Multivariate Meta-Analysis: Concepts and Applications

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KEY POINTS . . .

Clinical trials report multiple outcomes, many of which are correlated.

Accounting for correlations between outcomes in meta-analyses can be advantageous.

Multivariate meta-analysis methods are still under development, but may one day become the standard more routine for evidence synthesis

MVMA is an advanced technique that is still under development, but has the potential for use with economic modeling and decision making by providing (potentially narrower) joint uncertainty intervals.

The Evolution of Meta-Analyses

Evidence synthesis is increasingly common in health technology assessments (HTAs). The question of how one treatment compares relative to another is usually assessed via randomized controlled trials (RCTs). One familiar form of evidence synthesis is meta-analysis, defined as "the statistical analysis of a large collection of individual studies for the purposes of integrating the findings" or "a statistical analysis that combines or integrates the results of several independent clinical trials considered by the analyst to be 'combinable'" [1,2].

The simplest meta-analysis compares the effect of two treatments on a single outcome to determine whether the collective body of evidence demonstrates a meaningful difference (Fig. 1). Standard pairwise meta-analyses have been extended to what are called "network meta-analyses," which simultaneously examine the relative effects of more than two treatments [3]. Network meta-analyses allow simultaneous comparison of multiple treatments to understand how they compare relative to one another, rather than relative to only a single alternative.

Outcomes Collected from the Same Patient Are Usually Related

Comprehensive evaluation of comparative effectiveness usually includes assessing more than one outcome. Multiple pieces of data collected from the same individual could include outcomes such as systolic and diastolic blood pressure or time to disease progression and death. They may also collect the same outcome measured at multiple time points [4]. These outcomes are typically analyzed separately using univariate meta-analyses (UVMA), which implicitly assumes that the outcomes are independent. Expanding the analysis process to assess and account for the relationships (or correlations) among outcomes is the motivating factor behind multivariate meta-analysis (MVMA).

When two or more related outcomes are reported within the same study, the relationship between them is known as "within- study correlation," the measure of the association between the estimates of two outcomes within a study. Within-study correlation arises from two interrelated factors. First, different outcomes or the same outcome at different time points are measured on the same patient. Second, the outcomes are linked to the same disease or treatment process and hence they tend to be related.

Another type of correlation is "between-study correlation," which estimates how the outcomes on the population level are related across studies. Between-study correlation is caused by inherent relationships between variables as well as differences among studies, such as clinically important patient characteristics or study characteristics. Correlation can take a value in the range [-1,1] with positive values indicating a positive association and negative values indicating a negative association. The further the value is from zero, the greater the association. UMVA assumes the correlation is zero.

MVMA in Current Practice

The first multivariate model to incorporate within-study and between-study correlations is attributed to van Houwelingen et al. [5]. For additional technical details on MVMA model specification for the two-outcome case, we refer the reader to Roiz et al, who provides comparisons of UVMA and MVMA outcomes [6]. Details and examples of published applications of multivariate meta-analyses can be found in numerous other publications [5,7-13].

In the context of HTA, where the aim of the evidence synthesis is to characterize the uncertainty about inputs to decision-analytic models, an MVMA may provide a more realistic representation of the joint uncertainty than separate univariate analyses when the outcomes analyzed are expected to be correlated. Additionally, the uncertainty intervals of the MVMA results may be smaller than the UVMA results due to the sharing of information between outcomes via the correlation coefficient. It is also not necessary for all studies to provide information on all outcome measures to conduct an MVMA. The analysis will >

allow for borrowing of information from studies that do report all outcomes.

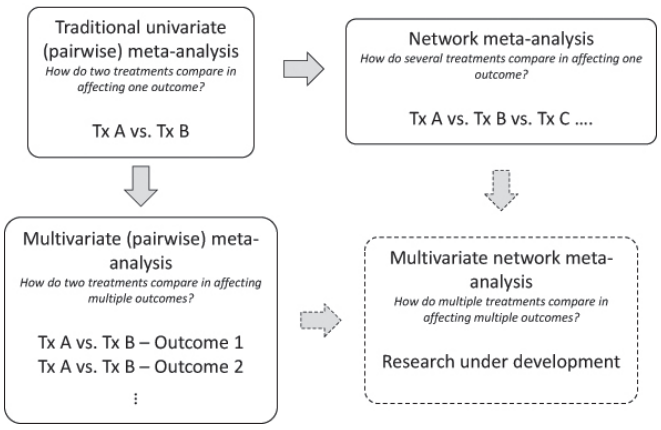
Methodology to Analyze MVMAS Is Emerging

Various methods are available for executing MVMAs, such as the commercial programs SAS/Stata and the shareware programs R and WinBUGS. The choice of software depends on the method of estimation. A detailed introduction to multivariate meta-analysis using Bayesian approach, which is showing an increasing trend, is described by Mavridis et al. [10]. SAS Proc Mixed was among the earliest and most popular programs for MVMA.

MVMA Implications and Some Limitations

A MVMA offers some advantages over separate UVMAs. MVMA estimates account for between-study correlations, so they may be used to estimate a joint distribution of analysis outcomes which can be used for modeling, testing, or the prediction of new outcomes from the associations between outcomes. Estimates of treatment effects also tend to have smaller uncertainty intervals in MVMA as a consequence of using correlations to borrow strength across studies. This can also reduce bias arising from partial reporting of outcome measures within studies [8].

Figure 1: The Evolution of Quantitative Evidence Synthesis



(Tx indicates treatment).

In spite of the potential advantages, there are several limitations to MVMA implementation [8]. First and foremost, UVMAs are easier to implement and understand. This and the general unavailability of the sample correlation between outcomes within studies is the largest barrier to MVMA adoption, with such correlations having to be assumed. Individual patient data can be used to estimate within-study correlations, but access to such data is unlikely for all studies within the meta-analysis. Alternative analysis methods for dealing with unknown within-study correlations have been proposed which may provide a partial solution for addressing the limitation. This alternative model, however, may also be limited by its own assumptions [14]. Between-study correlations may be postulated by the analyst as sensitivity analyses of varying assumptions or estimated by computing the correlation between the pair of aggregate (study-level) outcomes across studies.

There are also distinct disadvantages. MVMA may exacerbate publication or other sources of bias. For example, if outcomes are missing not at random (e.g., due to omission of non-significant outcomes within a publication), then inferences about all outcomes will be biased. MVMA can result potentially in narrower uncertainty intervals although these may only be marginally improved or even not at all, which could make the effort not worthwhile. In a meta-analysis simulation study, Trikalinos et al. [15] found that the numerical differences between UVMA and MVMA were almost always small and could or could not lead to smaller confidence intervals, depending on the estimated covariance between the effects. The authors concluded that it would be reasonable to assess and compare both univariate and multivariate approaches when possible.

Summary

In comparative-effectiveness analyses, multiple related outcomes for efficacy, safety, or utility are typically of interest. MVMA is an advanced technique that is still under development, but has the potential for use with economic modeling and decision making by providing (potentially narrower) joint uncertainty intervals. To date, guidelines and practical methodologies to conduct MVMA remain a work in progress. Research is ongoing and MVMA methods for pairwise and network analyses may one day become more routine for evidence synthesis [16,17].

References

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