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

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Abstract (116 out of 200 words)

Objective

To 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 IPD-MA, mixed effects fractional polynomials, splines, meta-stepp and glmm-trees.

Study Design and Setting

We applied the aforementioned approaches into two empirical data-sets. The first is investigating the effect of somatostatin treatment versus placebo in liver reduction percentage, on participants with polycystic liver disease. The second investigates the effect of antibiotics in fever/ear-pain reduction, on children with acute otitis media(AOM).

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 be present in both categorical and/or continuous covariates. For example, differences in the treatment effect may be present between smokers and non-smokers. In this case, subgroups are already defined and therefore, only hypothesis testing may be conducted. Then the investigation of subgroup effects is performed using statistical tools, such as generalised linear models combined with meta-analytical tools, or generalised linear mixed-effects models with interaction terms included. Subsequently, the estimated coefficients are checked for statistical significance. On the other hand, effect modification across a continuous covariate is more challenging, as the subgroups are non-existent or not be a-priori known. Besides confirming an effect modification, we may be compelled to further explore also the association of the variable with the outcome.

A common technique is to categorise the continuous covariate, using some prior knowledge. Thereto, subgroups are generated using prior knowledge driven from literature. Nevertheless, this technique is only reasonable when we wish to confirm a treatment effect difference across the levels of the dichotomous variable. Furthermore, 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 linearity over the link function, a method that may also lead to deterioration of power, misspecification and even spurious results [6]. Therefore, besides confirming a variable if is an effect modifier, we may have to the explore the functional form of the outcome-effect modifier association. Various approaches to 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, fractional polynomials and smoothing splines 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 covariate while accounting also for the shape of the association. 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 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 knots in which the treatment effect is altered. These knots 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. It is also unclear if the treatment effect function [12] or interaction term analysis [13] is most appropriate 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. Although confirmatory and exploratory data analyses are almost never conducted one without the other we wish to point out that we will focus on the exploratory part. For instance, we may explore for potential effect modification and/or functional form of outcome-effect modifier association, or for effect modification on a subgroup, or how many times does the effect change over a continuous variable, and at which cut-points. We will introduce the data and the methods we used in chapter 2 and apply them on real empirical data to illustrated their performance.

2. Data

We use 2 empirical IPD-sets. The first data-set [14] was investigating the effect of antibiotics in acute otitis media on children aged from 0 to 12 years old. 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). Rovers et al. 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 also investigated separately for potential effect modification and only bilateral acute otitis media showed a significant result.

The second data-set [15] was investigating the effect of somatostatin in the liver volume reduction. Gevers et al. collected IPD from 3 randomised placebo-controlled trials with a total of 107 participants. The outcome was continuous (liver volume reduction) and age, sex, baseline liver volume, and diagnosis of autosomal dominant polycystic liver or kidney disease has been investigated for effect modification. Gevers et al. concluded that therapy using somatostatin was more beneficial for young female patients. One of the included trials [Caroli et al.] had a cross-over design, therefore participants were in both treatment groups (control and treated) in different time periods. We matched the participants per age and gender and picked half on the treated and half on the control group. Therefore, some differences between our results and those reported in the original article may occur.

Table 1: Baseline Characteristics (Rovers et al.)

	Damoiseaux		Burke		Appelman		Little		Saux		McCormick	
	Placebo	**Antibiotics**	**Placebo**	**Antibiotics**	**Placebo**	**Antibiotics**	**Placebo**	**Antibiotics**	**Placebo**	**Antibiotics**	**Placebo**	**Antibiotics**
Number of participants	123	117	118	114	54	67	164	151	254	258	111	112
Age, median [range]	**1 [1,2]**	**1 [0,2]**	**5 [3,9]**	**5 [3,9]**	**4.16 [1.07,10.22]**	**3.83 [0.65,10.19]**	**4.74 [0,10.87]**	**5.03 [0.48,11.1]**	**2.71 [0.55,5.97]**	**2.86 [0.5,6.01]**	**1.82 [0.51,12.66]**	**1.46 [0.5,12.65]**
Males (%)	66 (54%)	64 (55%)	50 (42%)	59 (52%)	25 (46%)	31 (46%)	81 (49%)	74 (49%)	131 (52%)	129 (50%)	58 (52%)	54 (48%)
RAOM (%)	50 (41%)	34 (29%)	106 (90%)	100 (88%)	48 (89%)	62 (93%)	81 (49%)	69 (46%)	48 (19%)	49 (19%)	96 (86%)	88 (79%)
Sibling (%)	123 (100%)	117 (100%)	105 (89%)	96 (84%)	NA (NA%)	NA (NA%)	NA (NA%)	NA (NA%)	169 (67%)	169 (66%)	75 (68%)	73 (65%)
Winter season (%)	79 (64%)	76 (65%)	74 (63%)	71 (62%)	40 (74%)	50 (75%)	120 (73%)	118 (78%)	225 (89%)	228 (88%)	82 (74%)	80 (71%)
Being breastfed (%)	84 (68%)	79 (68%)	NA (NA%)	NA (NA%)	NA (NA%)	NA (NA%)	118 (72%)	108 (72%)	NA (NA%)	NA (NA%)	53 (48%)	57 (51%)
Passive smoking (%)	39 (32%)	46 (39%)	NA (NA%)	NA (NA%)	NA (NA%)	NA (NA%)	31 (19%)	24 (16%)	66 (26%)	68 (26%)	82 (74%)	76 (68%)
Crying (%)	105 (85%)	100 (85%)	78 (66%)	70 (61%)	NA (NA%)	NA (NA%)	NA (NA%)	NA (NA%)	230 (91%)	237 (92%)	NA (NA%)	NA (NA%)
Runny nose (%)	99 (80%)	104 (89%)	85 (72%)	79 (69%)	45 (83%)	58 (87%)	NA (NA%)	NA (NA%)	200 (79%)	187 (72%)	NA (NA%)	NA (NA%)
Ear pain (%)	85 (69%)	82 (70%)	112 (95%)	109 (96%)	53 (98%)	66 (99%)	158 (96%)	143 (95%)	230 (91%)	236 (91%)	86 (77%)	87 (78%)
Fever (%)	86 (70%)	82 (70%)	NA (NA%)	NA (NA%)	18 (33%)	22 (33%)	12 (7%)	14 (9%)	170 (67%)	162 (63%)	1 (1%)	2 (2%)
Otorrhoea (%)	19 (15%)	16 (14%)	NA (NA%)	NA (NA%)	NA (NA%)	NA (NA%)	46 (28%)	35 (23%)	NA (NA%)	NA (NA%)	NA (NA%)	NA (NA%)
Red tympanic membrane (%)	113 (92%)	109 (93%)	115 (97%)	111 (97%)	34 (63%)	47 (70%)	133 (81%)	118 (78%)	248 (98%)	254 (98%)	111 (100%)	112 (100%)
Bulging tympanic membrane (%)	30 (24%)	26 (22%)	14 (12%)	24 (21%)	2 (4%)	2 (3%)	77 (47%)	71 (47%)	186 (73%)	195 (76%)	33 (30%)	25 (22%)

Table 2: Baseline Characteristics (Gevers et al.)

	van Keimpema et al		Hogan et al		Caroli et al	
	Placebo	**Somatostatin**	**Placebo**	**Somatostatin**	**Placebo**	**Somatostatin**
Number of participants	27	27	14	28	6	6
Age, median [range]	48 [36,68]	49 [32,65]	49 [38,65]	47 [34,69]	39 [29,53]	40 [30,59]
Female	23 (85%)	24 (89%)	13 (93%)	23 (82%)	2 (33%)	1 (17%)
Male	4 (15%)	3 (11%)	1 (7%)	5 (18%)	4 (67%)	5 (83%)
ADPKD	20 (74%)	12 (44%)	10 (71%)	24 (86%)	6 (100%)	6 (100%)
PCLD	7 (26%)	15 (56%)	4 (29%)	4 (14%)	0 (0%)	0 (0%)
Liver volume, mL , median [range]	4838.68 [1704.38,10252.145]	4129.97 [1728.19,8183.12]	4031.5 [2238.56,13148.11]	5200.355 [2234.08,11766.05]	1521.45 [1109.24,2212.05]	1577.835 [1213.89,2808.57]

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 $\bar{Age}_j$, cut-point as κ

3.2. Recursive-partitioning (tree-based) methods

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

Generalised linear mixed model trees approach is a state-of-the-art technique, proposed by Fokkema et al [10] for the detection of treatment-effect modifier interaction. 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

We identify 2 assumptions that a researcher may a-priori have. The first is over the functional form the association of the outcome with the continuous covariate have and the second one over the knots 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.

		Assumptions made	
		Cut-points	
		Known	Unknown
Functional form	Known	Piecewise polynomials Categorisation (piecewise intercept)	MFP (treatment effect plot)
	Unknown	Splines (with fixed knots)	GLMM - trees Smoothing splines META-STEPP

Table 3: Characteristics of the methods

Statistical methods	Type of second stage pooling	Fit near the edges	Cut-points	Degrees of freedom spent
	Coefficient or fitted functions pooling			
Global methods				
Fractional Polynomials (FP)	Both	medium	None	((m+1)l-1) x j
Generalised linear models	Both	Bad	None	(2l-1) x j
Generalised linear mixed effects models	NA	Bad	None	(2l-1)[FE] (2l-1) + 2*Coefs [RE] ((2l-1) x j) [FEs]
Mixed effects fractional polynomials				((m+1)l-1)[FE] ((m+1)l-1) + 2*Coefs [RE] (((m+1)l-1) x j) [FEs]
Segmented methods				
Piecewise polynomials	Both	Good	Predifined	
Splines	only fitted functions	Good	Predifined	
Natural splines	only fitted functions	Special	Predifined	
Smoothing splines	only fitted functions	Best	Not necessary	
Generalised additive models	NA	Best	Not necessary	
				Abbreviations
				l: the levels of the treatment
				k: # of the cut-points
				j: # of trials
				i: # of participants per trial
				m: order of the FP
				Coef : Coefficients with random effects
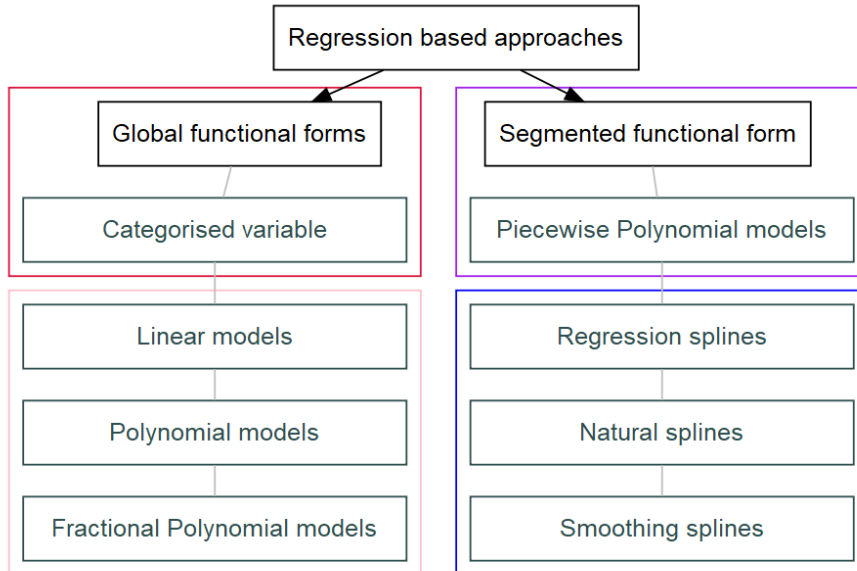
3.3.1. Two-stage approaches

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

$$g(Y_{ij}) = f_{1j}(X) + f_{2j}(X) \times Treatment$$

[1]

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 f_{1j}, f_{2j} 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 knots where the effect is altered we may fit:

For known functional form and known knots

- Piecewise-polynomials with m knots (knots)

$$f_1 = \sum_{\kappa=1}^{\kappa=m} f_{1\kappa}(X_{x_{k-1} \leq X < x_{k-1}}) f_2 = \sum_{\kappa=1}^{\kappa=m} f_{2\kappa}(X_{x_{k-1} \leq X < x_{k-1}})$$

Piecewise-polynomials mostly used are piecewise intercepts, linear, quadratic and cubic, where:
  - Piecewise-intercept: within each interval [a ,b] both f1, f2 have the form of $\beta_{[a,b]}$
  - Piecewise-linear: within each interval [a ,b] both f1, f2 have the form of $\beta_{0[a,b]} + \beta_{1[a,b]} \times X$
  - Piecewise-quadratic: within each interval [a ,b] both f1, f2 have the form of $\beta_{0[a,b]} + \beta_{1[a,b]} \times X + \beta_{2[a,b]} \times X^2$

Known functional form and no knots

- Global-polynomials:

$$f_1 = \sum_{p=1}^{p=m} \beta_{1p} \times X^p$$

$$f_2 = \sum_{p=1}^{p=m} \beta_{2p} \times X^p$$

  - linear: $f_1 = \beta_{10} + \beta_{11} \times X, f_2 = \beta_{20} + \beta_{21} \times X$
  - Quadratic: $f_1 = \beta_{10} + \beta_{11} \times X + \beta_{12} \times X^2, f_2 = \beta_{20} + \beta_{21} \times X + \beta_{22} \times X^2$
  - Cubic: $f_1 = \beta_{10} + \beta_{11} \times X + \beta_{12} \times X^2 + \beta_{13} \times X^3, f_2 = \beta_{20} + \beta_{21} \times X + \beta_{22} \times X^2 + \beta_{23} \times X^3$

Smoothing splines

Splines are a generalisation of piecewise polynomials and can offer great flexibility in the shape of the outcome-effect modifier association. Regression splines of an **m** degree, should be continuous, have **m-1** continuous derivatives and the mth derivative should constant with 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 in the edges κ_0, κ_m of the association is 0. This is a something that should be considered when the goal of our research is to forecast future outcomes such as in some longitudinal or time series studies.

Typically, when using splines the real underlying shape is not known. Furthermore, the knots may not be known already, and may be part of the exploratory analysis we are performing. We can introduce even more flexibility into our model a perform smoothing splines. Smoothing splines are by-pass the problem of knot selection by shrinking the coefficients to their basis expansion. In order to do so, they minimise a

penalised least squares criterion or equivalently the maximum likelihood with an extra parameter to penalise the wingliness of the line, $MLE + \lambda \int_0^1 [f''(x)]^2 dx$ equivalently $||y - X\beta||^2 + \lambda \int_0^1 [f''(x)]^2 dx$ or in algebraic form $||y - X\beta||^2 + \lambda \beta^T S \beta$.

Fractional polynomials

Unknown functional form and unknown knots

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 $f(x; \beta) = \sum_{k=1}^{k=m} \beta_k \times X^{p_k}$, where m is the degree of the fractional polynomial and the power is derived from a fixed set of powers $p_k \in S : \{-2,-1,-0.5, 0=(\log),0.5,1,2\}$. 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 χ^2 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, 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

3.3.1.2 Second-stage combination of the first stage elicitations

As a second-stage in the two-stage IPD-MA, we may either pool the estimates or the fitted functions extracted from the first stage. The coefficients β_i and SE_i, extracted in the first stage can be used in a multi-variate meta-analysis (CE or RE) to give an overall mean to extract the pooled b_0 and its 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 τ^2 estimation [21] and the HKSJ adjustment [22].

The fitted function g can be calculated per study $\hat{g}_i(x; \beta_i)$ and derive its standard error from S_i. Then we perform a meta-analysis, to get a pooled estimate $\hat{g}_i(x; \beta_i)$ and its 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 $X_{ij} = Age_{ij} - \bar{Age}_j$ the statistical model will be:

$g(Y_{ij}) = f_{1j}(X) + f_{2j}(X) \times Treatment$

The f_{1j} and f_{2j} can be either piecewise polynomials, global polynomials or splines as described in section *3.3.1.1*. This

For the β_{1kpj} and β_{2kpj} 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(b, σ^2).

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:

$g(Y_{ij}) = FP_{1j}(X) + FP_{2j}(X) \times Treatment$

Results

We illustrate the results of the aforementioned approaches by ascending order of assumptions made. Therefore, we will start with the tree-based approach and smoothing spline, as we believe that these should be the first "exploratory" steps. We increased the level of significance, due to small sample size per trial.

Gevers et al
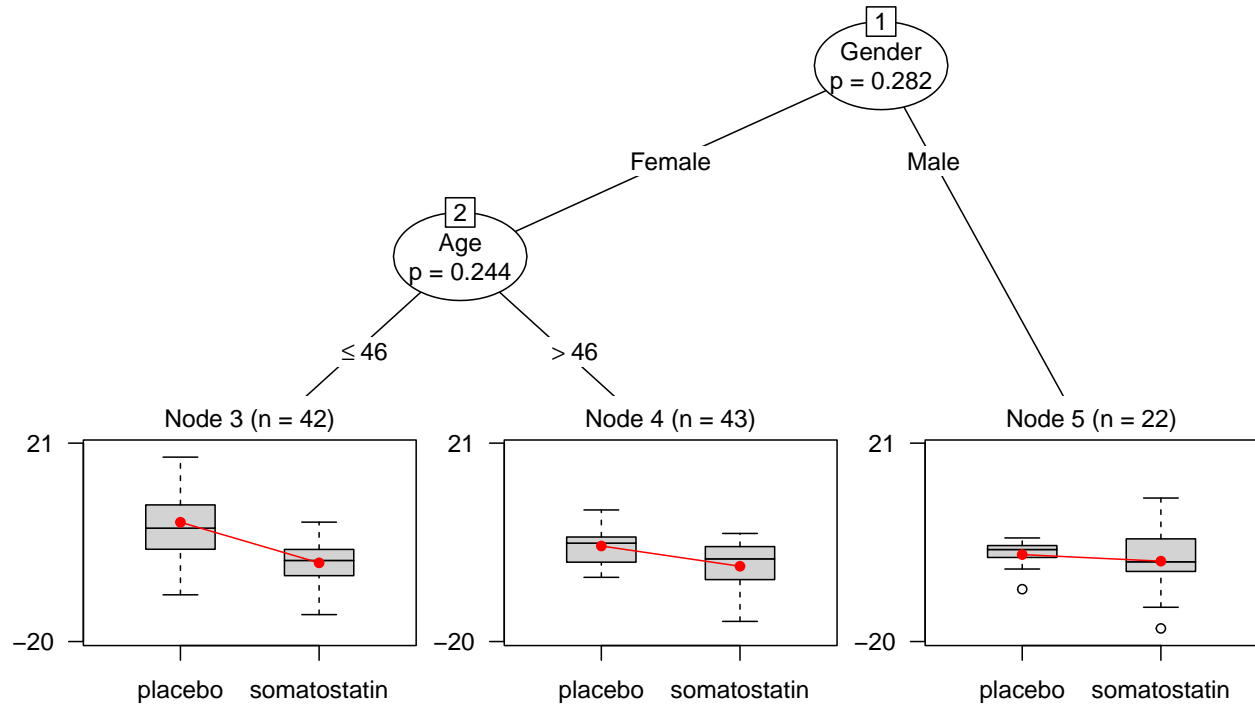
We show that there is a difference between the average outcomes of male and females. This difference seems to emanate from young women ($\leq$ 46 years).
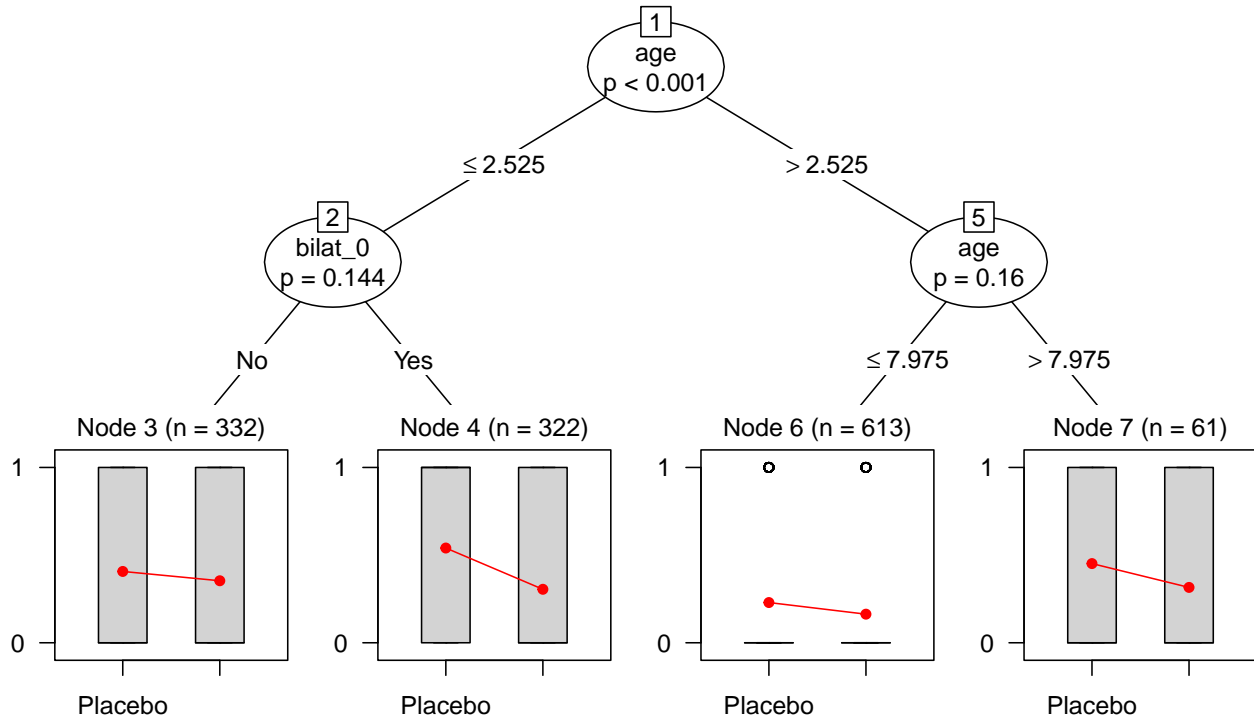
Rovers et al

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

Two-stage smoothing splines

In contrast with linear regression models, in nonlinear models we cannot interpret the shape of the regression line from the summary. Therefore, visualization is an important tool for interpretating nonlinear regression models. Here a selection of visualization functions is summarized. Detailed information on the functions and examples are found in the help files of each function.

```
Summary:
    * bilat_0 : factor; set to the value(s): Yes.
    * treat : factor; set to the value(s): Antibiotics.
    * age : numeric predictor; with 30 values ranging from 0.000000 to 12.655556.
    * study : factor; set to the value(s): Saux. (Might be canceled as random effect, check below.)
    * NOTE : The following random effects columns are canceled: s(age,study)


Summary:
    * bilat_0 : factor; set to the value(s): Yes.
    * treat : factor; set to the value(s): Placebo.
    * age : numeric predictor; with 30 values ranging from 0.000000 to 12.655556.
    * study : factor; set to the value(s): Saux. (Might be canceled as random effect, check below.)
    * NOTE : The following random effects columns are canceled: s(age,study)


Summary:
    * bilat_0 : factor; set to the value(s): No.
    * treat : factor; set to the value(s): Antibiotics.
    * age : numeric predictor; with 30 values ranging from 0.000000 to 12.655556.
    * study : factor; set to the value(s): Saux. (Might be canceled as random effect, check below.)
```
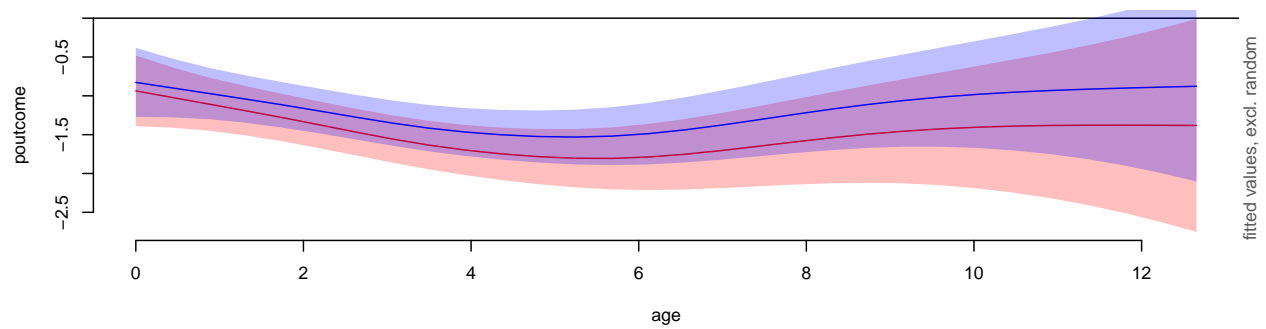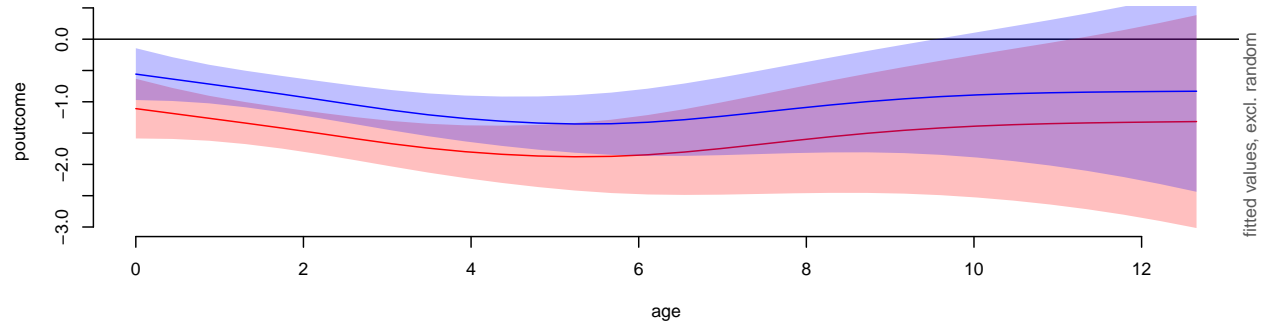
```
 * NOTE : The following random effects columns are canceled: s(age,study)
```



```
Summary:
    * bilat_0 : factor; set to the value(s): No.
    * treat : factor; set to the value(s): Placebo.
    * age : numeric predictor; with 30 values ranging from 0.000000 to 12.655556.
    * study : factor; set to the value(s): Saux. (Might be canceled as random effect, check below.)
    * NOTE : The following random effects columns are canceled: s(age,study)
```

Two-stage GLMs

In two-stage meta-analysis of interaction terms using linear assumptions, effect modification across age was not statistically significant.
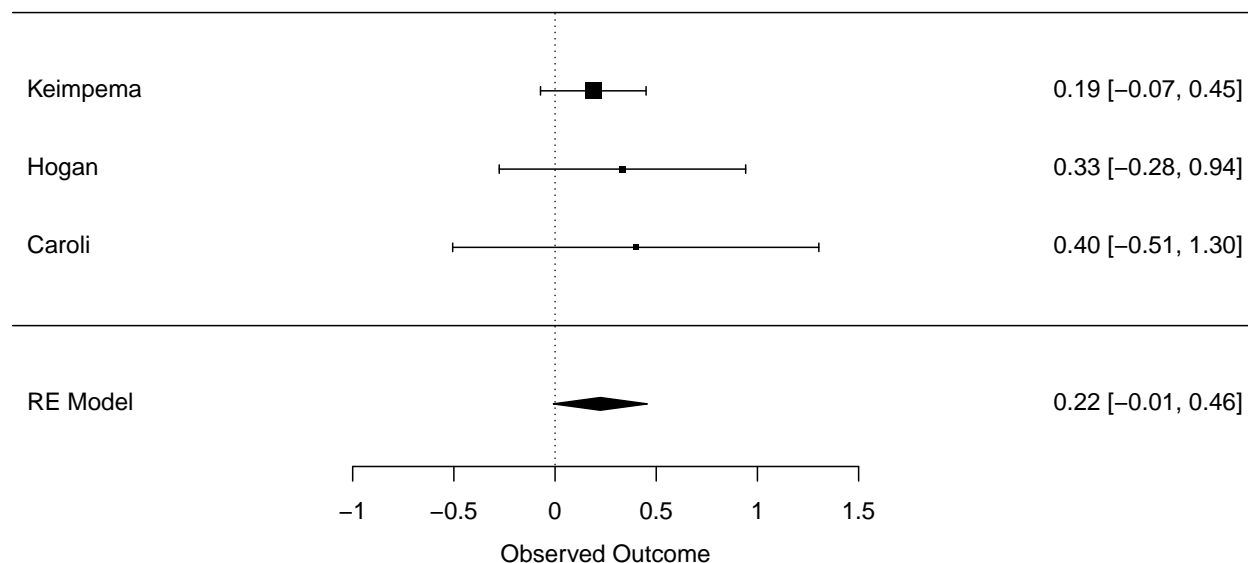
One-stage IPD-MA (linear assumption)

```
Linear mixed model fit by REML ['lmerMod']
Formula: dif_liver_perc ~ Drug * Age * Gender + (Drug | Study) + (1 |
    Study)
   Data: somatostatin
Control: lmerControl(calc.derivs = F)

REML criterion at convergence: 664.9

Scaled residuals:
    Min      1Q  Median      3Q     Max
-2.7131 -0.6030  0.0445  0.5571  2.4456

Random effects:
 Groups    Name              Variance Std.Dev. Corr
 Study     (Intercept)        0.000   0.000
           Drugsomatostatin   1.032   1.016         NaN
 Study.1   (Intercept)        0.000   0.000
 Residual                    31.339   5.598
Number of obs: 107, groups:  Study, 3

Fixed effects:
                              Estimate Std. Error t value
(Intercept)                    13.9046     5.7150   2.433
Drugsomatostatin              -15.7069     7.4472  -2.109
Age                            -0.2496     0.1196  -2.087
GenderMale                    -20.3847    10.7828  -1.891
Drugsomatostatin:Age            0.2011     0.1549   1.298
Drugsomatostatin:GenderMale    13.3882    14.4564   0.926
Age:GenderMale                  0.3350     0.2094   1.599
Drugsomatostatin:Age:GenderMale -0.1807    0.2796  -0.646

Correlation of Fixed Effects:
           (Intr) Drgsmt Age    GndrMl Drgs:A Drg:GM Ag:GnM
Drugsmtsttn -0.767
```

```
Age        -0.987  0.757
GenderMale  -0.530  0.407  0.523
Drgsmtstt:A  0.762 -0.982 -0.772 -0.404
Drgsmtst:GM  0.395 -0.514 -0.390 -0.746  0.502
Age:GendrMl  0.564 -0.433 -0.571 -0.980  0.441  0.731
Drgsmt:A:GM -0.422  0.547  0.428  0.734 -0.551 -0.981 -0.749
```

```
Generalized linear mixed model fit by maximum likelihood (Laplace
  Approximation) [glmerMod]
 Family: binomial  ( log )
Formula:
poutcome ~ treat * age * bilateral + (treat | study) + (1 | study)
   Data: IPDMA
Control: glmerControl(calc.derivs = F)

     AIC      BIC   logLik deviance df.resid
  1588.5   1650.8   -782.3   1564.5     1316


Scaled residuals:
    Min      1Q  Median      3Q     Max
-1.2318 -0.6599 -0.5449  1.0986  2.7717


Random effects:
 Groups  Name               Variance  Std.Dev.  Corr
 study   (Intercept)        5.627e-02 0.2372195
         treatAntibiotics   9.267e-04 0.0304419 1.00
 study.1 (Intercept)        1.139e-07 0.0003374
Number of obs: 1328, groups:  study, 5

Fixed effects:
```

	Estimate	Std. Error
(Intercept)	-1.05624	0.17275
treatAntibiotics	-0.09482	0.19328
age	-0.05066	0.03648
bilateralBilateral acute otitis	0.39116	0.16981
treatAntibiotics:age	-0.03742	0.05357
treatAntibiotics:bilateralBilateral acute otitis	-0.52329	0.27492
age:bilateralBilateral acute otitis	-0.05470	0.06316
treatAntibiotics:age:bilateralBilateral acute otitis	0.07214	0.10027

	z value	Pr(>|z|)	
(Intercept)	-6.114	9.71e-10	***
treatAntibiotics	-0.491	0.6237	
age	-1.389	0.1649	
bilateralBilateral acute otitis	2.304	0.0212	*
treatAntibiotics:age	-0.699	0.4848	
treatAntibiotics:bilateralBilateral acute otitis	-1.903	0.0570	.
age:bilateralBilateral acute otitis	-0.866	0.3865	
treatAntibiotics:age:bilateralBilateral acute otitis	0.719	0.4719	

```
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1


Correlation of Fixed Effects:
          (Intr) trtAnt age    bltBao trtAn: tA:Bao ag:Bao
tretAntbtcs -0.430
```
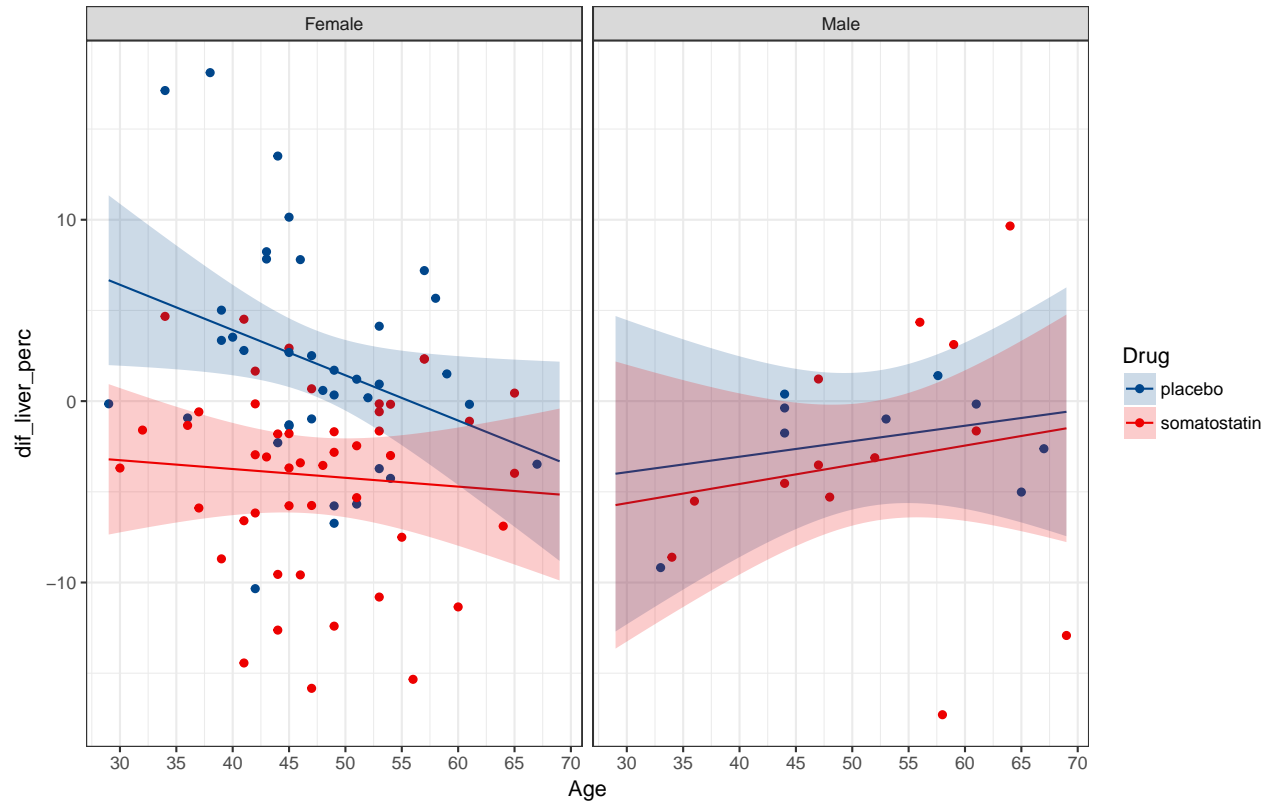
```
age           -0.656   0.494
bltrlBltrao  -0.534   0.494   0.546
trtAntbtcs:   0.380  -0.819  -0.584  -0.400
trtAntb:Bao   0.338  -0.699  -0.352  -0.599   0.576
ag:bltrlBao   0.334  -0.293  -0.505  -0.766   0.347   0.463
trtAnt::Bao  -0.205   0.438   0.312   0.475  -0.535  -0.769  -0.623
```
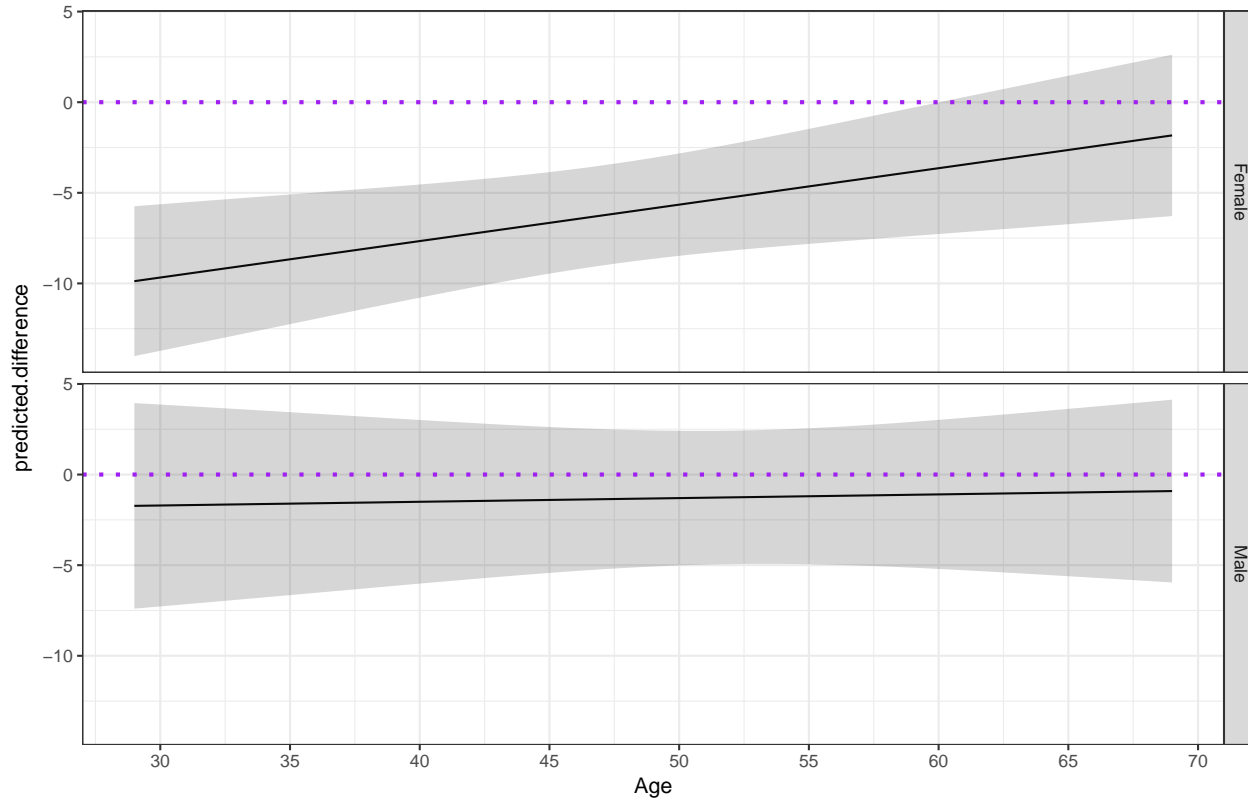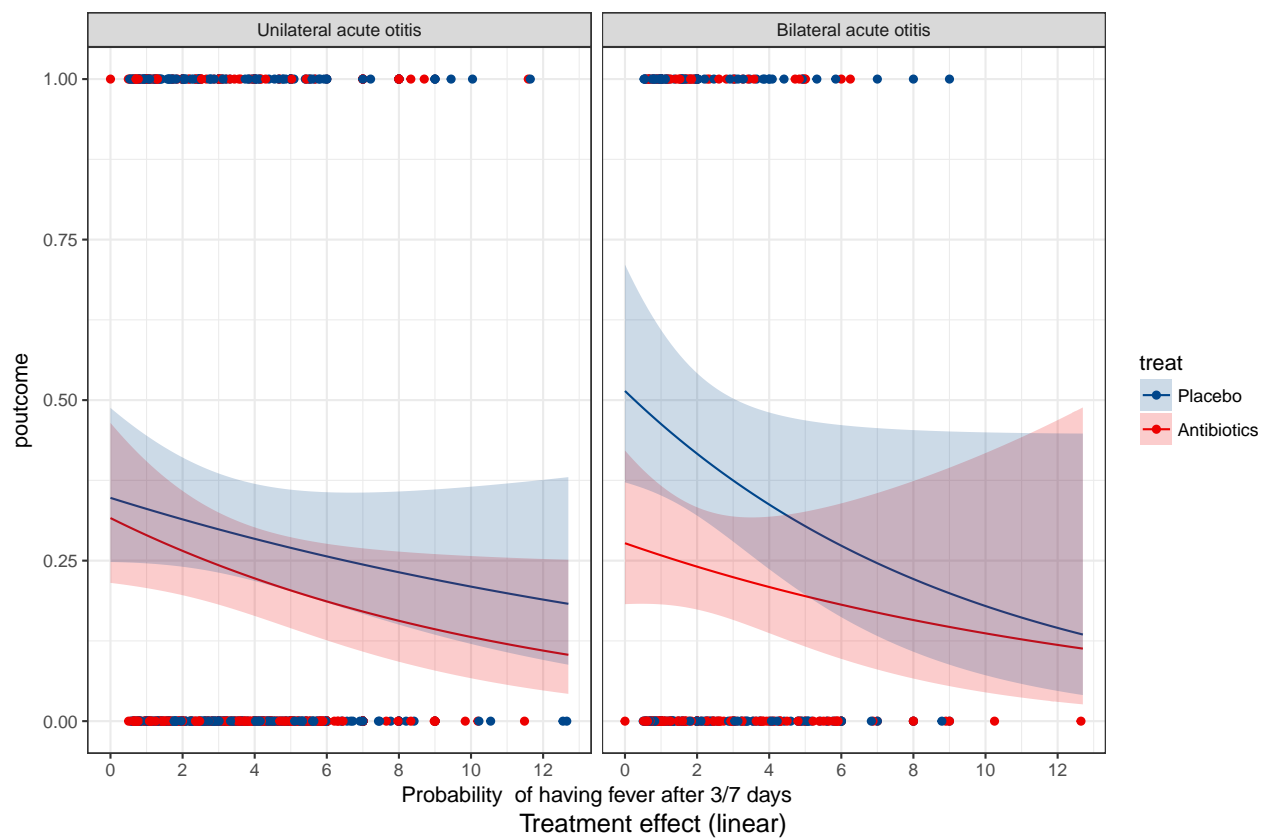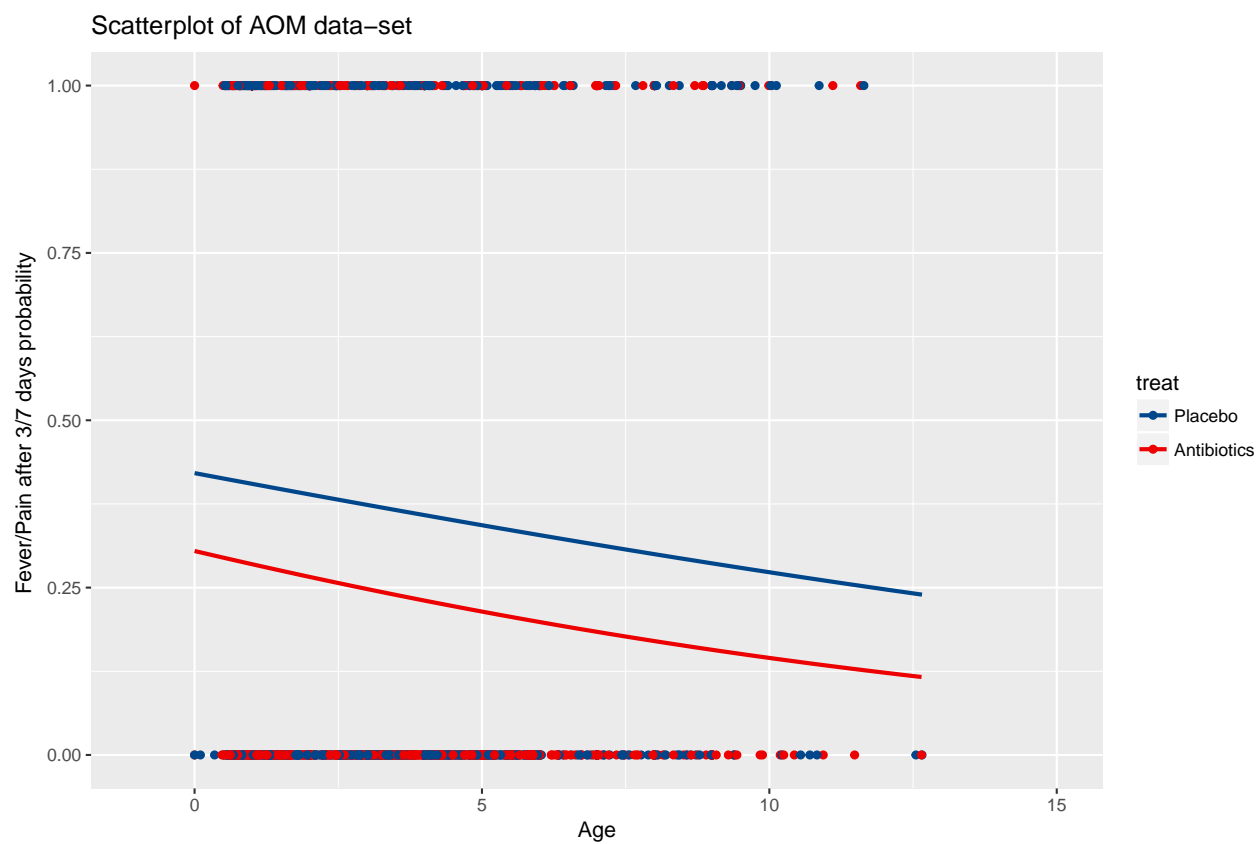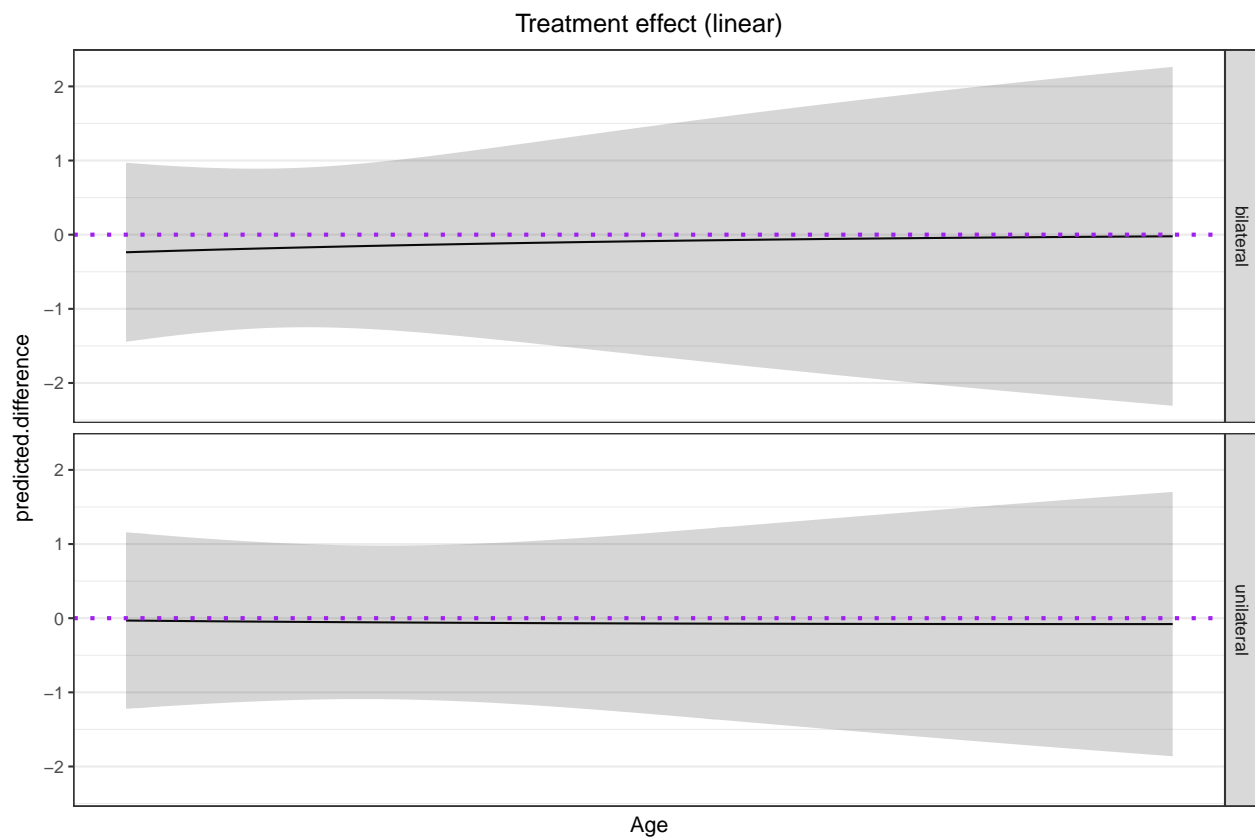

Liver difference over age

Fever probability across age

Treatment effect (linear)

Treatment effect (linear)

Scatterplot of AOM data−set

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.

[2] Altman DG. The cost of dichotomising continuous variables. BMJ 2006;332:1080–0. doi: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.

[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.

[5] Weinberg C. How bad is categorization? Epidemiology 1995;6:345–6. doi: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.

[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.

[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.

[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.

[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.

[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.

[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.

[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.

[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.

[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.

[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.

[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.

[18] Royston P, Altman DG. Regression using fractional polynomials of continuous covariates: Parsimonious parametric modelling. Applied Statistics 1994;43:429. doi: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.

[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.

[21] Stijnen T, Houwelingen JCV. Empirical bayes methods in clinical trials meta-analysis. Biometrical Journal 2007;32:335–46. doi: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.

[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.

[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.

[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.

[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.

[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.

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