A comparison of Fractional polynomials, meta-STEPP and smoothing splines to investigate effect modification in IPD-MA : a simulation study

Michail Belias

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Abstract

Introduction

Individual participant data (IPD) meta-analysis (MA) offer great opportunities, such as to simultaneously investigate effect modification while also modelling for potential non-linear association between the outcome and the effect modifier. Several regression based approaches have been proposed such as fractional polynomials, meta-STEPP and splines.

Objective

Our objective is to compare their properties and their precision to investigate effect modification in IPD-MA.

Methods

To that goal we first describe the aforementioned methods. Subsequently, we conduct a simulation study covering 3 distinct scenarios. All scenarios consist of 5 studies with 200 participants each and equal treatment allocation reflecting the design of a randomised clinical trial. In the first scenario we introduced heterogeneity but the domain of the continuous effect modifier was the same across the studies. In the second scenario we introduced heterogeneity and the the domain of the continuous effect modifier was the different across the studies, while in the third scenario we added ecological bias.

Results

Conclusions

Introduction

Individual participant data (IPD) meta-analysis (MA) is well established as the gold standard to synthesize evidence from multiple studies [1,2]. IPD-MA offers great opportunities and showed great increase over the last decades [3]. Two opportunities commonly addressed with IPD-MA is the investigation of effect modification and modelling non-linear associations with the outcome. Estimating correctly the real underlying functional shape between the outcome and a continuous variable is a important task, as failing to do so may lead to biased results and subsequently biased conclusions. Therefore, a plethora of modelling approaches have been developed such as polynomial regression, fractional polynomials, splines and sliding window techniques. Most of these approaches have been developed in a single study formats and extended in multi-level schemes to account for the within study clustering of the participants. The aforenmentioned approaches can be classified in two categories. Polynomial regression and fractional polynomials are **global** methods, while splines and sliding windows approaches are **fragmented** methods. Polynomial regression approach is the most simple and easy to perform. Hereby, higher than one powers (linear) of the continuous variable are generated and regressed with the outcome. Lower and higher degree polynomials are typically compared using tests such as likelihood ratio and Wald test or criteria such as AIC and BIC. Fractional polynomials [4,5] use the same approach as polynomial regression, but the powers that can be used come from a specific set $S : [-2; -1; -0 : 5; 0; 0 : 5; 1; 2; 3]$. Note that FPs introduce also negative powers, which offers great flexibility. Splines are based on piece-wise polynomials. As the term piece-wise implies the continuous variable is splitted into subdomains. The cut points for these splits are often called knots and the domains within each knot intervals. As simply fitting a polynomial within two adjacent interval would produce discontinuous fitted lines splines are constrained to be continuous and in most approaches smooth over the knots. Slines amy be also classified in two categories **regression splines** and **penalised splines**. The most commonly used **regression splines** are restricted splines [cit] and B-splines [6,7]. On the other hand, the most commonly used **penalised splines** are smoothing splines [8] and p-splines [9].

Sliding window approaches are often called non-parametric, as they make no distributional assumptions. Hereby, a number of observations or events is first chosen and a

References

The most popular splines are restricted splines, B-splines

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