Systematic reviews of meta-analyses: applications and limitations

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Systematic reviews of meta-analysis can provide helpful insights in several aspects of meta-analysis: quality of published meta-analyses, statistical methods, publication bias and its determinants, and on the causes of heterogeneity. However, they present limitations, mostly derived from the current statistical procedures applied to detect some facts, such as publication bias and heterogeneity.

Systematic review of meta-analyses can be defined as the study working with meta-analysis as the unit of analysis. During the past years meta-analysis has been a growing field, more and more papers appearing on it with time. For instance, the number of references in a PubMed search using the keyword meta-analysis has steadily increased: 329 in 1990, 769 in 1995, 1649 in 2000, and 2545 in 2004. With such amount of papers it is not strange that the number of papers using meta-analysis itself as unit of analysis has also increased. From time to time the term "meta-meta-analysis" has appeared in scientific literature. The first time I read it in epidemiological literature was in an excellent editorial by Spitzer¹ criticising the limitations of pooling data from observational studies. To follow properly the terminology currently applied the term meta-meta-analysis should be reserved for the combination of several meta-analyses in just one estimate. Katerndahl and Lawler² used this procedure to analyse the variability of 23 meta-analyses of the benefits of cholesterol reduction in coronary heart disease. They concluded that methodologically better meta-analyses showed a trend to report more beneficial odds ratios and the main fact supporting cholesterol reduction was the statistical significance of the odds ratios for cardiovascular mortality. Grissom³ applied it to study in psychology the superiority of experimental treatments compared with placebo and control treatments, suggesting that there is more to therapeutic success than placebo effects and that placebo is typically better than do-nothing control conditions.

Systematic reviews of meta-analyses are needed to study different aspects of research. Firstly, they help to test the validity of meta-analysis itself. For

instance, in the past there was a considerable debate about meta-analysis compared with large trials. An early systematic review of meta-analyses from the pregnancy and childbirth module of the Cochrane database showed the lack of agreement between meta-analyses (removing the largest trial) and largest trial results.⁴ Having in mind that publication bias occurs more frequently in small trials the consequences of this review are obvious: meta-analysis based only on small studies cannot be trusted.

Secondly, the analysis of the quality of published meta-analyses requires to draw a representative sample of meta-analyses. For instance, Jadad *et al*⁵ compared the quality of meta-analyses published in conventional journals and those in the Cochrane Library and concluded that Cochrane reviews seemed to have greater methodological rigour and were more frequently updated than systematic reviews published in conventional journals. Quality analysis of meta-analyses can also be focused in particular methodological aspects, such as the assessment of publication bias,⁶ or the criteria and tests used in the ascertainment of heterogeneity.⁷

Thirdly, meta-analysis from its beginnings boosted the research on publication bias and its determinants. However, systematic reviews of meta-analysis are needed to know how the different procedures to detect publication bias work. In this field, simulation procedures are preferred, although a sample of actual meta-analyses is required to establish the parameters to build the simulations. That is the way Egger *et al*⁸ suggested their method, Sterne *et al*⁹ compared it with the Begg-Mazumdar procedure, and Macaskill *et al*¹⁰ suggested their funnel plot regression as a more specific procedure than other

previous tests to detect publication bias. Notwithstanding, systematic reviews of meta-analyses are needed to determine the frequency of publication bias in meta-analysis. There have been published at least four papers with these goals. Surprisingly, although they explore very different fields, the results are similar, publication bias is suggested in around 20% of meta-analyses.¹¹⁻¹⁴

Systematic reviews of meta-analysis can also contribute to the assessment of determinants of publication bias. For instance, do observational studies show the same frequency of publication bias than experimental studies? Pharmaceutical industry funds clinical trials. A condition of this funding is that data are owned by the firm and this may lead to publication bias more frequently in clinical trials¹⁵⁻¹⁸ than in observational research where the presence of industry is much more scarce. However, the follow up of the researches approved by the Ethics Committee of Oxford found that observational studies were more prone to publication bias than trials.¹⁵ The opposite results have been reported in a random sample of French research ethics committees.¹⁹ One way may help to resolve this controversial subject is to apply one or more procedures to detect publication bias in a representative sample of meta-analyses. As observational studies show more heterogeneity than trials and heterogeneity interferes with the detection of publication bias,²⁰ this factor should be taken into account. The limitation of this approach relies in the weaknesses of the methods used to detect publication bias as they are not 100% sensitive and 100% specific.¹⁰ True differences cannot be disentangled from publication bias and the term small study effects instead of publication bias has been suggested.²¹

The frequency of regression to the mean (defined here as the decrease of the association reported in the first published paper with later studies on the same topic appear) can also be approached by systematic reviews of meta-analyses. This fact is related to publication bias: if an article with significant results is published it may trigger that other, remaining in researchers' drawers, to appear claiming that they do not find such association. It can be also attributable to a refinement of methods with time: a better methodology reduces bias and shows a trend to a lower strength of association. Isolated reports of this fact can be found; an example is the vaccine against malaria developed by Patarroyo.²² At present no systematic approach have been carried out to establish the frequency of this fact and the determinants

related to its occurrence. It has been suggested that cumulative meta-analysis can be a useful procedure to detect it.²³

Fourthly, systematic reviews of meta-analyses can be applied to better delineate the statistical methods used in meta-analysis. Several statistical models, under different assumptions, can be used in meta-analysis and their results do not necessarily agree. One early example of systematic review of 21 meta-analyses was the comparison of the DerSimonian-Laird method with Peto's procedure, yielding both procedures similar results,²⁴ although a bias in the latter method was described later.²⁵ There is still some controversy on whether to use the random effects model or the fixed effects model. Empirical work can help. A systematic review of 84 meta-analyses in perinatal medicine compared the two procedures to show their different behaviour under several circumstances with the goal to give a recommendation on what model should be used.²⁶ Another review compared risk difference with odds ratio in pooling across a set of 125 meta-analyses published in leading journals.²⁷ This review showed no major differences between the methods, although pooling risk differences yielded a statistically significant heterogeneity more frequently.

And fifthly, systematic reviews of meta-analysis can improve our knowledge of heterogeneity. Heterogeneity can be an important drawback of meta-analysis when a pooled estimate is the main objective. Otherwise, heterogeneity can be also a major goal in meta-analysis: to find the variables associated with variation across the primary studies can help future research on a topic. It was suggested one decade ago that this application of meta-analysis had received little attention.²⁸ With just one meta-analysis is difficult to get the whole picture of the determinants influencing heterogeneity. A systematic review of meta-analyses can help in establishing them. Several factors have been analysed using this technique. One of the first is the pioneer paper by Schulz *et al.*,²⁹ in which through the review of 33 meta-analyses of clinical trials they outlined the influence of several methodological characteristics of randomised clinical trials on their results: concealment of randomisation and blinding are associated with a closer to the null treatment effects—that is, the use of rigorous procedures to control bias reduces the efficacy of a treatment. Another example was the assessment of the effect of the control rate as a predictor of treatment efficacy in 115 meta-analyses of clinical trials: the higher the effect rate in the control group the greater the efficacy of treatment.³⁰ Another factor having an effect on variability across

studies and analysed using a systematic review of meta-analysis has been the quality of randomised trials: studies of low methodological quality have shown an increased efficacy of treatment compared with high quality trials.³¹

Although there are excellent narrative reviews of the causes of heterogeneity,^{28, 32} a systematic review analysing the determinants of heterogeneity in a representative sample of meta-analyses is lacking. Given that heterogeneity is more likely to be present in observational studies, these designs should be analysed separately from clinical trials; observational research lacks the control of bias existing in randomised controlled trials. Other particular fields may deserve specific reviews, such as meta-analysis of diagnostic tests, because the research approach applied here is rather different from other topics and flaws are very common. The application of common procedures to detect heterogeneity in this field has been published³³ and can be easily applied in a systematic review of meta-analyses. The estimation of the parameter I^2 , the proportion of total variation in study estimates that is attributable to heterogeneity,³⁴ can be a very useful figure in these systematic reviews. In the analysis of causes of heterogeneity in a series of meta-analyses a problem is the detection of the heterogeneity. Most of the statistical tests applied have low statistical power—that is, false negative results are common, although this drawback diminishes with the number of studies. This limitation may hinder the identification of variables influencing variability across studies.

In summary, systematic reviews of meta-analyses can improve our knowledge of several characteristics of research, such as publication bias and heterogeneity across the primary studies. Although some important studies have been carried out on these topics, systematic approaches for several factors are still lacking. Some of the potential contributions in these fields have been outlined.

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Pharmacology

Where now for pharmacist led medication review?

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Medication review has the potential to yield benefits but it is still unproved whether it is an effective use of scarce health resources even when optimally delivered.

Over the past century there has been a rapid growth in the size and proportion of the population aged over 65. Compared with younger people this group experiences worse health and consumes a disproportionate quantity of drugs, the volume and cost of which is increasing considerably.¹ These drugs are, of course, prescribed to reduce morbidity and mortality. However, drugs can also cause harm.² Older people especially are at risk of such harm, because of the number of drugs consumed, and age related changes in their physiology.³

Medication review has been advocated as a technique to ensure patients gain maximum benefit from their drugs, while simultaneously reducing the potential for harm. Achieving these aims is at the heart of successful "medication review" that has been defined as a: "structured, critical examination of a patient's medicines with the objective of reaching an agreement with the patient about treatment, optimising the impact of medicines, minimising the number of medication-related problems, and reducing waste."⁴ In theory, this should improve health outcomes. It has also been assumed, although based on little high quality evidence, that such measures will lead to important gains for health systems by reducing hospital admissions and inappropriate drug prescribing. Such gains hold great appeal for policymakers when taken in combination with the apparent benefits to patients.⁵ With this underpinning rationale in mind, medication reviews have been widely introduced and are

increasingly undertaken by pharmacists operating separately from the physicians involved in prescribing decisions.

Over the past five years a substantial quantity of trial evidence has appeared relating to pharmacist led medication review. These trials have varied in terms of target population (older people generally, or those with a specific disease), numbers of pharmacists, and location of the intervention (home, pharmacy, general practice, hospital, or a combination). The primary outcome has also varied, including reducing drug related problems, adverse drug reactions, and hospital admissions, or improving medication appropriateness. No study has yet been sufficiently large to test whether such interventions can reduce mortality and, although many studies have measured quality of life, this is rarely a primary outcome.

There have been eight large studies (involving over 500 patients) of medication review in broad older populations: three conducted in the UK,^{6–8} one across seven European countries,⁹ four in the USA,^{10–12} and one in Canada.¹³ All entailed some kind of face to face encounter between a pharmacist and a patient. Findings from these studies have been mixed: one study suggested improved medication appropriateness and adherence but no effect on hospital admission,¹⁰ one study showed a small increase in drug changes (2.2 compared with 1.9 over one year) but again no effect on hospital admission,⁷ one study increased the proportion of resolved drug related problems (81% compared with 30%) but showed no effect on hospital admission,⁸ one study

showed no effect on quality of life, but slightly decreased hospital admissions,¹¹ two studies showed no clear effect on a variety of outcomes,^{9,13} one study increased clinic visits and had no effect on quality of life or hospital admission,^{12,14} and most recently the HOMER trial increased hospital admissions and GP visits and failed to improve quality of life.⁶ No study found a positive effect on mortality or a clear improvement in quality life.

The evidence therefore presents us with a dilemma: those studies that have focused on medication related outcomes have shown some positive findings, but these do not seem to translate into measurable benefits to patients or health services. It could be argued that the quality of life measures used (often the SF-36) are too blunt to detect the impacts of these interventions, yet these interventions have been proposed as solutions to the important and costly problem of adverse drug reactions.

So is there a place for pharmacist led medication review? The most successful interventions have been delivered by small numbers of pharmacists working in close liaison with primary care physicians.^{7,8} Services, on the other hand, set up at a distance from physicians have either failed to deliver clear positive outcomes,⁹ or have potentially worsened health outcomes.⁶ Furthermore, no high quality health economic analysis has been published, making it impossible to assess if this is an effective use of scarce health resources even when optimally delivered.

Despite this, the UK government has decided to invest £40 million in providing pharmacist led services delivered within community pharmacy where pharmacists are at a distance from the physicians they hope to influence, and are unlikely to have ready access to patient records.¹⁵

Medication review, like drugs themselves, has the potential to yield benefits, but may also cause harm. This intervention delivered by professionals not primarily responsible for prescribing decisions, should be considered in the same way as other health technologies and be expected to adequately demonstrate not just effectiveness but also cost effectiveness before being introduced