest ways in which future developments in research synthesis can facilitate the most rapid progress in the fields in which it is employed.

Meta-analyses use well-documented methodologies

Systematic reviews aim to be transparent, reproducible and updatable, and to address well-defined questions. The systematic review process includes use of formal methodological guidelines for the literature search, study screening (including critical appraisal of eligible studies according to pre-defined criteria), data extraction, coding, and often statistical analysis (i.e. meta-analysis) along with detailed, transparent documentation of each step. Software, protocols and reporting guidelines for systematic reviews and meta-analyses (e.g., PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses[12]; www.prisma-statement.org) are well established in many fields. For instance, PRISMA is "an evidence-based minimum set of items for reporting in systematic reviews and meta-analyses" and includes a checklist of 27 items and a template flow chart for systematic review presentation (i.e. a PRISMA diagram; Fig. 1a). Guidelines for developing and preparing systematic review protocols are published in PRISMA-P (-Protocols; http://www.prisma-statement.org/Extensions/Protocols.aspx)[13].

If the systematic review reveals sufficient and appropriate quantitative data from the studies summarized, a meta-analysis can be conducted. In a meta-analysis, one or more outcomes in the form of effect sizes are extracted from each study. Effect sizes are designed to put the outcomes of the different studies being combined on the same scale, using a suite of metrics including odds and risk ratios, standardized mean difference, *z*-transformed correlation coefficients, log response ratios, and others[14,15]. It is essential for the effect size metric used to be readily interpretable, scientifically meaningful, comparable among meta-analyses, and for its sampling distribution to be known, so that statistical models can be appropriately constructed.

The effect sizes are then entered into a statistical model with the goals of assessing overall effects and heterogeneity in outcomes. These models are based on either an assumption of a common effect ("fixed effect ") or random effects (Fig. 1 b)[16]. The common-effect (fixed-effect) model assumes that variation in effect sizes among studies is due to within-study (sampling) variance, and that all studies share a common 'true' effect. The random-effects model assumes that the true effects from different studies also differ from one another, and represent a random sample of a population of outcomes, analogous to random effects models in ANOVA. Thus, random-effects models include an extra variance component to account for between-study variance in addition to within-study variance. Common-effect models imply that the results apply only to a given group of studies. Random-effects models apply more generally. In carrying out a meta-analysis one evaluates the central tendency (the mean) and its confidence limits, and the heterogeneity in the effect across studies. To identify the magnitude and sources of variation among studies in the effect sizes (Fig. 1 c), earlier studies relied on simple heterogeneity tests[16], while more recent work often uses meta-regressions[17]. The "main effect" or "grand mean" may be of critical importance or largely irrelevant, depending on the goals of the meta-analysis and the magnitude and sources of heterogeneity (see below). While these differ considerably among disciplines, quantifying heterogeneity is universally important.

Both heterogeneity tests and meta-regression employ weighting by the precision of the estimate of the effect, where large studies with high precision are weighted more heavily than smaller and more variable studies[18] (Fig. 1 b,d). There are many issues to consider in constructing these statistical models, including appropriate weighting and accounting for non-independence (below). In addition, tools have been developed for evaluating publication bias and power, and conducting sensitivity analyses[19-21] (Fig. 1 e,f).

Meta-analysis is essential for progress in science

Meta-analysis has generally been used for two different fundamental goals, employing contrasting approaches. The first of these goals is to assess the evidence for the effectiveness of specific interventions for a particular problem or hypothesized causal associations for a condition, often over a relatively small number (ca. <25) of studies. The second, quite different, fundamental goal is to reach broad generalizations across larger numbers (dozens to hundreds) of study outcomes to provide a more comprehensive picture than is possible in an individual primary study. The differences in approach and goals affect not only the scale of meta-analyses, but every step of the research synthesis, from study inclusion criteria to the statistical models used. In both approaches, meta-analysis is used to synthesize evidence across studies to detect effects, estimate their magnitudes and variation, and analyse the factors (covariates or moderators) influencing those effects.

Where the goal is to assess evidence for specific interventions, the focus is on accurately estimating an overall mean effect, and may include identifying factors that modify that effect. This approach is exemplified by the PICO (Population, Intervention, Comparator, Outcome) framework (and its extensions) for question formulation, where specification of these elements is central to the purpose of the synthesis[22], for example in assessing clinical effectiveness, and the effectiveness of interventions in other disciplines. Question formulation using PICO has been widely adopted in fields ranging from medicine to the social sciences (e.g. the Campbell Collaboration). While moderating factors may be important to understanding how the overall effect is influenced by study or population characteristics, such meta-analyses tend to emphasize the consequences of implementing a specific intervention for a specific population. This implies clearly delineating that population, very specifically and often narrowly.

In the second case, where the goal is to reach broad generalizations, the population of studies may be large and heterogeneous, and although estimating the main effect of a particular phenomenon or experimental treatment may be important, identifying sources of heterogeneity in outcomes is often central to understanding the overall phenomenon[23]. Such meta-analyses deliberately incorporate results on heterogeneous populations so that broad generalizations and the factors modifying them can be examined and tested. This approach is common in the fields of EEC and in some social sciences, where meta-analysis has been used to address fundamental problems, weigh the evidence for prominent theories or hypotheses, and consider the generality of common findings, observations or phenomena[23,24]. Of course, to some extent there is a continuum rather than an absolute dichotomy in meta-analytic approaches, with overlap between disciplines. A limitation of using broad inclusion criteria is adequately accounting for high heterogeneity. A limitation of a reductionist scope and narrow focus can be the limited inference possible outside of a narrowly specified population or for factors modifying outcomes, where inclusion of a broader definition of the population of interest and potential factors affecting outcomes might be highly revealing. Either approach can be limited or even biased. A collection of many narrowly focused reviews of what is essentially the same intervention can generate spurious results, as can the opposite approach of 'fishing' for significance among many hypothesized explanatory factors or covariates in an excessively broad study.

For both of these basic goals (evaluation of specific interventions, or reaching a broad understanding of a general problem), meta-analysis has been a more powerful and less biased means for clarifying, quantifying and disproving (or confirming) assumed wisdom than have previous conventional approaches[25], such as narrative reviews and flawed quantitative methods such as 'vote counts' (discussed below). Meta-analytic methods have resolved apparently inconclusive data to arrive at a clearer picture, often sooner than other approaches. In medicine, meta-analyses can unambiguously assess the effectiveness of particular surgical or pharmaceutical interventions or the significance of hypothesized causal associations.. For example, a meta-analysis of 20 clinical studies was able to conclusively demonstrate a clear relationship between maternal obesity and increased risk of neural tube defects (NTDs) despite considerable variation in effects reported in individual studies (from 0 to 3-fold increase in the risk of NTDs)[26]. Similarly, primary studies of the value of a family-based intervention approach for serious juvenile offenders called multi-systemic therapy (MST) were seemingly inconsistent. Despite the logical and theoretical basis for MST, a meta-analysis found no significant differences between MST and conventional social services in the success of outcomes [27]. Both meta-analyses have had ramifications for evidence-based practice.

The most consequential impact of the introduction of formal research synthesis methodology has been a profound change in the way scientists think about the outcome of scientific research. An individual primary study may be seen as a contribution toward the accumulation of evidence, rather than revealing the conclusive answer to a scientific problem [25,28]. Clearly there are cases where a single revelatory study completely illuminates and resolves a major problem. However, in many cases syntheses can provide a more general and complete picture of the evidence than can any one individual study. The results of initial studies are too often not confirmed by those of subsequent studies or by syntheses of a body of research. Additional major contributions of the introduction of meta-analysis have been increased attention to reporting standards in primary studies, including full and transparent reporting of data, and recognition that studies reporting "no significant effect" are as potentially interesting and valuable as those reporting low p values [29,30].

Meta-analysis in EEC as a case study

Meta-analysis was first adopted by ecologists and evolutionary biologists some 25 years ago (Table 1), and has had a considerable impact on this research field in both fundamental and applied areas. Meta-analytic approaches in ecology were introduced at the same time as it has become increasingly urgent to provide accurate quantitative assessments, predictions and practical solutions to pressing environmental issues including biodiversity losses, the increase in invasive species and biotic responses to climate change. Meta-analysis provided tools for summarizing evidence for these effects, their impacts, and the effectiveness of interventions. An increased use of meta-analyses and systematic reviews in conservation and applied ecology has been facilitated by the promotion of evidence-based approaches in this field [31,32], especially through organizations such as the *Centre for Evidence Based Conservation* (www.cebc.bangor.ac.uk) and the *Collaboration for Environmental Evidence* (www.environmentalevidence.org; Table 1).

Applications of meta-analysis and more recently, systematic reviews in EEC have highlighted major research gaps[33], provided assessments of the impacts of major environmental drivers (e.g., climate change[34]), the effectiveness of conservation and management strategies[31], and evaluation of the evidence for ecological and evolutionary theories[35]. Examples of influential ecological meta-analyses include quantification of the effects of biodiversity on ecosystem functioning and services[36,37], demonstrating that declines in species richness have negative impacts on the functioning of ecosystems. Benayas and colleagues[38] found that ecological restoration can reverse environmental degradation and increase biodiversity and provisioning of ecosystem services in a wide range of ecosystems globally, although not to full recovery compared to reference ecosystems.

Similarly, meta-analysis offered evolutionary biologists the tools to test major hypotheses based on theories of natural selection, sexual selection and animal social behaviour at unprecedented scales [35]. Examples of prominent evolutionary meta-analyses include assessments of correlations between measures of genetic diversity, fitness and population size[39]. One conclusion is that reduction in population size due to habitat fragmentation reduces genetic variation, and that these losses of genetic diversity have a negative impact on fitness in affected populations.

Meta-analysis has been important in EEC for greatly expanding the capability to evaluate large scale overviews of study outcomes—over larger spatial scales, different time periods, multiple systems, and a diversity of organisms that are beyond the scope of any one researcher or research group. For example, Hillebrand carried out a global meta-analysis of almost 600 latitudinal gradients in species diversity, verifying the high degree of generality of the decline in diversity with latitude, but also identifying important factors modifying this pattern[40]. Meta-analysis has also been a valuable tool for practitioners in EEC involved in collaborative research who wish to combine original results from experiments carried out across multiple study sites[41,42].

Unlike clinical medicine and social sciences where the research is on a single species, the multi-species nature of much of EEC research and therefore of meta-analyses has led practitioners to integrate phylogenetic comparative methods with meta-analytic models to take into account potential non-independence among lineages due to shared evolutionary history[43-45]. Non-independence among outcomes due to a variety of sources may be more obvious in EEC than in other fields because of the large size and complex data structure of many EEC meta-analyses. However, non-independence is a ubiquitous problem for research synthesis in most research fields, and much work remains to be done to better model and account for sources of non-independence.

The structural characteristics of data in EEC and the goals of generality typically result in high heterogeneity. Rather than seeking to explain all of the heterogeneity among studies, the goal is often to identify major factors of commonality — to detect the signals amid the noise where the gain in information is more important than achieving a clean accounting of all sources of variability. This is a different perspective than meta-analyses narrowly focused on detecting the efficacy of a specific intervention, for instance.

Advances in meta-analyses in EEC have been stimulated by many factors, including learning from practitioners in other disciplines, effective and widespread short courses for training advanced students and practicing scientists, and development of software specifically tailored for this field[46,47]. Methodological innovations incorporated or developed in meta-analysis in EEC include the meta-analysis of factorial experiments[48], introduction of randomization (permutation) tests in meta-analysis[49], early embrace of random-effects and mixed-effects models when these were still highly controversial in other disciplines[50], and methods for inclusion of qualitative information such as expert opinions[51].

The introduction and incorporation of meta-analysis in ecological research have raised similar objections to those raised in other disciplines, and these criticisms and others have been similarly refuted across disciplines[11]. For instance, critics have claimed that the potential for publication bias in the literature (i.e. the underreporting of non-significant results or disconfirming evidence[21]) invalidates the use of meta-analysis. This objection has been refuted by research synthesists in many fields who point out that if publication bias exists, it is not a problem unique to meta-analysis, but affects any attempt not only to summarize the results of the literature, but to reach any valid conclusions from it. In another instance, as in the early criticisms of meta-analyses in social sciences[52], some ecologists have claimed that ecological studies are too heterogeneous to be meaningfully combined statistically[9] and that ecology is best served by accumulating a catalogue of case studies[53]. Analogously, the basis for early objections to the introduction of statistics to ecology in mid-20th century was the inability to fully account for the uniqueness of individual organisms and micro-site environmental variation using means and statistical tests. . Despite the above criticism, introduction of meta-analysis in EEC has been enthusiastically embraced by the majority of scientists in these disciplines as a “remote sensing tool” helping scientists to generalize the findings of individual studies to reach a broader understanding[11], and the number of meta-analyses published in EEC has increased exponentially over time[54].

Limitations, controversies and challenges

Despite both its current utility and future potential, meta-analysis also has various limitations as a tool for research synthesis and for informing decisions. Meta-analysis and systematic reviews can highlight areas where evidence is deficient but cannot overcome these deficiencies; they are statistical and scientific procedures rather than magical techniques. For example, in a systematic review of the literature on hypotheses explaining biological invasions, Lowry and colleagues found a major gap in published studies on invasive species in the tropics, highlighting not only what is known but also what is unknown globally about this problem[33]. Other challenges for meta-analysis and systematic reviews include publication bias and research bias[50], the latter where populations, species, or systems are over- or under-represented in the literature, giving a biased view of the totality. These issues may be strongly suspected and their magnitude can sometimes be estimated[19,20], but cannot truly be corrected by the meta-analyst[55,56]. Similarly, a synthesis may be constrained by either selective or incomplete reporting in the primary literature [30].

One undesirable consequence of the growing recognition and high impact of meta-analyses is an increase in less-than-rigorous applications of these methods as well as the application of arbitrary and less-well-justified methodology, inaccurately termed ”meta-analysis.“ The use of statistically flawed approaches can lead to erroneous and misleading results that masquerade as serious research syntheses. The term “meta-analysis” should be applied only to studies employing well-justified statistical procedures such as appropriate effect size calculation, weighting and heterogeneity analysis[57] and use statistical models that take into account the distinct hierarchical structure of meta-analytic data. Unfortunately, the term has been misapplied to any study using data from a number of primary publications, regardless of the rigor of the methodology. Statistically flawed procedures such as vote-counting, which provide only limited information about study outcomes, can be highly misleading and have long been discredited, are still employed in published papers[6,50]. Vote-counting is a deceptively convenient procedure in which the generality of findings in a group of studies is assessed by counting up the number of significant and non-significant results in individual studies (and by elaborations on this approach). Although it is vulnerable to erroneous inferences and provides unreliable information on effect magnitudes or heterogeneity, it persists zombie-like, returning like the undead to haunt the naïve or determinedly uninformed. Vote-counting is not meta-analysis, and is not an acceptable basis for meaningfully summarizing research results in published papers.

Meta-analyses that are not weighted by inverse variances are common, often unjustified, and present different problems. Unlike vote-counts, unweighted meta-analyses can be unbiased and may provide information on the magnitude of the effects[8]. However, in an unweighted analysis, within- and between-study variation cannot be separated, and therefore common- and random-effects models cannot be employed and heterogeneity is difficult to assess properly. Unweighted meta-analyses also increase the influence of small studies[29], which have often been found to report larger and more variable effects than those of larger studies (both due to incorporating more random noise, and possibly due to publication bias). An alternative when variances are unavailable from primary studies is weighting by sample size or other metrics, but this does not incorporate the information that an inverse-variance weighted analysis provides, and may introduce unknown biases. These problems are particularly acute with small sample sizes. One argument often made in support of unweighted meta-analyses is that the variances needed for a weighted meta-analysis are frequently unavailable due to poor primary study reporting, and it is undesirable to leave studies with missing data out of the meta-analysis. One solution is use of the various methods developed for imputing or otherwise modelling missing data. And, although data reporting practices are being slowly improved, it may be that many older studies are simply inadequate for accurate quantitative reviews. Another argument for unweighted meta-analyses is that when between-study variation is much higher than within-study variation, this simplifies to an essentially unweighted analysis[58]. However, we note that it requires a weighted meta-analysis to assess the two types of variation in the first place, and it would be preferable to report both weighted and unweighted results in such cases.

Another unfortunate outcome of the high impact and growing prestige of meta-analyses[59], coupled with use of metrics such as citation numbers and *h*-indices in evaluations of research accomplishments, is an unease among some primary researchers about the fairness and rewards of the scientific process[8,60]. Some have decried reviews as “the black-market of scientific currency” with calls to replace citations to reviews and meta-analyses by citations of primary studies[61]. Worse, research synthesists in medicine have been recently described as "research parasites"[62] of primary studies and the researchers who conduct them. On the other hand, primary studies without context, comparison or summary are ultimately of limited value. Moreover, research synthesis methods are not the exclusive province of any one group, but can also be conducted by primary researchers in their own areas of expertise. The introduction of more explicit guidelines and standards for conducting and reporting meta-analysis could address some of these grievances, and we agree that better methods for citing primary studies in meta-analysis should be implemented to give full credit for the original studies. "Research parasites" can also serve to increase scientific diversity by the addition of another "trophic level," improving scientific ecosystem functioning.

Advances, developments and future promises

Meta-analysis is the grandmother of both the Big Data and the Open Science movements. For hundreds of years, scientists have collected data in individual studies, based on observations and experimentation[63]. The introduction and implementation of meta-analysis was the first large-scale, coordinated effort to collect and synthesize pre-existing data to determine patterns, make predictions, reach generalizations, and make evidence-based decisions. Discoveries resulting from the analysis of 'Big Data' and in parallel, development of Open Science practices, transparency, and replication of research are transforming many research areas. Big Data refers to large, complex data sets that may be mined for patterns or for making predictions, and has been influential in areas from genomics to climatology to advertising. Data searching, curating, evaluation and quality control are essential components of Big Data practice, and all of these have been the subject of conceptual exploration and formal methodological development in meta-analysis for many years[64]. However, the approach has been somewhat different. Meta-analysis is inherently statistical, while Big Data has been framed within computer science. Greater cross-fertilization between the two fields should prove productive.

Open Science practices have emphasized full and unbiased access to scientific data[65]; these issues are central to future progress in meta-analysis. Pre-registration (called 'registration' in some fields) of planned studies can reduce selective outcome reporting; publication of "registered reports" in which a study's methods and proposed analyses are peer-reviewed and published prior to research being conducted can reduce publication bias. Limitations placed on accessing information are serious impediments for best practices in meta-analysis. By minimising selective and poor reporting and advocating full access to data and coding of analyses, Open Science standards, including guidelines such as those in the Equator Network (http://www.equator-network.org) [30,66] can ameliorate many problems in research synthesis and propel rapid advances.

In addition to the benefits accruing from the increased availability of unbiased information, advances in meta-analysis are being propelled by methodological developments, and include the use of machine learning and artificial intelligence (AI) to screen studies for inclusion in systematic reviews and meta-analyses[67], increasingly sophisticated software and models for complex meta-regression[17,47], robust variance estimation to better account for studies with small sample sizes [68], meta-analysis of individual participant data, and integration of meta-analysis with decision support in medicine and other domains[69]. Bayesian meta-analysis has been implemented in many fields and is a particularly important approach when external sources of information can provide priors [70]. Meta-analysis methodology has been used to synthesize data to address methodological issues including heterogeneity and its interpretation[71], the implications of inclusion/exclusion of unpublished literature[72], and other issues. The integration of Big Data, AI and meta-analysis are important conceptual as well as methodological developments reliant on larger trans-disciplinary linkages between statistics, computer science, biological sciences, social sciences and other scientific fields. It is not impossible to envisage automated systems where AI aids not only in the real-time acquisition, but in the critical appraisal and meta-analysis of data, potentially integrating different information streams to inform tailored decisions in all areas of applied science.

The statistical methodologies underpinning and supporting meta-analysis have been undergoing nearly constant methodological development. Areas of particular current interest include multiple imputation to model missing data, advanced use of meta-regression and model selection to evaluate the influence of more complex data structures and multiple covariates, and hierarchical modelling of multi-level data, including that from individual "participant" data in medicine[22] and in EEC[73]. Network meta-analyses seek to provide comparisons of multiple interventions, including indirect comparisons[74]. These methods are particularly useful when a set of randomized control trials with pairwise comparisons of interventions has been carried out with common interventions among the studies, but where not all studies include all interventions. Developments in and applications of this powerful approach have increased dramatically in clinical medicine over the last 10 years[75] allowing meta-analysis to more usefully inform decision models about which treatment is most effective when there are multiple treatment options and pathways. "Living reviews" which are constantly updated can prevent cementing stale information and have the potential to result in a paradigm shift, because knowledge is constantly being updated and new papers are constantly being published[76]. Rather than summarising information in a plethora of individual papers, living reviews and living cumulative network meta-analyses may also help to reduce waste in research by using available primary studies more efficiently, identifying research gaps and determining when the evidence is sufficient for decision and policy making[77]. Their full implementation may require a reward shift for both primary researchers and synthesists.

Perhaps the most important foundation for advances in meta-analysis is education in high quality research synthesis methods. Training in meta-analysis should be part of the basic training for higher degree candidates in basic and applied scientific fields, including research post-graduates, medical doctors and other professional science practitioners (e.g. environmental consultants). This would formally embed their work in the context of existing evidence and facilitate learning of both statistical and critical appraisal skills. Those involved in primary research also need better understanding of meta-analysis to fully exploit the revolution in open data. Most importantly, a new generation of scientists, peer-reviewers, editors, and science-policy practitioners would benefit from increased understanding of evidence synthesis and interpretation.

Meta-analysis can be a key tool in facilitating rapid progress in science by quantifying what is known and identifying what is not yet known. Evidence synthesis should become a regular companion to primary scientific research to maximize the effectiveness of scientific inquiry. An evidence-based approach is important for progress in science, policy and medical and conservation practice. It requires collaboration between statisticians, primary researchers and research synthesists as well as collaboration of meta-analysts across different disciplines and stakeholders. If such collaborations are successful, we are confident that meta-analysis will survive its 'midlife crisis' and will emerge stronger and with a new-found purpose.

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Table 1. Milestones of systematic review and meta-analytic development in ecology, evolution and conservation.

Year	Milestone
1991	First meta-analysis in ecology published[78]
1995	Seminal paper by Arnqvist and Wooster published in *Trends in Ecology and Evolution* introducing meta-analysis to many ecologists[79]
1995	National Center for Ecological Analysis and Synthesis established in USA
1997	MetaWin, 1st software for ecological meta-analysis created[46]
1999	Special feature on meta-analysis published in the journal *Ecology*, including an influential paper on statistical issues in ecological meta-analysis[50] and introducing log response ratio as a new effect size metric[80]
2001	First general review of meta-analysis in ecology published[81]
2003	Centre for Evidence-Based Conservation (CEBC) established in UK
2007	Collaboration for Environmental Evidence created
2008/9	Seminal papers on phylogenetic meta-analysis are published [43,45] and phylometa software for integrating phylogeny into meta-analysis created[82]
2011	Environmental Evidence (the official journal of the Collaboration for Environmental Evidence) established
2013	First Handbook of meta-analysis in ecology and evolution published [73]
2014	OpenMEE, software for ecological and evolutionary meta-analysis, released[47]
2016	1st International Conference of the Collaboration for Environmental Evidence, in Stockholm

Figure Legends

Figure 1. A variety of charts and plots common in meta-analysis. a. PRISMA diagram, **b.** a forest plot showing means, confidence limits (CIs) and precision (indicated by the size of the square symbols) for individual studies, and overall meta-analysis means and CIs based on a common-effect (fixed-effect) model and random-effects model **c.** summary forest plot presenting mean effect sizes and CIs for different groups of studies, common in EEC and some social sciences, **d.** a bubble plot to show a predicted line from a meta-regression analysis where the size of the bubble reflect study sample size, **e.** a funnel plot of original data (red points) showing some funnel asymmetry, which may indicate publication bias, with augmented data (open circles) from the trim-and-fill method, which is a sensitivity analysis correcting for a potential publication bias and, **f.** a forest plot of a cumulative meta-analysis where outcomes are added into the analysis in chronological order, demonstrating increasing precision and a temporal trend or convergence of effect sizes across studies.

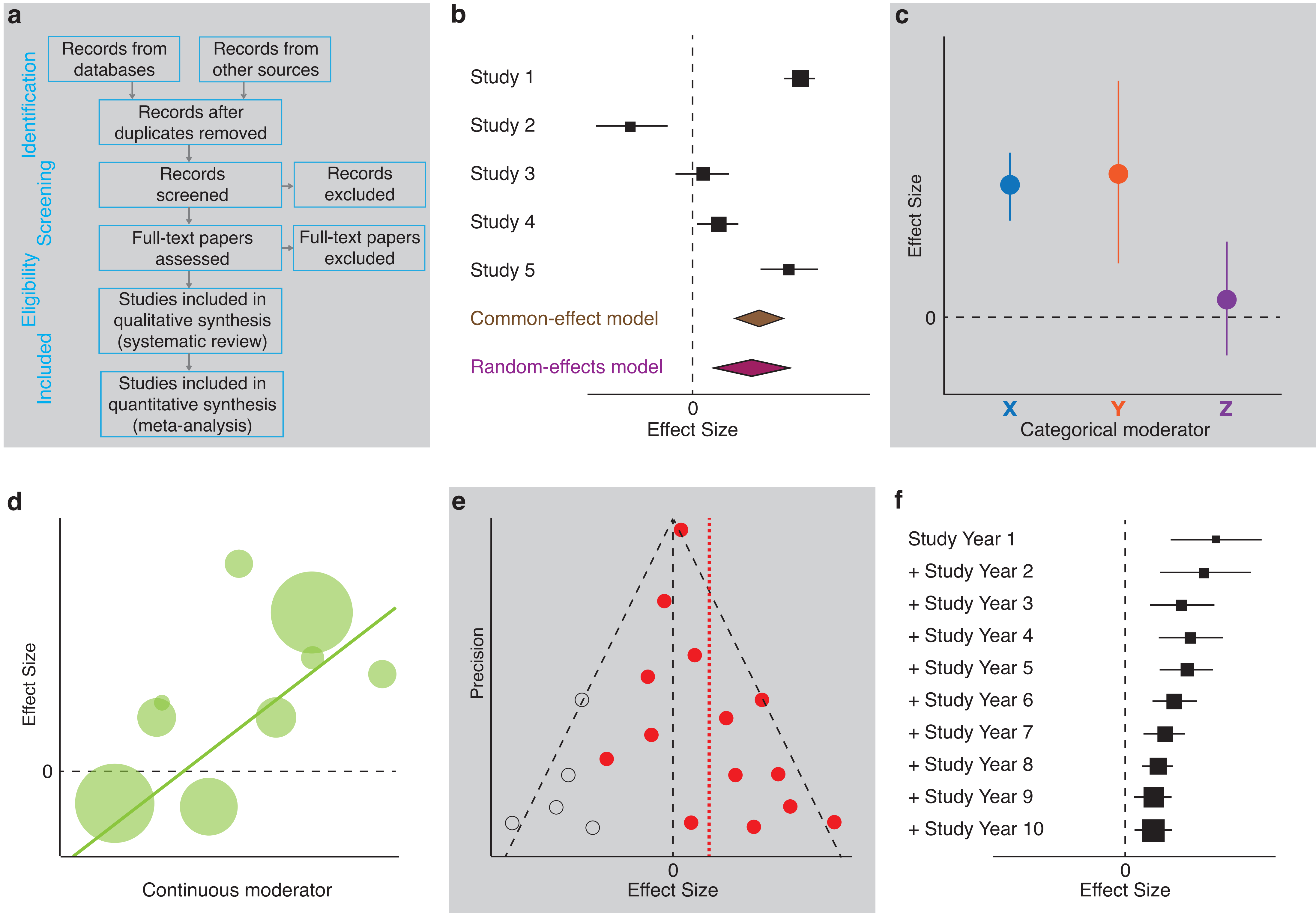
Box 1. *A brief history of meta-analysis*

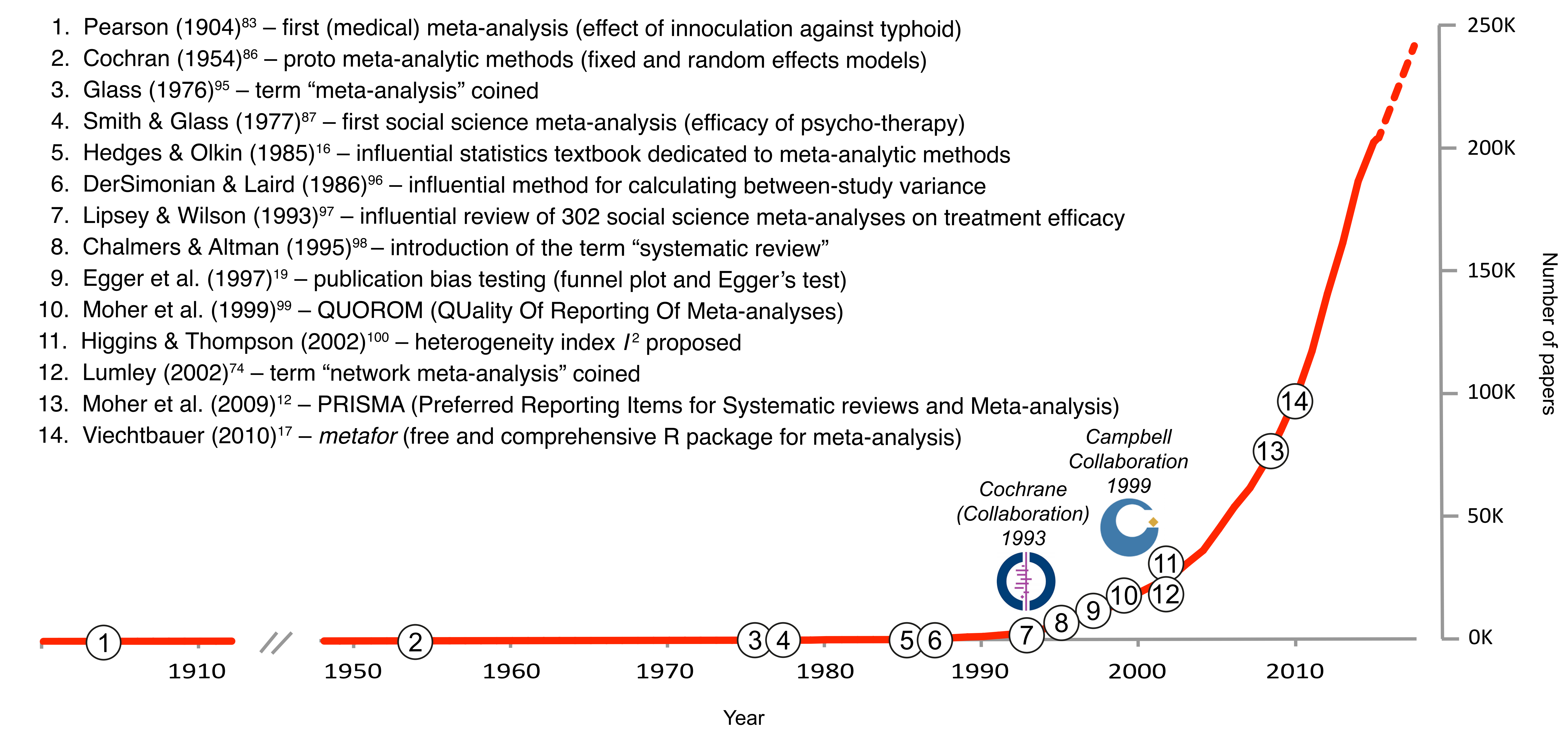
The first formal attempt to combine information from multiple sources (Fig. I) was made in 1904 by Karl Pearson[83] to ascertain the effectiveness of vaccination in preventing soldiers from contracting typhoid. R.A. Fisher, another major figure in the development of modern statistical science, introduced a method to combine probabilities from different studies[84]. In the late 1930s, William Cochran and Frank Yates described approaches that were essentially the same as modern fixed-effect and random-effects models[85], later formalized and generalized by Cochran[86]. However, not until the insight of psychologists Gene Glass and Mary Smith — that outcome measures from different experiments could be standardized and put on the same scale[87] – did meta-analysis begin to really impact scientific research. Meta-analysis was initiated almost simultaneously in medicine and the social sciences[88] and was initially met in all fields with a combination of great enthusiasm and condemnation[52,88]. Methodology was formalized and developed in the following two decades in multiple fields[16,89-91], with influential studies spreading from medical and social sciences to EEC in the early 1990s[23,92] (Table 1).

Rapid methodological and procedural developments have followed, where truly cross-disciplinary interactions and fertilization have been major drivers of progress. The introduction of electronic literature databases and journal articles were central to the development of current practices; lack of access in poorer institutions and countries hinders scientific progress. The highly interdisciplinary *Society for Research Synthesis Methodology* (www.srsm.org) was established in 2005 followed by its publication of *Research Synthesis Methods*. Major collaborative networks, the *Cochrane Collaboration* (now known as *Cochrane*; www.cochrane.org) and *Campbell Collaboration* (www.campbellcollaboration.org) oversee systematic reviews in medical and social sciences, respectively, bringing practitioners and methodologists together and setting standards for research synthesis publications and evidence-based guidelines for practice and policy.

(part of Box 1)

Figure I. Milestones in meta-analytic history. Red line shows the number of papers from a Scopus search. These historical milestone publications are chosen based on two main criteria, precedence and influence (we relied heavily on these references[93,94]).


a
Identification
Screening
Eligibility
Included
Records from databases
Records from other sources
Records after duplicates removed
Records screened
Records excluded
Full-text papers assessed
Full-text papers excluded
Studies included in qualitative synthesis (systematic review)
Studies included in quantitative synthesis (meta-analysis)
b
Study 1
Study 2
Study 3
Study 4
Study 5
Common-effect model
Random-effects model
0
Effect Size
c
Effect Size
0
X
Y
Z
Categorical moderator
d
Effect Size
0
Continuous moderator
e
Precision
0
Effect Size
f
Study Year 1
+ Study Year 2
+ Study Year 3
+ Study Year 4
+ Study Year 5
+ Study Year 6
+ Study Year 7
+ Study Year 8
+ Study Year 9
+ Study Year 10
0
Effect Size


1. Pearson (1904)[83] – first (medical) meta-analysis (effect of innoculation against typhoid)
2. Cochran (1954)[86] – proto meta-analytic methods (fixed and random effects models)
3. Glass (1976)[95] – term “meta-analysis” coined
4. Smith & Glass (1977)[87] – first social science meta-analysis (efficacy of psycho-therapy)
5. Hedges & Olkin (1985)[16] – influential statistics textbook dedicated to meta-analytic methods
6. DerSimonian & Laird (1986)[96] – influential method for calculating between-study variance
7. Lipsey & Wilson (1993)[97] – influential review of 302 social science meta-analyses on treatment efficacy
8. Chalmers & Altman (1995)[98] – introduction of the term “systematic review”
9. Egger et al. (1997)[19] – publication bias testing (funnel plot and Egger’s test)
10. Moher et al. (1999)[99] – QUOROM (QUality Of Reporting Of Meta-analyses)
11. Higgins & Thompson (2002)[100] – heterogeneity index I^2 proposed
12. Lumley (2002)[74] – term “network meta-analysis” coined
13. Moher et al. (2009)[12] – PRISMA (Preferred Reporting Items for Systematic reviews and Meta-analysis)
14. Viechtbauer (2010)[17] – *metafor* (free and comprehensive R package for meta-analysis)
Cochrane
(Collaboration)
1993
Campbell
Collaboration
1999
250K
200K
150K
100K
50K
0K
Number of papers
1910
1950
1960
1970
1980
1990
2000
2010
Year