Overview and illustration of methods to investigate effect modification across a continuous covariate

Michail Belias

14 October, 2018

# Abstract (116 out of 200 words)

## Objective

To give an overview and illustrate a variety of tree-based and regression-based approaches to detect and model effect-modification in meta-analysis(MA) of individual participant data(IPD), such as: covariate-centred one-stage IPD-MA, mixed effects fractional polynomials, splines, meta-stepp and glmm-trees.

## Study Design and Setting

We applied the approaches on two empirical examples. In the first we investigate possible modification of the effect of somatostatin on liver reduction in participants with polycystic liver disease, in the second effect modification of antibiotics on fever/ear-pain reduction in children with acute otitis media.

## Results

Non-linear association was detected in AOM IPD-MA.

## Conclusion

We conclude that subgroup detection in IPD-MA requires knowing the underlying assumptions and careful modelling. Effect modification may be distorted by a non-linear association if left unadjusted.

##### 

# 1. Introduction

Individual participant data meta-analysis (IPD-MA) is a type of systematic review where data gathered from multiple studies are combined and analysed centrally. The capability to standardise subgroup definitions and outcomes across studies, the increased power to investigate other than linear associations, the increased validity and reliability of the subgroups and the flexibility to search for subgroups based on combinations of patient and/or disease characteristics are some of the benefits of using IPD of multiple trials rather than traditional (aggregate) meta-analysis. A vivid field of research towards personalised healthcare is the investigation of effect modification. For this task, IPD-MA is considered a gold standard as single trials rarely have sufficient power to identify relevant effect modification.

Effect modification may occur in categorical and/or continuous covariates: differences in the treatment effect may be present between smokers and non-smokers, or may depend on the age of the patient. The investigation of subgroup effects is frequently performed using statistical models, but challenges do exist. For example, a common first step is to categorize a continuous covariate. However, categorisation has been criticised for misspecification, loss of information and power, inflation of the type I error rate when adjusting for confounding, and biased results [1–5]. Another common practice is to assume a linear relation between the continuous covariate and (the logit or other transformation of) the outcome, a method that may also lead to deterioration of power, misspecification and even spurious results [6]. A better practice would be to start with exploring the functional form of the outcome-effect modifier association. Various approaches to investigate and if needed account for non-linear associations have been developed, such as fractional polynomials (FPs) [7] and splines.

Regression based approaches such as linear models, piecewise polynomials or fractional polynomials may be performed either in one or two stages. In two-stage approach, each trial is first modelled separately, using an appropriate statistical model of choice. Subsequently, we pool either the extracted estimates or the fitted functions across trials using standard meta-analytical tools. In contrast, in one-stage IPD-MA all IPD from every trial are analysed simultaneously whilst accounting for the clustering of participants within studies. Hereto, researchers may model interactions between treatment and patient-level covariates. Recent recommendations, suggest mean-centring the potential effect modifiers per trial in order to account for potential ecological bias due to unadjusted confounding. Within trials clustering can be accounted using either fixed effect**s** (stratified intercept/slope), fixed effect (common intercept/slope) or random effects (intercept and/slopes driven from a common Normal distribution) [9]. Finally, state-of-the-art plot and tree-based methods have been developed for exploring and confirming effect modification. Generalised linear mixed-effects model trees (glmertree) introduced by Fokkema et al.[10] can handle non-linear associations, whilst accounting for within studies clustering of the participants. Meta-stepp is a plot based moving average (sliding window) method that approximates non-linear effects from clustered data [11]. Finally, although, providing the whole information of the outcome-continuous effect modifier association is more informative clinical decisions are based in cut-points in which the treatment effect is altered. These cut-points may be altered if the assumptions are altered or if the outcome-effect modifier functional form is mis-specified.

It is often unclear when each method should be preferred. Also, it is unclear if the treatment effect function [12] or interaction term analysis [13] is most appropriate and in randomised clinical trials (RCT) meta-analysis framework. We aim to describe and illustrate the aforementioned methods. For that task, we will use both regression-based approaches such as meta-stepp, centred one-stage IPD-MA, mixed effects fractional polynomials and splines, and tree-based approaches such as generalised linear mixed-effects model trees.

# 2. Example datasets

We use 2 empirical IPD-sets to illustrate the methods. The first data-set [14] was used to investigate the effect of antibiotics on acute otitis media in children aged from 0 to 12 years old. Rovers et al. collected IPD from 6 randomised clinical trials with a total of 1643 children. The primary outcome was fever and/or ear-pain after 3-7 days (yes/no). They concluded that antibiotics were more beneficial in young children (less than 2 years old) with bilateral acute otitis media. Presence of bilateral acute otitis media (yes/no), age, and otorrhea were also investigated separately for potential effect modification and only the presence of bilateral acute otitis media showed a significant effect modification?.

The second data-set [15] was used to investigate the effect of Somatostatin on liver volume reduction. Gevers et al. collected IPD from 3 randomised placebo-controlled trials with a total of 107 participants. In this example, the outcome was continuous (liver volume reduction), and age, sex, baseline liver volume, and diagnosis of either autosomal dominant polycystic liver or kidney disease were investigated for effect modification. They concluded that use of Somatostatin was more beneficial for younger (<47) female patients. One of the 3 trials [Caroli et al.] had a cross-over design, therefore participants were treated both with the active and the control treatment in different time periods. In order to use these data for our illustrative purposes, we removed the cross-over design and used all patients only once, by selecting half of the patients from the active period and the other half (sex and age-matched) from the control period. Therefore, differences between our results and those reported in the original article will occur.

# 3. Methods

## 3.1 Notation

We are denoting the studies as j = 1,2,…,J, individuals as i=1,2…,I, the per trial mean of age as , cut-point as

## 3.2. Recursive-partitioning (tree-based) methods

### 3.2.1 Generalised Linear Mixed Model Trees (glmm or glmer trees)

The Generalised linear mixed model (GLMM) tree approach is a state-of-the-art technique, proposed by Fokkema et al. [10] for the detection of treatment-effect modifier interactions in clustered data???. A model-based recursive partitioning [16,17] algorithm is applied, while also considering the clustered structure of datasets.

The GLMM tree algorithm:

1. fit the parametric model to the dataset,
2. statistically test for parameter instability with respect to each of a set of partitioning variables,
3. if there is some overall parameter instability, split the dataset with respect to the variable associated with the highest instability,
4. repeat the procedure in each of the resulting subgroups.

##### 

## 3.3 Regression based approaches

In regression based approaches it is important to model the appropriate functional form of the association between the effect modifier and the outcome. If the appropriate form is already known, modeling will be straightforward. However, if not, splines or FPs may be used to evaluate the functional form of the association.

Another aspect to take into consideration while modeling the functional form, is whether there may be cut-points where the shape of the association changes. If these may exist, this should be taken into account. Again, if the cut-points are known, modeling will be more straightforward then when they are unknown. These two dimensions define how to proceed with the regression model.

Also some introduction on two-stage vs one-stage….

We identify 2 assumptions that a researcher may apriori have. The first is over the functional form the association of the outcome with the continuous covariate have and the second one over the cut-points known also as cut-offs or knots, where the effect is modified. In this framework, we consider that given the assumptions made we may choose the appropriate analysis to perform.

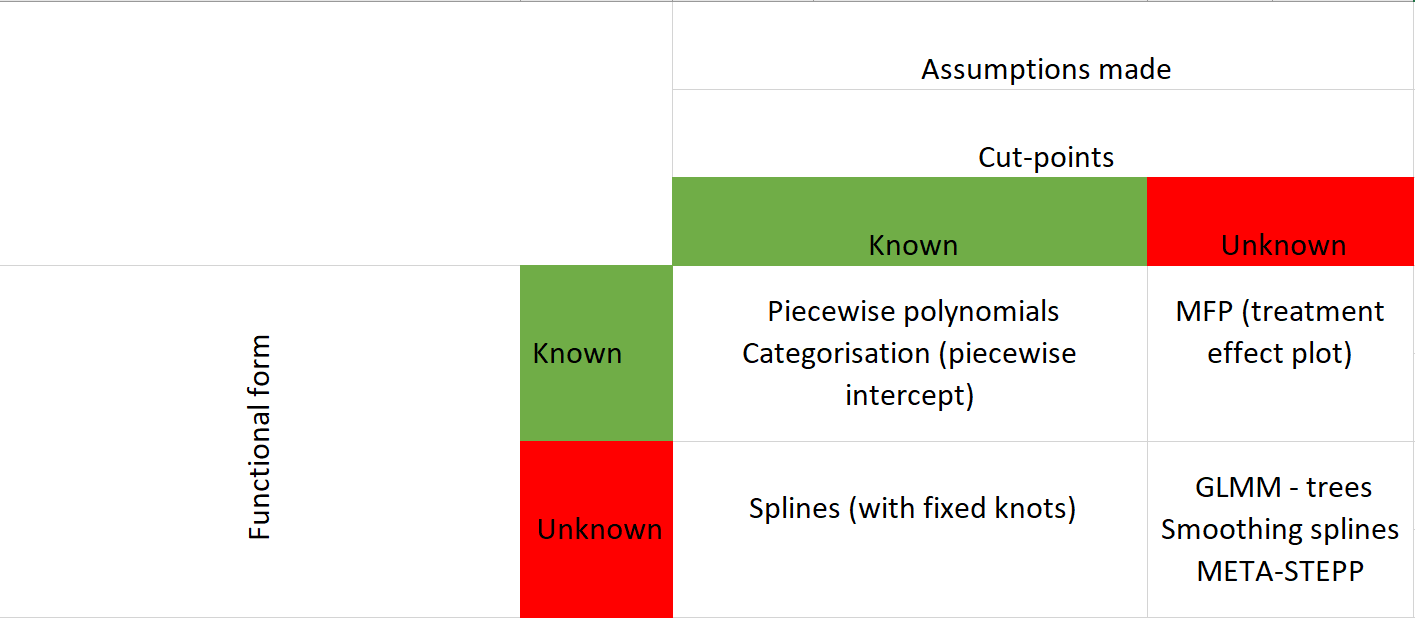


Table 1

### 3.3.1. Two-stage approaches

In two-stage approaches a statistical model of choice is directly fitted per trial. The statistical model per trial j is as follows:

Subsequently, we can either pool the coefficients or the fitted functions using typical meta-analytical tools.

#### 3.3.1.1 First stage: Per-trial modeling

The functions are providing the functional shape of the outcome-effect modifier association per trial j for the treated and the control respectively. Depending on the a priori knowledge of the association’s functional form and the cut-points where the effect is altered we may fit.

*Known functional form and known cut-points*

* Piecewise-polynomials with m cut-points (knots)
  + Piecewise constant: within each interval both f1, f2 have the form of (for k=2 equivalent to Dichotomisation and for k>2 categorisation)
  + Piecewise-linear: within each interval both f1, f2 have the form of
  + Piecewise-quadratic: within each interval both f1, f2 have the form of

*Known functional form and unknown cut-points*

* Global-polynomials:
  + linear:
  + Quadratic:

#### 

#### Fractional polynomials

*Unknown functional form and unknown cut-points*

Fractional polynomials [18] are an extension of polynomials, that also include negative powers. FPs provide a global functional form. FPs model the effect of a covariate X as , where m is the degree of the fractional polynomial and the power is derived from a fixed set of powers {-2,-1,-0.5, 0=(log),0.5,1,2}. The Fractional selection procedure FSP algorithm (FSP) has been proposed [19] to explore the best fitting fractional polynomial. The fractional polynomials of a common degree **m** are tested using the deviance difference criterion, whilst fractional polynomials of different degree are compared using a test. When multiple data-sets are present Sauerbrei and Royston [7], have proposed 3 methods to evaluate the general functional form.

* Overall FP, where the FSP is applied in the pooled data (stratified by study), in order to find the best FP
* Study-wise FP2, the best FP2 is selected for each study
* Study wise selected FP, where the best fitting FP is extracted per study

#### 

#### 3.3.1.2 Second-stage: combination of the first stage results

As a second-stage in the two-stage IPD-MA, we either pool the estimates or the fitted functions extracted from the first stage. The coefficients and , extracted in the first stage, can be used in a multivariate meta-analysis(CE or RE) to give an overall mean to extract the pooled and it’s SE. This approach only works when common powers have been used across studies. Therefore, it is applicable in piecewise and global polynomials, and fractional polynomials fitted using the overall FP procedure. we applied a random-effects meta-analysis, using the EB method for the estimation [21] and the HKSJ adjustment [22].

The fitted function g can be calculated per study and derive its standard error from . Then we perform a meta-analysis, to get a pooled estimate and it’s variance.

### 

### 3.3.2. One-stage approaches

#### 

#### 3.3.2.1 Centred One-stage IPD-MA

We follow recent recommendations [24] and centre per trial the effect modifier. This way we can separate the within and across trial information of the effect modification. As in the two stage methods we can fit piecewise and global polynomials, but using a mixed-effect model to account for within trials clustering.

Therefore, assuming that the statistical model will be:

where given cut-points and p degree of polynomial,

and

For the and we can assume, either fixed (common) effect, fixed effect*s* (stratified betas), or random effects. If we choose the fixed effect approach a common beta is assumed, in the stratified approach j betas will be generated which correspond to the per trial beta, while in the random effects we assume that the per trial coefficients are driven from a common Normal distribution N().

#### 3.3.2.2 Multilevel Fractional polynomials

Fractional polynomials may be used using one stage approach[25]. In this case, we use the same set of powers as in the FSP method. Furthermore, we fit a mixed effect model of our choice, with either stratified, fixed or random effects. For model selection we can use the lowest deviance or the Akaike Information Criterion (AIC) [27], or Bayesian Information Criterion (BIC) [28].

Therefore the statistical model applied is:

##### 

# Results

##### 

# Discussion

##### 

# References

[1] Royston P, Altman DG, Sauerbrei W. Dichotomizing continuous predictors in multiple regression: A bad idea. Statistics in Medicine 2005;25:127–41. doi:[10.1002/sim.2331](https://doi.org/10.1002/sim.2331).

[2] Altman DG. The cost of dichotomising continuous variables. BMJ 2006;332:1080–0. doi:[10.1136/bmj.332.7549.1080](https://doi.org/10.1136/bmj.332.7549.1080).

[3] Austin PC, Brunner LJ. Inflation of the type i error rate when a continuous confounding variable is categorized in logistic regression analyses. Statistics in Medicine 2004;23:1159–78. doi:[10.1002/sim.1687](https://doi.org/10.1002/sim.1687).

[4] Maxwell SE, Delaney HD. Bivariate median splits and spurious statistical significance. Psychological Bulletin 1993;113:181–90. doi:[10.1037/0033-2909.113.1.181](https://doi.org/10.1037/0033-2909.113.1.181).

[5] Weinberg C. How bad is categorization? Epidemiology 1995;6:345–6. doi:[10.1097/00001648-199507000-00002](https://doi.org/10.1097/00001648-199507000-00002).

[6] Jørgensen TSH, Osler M, Ängquist LH, Zimmermann E, Christensen GT, Sørensen TI. The u-shaped association of body mass index with mortality: Influence of the traits height, intelligence, and education. Obesity 2016;24:2240–7. doi:[10.1002/oby.21615](https://doi.org/10.1002/oby.21615).

[7] Sauerbrei W, Royston P. A new strategy for meta-analysis of continuous covariates in observational studies. Statistics in Medicine 2011;30:3341–60. doi:[10.1002/sim.4333](https://doi.org/10.1002/sim.4333).

[8] Royston P, Sauerbrei W. Interaction of treatment with a continuous variable: Simulation study of significance level for several methods of analysis. Statistics in Medicine 2013;32:3788–803. doi:[10.1002/sim.5813](https://doi.org/10.1002/sim.5813).

[9] Legha A, Riley RD, Ensor J, Snell KI, Morris TP, Burke DL. Individual participant data meta-analysis of continuous outcomes: A comparison of approaches for specifying and estimating one-stage models. Statistics in Medicine n.d. doi:[10.1002/sim.7930](https://doi.org/10.1002/sim.7930).

[10] Fokkema M, Smits N, Zeileis A, Hothorn T, Kelderman H. Detecting treatment-subgroup interactions in clustered data with generalized linear mixed-effects model trees. Behavior Research Methods 2017. doi:[10.3758/s13428-017-0971-x](https://doi.org/10.3758/s13428-017-0971-x).

[11] Wang XV, Cole B, Bonetti M, Gelber RD. Meta-STEPP: Subpopulation treatment effect pattern plot for individual patient data meta-analysis. Statistics in Medicine 2016;35:3704–16. doi:[10.1002/sim.6958](https://doi.org/10.1002/sim.6958).

[12] Royston P, Sauerbrei W. Interactions between treatment and continuous covariates: A step toward individualizing therapy. Journal of Clinical Oncology 2008;26:1397–9. doi:[10.1200/jco.2007.14.8981](https://doi.org/10.1200/jco.2007.14.8981).

[13] Sun X, Briel M, Walter SD, Guyatt GH. Is a subgroup effect believable? Updating criteria to evaluate the credibility of subgroup analyses. BMJ 2010;340:c117–7. doi:[10.1136/bmj.c117](https://doi.org/10.1136/bmj.c117).

[14] Rovers MM, Glasziou P, Appelman CL, Burke P, McCormick DP, Damoiseaux RA, et al. Antibiotics for acute otitis media: A meta-analysis with individual patient data. The Lancet 2006;368:1429–35. doi:[10.1016/s0140-6736(06)69606-2](https://doi.org/10.1016/s0140-6736(06)69606-2).

[15] Gevers TJ, Inthout J, Caroli A, Ruggenenti P, Hogan MC, Torres VE, et al. Young women with polycystic liver disease respond best to somatostatin analogues: A pooled analysis of individual patient data. Gastroenterology 2013;145:357–365.e2. doi:[10.1053/j.gastro.2013.04.055](https://doi.org/10.1053/j.gastro.2013.04.055).

[16] Zeileis A, Hothorn T, Hornik K. Model-based recursive partitioning. Journal of Computational and Graphical Statistics 2008;17:492–514. doi:[10.1198/106186008x319331](https://doi.org/10.1198/106186008x319331).

[17] Su X, Tsai C-L, Wang H, Nickerson DM, Li B. Subgroup analysis via recursive partitioning. SSRN Electronic Journal 2009. doi:[10.2139/ssrn.1341380](https://doi.org/10.2139/ssrn.1341380).

[18] Royston P, Altman DG. Regression using fractional polynomials of continuous covariates: Parsimonious parametric modelling. Applied Statistics 1994;43:429. doi:[10.2307/2986270](https://doi.org/10.2307/2986270).

[19] Ambler G, Royston P. Fractional polynomial model selection procedures: Investigation of type i error rate. Journal of Statistical Computation and Simulation 2001;69:89–108. doi:[10.1080/00949650108812083](https://doi.org/10.1080/00949650108812083).

[20] Sauerbrei W, Royston P. Building multivariable prognostic and diagnostic models: Transformation of the predictors by using fractional polynomials. Journal of the Royal Statistical Society: Series A (Statistics in Society) 1999;162:71–94. doi:[10.1111/1467-985x.00122](https://doi.org/10.1111/1467-985x.00122).

[21] Stijnen T, Houwelingen JCV. Empirical bayes methods in clinical trials meta-analysis. Biometrical Journal 2007;32:335–46. doi:[10.1002/bimj.4710320316](https://doi.org/10.1002/bimj.4710320316).

[22] Hartung J, Knapp G. A refined method for the meta-analysis of controlled clinical trials with binary outcome. Statistics in Medicine 2001;20:3875–89. doi:[10.1002/sim.1009](https://doi.org/10.1002/sim.1009).

[23] IntHout J, Ioannidis JP, Borm GF. The hartung-knapp-sidik-jonkman method for random effects meta-analysis is straightforward and considerably outperforms the standard DerSimonian-laird method. BMC Medical Research Methodology 2014;14. doi:[10.1186/1471-2288-14-25](https://doi.org/10.1186/1471-2288-14-25).

[24] Hua H, Burke DL, Crowther MJ, Ensor J, Smith CT, Riley RD. One-stage individual participant data meta-analysis models: Estimation of treatment-covariate interactions must avoid ecological bias by separating out within-trial and across-trial information. Statistics in Medicine 2016;36:772–89. doi:[10.1002/sim.7171](https://doi.org/10.1002/sim.7171).

[25] Long J, Ryoo J. Using fractional polynomials to model non-linear trends in longitudinal data. British Journal of Mathematical and Statistical Psychology 2010;63:177–203. doi:[10.1348/000711009x431509](https://doi.org/10.1348/000711009x431509).

[26] Johnson W, Balakrishna N, Griffiths PL. Modeling physical growth using mixed effects models. American Journal of Physical Anthropology 2012;150:58–67. doi:[10.1002/ajpa.22128](https://doi.org/10.1002/ajpa.22128).

[27] Akaike H. A new look at the statistical model identification. In:. Springer series in statistics, Springer New York; 1974, pp. 215–22. doi:[10.1007/978-1-4612-1694-0\_16](https://doi.org/10.1007/978-1-4612-1694-0_16).

[28] Schwarz G. Estimating the dimension of a model. The Annals of Statistics 1978;6:461–4. doi:[10.1214/aos/1176344136](https://doi.org/10.1214/aos/1176344136).