Efficient estimation of breakpoints in piecewise-linear mixed-effects models for longitudinal ophthalmic studies

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Abstract

Purpose: Broken stick analysis is a useful approach to detect the unknown breakpoints where association between measurements change. Currently, most longitudinal studies aggregate measurements obtained from all visits without considering the repeated measurements from a given eye so that segmented linear models can be applied to such "compressed" cross-sectional data. The purpose of this study is to introduce an advanced **r**obust **s**egmented **m**ixed **m**odel (RSMM) which accommodates longitudinal measurements from both eyes, and is robust to outliers.

Methods: The model setup and parameter estimation algorithm of RSMM was introduced. The performance of all competing methods were assessed via comprehensive simulation studies and application to a longitudinal ophthalmic study with 216 eyes (145 subjects) followed for 3.7±1.3 years to examine the longitudinal association between structural and functional measurements.

Results: In the simulation studies, the breakpoint estimates of RSMM exhibit smallest bias and mean squared error (MSE), with empirical coverage probability closest to the nominal level for scenarios with and without outlier data points. In the application to the longitudinal ophthalmic study, results of RSMM indicated the existence of two breakpoints between visual field mean deviation (MD) and retinal nerve fiber layer thickness (RNFL) and one breakpoint between MD and cup to disc ratio (CDR) while the cross-sectional analysis approach only detected one and none, respectively.

Conclusions: RSMM improves the estimation accuracy of breakpoints for longitudinal ophthalmic studies. The conventional cross-sectional analysis approach is not recommended for future studies.

Introduction

Broken stick analysis is an analytical tool for investigating piecewise-linear association between continuous variables primarily useful in the presence of inconsistent association. An example for its use in ophthalmology is the association between structural and functional measurements in glaucoma. Numerous studies demonstrated varying level of association between structural measurements obtained by OCT, such as average retinal nerve fiber layer (RNFL) thickness, and functional measurements obtained with visual field tests, at different stages of disease severity[1-6]. The current methodologies used in broken stick analysis mainly employ cross-sectional approach where observations from one eye per subject from a single visit are included in the analysis. This negates the possibility of maximizing available data by using information obtained from both eyes of the same subject and evaluating longitudinal processes such as disease trajectory. Alternatively, aggregate of all eyes from all visits are used without considering the inter-eye correlation and the use of repeated measurements. Without considering the correlations of repeated measurements from two eyes within a subject, the breakpoint estimation may be misleading.

We propose a new and robust segmented mixed-effects model (RSMM) that can overcome these shortfalls and provide accurate breaking point analysis for longitudinal datasets that include data from both eyes. This method is built upon the segmented mixed model[7], while incorporating least trimmed squares (LTS) technique[8] to accommodate potential outliers within the dataset. We also propose a new standard error estimator for RSMM to improve the coverage probability of confidence interval estimate. The segmented mixed model is an iterative procedure that estimates unknown breakpoints utilizing a linearization technique and mixed effect regression. However, the estimation is often impacted by outliers in the data. We address this with the LTS technique

which is a robust statistical method that mitigates the impact in the presence of outliers. While LTS can effectively reducing or eliminating the influence of outliers on point estimations, the design of this technique is to find the lowest sum of squared residuals which can lead to underestimation of the standard errors of the unknown parameters. To reduce the effects, we propose an algorithm to improve the estimate of standard errors and confidence intervals (CIs) of unknown parameters (including breakpoints and their associated slopes).

A simulation study was conducted to evaluate the performance of the proposed method against competing methods by comparing the finite sample bias, mean square error (MSE), and the empirical coverage probabilities of 95% CI estimates. We applied these methods to a longitudinal assessment of the association between visual field mean deviation (MD) and OCT RNFL thickness and between MD and cup to disc ratio and analyzed the piecewise association.

Methods

Model specification of RSMM

The framework of segmented mixed effects model was adopted to characterize the longitudinal, non-linear association relationship between variables. Following notation of Muggeo (2003)[7], we consider data $(y_{ijk}, x_{ijk}, z_{ijk})$ observed from subject i $(= 1, \dots, n)$ at visit time t_{ijk} $(j = 1, \dots, n_i)$ for eye k (= OD, OS). Here x_{ijk} and y_{ijk} denotes the two key variables of interest in the association analysis, where the primary goal is to detect the unknown yet important breakpoints of association changes. z_{ijk} denotes the time-dependent covariates including visit time t_{ijk}. The segmented mixed effects regression model with P breakpoints $\varphi_1, \cdots, \varphi_P$ can be written as

$$y_{ijk} = \beta_0 + \beta_1 \cdot x_{ijk} + \sum_{p=1}^{P} \xi_p \cdot \left(x_{ijk} - \varphi_p\right) \cdot I_{(x_{ijk} > \varphi_p)} + \beta_2 \cdot z_{ijk} + \gamma_i \cdot s_{ij} + \gamma'_{ij} \cdot s'_{ijk} + \varepsilon_{ijk}, \quad (1)$$

where $\boldsymbol{\beta} = (\beta_0, \beta_1, \beta_2)^t$ corresponds to the intercept and random effects of x_{ijk}, z_{ijk} respectively, $\boldsymbol{\Psi} = (\beta_1, \beta_1 + \xi_1, \cdots, \beta_1 + \xi_1 + \xi_2 + \cdots + \xi_P)^t$ are the $P + 1$ slopes (association effects) for each of the segments between P breakpoints. $\gamma_i \sim N\left(0, \Sigma_\gamma\right)$ and $\gamma'_{ij} \sim N\left(0, \Sigma_{\gamma'}\right)$ are the random effects for covariate s_{ij} and s'_{ijk}. $\varepsilon_{ijk} \sim N(0, \sigma^2)$ are the independent individual errors. The model will shrink to the standard linear mixed-effects model when no breakpoint is detected (i.e., $P = 0$). The detailed algorithms **Error! Reference source not found.** and **Error! Reference source not found.** for estimating breakpoints $\Phi = (\varphi_1, \cdots, \varphi_P)^t$, other unknown parameters $\boldsymbol{\Theta} = \left(\boldsymbol{\beta}^t, \xi_1, \cdots, \xi_P, \mathrm{diag}\left(\Sigma_\gamma\right), \mathrm{diag}\left(\Sigma_{\gamma'}\right), \sigma^2\right)^t$, and their corresponding 95% CIs are detailed in the following.

2.2 Efficient estimation of breakpoints and other parameters

For the standard linear mixed-effects model, the unknown parameters can be estimated through maximum likelihood estimation (MLE) approach using the derived log-likelihood function[11]. However, the strategy is not applicable for segmented mixed effects model (1) because the corresponding log-likelihood function is not differentiable at $\varphi_p{}'s$. Additionally, linear model fitting is sensitive to outliers which can occur due to measurement error, reading error, instrumental error, etc. Therefore, we propose a robust estimation approach that accounts for multiple breakpoints and potential outliers.

Given a value $\varphi_p^{(s)}$, the breakpoint estimation can be performed via a first order Taylor expansion around $\varphi_p^{(s)}$,

$$\left(x_{ijk}-\varphi_p\right)\cdot I\left(x_{ijk}>\varphi_p\right)\approx\left(x_{ijk}-\varphi_p^{(s)}\right)\cdot I\left(x_{ijk}>\varphi_p^{(s)}\right)+(\varphi_p-\varphi_p^{(s)})(-1)I\left(x_{ijk}>\varphi_p^{(s)}\right)$$

where $(-1)I(x_{ijk}>\varphi_p^{(s)})$ can be considered as the first derivative of $\left(x_{ijk}-\varphi_p\right)\cdot I\left(x_{ijk}>\varphi_p\right)$. This motivates us to solve the estimation problem by iteratively estimating breakpoints Φ and $\boldsymbol{\Theta}$. Given a pre-determined proportion of outlier data points $\boldsymbol{\alpha}\in(0,1)$, the iterative procedure of parameter estimates of RSMM is given as

Algorithm 1 (A1) point estimate of parameters for the robust segmented mixed model (RSMM)

1. Randomly sample $(1-\alpha)\%$ observations from the full data set;

For m'th iteration:

2. Set initial values of $\Phi^{(0)}=\left(\varphi_1^{(0)},\cdots,\varphi_P^{(0)}\right)$;
3. Given current $\varphi_p^{(s)}, p=1,\cdots P$, calculate $U_{ijk,p}^{(s)}=(x_{ijk}-\varphi_p^{(s)})\cdot I_{(x_{ijk}>\varphi_p^{(s)})}$ and $V_{ijk,p}^{(s)}=-I_{\left(x_{ijk}>\varphi_p^{(s)}\right)}$.

The segmented model can then be re-expressed as $y_{ijk}=\beta_0+\beta_1\cdot x_{ijk}+\sum_{p=1}^{P}\xi_p\cdot U_{ijk,p}^{(s)}+\sum_{p=1}^{P}\eta_p\cdot V_{ijk,p}^{(s)}+\beta_2\cdot z_{ijk}+\gamma_i\cdot s_{ij}+\gamma'_{ij}\cdot s'_{ijk}+\varepsilon_{ijk}$, and MLE estimate of parameter $\boldsymbol{\Theta}$ were obtained as $\boldsymbol{\Theta}^{(s)}$;

4. Update φ_p with $\varphi_p^{(s+1)}=\frac{\hat{\eta}_p^{(s)}}{\hat{\xi}_p^{(s)}}+\varphi_p^{(s)}$;
5. Repeat 3 and 4 until $\hat{\eta}_p^{(s)}\to 0$. Denote the resulted parameters as $\Phi^{[m]}$ and $\boldsymbol{\Theta}^{[m]}$;
6. Use the m'th estimates and corresponding model to predict the full data and calculate the squared residuals $(y_{ijk}-\hat{y}_{ijk})^2$ for each observation;
7. Select the $(1-\alpha)\%$ observations that have smallest squared residuals and repeat steps 2-6 until the sampled observations achieve the smallest squared residuals.

This iterative procedure comprises of two layers, where the outer layer (Steps 1 and 7) employs the least trimmed squares technique to accommodates the potential effects of outliers on the model fitting, and the inter layer (Steps 2-6) adopts the iterative optimization algorithm from the segmented mixed model we will introduce later in the competing method. This algorithm is efficient and adapted the bootstrap restarting[12] to make the algorithm less sensitive to starting values such that this procedure does not need to manually set initial values of $\Phi^{(0)}$ and is computational stable.

We further propose the following algorithm for the confidence interval estimation of parameters for RSMM to reduce the impact of under-estimates of SE from the original Least trimmed square technique.

Algorithm 2 (A2) The 95% confidence interval (CI) estimator of RSMM

1. Average the absolute maximal and minimal values of the residuals from RSMM (**Error! Reference source not found.**), and consider it as $\left(1-\frac{\alpha}{2}\right)$% quartile of the full distribution of the residual;**Error! Reference source not found.Error! Reference source not found.Error! Reference source not found.Error! Reference source not found.Error! Reference source not found.Error! Reference source not found.Error! Reference source not found.Error! Reference source not found.**
2. Recover the estimated standard deviation $\hat{\sigma}$ of residuals and generate pseudo-random error $\hat{\varepsilon}_{ijk} \sim N(0,\ \hat{\sigma}^2)$;
3. Let $y_{new,ijk} = \hat{y}_{ijk} + \hat{\varepsilon}_{ijk}$ be the updated full dataset and re-run steps 2-5 of A1 accordingly;
4. Employ the standard errors (SE) of Φ, Θ from the resulted model as the corrected SEs.
5. The 95% CI of Φ, Θ can then be derived by the estimates $\pm 1.96 \cdot \mathrm{SE}$.

2.3 Competing methods

We compare our proposed method with two representative broken stick analysis methods for estimating breakpoints in longitudinal studies used in other study fields: 1) Segmented mixed model (**SMM**), proposed by Muggeo et al[9]. Iterative optimization algorithm implemented in SMM for parameter estimation does not account for outlier data points, therefore the effect of outliers on the estimate of breakpoints needs to be evaluated; and 2) Robust mixed-effect segmented model (**RMSER**), proposed by Zhou et. al.[10] which combines the estimates from both segmented linear model and segmented linear mixed-effects model. The least trimmed squares technique was incorporated in RMSER to accommodate outliers. We also compared with the conventional method (named **Cross**) in which longitudinal measurements were aggregated cross-sectionally and analyzed with segmented linear regression model[7]. The detailed description of the algorithm for each method can be found in **Supplementary material Appendix A**.

2.4 Simulation setup

The simulation was designed to mimic structural and functional data from real longitudinal ophthalmic studies. Specifically, for both Scenario 1 and 2, two breakpoints, i.e., φ_1 and φ_2 were simulated for covariate x (termed the breakpoint variable hereafter). Time variable t was

included to impersonate the time from baseline visit by year, and random effects within each subject and within each eye were considered. The outcome y can be generated from the model:

$$y_{ijk} = \beta_0 + \beta_1 \cdot x_{ijk} + \xi_1(x_{ijk} - \varphi_1)I(x_{ijk} > \varphi_1) + \xi_2(x_{ijk} - \varphi_2)I(x_{ijk} > \varphi_2) + \beta_2 \cdot d_{ijk} + \mathrm{ID}_i + \mathrm{Eye{:}ID}_{ij} + \varepsilon_{ijk}$$

where $(\beta_0, \beta_1, \beta_2) = (50, 1, -0.5)$, $(\xi_1, \xi_2) = (2, 3)$, $(\varphi_1, \varphi_2) = (-10, 2)$, $x \sim N(-4, 6^2)$, $t = 0, 1, 2, 3$, $\mathrm{ID} \sim N(0, 1)$, $\mathrm{Eye{:}ID} \sim N(0, 2^2)$, and $\varepsilon_{ijk} \sim N(0, 0.5^2)$. To simulate outliers under Scenario 2, we randomly selected 5% of observations in the simulated dataset and added $(\max(y) - \min(y))/4$ to the outcome variable y and $(\max(x) - \min(x))/4$ to the breakpoint variable x. The data from 3-4 visits and from two eyes for 60% of totaling 300 subjects were simulated. N = 1000 replications were conducted to assess the point and confidence interval estimates of breakpoints and slopes for the proposed method RSMM, and competing methods including SMM, RMSER, and Cross.

2.5 The longitudinal ophthalmic study

This longitudinal clinical study examined 216 eyes (163 open angle glaucoma, 44 glaucoma suspects, and 9 healthy eyes) from 145 subjects aiming to assess ocular structural and functional changes over time. All subjects had undergone comprehensive ophthalmic in at least 5 visits (in average 3.7 years) with qualified visual fields, and OCT optic nerve head (ONH) and macular scans. The piecewise association between visual field mean deviation (MD) and retinal nerve fiber layer (RNFL) thickness and between MD and cup to disc ratio (CDR) were assessed (**Table 1**). All break-point analysis methods were adjusted for time to baseline visit (year), age at baseline, signal strength of scans, and eye. Bayesian information criterion (BIC) was used to determine the optimal number of breakpoints for each method. The model that has smallest BIC was selected and corresponding estimated breakpoints, slopes were reported.

3. Results

3.1 Simulation results

Table 2 and Table demonstrate the estimation performance of all assessed methods with respect to the mean value, empirical bias, and MSE for point estimates, and the empirical coverage probability (ECP) for 95% confident interval estimates of the detected breakpoints.

In the first scenario without outliers in the synthetic dataset (**Table**), the point estimates of RSMM (proposed method), SMM, and RMESR are statistically efficient in terms of negligible bias and small MSE, while the point estimate of Cross has a much larger bias and MSE comparing with other methods. The CI estimates of RSMM and SMM have satisfactory ECP close to the nominal level of 95%. However, the CI estimates of RMESR, and Cross tend to have much lower ECP than nominal.

In the second scenario where outliers do occur (**Table**), the point estimate of the proposed method RSMM has markedly smallest bias and MSE, indicating the statistical efficiency and superior robustness to outliers. The point estimates of all competing methods have large bias and MSE that indicate the failure of accurately detecting breakpoint under this scenario. The ECPs of all competing methods are substantially lower than nominal, while RSMM maintained ECP closest to the nominal. However, slightly over-coverage of the CI estimate of RSMM is detected.

3.2 Broken stick analysis results of the longitudinal ophthalmic study

Piecewise association analysis between RNFL and MD. Figure 1 and Table 4 shows the piecewise association analysis results of four assessed methods. RSMM, SMM, and RMESR demonstrate consistent results that two breakpoints were detected in the association relationship between RNFL thickness and MD. The corresponding estimated breakpoints and slopes of the

piecewise association between RNFL and MD were comparable. Specifically, the result of RSMM suggested that RNFL thickness decreases significantly and rapidly at the rate of 1.9 [1.52,2.29] μm/dB before reaching the first breakpoint of -4.31 dB. After that, RNFL thickness still significantly decreases but in a slower rate of 1.05 [0.81,1.29] μm/dB until the second breakpoint of -15.70 dB. The association approaches plateau with insignificance rate of change when MD is smaller than -15.70 dB.

In contrast, the conventional method, Cross, only captured one breakpoint at MD= -4.08 dB that is inconsistent with the other three competing methods. The estimated slope from Cross indicates that RNFL thickness decreases significantly with MD when MD is larger than -4.08 dB, which is not typically observed clinically.

Piecewise association analysis between CDR and MD. Figure and Table 5 shows that RSMM, SMM, and RMESR discovered one breakpoint while Cross detected none in the piecewise association analysis between CDR and MD. RSMM and RMESR, two methods designed to accommodate outliers, report breakpoints close to each other at -8.61 dB, and -9.83 dB respectively. The corresponding slope estimates from RSMM and RMESER indicated that CDR increases at the rate of 0.0131[0.0107,0.0155] per dB and (0.0099[0.0089,0.0109] per dB) before MD decreases to the breakpoint. After that the increasing trend slows down with a rate of 0.0023[0.0008,0.0038] per dB and (0.0022[0.0014,0.0030] per dB). In comparison, SMM showed that CDR increases at the rate 0.0159[0.0140,0.0178] per dB when MD decreases before reaching the breakpoint of -12.46 dB. After the breakpoint, CDR decreases at the rate 0.0019[-0.0011,0.0048] per dB when MD declined. In this case, RSMM and RMESR demonstrated a pattern that complied with clinical observation while SMM described a trend less often observed.

4. Conclusion

In this manuscript, we proposed a novel robust segmented mixed model (RSMM) for broken stick analysis of longitudinal studies. This method enables efficient estimation of breakpoints for longitudinal dataset, largely mitigating the impact of outliers, and improving the estimation of CIs of breakpoints and slopes. A comprehensive simulation study was conducted to compare the proposed method with three competing methods. In the scenarios with and without outliers, RSMM achieved negligible bias, smallest MSE, and ECPs closest to the nominal level of 95% comparing with the other methods.

In the application to broken stick analysis of the longitudinal clinical study, the piecewise associations between RNFL thickness and MD estimated by RSMM, SMM, and RMESR were comparable and compatible with clinical observations. In the piecewise associations between RNFL thickness and CDR, RSMM and RMESR demonstrated a pattern that complied with clinical observation while SMM described a less likely clinical pattern. The results of Cross, however, were inconsistent with three other methods.

In conclusion, RSMM exhibits the most favorable results in both simulation scenarios with and without outliers occurred and illustrated a pattern that complied with clinical observation in the longitudinal clinical study while other methods delineated a doubtful clinical pattern. A user-friendly R package "RSMM" is publicly available at https://github.com/JiyuanHu/. The conventional cross-sectional method fails to estimate the breakpoints in all simulation scenarios and therefore is not recommend for use in future longitudinal studies.

Tables and Figures

Table 1. Characteristics of the longitudinal clinical study.

Parameters	Ns or Mean ± standard deviation (SD)
Eyes/subjects	214/145
N visits during f/u	5.8±0.9
N observations	1221
Age (years)	69.7±10.6
follow up (years)	3.7±1.3
ONH signal strength	8.3±0.8
baseline RNFL (μm)	73.8±14.4
baseline MD (dB)	-4.23±6.29
baseline CDR	0.67±0.15

Table 2: Simulation results for Scenario 1: synthetic dataset without outliers with breaking points at -10 and 2. Shown are the comparisons of point and CI estimation of breakpoints among different statistical methods.

	$\varphi_1 = -10$					$\varphi_2 = 2$				
	Est	Bias	MSE	SE	ECP	Est	Bias	MSE	SE	ECP
RSMM	-10.0005	-0.0005	0.0010	0.0291	0.923	2.0000	<0.0001	0.0005	0.0193	0.928
SMM	-10.0007	-0.0007	0.0008	0.0284	0.943	1.9999	-0.0001	0.0004	0.0189	0.942
RMESR	-10.0383	-0.0383	0.0027	0.0189	0.485	2.0340	0.0340	0.0017	0.0126	0.349
Cross	-5.9814	4.0186	19.753	0.8238	0.141	-1.6171	-3.6171	16.524	0.8236	0.141

Est, bias and MSE: Mean value, bias and mean squared error of the point estimate of the breakpoint respectively; SE: Mean value of the standard error estimate of the breakpoint; ECP: Empirical coverage probability of the 95% confidence interval estimate.

Table 3: Simulation results for Scenario 2: synthetic dataset with outliers with breaking points at -10 and 2. Shown are the comparisons of point and CI estimation of breakpoints among

different statistical methods.

	$\varphi_1 = -10$					$\varphi_2 = 2$				
	Est	Bias	MSE	SE	ECP	Est	Bias	MSE	SE	ECP
RSMM	-9.9963	0.0037	0.0817	0.0705	0.996	2.0080	0.0080	0.1169	0.0662	0.998
SMM	-10.3361	-0.3361	7.2465	0.8715	0.747	1.7874	-0.2126	4.8063	0.7424	0.778
RMESR	-10.0732	-0.0732	1.2084	0.0197	0.597	1.9793	-0.0207	0.6337	0.0139	0.567
Cross	-5.5309	4.4691	28.427	1.2464	0.218	-1.9612	-3.9612	22.879	1.7822	0.231

Est, bias and MSE: Mean value, bias and mean squared error of the point estimate of the breakpoint respectively; SE: Mean value of the standard error estimate of the breakpoint; ECP: Empirical coverage probability of the 95% confidence interval estimate.

Table 4. Parameter estimates [95% Cis] for the broken stick association analysis between MD and RNFL. Breakpoints are reported as dB and slopes as μm/dB.

	Breakpoint 1	Breakpoint 2	Slope 1	Slope 2	Slope 3
RSMM	-4.31	-15.70	1.90*	1.05*	-0.21
	[-6.19, -2.42]	[-17.86, -13.53]	[1.52, 2.29]	[0.81, 1.29]	[-0.63, 0.22]
SMM	-4.93	-15.73	2.19*	0.95*	-0.16
	[-6.25, -3.62]	[-17.87, -13.58]	[1.90, 2.48]	[0.70, 1.2]	[-0.51, 0.18]
RMESR	-5.47	-15.64	1.64*	1.04*	-0.19
	[-7.16, -3.78]	[-16.95, -14.34]	[1.40, 1.87]	[0.87, 1.21]	[-0.42, 0.05]
	Breakpoint		Slope 1		Slope 2
Cross	-4.08		3.91*		0.48
	[-6.26, -1.89]		[1.93, 5.90]		[-0.03, 0.98]

* p-value <0.05 for the statistical test against the null hypothesis of slope equal to zero.

Table 5. Parameter estimates [95% Cis] for the broken stick association analysis between MD and CDR. Breakpoints are reported as dB and slopes as cup-to-disc-ratio/dB.

	Breakpoint 1	Slope 1	Slope 2
RSMM	-8.61	-0.0131*	-0.0023*
	[-10.09, -7.14]	[-0.0155, -0.0107]	[-0.0038, -0.0008]
SMM	-12.46	-0.0159*	0.0019
	[-13.85, -11.07]	[-0.0178, -0.014]	[-0.0011, 0.0048]
RMESR	-9.83	-0.0099*	-0.0022*

	[-10.69, -8.98]	[-0.0109, -0.0089]	[-0.0030, -0.0014]
		Slope	
Cross	Breakpoint not detected	-0.0109* [-0.0141, -0.0077]	

* p-value <0.05 for the statistical test against the null hypothesis of slope equal to zero.

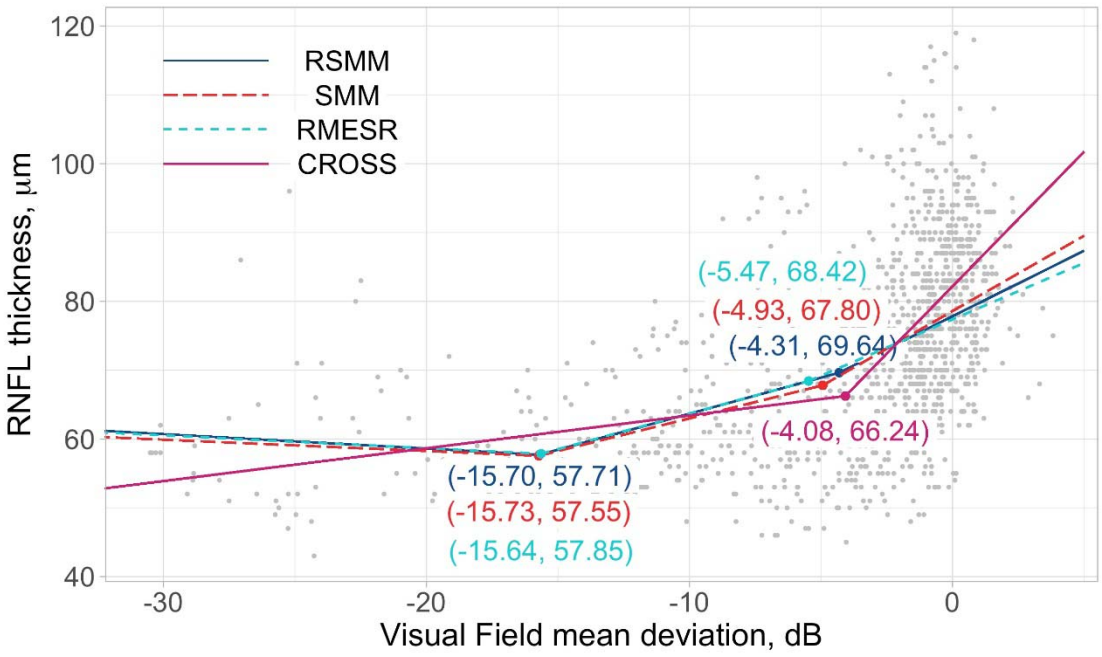

Figure 1. The estimated piecewise associations between visual field mean deviation and RNFL thickness and from all assessed methods.

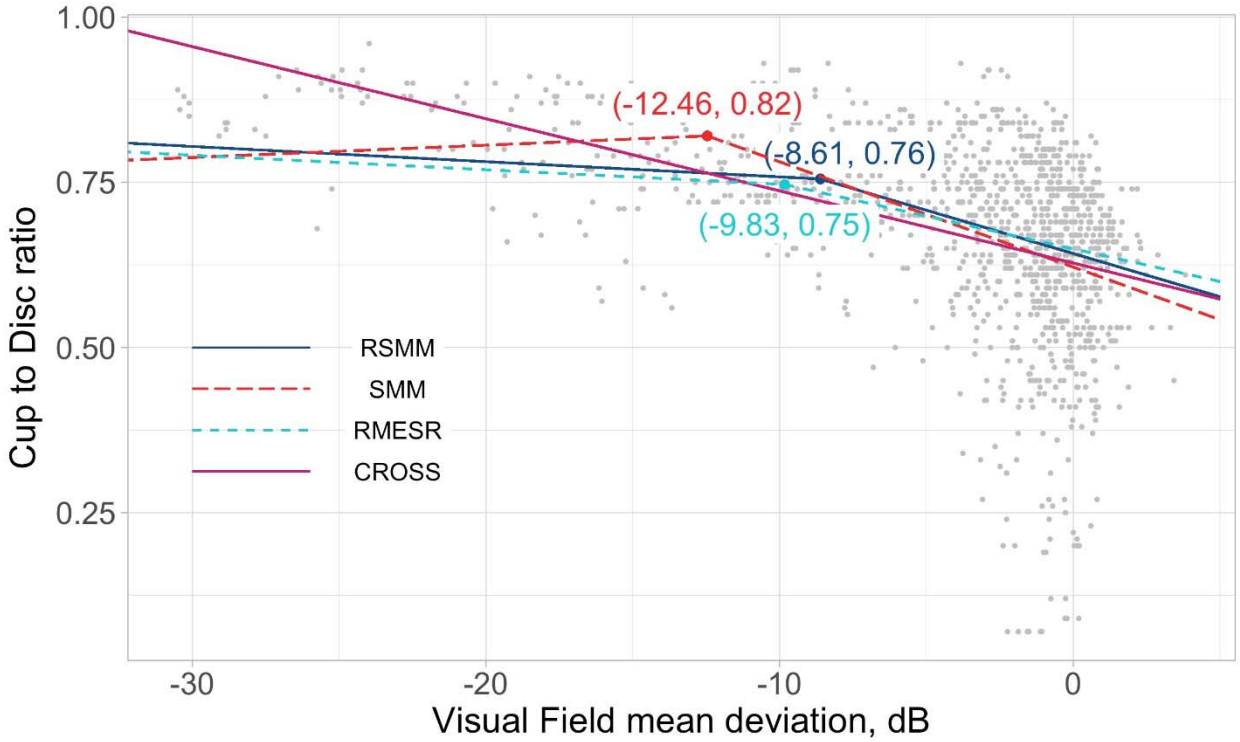

Figure 2. The estimated piecewise associations between visual field mean deviation and cup to disc ratio from all assessed methods.

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