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A critical review of methods for the assessment of patient-level interactions in individual participant data meta-analysis of randomized trials, and guidance for practitioners

D.J. Fisher*, A.J. Copas, J.F. Tierney, M.K.B. Parmar

Medical Research Council Clinical Trials Unit, London NW1 2DA, UK

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Abstract

Objective: Treatments may be more effective in some patients than others, and individual participant data (IPD) meta-analysis of randomized trials provides perhaps the best method of investigating treatment-covariate interactions. Various methods are used; we provide a comprehensive critique and develop guidance on method selection.

Study Design and Setting: We searched MEDLINE to identify all frequentist methods and appraised them for simplicity, risk of bias, and power. IPD data sets were reanalyzed.

Results: Four methodological categories were identified: PWT: pooling of within-trial covariate interactions; OSM: ''one-stage'' model with a treatment-covariate interaction term; TDCS: testing for difference between covariate subgroups in their pooled treatment effects; and CWA: combining PWT with meta-regression. Distinguishing across- and within-trial information is important, as the former may be subject to ecological bias. A strategy is proposed for method selection in different circumstances; PWT or CWA are natural first steps. The OSM method allows for more complex analyses; TDCS should be avoided. Our reanalysis shows that different methods can lead to substantively different findings.

Conclusion: The choice of method for investigating interactions in IPD meta-analysis is driven mainly by whether across-trial information is considered for inclusion, a decision, which depends on balancing possible improvement in power with an increased risk of bias. © 2011 Elsevier Inc. All rights reserved.

Keywords: Meta-analysis; IPD; RCT; Interaction; Subgroup; Methodology

1. Introduction

The main aim of meta-analysis is to combine estimates of a particular effect across independent studies—frequently the effect of a treatment assessed in randomized controlled trials (RCTs)—to obtain a summary estimate of effect and standard error. Because of the inevitable differences in trial design and population, some variation in effect is to be expected. The widely used random-effect model of DerSimonian and Laird [1] was proposed to account for this. There are, however, statistical and clinical benefits to be had from investigating *how* factors influence the treatment effect—in other words, the nature of interactions between such factors and treatment. In meta-analysis of aggregate data (from publications or supplied by investigators), trial-level heterogeneity is often explored using subgroup analyses or meta-regression [2]. However, to assess *patient*-level heterogeneity in this framework, individual patients must be assigned trial-level average values, which is inefficient and risks bias because of the ''ecological fallacy'' [3].

We may overcome some of these problems by obtaining individual participant data (IPD) for each trial. Treatment, outcome, and covariate measurements are then known for each patient within each trial, representing the best opportunity to explore treatment-covariate interactions. More powerful and flexible analyses can be done and, in particular, patient-level heterogeneity in the treatment effect can be separated from trial-level heterogeneity and investigated directly. Various methods of accomplishing this are used in practice and, as previously observed [4], most IPD literature concentrates either on documenting these methods or on proposing

* Corresponding author. Tel.: +44-207-670-4646; fax: +44-207-670-4949.

E-mail address: df@ctu.mrc.ac.uk (D.J. Fisher).

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What is new?

Key findings

- Methodology for analyzing treatment by patient-level covariate interactions in individual participant data (IPD) meta-analysis is not yet fully established, and practical guidance is limited.
- A common approach, that estimates treatment effects within covariate subgroups and tests the differences between these subgroup estimates, is shown to be at risk of bias and should be discouraged.
- An approach that estimates a ''within-trial'' patient-level interaction only is recommended. ''Across-trial'' information is at risk of bias, and if it is to be used to supplement the ''within-trial'' information it should be done with caution.

What this adds to what was known?

- Although methodology in this area is discussed elsewhere, this is generally of a technical nature without a clear presentation of each distinct methodological approach.
- Clear guidance is given to help systematic reviewers assess whether a treatment effect varies across patient-level covariates using appropriate methodology.

What is the implication, what should change now?

- Estimating treatment effects within covariate subgroups and testing the differences between these subgroup estimates should not be used further. Instead, the guidance given in this article should be followed to select an appropriate method.
- If the data are unsuitable for assessing patient-level covariate interactions (e.g., sparse categories or large heterogeneity across trials), reviewers should state this rather than attempt to draw conclusions, which would likely be unreliable.

new statistically advanced techniques (e.g., [5]). A recent article by Thompson et al. [6] discusses most of these methods for IPD meta-analysis of time-to-event data, but we focus specifically on treatment-covariate interaction estimation in trials, describing the relevant issues in greater detail and including in our critique one further commonly used method.

In this article, we identify the principal published methods to assess treatment-covariate interactions, and critically appraise them to summarize their advantages and disadvantages. We then develop guidance on which approach might be used in different circumstances. We apply the methods to IPD data sets comparing interventions for cancer to illustrate their use in practice, before making some concluding remarks. Because these data sets all relate to time-to-event outcome measures, this article will focus on such outcome measures while also providing broader guidance.

2. Methods in the literature to analyze treatment-covariate interactions

A literature search of Medline (1966–2009) was performed to identify the main approaches for analyzing patient-level treatment-covariate interactions, both proposed in theory and used in practice, and also previous methodological reviews (see Appendix A). However, our search was not planned to quantify the number of reviews using these approaches in practice. We limited ourselves to frequentist approaches as these are most commonly used by systematic reviewers. Four categories of methods were identified, all of which may be fitted using standard statistical software unless otherwise stated. For simplicity, in this section we consider two competing treatments and a patient covariate that is binary, continuous, or ordered categorical. We assume that if the covariate is not binary then the interaction can be adequately represented by a linear interaction term. A mathematical presentation of the four methods is provided in Appendix B.

2.1. Pooling of within-trial covariate interactions (PWT)

This approach is based on the familiar weighted-average meta-analysis of aggregate data, but here we pool treatment-covariate interaction effects instead of main study effects [7]. Interactions are estimated independently within each trial using regression models or contingency tables, and are pooled using inverse-variance meta-analysis. Like the equivalent technique for main effects, this method can be described as ''*two-stage*'' [8] in that two separate sets of calculations must be carried out, the second using the output of the first.

2.2. "One-stage" model with a covariate interaction term (OSM)

An alternative approach is to estimate the treatment-covariate interaction using all available data in a single model containing terms representing trial membership, treatment, covariate, and treatment-covariate interaction [9], as detailed in Appendix B. Alternatively, the interaction term may be replaced by two independent terms, representing across- and within-trial interaction effects [5]. The treatment effect may be fixed or random, but the latter is computationally difficult for time-to-event data (see next section).

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