Supplementary Online Content

Mohammadzadeh V, Su E, Mohammadi M, et al. Association of blood pressure with rates of macular ganglion cell complex thinning in patients with glaucoma. *JAMA Opthalmol*. Published online February 9, 2023. doi:0.1001/jamaophthalmol.2022.6092

This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods: Bayesian Hierarchical Longitudinal Model With Random Intercepts, Slopes, and Residual Variances

For this study, we fit longitudinal ganglion cell complex (GCC) measurements from all participants and superpixels together in a Bayesian hierarchical random-effects model. Let y_{ijk} denote the GCC thickness measured on subject i at time t_{ij} in superpixel k for $k = 1, \dots, 49$. Time since baseline t_{ij} is measured in years, where the first visit $j = 1$ for all participants is at $t_{i1} = 0$ years. We extend our previous Bayesian hierarchical model to include covariates. [1]

In each superpixel, our model has 7 interpretable superpixel-level population parameters, the (i) population intercept α_{0k}, (ii) standard deviation (SD) of the random intercepts $D_{00k}^{1/2}$, (iii) population slope α_{1k}, (iv) SD of the random slopes $D_{11k}^{1/2}$, (v) correlation ρ_k between random intercepts and slopes, (vi) mean σ_{mk} of the random residual SDs, and (vii) SD σ_{sk} of the random residual SDs. We transformed the random intercepts and slopes correlation ρ_k and variance D_{11k} of the random slopes to the regression coefficient $\gamma_k = \rho_k D_{11k}^{1/2} D_{00k}^{-1/2}$ of the random slopes given the random intercept and the remaining slope variance $D_{11.0k} = (1 - \rho_k^2) D_{11k}$ of the random slopes (variance of the random slopes adjusted for the random intercepts). We log transformed the random intercept and remaining slope variances D_{00k}, $D_{11.0k}$, and the population mean σ_{mk} and SD σ_{sk} of the random residual SDs. We term these 7 superpixel parameters (or their transformations) population parameters. The 7 transformed parameters in superpixel $k = 1, \dots, 49$ were given hierarchical normal priors with unknown global mean and variance. Three parameters, $\alpha_{0k}, \log D_{00k}, \log D_{11.0k}$, were given a joint multivariate normal prior, the other four parameters were given independent normal priors.

For superpixel k, α_{0k} is the population average intercept at baseline $t_{i1} = 0$; α_{1k} is the population average slope; β_{0ik} is the ith subject's random intercept: the unknown difference between subject i's intercept and the population intercept α_{0k}; β_{1ik} is the ith subject's random slope: the unknown difference between subject i's slope and α_{1k}; and the residual variance for subject i is σ^2_{ik}. For subject i, $x_i = (x_{i1}, \ldots, x_{iQ})'$ are the Q standardized covariates of interest; $\eta_0 = (\eta_{01}, \ldots, \eta_{0Q})'$ is the vector of regression coefficients for the covariate effects on the intercepts; and $\eta_1 = (\eta_{11}, \ldots, \eta_{1Q})'$ is the vector of regression coefficients for the covariate effects on the slopes. We standardized all covariates by subtracting the covariate sample mean m_p and then dividing by the covariate sample SD s_p. We report inferences for coefficients by transforming coefficients back to being coefficients of unstandardized coefficients $\eta^*_p = \eta_p/s_p$ in the absence of an interaction. For models with interactions between two covariates, we multiply both standardized covariates together, and do not further standardize the interaction term. To transform standardized coefficients of covariates labeled 1 and 2, and the interaction term between covariate 1 and 2 back to being unstandardized coefficients, we use the following formulas

$$\eta^*_1 = \left(\frac{\eta_1}{s_1}\right) - \left(\frac{m_2}{s_1 s_2}\right)\eta_{1\times 2}$$

$$\eta^*_2 = \left(\frac{\eta_2}{s_2}\right) - \left(\frac{m_1}{s_1 s_2}\right)\eta_{1\times 2}$$

$$\eta^*_{1\times 2} = \left(\frac{\eta_{1x2}}{s_1 s_2}\right).$$

Let $N(a, b^2)$ be a normal random variable with mean a and variance b^2; $IG(a, b)$ be an inverse gamma random variable with shape parameter a, scale parameter b, and mean $b/(a-1)$

for $a > 1$; $C^+(a, b)$ be a half-Cauchy random variable (a Cauchy or t with 1 degree of freedom restricted to the positive real line) with location a and scale b; and $\text{Wish}(V, n)$ for Wishart distribution with inverse scale matrix V, degrees of freedom n, and mean $(nV)^{-1}$. For the univariable models, we fit a separate model for each covariate ($Q = 1$). The full multivariable model is

$$y_{ijk} = \alpha_{0k} + \alpha_{1k}t_{ij} + \beta_{0ik} + \beta_{1ik}t_{ij} + \eta_0' x_i + \eta_1' x_i t_{ij} + \epsilon_{ijk}$$

$$\epsilon_{ijk} | \sigma_{ik}^2 \sim N(0, \sigma_{ik}^2)$$

$$\beta_{0ik} | D_{00k} \sim N(0, D_{00k})$$

$$\beta_{1ik} | \gamma_k, \beta_{0ik}, D_{11.0k} \sim N(\gamma_k \beta_{0ik}, D_{11.0k})$$

$$\log \sigma_{ik} \mid \sigma_{mk}, \sigma_{sk} \sim N(\mu^*, \sigma^{*2})$$

$$\mu^* = 2 \log \sigma_{mk} - 0.5 \log(e^{2 \log \sigma_{mk}} + e^{2\sigma_{sk}})$$

$$\sigma^{*2} = \log e^{2(\log \sigma_{sk} - \log \sigma_{mk}) + 1}$$

$$(\alpha_{0k}, \log D_{00k}, \log D_{11.0k})' \mid (\mu_1, \mu_2, \mu_4)', \Sigma \sim N((\mu_1, \mu_2, \mu_4)', \Sigma)$$

$$\alpha_{1k} | \mu_3, \sigma_3^2 \sim N(\mu_3, \sigma_3^2)$$

$$\gamma_k | \mu_5, \sigma_5^2 \sim N(\mu_5, \sigma_5^2)$$

$$\log \sigma_{mk} | \mu_6, \sigma_6^2 \sim N(\mu_6, \sigma_6^2)$$

$$\log \sigma_{sk} | \mu_7, \sigma_7^2 \sim N(\mu_7, \sigma_7^2)$$

Regression coefficients have horseshoe priors [2,3]

$$\eta_{0p} | \lambda_{0p}, \tau_0 \sim N(0, \lambda_{0p}^2 \tau_0^2)$$

$$\eta_{1p} | \lambda_{1p}, \tau_1 \sim N(0, \lambda_{1p}^2 \tau_1^2)$$

for $p = 1, \ldots, Q$, $N(0, \lambda_p^2 \tau^2)$, with separate λ_{0p} and λ_{1p} for covariate p for the intercept and slope respectively, and global parameters τ_0 and τ_1, where λ_p and τ are a priori distributed as independent half-Cauchy random variables with location zero and scale parameter 1.

Matrix D_k is a $2x2$ variance-covariance matrix of the random intercepts and slopes with elements

$$\mathrm{D_k} = \begin{pmatrix} \mathrm{D_{00k}} & \mathrm{D_{01k}} \\ \mathrm{D_{10k}} & \mathrm{D_{11k}} \end{pmatrix}$$

and $D_{11.0k} = D_{11k} - D_{10k}D_{00k}^{-1}D_{01k}$ is the variance of the conditional distribution of $\beta_{1ik}|\beta_{0ik}$.

The correlation between the random intercepts and slopes is

$$\rho_{\mathrm{k}} = \frac{\mathrm{D_{01k}}}{(\mathrm{D_{00k}}\,\mathrm{D_{11k}})^{1/2}} = \gamma_{\mathrm{k}}\sqrt{\frac{\mathrm{D_{00k}}}{\mathrm{D_{11k}}}}.$$

The priors are

$$\mu_1 \sim \mathrm{N}(90, 400)$$

$$\mu_2 \sim \mathrm{N}(5.4161, 0.804719)$$

$$\mu_3 \sim \mathrm{N}(-0.8, 0.36)$$

$$\mu_4 \sim \mathrm{N}(-0.4462871, 0.804719)$$

$$\mu_5 \sim \mathrm{N}(0, 9\mathrm{e}-04)$$

$$\mu_6 \sim \mathrm{N}(0.7, 0.09)$$

$$\mu_7 \sim \mathrm{N}(-0.25, 0.09)$$

$$\Sigma^{-1} \sim \mathrm{Wish}(5\mathrm{V}, 5)$$

$$\mathrm{V} = \begin{pmatrix} 135 & 0 & 0 \\ 0 & 0.15 & 0 \\ 0 & 0 & 0.384 \end{pmatrix}$$

$$\sigma_3^2 \sim \mathrm{IG}(2.5, 0.1666667)$$

$$\sigma_5^2 \sim \mathrm{IG}(2.5, 0.00135)$$

$$\sigma_6^2 \sim \mathrm{IG}(2.5, 0.06)$$

$$\sigma_7^2 \sim \mathrm{IG}(2.5, 0.135)$$

$$\lambda_{0\mathrm{p}} \sim \mathrm{C}^{+}(0, 1)$$

$$\lambda_{1p} \sim C^{+}(0,1)$$

$$\tau_0 \sim C^{+}(0,1)$$

$$\tau_1 \sim C^{+}(0,1).$$

eTable 1. Association of individual covariates with ganglion cell complex baseline thickness in univariable prognostic models.

	Intercepts		
Variable	*Posterior Mean*	*95% CrI*	*p-value*
Age at Baseline (/10 years)	–0.784	(–1.158, –0.401)	<.001
Female Sex	0.647	(–0.015, 1.366)	.04
Ethnicity			
White Participants (reference)			
African American Participants	–3.514	(–4.449, –2.594)	<.001
Hispanic Participants	0.534	(–0.197, 1.563)	.12
Asian Participants	3.213	(2.453, 3.974)	<.001
Diastolic Blood Pressure (/10 mmHg)	–0.179	(–0.526, 0.061)	.13
Systolic Blood Pressure (/10 mmHg)	–0.110	(–0.305, 0.016)	.11
History of Blood Pressure Medication	–0.647	(–1.378, 0.012)	.03
Hypertension	0.035	(–0.319, 0.485)	.44
Diabetes Mellitus	–1.487	(–2.347, –0.581)	<.001
Intraocular Pressure (/1 mmHg)	0.161	(0.071, 0.248)	<.001
Central Corneal Thickness (/10 µm)	0.120	(0.031, 0.204)	<.001
Axial Length (/1 mm)	0.037	(–0.096, 0.224)	.32
Contrast Sensitivity at 12 cycles per degree (/log unit)	0.451	(0.275, 0.630)	<.001
Mean Deviation 10–2 Visual Field (/1 dB)	0.605	(0.546, 0.664)	<.001

CrI = credible interval

eTable 2. Final multivariable model including diastolic blood pressure and its interaction with intraocular pressure and all other covariate effects on ganglion cell complex baseline thickness.

	Intercepts		
Variable	*Posterior Mean*	*95% CrI*	*p-value*
Age at Baseline (/10 years)	–0.769	(–1.165, –0.364)	<.001
Female Sex	0.529	(–0.070, 1.239)	.06
Ethnicity			
White participants (reference)			
African American participants	–4.248	(–5.225, –3.267)	<.001
Hispanic participants	1.484	(0.299, 2.609)	.005
Asian participants	2.222	(1.424, 3.004)	<.001
Hypertension	0.943	(0.038, 1.819)	.02
Diabetes Mellitus	–0.856	(–1.754, 0.001)	.03
Central Corneal Thickness (/10 µm)	0.125	(0.039, 0.208)	.002
Axial Length (/1 mm)	0.013	(–0.167, 0.207)	.44
Contrast Sensitivity 12 cycles per degree (/log unit)	–0.016	(–0.176, 0.128)	.41
10–2 Visual Field Mean Deviation (/1 dB)	0.615	(0.551, 0.680)	<.001
History of Blood Pressure Medication	0.747	(–0.035, 1.620)	.04
Intraocular Pressure	–0.525	(–1.316, 0.099)	.06
Diastolic Blood Pressure (/10 mmHg)	–0.861	(–2.066, 0.108)	.05
DBP/10 × IOP Interaction	0.056	(–0.019, 0.152)	.10

CrI = credible interval; DBP = diastolic blood pressure; IOP = intraocular pressure

eTable 3. Multivariable model including systolic blood pressure and its interaction with intraocular pressure and all other covariate effects on ganglion cell complex baseline thickness.

	Intercepts		
Variable	*Posterior Mean*	*95% CrI*	*p-value*
Age at Baseline (/10 years)	–0.767	(–1.192, –0.331)	<.001
Female Sex	0.534	(–0.101, 1.279)	.07
Ethnicity			
White participants (reference)			
African American participants	–3.886	(–4.920, –2.832)	<.001
Hispanic participants	1.624	(0.421, 2.782)	.004
Asian participants	2.708	(1.859, 3.553)	<.001
Hypertension	1.041	(0.066, 2.014)	.01
Diabetes Mellitus	–1.447	(–2.355, –0.504)	.001
Central Corneal Thickness (/10 µm)	0.122	(0.032, 0.207)	.003
Axial Length (/1 mm)	–0.010	(–0.211, 0.188)	.46
Contrast Sensitivity 12 cycles per degree (/log unit)	–0.053	(–0.236, 0.090)	.27
10–2 Visual Field Mean Deviation (/1 dB)	0.648	(0.581, 0.714)	<.001
History of Blood Pressure Medication	1.219	(0.214, 2.130)	.008
Intraocular Pressure	–1.940	(–2.623, –1.245)	<.001
Systolic Blood Pressure (/10 mmHg)	–1.648	(–2.245, –1.049)	<.001
SBP/10 × IOP Interaction	0.132	(0.083, 0.180)	<.001

CrI = credible interval; SBP = systolic blood pressure; IOP = intraocular pressure

eTable 4. Multivariable model including systolic blood pressure and its interaction with intraocular pressure and all other covariates on the rates of change of ganglion cell complex.

	Slopes		
Variable	*Posterior Mean*	*95% CrI*	*p-value*
Age at Baseline (/10 years)	–0.013	(–0.048, 0.014)	.22
Female Sex	–0.125	(–0.188, –0.059)	<.001
Ethnicity			
White participants (reference)			
African American participants	0.401	(0.310, 0.495)	<.001
Hispanic participants	–0.105	(–0.209, –0.001)	.02
Asian participants	–0.010	(–0.074, 0.046)	.38
Hypertension	0.080	(0.001, 0.162)	.02
Diabetes Mellitus	–0.002	(–0.066, 0.061)	.47
Central Corneal Thickness (/10 µm)	–0.030	(–0.037, –0.023)	<.001
Axial Length (/1 mm)	0.012	(–0.005, 0.034)	.12
Contrast Sensitivity 12 cycles per degree (/log unit)	–0.008	(–0.023, 0.005)	.16
10–2 Visual Field Mean Deviation (/1 dB)	–0.009	(–0.015, –0.003)	.001
History of Blood Pressure Medication	–0.301	(–0.376, –0.224)	<.001
Intraocular Pressure	–0.007	(–0.055, 0.040)	.34
Systolic Blood Pressure (/10 mmHg)	0.039	(–0.002, 0.079)	.03
SBP/10 × IOP Interaction	0.000	(–0.003, 0.003)	.49

CrI = credible interval; SBP = systolic blood pressure; IOP = intraocular pressure

eResults: Univariable and multivariable Bayesian hierarchical model for the subset of eyes with open-angle glaucoma (N= 98).

We ran the entire analysis on the subset of the eyes with the diagnosis of open-angle glaucoma (N= 98). Overall, the results were similar to the model evaluating all 105 eyes. The results of the univariable model is given in eTable 5. We found that female sex, African American descent, history of BP medications, higher IOP, thicker CCT, shorter AL and higher (better) 10-2 visual field MD were associated with faster (worse) rates of GCC thinning over time. Every 10 mmHg lower DBP was associated with 0.071 µm/year faster rates of GCC thinning. The effects of predictors on the intercepts in this cohort is presented in eTable 6.

eTable 7 gives results of the multivariable model adjusting for confounding factors. The interaction DBP*IOP had a significant effect on the rate of GCC thinning; eyes with higher DBP, lower IOP, or both had similar negative slopes. For example, at an IOP of 8 mmHg (16 mmHg), every 10 mmHg decrease in DBP was associated with a slower 0.026 µm/year (faster –0.171 µm/year) rate of GCC thinning. The effect of predictors on the GCC population intercept for the multivariable model is presented in eTable8.

eTable 5. Association of individual covariates with ganglion cell complex rates of change in univariable prognostic models for the subset of eyes with open-angle glaucoma (N= 98).

	Slopes		
Variable	*Posterior Mean*	*95% CrI*	*p-value*
Age at Baseline (/10 years)	–0.005	(–0.034, 0.023)	.38
Female Sex	–0.133	(–0.192, –0.077)	<.001
Ethnicity			
White Participants (reference)			
African American Participants	0.337	(0.252, 0.424)	<.001
Hispanic Participants	–0.052	(–0.141, 0.024)	.11
Asian Participants	0.042	(–0.022, 0.113)	.11
Diastolic Blood Pressure (/10 mmHg)	0.071	(0.042, 0.100)	<.001
Systolic Blood Pressure (/10 mmHg)	0.014	(–0.001, 0.030)	.04
History of Blood Pressure Medication	–0.130	(–0.188, –0.072)	<.001
Hypertension	0.002	(–0.044, 0.049)	.47
Diabetes Mellitus	–0.022	(–0.093, 0.042)	.26
Intraocular Pressure (/1 mmHg)	–0.017	(–0.025, –0.010)	<.001
Central Corneal Thickness (/10 µm)	–0.030	(–0.037, –0.023)	<.001
Axial Length (/1 mm)	0.034	(0.015, 0.053)	.001
Contrast Sensitivity at 12 cycles per degree (/log unit)	–0.007	(–0.022, 0.006)	.17
Mean Deviation 10–2 Visual Field (/1 dB)	–0.006	(–0.012, –0.001)	.01

CrI = credible interval

eTable 6. Association of individual covariates with ganglion cell complex intercepts (i.e., estimated baseline thickness) in univariable prognostic models for the subset of eyes with open-angle glaucoma (N= 98).

	Intercepts		
Variable	*Posterior Mean*	*95% CrI*	*p-value*
Age at Baseline (/10 years)	–0.603	(–1.004, –0.175)	.004
Female Sex	0.507	(–0.067, 1.263)	.07
Ethnicity			
White Participants (reference)			
African American Participants	–2.818	(–3.829, –1.822)	<.001
Hispanic Participants	0.780	(–0.104, 1.867)	.06
Asian Participants	3.563	(2.724, 4.390)	<.001
Diastolic Blood Pressure (/10 mmHg)	–0.044	(–0.345, 0.176)	.38
Systolic Blood Pressure (/10 mmHg)	–0.031	(–0.189, 0.068)	.33
History of Blood Pressure Medication	–0.434	(–1.194, 0.101)	.10
Hypertension	0.067	(–0.272, 0.598)	.39
Diabetes Mellitus	–1.783	(–2.666, –0.890)	<.001
Intraocular Pressure (/1 mmHg)	0.162	(0.062, 0.257)	.002
Central Corneal Thickness (/10 µm)	0.154	(0.068, 0.241)	<.001
Axial Length (/1 mm)	0.086	(–0.060, 0.318)	.20
Contrast Sensitivity at 12 cycles per degree (/log unit)	0.435	(0.253, 0.617)	<.001
Mean Deviation 10–2 Visual Field (/1 dB)	0.612	(0.551, 0.672)	<.001

CrI = credible interval

eTable 7. Final multivariable model including diastolic blood pressure and its interaction with intraocular pressure and all other covariate effects on the rates of change of ganglion cell complex for the subset of eyes with open-angle glaucoma (N= 98).

	Slopes		
Variable	*Posterior Mean*	*95% CrI*	*p-value*
Age at Baseline (/10 years)	0.000	(–0.029, 0.028)	.49
Female Sex	–0.124	(–0.187, –0.061)	<.001
Ethnicity			
White participants (reference)			
African American participants	0.398	(0.306, 0.490)	<.001
Hispanic participants	–0.100	(–0.196, –0.002)	.02
Asian participants	–0.004	(–0.067, 0.053)	.45
Hypertension	0.117	(0.038, 0.194)	.003
Diabetes Mellitus	0.005	(–0.056, 0.070)	.44
Central Corneal Thickness (/10 µm)	–0.029	(–0.036, –0.022)	<.001
Axial Length (/1 mm)	0.023	(0.001, 0.044)	.02
Contrast Sensitivity 12 cycles per degree (/log unit)	–0.025	(–0.042, –0.006)	.004
10–2 Visual Field Mean Deviation (/1 dB)	–0.008	(–0.013, –0.002)	.006
History of Blood Pressure Medication	–0.309	(–0.385, –0.230)	<.001
Intraocular Pressure	–0.160	(–0.244, –0.075)	<.001
Diastolic Blood Pressure (/10 mmHg)	–0.119	(–0.237, 0.001)	.03
DBP/10 × IOP Interaction	0.018	(0.008, 0.028)	<.001

CrI = credible interval; DBP = diastolic blood pressure; IOP = intraocular pressure

eTable 8. Final multivariable model including diastolic blood pressure and its interaction with intraocular pressure and all other covariate effects on the intercepts of ganglion cell complex (i.e., estimated baseline thickness) for the subset of eyes with open-angle glaucoma (N= 98).

	Intercepts		
Variable	*Posterior Mean*	*95% CrI*	*p-value*
Age at Baseline (/10 years)	–0.803	(–1.215, –0.387)	<.001
Female Sex	0.486	(–0.115, 1.230)	.08
Ethnicity			
White participants (reference)			
African American participants	–4.020	(–5.075, –2.945)	<.001
Hispanic participants	1.918	(0.769, 3.032)	.001
Asian participants	2.860	(2.023, 3.675)	<.001
Hypertension	0.842	(–0.030, 1.823)	.04
Diabetes Mellitus	–1.077	(–1.976, –0.127)	.01
Central Corneal Thickness (/10 µm)	0.146	(0.061, 0.230)	.001
Axial Length (/1 mm)	0.019	(–0.165, 0.220)	.43
Contrast Sensitivity 12 cycles per degree (/log unit)	–0.005	(–0.162, 0.152)	.47
10–2 Visual Field Mean Deviation (/1 dB)	0.641	(0.577, 0.708)	<.001
History of Blood Pressure Medication	1.352	(0.394, 2.268)	.003
Intraocular Pressure	–1.473	(–2.454, –0.415)	.001
Diastolic Blood Pressure (/10 mmHg)	–2.194	(–3.635, –0.692)	.002
DBP/10 × IOP Interaction	0.164	(0.038, 0.280)	.003

CrI = credible interval; DBP = diastolic blood pressure; IOP = intraocular pressure

References

1. Mohammadzadeh V, Su E, Shi L, et al. Multivariate Longitudinal Modeling of Macular Ganglion Cell Complex: Spatiotemporal Correlations and Patterns of Longitudinal Change. *Ophthalmology Science*. 2022;doi:10.1016/j.xops.2022.100187
2. Carvalho CM, Polson NG, Scott JG. Handling sparsity via the horseshoe. *In Proceedings of the Twelth International Conference on Artificial Intelligence and Statistics, PMLR 5*. 2009 Apr 16-18 pp. 73-80.
3. Carvalho CM, Polson NG, Scott JG. The horseshoe estimator for sparse signals. *Biometrika*. 2010 Jun 1;97(2):465-80.

Commented [MV1]: eReferences