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Predictive distributions were developed for the extent of heterogeneity in meta-analyses of continuous outcome data

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Abstract

Objectives: Estimation of between-study heterogeneity is problematic in small meta-analyses. Bayesian meta-analysis is beneficial because it allows incorporation of external evidence on heterogeneity. To facilitate this, we provide empirical evidence on the likely heterogeneity between studies in meta-analyses relating to specific research settings.

Study Design and Setting: Our analyses included 6,492 continuous-outcome meta-analyses within the Cochrane Database of Systematic Reviews. We investigated the influence of meta-analysis settings on heterogeneity by modeling study data from all meta-analyses on the standardized mean difference scale. Meta-analysis setting was described according to outcome type, intervention comparison type, and medical area. Predictive distributions for between-study variance expected in future meta-analyses were obtained, which can be used directly as informative priors.

Results: Among outcome types, heterogeneity was found to be lowest in meta-analyses of obstetric outcomes. Among intervention comparison types, heterogeneity was lowest in meta-analyses comparing two pharmacologic interventions. Predictive distributions are reported for different settings. In two example meta-analyses, incorporating external evidence led to a more precise heterogeneity estimate.

Conclusion: Heterogeneity was influenced by meta-analysis characteristics. Informative priors for between-study variance were derived for each specific setting. Our analyses thus assist the incorporation of realistic prior information into meta-analyses including few studies.

Keywords: Meta-analysis; Heterogeneity; Intervention studies; Bayesian analysis; Continuous data; Standardized mean difference

1. Introduction

Policy decision makers are becoming increasingly reliant on the findings from systematic reviews [1]. Within systematic reviews are meta-analyses that combine results from similar studies to synthesize available evidence in a specific research area. Variation among the results of included studies, known as heterogeneity, is inevitable. The studies have likely been conducted using different methods, at various locations, and by different teams. Statistical heterogeneity occurs when the variation between study results is greater than that expected by chance. Several possible approaches are available to deal with heterogeneity: we can ignore it, investigate it, or we may decide not to perform a meta-analysis at all. Alternatively, we can allow for heterogeneity in a random-effects meta-analysis, estimating the summary effect and the between-study variance [2].

In many meta-analyses, there are few studies available to include, perhaps because the disease is rare or the treatment under assessment is new. Of 22,453 meta-analyses from the Cochrane Database of Systematic Reviews (CDSR), containing at least two studies, just under 75% contained five or fewer studies [3]. When there are only a small number of studies included in a meta-analysis, estimation of the between-study variance is difficult. In a conventional random-effects meta-analysis, the uncertainty in the between-study variance is not accounted for [2]. However, within a Bayesian framework, we can allow for all sources of uncertainty and incorporate external evidence on

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What is new?

Key findings

- This article represents a very large empirical study of continuous-outcome meta-analyses, showing that meta-analysis characteristics strongly influence the extent of heterogeneity.
- Predictive distributions have been obtained for the expected between-study variance in future meta-analyses, and these differ substantially across settings defined by outcome type, type of intervention comparison, and medical area.

What this adds to what was known?

- When a meta-analysis includes a small number of studies, estimation of the between-study variance is difficult. The existing literature on heterogeneity in meta-analyses of continuous outcomes is sparse, and so little is known as to what forms a realistic prior distribution for the between-study variance. This article proposes a new set of informative prior distributions for use in specific research areas.

What is the implication and what should change now?

- We have demonstrated how an informative prior for heterogeneity can be used in a future meta-analysis. In each of two illustrative examples, incorporation of external information led to more precise estimates for the between-study variance.
- In view of the strong associations between meta-analysis characteristics and the extent of heterogeneity observed in our data set, the use of an empirically derived informative prior for heterogeneity in future meta-analyses would be perfectly reasonable.

heterogeneity. To perform a Bayesian random-effects meta-analysis, prior distributions need to be specified for unknown parameters. It has been recommended that a realistic prior distribution should be used for the between-study variance [4–6].

To facilitate Bayesian meta-analysis with an informative prior for the between-study variance, we provide empirical evidence on the likely extent of heterogeneity in meta-analyses of particular settings, defined by outcome type, types of interventions evaluated, and medical area. Study data from the binary outcome meta-analyses in the CDSR have already been analyzed by Turner et al. [5]. Turner et al. summarized a set of informative prior distributions for the between-study variance τ^2 for use in future binary outcome meta-analyses on the log odds ratio scale.

Here, we analyze data from a large collection of published continuous-outcome meta-analyses and investigate the influence of meta-analysis characteristics on between-study heterogeneity. We provide predictive distributions for the extent of heterogeneity expected in future continuous-outcome meta-analyses in particular settings. These distributions can be used in new meta-analyses as ''off-the-shelf'' informative prior distributions for the between-study variance [4,7].

2. Methods

2.1. Data description

CDSR is a rich resource of systematic reviews in areas of health care. These reviews have been prepared by the Cochrane Collaboration, with the objective to make the most up-to-date and reliable evidence conveniently available to health care consumers, professionals, and providers [3]. In this research, data from the CDSR (issue 1, 2008) were provided by the Nordic Cochrane Centre.

Cochrane reviews typically include multiple meta-analyses, which correspond to the comparisons of different pairs of interventions or the assessment of different outcomes within the same research area. For example, a review examining antibiotics could report separate meta-analyses comparing each of several antibiotics against a placebo, with respect to both infection severity and adverse effects. Meta-analyses were included in our analyses if they consisted of data from at least two studies. In some reviews, results from studies eligible for a meta-analysis were available, but no pooled results were published in the Cochrane review. Such data were regarded in the same way as meta-analyses to maximize the amount of information available. The review authors may have decided not to perform a meta-analysis based on the degree of heterogeneity between studies [3].

Reviews sometimes present results for several subgroup analyses within meta-analyses. Because we are interested in the overall between-study heterogeneity in a meta-analysis, study results were combined across subgroups. In some reviews, the subgroups presented within a meta-analysis were not mutually exclusive; therefore, we checked for study duplications and used data for only the first occurrence of each study in each meta-analysis [3].

All meta-analyses in the original CDSR database have been classified according to the type of outcome, types of interventions involved in the pairwise comparison, and medical specialty, as described in an earlier article [3]. In previous work conducted on binary outcome meta-analyses, Turner et al. [5] classified types of outcome according to three categories (objective, semiobjective, and subjective). When grouping outcomes for the analyses of continuous data, we decided to use narrower outcome groupings because there were no continuous outcomes we judged to be objective and fewer outcome categories in total.

For each study measured as a continuous outcome, we have study data consisting of means and standard