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 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.

4. 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 instance, differences in the treatment effect may be present between smokers and non-smokers, or across the levels of the age of the patient. If subgroups are already defined only hypothesis testing may be conducted, using statistical tools such as generalised linear models combined with meta-analytical tools, or generalised linear mixed-effects models with interaction terms included. On the other hand, effect modification across a continuous variable is more challenging, as the subgroups are non-existent. Furthermore, besides confirming an effect modification, we may be compelled to state at what point does the treatment effect changes.

A common technique is to categorise the continuous covariate. Thereto, subgroups are created using prior knowledge driven from literature. Nevertheless, this technique is only reasonable when we wish to confirm that the treatment effect is different between the levels of the categorised variable. For example, if we want to investigate women before and after menopause, we can categorise age in a fixed value between 40 and 50, according to our beliefs. As a consequence, categorisation has been criticised for misspecification, loss of information and power, inflation of the type I error rate when adjusting for confounding and even 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 whether a variable is an effect modifier, we have to 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 (FP) [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 coefficients, if commone across the trials, or their fitted functions 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 model interactions between treatment and patient-level variables, while accounting also for the shape of its association 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. Within trials clustering can be accounted using either fixed effects (stratified intercept/slope), fixed effect (common intercept/slope) or random effects (intercept and/slopes driven from a common Normal distribution) [9]. Furthermore, state-of-the-art plot and tree-based methods have been developed for exploring effect modification. Generalised linear mixed-effects model trees (GLMM-tree) introduced by Fokkema et al. [10] can handle non-linear associations, whilst accounting for within studies clustering of the participants. Furthermore, since they don't use assumptions GLMM-trees can be used for exploratory data-analysis. Finally, meta-stepp is a plot based moving average (sliding window) method that approximates non-linear effects from clustered data [11]. Although, providing the whole information of the outcome-continuous effect modifier association is more informative, clinical decisions are based in cut-points (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 more appropriate and when. We aim to describe and illustrate the aforementioned methods. We will introduce the IPD-sets and the methods we used in chapter 2.

2. Example datasets

We used 2 IPD-sets to illustrate our methods. 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 investigated also separately for potential effect modification and only bilateral acute otitis media showed a significant result.

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. 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.

Table 1: 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%)
Log-scaled Liver volume difference, median [range]	0.011 [-0.038,0.079]	-0.018 [-0.19,0.043]	-0.006 [-0.109,0.166]	-0.034 [-0.172,0.092]	-0.006 [-0.096,0.158]	-0.05 [-0.09,0.031]

Table 2: 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%)
Bilateral AOM (%)	76 (62%)	75 (64%)	16 (14%)	16 (14%)	6 (11%)	14 (21%)	NA (NA%)	NA (NA%)	74 (29%)	79 (31%)	48 (43%)	52 (46%)
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%)

3. Methods

3.1 Notation

As described in section 2, both our datasets are composed of multiple trials. Therefore, we introduce some notation that will be used hereto.

We are denoting:

- The studies as j = 1,2 ,. . . ,J,
- Individuals as i = 1,2 ,. . . ,I,
- The per trial mean of age as $\bar{Age}_j$
- The per trial centred age as X = $\bar{Age}_j - Age_{ij}$
- Knot (cut-point) as κ
- The degree of a fractional polynomial as m
- The degree of a polynomial as p

3.2. Recursive-partitioning (tree-based) methods

Recursive partitioning is a statistical method typically used in multivariable analysis [16]. A decision tree is generated by dichotomising the variable in cut-points were the outcome is differed. Recursive partitioning techniques can handle non-linear associations as they make no functional form assumptions and 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. However, splitting the data-set into clusters is sensitive and minor changes in the data may lead to completely different trees. Therefore, leaving the within trial clustering unaccounted may lead to erroneous results.

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 when we have clustered data. In our case, we assume that the participants are clustered within the trials A model-based recursive partitioning [17,18] algorithm is applied, while also considering the clustered structure of datasets.

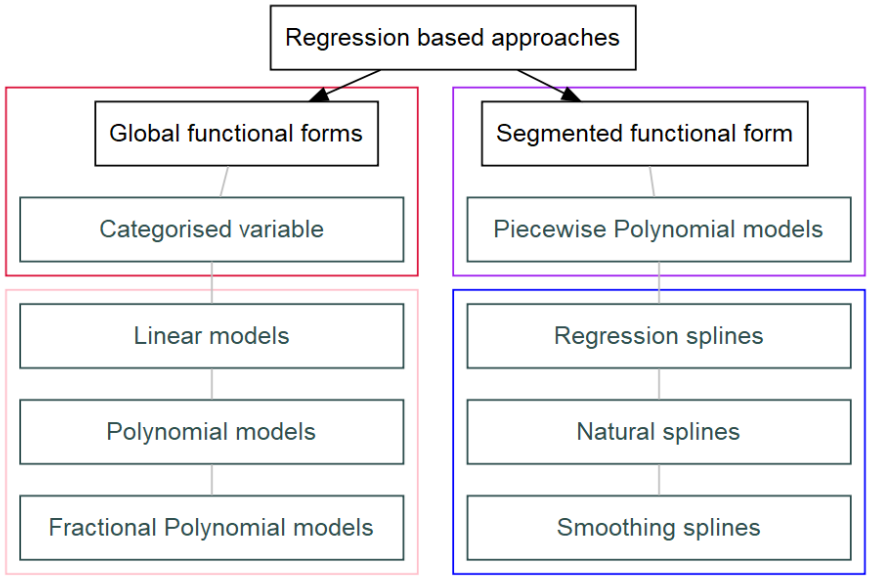
The GLMM tree algorithm:

(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, modelling will be straightforward. However, if not, splines and/or fractional polynomials may be used to evaluate the functional form of the association. Another aspect to take into consideration while modelling the functional form, is whether there may be cut-points (knots) where the shape of the association changes. If these exist, this should be also taken into consideration. Again, if the cut-points are known, modelling will be more straightforward than when they are unknown. These two dimensions define how to proceed with the regression model.

		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



Finally, within trial clustering should be accounted [19]. This may be achieved, as described in introduction, either by conducting a two-stage meta-analysis, or using a mixed effects models or an equivalent method in one-stage approaches. Therefore, we will begin the two-stage methods and then describe the one-stage approaches. Within each section we will begin with the global functional forms as they make more assumptions and gradually describe methods that offer more flexibility.

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:

$$g(Y_{ij}) = \hat{f}_{1j}(X) + \hat{f}_{2j}(X) \times Treatment \quad [1]$$

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

Table 3: Characteristics of the methods

Statistical methods	Type of second stage pooling	Fit near the edges	Cut-points	Degrees of freedom spent	Difficulty	Converged	Trials excluded
	Coefficient or fitted functions pooling			[Liver data, AOM data]			[Liver data, AOM data]
Global methods							
Fractional Polynomials (FP)	Both	medium	None	[21 , 32]	Easy	Only overall FP method	[0 , 3]
Generalised linear models	Both	Bad	None	[21,]	Easy		
Generalised linear mixed effects models	NA	Bad	None		Moderate		
Mixed effects fractional polynomials					Moderate		
Segmented methods							
Piecewise polynomials	Both	Good	Predifined		Difficult		
Splines	only fitted functions	Good	Predifined	[8.6, 13.79]	Moderate		
Natural splines	only fitted functions	Special	Predifined		Moderate		
Smoothing splines	only fitted functions	Best	Not necessary		Moderate		
Generalised additive models	NA	Best	Not necessary	[8.6, 13.79]	Difficult		
				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			

The functions $\hat{f}_{1j}, \hat{f}_{2j}$ 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 cut-points where the effect is altered we may fit.

Known functional form and known $\kappa = 0$ knots (global functions)

- Global-polynomials:

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

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

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

Known functional form and known $\kappa \geq 1$ knots and known position of the knots (segmented functions)

- Piecewise-polynomials with κ knots

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

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

Unknown functional form and known $\kappa = 0$ knots (global function)

Fractional polynomials [20] 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 [21] 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

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 p^{th} 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 k_0, k_κ 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, $MLE + \lambda \int_0^1 [f^{''}(x)]^2 dx$ equivalently $||y - X\beta||^2 + \lambda \int_0^1 [f^{''}(x)]^2 dx$ or in algebraic form $||y - X\beta||^2 + \lambda \beta^T S \beta$.

3.3.1.2 Second-stage combination of the first stage results

As a second-stage in the two-stage IPD-MA, we may either pool the estimates or the fitted functions $\hat{f}_{1j}(X)$, $\hat{f}_{2j}(X)$ extracted from the first stage. The simplest approach is to pool the extracted per trial $beta_{kj}$ into one b_k, using a multi-variate meta-analysis, whilst assuming common effect or random effects. 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. We applied a random-effects meta-analysis, using the EB method for the τ^2 estimation [23] and the HKSJ adjustment [24].

Another suggested pooling method is to pool the fitted functions. For each x in the data (pointwise) we calculate per study the fitted function $\hat{g_j}(x; \beta_j)$ and its standard error from $SE_j(x)$. This $\hat{g_j}(x; \beta_j)$ is the per trial predicted line or equivalently the mean expected outcome for given X E(g(x)|X) and the $S_j(x)$ is the confidence intervals of the predicted line. Afterwards, for each x in the data (pointwise), we calculate the pooled estimate $\hat{g}(x)$ and its SE(x), using either common or random-effects meta-analysis [26].

3.3.2. One-stage approaches

3.3.2.1 Centred One-stage IPD-MA

We follow recent recommendations [27] 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 $X_{ij} = Age_{ij} - \bar{A}ge_j$ the statistical model will be:

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

The $\hat{f}_{1j}$ and $\hat{f}_{2j}$ 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 $\mathrm{N}(b, \sigma^2)$.

3.3.2.2 Multilevel Fractional polynomials

Fractional polynomials may be used using 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 lowest deviance or the Akaike Information Criterion (AIC) [30], or Bayesian Information Criterion (BIC) [31].

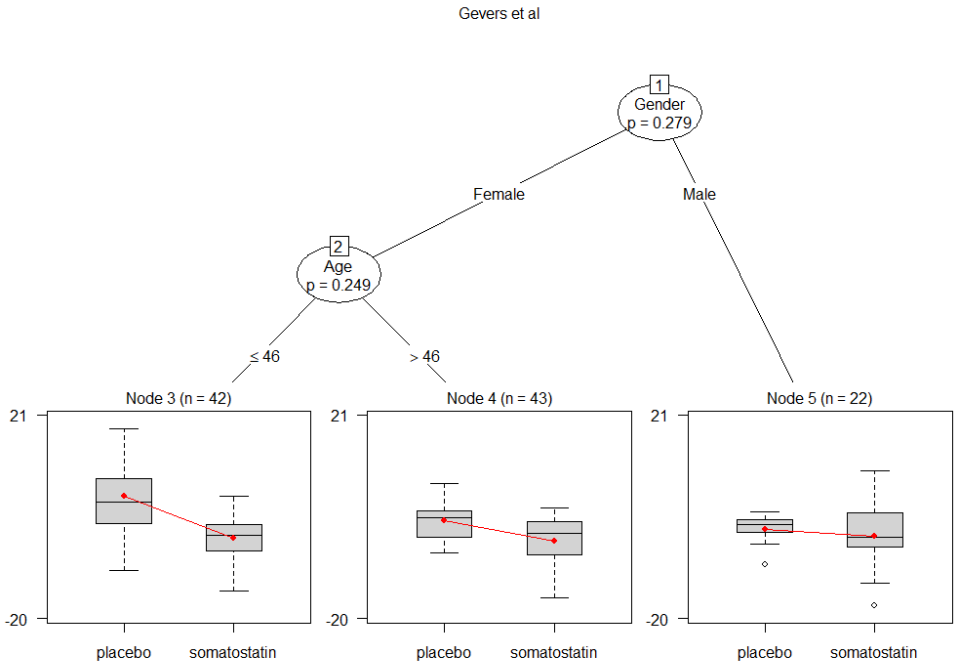
Therefore, the statistical model applied is:

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

Results

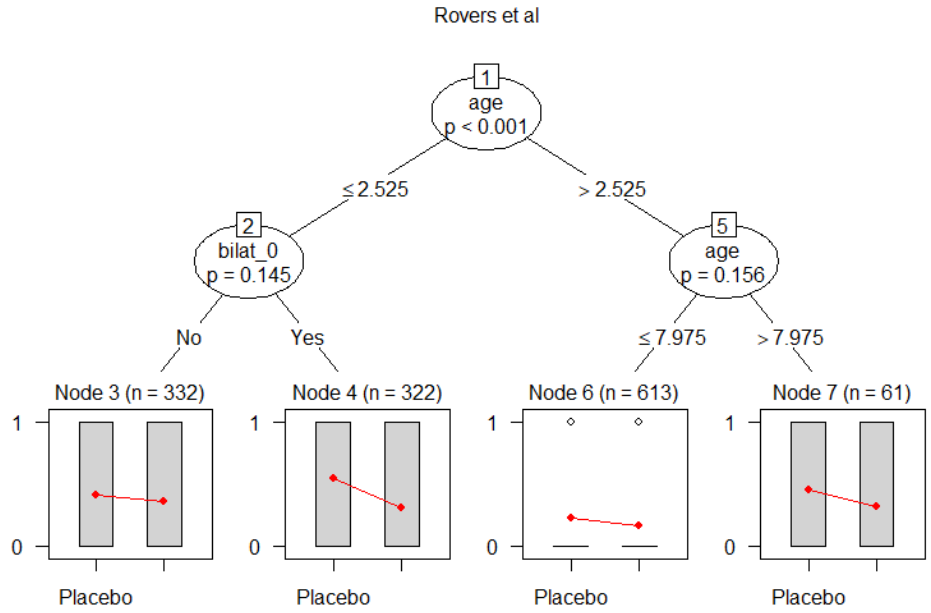
We will illustrate the results of the aforementioned approaches by ascending order of assumptions made. Therefore, we will start with the tree-based approach and smoothing splines, as we believe that these should be the first "exploratory" steps. In the Gevers et al. data-set we increased the level of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

Lmer trees



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).

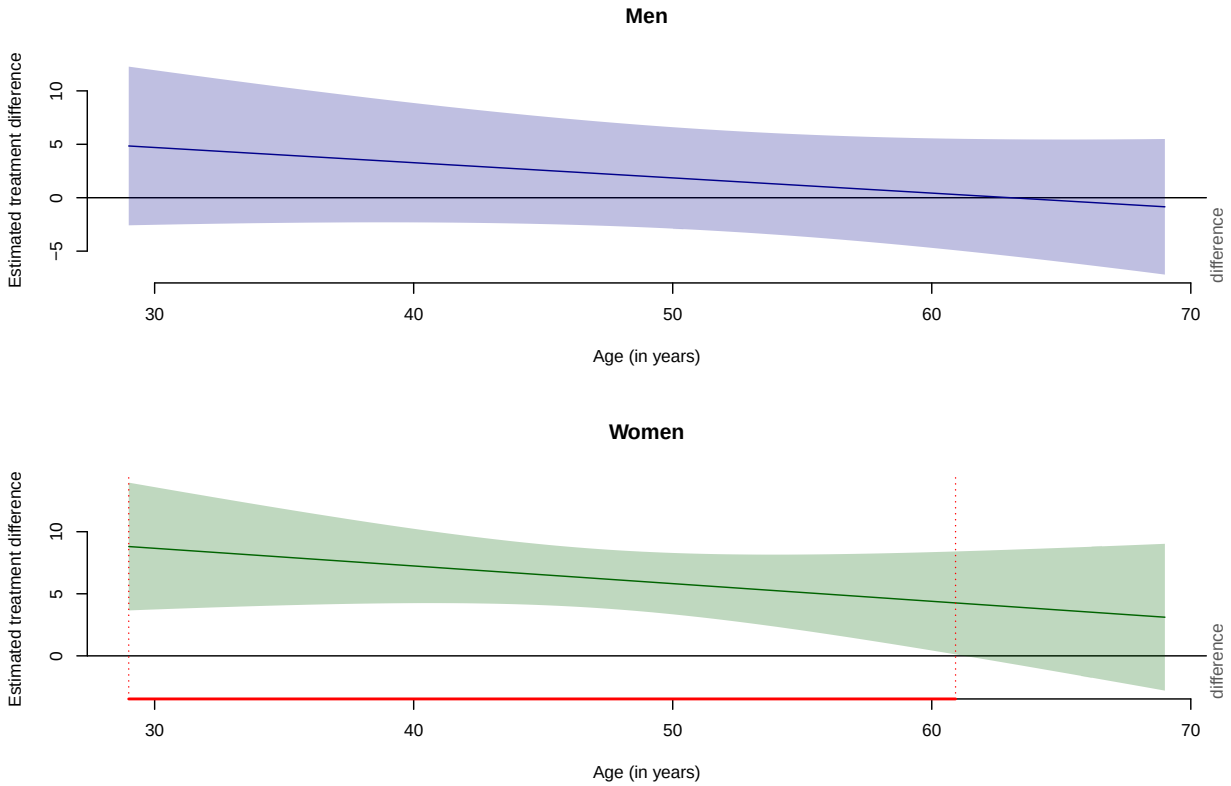
Glmer trees



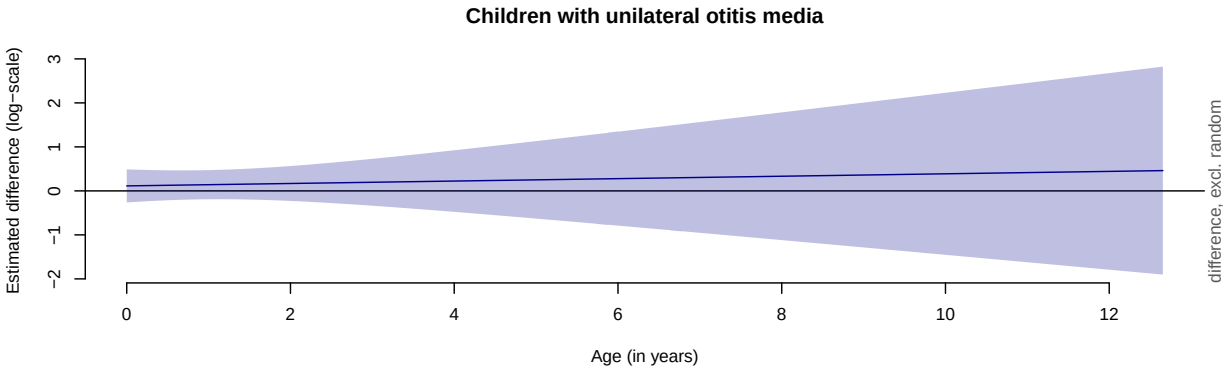
On the Rovers et al., dataset we show that age is a potential effect modifier and we may also have a tree-way interaction with bilateral otitis.

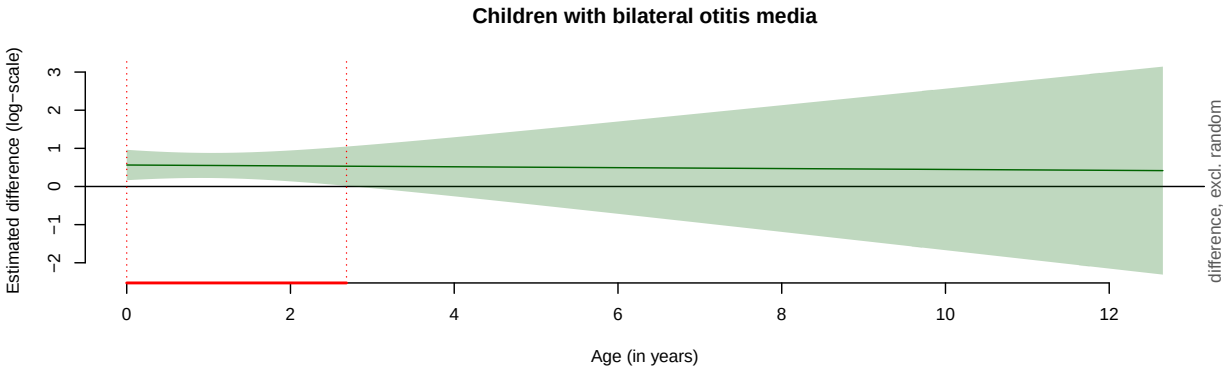
Two-stage smoothing splines (I need to explain her some things)

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 to investigate effect modification. We show that women younger than 57 have a treatment benefit, probably due to menopause.

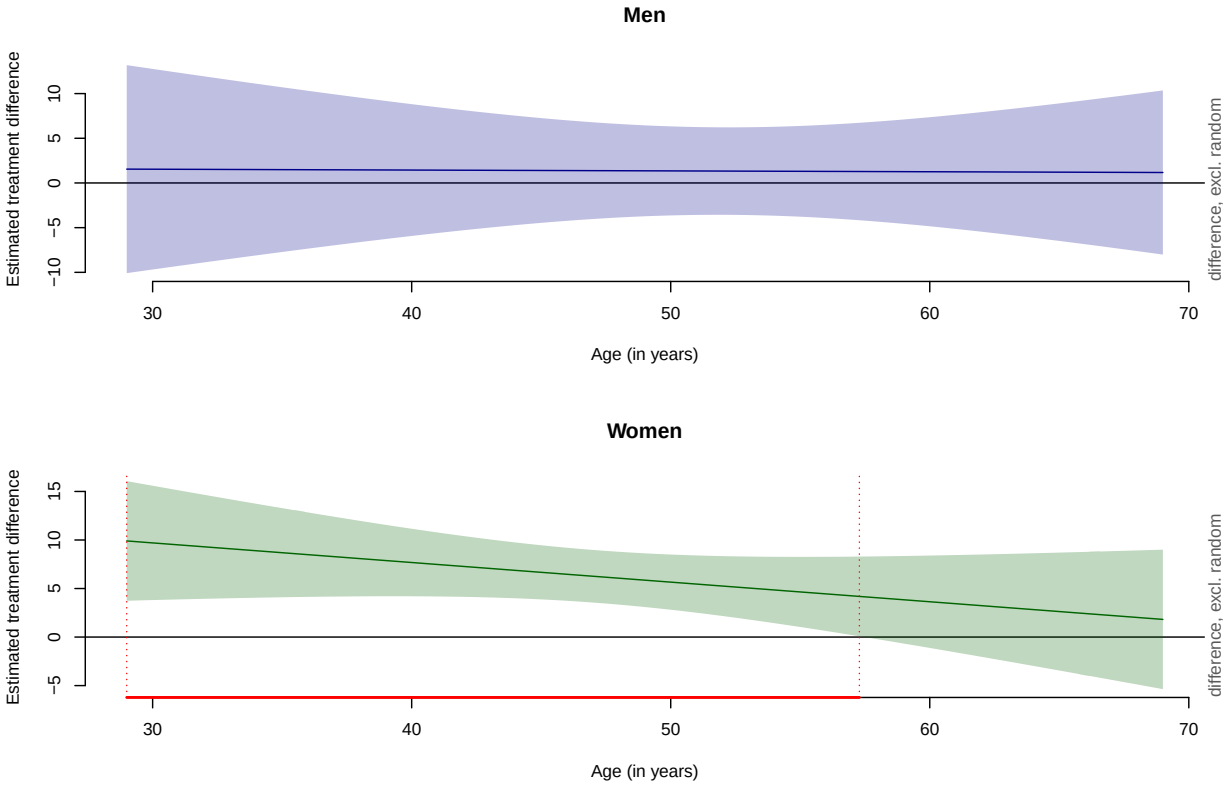


In the acute otitis media data-set we show that children 0-5 years have a treatment benefit.


Children with unilateral otitis media
Estimated difference (log−scale)
−2
−1
0
1
2
3
0
2
4
6
8
10
12
Age (in years)
difference, excl. random


Children with bilateral otitis media
Estimated difference (log−scale)
−2
−1
0
1
2
3
0
2
4
6
8
10
12
Age (in years)
difference, excl. random

One-stage smoothing splines



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.

	Estimate	Std. Error	z	Pr(>|z|)	95%ci.lb	95%ci.ub
Intercept	-0.6841942	0.2488971	-2.7489040	0.0059795	-1.1720235	-0.1963649
Treatment	-0.3496952	0.1740573	-2.0090804	0.0445286	-0.6908413	-0.0085491
FP(Age)	-0.0673286	0.5740890	-0.1172791	0.9066389	-1.1925224	1.0578651
Bilateral	0.1843859	0.3046302	0.6052777	0.5449945	-0.4126784	0.7814501
Treatment x FP(Age)	-0.4340268	0.7659547	-0.5666482	0.5709532	-1.9352705	1.0672168
Treatment x Bilateral	-0.3526736	0.3220061	-1.0952388	0.2734120	-0.9837939	0.2784468
Treatment x FP(Age)	-3.3004523	1.3664947	-2.4152690	0.0157236	-5.9787327	-0.6221719
Treatment x FP(Age) x Bilateral	0.6060753	1.9562187	0.3098198	0.7566980	-3.2280429	4.4401936

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Chi-squared test:
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X2 = 9.314, df = 3, P(> X2) = 0.0254
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We couldn't show that age is an effect modifier on 0.05 α.

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 $2 \times p$ (degree of polynomial) $\times J$ (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.

In two-stage meta-analysis using linear assumptions, effect modification across age was not statistically significant.

For the Gevers et al the two-stage meta-analysis of interaction terms showed no statistically significant results.

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

	Estimate	Std. Error	z	Pr(>|z|)	95%ci.lb	95%ci.ub
Intercept	0.0619771	0.2817542	0.2199688	0.8258955	-0.4902509	0.6142051
Treatment	0.1167730	0.4138136	0.2821875	0.7777997	-0.6942867	0.9278328
Age	-0.4628689	0.1393645	-3.3212824	0.0008960	-0.7360184	-0.1897195
Bilateral	0.5632859	0.4473928	1.2590411	0.2080155	-0.3135879	1.4401597
Age^2	0.0426999	0.0142068	3.0056027	0.0026506	0.0148551	0.0705446
Treatment x Age	-0.2772199	0.2187374	-1.2673639	0.2050252	-0.7059373	0.1514976
Treatment x Bilateral	-1.7005663	0.7163822	-2.3738254	0.0176049	-3.1046497	-0.2964830
Age x Bilateral	0.0019461	0.3021292	0.0064413	0.9948606	-0.5902162	0.5941084
Treatment x Age^2	0.0314613	0.0232316	1.3542436	0.1756587	-0.0140719	0.0769944
Age^2 x Bilateral	-0.0052413	0.0381155	-0.1375116	0.8906265	-0.0799464	0.0694637
Treatment x Age x Bilateral	0.9142263	0.5348389	1.7093491	0.0873863	-0.1340386	1.9624912
Treatment x Age^2 x Bilateral	-0.1095269	0.0766428	-1.4290571	0.1529878	-0.2597439	0.0406902

```
Chi-squared test:
X2 = 3.968, df = 4, P(> X2) = 0.4103
```

One-stage IPD-MA

Discussion

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