

Recent developments in meta-analysis

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SUMMARY

The art and science of meta-analysis, the combination of results from multiple independent studies, is now more than a century old. In the last 30 years, however, as the need for medical research and clinical practice to be based on the totality of relevant and sound evidence has been increasingly recognized, the impact of meta-analysis has grown enormously. In this paper, we review highlights of recent developments in meta-analysis in medical research. We outline in particular how emphasis has been placed on (i) heterogeneity and random-effects analyses; (ii) special consideration in different areas of application; (iii) assessing bias within and across studies; and (iv) extension of ideas to complex evidence synthesis. We conclude the paper with some remarks on ongoing challenges and possible directions for the future. Copyright © 2007 John Wiley & Sons, Ltd.

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INTRODUCTION

The art and science of meta-analysis, the combination of results from multiple independent studies, is now more than a century old. The earliest specific example thus far identified is a combination of studies of typhoid vaccine effectiveness by Karl Pearson in 1904 [1], and there were sporadic cases of similar syntheses in subsequent decades [2]. In the last 30 years, however, as the need for medical research and clinical practice to be based on the totality of relevant and sound evidence has been increasingly recognized, the impact of meta-analysis has grown enormously. Numbers of published, health-related, meta-analyses, charted by Lee *et al.* [3], had increased to 400 per year in the year 2000. In Figure 1, we illustrate crude numbers of meta-analyses as publication types in PubMed, along with numbers of meta-analysis-related methodological papers in this journal, since 1990. It can be seen that the number of meta-analyses has increased throughout this period.

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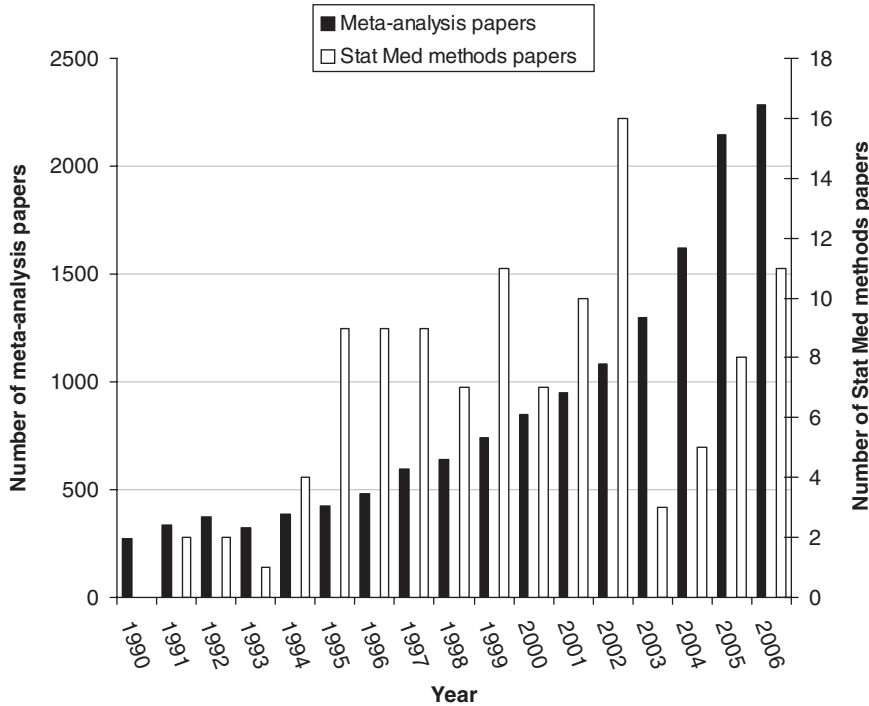


Figure 1. Graph showing crude numbers of meta-analyses as publication types in PubMed, along with numbers of methodological papers in this journal, for years 1990–2006.

The trend for the methodological papers is less clear, probably due in part to the much smaller numbers; however, a sustained output of approximately 10 papers a year can be observed over the last decade.

Areas of application of meta-analysis extend beyond medicine and health, and indeed span from ‘astronomy to zoology’ [4]. They have been identified as the most cited types of research paper [5], and represent a significant proportion of articles in major general medical journals. With the ever-expanding literature of medical research studies, and the suggestion that the majority of such findings may be false [6], the need for critical evaluations and considered syntheses of multiple studies is an easy case to make.

Almost 10 years ago, in a consideration of the future of biostatistics in this journal, van Houwelingen listed meta-analysis among his ‘nightmares’, which he hoped would not come back to haunt us [7]. While supporting the idea of combining evidence from different sources, van Houwelingen’s concern was about analysing summary measures from selective studies, and he looked forward to a time when individual participant data (IPD) from *all* studies were available to be synthesized using appropriate random-effects models. Although we have not achieved this vision, one might argue that the process of systematic review, within which the majority of meta-analyses are now undertaken, has to some extent reduced bias due to selective inclusion of studies, and analyses involving IPD continue to increase in number [8]. The QUOROM statement [9] offers guidelines for reporting of meta-analyses of randomized controlled trials. Similar statements

address reporting of constituent studies; [10–12] and along with a variety of major texts on meta-analysis [13–16] this should increase the quality of meta-analyses beyond the fears of van Houwelingen.

Meta-analyses are undertaken for a variety of reasons. A large number of them are undertaken with the broad aim of summarizing existing evidence. For example, The Cochrane Collaboration endeavours to collate and synthesize high-quality evidence on the effects of important health-care interventions for a worldwide, multi-disciplinary audience, and publishes these in the Cochrane Database of Systematic Reviews [17]. Cochrane reviews are not intended to provide recommendations for practice in any particular clinical context. On the other hand, many meta-analyses are undertaken to inform specific decisions, and may be extended to incorporate economic considerations in a decision analysis framework. Bayesian tools offer great flexibility in such applications, and encourage a model-based approach to the combination of information from multiple sources.

In this paper, we review highlights of recent developments in meta-analysis in medical research. We outline in particular how emphasis has been placed on (i) heterogeneity and random-effects analyses; (ii) special consideration in different areas of application; (iii) assessing bias within and across studies; (iv) extension of ideas to complex evidence synthesis.

METHODOLOGICAL DEVELOPMENTS

Core methods

The basic, widely applicable, meta-analysis method is a weighted average of point estimates (one from each study), with weights based on the standard errors of the estimates [18]. This is often described as the ‘two-stage’ approach to meta-analysis, in which each study is analysed separately prior to the meta-analysis itself. Combination of estimates of a common quantity is usually achieved using one of two assumptions, yielding a fixed-effect and a random-effects meta-analysis, respectively. A fixed-effect meta-analysis usually takes the inverse variances of the estimates as weights, and interpretation relies on an assumption of a common effect underlying every study. A random-effects meta-analysis incorporates the underlying among-study variation of effects into the weights [19]. Either method can be extended to incorporate study-level covariates. Controversy surrounds the fixed-effect method because it does not specifically allow for variation not explained by covariates. However, fixed-effect methods are relatively standardized (including the Mantel–Haenszel method [20] and Peto method [21] for multiple 2×2 tables, and standard weighted regression), and have not recently been the subject of many methodological developments.

Alternatives and extensions to a simple two-stage procedure are frequently encountered. First, data might be modelled at a more detailed level than the effect estimate. In many applications, the basic available information comprises group-level aggregate data, such as means and standard deviations, or event counts, for each treatment group in a clinical trial. A bivariate meta-analysis method lends itself to this situation [22, 23], as do methods that can specifically model group-level outcome data, such as logistic regression or the Mantel–Haenszel procedure for binary data. On occasion, a much finer level of detail is available in the form of a so-called IPD meta-analysis, for which original data from each participant in each study are collected.

Second, there may be more than one effect estimate per study. Such multivariate meta-analyses should account for any correlation between effect estimates and, in a random-effects model, between parameters relating to the same study. Third, a meta-analysis may be designed to analyse

fundamentally different quantities simultaneously. For example, studies of prevalence may be combined with studies of epidemiologic association, or clinical trials making different treatment comparisons may be combined. We refer to these types of extensions as ‘complex synthesis’ and address them in a separate section.

Assessing heterogeneity. Prior to performing a meta-analysis, or as part of the process, it is customary to assess evidence of variation in the underlying effects [24, 25]. Usually termed ‘heterogeneity’, this variation arises due to differences across studies in populations, exposures/interventions, outcomes, design and/or conduct [26]. A forest plot is useful for visual assessment of consistency of results across studies. Other graphical methods can help identify unusual studies, including a plot of influence on the heterogeneity test statistic (see below) *versus* influence on the meta-analytic combined estimate, [27] and an L’Abbé plot when the data are in the form of a series of 2×2 tables [28].

Traditionally, a chi-squared test is undertaken to determine whether there is statistically significant evidence against a null hypothesis of no heterogeneity. Simulation studies of the properties of tests for heterogeneity are plentiful, yet no overview of their findings seems to have been produced. On the other hand, two theoretically derived discussions of power have appeared recently [29, 30], and highlight the low power of the test in the typical situation of having few studies in a meta-analysis. Perhaps a stronger argument against using the test for heterogeneity is the expectation that the null hypothesis (of homogeneity) is rather unlikely to be true [31]. Measures of the extent of heterogeneity might be considered preferable to tests of its presence, and indeed a statistic, I^2 , that measures the consistency of findings as the proportion of total variation in point estimates attributable to heterogeneity (rather than sampling error) is now used very widely [32].

Random-effects methods. The popular DerSimonian–Laird approach to random-effects meta-analysis uses a simple moment-based estimate of the among-study variance, and does not incorporate uncertainty in the variance estimate when making inference on the mean of the random-effects distribution. The simple moment estimator is a special case of a more general moment-based approach [33]. Modern computing allows for a more appropriate, iterative estimate to be used instead. It is well-recognized by statisticians, though less often by applied researchers, that the among-study variance is a key parameter in a random-effects meta-analysis, and provides probably the most appropriate measure of the extent of heterogeneity. Thus, attempts to investigate the properties of estimates of this variance are welcome. Sidik and Jonkman compare seven different estimators in a simulation study [34]. Viechtbauer reviews seven approaches for obtaining confidence intervals for the variance, including a self-proposed method that is demonstrated to have accurate coverage [35]. Concerns of bias in estimation of this variance have been raised as a consequence of using inappropriate within-study variance estimates [36].

The random-effects method has long been associated with problems due to the poor estimation of among-study variance when there is little information [37, 38]. Several suggestions for adapting the random-effects method have appeared recently. Notable among these is the proposal of Hartung and Knapp [39–41], also proposed by Sidik and Jonkman [42, 43]. This involves a simple adjustment to the standard error of the estimated random-effects mean and use of a T distribution rather than a standard normal distribution for statistical tests and confidence intervals. (However, concerns have been expressed at the substitution of estimates for unknown quantities [44].) More long-standing approaches include those of Biggerstaff–Tweedie [45] and Hardy–Thompson [37], and it is disappointing that these have seldom been implemented. Alternatively, Bayesian models that

incorporate in a natural way the uncertainty in estimation of the among-study variance have been described [46]. The extent of among-study variation should also be built into *interpretation* of random-effects meta-analyses more often than they are [47].

It is conventional to assume a normal distribution for the underlying effects in a random-effects distribution, and important to appreciate that this is a distributional assumption. It is difficult to assess the suitability of the distribution; some diagnostics can help if there are sufficient studies [48]. In general, little formal assessment of the goodness-of-fit of meta-analysis models to the data is carried out. This may be partly because many non-statisticians conduct meta-analysis, and to such applied researchers meta-analysis may be seen as a necessary data-processing procedure rather than a model-fitting exercise. Furthermore, the small number of studies typically involved in a meta-analysis precludes an informative investigation of model fit. Developments in the use of flexible random-effects approaches offer a means of avoiding a specific model assumption, for example, using non-parametric maximum likelihood [49].

Meta-regression. A notable paradigm shift in recent years has been the movement away from simple meta-analyses in favour of explorations of among-study differences [25, 50]. A key tool in this endeavour is meta-regression, which is a combination of meta-analytic principles (of combining results from multiple studies with due attention to within-study precision and among-study variation) with regression ideas (of predicting study effects using study-level covariates). A key early paper was produced by Berkey and colleagues [51], and other general discussions are available [52, 53]. A comparison of specific methods concluded that additive models for unexplained heterogeneity are preferable, and that methods that are tailored to the precise type of outcome data are preferable in principle [54]. A body of literature has explored methods for relating odds ratios to the underlying risk for clinical trials with binary data [55–59]. Naïve application of meta-regression methods should be avoided for such analyses, due to the inherent correlation between the observed odds ratio and the observed risk in the control group [60]. Recent developments in meta-regression have seen an improved variance estimator for association [61, 62], a permutation test to establish the true statistical significance of a positive finding [63] and discussions of advanced models, such as fractional polynomials and splines [64] to quantify non-linear associations.

Sequential approaches and statistical power. Sometimes advocated for situations better suited to meta-regression [65], cumulative meta-analysis has been used to illustrate important gaps between accumulated evidence and the behaviour of researchers and practitioners [66]. Cumulative meta-analysis typically refers to the retrospective undertaking of a series of meta-analyses, each one repeated upon the inclusion of an additional study. The statistical basis of cumulative meta-analysis is weak, and we advise its use only for illustrative purposes. For instance, an infinitely updated cumulative meta-analysis would eventually yield a statistically significant finding even under the null hypothesis [67]. To overcome the limitations of performing cumulative meta-analyses prospectively, formal sequential methods have been developed for consideration of accumulating knowledge across studies [68–70]. Although some argue that formal stopping rules are inappropriate when the meta-analyst is not directly responsible for the production of new evidence, these methods have found favour in general use [71] and in the prospective design of a series of studies with the purpose of integrating the findings [69].

Sequential methods attempt to retain overall type I and type II error rates over the repeated analyses. Significance levels are frequently reported with the results of meta-analyses in the form of *P* values. The generally accepted cut-point for declaration of statistical significance appears to be 5

per cent, despite the frequent supposition that meta-analyses should provide authoritative evidence (suggesting perhaps that more stringent criteria should be used). On the other hand, the statistical power of a particular meta-analysis is very rarely discussed, other than *via* the common proclamation that combining the results of multiple studies increases the power over that of any individual study. The power of standard meta-analytic methods has been studied by Hedges and Pigott [29, 72]. A related problem is sample-size calculation, and there have been recent developments in feeding meta-analyses into evidence-based sample-size calculations for new primary research studies, with a view of powering the updated meta-analysis [73].

Bayesian methods. The use of Bayesian methods for meta-analysis has been reviewed elsewhere [74], is discussed at some length in a recent text on Bayesian methods [75] and has been reviewed from a historical perspective as part of this series [76]. Advances in software for evaluating Bayesian models, most notably WinBUGS [77], which uses Markov Chain Monte Carlo (MCMC) methods, has led to a proliferation of meta-analysis models fitted under this framework. These analyses harness the great flexibility of WinBUGS in the specification of parametric models, and exploit the advantages of allowing for full uncertainty in all quantities, and of offering a natural means of interpreting the results. However, they tend not to subscribe to a ‘fully’ Bayesian approach of incorporating external information *via* informative prior distributions for model parameters. For this reason, such developments are discussed in the current paper alongside those using more traditional statistical methods. Research on the use of a Bayesian tools, and on using WinBUGS in particular, includes a simulation study showing that care should be taken in random-effects meta-analysis models, particularly when the number of studies included in the analysis is small, since it is difficult to specify prior distributions for the variances of such random effects that are truly non-informative [78].

Fully Bayesian approaches to meta-analysis that incorporate informative prior distributions have included:

- a re-analysis of the controversial magnesium trials, demonstrating that unreasonable prior scepticism would have been necessary to disbelieve the early, positive, trial results [79];
- placing prior distributions on unknown correlation coefficients [80, 81];
- use of data-based prior distributions for the heterogeneity parameter in a random-effects analysis, particularly when the number of studies is small [82].

Methods for specific types of data

We have noted that meta-analyses may be based on effect estimates, aggregate data or IPD. Methods for the first of these are generic, and depend usually on the availability of estimates that are approximately normally distributed, with a given standard error (assumed to be known). Sometimes, these effect estimates are all that are available from published reports; a common example is an adjusted measure of association from an observational epidemiological study. Often, however, the meta-analyst calculates these effect estimates prior to performing the meta-analysis; this is more often the case for randomized controlled trials. A challenge here is that there can be several effect measures to choose from, and different ways of estimating each. Over the years, much consideration has been given to these choices. Methods based on the specific nature of aggregate- or individual-level data can offer advantages over generic methods. For example, logistic regression approaches for event counts may be preferable to an assumption of normality for the log-odds

ratios from each study. Here, we review some developments to help these considerations for various specific types of data, although we delay discussion of IPD methods until a later section.

Binary data. Numerous metrics are available for the comparison of two groups with binary data [83]. The usual choice is between an odds ratio, a probability ratio (relative risk) and a probability difference (risk difference). Deeks discusses this choice at length [84]. Empirical studies have demonstrated a higher consistency of the ratio measures than the risk difference across studies in the same meta-analysis [84, 85]. Nevertheless, a comparative study of different ways of estimating the risk difference has been undertaken [86], and methods have been developed for meta-analysing risk differences based on binomial modelling of the data [87]. A Bayesian implementation of the Mantel–Haenszel method for relative risks has been developed using Laplacian procedures [88]. The performance of competing methods for meta-analysis of binary outcome data has been evaluated specifically in a sparse data context [89], typical in the evaluation of adverse drug effects (see also below). A separate related evaluation focused on the performance of alternative continuity correction factors when zero events are present in study arms [90]. If the measure chosen for the meta-analysis conflicts with the format in which results are available, methods are available for re-constructing a 2×2 table from estimates and confidence intervals [91]. Related techniques are available for checking for errors in reported estimates and confidence intervals [92]. Finally, we note that methods have been advanced for meta-analysis of single risks across studies, such as prevalence, or a simple success rate [93, 94].

Continuous data. Whereas binary data are common in medicine, quantitative outcome measures are common in the social sciences. In both fields, quantitative data are typically assumed to be continuous, and methods based on means and standard deviations are the norm. The two common effect measures are a simple difference between mean response in two groups and, to allow combination of data from different scales, a standardized version of this difference in which it is divided by the standard deviation of responses. In the social sciences, a common approach to meta-analysis is to transform results of all studies to the latter ‘effect size’ scale. Correlations, both independent and matched pairs of means, and even odds ratios can be transformed to effect sizes with certain assumptions [95, 96]. In contrast, meta-analyses in medicine are more often transformed from the continuous to the binary scale for ease of clinical interpretation [97]. A common problem in meta-analyses of continuous data is that of missing data on variances. A variety of methods for imputing these variances have been observed [98, 99], and methods for imputing them for the specific case of change-from-baseline measures have been proposed in a Bayesian framework [80].

Ordinal data, time-to-event data and rates. Meta-analyses of ordinal data, time-to-event data and rates are less straightforward and (perhaps therefore) less common than meta-analyses of binary and continuous data. Methods for ordinal data have been described [100–102], although our impression is that it is rare to have access to the required multinomial data [8]. Meta-analysis of published results is particularly challenging for time-to-event data, because of the lack of appropriate group-level summary statistics. If hazard ratios (and confidence intervals) are available for each study, then it is straightforward to implement generic methods. A variety of transformations and approximations have been proposed for dealing with other summary statistics [103] and for extracting information from survival curves [104, 105]. Empirical studies of these and other methods have been carried out, and are important to delineate their properties in practice [106, 107]. After a long period

with virtually no discussion in the literature, meta-analyses of rates (events over person–time) have recently received more attention, with simple estimates and Poisson models being proposed [108, 109].

Methods for the consideration of bias

Biases within studies. Work continues on identifying sources of bias in the conduct, analysis and reporting of studies. Accounting for variability in study quality in meta-analysis has been considered, but with little consensus on best practice. Alternatives proposed include (i) restricting those studies meta-analysed to only the best quality, either as a primary or sensitivity analysis; (ii) down-weighting studies based on a quantitative assessment of quality [110]; (iii) exploring the effect of components of quality *via* meta-regression [111]. While these approaches take a rather generic approach to the problem, there have been isolated examples in epidemiology where detailed modelling of context-specific biases has been incorporated into each study included in the meta-analysis [112, 113]. Recently, an investigation of the use of ‘assay sensitivity’ as an inclusion criterion for meta-analysis (i.e. in an attempt to limit inclusion to high-quality studies) was assessed and considered non-robust [114].

Reporting biases. The issue of publication and related biases continues to be a concern for those conducting and using results of meta-analysis, since, if statistically significant or ‘positive’ results are more likely to be published, a meta-analysis based on the resulting literature will be biased. A whole book has recently been devoted to this topic [115]. There is general agreement that alleviation is the best solution to this problem, but there is little to suggest that the problem will disappear in the future.

The funnel plot is generally considered a good exploratory tool for investigating publication bias [116]. It plots a measure of effect size against a measure of study precisions (the most appropriate axes for such a plot have been discussed [117]) and should appear symmetric if no bias is present. By its nature, assessment of such a plot is subjective, and a recent empirical evaluation would suggest that interpretation of such a plot can be limited [118]. Unfortunately, there is still widespread lack of appreciation that funnel plot asymmetry can be due to causes other than publication bias; any influential covariate that is related to precision (or sample size) can induce such a pattern through confounding.

Non-parametric [119] and parametric ‘Egger’s test’ [120] methods to formally test for such funnel plot asymmetry are now commonplace. Although widely studied, the performance characteristics of these and related tests seem to be less well appreciated. While parametric tests generally appear to be more powerful than non-parametric [121], Egger’s test has highly inflated type 1 errors in some circumstances when binary outcomes are considered [122–124]. This has led to a number of modified tests being developed for binary outcomes [122, 123, 125, 126], and more generally [127]. A further comparative evaluation of these modified tests is required, with optimal test choices for given meta-analysis situations programmed into user-friendly software.

Methodological work developing selection modelling approaches for adjusting meta-analyses for publication bias is ongoing, with detailed reviews available elsewhere [128, 129]. While it has been suggested that correcting for publication bias is not possible without making untestable assumptions [130], a bound for the bias as a function of the fraction of missing studies has been proposed [131], as has the use of *a priori* specified selection models [132]. A further recent development is the use of simulated pseudo-data to correct for publication bias [133]. This method

assumes that the selection process is known, but allows arbitrarily complex selection processes to be modelled.

The alternative, non-parametric Trim and Fill method [134] for adjusting for publication bias would appear to be used more frequently than selection modelling in practice, probably due to the availability of software that implements it. However, simulations suggest that it performs poorly in the presence of among-study heterogeneity [135].

There would seem to be some disagreement as to whether adjustment for publication bias should be encouraged. Many authors have put forward their adjustment methods as a form of sensitivity analysis, although this sentiment was perhaps not as clearly expressed as it could have been, perhaps resulting in the polarization of researchers. The context of the meta-analysis is an important issue here, since sensitivity analysis is only of limited use in a decision-making context.

Novel areas of research in publication bias include (i) an investigation of how publication bias affects the estimation of the among-study heterogeneity parameter in a random-effects meta-analysis model [136]; (ii) allowing for differential levels of publication bias across studies of different designs [137]; and (iii) The use of capture–recapture methods across electronic databases in order to estimate the number of missing studies [138].

The issue of within-study reporting bias has received a lot of attention in recent years. Empirical research has revealed that outcome reporting bias is a serious issue, at least in randomized controlled trials [139–142]. Statistical methods have been put forward to assess the likely impact of selective outcome [143–145] and subgroup [146] reporting.

Complex synthesis

The boundary between what is considered to be meta-analysis and what is considered to be quantitative synthesis ‘beyond’ meta-analysis is somewhat blurred. Here, we consider complex evidence synthesis as involving models that incorporate evidence on multiple parameters and/or that specifically model data from different study designs. In addition to the summary of this area below, the interested reader is directed to a more in-depth review of this area [147].

Early work on complex evidence synthesis was undertaken under the name of the confidence profile method [148]. This is a general framework for carrying out multi-parameter meta-analysis, which, among other things, allowed quantities defined by, potentially complex, functions of parameters to be evaluated. While rarely used under that heading, many of the rudiments of the approach are present in more recent work, including the integration of evidence synthesis and (economic) decision modelling into a single process [149–153] and extrapolation of survival estimates in cost-effectiveness studies [154].

Cross-design synthesis [155] was put forward as a way of addressing the concern that results obtained from randomized clinical trials (RCTs) may not generalize to wider groups of patients. The proposal was to use other, observational, data sources to complement that from the RCTs, while attempting to model any existing biases. Other attempts have been made to synthesize studies with different designs, while acknowledging the differences in design using hierarchical models [156–159]. However, such methods are still in their infancy and have yet to gain widespread acceptance.

Several extensions to meta-analysis have been described that simultaneously combine information on multiple parameters or outcome measures. In clinical trials, for example, there may be advantages of modelling each trial arm separately, fitting a model that assumes the study data to be bivariate normally distributed, for example, when investigating relationships between treatment

effect and participant baseline risk as discussed above [23], when allowing single-arm studies to be combined with comparative studies [160], or allowing for heterogeneous study designs [161]. Similar statistical models can be fitted to multiple outcomes reported by the studies in the meta-analysis [81, 162–164]. When the correlations among outcome variables are known and all studies report all outcomes, this can lead to modest increases in efficiency of estimation [163]. Further gains in efficiency can be gained if outcome reporting is less complete across studies [165].

Another application of multiple outcome meta-analysis is to estimate the relationship between outcome of ultimate interest and a surrogate marker. A bivariate model, assuming surrogate and clinical outcome were related *via* linear regression, was proposed initially [166]. Since then, modifications allowing separate relationships between surrogate and clinical outcome within each treatment have been described [167, 168]; see Burzykowski *et al.* [169] for more details on this topic. Evaluation of multiple-related parameters in a screening context using multiple studies has also been described [170].

‘Chain-of-evidence’ models have been described [171], where fixed relationships are specified among related parameters and evidence synthesis is conducted for each of these parameters. For example, statins reduce cardiac mortality through lowering serum cholesterol. Studies estimating the effect of statins on cholesterol levels, cholesterol levels on cardiac mortality and statins (directly) on cardiac mortality could all be synthesized in a chain of evidence.

Perhaps the most important development in this field is mixed treatment comparisons (MTC) meta-analysis. These methods allow all treatment options in a therapeutic area to be compared with each other, while respecting the randomization of the included trials [82, 172–177]. As well as efficiently combining the data, using Bayesian MCMC methods to evaluate such models readily yields probability statements on how likely each treatment is to be the most effective, resolving the inherent difficulties that are created by the multiple comparisons. Time will tell whether this is how efficacy of treatments will be routinely compared in the future.

The importance of establishing coherence, or consistency, of evidence becomes more difficult and more crucial as more complex models are fitted. Recently, statistical tools are being applied to assess how well a synthesis model fits to the data and to provide a means of deciding among competing models [178]. A detailed illustrative example of these techniques in an evidence synthesis context is available [179].

DEVELOPMENTS IN SPECIFIC APPLICATION AREAS

Within the medical research area, meta-analyses are most frequently applied to questions of the effects of interventions, to aetiology, to diagnosis and to prognosis. However, simple meta-analytic techniques can be applied to any set of studies yielding an estimate and standard error of a similar parameter; for example, difference estimates from method comparison studies [180] or predicted effects of interventions from surrogate endpoint studies [181].

There have been some brave initial attempts to synthesize qualitative with quantitative data using Bayesian meta-analysis [182] and other methods [183, 184]. Potential biases in meta-analyses have been examined through analysis of data from (large) collections of meta-analyses. Meta-meta-analytic approaches have been proposed for this, which allow for between- and within-meta-analysis heterogeneity [185]. A hierarchical model has been described, which allows for inconsistent reporting of effect sizes and standard errors through heterogeneous methods of analysis [186].

Effects of interventions

The majority of methodological papers on meta-analysis in medical research have focussed on meta-analysis of clinical trials, and we have discussed many of them under different headings in this paper. We have already noted the importance of recent developments in MTC meta-analysis. Another practically important area of the literature, although still quite small, is specific methodological guidance for non-standard trial designs, such as cross-over trials [187–190] and cluster-randomized trials [191]. The use of meta-analysis to identify and quantify adverse effects of interventions has received considerable attention recently [192–197]. In such a context, it is commonplace for data to be pooled across studies without regard to the different trials from which they arose, despite warnings against such a non-meta-analytic approach [196, 198]. Adverse event data solely from RCTs may be patchy and inconclusive, and the difficult question raised is whether they should be complemented with data from observational studies [192–194]; this is far from resolved and more research is needed.

Aetiology

Methods for meta-analysis of epidemiological studies differ little, in general, from those used for clinical trials. Several discussions of the role of meta-analysis in this area focus on the less statistical aspects of comparability of studies (heterogeneity) and biases [199–204]. Although logistic regression methods are appropriate for analysis of retrospective studies, Bayesian meta-analysis methods may use a specifically retrospective likelihood, modelling the exposures conditional on the outcome [205] for analysing case–control studies. An exact method has been developed for combining case–control with cohort studies [206]. Methodological developments in the field of observational epidemiology relate mainly to different types of exposure measurement. For example, combination of results from studies comparing different doses requires a dose–response meta-analytic methodology [207–211]. Methods have also been developed for interval-censored exposure data [212], and for exposures that are merged in different ways [213]. The latter is exemplified in a synthesis of genetic association studies, and this is a field that is receiving particular attention at present [214, 215]. The Human Genome Epidemiology Network has embarked on a programme of systematic reviews and meta-analyses comparable with that of The Cochrane Collaboration [216], and is accompanied by developments of novel methods including (i) Mendelian randomization, in which gene–disease and gene–biomarker information are combined to infer about biomarker–disease relationships [217–219]; (ii) inference about modes of genetic inheritance [220]; and (iii) examination of departure from Hardy–Weinberg equilibrium [221]. In addition, meta-analysis methods have been developed for linkage and genome-wide association studies [222–225].

Diagnosis and screening

Meta-analysis is being used increasingly in studies of the accuracy of diagnostic and screening tools, although there is currently little standardization of methods. Methods for synthesis of diagnostic test/screening studies are more complicated than those for intervention studies because test performance cannot be adequately summarized in a single measure. While there have been many developments in this area over recent years, such methods are potentially underused [226], and further methodological work is still needed [227]. The majority of methods assume that data available from every study consist of the four numbers—true positives, false positives, true

negatives, and false negatives—relating to how the test categorizes individuals at a particular threshold (which may or may not be defined or even be definable) *versus* a gold standard.

Deeks [228] describes basic methods for meta-analysis of diagnostic studies, including: (a) combining sensitivity and specificity independently assuming no heterogeneity or threshold differences among studies; (b) combining diagnostic odds ratios, which allows for varying thresholds among studies, but assumes the variability in test values to be the same in diseased and non-diseased populations; and (c) a more general regression framework [229] that makes no such assumptions about the equality of variances. Methods (b) and (c) allow summary receiver operating characteristic curves (SROCs) to be constructed to illustrate how test performance varies with threshold. The statistical properties of SROCs have been explored elsewhere [230, 231].

More recent work has included the development of a hierarchical SROC approach [232, 233] that incorporates random effects to allow for among-study heterogeneity and an approach treating sensitivity and specificity as bivariate normally distributed [234]. These approaches have been shown to be mathematically equivalent, alternative parameterizations of the same model (unless, in an attempt to explain heterogeneity [235], different covariates are allowed to affect sensitivity/specificity or accuracy/cut-point in the bivariate or hierarchical SROC parameterizations, respectively [236]).

Although several of these methods allow for different test thresholds to be used across the primary studies, none have been used to incorporate threshold values explicitly, a notable limitation. An extension of the hierarchical SROC approach to allow for synthesis of test performance data reported at multiple thresholds within each primary study has been developed [237]. Yet to be used extensively, this would appear to offer increases in efficiency by combining more information from the primary studies. However, reporting practices need to improve before the necessary data are commonly available. Although rarely, if ever, carried out, the theoretical benefits of obtaining IPD (see below) for diagnostic test meta-analysis have been laid out [238]. Extensions to synthesis methods which allow for (i) test comparison with imperfect reference standards [239] or alternative tests [240]; and (ii) incorporation of studies which compare more than one test [241, 242], have been described. Methods for assessing publication bias in diagnostic test studies are in their infancy; however, it has been shown that standard methods may produce misleading results in this context [243].

Prognosis

Meta-analysis of prognostic studies has received relatively little attention, and applications in this area are hampered due to methodological limitations in the conduct of primary studies. Variation in the way studies are reported and concerns regarding selective reporting bias [244] also currently limit the use of meta-analysis in this context [245].

Obtaining IPD may overcome some problems, including standardization of marker values and outcome definitions across studies, as would the use of prospectively planned meta-analysis [246]. The recently published reporting recommendations for tumour marker prognostic studies are an important initiative that will hopefully raise the quality of primary studies aiding the meta-analyst's task in the future [247].

INDIVIDUAL PARTICIPANT DATA

Collecting IPD from original study investigators is widely regarded as the gold standard approach to meta-analysis. The approach has been used most extensively for time-to-event therapy

outcomes, although their potential usefulness in other contexts has been noted [238, 248, 249]. Despite this, little attention has been paid to the statistical methods for such syntheses. In a recent survey of methods used in practice [8], the majority of meta-analyses used simple fixed-effect pooling after obtaining an effect size from each study data set, with only a small proportion considering among-study heterogeneity and adopting a random-effects approach. However, IPD random-effects models have been developed for continuous, binary, survival, and ordinal outcome variables [101, 250–252].

While there are unquestionable practical benefits of an IPD approach over using (published) summary data—including standardization and updating of data sets [253]—it is often unclear whether these outweigh the extra cost of taking such an approach [254]. The statistical issues that contribute to this debate are perhaps under-appreciated. If mean effects are of interest, then, in some situations, using the corresponding IPD and summary data will produce identical results [255]. However, if exploration of participant-level covariates is of interest, then an IPD meta-analysis will typically have higher power than a meta-regression approach incorporating study-level covariates representing the average covariate response for each study [256, 257]. Through simulation, it has been shown that the power of the summary level analysis will often be extremely low for typical meta-analysis data sets implying the IPD would be necessary to detect covariate effects [257]. A theoretical consideration of these issues has led to simple criteria for determining the potential benefits of IPD to assess participant-level covariates [258].

One practical limitation of carrying out an IPD regression analysis is that it relies on data sets for all studies in the meta-analysis being available. For various reasons, including old data being destroyed and reluctance of researchers to part with data, this will often not be the case. Recently, methods have been developed for this [259] and other situations [260] to synthesize individual and aggregated data to maximize statistical efficiency [261, 262].

SOFTWARE

Considerable developments in software for meta-analysis have been made in recent years. This paragraph updates the detailed reviews published previously [263, 264]. Due to the fact that meta-analysis of summary data needs a unique set of analysis tools, the large developers of general statistical software have been reticent about providing the required routines. Fortunately, users have developed collections of macros, e.g. for SAS [265–267] and, most comprehensively, for STATA [268]. Stand-alone packages have also been developed, the most sophisticated of which is probably the commercial Comprehensive Meta Analysis [269]. The Cochrane Collaboration software, RevMan [270], continues to be developed and a new freely downloadable Excel add-in MIX [271] offers excellent functionality and educational content for those on a tight budget. The authors have found MetaDiSc [272] very useful for carrying out the specialized analyses required meta analysis of for diagnostic tests meta-analyses.

DISCUSSION

Although not without its detractors in the past [273], there seems little doubt that meta-analysis has become firmly established and will continue to be used as a tool for quantitatively synthesizing and summarizing information in the medical literature. Meta-analyses are often put at the top of

hierarchies of evidence [274], but also have a key role to play in the research process. They should inform the need for primary research, and should be updated on completion of a study to place their results in context [275–277]. However, there is empirical evidence to suggest that the use of existing meta-analyses when designing new studies is low [278]. With the exception of a few prospectively planned meta-analyses, there is little formal consideration of future meta-analyses when individual studies are being designed, despite the likelihood that an updated meta-analysis may well be more influential than the results of the new study in isolation. Hence, while meta-analysis currently underpins much evidence-based medicine, its role in informing ‘evidence-based’ research is suboptimal. To this end, we hope the use of meta-analysis to inform future research will greatly increase in the future.

The key to a sound meta-analysis is the availability of unbiased and suitably detailed data. For many applications, summary data—as reported in published papers—are sufficient, or they would be if they were better reported. IPD data are valuable, if not essential, in other situations. It is now established that meta-regression of summary covariate data is in many situations highly inefficient, compared with exploration of participant-level covariates using IPD. In the evaluation of diagnostic tests, IPD allow individual study ROC curves to be combined, providing a much more meaningful analysis than can be obtained using a single-threshold-based 2×2 table from each study. Furthermore, with the decoding of the human genome comes accelerated interest in the possibility of health care that is genuinely tailored to the individual; challenges await the design and analysis of individual studies, as well as their meta-analyses. For such situations in which IPD are likely to be considerably more useful than summary data, some practical questions arise. For example, in what circumstances might limited resources be better focused on seeking IPD from a selection of good, or large, studies rather than summary data from all of them? Of course, we might prefer to see IPD being analysed from all relevant studies. At present, great efforts are needed to obtain IPD, and the pay-off for small, or low-quality, studies may be low. Issues of ownership and access to data for use in meta-analyses need to be addressed, and we hope initiatives will be set in place to make meta-analyses using IPD easier in the future.

The vast volume of genetic data being generated in epidemiological studies raises further questions around the suitability of literature-based meta-analysis. It is not feasible to publish all findings from a genome-wide association study in traditional paper formats without (legitimately) reporting only those that appear most promising. This is an extreme example of the selective reporting problem that likely permeates all published medical research, including the suppression of entire studies on the basis of their findings (publication bias). Registration of clinical trials and other studies, and on-line repositories of full results provide natural means of making more findings available. High-output research will present a considerable challenge in the foreseeable future, and methods that pay due attention to multiple testing issues are needed.

Given the availability of reliable data, a meta-analysis should employ sound methods to synthesize them. Our review has demonstrated considerable research activity in the field of meta-analysis in recent years. But how should ‘optimal’ methods be chosen? Non-statistical considerations have an important role in choosing plausible models (e.g. choosing between fixed and random effects; or selecting suitable covariates). Purely theoretical considerations can sometimes be employed (e.g. selection of an unbiased, minimum-variance estimator). For many other questions, however, simulation studies are required to compare the behaviour of candidate analysis methods in realistic scenarios. Simulation studies need to be carefully designed to evaluate the appropriate aspect of a proposed method; we have observed examples that do not. For example, to evaluate the specific properties of a meta-analysis method based on estimates and standard errors from each study,

it might be more appropriate to generate estimates and standard errors than to generate 2×2 tables and calculate odds ratios. Otherwise, the influence of different weights awarded to studies with different event probabilities is difficult to separate from the properties of the meta-analysis method of primary interest. Similarly, to evaluate the implication of applying a method to a specific type of outcome data requires those outcome data to be simulated—a standard example being tests for funnel plot asymmetry, which have particular properties when applied to binary outcome data. Compilation of standardized meta-analysis scenarios would be a helpful resource for those undertaking, and trying to interpret, simulation studies to compare methods. These could include proposed selections of study sample sizes, numbers of studies, heterogeneity parameters, effect sizes, and, where appropriate, quantities such as probabilities for binary outcome data or standard deviations for continuous outcome data.

Looking to the future, we have little doubt that the development and use of these often ‘tailor-made’ evidence synthesis models will increase. The use of MTC to compare all trials in an area is starting to be recognized by prominent general medical journals [172]. While methodological work in this area is ongoing, this approach has the considerable appeal of being able to address the relative benefits of competing treatments, and can address questions such as the probability that a particular treatment is superior to all the alternatives. Whether ‘traditional’ pair-wise comparison meta-analyses will be discouraged in favour of the new methodology is unclear. Such methods do introduce new modelling assumptions that need careful consideration, and more experience with their use is required before the scope of their applicability can be established. There is less evidence that other complex synthesis methods are being adopted, and it is unclear whether they will ever enter the mainstream. David Eddy and colleagues saw the potential for such models perhaps earlier than anyone else [148]. It is exciting to see that his current work is even more ambitious than the Confidence Profile method, and arguably even further ahead of its time. His current collaborative work includes the creation of the Archimedes simulation model, which simultaneously considers biologic modelling, clinical medicine, care processes and system resources for the evaluation of new treatments in the major disease areas [279, 280]. This detailed person-level simulation includes variables as specific as to pertain to the modelling of individual organs, but, at the same time, is broad enough to consider issues such as the implications of new treatments on hospital resources. In order to do this, information from a whole array of sources is synthesized by the model. The core equations of the model have been impressively validated by results from published RCTs [281]. There is at least a chance that this pioneering work may again be seen in the future as visionary and hugely influential and revolutionize our understanding of what is possible when combining information from multiple sources to inform all aspects of health care.

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