A method for IPD meta-analysis of treatment-covariate interaction with a continuous predictor in randomised trials

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Aims
In clinical trials, there is considerable interest in investigating whether a treatment effect is similar in all patients, or that some prognostic variable indicates a differential response to treatment. To examine this, a continuous predictor is usually categorized into groups according to one or more cut-points. Several weaknesses of categorisation are well known. To avoid the disadvantages of cut-points and to retain full information of the variable, it is preferable to keep continuous variables continuous in the analysis. We propose a statistical procedure to handle such situations when individual patient data (IPD) are available from several studies and we will illustrate practical issues using an IPD meta-analysis of three randomised trials in acute lung injury as an example.

Methods
For continuous variables, the multivariable fractional polynomial interaction (MFPI) method provides a treatment effect function, that is a measure of the treatment effect on the continuous scale of the covariate (R+S 2004, S+R 2007). MFPI is applicable to most of the popular regression models, including Cox and logistic regression. A meta-analysis approach for
averaging risk functions across several studies has recently been proposed (S+R 2011). Here we combine the two techniques to produce a method of IPD meta-analysis in which treatment-effect functions are averaged across studies. Issues such as type I error of MFPI (R+S 2013), influential points or the role of differences in patient populations across studies will be discussed. More details can be found in the registered protocol (Kasenda et al 2012).

**Results**

We used the new approach to investigate four potential treatment effect modifiers in a meta-analysis of IPD from three randomised trials in acute lung injury, where the main outcome of interest was 60-day in-hospital mortality. In contrast to cut-point based analyses, the results give more detailed insight into whether treatment effects are influenced by any of the four factors considered.

**Conclusions**

The proposed method appears to be first to address the problem of retaining full information when performing IPD meta-analyses to examine continuous effect modifiers in randomised trials. Early experience suggests that it is a promising approach with broad applications. Adjustment for confounders is possible with MFPI, therefore this approach also allows investigating interactions between a binary (extension to categorical variable is straightforward) and a continuous variable in observational studies. Functions from several observational studies can be averaged as illustrated for randomised trials here.

**References**


