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

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# Abstract (116 out of 200 words)

## Objective

To provide 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). For instance, covariate-centred one-stage IPD-MA, mixed effects fractional polynomials, splines, meta-stepp and GLMM-trees, using both two and one stage approach when possible.

## 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

We show that GLMM-trees is a helpful exploratory tool, providing evidence for three-way interactions. On the regression-based methods two-stage approaches showed increased risk of non-convergance and dropping whole trials due to missing data. On the other hand one-stage methods produced results using all information available. Nevertheless, they produced varying results over the power to detect the effect modification, the modeling efficiency and the produced cut-points.

## Conclusion

We conclude that subgroup detection in IPD-MA requires knowing the underlying assumptions and careful modelling. Effect modification may be distorted by unadjusted non-linear associations. We propose the use of more flexible apporaches such GLMM-trees and splines to explore and investigate effect modification.

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# 1. Introduction

Individual participant data meta-analysis (IPD-MA) is a type of statistical analysis, where data are gathered from multiple studies are combined and analysed 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 [1–3]. A vivid field of research towards personalised healthcare is the investigation of effect modification. For this, IPD-MA is considered the gold standard as single trials rarely have sufficient power to properly detect effect modification. Effect modification may be present in both categorical and/or continuous covariates. For instance, differences in the treatment effect may be present between smokers and non-smokers, or across the age of the patients. If subgroups have been predefined, hypothesis testing may be performed using traditional regression-based methods. For single trials, this typically involves the estimation of (linear) interaction terms between treatment and the modifier of interest. In an IPD-MA, these interaction effects may be estimated either separately within studies and subsequently be pooled across studies (two-stage IPDMA), or directly across all studies (one-stage IPDMA. However, effect modification across continuous variables is more challenging, since we may need to evaluate effect modification and at the same time want to define a threshold from which point the treatment effect is relevantly different. Categorization is a common technique to investigate effect modification, by splitting the continuous covariate into subgroups. Nevertheless, these subgroups should always be created based on good prior knowledge from literature. If so, this approach may provide meaningful insight into effect modification. Nevertheless, categorization has been criticised for misspecification, loss of information and power, inflation of the type I error rate and even biased results [4–8].Another common practice is using the covariable as it is, but assuming linearity over the link function, a method that may also lead to deterioration of power, misspecification, and even spurious results [9]. Ideally, when continuous covariates are included, we would like to account for their functional form while simultaneously making inferences over the presence of the effect modification. Furthermore, although the association between the outcome and the continuous effect modifier is highly informative, clinical decisions are based on subgroups of participants the differ in treatment response. Finally, subgroups generated from continuous variables are defined by the cut-points were the treatment effect is considered to change. These cut-points may be based on the treatment effect function [10], i.e. the difference between the two treatments over the range of the covariable or the treatment-effect modifier interaction terms [11]. For this, various approaches to account for non-linear associations have been developed, such as splines and fractional polynomials (FP) [12].

For IPD-MA, regression-based approaches such as linear models, piecewise polynomials, FPs and smoothing splines may be performed either in one or two stages. In a two-stage approach, first each trial is modelled separately using an appropriate statistical model. Subsequently, we pool either the extracted coefficients if shared across the trials or their fitted functions, using standard meta-analytical tools. In contrast, in one-stage IPD-MA the IPD from all trials are analysed simultaneously whilst accounting for the clustering of participants within studies and the potential of ecological bias . Hereto, we model interactions between treatment and patient-level variables while accounting also for the shape of the associations with the outcome. Recent recommendations suggest mean-centring the potential effect modifiers per trial in order to account for potential ecological bias due to unadjusted confounding. In such a one-stage model, within-trial clustering can be accounted for using either a fixed effect (common intercept/slope), fixed effects (stratified intercept/slope), or random effects [14]. Other methods to explore effect modification are plot- and tree-based methods such as the generalised linear mixed-effects model tree (GLMM-tree) method [15] or meta-stepp, a plot based moving average (sliding window) method.

Although there is a large variety of methods to explore effect modification for continuous covariates, little guidance exists on their use. We aim to describe and illustrate the aforementioned methods by applying them on two empirical examples, while discussing their (potential) advantages and limitations.

# 2. Empirical examples

We use 2 IPD-sets to illustrate aforementioned methods. The first empirical example [16] considers an IPD-MA where the effect of antibiotics in acute otitis media was investigated in children. Rovers et al. collected IPD from 6 randomised clinical trials with a total of 1643 children, aged from 0-12 years old. The primary outcome was fever and/or ear-pain after 3-7 days (yes/no). They concluded that antibiotics were more beneficial in younger children (less than 2 years old) with bilateral acute otitis media. Bilateral acute otitis media (yes/no), age, otorrhea were investigated also separately for potential effect modification and only bilateral acute otitis media showed a significant result. The second empirical example [17] considers an IPD-MA 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 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 may occur.

# 3. Methods

## 3.1 Notation

As described in section 2, both empirical example datasets are composed of multiple randomised trials. We will adopt the following notation throughout our manuscript:

* The trials as j = 1,2, …,J,
* Trial participants as i = 1,2, …,I,
* The per trial mean of age as
* The per trial centred age as =
* Cut-point (knot) as
* The degree of a fractional polynomial as m
* The degree of a polynomial as p

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

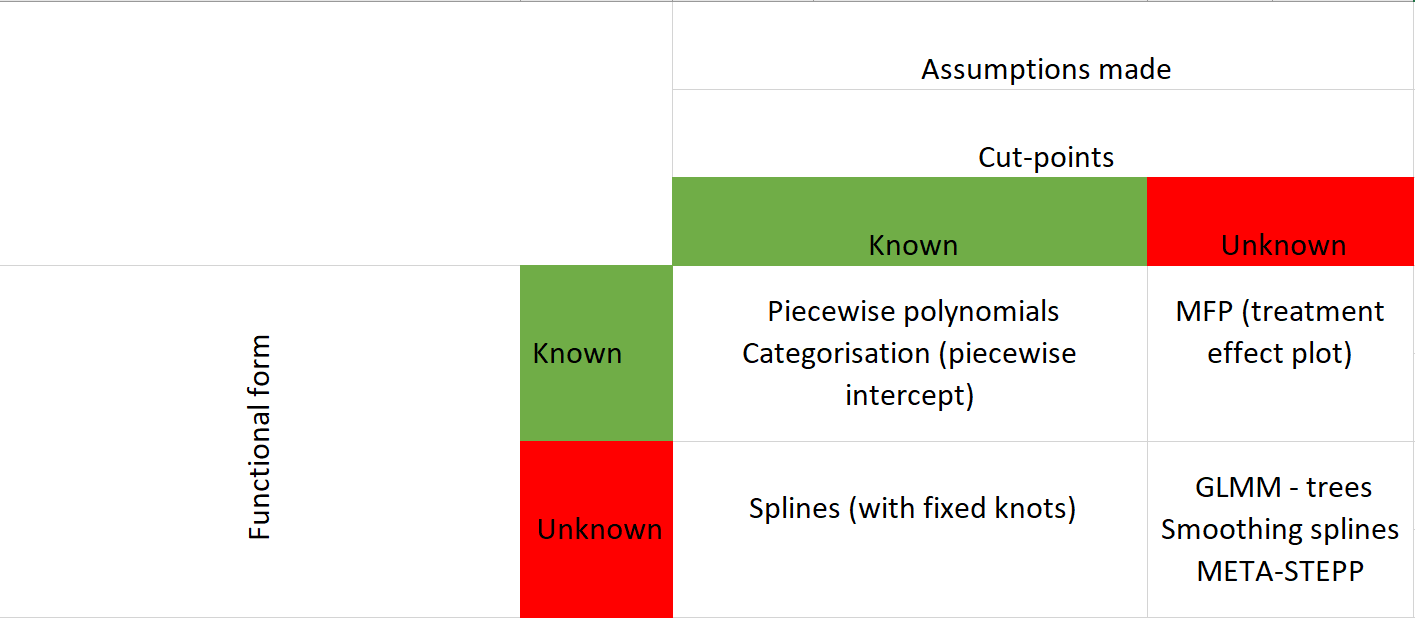
Recursive partitioning can be a first step to explore the underlying structure of the data, such as whether there are outcome differences across the levels of a continuous or categorical variable. It is a statistical method typically used in multivariable analysis[18]. A decision tree is generated by dichotomising the variable by cut-points, thus creating subgroups where the treatment effect is altered. Recursive partitioning techniques can handle non-linear associations as they make no functional form assumption a-priori.

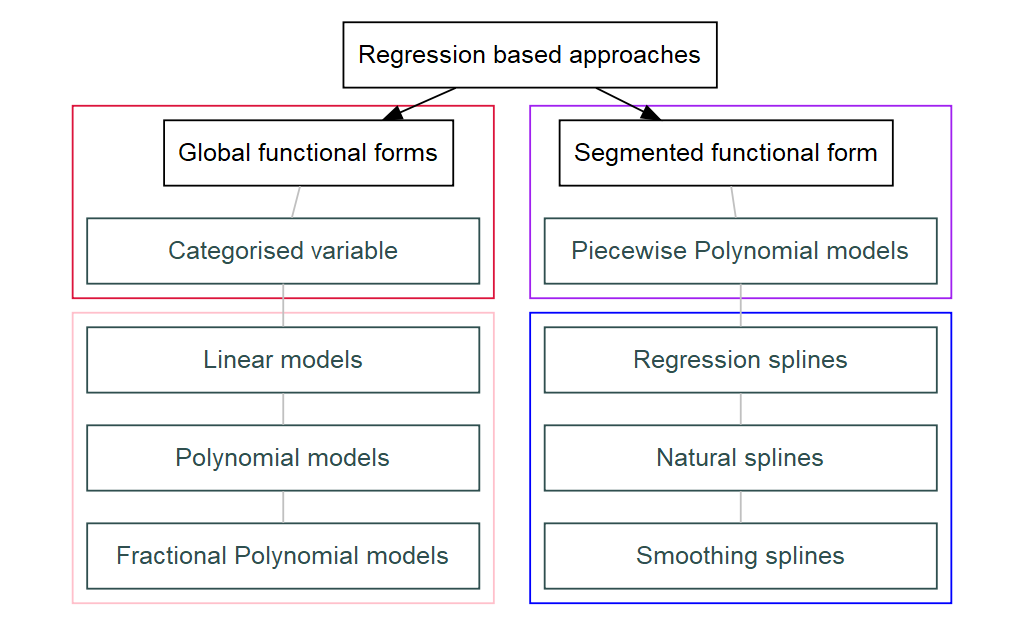
Splitting the data-set into subgroups is a sensitive process though. Therefore, it is highly important to account for within trial clustering of the participants. The Generalised linear mixed model (GLMM) tree approach is a state-of-the-art technique using a model-based recursive partitioning [19,20] algorithm. It was proposed by Fokkema et al. [21] to detect treatment-effect modifier interactions in the presence of clustered data, as is the case in IPD-MA. Since this approach is exploratory, we can play with the significance level for the splitting criterion, to be more or less liberal. Furthermore, we can use GLMM-trees to detect the possibly relevant variables, their crude cut-points and their underlying subgroups. If GLMM-tree results in subgroups, we can evaluate the corresponding variable using a more sophisticated approach. For example, if we identify age and gender as subgrouping variables using the GLMM-tree, we can use a regression technique to model this relationship. The GLMM tree algorithm (1) starts by fitting a regression model with interaction terms (treatment x subgroup variables) included (2) statistically tests the interaction terms using a user-defined α, i.e. whether treatment is modified with respect to the subgroup variables, then (3) if test indicates modification, splits the dataset in order to create 2 subgroups with the largest difference in treatment effect. This procedure is (4) repeated in each of the resulting subgroups, until a user-defined convergence is achieved.

## 3.3 Regression based approaches

In regression-based approaches it is important to specify an appropriate functional form for the association between the effect modifier and the outcome. If the functional form is known a priori (e.g. linear, log-linear), modelling is fairly straightforward. However, if the functional form is not properly be predefined, splines and/or fractional polynomials may be used to evaluate the functional form of the association.

When using segmented functions, another concern is the selection and placing of the cut-points (knots), which are used to model changes in the shape of the association. The location and number of knots could be either predefined or estimated. In first case, we split the variable in these knots and fit an appropriate polynomial regression within. In the later, we may either use cross-validation or penalised maximum likelihood approaches.





Finally, for any regression-based approach, the presence of within-trial clustering should be accounted for [22]. Below, we describe how this can be done in an IPD-MA.

### 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 modelling

The functions are providing the functional shape of the outcome-effect modifier association per trial j for the treated and the control group respectively. Depending on the a priori knowledge of the association’s functional form and the cut-points where the effect is altered, we may either fit a generalised additive model with splines included, a fractional polynomial model or a polynomial model (including linear shapes and categorised variable). The approaches mentioned above, besides FPs, can be also performed using the continuous variable split in predefined cut-points, also called knots.

*Unknown functional form and known knots*

Splines are a generalisation of piecewise polynomials and can offer great flexibility to explore the shape of the outcome-effect modifier association. Regression splines of **p** degree should be continuous, have **p-1** continuous derivatives and the derivative should constant across the knots. They are quite similar to piecewise polynomials, with the difference that they are continuous across the knots. A natural spline has an extra assumption that the second derivative of the function over the edges of the association is 0. This is a something that should be considered when the goal of our research is to forecast future outcomes, as for instance in longitudinal or time series studies. When using splines, the real underlying shape is not known or we don’t want to assume it is known, therefore, we explore it. However, information over the position of the knots and their number may be also unknown. Thus, we can introduce even more flexibility into our model by fitting smoothing splines. Smoothing splines by-pass the problem of knot selection by shrinking the coefficients to their basis expansion, which is a piecewise polynomial. In order to do so, they minimise the penalised least squares criterion or equivalently the maximum likelihood criterion with an extra parameter representing the wingliness of the line, equivalently or in algebraic form .

*Unknown functional form and known knots (global function)*

Fractional polynomials [23] 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 [24] 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 [12], have proposed 3 methods to evaluate the general functional form.

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

*Known functional form and known knots and known position of the knots (segmented functions)*

* Piecewise-polynomials with knots
* Piecewise-polynomials mostly used are piecewise constant, linear, quadratic and cubic.

*Known functional form and known knots (global functions)*

* Global-polynomials:

- Global polynomials typically are limited to either linear, Quadratic or Cubic, but can go to higher degrees.

#### 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 simplest approach is to pool the extracted trial into one , using a multi-variate meta-analysis, whilst assuming a common effect or random effects . When using random effects approach, a variety of methods is available to estimate the pooled coefficients, such as maximum likelihood, restricted maximum likelihood, method of moments or variance components. We preferred the restricted maximum likelihood, in order to be consistent with one-stage approaches. This approach only works when common powers are present across studies. Therefore, it is applicable in piecewise, global polynomials, and fractional polynomials fitted using the overall FP procedure.  
Another suggested pooling method is to pool the fitted functions. For each x in the data (pointwise) we calculate per study the fitted function and its standard error from . This is the per trial predicted line or equivalently the mean expected outcome for given x E(g(x)|X=x) and the is the confidence intervals of the predicted line. Afterwards, for each x in the data (pointwise), we calculate the pooled estimate and its SE(x), using either common or random-effects meta-analysis [26].

### 3.3.2. One-stage approaches

####3.3.2.1 Generalised additive mixed effects models

Generalised additive models are a form of penalised generalised linear models. One type of penalization is identical to the random effects’ technique introduced by McCullagh et al. [27] in the generalised mixed effects models. There we can estimate a separate functional form per trial, given the fixed effects parameters.

#### 3.3.2.2 Multilevel Fractional polynomials

Fractional polynomials may be used using a one stage approach [28]. 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 model with the lowest deviance or the Akaike Information Criterion (AIC) [30], or Bayesian Information Criterion (BIC) [31].

Therefore, the statistical model applied is:

#### 3.3.2.3 Centred One-stage IPD-MA

We follow recent recommendations [32] 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:

The and can be either piecewise polynomials, global polynomials or splines as described in section *3.3.1.1*.

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().

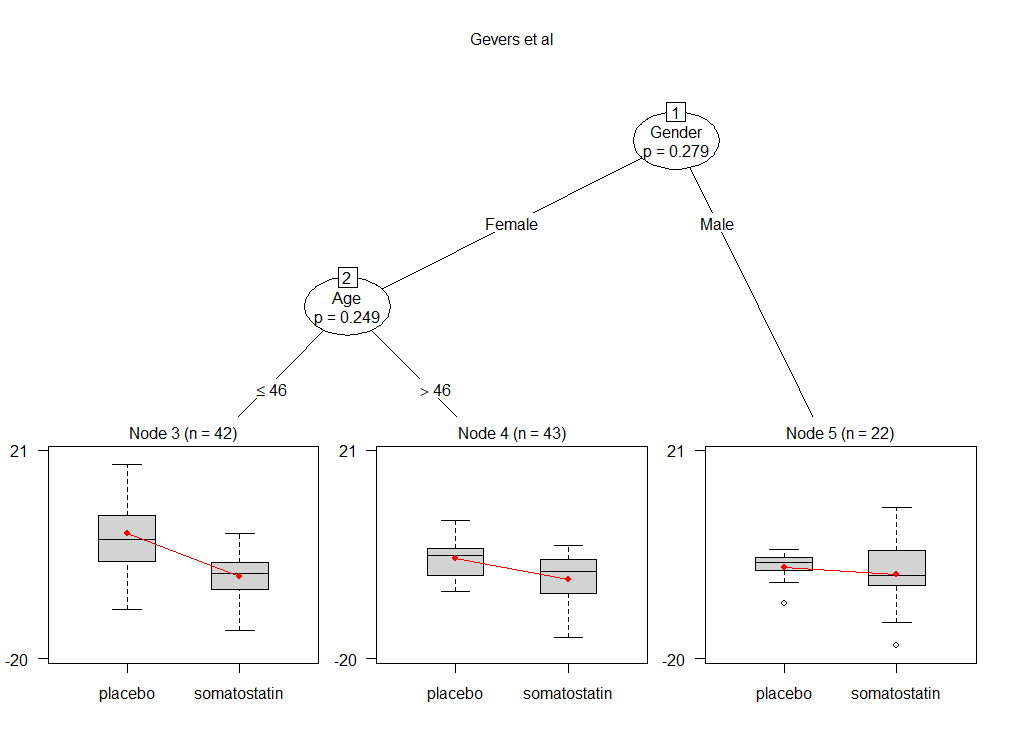
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# Results

We will illustrate the results of the aforementioned approaches beginning with the more exploratory to the more confirmatory methods. Therefore, we will start with the tree-based approach and smoothing splines, as we believe that these should be the first exploratory steps. Subsequently, we will show the results of FPs and we end with generalised linear models.

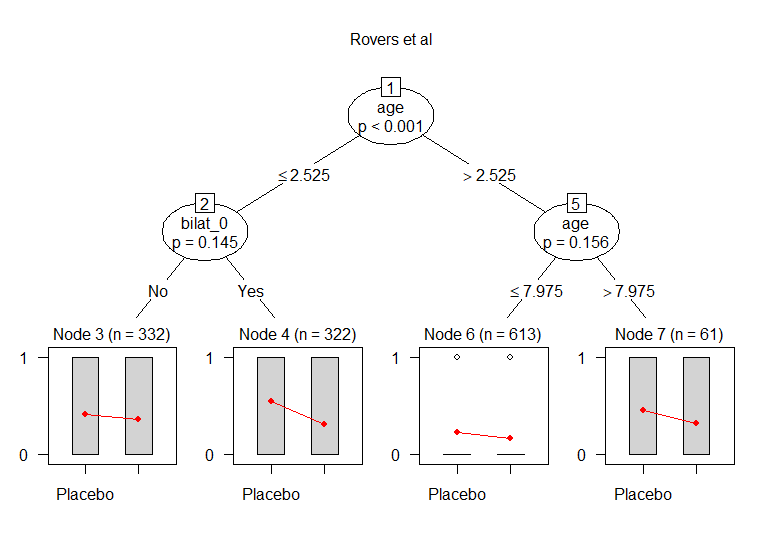
## GLMM-Trees

In the Gevers et al . data-set we increased the level of significance into α =0.3 , due to small sample size per trial.



**Figure.1 GLMM-tree for the liver data set**

We show that there is a difference between the treatment effects of males and females. Furthermore, age seems to be an effect modifier in the subgroup of females (cut-point at 46 years).

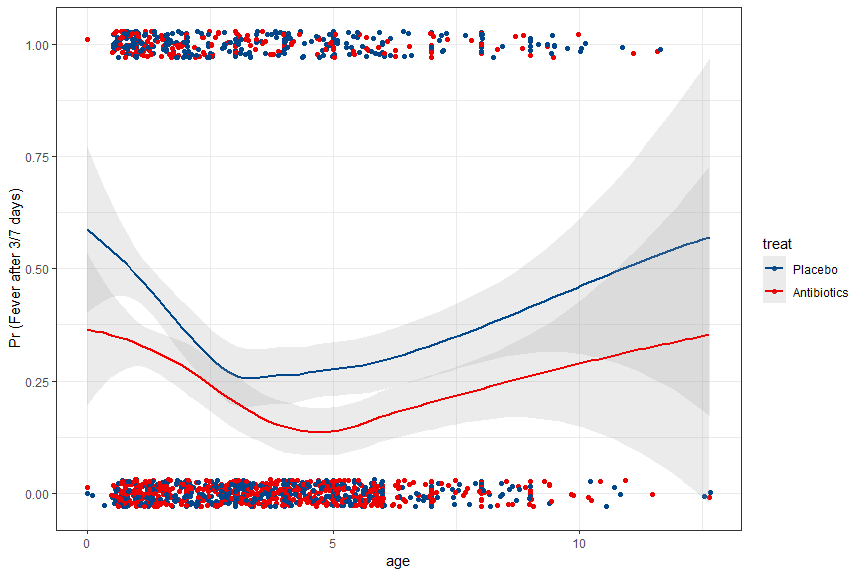
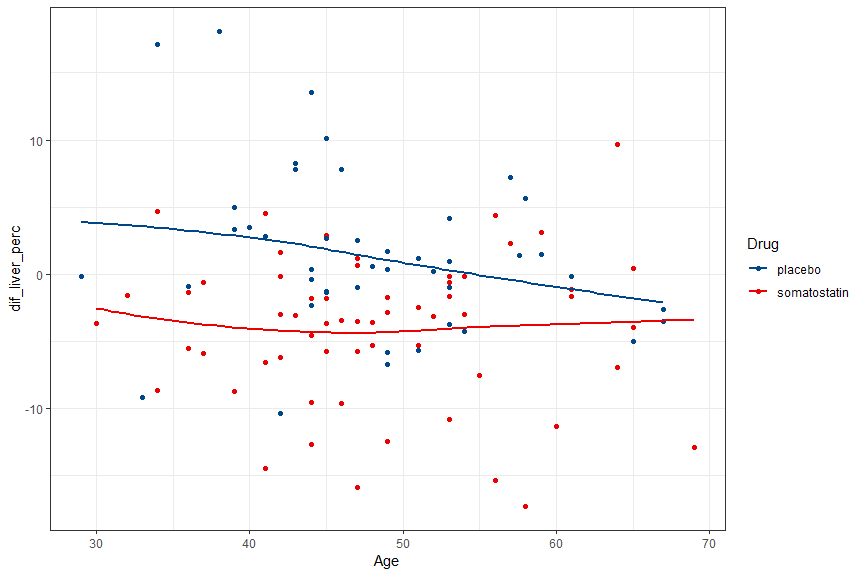


**Figure.2 GLMM-tree for the acute otitis media data set**

On the Rovers et al., dataset we show that age is a potential effect modifier and we may also have a three-way interaction with bilateral otitis.

## Regression-based approaches

We will show the results for each approach, first when performing a two-stage and then when using a one-stage method. The liver disease data set contained trials with limited number of participants, see table 1. For instance, Caroli et.al had only 1 female participant in the somatostatin group. On the other hand, Keimpema et al. and Hogan et al. had limited participation of men. Therefore, the liver data set was impossible to be analysed using two-stage approaches, for the three-way interaction we observed above. We present only the acute otitis media approach. Before starting applying regression-based techniques to model or identify interactions, we suggest to plot the data using a locally estimated scatterplot smoothing (loess) approach, in order to have a first touch with the variables and how they are associated. We will show the results for each approach, first when performing a two-stage and then when using a one-stage method. The liver disease data set contained trials with limited number of participants, see table 1. For instance, Caroli et.al had only 1 female participant in the somatostatin group. On the other hand, Keimpema et al. and Hogan et al. had limited participation of men. Therefore, the liver data set was impossible to be analysed using two-stage approaches, for the three-way interaction we observed above. We present only the acute otitis media approach. Before starting applying regression-based techniques to model or identify interactions, we suggest to plot the data using a locally estimated scatterplot smoothing (loess) approach, in order to have a first touch with the variables and how they are associated.



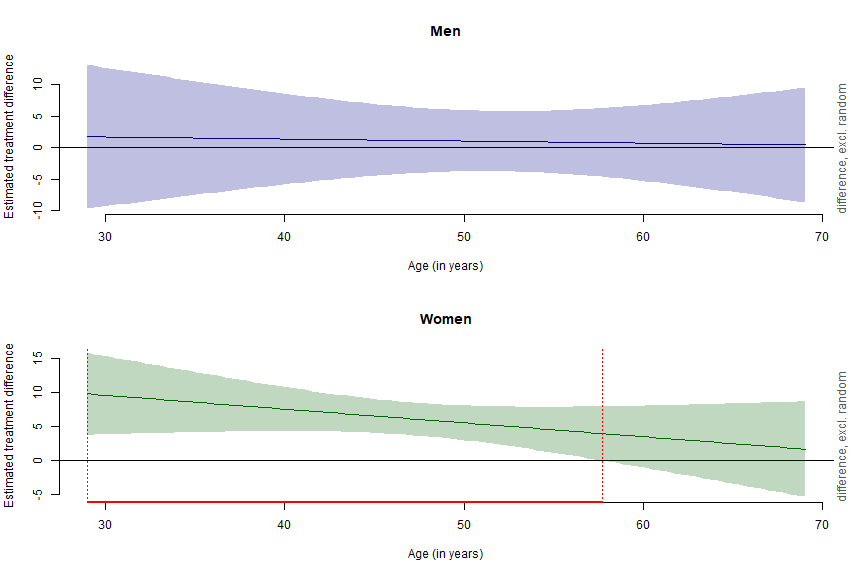
We can see a linear association in the liver data set, while in the acute otitis media data set a quadratic.

## Two-stage smoothing splines

In the acute otitis media data-set we had convergence problems and some results were unrealistic… *Interactions are problematic. This approach is difficult and needs more attention*.

## One-stage smoothing splines

In contrast with linear regression models, in smoothing spline models we cannot directly interpret the shape of the regression line from the summary estimates describing the spline function. Therefore, visualization is an important tool to investigate effect modification. We show that women younger than 57 have a treatment benefit, probably due to menopause.

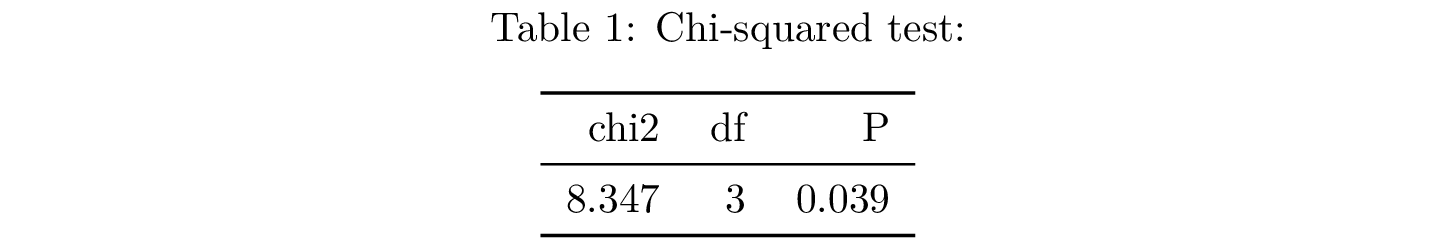
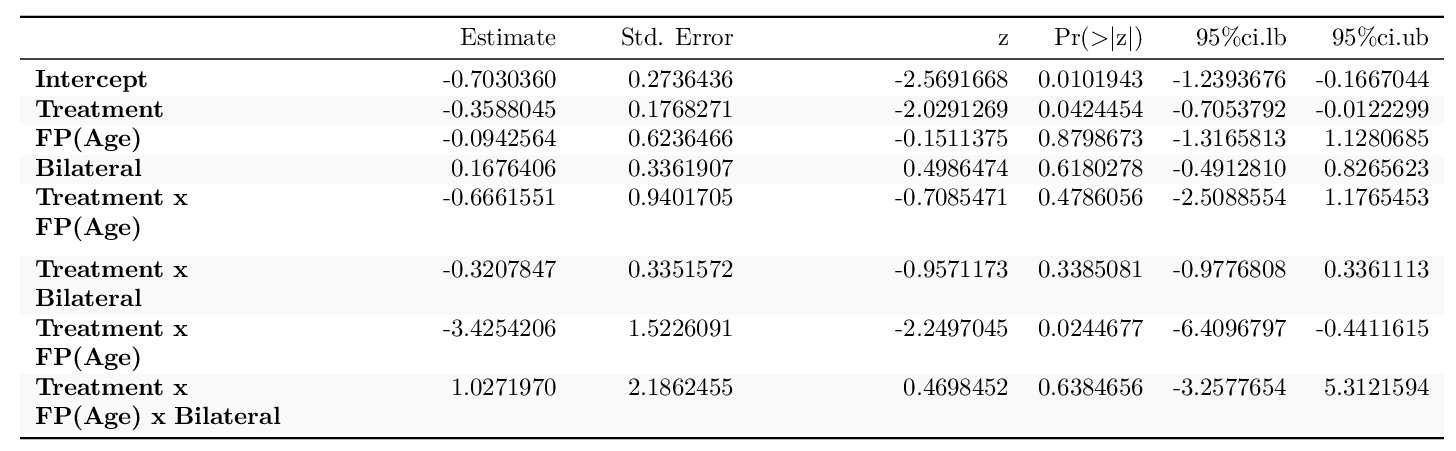


## Two-stage Fractional Polynomials

*Overall FP, where the FSP is applied in the pooled data, in order to find the best FP (stratified by data-set).*

We extracted the fractional polynomial transformations for age per treatment group and stratified per Study. Then we fit a GLM per trial with this overall FP. The FP for the somatostatin data was linear. In this method we couldn’t investigate threeway interactions, as 2 studies had insufficient **female** participants and limited sample size.

Little et al. had no information over the bilateral otitis media and Appelman et al. didn’t have enough participants to investigate the FP shape. So we droped these studies.



We couldn’t show that age is an effect modifier on 0.05 significance level.

## Study-wise FP2, the best FP2 is selected for each study

The best fitting FP2s for the somatostatin per trial suffered from the same problems as the overall FP.

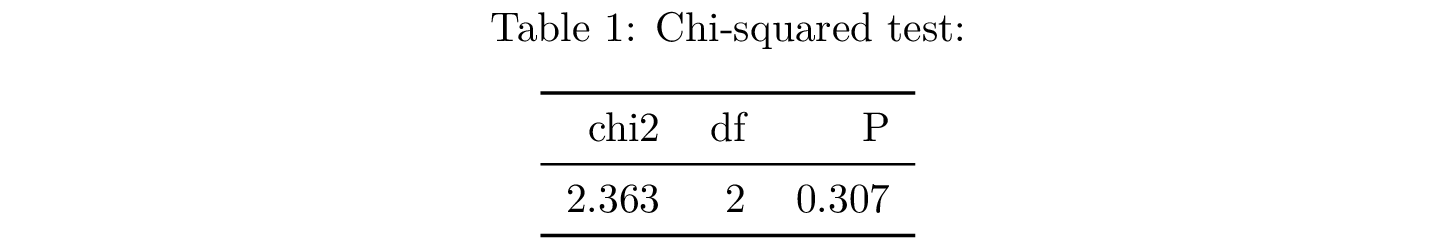
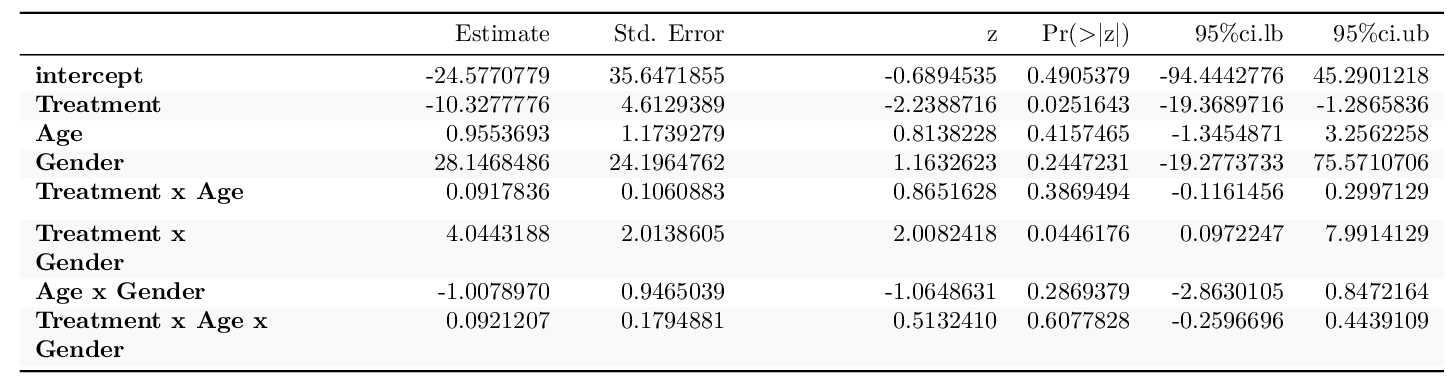
Only 2 studies (Damoiseaux, Burke) could converge using the FP2 method.

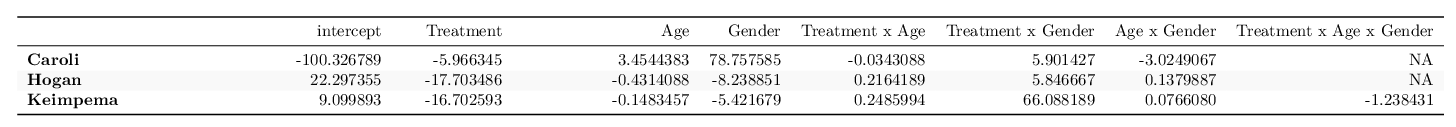
*Study wise selected FP, where the best fitting FP is extracted per study*

The best fitting FPs for the somatostatin per trial were linear, so the analysis is identical with the two-stage global polynomial.

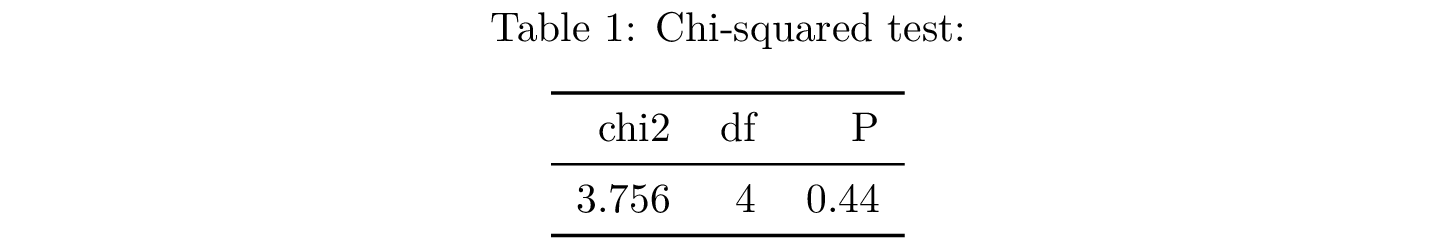
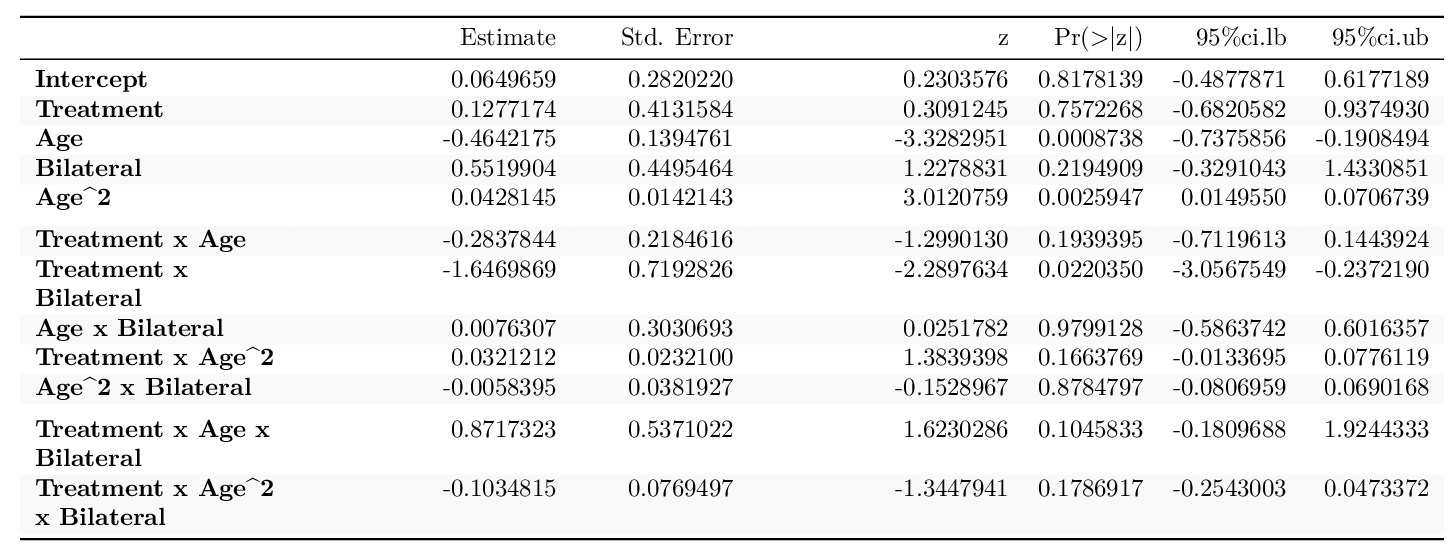
*Two-stage Global polynomials (coefficient pooling)*

For the Gevers et al. data-analysis, we assumed a linear functional form, as we had limited data (108 observations) and spending (degree of polynomial) (trial number) was considered inefficient. Furthermore, the initial pooled plot showed no significant non-linearity. In contrast, for the Rovers et al. we observed an overall quadratic shape. Damoiseaux et al. had age rounded and the participants were only 1- and 2-years old children. To avoid non-convergence of the log-binomial models we created a slight artificial deviation for the Damoiseaux et al. using the **jitter()** command.



For the liver data set the two-stage meta-analysis of interaction terms showed no statistically significant results. The reason we the same as in splines and FPs. The per trial  coefficients

Little et al had no bilateral information. The study was dropped.



*One-stage IPD-MA*

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# Discussion

In our paper, we described and illustrated a variety of approaches to explore, confirm, model or investigate for effect modification by a continuous variable. Since clinical decision making often needs to consider treatment effect in terms of available infrastructure, costs, ethical constraints and other issues, it is important to assess how treatment effect varies across relevant patient characteristics (rather than merely establishing it does vary, as is commonly done in subgroup analysis). Policy makers can then integrate all relevant evidence (such as costs) to assess which cut-points should be recommended for decision making. Our results showed that it is important to account for the outcome-variable functional shape. Furthermore, we showed that GLMM-trees can be a valuable exploratory tool to detect a potential higher-level interaction. Also, two-stage methods suffered from trial drop-outs and non-convergence, when trials with few participants were analysed.

## 5.1 Comparison with literature

Help needed

## 5.2 Strengths and limitations

The major strength of our paper is the variety of approaches we illustrated. In particular, we beside generalised linear mixed effects models we also described and illustrated one and two-stage generalised additive models using splines, two-stage fractional polynomials and we proposed a one-stage fractional polynomial approach using a similar intuitive method as Royston et al. To our knowledge this the first study describing and illustrating in empirical data sets the approaches mentioned above. Furthermore, we also wish to point out some limitations. I am writing them in bullets so that we extend them and order them and write more:

* GAM approach identifies the point where E( Y┴^\_treated-Y┴*control±1.96×SE*(Y\_treated-Y┴\_control )) crosses 0. This measure can be further developed (ideas are welcome) for example, the percentage of the wrongly treated (Joanna’s idea), posterior confidence bands (Bayesian approach)
* Our data were limited in linear and quadratic shapes
* Liver data set had small trials and didn’t converge (in two-stage approach)
* GAMs have a lot of variations nevertheless, we used the most reasonable
* No simulation so we don’t really know the truth

## 5.3 Implications for practice

## 5.4 Conclusions

We propose the use of one-stage generalised additive model with smoothing spline. This approach makes no assumptions over the functional shape and the cut-point where it changes, as its primary goal is to estimate them both. Furthermore, combined with the treatment effect plot we can easily identify the point where the treatment effect is altered, (equivalent to the CIs of the RD).

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