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Ophthalmology

Relationship between intraocular pressure fluctuation and visual field progression rates in the United Kingdom Glaucoma Treatment Study --Manuscript Draft--

Manuscript Number:	OPHTHA-D-23-01872R3
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Keywords:	visual field progression; ocular pulse amplitude; Risk factors; linear mixed models.
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Abstract:	<p>Purpose. To investigate whether intraocular pressure (IOP) fluctuation is independently associated with the rate of visual field (VF) progression in the United Kingdom Glaucoma Treatment Study.</p> <p>Design. Randomized, double-masked, placebo-controlled multicenter trial.</p> <p>Participants: Participants with ≥ 5 VFs (213 placebo, 217 treatment).</p> <p>Methods. Associations between IOP metrics and the VF progression rates (mean deviation (MD) and five fastest locations) were assessed with linear mixed models. Fluctuation variables were mean ocular pulse amplitude (OPA), standard deviation (SD) of diurnal IOP (diurnal fluctuation), and SD of IOP at all visits (long-term fluctuation). Fluctuation values were normalized for mean IOP to make them independent from mean IOP. Correlated non-fluctuation IOP metrics (baseline, peak, mean, supine and peak phasing IOP) were combined with principal component analysis (PCA), and principal component 1 (PC1) was included as a covariate. Interactions between covariates and time from baseline modelled the effect of the variables on VF rates. IOP was measured with Goldmann applanation tonometry and OPA with Pascal tonometry. Analyses were conducted separately in the two treatment arms.</p> <p>Main Outcome Measures. Associations between IOP fluctuation metrics and rates of MD and five fastest test locations.</p> <p>Results. In the placebo arm, only PC1 was significantly associated with the MD rate (estimate [standard error (SE)]: -0.19 [0.04] dB/year, $p < 0.001$), while normalized IOP fluctuation metrics were not. No variable was significantly associated with MD rates in the treatment arm. For the fastest five locations in the placebo group, PC1 (estimate [SE]: -0.58 [0.16] dB/year, $p < 0.001$), CCT (estimate [standard error (SE)]: 0.26 [0.10] dB/year for 10 μm thicker, $p = 0.01$) and normalized OPA (estimate [SE]: -3.50 [1.04] dB/year, $p = 0.001$) were associated with rates of progression; normalized diurnal and long-term IOP fluctuations were not. In the treatment group, only PC1 (estimate [SE]: -0.27 [0.12] dB/year, $p = 0.028$) was associated with the rates of progression.</p> <p>Conclusions. There is no evidence to support that either diurnal or long-term IOP fluctuation, as measured in clinical practice, are independent factors for glaucoma progression; other aspects of IOP, including mean IOP and peak IOP, may be more informative. OPA may be an independent factor for faster glaucoma progression.</p>
Suggested Reviewers:	
Opposed Reviewers:	
Response to Reviewers:	AE Comment: Dear authors, Congratulations on your work. I have one suggestion. In the Precis (and everywhere else where the same issue is present), please insert "either" in front of "diurnal" and replace "and" with "or" in front of "long-term". The way it now stands, one could conclude that diurnal fluctuation and long-term fluctuation are risk factors, but are not independent of one another. Does that make sense? Best

wishes, Henry Jampel

Authors' Response: We thank the Associate Editor for his positive feedback. We have now modified the precis, abstract, and discussion accordingly.

Change in the Manuscript:

Precis

"This exploratory analysis of the multicenter randomized placebo-controlled United Kingdom Glaucoma Treatment Study found no evidence to support that either diurnal or long-term IOP fluctuation are independent factors for glaucoma progression."

Abstract, page 4, lines 30-33

"Conclusions. There is no evidence to support that either diurnal or long-term IOP fluctuation, as measured in clinical practice, are independent factors for glaucoma progression; other aspects of IOP, including mean IOP and peak IOP, may be more informative."

Discussion, page 29, lines 595-597

"In conclusion, this study finds no evidence to support that either diurnal or long-term IOP fluctuation, defined in a clinically relevant manner, are independent factors for glaucoma progression."

February 3rd, 2024

Russell N. Van Gelder, MD PhD
Chief Editor
Ophthalmology

Dear Editor,

Thank you for considering our manuscript OPTHHA-D-23-01872, "**Intraocular pressure fluctuation and rates of visual field progression in primary open-angle glaucoma: an exploratory analysis from the United Kingdom Glaucoma Treatment Study (UKGTS)**" for publication in the *Ophthalmology* journal. The points raised by the Associate Editor and Editorial office have all been considered and changes incorporated into the revised manuscript where appropriate. Attached is a point-by-point response to each of these comments. Any changes to the manuscript are italicized and in quotes in the response letter.

All the authors have approved the revised manuscript for submission to the *Ophthalmology* journal. As Corresponding Author, I had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis, as well as the decision to submit it for publication.

Thank you for your consideration of our manuscripts and we look forward to your response.

Yours sincerely,

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POINT-BY-POINT RESPONSE FORM

Please list the editor's, reviewer(s)', and editorial office's comments in the left-hand column, spacing them so that you can insert the relevant response in the center column and the respective point(s) in the text (and tables or legends, if appropriate) in the right-hand column. Adding line numbers to the manuscript file and referring to specific line numbers will be useful in determining which parts of the manuscript changed.

Manuscript #: OPHTHA-D-23-01872

Manuscript title: Relationship between intraocular pressure fluctuation and visual field progression rates in the United Kingdom Glaucoma Treatment Study

Suggestion, Question, or Comment from the Editor	Author's Response	Change in the Manuscript
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Suggestion, Question, or Comment from the Editorial Office	Author's Response	Change in the Manuscript
If your paper includes a study group/writing committee authorship, please upload the complete study group/writing committee list as a Word document "Collaborators" file to the submission.	We have now included a Word document "Collaborators" file listing the UKGTS investigators.	N/A

PRECIS

This exploratory analysis of the multicenter randomized placebo-controlled United Kingdom Glaucoma Treatment Study found no evidence to support that either diurnal ~~and-or~~ long-term IOP fluctuation are independent factors for glaucoma progression.

- Manuscript -

Relationship between intraocular pressure fluctuation and visual field progression rates in the United Kingdom Glaucoma Treatment Study

Authors: Alessandro Rabiolo, MD, FEBO¹⁻³; Giovanni Montesano, MD^{1,4}; David P Crabb PhD⁴; David F Garway-Heath, MD, FRCOphth¹, on behalf of the United Kingdom Glaucoma Treatment Study Investigators

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Short title: IOP fluctuation and glaucoma progression rates in the UKGTS

Conflict of Interest: None of the authors has any competing interest.

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Annual Meeting, May 2022, Denver, Canada; 15th European Glaucoma Society

Congress, June 2022, Athens, Greece.

ABSTRACT

1 **Purpose.** To investigate whether intraocular pressure (IOP) fluctuation is
2 independently associated with the rate of visual field (VF) progression in the United
3 Kingdom Glaucoma Treatment Study.

4 **Design.** Randomized, double-masked, placebo-controlled multicenter trial.

5 **Participants:** Participants with ≥ 5 VFs (213 placebo, 217 treatment).

6 **Methods.** Associations between IOP metrics and the VF progression rates (mean
7 deviation (MD) and five fastest locations) were assessed with linear mixed models.
8 Fluctuation variables were mean ocular pulse amplitude (OPA), standard deviation
9 (SD) of diurnal IOP (diurnal fluctuation), and SD of IOP at all visits (long-term
10 fluctuation). Fluctuation values were normalized for mean IOP to make them
11 independent from mean IOP. Correlated non-fluctuation IOP metrics (baseline, peak,
12 mean, supine and peak phasing IOP) were combined with principal component
13 analysis (PCA), and principal component 1 (PC1) was included as a covariate.
14 Interactions between covariates and time from baseline modelled the effect of the
15 variables on VF rates. IOP was measured with Goldmann applanation tonometry and
16 OPA with Pascal tonometry. Analyses were conducted separately in the two
17 treatment arms.

18 **Main Outcome Measures.** Associations between IOP fluctuation metrics and rates
19 of MD and five fastest test locations.

20 **Results.** In the placebo arm, only PC1 was significantly associated with the MD rate
21 (estimate [standard error (SE)]: -0.19 [0.04] dB/year, $p < 0.001$), while normalized IOP
22 fluctuation metrics were not. No variable was significantly associated with MD rates
23 in the treatment arm. For the fastest five locations in the placebo group, PC1
24 (estimate [SE]: -0.58 [0.16] dB/year, $p < 0.001$), CCT (estimate [standard error (SE)]:

25 0.26 [0.10] dB/year for 10 μ m thicker, $p=0.01$) and normalized OPA (estimate [SE]: -
26 3.50 [1.04] dB/year, $p=0.001$) were associated with rates of progression; normalized
27 diurnal and long-term IOP fluctuations were not. In the treatment group, only PC1
28 (estimate [SE]: -0.27 [0.12] dB/year, $p=0.028$) was associated with the rates of
29 progression.

30 **Conclusions.** There is no evidence to support that either diurnal ~~and or~~ long-term
31 IOP fluctuation, as measured in clinical practice, are independent factors for
32 glaucoma progression; other aspects of IOP, including mean IOP and peak IOP,
33 may be more informative. OPA may be an independent factor for faster glaucoma
34 progression.

35

36 **Keywords:** visual field progression; ocular pulse amplitude; risk factors; linear
37 mixed models.

38 INTRODUCTION

39 Intraocular pressure (IOP) is an established risk factor for glaucoma
40 progression, and lowering IOP is currently the only available treatment to slow the
41 disease progression.¹⁻⁴ Longitudinal measurement of IOP is crucial in evaluating
42 glaucoma patients, estimating their risk of developing progressive glaucomatous
43 damage, and assessing their response to treatment.

44 IOP is subject to fluctuations over time. Several IOP-derived parameters are
45 commonly used in clinical practice and research to summarize the behavior of IOP,
46 including mean IOP (average of IOP over multiple visits), peak IOP (highest IOP
47 reading over follow-up), and IOP fluctuation (standard deviation [SD] or range IOP
48 over time). Many studies have shown that mean IOP and peak IOP are
49 independently associated with glaucoma progression;^{1, 2, 5, 6} on the other hand, the
50 exact role of IOP fluctuation is still debated, with discordant results reported in the
51 literature.⁵⁻¹⁰ Elucidating the role of IOP fluctuation is difficult for several reasons.
52 IOP fluctuation is tightly correlated with other IOP-related metrics (e.g., mean IOP),
53 making it difficult to isolate its role as an independent factor. IOP fluctuation may be
54 artificially increased by escalating treatment in patients with suspect progression.
55 The effect of IOP fluctuation may not be uniform, varying as a function of the disease
56 stage, treatment status, mean IOP values, and definition of fluctuation.¹¹

57 This planned secondary analysis of the United Kingdom Glaucoma Treatment
58 Study (UKGTS) randomized controlled trial aimed to evaluate whether IOP
59 fluctuation, as assessed by ocular pulse amplitude (OPA), diurnal variation and
60 between-visit variation, is independently associated with the rate of visual field
61 progression. The UKGTS is ideal for this purpose because there were no treatment

- 62 escalations artificially increasing IOP fluctuation, and the dataset allows evaluation of
- 63 IOP metrics in both untreated and treated glaucoma patients.

64 **METHODS**

65 *Study Population and Procedures*

66 This study was a planned secondary analysis of data from the UKGTS, which
67 was a multicenter, randomized, triple-masked, placebo-controlled trial investigating
68 the ability of Latanoprost, an IOP lowering medication, to preserve visual function in
69 newly diagnosed open-angle glaucoma patients (trial registration number,
70 ISRCTN96423140). The UKGTS and the subsequent analysis of anonymized data in
71 this study complied with the tenets of the Declaration of Helsinki and were approved
72 by local institutional review boards (Moorfields and Whittington Research Ethics
73 Committee on June 1, 2006, ethics approval reference, 09/H0721/56). All patients
74 provided written informed consent at the time of enrolment in the trial.

75 The UKGTS study protocol, baseline characteristics, and outcomes have
76 been published elsewhere.^{3, 12, 13} Participants recruited in 10 ophthalmology
77 institutions across the United Kingdom were randomized 1:1 to receive latanoprost
78 0.005% or placebo eye drops once in the evening in both eyes for 24 months or until
79 meeting an endpoint. The UKGTS included patients ≥ 18 years of age and newly
80 diagnosed treatment-naïve open-angle glaucoma, including primary open-angle and
81 pseudoexfoliation glaucoma. Exclusion criteria were: advanced glaucoma, as
82 defined by visual field mean deviation < -10 dB in the better eye or < -16 dB in the
83 worse eye, mean baseline IOP ≥ 30 mmHg, Snellen best-corrected visual acuity
84 (BCVA) $< 6/12$, and poor image quality (>40 μm mean pixel height standard
85 deviation) with the Heidelberg retina tomograph (Heidelberg Engineering,
86 Heidelberg, Germany).

87 Potentially eligible participants underwent two pre-randomization visits. After
88 meeting the study criteria and signing the written informed consent, participants were

89 randomized either to receive latanoprost 0.005% or placebo eye drops. Enrolled
90 subjects underwent IOP measurement, VF, and imaging at eleven post-
91 randomization visits over 24 months or until meeting an endpoint. Standard
92 automated perimetry with the Humphrey Field Analyzer (Carl Zeiss Meditec, Dublin,
93 CA) was performed with stimulus size III, Swedish Interactive Threshold Algorithm
94 (SITA) standard strategy, and 24-2 grid. VF testing was performed at all 11
95 scheduled visits over 24 months, and tests were clustered (2 VFs on the same day)
96 at baseline, 2 months, 16 months, 18 months, and 24 months. In this exploratory
97 analysis, we included participants from the UKGTS with ≥ 5 reliable visual fields
98 (VFs). Reliable VFs were defined as those with false positives less than 15%, while
99 no limits for false negatives and fixation losses were applied. At the first post-
100 randomization visit, the following demographic variables were collected: age, sex,
101 ethnicity, family history of glaucoma, history of systemic diseases (i.e., systemic
102 hypertension, cardiovascular disease, diabetes, heart attack, stroke, sleep apnea,
103 migraine, Raynaud's phenomenon, vasospasm, angina, claudication), and smoking
104 status. The following investigations were also performed: blood pressure
105 measurements with the Omron M7 Blood Pressure Monitor (Matsusaka, Mie, Japan),
106 weight, height, slit-lamp examination, refractive error measured either with an
107 autorefractor or from spectacle focimetry (if not available, the spherical equivalent of
108 the trial lens was used in the visual field test, based on participants' age), axial
109 length measurement with the IOL Master (Carl Zeiss Meditec, Dublin, CA), and
110 central corneal thickness (CCT) measured with an ultrasound pachymeter. We
111 included one eye per patient; specifically, the eye with the worst baseline VF mean
112 deviation (MD).

113

114 *IOP Metrics*

115 At all visits, IOP was measured with Goldmann applanation tonometry (GAT;
116 Haag Streit, Koeniz, Switzerland), Pascal dynamic contour tonometry (Ziemer
117 Ophthalmic Systems AG, Zurich, Switzerland), and the Ocular Response Analyzer
118 (Reichert, Inc., Buffalo, NY). Diurnal GAT phasing with IOP measured every 2 hours
119 from 9 am to 5 pm was performed at the first post-randomization and at the final visit.
120 At the first post-randomization visit, supine IOP was measured with Perkins
121 applanation tonometer.

122 The following IOP metrics were calculated and used for the analyses:

- 123 • Baseline pretreatment IOP, defined as the average of the IOP readings obtained
124 in the two pre-randomization visits.
- 125 • Mean IOP, defined as the average of all post-randomization IOP readings.
- 126 • Peak IOP, defined as the highest IOP reading of all post-randomization IOP
127 readings.
- 128 • Supine IOP, defined as the Perkins applanation tonometry IOP readings
129 measured at the first post-randomization visit.
- 130 • Phasing peak IOP, defined as the highest IOP reading of the diurnal phasing
131 performed at the first post-randomization visit.
- 132 • Diurnal IOP fluctuation, defined as the SD of IOP measurements obtained from
133 the diurnal IOP phasing performed at the first post-randomization visit. Diurnal
134 IOP fluctuation was also calculated using the IOP measurements from the last
135 post-randomization visit.
- 136 • Long-term IOP fluctuation, defined as the SD of post-randomization IOP
137 readings.

- 138 • Mean ocular pulse amplitude (OPA) from the Pascal Dynamic Contour tonometry.
139 OPA was defined as the range of the pulse wave contour and provides a
140 measure of how IOP fluctuates over cardiac cycle. We used the average of all
141 post-randomization ORA values.

142

143 *Statistical Analysis*

144 We performed all statistical analyses with the open-source software R (R
145 Foundation for Statistical Computing, Vienna, Austria). Variable distributions were
146 inspected with histograms and quantile-quantile plots. We reported mean (\pm
147 Standard deviation [SD]) and median (interquartile range [IQR]) for Gaussian and
148 non-Gaussian variables, respectively. We reported frequencies and proportions for
149 discrete variables. Proportion and pattern of missing data were analyzed. All
150 analyses were conducted with complete cases. All tests were 2-tailed, and p-values
151 <0.05 were considered statistically significant.

152 Demographic and clinical characteristics between the two treatment groups
153 were compared with t-test and chi-squared test for continuous and categorical
154 variables, respectively. Agreement between diurnal IOP fluctuation calculated on the
155 first and last post-randomization visit was investigated with Bland-Altman statistics.
156 We also collected the timing of each IOP measurement and calculated the absolute
157 differences from each measurement and the mean time of day for each patient's IOP
158 measurements.

159 Linear models were used to evaluate the relationship between (i) mean IOP and
160 long-term IOP fluctuation, (ii) mean IOP and long-term IOP fluctuation/mean IOP, (iii)
161 mean diurnal IOP and diurnal IOP fluctuation, (iv) mean diurnal IOP and diurnal IOP

162 fluctuation/mean diurnal IOP, (v) mean OPA and mean IOP, and (vi) mean
163 OPA/GAT IOP and mean IOP.

164 IOP fluctuation is known to be positively correlated with mean IOP. Additionally,
165 measurement error can contribute to the variability in IOP measurements, potentially
166 confounding true IOP fluctuation. To obtain a measure of IOP fluctuation which is
167 independent from mean IOP, we performed a normalization of IOP fluctuation
168 values. Specifically, we ran a linear regression of IOP fluctuation against mean IOP.
169 We then divided the observed IOP fluctuation values by the corresponding predicted
170 values. This process was applied distinctly for each fluctuation metric. For long-term
171 fluctuation, we utilized the SD of all post-randomization IOP readings and their
172 corresponding mean IOP values from all post-randomization readings. For diurnal
173 fluctuation, we used the SD and mean IOP measurements from the diurnal IOP
174 phasing conducted during the first post-randomization visit. For the OPA, we used
175 the average of all post-randomization ORA values for each subject and their
176 corresponding mean IOP across all available post-randomization visits. For OPA, we
177 calculated the average of all post-randomization ORA values for each subject,
178 alongside their corresponding mean IOP from all available post-randomization visits.

179 As shown in Figure S1, normalized IOP fluctuation was unrelated to mean IOP.
180 Normalization was further performed on the two study arms separately, leading to
181 almost identical results (data not shown). All analyses were conducted on both
182 normalized and unnormalized IOP fluctuations values.

183 Linear mixed models with random slopes and random intercepts were used to
184 estimate the rates of progression and investigate associations between the rate of
185 visual field progression and variables of interest. Linear mixed models are an
186 extension of traditional linear models, which can accommodate the repeated-

187 measure (e.g., multiple measurements from the same eye over time) and clustered
188 (multiple test locations from the same VF) nature of data. We first look at univariable
189 associations between the MD rate of change and each variable of interest. In all
190 models, the MD value at each visit was the outcome variable; the follow-up time in
191 years, the covariate of interest, and their interaction were the fixed effects; the eye
192 identification number and follow-up time were the random intercept and random
193 slope terms, respectively, to account for the repeated measure of data and for the
194 fact that different eyes may have different rates of progression over time. Interactions
195 between covariates and time from baseline modeled the variables' effect on the
196 progression rate. We then built multiple variable linear mixed models to account for
197 the impact of fluctuation metrics after adjusting for all other potentially confounding
198 factors, including other IOP metrics. Correlations among candidate covariates were
199 tested with a hierarchical cluster analysis based on the absolute value of Spearman
200 correlations (Figure S2). Some of the variables measuring the magnitude of IOP
201 elevation exhibited high correlations. Highly correlated variables are a source of
202 multicollinearity, causing unstable regression coefficients and large standard errors.
203 To address this issue, all correlated metrics measuring IOP (baseline IOP, peak IOP,
204 mean IOP, supine IOP, peak phasing IOP) were combined using Principal
205 Component Analysis (PCA). These variables had a |Spearman rho| of 0.50 or
206 greater. PCA extracts uncorrelated orthogonal vectors (Principal Components [PCs])
207 from multiple correlated variables. PCs are ranked, with the first PC (PC1) being the
208 one containing the largest amount of combined information from the correlated
209 variables. PCA was performed on standardized data, with zero mean and unit
210 variance. We inspected the PCA model with biplots and scree plots (Figure S3).
211 Scree plots were used to visualize the amount of variance explained by the various

212 Principal Components and to select the number of PCs to retain for subsequent
213 analyses. PC1 was selected for further analyses, as it explained 81% of the overall
214 variance in the PCA, and used as a fixed effect in the multivariable linear mixed
215 models. The Interaction between PC1 and follow-up time modelled the effect of PC1
216 on visual field progression rates, as previously explained. PCA was also performed
217 on the two study arms separately, leading to similar results (data not shown).

218 Similar analyses were run in a pointwise manner, including: (i) all 52 VF test
219 locations of the 24-2 grid (after excluding the two locations corresponding to the blind
220 spot), and (ii) the five fastest progressing locations for each study eye (which is
221 conceptually similar to the event-based GPA analysis which identifies the 3 or more
222 locations most different from baseline). Models conducted on the pointwise threshold
223 sensitivity data had a nested random intercept with eye identification number over
224 the test location number to account for the inclusion of multiple pointwise series from
225 the same eye. All models were run separately in the placebo and treatment arms.
226 Regression estimates along with their 95% confidence intervals (95% CIs) and p-
227 values were reported.

228 RESULTS

229 Of the 461 participants with longitudinal data included in the primary UKGTS
230 analysis, 31 were excluded because of an insufficient number of VFs. The remaining
231 430 (placebo arm: 213, treatment arm: 217) participants were included in this study.
232 As shown in Figure S4, most variables had complete observations, with only a few
233 variables having missing observations. Spherical equivalent, CCT, and supine IOP
234 values were missing in 26 eyes (6%), 16 (3.7%), and 15 eyes (3.5%), respectively.
235 Mean arterial pressure, body mass index, ethnicity, corneal hysteresis, peak and
236 mean phasing IOP, and diurnal fluctuation were missing in less than 2% of patients.
237 All other variables had no missing data.

238 Baseline characteristics of the UKGTS study population have been published
239 elsewhere.^{3, 12} Table 1 illustrates the main demographic and clinical characteristics
240 of the patient cohort. Patients in the treatment cohort had significantly longer follow-
241 up time than those in the placebo cohort, with a median (IQR) of 1.9 (1.3 to 2.0) and
242 1.6 (1.0 to 2.0) years, respectively ($p=0.004$). The number of VFs was also
243 significantly greater ($p=0.027$) in the treatment arm (median [IQR]: 15 [10-16]) than in
244 the placebo arm (median [IQR]: 13 [10-16]). In the post-randomization study period,
245 patients in the treatment arm showed higher mean corneal hysteresis than those in
246 the placebo arm (mean [\pm SD]: 9.4 [\pm 1.6] vs. 8.9 [\pm 1.6] mmHg, $p=0.003$). As shown in
247 Figure 5, all post-randomization IOP metrics were significantly different between the
248 two arms ($p<0.045$ or below), except for normalized diurnal IOP fluctuation ($p=0.89$)
249 and normalized OPA ($p=0.93$). The median of the absolute differences from the
250 mean time of day for each patient's IOP measurements was 1.1 hours, with an
251 interquartile range (IQR) of 0.5 hours (30 minutes) to 2.0 hours.

252

253 *Global MD rate*

254 The distribution of MD rates in the two groups as estimated with linear mixed
255 models is illustrated in Figure 6. Median (IQR) MD rates in the placebo and
256 treatment cohort were -0.23 (-0.73 to 0.11) dB/year and 0.13 (-0.30 to 0.37) dB/year,
257 respectively ($p < 0.001$).

258 In the univariable analysis (Table S2), higher values of all non-fluctuation IOP
259 parameters, including pretreatment baseline IOP (estimate [standard error (SE)]: -
260 0.06 [0.02] dB/year for 1 mmHg increase, $p < 0.001$), mean IOP (estimate [SE]: -0.08
261 [0.02] dB/year for 1 mmHg increase, $p < 0.001$), peak IOP (estimate [SE]: -0.07 [0.01]
262 dB/year for 1 mmHg increase, $p < 0.001$), peak phasing IOP (estimate [SE]: -0.05
263 [0.02] dB/year for 1 mmHg increase, $p < 0.001$), and supine IOP (estimate [SE]: -0.06
264 [0.01] dB/year for 1 mmHg increase, $p < 0.001$), were significantly associated with
265 faster MD rates in the placebo group. With regards to the IOP fluctuations
266 parameters, higher long-term IOP fluctuation (estimate [SE]: -0.27 [0.07] dB/year for
267 1 mmHg increase, $p < 0.001$) and OPA (estimate [SE]: -0.32 [0.09] dB/year for 1
268 mmHg increase, $p < 0.001$) were associated with faster MD rates of change, while
269 diurnal IOP fluctuation was not ($p = 0.23$). None of the fluctuation parameters was
270 associated with the MD rate after normalizing for the mean IOP ($p = 0.11$ or above). In
271 the treatment arm, none of the variables was significantly associated with the MD
272 rate, except for long-term IOP fluctuation (estimate [SE]: -0.12 [0.06] dB/year for 1
273 mmHg increase, $p = 0.047$).

274 Results of the multivariable model for factors associated with MD rate of
275 progression are illustrated in Figure 7 and detailed in Table S3. In the placebo arm,
276 PC1, which combined information from all the non-fluctuation IOP parameters, was
277 the only factor associated with the MD rate (estimate [SE]: -0.19 [0.08] dB/year for 1

278 unit increase, $p < 0.001$), while the various normalized IOP fluctuation metrics were
279 not. Thinner CCT had an association of borderline statistical significance with faster
280 VF progression rates (estimate [SE]: 0.05 [0.02] dB/year for 10 μm thicker, $p = 0.06$).
281 None of the variables was significantly associated with the MD rate of progression in
282 the treatment arm. Older age was associated with faster MD rates (estimate [SE]: -
283 0.12 [0.06] dB/year for a 10-year increase) in the treatment arm, but this only
284 approached nominal statistical significance ($p = 0.06$). Similar results were obtained
285 when analyzing unnormalized IOP fluctuation metrics (Table S4).

286

287 *Pointwise Rates*

288 Figure 6 illustrates the distribution of pointwise progression rates in the two
289 groups. Pointwise rates were significantly faster in the placebo group than in the
290 treatment group (median [IQR]: -0.42 [-0.59 to -0.26] dB/year vs. 0.03 [-0.14 to 0.19]
291 dB/year, $p < 0.001$). Results of the univariable analysis for factors associated with the
292 pointwise rates of change are illustrated in Table S5. In the placebo group, all the
293 non-fluctuation IOP parameters were significantly associated with the pointwise rates
294 ($p = 0.003$ or below). Higher unnormalized long-term IOP fluctuation (estimate [SE]: -
295 0.34 [0.13] dB/year for 1 mmHg increase, $p = 0.008$) and OPA (estimate [SE]: -0.65
296 [0.15] dB/year for 1 mmHg increase, $p < 0.001$) were associated with faster pointwise
297 rates of progression. After normalizing IOP fluctuations for mean IOP, only OPA was
298 associated with the rate of progression (estimate [SE]: -1.36 [0.48] dB/year for 1 unit
299 increase, $p = 0.005$). In the treatment arm, none of the IOP variables was associated
300 with the pointwise rates of progression. In the multiple variable model (Figure 8 and
301 Table S6), normalized mean OPA was associated with the pointwise rates of
302 progression in the placebo arm (estimate [SE]: -1.23 [0.46] dB/year for 1 unit

303 increase, $p=0.009$), but not in the treatment arm. None of the other fluctuation
304 metrics was associated with the rate of progression in either group. The combined
305 IOP metric, PC1, was associated with the pointwise rate of change in the placebo
306 group ($p<0.001$), but not in the treatment group ($p=0.42$). Similarly, none of the
307 unnormalized IOP fluctuation metrics was associated with the pointwise rate of
308 change metrics (Table S7), except for mean OPA in the placebo group (estimate
309 [SE]: $-0.47 [0.17]$ dB/year for 1 mmHg increase, $p=0.008$).

310 For the five fastest progressing locations, median (IQR) pointwise rates of the
311 five in the placebo and treatment cohort were $-1.00 (-1.49 \text{ to } -0.80)$ dB/year and -
312 $0.52 (-0.93 \text{ to } -0.34)$ dB/year, respectively ($p<0.001$). Results of the univariable
313 analysis for factors associated with the rates of the fastest five locations are
314 illustrated in Table S8. In the placebo group, all the non-fluctuation IOP parameters
315 were significantly associated with the pointwise rates ($p=0.003$ or below). Higher
316 unnormalized (estimate [SE]: $-1.67 [0.34]$ dB/year for 1 mmHg increase, $p<0.001$)
317 and normalized OPA (estimate [SE]: $-3.95 [1.10]$ dB/year for 1 unit increase,
318 $p<0.001$) were associated with faster rates of progression. In the treatment arm,
319 higher unnormalized long-term IOP fluctuation was associated with faster rates of
320 progression (estimate [SE]: $-0.46 [0.17]$ dB/year for 1 mmHg increase, $p=0.006$), but
321 the association was no longer significant after normalizing IOP fluctuation (estimate
322 [SE]: $-0.81 [0.44]$ dB/year for 1 unit increase, $p=0.06$). In the multiple variable model
323 (Figure 9 and Table S9), CCT (estimate [SE]: $0.26 [0.10]$ dB/year for 10 μm thicker,
324 $p=0.01$), normalized OPA (estimate [SE]: $-3.50 [1.04]$ dB/year for 1 unit increase,
325 $p=0.001$), and PC1 (estimate [SE]: $-0.58 [0.16]$ dB/year for 1 PC1 unit increase,
326 $p<0.001$) were associated with the rates of progression of the fastest five test
327 locations in the placebo group; while normalized diurnal and long-term IOP

328 fluctuations were not. In the treatment group, PC1 (estimate [SE]: -0.27 [0.12]
329 dB/year for 1 PC1 unit increase, $p=0.028$) was the only factor associated with
330 progression rates. Results of the nonnormalized models are shown in Table S10.
331 All analyses were repeated with mean IOP, peak IOP and normalized LTF fluctuation
332 calculated from corneal compensated IOP as measured with the Ocular Response
333 Analyzer (Reichert, Inc, Buffalo, NY) and lead to similar results (Figures S10-S14).

334 **DISCUSSION**

335 In this study, we evaluated whether IOP fluctuation was associated with the
336 rate of glaucomatous visual field progression. We provided a comprehensive
337 evaluation of clinically relevant definitions of IOP fluctuation over the course of
338 seconds (OPA), office hours (diurnal fluctuation), and multiple visits over the entire
339 follow-up (long-term fluctuation). We found that higher OPA was associated with
340 faster rates of progression, while diurnal or long-term IOP fluctuations were not
341 associated with the rate of progression. Elevated IOP metrics (e.g., mean IOP, peak
342 IOP) were consistently associated with the rate of VF progression.

343 Establishing the relationship between IOP fluctuation and the rates of visual
344 field progression is not an easy task for many reasons. First, IOP fluctuation may
345 vary as a function of the time frame over which it is calculated, and there is no
346 consensus on which type of fluctuation is most informative. Our study provided a
347 comprehensive approach, analyzing three measures of fluctuations. Second, the
348 definition of IOP fluctuation is not uniform across studies, with IOP range and SD
349 IOP usually used as measures for IOP fluctuation. It has been suggested that SD
350 IOP could be a more robust metric than range IOP as the latter may be heavily
351 influenced by outliers and does not account for the number of IOP measurements.⁸
352 In this study, we used SD IOP to calculate diurnal and long-term IOP fluctuation; on
353 the other hand, OPA, a measure of very short-term fluctuation, was an average
354 range of several cardiac cycles. We further mitigated the effect of potential outliers
355 on OPA by obtaining two consecutive OPA measurements at each time point,
356 averaging them to have a single value, and then averaging the resulting values
357 throughout all available follow-up visits. Third, isolating the impact of fluctuation from
358 the level of IOP may be challenging because of the intimate relationship between

359 these two variables. IOP fluctuation is known to be positively correlated with mean
360 IOP. In a retrospective study performed on non-human primates of experimental
361 glaucoma, Gardiner and colleagues¹⁰ used the coefficient of variation (SD IOP
362 divided by mean IOP) to remove the relationship between these two variables. In our
363 cohort, the coefficient of variation reversed the association with mean IOP values,
364 leading to a negative relationship between IOP fluctuation and mean IOP. The
365 explanation for this is likely that there are two components of variability
366 (measurement error and true IOP fluctuation), one of which (true fluctuation) is
367 related to mean IOP and the other (measurement error) is not.¹⁴ Dividing the
368 measurement error by the mean IOP induces the negative association. The method
369 of normalization used in our study likely respects both the increased fluctuations at
370 higher mean IOP and constant measurement errors. Fourth, IOP-related metrics
371 tend to be highly correlated because they are related to the same original quantity.
372 Modeling highly correlated variables may lead to a statistical issue called
373 multicollinearity. In the presence of multicollinearity, regression models may become
374 inefficient with loss of statistical power, greater computation inaccuracy, unstable
375 estimates, and high variance.¹⁵ Various methods have been proposed to deal with
376 multicollinearity. One or more highly collinear covariates may be omitted from the
377 regression model, which may cause information loss. Ridge regression, a form of
378 penalized linear regression, is another popular method to handle multicollinearity;
379 however, it produces biased estimates and is better suited for predictive rather than
380 explanatory models.¹⁶ In our study, we addressed the issue of multicollinearity with
381 PCA, which creates a new set of orthogonal linear combinations of the original
382 variables (PCs), by definition perfectly uncorrelated to each other.¹⁷ In this study, we
383 used PCA to obtain a maximally informative combined metric of IOP control. Fifth,

384 clinicians are more likely to escalate treatment in progressing patients, inducing IOP
385 fluctuation. This may be easily overlooked in retrospective cohort studies and even in
386 prospective studies if countermeasures are not adopted. The findings of previous
387 studies have been greatly questioned because of the possible bias caused by
388 medical and surgical treatment escalation. Our study is not vulnerable to the
389 potential confounding effect of treatment escalation as patients in the UKGTS took
390 either latanoprost or placebo for their entire study period. In addition, our study is in
391 the unique position to elucidate the role of IOP fluctuation on glaucomatous
392 progression in untreated patients.

393 The relationship between IOP fluctuation and glaucomatous progression
394 remains highly controversial, with contrasting results reported in the literature.
395 Comparisons of results from different studies, including ours, should be done with
396 caution because of heterogeneity in study populations, designs, definitions of
397 fluctuation and progression, and statistical analysis. Most of the previous studies
398 focused on long-term (intervisit) IOP fluctuation, which is the most accessible
399 fluctuation metric to obtain as it can be estimated from single IOP measurements
400 from multiple visits. Our study did not find any relationship between long-term IOP
401 fluctuation and VF progression rates. Bengtsson et al.⁵ conducted a post-hoc
402 analysis from the Early Manifest Glaucoma Trial (EMGT); they found that mean IOP
403 was a strong predictor of glaucoma progression, while IOP fluctuation was not.
404 EMGT and UKGTS share many similarities, including the mild disease stage, type of
405 treatment (i.e., nonsurgical intervention), and mean IOP values. An observational
406 study by Medeiros et al.¹⁸ investigated whether IOP fluctuations were associated
407 with the risk of conversion from ocular hypertensive to glaucoma and found that
408 mean IOP, but not long-term IOP fluctuation, was associated with glaucoma

409 development. Other studies found contrasting results, showing a positive association
410 between long-term IOP fluctuation and VF progression. In a post-hoc analysis of the
411 Advanced Glaucoma Intervention Study (AGIS), Nouri-Mahdavi and colleagues⁹
412 found that long-term IOP fluctuation was an independent risk factor for glaucoma
413 progression, while mean IOP was not. The results of this study were criticized
414 because the authors analyzed the entire available follow-up, including time points
415 after treatment escalation. Further intervention, either in the form of trabeculectomy
416 or laser trabeculoplasty as per AGIS protocol, might have been itself a cause of
417 clinician-induced increased fluctuation in patients at high risk of progression. In a
418 subsequent post-hoc analysis of the AGIS, Caprioli and Coleman⁸ investigated the
419 relationship between long-term IOP fluctuation and VF progression, excluding those
420 patients having multiple interventions; they found that long-term IOP fluctuations was
421 significantly associated with VF progression in patients with low mean IOP, but not in
422 those with high IOP. A post-hoc analysis from the Collaborative Initial Glaucoma
423 Treatment Study (CIGTS)⁶ examined the role of various IOP parameters on VF
424 progression and found that long-term IOP fluctuation and peak IOP were associated
425 with VF progression, while mean IOP was not.

426 The literature on the role of diurnal (or diurnal-nocturnal) IOP fluctuation is
427 scarce, of lower quality, and with conflicting reports. In the Malmö Ocular
428 Hypertension study,¹⁹ diurnal IOP fluctuation was not an independent risk factors for
429 the development of glaucoma; conversely, mean IOP was associated with the
430 incidence of glaucomatous visual field loss in patients with OHT. Our study did not
431 find an association between diurnal IOP fluctuation and the rate of glaucomatous
432 progression in any of the models, corroborating the findings of the Malmö Ocular
433 Hypertension study. In a secondary analysis from a Swedish clinical trial

434 randomizing patients to either pilocarpine or argon laser trabeculoplasty, Bergea et
435 al.²⁰ investigated the relationship between visual field progression and different IOP
436 variables, and they found that both mean IOP and diurnal IOP fluctuation were
437 associated with visual field progression. That study, however, had several limitations,
438 including the small sample size (76 eyes), high proportion of pseudoexfoliation
439 glaucoma (72%), and the use of range IOP as a measure of fluctuation, which is
440 vulnerable to outlier and highly related to peak IOP. A retrospective study by Matlach
441 and colleagues²¹ assessed the impact of long-term and diurnal-nocturnal IOP
442 fluctuation on glaucoma progression in a cohort of 120 glaucoma patients randomly
443 selected from a tertiary referral center; they found that diurnal-nocturnal IOP
444 fluctuation was associated with glaucoma progression, while long-term IOP
445 fluctuation and mean IOP were not. A retrospective study by Kim et al.²² found
446 similar results in a cohort of NTG patients, with higher diurnal IOP fluctuations and
447 disc hemorrhages being associated with higher hazard of visual field progression.
448 Both these studies are limited by their retrospective nature, making them vulnerable
449 to potential confounders and selection bias. Also, these studies did not employ any
450 statistical method to mitigate multicollinearity.

451 Besides including these two established measures of IOP fluctuation, we also
452 investigated the role of very short-term fluctuation, as measured by the mean ocular
453 pulse amplitude (OPA) over follow-up. OPA is calculated as the difference between
454 systolic and diastolic IOP, as measured by the Pascal dynamic contour tonometer,
455 and informs on how IOP varies across the cardiac cycle, secondary to the pulsatile
456 influx/efflux of blood volume into the eye (mainly to choroid). Ocular pulse may be
457 determined by various ocular and systemic factors, including ocular tissue rigidity,²³⁻
458 ²⁵ axial length,²⁶ IOP,^{23, 27} blood pressure pulse amplitude,^{28, 29} left ventricular

459 ejection time,³⁰ heart rate,^{31, 32} and conditions influencing ocular perfusion (e.g.,
460 carotid artery stenosis, tight encircling band).^{33, 34} To the best of our knowledge,
461 there are currently no clinical studies investigating the role of OPA (or any metric for
462 very short IOP fluctuation) on glaucoma progression. We found that higher OPA was
463 significantly associated with faster pointwise rates of progression in the placebo
464 group. Reasons for this finding are speculative. This association may result from an
465 effect of the OPA itself or be related to one or more of its determinants. Animal
466 studies have shown that acute IOP elevation may induce structural optic nerve head
467 deformations and functional electrophysiological changes. Hence, multiple transient
468 IOP spikes may cause faster glaucoma progression in vulnerable eyes. This
469 explanation seems unlikely as these studies investigated large IOP changes, much
470 larger than those measured with OPA. Higher OPA is associated with increased
471 scleral rigidity and stiffer ocular tissues, which may be less compliant to IOP
472 changes, causing larger stress within the lamina cribrosa secondary to IOP
473 elevation.^{35, 36} In a simulation study based on finite element analysis reconstructing a
474 healthy eye model, Jin et al.³⁶ found that stiffer sclera was associated with higher
475 OPA, larger ONH deformation, and increased shearing forces to neural axons of the
476 neuroretinal rim. OPA has been proposed as a surrogate measure for
477 hemodynamics, being influenced by the arterial pulse pressure, heart rate, and left-
478 ventricular ejection time. Low diastolic blood pressure, vascular dysregulation and
479 optic nerve hypoperfusion have been associated with glaucoma progression,
480 especially in some phenotypes of open-angle glaucoma. However, one would expect
481 an opposite association to that found in this study, as lower OPA has been
482 associated with lower ocular blood supply. On the other hand, larger arterial pulse
483 pressure is associated with systemic hypertension, which may lead to vascular

484 damage. So, high OPA might be a surrogate for hypertensive vascular damage, and
485 previous studies^{37, 38} have shown that high blood pressure may be a risk factors for
486 primary open-angle glaucoma.

487 Our study confirms the importance of elevated IOP on glaucoma progression.
488 PC1, which combined information from various IOP parameters (i.e., mean IOP,
489 peak IOP, baseline IOP, peak phasing IOP, and supine IOP), was consistently
490 associated with the rate of visual field progression in the placebo group. On the other
491 hand, such a relationship was significant in the treatment group only for the rates of
492 the fastest five visual field locations, but not for global rates of change. The
493 progression rate of the treatment arm was extremely slow during the trial duration,
494 and the signal from a few progressing locations may be obscured by the overall
495 stability of most test locations. Comparative studies^{39, 40} have shown that pointwise
496 methods (especially those considering only locations with significant deterioration)
497 have higher sensitivity and require less time to detect progression than those based
498 on global indices or all test locations. Our study does not provide any information on
499 which IOP metric is the most important for disease progression; this is arduous to
500 tackle because of the intimate relationship among these variables. De Moraes and
501 colleagues² evaluated the effect of mean IOP, peak IOP, and SD IOP in a large
502 retrospective cohort of glaucoma patients under clinical care; they found that all
503 these variables were associated with disease progression in the univariable analysis,
504 but only peak IOP was significantly associated with VF progression in the
505 multivariable model. However, mean IOP and peak IOP are highly correlated, and a
506 multivariable model containing both variables would likely suffer from
507 multicollinearity. Treatment modifications highly influence mean IOP and SD IOP in

508 real-world settings; although the occurrence of glaucoma surgery during follow-up
509 was taken into consideration, medical treatment escalation was not.

510 We also investigated the impact of non-IOP and other ocular factors on
511 glaucomatous progression rates, including age, CCT, and corneal hysteresis. The
512 evidence for role of CCT as a risk factor for glaucoma progression is often
513 misunderstood. A thinner cornea causes artifacts in applanation tonometry, with
514 underestimation of the true IOP.⁴¹ Alternatively, corneal thickness may serve as a
515 biomarker of the biomechanical properties of the lamina cribrosa and peripapillary
516 sclera, providing insights into the vulnerability of the optic nerve to increased IOP.⁴²
517 An experimental study by Wells and colleagues⁴³ investigated whether CCT was
518 associated with optic disc compliance after inducing acute IOP rise and found no
519 significant association, indicating that CCT may not reflect ocular biomechanics. In
520 our cohort, thinner CCT was associated with faster progression rates in some
521 multivariable models (which included IOP metrics), while it did not show significance
522 in any of the univariable models. This suggests that CCT alone is not directly
523 associated with glaucoma progression: rather, it becomes statistically significant
524 when measured IOP is included in the model due to the effect of CCT on measured
525 IOP. Other studies, including the Early Manifest Glaucoma Treatment (EMGT)⁴⁴ and
526 the Los Angeles Latino Eye Study (LALES),⁴⁵ found similar finding, associating thin
527 CCT with conversion to glaucoma and incident glaucoma in multivariable models,
528 but not in univariable models. Khawaja and Jansonius⁴⁶ performed a simulation
529 study that mimicked datasets similar to the LALES and Ocular Hypertensive
530 Treatment Study so that IOP, but not CCT, was not associated with glaucoma risk.
531 Consistent with our findings and those from other studies, they found that CCT was
532 not associated with the risk of glaucoma in the univariable model, but a spurious

533 association between CCT and glaucoma appeared when measured IOP was added
534 to the model.

535 Although previous studies⁴⁷⁻⁴⁹ have shown a relationship between corneal
536 hysteresis and visual field progression rates, we were not able to confirm such
537 association in our cohort. In any given eye, corneal hysteresis is inversely related to
538 IOP. Therefore, low corneal hysteresis may reflect high IOP, which is an established
539 risk factors for faster glaucoma progression. Also, corneal hysteresis is directly
540 related to corneal stiffness and thickness. Hence, IOP might have underestimated in
541 patients with low corneal hysteresis, with consequent undertreatment leading to
542 faster progression.

543 Many studies have reported an association between older age and faster
544 progression rates.^{1, 44, 50, 51} In our study, older age was associated with faster MD
545 (but not pointwise) progression rates in the latanoprost group but not in the placebo
546 group. Ageing causes the lamina cribrosa to become stiffer and less compliant,
547 potentially reducing its ability and that of peripapillary sclera to comply with IOP
548 changes. Girard and colleagues³⁵ investigated the age-related biomechanical
549 differences in monkey posterior sclera and found that older animals had higher
550 tensile stress secondary to IOP elevation than younger ones. As tensile stress
551 increased non-linearly with IOP rise, the impact of ageing should theoretically be
552 more pronounced in patients with higher mean IOP; however, we found that older
553 age was associated with worse progression rates in the treatment arm, which had
554 lower mean IOP than the placebo arm. This finding is in agreement with a large
555 retrospective cohort study by De Moraes and colleagues², reporting that older age
556 was independently associated with glaucomatous VF progression only in patients
557 with lower mean IOP. Similar findings were found in the JAMDIG study, a large

558 retrospective study conducted in Japanese patients with fairly low mean IOP
559 values.⁵⁰ An explanation to these findings may be that the impact of non-IOP factors,
560 including age, becomes more important only after substantially lowering the IOP.

561 This study has limitations. This was a planned secondary analysis based on
562 the UKGTS dataset and the number of subjects and the duration of follow-up may
563 not provide enough statistical power to identify a meaningful relationship between
564 IOP fluctuation and visual field progression, especially in the treatment arm, where
565 progression rates were extremely slow over the study period. The study cohort
566 included treatment-naïve primary open-glaucoma patients, mainly of European
567 descent and with early glaucomatous damage. Some authors¹¹ have hypothesized
568 that the effect of IOP fluctuation on the rates of visual progression might vary as a
569 function of disease stage, mean IOP, glaucoma subtype, ethnicity, and treatment
570 modality (medical vs surgical intervention); hence, the results of this study may be
571 not entirely generalizable to other populations. Nevertheless, the results of this study
572 are in agreement with those from the EMGT analysis.⁵ The diurnal IOP fluctuation
573 calculation was based on five measurements obtained during the morning and
574 afternoon, and this study provides only IOP snapshots across the day and no
575 information on IOP fluctuation outside office hours. Although we used clinically
576 relevant definitions of IOP fluctuation, these measurements may not adequately
577 characterize short-term IOP variability. Diurnal phasing has been shown to be poorly
578 reproducible, indicating that single-day IOP measurements may not be sufficient to
579 accurately assess short-term fluctuations.⁵²⁻⁵⁵ Our findings are consistent with
580 existing literature in this field. A comparison between the two available diurnal IOP
581 curves revealed that the 95% limits of agreement were around 4 mmHg, aligning
582 closely with the most pronounced fluctuation extremes observed in this dataset

583 (Figure S15). Differences between diurnal IOP fluctuation calculated in the first and
584 last post-randomization visits were random and approximate a normal distribution
585 (Figure S16). Several studies^{56, 57} have documented a nocturnal peak in IOP,
586 primarily attributed to an increase in episcleral venous pressure when the body is in
587 a horizontal position. Although our study did not include night-time IOP
588 measurements, we did record IOP in a supine position, which is recognized as a
589 reasonable proxy for estimating nocturnal peak levels.⁵⁸ While devices for home IOP
590 monitoring^{59, 60} or continuous IOP tracking^{61, 62} have been introduced, they were not
591 collected in the UKGTS study and are generally reserved for research rather than
592 routine clinical use. Although the methodology employed in this study may not
593 capture the entire spectrum or precise patterns of IOP fluctuations, we adopted a
594 clinically relevant approach to defining diurnal IOP fluctuation.

595 In conclusion, this study finds no evidence to support that either diurnal and-or
596 long-term IOP fluctuation, defined in a clinically relevant manner, are independent
597 factors for glaucoma progression. Other aspects of IOP, such as mean IOP and
598 peak IOP, may be more informative. Higher OPA may be an independent factor for
599 faster glaucoma progression.

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611

612 During the preparation of this work the authors used chatGPT3.5 in order to improve
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790

791 **FIGURE LEGENDS**

792

793 **Figure 5.** Boxplots comparing the various IOP metrics in the placebo and treatment
794 groups. IOP: intraocular pressure; MD: mean deviation; OPA: ocular pulse
795 amplitude; SD: standard deviation.

796

797 **Figure 6.** Density plots for the distribution of MD (**left panel**) and pointwise (**right**
798 **panel**) rates of progression in the placebo and latanoprost groups. MD: mean
799 deviation. PLR: pointwise linear rates.

800

801 **Figure 7.** Forest plots for factors associated with the MD rates of progression in the
802 placebo (**left panel**) and treatment (**right panel**) group. Dots and bars indicate point
803 estimates and 95% confidence intervals, respectively. Estimates are intended for 1-
804 unit increase, unless specified otherwise. Combined IOP metrics PC1 is an unitless
805 variable, which combines fluctuation unrelated IOP metrics (baseline IOP, peak IOP,
806 mean IOP, supine IOP, peak phasing IOP) through Principal Component Analysis.
807 CCT: central corneal thickness; CH: corneal hysteresis; IOP: intraocular pressure;
808 MD: mean deviation; OPA: ocular pulse amplitude; PC1: principal component 1.

809

810 **Figure 8.** Forest plots for factors associated with the pointwise rates of progression
811 in the placebo (**left panel**) and treatment (**right panel**) group. Dots and bars indicate
812 point estimates and 95% confidence intervals, respectively. Estimates are intended
813 for 1-unit increase, unless specified otherwise. Combined IOP metrics PC1 is an
814 unitless variable, which combines fluctuation unrelated IOP metrics (baseline IOP,
815 peak IOP, mean IOP, supine IOP, peak phasing IOP) through Principal Component

816 Analysis. CCT: central corneal thickness; CH: corneal hysteresis; IOP: intraocular
817 pressure; OPA: ocular pulse amplitude; PC1: principal component 1; PLR: pointwise
818 linear rates.

819

820 **Figure 9.** Forest plots for factors associated with the pointwise rates of progression
821 of the five fastest locations in the placebo (**left panel**) and treatment (**right panel**)
822 group. Dots and bars indicate point estimates and 95% confidence intervals,
823 respectively. Estimates are intended for 1-unit increase, unless specified otherwise.
824 Combined IOP metrics PC1 is an unitless variable, which combines fluctuation
825 unrelated IOP metrics (baseline IOP, peak IOP, mean IOP, supine IOP, peak
826 phasing IOP) through Principal Component Analysis. CCT: central corneal thickness;
827 CH: corneal hysteresis; IOP: intraocular pressure; OPA: ocular pulse amplitude;
828 PC1: principal component 1; PLR: pointwise linear rates.

- Manuscript -

Relationship between intraocular pressure fluctuation and visual field progression rates in the United Kingdom Glaucoma Treatment Study

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ABSTRACT

1 **Purpose.** To investigate whether intraocular pressure (IOP) fluctuation is
2 independently associated with the rate of visual field (VF) progression in the United
3 Kingdom Glaucoma Treatment Study.

4 **Design.** Randomized, double-masked, placebo-controlled multicenter trial.

5 **Participants:** Participants with ≥ 5 VFs (213 placebo, 217 treatment).

6 **Methods.** Associations between IOP metrics and the VF progression rates (mean
7 deviation (MD) and five fastest locations) were assessed with linear mixed models.
8 Fluctuation variables were mean ocular pulse amplitude (OPA), standard deviation
9 (SD) of diurnal IOP (diurnal fluctuation), and SD of IOP at all visits (long-term
10 fluctuation). Fluctuation values were normalized for mean IOP to make them
11 independent from mean IOP. Correlated non-fluctuation IOP metrics (baseline, peak,
12 mean, supine and peak phasing IOP) were combined with principal component
13 analysis (PCA), and principal component 1 (PC1) was included as a covariate.
14 Interactions between covariates and time from baseline modelled the effect of the
15 variables on VF rates. IOP was measured with Goldmann applanation tonometry and
16 OPA with Pascal tonometry. Analyses were conducted separately in the two
17 treatment arms.

18 **Main Outcome Measures.** Associations between IOP fluctuation metrics and rates
19 of MD and five fastest test locations.

20 **Results.** In the placebo arm, only PC1 was significantly associated with the MD rate
21 (estimate [standard error (SE)]: -0.19 [0.04] dB/year, $p < 0.001$), while normalized IOP
22 fluctuation metrics were not. No variable was significantly associated with MD rates
23 in the treatment arm. For the fastest five locations in the placebo group, PC1
24 (estimate [SE]: -0.58 [0.16] dB/year, $p < 0.001$), CCT (estimate [standard error (SE)]:

25 0.26 [0.10] dB/year for 10 μ m thicker, $p=0.01$) and normalized OPA (estimate [SE]: -
26 3.50 [1.04] dB/year, $p=0.001$) were associated with rates of progression; normalized
27 diurnal and long-term IOP fluctuations were not. In the treatment group, only PC1
28 (estimate [SE]: -0.27 [0.12] dB/year, $p=0.028$) was associated with the rates of
29 progression.

30 **Conclusions.** There is no evidence to support that either diurnal or long-term IOP
31 fluctuation, as measured in clinical practice, are independent factors for glaucoma
32 progression; other aspects of IOP, including mean IOP and peak IOP, may be more
33 informative. OPA may be an independent factor for faster glaucoma progression.

34

35 **Keywords:** visual field progression; ocular pulse amplitude; risk factors; linear
36 mixed models.

37 INTRODUCTION

38 Intraocular pressure (IOP) is an established risk factor for glaucoma
39 progression, and lowering IOP is currently the only available treatment to slow the
40 disease progression.¹⁻⁴ Longitudinal measurement of IOP is crucial in evaluating
41 glaucoma patients, estimating their risk of developing progressive glaucomatous
42 damage, and assessing their response to treatment.

43 IOP is subject to fluctuations over time. Several IOP-derived parameters are
44 commonly used in clinical practice and research to summarize the behavior of IOP,
45 including mean IOP (average of IOP over multiple visits), peak IOP (highest IOP
46 reading over follow-up), and IOP fluctuation (standard deviation [SD] or range IOP
47 over time). Many studies have shown that mean IOP and peak IOP are
48 independently associated with glaucoma progression;^{1, 2, 5, 6} on the other hand, the
49 exact role of IOP fluctuation is still debated, with discordant results reported in the
50 literature.⁵⁻¹⁰ Elucidating the role of IOP fluctuation is difficult for several reasons.
51 IOP fluctuation is tightly correlated with other IOP-related metrics (e.g., mean IOP),
52 making it difficult to isolate its role as an independent factor. IOP fluctuation may be
53 artificially increased by escalating treatment in patients with suspect progression.
54 The effect of IOP fluctuation may not be uniform, varying as a function of the disease
55 stage, treatment status, mean IOP values, and definition of fluctuation.¹¹

56 This planned secondary analysis of the United Kingdom Glaucoma Treatment
57 Study (UKGTS) randomized controlled trial aimed to evaluate whether IOP
58 fluctuation, as assessed by ocular pulse amplitude (OPA), diurnal variation and
59 between-visit variation, is independently associated with the rate of visual field
60 progression. The UKGTS is ideal for this purpose because there were no treatment

- 61 escalations artificially increasing IOP fluctuation, and the dataset allows evaluation of
- 62 IOP metrics in both untreated and treated glaucoma patients.

63 **METHODS**

64 *Study Population and Procedures*

65 This study was a planned secondary analysis of data from the UKGTS, which
66 was a multicenter, randomized, triple-masked, placebo-controlled trial investigating
67 the ability of Latanoprost, an IOP lowering medication, to preserve visual function in
68 newly diagnosed open-angle glaucoma patients (trial registration number,
69 ISRCTN96423140). The UKGTS and the subsequent analysis of anonymized data in
70 this study complied with the tenets of the Declaration of Helsinki and were approved
71 by local institutional review boards (Moorfields and Whittington Research Ethics
72 Committee on June 1, 2006, ethics approval reference, 09/H0721/56). All patients
73 provided written informed consent at the time of enrolment in the trial.

74 The UKGTS study protocol, baseline characteristics, and outcomes have
75 been published elsewhere.^{3, 12, 13} Participants recruited in 10 ophthalmology
76 institutions across the United Kingdom were randomized 1:1 to receive latanoprost
77 0.005% or placebo eye drops once in the evening in both eyes for 24 months or until
78 meeting an endpoint. The UKGTS included patients ≥ 18 years of age and newly
79 diagnosed treatment-naïve open-angle glaucoma, including primary open-angle and
80 pseudoexfoliation glaucoma. Exclusion criteria were: advanced glaucoma, as
81 defined by visual field mean deviation < -10 dB in the better eye or < -16 dB in the
82 worse eye, mean baseline IOP ≥ 30 mmHg, Snellen best-corrected visual acuity
83 (BCVA) $< 6/12$, and poor image quality (>40 μm mean pixel height standard
84 deviation) with the Heidelberg retina tomograph (Heidelberg Engineering,
85 Heidelberg, Germany).

86 Potentially eligible participants underwent two pre-randomization visits. After
87 meeting the study criteria and signing the written informed consent, participants were

88 randomized either to receive latanoprost 0.005% or placebo eye drops. Enrolled
89 subjects underwent IOP measurement, VF, and imaging at eleven post-
90 randomization visits over 24 months or until meeting an endpoint. Standard
91 automated perimetry with the Humphrey Field Analyzer (Carl Zeiss Meditec, Dublin,
92 CA) was performed with stimulus size III, Swedish Interactive Threshold Algorithm
93 (SITA) standard strategy, and 24-2 grid. VF testing was performed at all 11
94 scheduled visits over 24 months, and tests were clustered (2 VFs on the same day)
95 at baseline, 2 months, 16 months, 18 months, and 24 months. In this exploratory
96 analysis, we included participants from the UKGTS with ≥ 5 reliable visual fields
97 (VFs). Reliable VFs were defined as those with false positives less than 15%, while
98 no limits for false negatives and fixation losses were applied. At the first post-
99 randomization visit, the following demographic variables were collected: age, sex,
100 ethnicity, family history of glaucoma, history of systemic diseases (i.e., systemic
101 hypertension, cardiovascular disease, diabetes, heart attack, stroke, sleep apnea,
102 migraine, Raynaud's phenomenon, vasospasm, angina, claudication), and smoking
103 status. The following investigations were also performed: blood pressure
104 measurements with the Omron M7 Blood Pressure Monitor (Matsusaka, Mie, Japan),
105 weight, height, slit-lamp examination, refractive error measured either with an
106 autorefractor or from spectacle focimetry (if not available, the spherical equivalent of
107 the trial lens was used in the visual field test, based on participants' age), axial
108 length measurement with the IOL Master (Carl Zeiss Meditec, Dublin, CA), and
109 central corneal thickness (CCT) measured with an ultrasound pachymeter. We
110 included one eye per patient; specifically, the eye with the worst baseline VF mean
111 deviation (MD).

112

113 *IOP Metrics*

114 At all visits, IOP was measured with Goldmann applanation tonometry (GAT;
115 Haag Streit, Koeniz, Switzerland), Pascal dynamic contour tonometry (Ziemer
116 Ophthalmic Systems AG, Zurich, Switzerland), and the Ocular Response Analyzer
117 (Reichert, Inc., Buffalo, NY). Diurnal GAT phasing with IOP measured every 2 hours
118 from 9 am to 5 pm was performed at the first post-randomization and at the final visit.
119 At the first post-randomization visit, supine IOP was measured with Perkins
120 applanation tonometer.

121 The following IOP metrics were calculated and used for the analyses:

- 122 • Baseline pretreatment IOP, defined as the average of the IOP readings obtained
123 in the two pre-randomization visits.
- 124 • Mean IOP, defined as the average of all post-randomization IOP readings.
- 125 • Peak IOP, defined as the highest IOP reading of all post-randomization IOP
126 readings.
- 127 • Supine IOP, defined as the Perkins applanation tonometry IOP readings
128 measured at the first post-randomization visit.
- 129 • Phasing peak IOP, defined as the highest IOP reading of the diurnal phasing
130 performed at the first post-randomization visit.
- 131 • Diurnal IOP fluctuation, defined as the SD of IOP measurements obtained from
132 the diurnal IOP phasing performed at the first post-randomization visit. Diurnal
133 IOP fluctuation was also calculated using the IOP measurements from the last
134 post-randomization visit.
- 135 • Long-term IOP fluctuation, defined as the SD of post-randomization IOP
136 readings.

- 137 • Mean ocular pulse amplitude (OPA) from the Pascal Dynamic Contour tonometry.
138 OPA was defined as the range of the pulse wave contour and provides a
139 measure of how IOP fluctuates over cardiac cycle. We used the average of all
140 post-randomization ORA values.

141

142 *Statistical Analysis*

143 We performed all statistical analyses with the open-source software R (R
144 Foundation for Statistical Computing, Vienna, Austria). Variable distributions were
145 inspected with histograms and quantile-quantile plots. We reported mean (\pm
146 Standard deviation [SD]) and median (interquartile range [IQR]) for Gaussian and
147 non-Gaussian variables, respectively. We reported frequencies and proportions for
148 discrete variables. Proportion and pattern of missing data were analyzed. All
149 analyses were conducted with complete cases. All tests were 2-tailed, and p-values
150 <0.05 were considered statistically significant.

151 Demographic and clinical characteristics between the two treatment groups
152 were compared with t-test and chi-squared test for continuous and categorical
153 variables, respectively. Agreement between diurnal IOP fluctuation calculated on the
154 first and last post-randomization visit was investigated with Bland-Altman statistics.
155 We also collected the timing of each IOP measurement and calculated the absolute
156 differences from each measurement and the mean time of day for each patient's IOP
157 measurements.

158 Linear models were used to evaluate the relationship between (i) mean IOP and
159 long-term IOP fluctuation, (ii) mean IOP and long-term IOP fluctuation/mean IOP, (iii)
160 mean diurnal IOP and diurnal IOP fluctuation, (iv) mean diurnal IOP and diurnal IOP

161 fluctuation/mean diurnal IOP, (v) mean OPA and mean IOP, and (vi) mean
162 OPA/GAT IOP and mean IOP.

163 IOP fluctuation is known to be positively correlated with mean IOP. Additionally,
164 measurement error can contribute to the variability in IOP measurements, potentially
165 confounding true IOP fluctuation. To obtain a measure of IOP fluctuation which is
166 independent from mean IOP, we performed a normalization of IOP fluctuation
167 values. Specifically, we ran a linear regression of IOP fluctuation against mean IOP.
168 We then divided the observed IOP fluctuation values by the corresponding predicted
169 values. This process was applied distinctly for each fluctuation metric. For long-term
170 fluctuation, we utilized the SD of all post-randomization IOP readings and their
171 corresponding mean IOP values from all post-randomization readings. For diurnal
172 fluctuation, we used the SD and mean IOP measurements from the diurnal IOP
173 phasing conducted during the first post-randomization visit. For the OPA, we used
174 the average of all post-randomization ORA values for each subject and their
175 corresponding mean IOP across all available post-randomization visits. For OPA, we
176 calculated the average of all post-randomization ORA values for each subject,
177 alongside their corresponding mean IOP from all available post-randomization visits.

178 As shown in Figure S1, normalized IOP fluctuation was unrelated to mean IOP.
179 Normalization was further performed on the two study arms separately, leading to
180 almost identical results (data not shown). All analyses were conducted on both
181 normalized and unnormalized IOP fluctuations values.

182 Linear mixed models with random slopes and random intercepts were used to
183 estimate the rates of progression and investigate associations between the rate of
184 visual field progression and variables of interest. Linear mixed models are an
185 extension of traditional linear models, which can accommodate the repeated-

186 measure (e.g., multiple measurements from the same eye over time) and clustered
187 (multiple test locations from the same VF) nature of data. We first look at univariable
188 associations between the MD rate of change and each variable of interest. In all
189 models, the MD value at each visit was the outcome variable; the follow-up time in
190 years, the covariate of interest, and their interaction were the fixed effects; the eye
191 identification number and follow-up time were the random intercept and random
192 slope terms, respectively, to account for the repeated measure of data and for the
193 fact that different eyes may have different rates of progression over time. Interactions
194 between covariates and time from baseline modeled the variables' effect on the
195 progression rate. We then built multiple variable linear mixed models to account for
196 the impact of fluctuation metrics after adjusting for all other potentially confounding
197 factors, including other IOP metrics. Correlations among candidate covariates were
198 tested with a hierarchical cluster analysis based on the absolute value of Spearman
199 correlations (Figure S2). Some of the variables measuring the magnitude of IOP
200 elevation exhibited high correlations. Highly correlated variables are a source of
201 multicollinearity, causing unstable regression coefficients and large standard errors.
202 To address this issue, all correlated metrics measuring IOP (baseline IOP, peak IOP,
203 mean IOP, supine IOP, peak phasing IOP) were combined using Principal
204 Component Analysis (PCA). These variables had a |Spearman rho| of 0.50 or
205 greater. PCA extracts uncorrelated orthogonal vectors (Principal Components [PCs])
206 from multiple correlated variables. PCs are ranked, with the first PC (PC1) being the
207 one containing the largest amount of combined information from the correlated
208 variables. PCA was performed on standardized data, with zero mean and unit
209 variance. We inspected the PCA model with biplots and scree plots (Figure S3).
210 Scree plots were used to visualize the amount of variance explained by the various

211 Principal Components and to select the number of PCs to retain for subsequent
212 analyses. PC1 was selected for further analyses, as it explained 81% of the overall
213 variance in the PCA, and used as a fixed effect in the multivariable linear mixed
214 models. The Interaction between PC1 and follow-up time modelled the effect of PC1
215 on visual field progression rates, as previously explained. PCA was also performed
216 on the two study arms separately, leading to similar results (data not shown).

217 Similar analyses were run in a pointwise manner, including: (i) all 52 VF test
218 locations of the 24-2 grid (after excluding the two locations corresponding to the blind
219 spot), and (ii) the five fastest progressing locations for each study eye (which is
220 conceptually similar to the event-based GPA analysis which identifies the 3 or more
221 locations most different from baseline). Models conducted on the pointwise threshold
222 sensitivity data had a nested random intercept with eye identification number over
223 the test location number to account for the inclusion of multiple pointwise series from
224 the same eye. All models were run separately in the placebo and treatment arms.
225 Regression estimates along with their 95% confidence intervals (95% CIs) and p-
226 values were reported.

227 RESULTS

228 Of the 461 participants with longitudinal data included in the primary UKGTS
229 analysis, 31 were excluded because of an insufficient number of VFs. The remaining
230 430 (placebo arm: 213, treatment arm: 217) participants were included in this study.
231 As shown in Figure S4, most variables had complete observations, with only a few
232 variables having missing observations. Spherical equivalent, CCT, and supine IOP
233 values were missing in 26 eyes (6%), 16 (3.7%), and 15 eyes (3.5%), respectively.
234 Mean arterial pressure, body mass index, ethnicity, corneal hysteresis, peak and
235 mean phasing IOP, and diurnal fluctuation were missing in less than 2% of patients.
236 All other variables had no missing data.

237 Baseline characteristics of the UKGTS study population have been published
238 elsewhere.^{3, 12} Table 1 illustrates the main demographic and clinical characteristics
239 of the patient cohort. Patients in the treatment cohort had significantly longer follow-
240 up time than those in the placebo cohort, with a median (IQR) of 1.9 (1.3 to 2.0) and
241 1.6 (1.0 to 2.0) years, respectively ($p=0.004$). The number of VFs was also
242 significantly greater ($p=0.027$) in the treatment arm (median [IQR]: 15 [10-16]) than in
243 the placebo arm (median [IQR]: 13 [10-16]). In the post-randomization study period,
244 patients in the treatment arm showed higher mean corneal hysteresis than those in
245 the placebo arm (mean [\pm SD]: 9.4 [\pm 1.6] vs. 8.9 [\pm 1.6] mmHg, $p=0.003$). As shown in
246 Figure 5, all post-randomization IOP metrics were significantly different between the
247 two arms ($p<0.045$ or below), except for normalized diurnal IOP fluctuation ($p=0.89$)
248 and normalized OPA ($p=0.93$). The median of the absolute differences from the
249 mean time of day for each patient's IOP measurements was 1.1 hours, with an
250 interquartile range (IQR) of 0.5 hours (30 minutes) to 2.0 hours.

251

252 *Global MD rate*

253 The distribution of MD rates in the two groups as estimated with linear mixed
254 models is illustrated in Figure 6. Median (IQR) MD rates in the placebo and
255 treatment cohort were -0.23 (-0.73 to 0.11) dB/year and 0.13 (-0.30 to 0.37) dB/year,
256 respectively ($p < 0.001$).

257 In the univariable analysis (Table S2), higher values of all non-fluctuation IOP
258 parameters, including pretreatment baseline IOP (estimate [standard error (SE)]: -
259 0.06 [0.02] dB/year for 1 mmHg increase, $p < 0.001$), mean IOP (estimate [SE]: -0.08
260 [0.02] dB/year for 1 mmHg increase, $p < 0.001$), peak IOP (estimate [SE]: -0.07 [0.01]
261 dB/year for 1 mmHg increase, $p < 0.001$), peak phasing IOP (estimate [SE]: -0.05
262 [0.02] dB/year for 1 mmHg increase, $p < 0.001$), and supine IOP (estimate [SE]: -0.06
263 [0.01] dB/year for 1 mmHg increase, $p < 0.001$), were significantly associated with
264 faster MD rates in the placebo group. With regards to the IOP fluctuations
265 parameters, higher long-term IOP fluctuation (estimate [SE]: -0.27 [0.07] dB/year for
266 1 mmHg increase, $p < 0.001$) and OPA (estimate [SE]: -0.32 [0.09] dB/year for 1
267 mmHg increase, $p < 0.001$) were associated with faster MD rates of change, while
268 diurnal IOP fluctuation was not ($p = 0.23$). None of the fluctuation parameters was
269 associated with the MD rate after normalizing for the mean IOP ($p = 0.11$ or above). In
270 the treatment arm, none of the variables was significantly associated with the MD
271 rate, except for long-term IOP fluctuation (estimate [SE]: -0.12 [0.06] dB/year for 1
272 mmHg increase, $p = 0.047$).

273 Results of the multivariable model for factors associated with MD rate of
274 progression are illustrated in Figure 7 and detailed in Table S3. In the placebo arm,
275 PC1, which combined information from all the non-fluctuation IOP parameters, was
276 the only factor associated with the MD rate (estimate [SE]: -0.19 [0.08] dB/year for 1

277 unit increase, $p < 0.001$), while the various normalized IOP fluctuation metrics were
278 not. Thinner CCT had an association of borderline statistical significance with faster
279 VF progression rates (estimate [SE]: 0.05 [0.02] dB/year for 10 μm thicker, $p = 0.06$).
280 None of the variables was significantly associated with the MD rate of progression in
281 the treatment arm. Older age was associated with faster MD rates (estimate [SE]: -
282 0.12 [0.06] dB/year for a 10-year increase) in the treatment arm, but this only
283 approached nominal statistical significance ($p = 0.06$). Similar results were obtained
284 when analyzing unnormalized IOP fluctuation metrics (Table S4).

285

286 *Pointwise Rates*

287 Figure 6 illustrates the distribution of pointwise progression rates in the two
288 groups. Pointwise rates were significantly faster in the placebo group than in the
289 treatment group (median [IQR]: -0.42 [-0.59 to -0.26] dB/year vs. 0.03 [-0.14 to 0.19]
290 dB/year, $p < 0.001$). Results of the univariable analysis for factors associated with the
291 pointwise rates of change are illustrated in Table S5. In the placebo group, all the
292 non-fluctuation IOP parameters were significantly associated with the pointwise rates
293 ($p = 0.003$ or below). Higher unnormalized long-term IOP fluctuation (estimate [SE]: -
294 0.34 [0.13] dB/year for 1 mmHg increase, $p = 0.008$) and OPA (estimate [SE]: -0.65
295 [0.15] dB/year for 1 mmHg increase, $p < 0.001$) were associated with faster pointwise
296 rates of progression. After normalizing IOP fluctuations for mean IOP, only OPA was
297 associated with the rate of progression (estimate [SE]: -1.36 [0.48] dB/year for 1 unit
298 increase, $p = 0.005$). In the treatment arm, none of the IOP variables was associated
299 with the pointwise rates of progression. In the multiple variable model (Figure 8 and
300 Table S6), normalized mean OPA was associated with the pointwise rates of
301 progression in the placebo arm (estimate [SE]: -1.23 [0.46] dB/year for 1 unit

302 increase, $p=0.009$), but not in the treatment arm. None of the other fluctuation
303 metrics was associated with the rate of progression in either group. The combined
304 IOP metric, PC1, was associated with the pointwise rate of change in the placebo
305 group ($p<0.001$), but not in the treatment group ($p=0.42$). Similarly, none of the
306 unnormalized IOP fluctuation metrics was associated with the pointwise rate of
307 change metrics (Table S7), except for mean OPA in the placebo group (estimate
308 [SE]: $-0.47 [0.17]$ dB/year for 1 mmHg increase, $p=0.008$).

309 For the five fastest progressing locations, median (IQR) pointwise rates of the
310 five in the placebo and treatment cohort were $-1.00 (-1.49 \text{ to } -0.80)$ dB/year and $-$
311 $0.52 (-0.93 \text{ to } -0.34)$ dB/year, respectively ($p<0.001$). Results of the univariable
312 analysis for factors associated with the rates of the fastest five locations are
313 illustrated in Table S8. In the placebo group, all the non-fluctuation IOP parameters
314 were significantly associated with the pointwise rates ($p=0.003$ or below). Higher
315 unnormalized (estimate [SE]: $-1.67 [0.34]$ dB/year for 1 mmHg increase, $p<0.001$)
316 and normalized OPA (estimate [SE]: $-3.95 [1.10]$ dB/year for 1 unit increase,
317 $p<0.001$) were associated with faster rates of progression. In the treatment arm,
318 higher unnormalized long-term IOP fluctuation was associated with faster rates of
319 progression (estimate [SE]: $-0.46 [0.17]$ dB/year for 1 mmHg increase, $p=0.006$), but
320 the association was no longer significant after normalizing IOP fluctuation (estimate
321 [SE]: $-0.81 [0.44]$ dB/year for 1 unit increase, $p=0.06$). In the multiple variable model
322 (Figure 9 and Table S9), CCT (estimate [SE]: $0.26 [0.10]$ dB/year for 10 μm thicker,
323 $p=0.01$), normalized OPA (estimate [SE]: $-3.50 [1.04]$ dB/year for 1 unit increase,
324 $p=0.001$), and PC1 (estimate [SE]: $-0.58 [0.16]$ dB/year for 1 PC1 unit increase,
325 $p<0.001$) were associated with the rates of progression of the fastest five test
326 locations in the placebo group; while normalized diurnal and long-term IOP

327 fluctuations were not. In the treatment group, PC1 (estimate [SE]: -0.27 [0.12]
328 dB/year for 1 PC1 unit increase, $p=0.028$) was the only factor associated with
329 progression rates. Results of the nonnormalized models are shown in Table S10.
330 All analyses were repeated with mean IOP, peak IOP and normalized LTF fluctuation
331 calculated from corneal compensated IOP as measured with the Ocular Response
332 Analyzer (Reichert, Inc, Buffalo, NY) and lead to similar results (Figures S10-S14).

333 **DISCUSSION**

334 In this study, we evaluated whether IOP fluctuation was associated with the
335 rate of glaucomatous visual field progression. We provided a comprehensive
336 evaluation of clinically relevant definitions of IOP fluctuation over the course of
337 seconds (OPA), office hours (diurnal fluctuation), and multiple visits over the entire
338 follow-up (long-term fluctuation). We found that higher OPA was associated with
339 faster rates of progression, while diurnal or long-term IOP fluctuations were not
340 associated with the rate of progression. Elevated IOP metrics (e.g., mean IOP, peak
341 IOP) were consistently associated with the rate of VF progression.

342 Establishing the relationship between IOP fluctuation and the rates of visual
343 field progression is not an easy task for many reasons. First, IOP fluctuation may
344 vary as a function of the time frame over which it is calculated, and there is no
345 consensus on which type of fluctuation is most informative. Our study provided a
346 comprehensive approach, analyzing three measures of fluctuations. Second, the
347 definition of IOP fluctuation is not uniform across studies, with IOP range and SD
348 IOP usually used as measures for IOP fluctuation. It has been suggested that SD
349 IOP could be a more robust metric than range IOP as the latter may be heavily
350 influenced by outliers and does not account for the number of IOP measurements.⁸
351 In this study, we used SD IOP to calculate diurnal and long-term IOP fluctuation; on
352 the other hand, OPA, a measure of very short-term fluctuation, was an average
353 range of several cardiac cycles. We further mitigated the effect of potential outliers
354 on OPA by obtaining two consecutive OPA measurements at each time point,
355 averaging them to have a single value, and then averaging the resulting values
356 throughout all available follow-up visits. Third, isolating the impact of fluctuation from
357 the level of IOP may be challenging because of the intimate relationship between

358 these two variables. IOP fluctuation is known to be positively correlated with mean
359 IOP. In a retrospective study performed on non-human primates of experimental
360 glaucoma, Gardiner and colleagues¹⁰ used the coefficient of variation (SD IOP
361 divided by mean IOP) to remove the relationship between these two variables. In our
362 cohort, the coefficient of variation reversed the association with mean IOP values,
363 leading to a negative relationship between IOP fluctuation and mean IOP. The
364 explanation for this is likely that there are two components of variability
365 (measurement error and true IOP fluctuation), one of which (true fluctuation) is
366 related to mean IOP and the other (measurement error) is not.¹⁴ Dividing the
367 measurement error by the mean IOP induces the negative association. The method
368 of normalization used in our study likely respects both the increased fluctuations at
369 higher mean IOP and constant measurement errors. Fourth, IOP-related metrics
370 tend to be highly correlated because they are related to the same original quantity.
371 Modeling highly correlated variables may lead to a statistical issue called
372 multicollinearity. In the presence of multicollinearity, regression models may become
373 inefficient with loss of statistical power, greater computation inaccuracy, unstable
374 estimates, and high variance.¹⁵ Various methods have been proposed to deal with
375 multicollinearity. One or more highly collinear covariates may be omitted from the
376 regression model, which may cause information loss. Ridge regression, a form of
377 penalized linear regression, is another popular method to handle multicollinearity;
378 however, it produces biased estimates and is better suited for predictive rather than
379 explanatory models.¹⁶ In our study, we addressed the issue of multicollinearity with
380 PCA, which creates a new set of orthogonal linear combinations of the original
381 variables (PCs), by definition perfectly uncorrelated to each other.¹⁷ In this study, we
382 used PCA to obtain a maximally informative combined metric of IOP control. Fifth,

383 clinicians are more likely to escalate treatment in progressing patients, inducing IOP
384 fluctuation. This may be easily overlooked in retrospective cohort studies and even in
385 prospective studies if countermeasures are not adopted. The findings of previous
386 studies have been greatly questioned because of the possible bias caused by
387 medical and surgical treatment escalation. Our study is not vulnerable to the
388 potential confounding effect of treatment escalation as patients in the UKGTS took
389 either latanoprost or placebo for their entire study period. In addition, our study is in
390 the unique position to elucidate the role of IOP fluctuation on glaucomatous
391 progression in untreated patients.

392 The relationship between IOP fluctuation and glaucomatous progression
393 remains highly controversial, with contrasting results reported in the literature.
394 Comparisons of results from different studies, including ours, should be done with
395 caution because of heterogeneity in study populations, designs, definitions of
396 fluctuation and progression, and statistical analysis. Most of the previous studies
397 focused on long-term (intervisit) IOP fluctuation, which is the most accessible
398 fluctuation metric to obtain as it can be estimated from single IOP measurements
399 from multiple visits. Our study did not find any relationship between long-term IOP
400 fluctuation and VF progression rates. Bengtsson et al.⁵ conducted a post-hoc
401 analysis from the Early Manifest Glaucoma Trial (EMGT); they found that mean IOP
402 was a strong predictor of glaucoma progression, while IOP fluctuation was not.
403 EMGT and UKGTS share many similarities, including the mild disease stage, type of
404 treatment (i.e., nonsurgical intervention), and mean IOP values. An observational
405 study by Medeiros et al.¹⁸ investigated whether IOP fluctuations were associated
406 with the risk of conversion from ocular hypertensive to glaucoma and found that
407 mean IOP, but not long-term IOP fluctuation, was associated with glaucoma

408 development. Other studies found contrasting results, showing a positive association
409 between long-term IOP fluctuation and VF progression. In a post-hoc analysis of the
410 Advanced Glaucoma Intervention Study (AGIS), Nouri-Mahdavi and colleagues⁹
411 found that long-term IOP fluctuation was an independent risk factor for glaucoma
412 progression, while mean IOP was not. The results of this study were criticized
413 because the authors analyzed the entire available follow-up, including time points
414 after treatment escalation. Further intervention, either in the form of trabeculectomy
415 or laser trabeculoplasty as per AGIS protocol, might have been itself a cause of
416 clinician-induced increased fluctuation in patients at high risk of progression. In a
417 subsequent post-hoc analysis of the AGIS, Caprioli and Coleman⁸ investigated the
418 relationship between long-term IOP fluctuation and VF progression, excluding those
419 patients having multiple interventions; they found that long-term IOP fluctuations was
420 significantly associated with VF progression in patients with low mean IOP, but not in
421 those with high IOP. A post-hoc analysis from the Collaborative Initial Glaucoma
422 Treatment Study (CIGTS)⁶ examined the role of various IOP parameters on VF
423 progression and found that long-term IOP fluctuation and peak IOP were associated
424 with VF progression, while mean IOP was not.

425 The literature on the role of diurnal (or diurnal-nocturnal) IOP fluctuation is
426 scarce, of lower quality, and with conflicting reports. In the Malmö Ocular
427 Hypertension study,¹⁹ diurnal IOP fluctuation was not an independent risk factors for
428 the development of glaucoma; conversely, mean IOP was associated with the
429 incidence of glaucomatous visual field loss in patients with OHT. Our study did not
430 find an association between diurnal IOP fluctuation and the rate of glaucomatous
431 progression in any of the models, corroborating the findings of the Malmö Ocular
432 Hypertension study. In a secondary analysis from a Swedish clinical trial

433 randomizing patients to either pilocarpine or argon laser trabeculoplasty, Bergea et
434 al.²⁰ investigated the relationship between visual field progression and different IOP
435 variables, and they found that both mean IOP and diurnal IOP fluctuation were
436 associated with visual field progression. That study, however, had several limitations,
437 including the small sample size (76 eyes), high proportion of pseudoexfoliation
438 glaucoma (72%), and the use of range IOP as a measure of fluctuation, which is
439 vulnerable to outlier and highly related to peak IOP. A retrospective study by Matlach
440 and colleagues²¹ assessed the impact of long-term and diurnal-nocturnal IOP
441 fluctuation on glaucoma progression in a cohort of 120 glaucoma patients randomly
442 selected from a tertiary referral center; they found that diurnal-nocturnal IOP
443 fluctuation was associated with glaucoma progression, while long-term IOP
444 fluctuation and mean IOP were not. A retrospective study by Kim et al.²² found
445 similar results in a cohort of NTG patients, with higher diurnal IOP fluctuations and
446 disc hemorrhages being associated with higher hazard of visual field progression.
447 Both these studies are limited by their retrospective nature, making them vulnerable
448 to potential confounders and selection bias. Also, these studies did not employ any
449 statistical method to mitigate multicollinearity.

450 Besides including these two established measures of IOP fluctuation, we also
451 investigated the role of very short-term fluctuation, as measured by the mean ocular
452 pulse amplitude (OPA) over follow-up. OPA is calculated as the difference between
453 systolic and diastolic IOP, as measured by the Pascal dynamic contour tonometer,
454 and informs on how IOP varies across the cardiac cycle, secondary to the pulsatile
455 influx/efflux of blood volume into the eye (mainly to choroid). Ocular pulse may be
456 determined by various ocular and systemic factors, including ocular tissue rigidity,²³⁻
457 ²⁵ axial length,²⁶ IOP,^{23, 27} blood pressure pulse amplitude,^{28, 29} left ventricular

458 ejection time,³⁰ heart rate,^{31, 32} and conditions influencing ocular perfusion (e.g.,
459 carotid artery stenosis, tight encircling band).^{33, 34} To the best of our knowledge,
460 there are currently no clinical studies investigating the role of OPA (or any metric for
461 very short IOP fluctuation) on glaucoma progression. We found that higher OPA was
462 significantly associated with faster pointwise rates of progression in the placebo
463 group. Reasons for this finding are speculative. This association may result from an
464 effect of the OPA itself or be related to one or more of its determinants. Animal
465 studies have shown that acute IOP elevation may induce structural optic nerve head
466 deformations and functional electrophysiological changes. Hence, multiple transient
467 IOP spikes may cause faster glaucoma progression in vulnerable eyes. This
468 explanation seems unlikely as these studies investigated large IOP changes, much
469 larger than those measured with OPA. Higher OPA is associated with increased
470 scleral rigidity and stiffer ocular tissues, which may be less compliant to IOP
471 changes, causing larger stress within the lamina cribrosa secondary to IOP
472 elevation.^{35, 36} In a simulation study based on finite element analysis reconstructing a
473 healthy eye model, Jin et al.³⁶ found that stiffer sclera was associated with higher
474 OPA, larger ONH deformation, and increased shearing forces to neural axons of the
475 neuroretinal rim. OPA has been proposed as a surrogate measure for
476 hemodynamics, being influenced by the arterial pulse pressure, heart rate, and left-
477 ventricular ejection time. Low diastolic blood pressure, vascular dysregulation and
478 optic nerve hypoperfusion have been associated with glaucoma progression,
479 especially in some phenotypes of open-angle glaucoma. However, one would expect
480 an opposite association to that found in this study, as lower OPA has been
481 associated with lower ocular blood supply. On the other hand, larger arterial pulse
482 pressure is associated with systemic hypertension, which may lead to vascular

483 damage. So, high OPA might be a surrogate for hypertensive vascular damage, and
484 previous studies^{37, 38} have shown that high blood pressure may be a risk factors for
485 primary open-angle glaucoma.

486 Our study confirms the importance of elevated IOP on glaucoma progression.
487 PC1, which combined information from various IOP parameters (i.e., mean IOP,
488 peak IOP, baseline IOP, peak phasing IOP, and supine IOP), was consistently
489 associated with the rate of visual field progression in the placebo group. On the other
490 hand, such a relationship was significant in the treatment group only for the rates of
491 the fastest five visual field locations, but not for global rates of change. The
492 progression rate of the treatment arm was extremely slow during the trial duration,
493 and the signal from a few progressing locations may be obscured by the overall
494 stability of most test locations. Comparative studies^{39, 40} have shown that pointwise
495 methods (especially those considering only locations with significant deterioration)
496 have higher sensitivity and require less time to detect progression than those based
497 on global indices or all test locations. Our study does not provide any information on
498 which IOP metric is the most important for disease progression; this is arduous to
499 tackle because of the intimate relationship among these variables. De Moraes and
500 colleagues² evaluated the effect of mean IOP, peak IOP, and SD IOP in a large
501 retrospective cohort of glaucoma patients under clinical care; they found that all
502 these variables were associated with disease progression in the univariable analysis,
503 but only peak IOP was significantly associated with VF progression in the
504 multivariable model. However, mean IOP and peak IOP are highly correlated, and a
505 multivariable model containing both variables would likely suffer from
506 multicollinearity. Treatment modifications highly influence mean IOP and SD IOP in

507 real-world settings; although the occurrence of glaucoma surgery during follow-up
508 was taken into consideration, medical treatment escalation was not.

509 We also investigated the impact of non-IOP and other ocular factors on
510 glaucomatous progression rates, including age, CCT, and corneal hysteresis. The
511 evidence for role of CCT as a risk factor for glaucoma progression is often
512 misunderstood. A thinner cornea causes artifacts in applanation tonometry, with
513 underestimation of the true IOP.⁴¹ Alternatively, corneal thickness may serve as a
514 biomarker of the biomechanical properties of the lamina cribrosa and peripapillary
515 sclera, providing insights into the vulnerability of the optic nerve to increased IOP.⁴²
516 An experimental study by Wells and colleagues⁴³ investigated whether CCT was
517 associated with optic disc compliance after inducing acute IOP rise and found no
518 significant association, indicating that CCT may not reflect ocular biomechanics. In
519 our cohort, thinner CCT was associated with faster progression rates in some
520 multivariable models (which included IOP metrics), while it did not show significance
521 in any of the univariable models. This suggests that CCT alone is not directly
522 associated with glaucoma progression: rather, it becomes statistically significant
523 when measured IOP is included in the model due to the effect of CCT on measured
524 IOP. Other studies, including the Early Manifest Glaucoma Treatment (EMGT)⁴⁴ and
525 the Los Angeles Latino Eye Study (LALES),⁴⁵ found similar finding, associating thin
526 CCT with conversion to glaucoma and incident glaucoma in multivariable models,
527 but not in univariable models. Khawaja and Jansonius⁴⁶ performed a simulation
528 study that mimicked datasets similar to the LALES and Ocular Hypertensive
529 Treatment Study so that IOP, but not CCT, was not associated with glaucoma risk.
530 Consistent with our findings and those from other studies, they found that CCT was
531 not associated with the risk of glaucoma in the univariable model, but a spurious

532 association between CCT and glaucoma appeared when measured IOP was added
533 to the model.

534 Although previous studies⁴⁷⁻⁴⁹ have shown a relationship between corneal
535 hysteresis and visual field progression rates, we were not able to confirm such
536 association in our cohort. In any given eye, corneal hysteresis is inversely related to
537 IOP. Therefore, low corneal hysteresis may reflect high IOP, which is an established
538 risk factors for faster glaucoma progression. Also, corneal hysteresis is directly
539 related to corneal stiffness and thickness. Hence, IOP might have underestimated in
540 patients with low corneal hysteresis, with consequent undertreatment leading to
541 faster progression.

542 Many studies have reported an association between older age and faster
543 progression rates.^{1, 44, 50, 51} In our study, older age was associated with faster MD
544 (but not pointwise) progression rates in the latanoprost group but not in the placebo
545 group. Ageing causes the lamina cribrosa to become stiffer and less compliant,
546 potentially reducing its ability and that of peripapillary sclera to comply with IOP
547 changes. Girard and colleagues³⁵ investigated the age-related biomechanical
548 differences in monkey posterior sclera and found that older animals had higher
549 tensile stress secondary to IOP elevation than younger ones. As tensile stress
550 increased non-linearly with IOP rise, the impact of ageing should theoretically be
551 more pronounced in patients with higher mean IOP; however, we found that older
552 age was associated with worse progression rates in the treatment arm, which had
553 lower mean IOP than the placebo arm. This finding is in agreement with a large
554 retrospective cohort study by De Moraes and colleagues², reporting that older age
555 was independently associated with glaucomatous VF progression only in patients
556 with lower mean IOP. Similar findings were found in the JAMDIG study, a large

557 retrospective study conducted in Japanese patients with fairly low mean IOP
558 values.⁵⁰ An explanation to these findings may be that the impact of non-IOP factors,
559 including age, becomes more important only after substantially lowering the IOP.

560 This study has limitations. This was a planned secondary analysis based on
561 the UKGTS dataset and the number of subjects and the duration of follow-up may
562 not provide enough statistical power to identify a meaningful relationship between
563 IOP fluctuation and visual field progression, especially in the treatment arm, where
564 progression rates were extremely slow over the study period. The study cohort
565 included treatment-naïve primary open-glaucoma patients, mainly of European
566 descent and with early glaucomatous damage. Some authors¹¹ have hypothesized
567 that the effect of IOP fluctuation on the rates of visual progression might vary as a
568 function of disease stage, mean IOP, glaucoma subtype, ethnicity, and treatment
569 modality (medical vs surgical intervention); hence, the results of this study may be
570 not entirely generalizable to other populations. Nevertheless, the results of this study
571 are in agreement with those from the EMGT analysis.⁵ The diurnal IOP fluctuation
572 calculation was based on five measurements obtained during the morning and
573 afternoon, and this study provides only IOP snapshots across the day and no
574 information on IOP fluctuation outside office hours. Although we used clinically
575 relevant definitions of IOP fluctuation, these measurements may not adequately
576 characterize short-term IOP variability. Diurnal phasing has been shown to be poorly
577 reproducible, indicating that single-day IOP measurements may not be sufficient to
578 accurately assess short-term fluctuations.⁵²⁻⁵⁵ Our findings are consistent with
579 existing literature in this field. A comparison between the two available diurnal IOP
580 curves revealed that the 95% limits of agreement were around 4 mmHg, aligning
581 closely with the most pronounced fluctuation extremes observed in this dataset

582 (Figure S15). Differences between diurnal IOP fluctuation calculated in the first and
583 last post-randomization visits were random and approximate a normal distribution
584 (Figure S16). Several studies^{56, 57} have documented a nocturnal peak in IOP,
585 primarily attributed to an increase in episcleral venous pressure when the body is in
586 a horizontal position. Although our study did not include night-time IOP
587 measurements, we did record IOP in a supine position, which is recognized as a
588 reasonable proxy for estimating nocturnal peak levels.⁵⁸ While devices for home IOP
589 monitoring^{59, 60} or continuous IOP tracking^{61, 62} have been introduced, they were not
590 collected in the UKGTS study and are generally reserved for research rather than
591 routine clinical use. Although the methodology employed in this study may not
592 capture the entire spectrum or precise patterns of IOP fluctuations, we adopted a
593 clinically relevant approach to defining diurnal IOP fluctuation.

594 In conclusion, this study finds no evidence to support that either diurnal or
595 long-term IOP fluctuation, defined in a clinically relevant manner, are independent
596 factors for glaucoma progression. Other aspects of IOP, such as mean IOP and
597 peak IOP, may be more informative. Higher OPA may be an independent factor for
598 faster glaucoma progression.

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610

611 During the preparation of this work the authors used chatGPT3.5 in order to improve
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789

790 **FIGURE LEGENDS**

791

792 **Figure 5.** Boxplots comparing the various IOP metrics in the placebo and treatment
793 groups. IOP: intraocular pressure; MD: mean deviation; OPA: ocular pulse
794 amplitude; SD: standard deviation.

795

796 **Figure 6.** Density plots for the distribution of MD (**left panel**) and pointwise (**right**
797 **panel**) rates of progression in the placebo and latanoprost groups. MD: mean
798 deviation. PLR: pointwise linear rates.

799

800 **Figure 7.** Forest plots for factors associated with the MD rates of progression in the
801 placebo (**left panel**) and treatment (**right panel**) group. Dots and bars indicate point
802 estimates and 95% confidence intervals, respectively. Estimates are intended for 1-
803 unit increase, unless specified otherwise. Combined IOP metrics PC1 is an unitless
804 variable, which combines fluctuation unrelated IOP metrics (baseline IOP, peak IOP,
805 mean IOP, supine IOP, peak phasing IOP) through Principal Component Analysis.
806 CCT: central corneal thickness; CH: corneal hysteresis; IOP: intraocular pressure;
807 MD: mean deviation; OPA: ocular pulse amplitude; PC1: principal component 1.

808

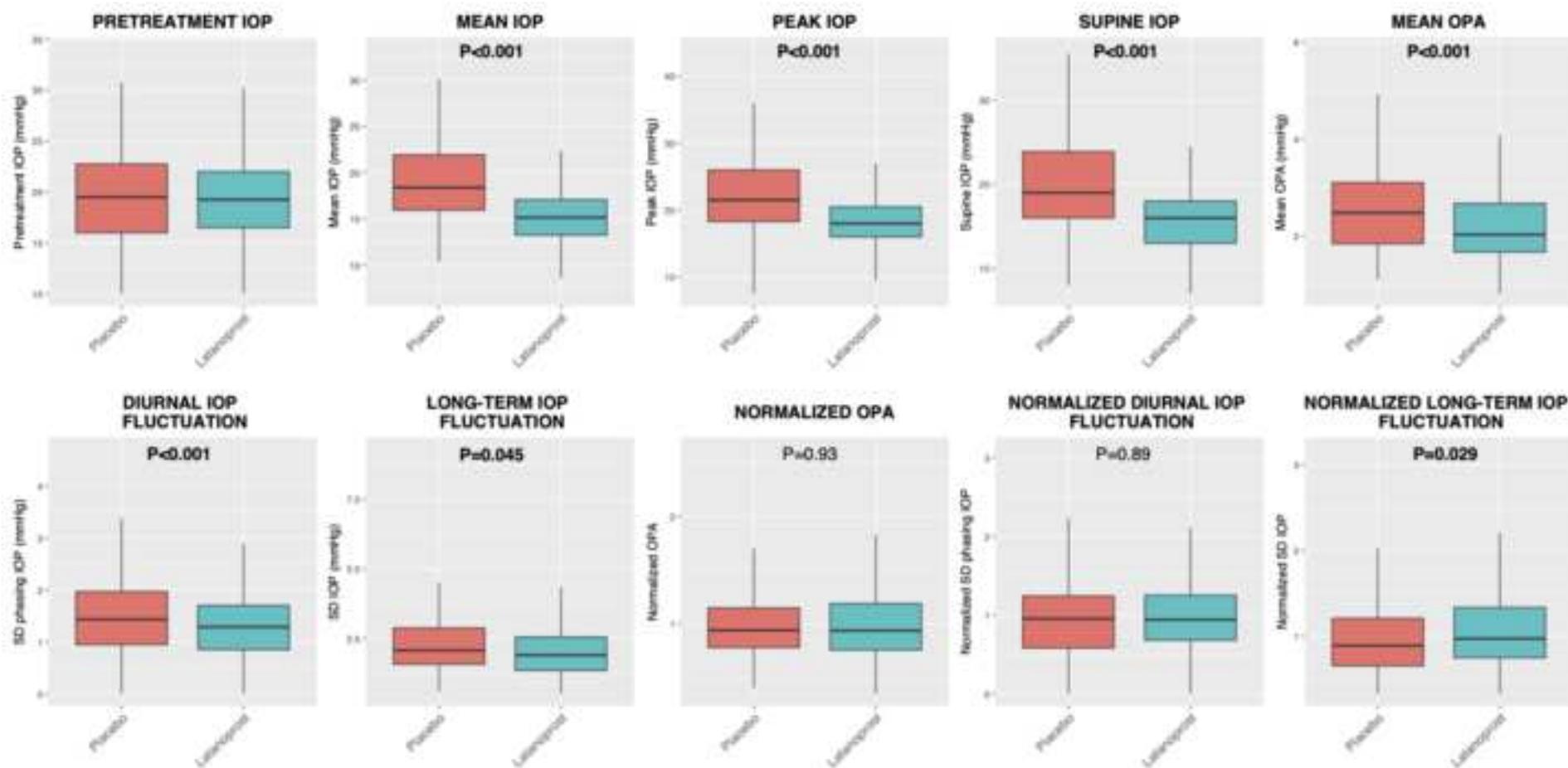
809 **Figure 8.** Forest plots for factors associated with the pointwise rates of progression
810 in the placebo (**left panel**) and treatment (**right panel**) group. Dots and bars indicate
811 point estimates and 95% confidence intervals, respectively. Estimates are intended
812 for 1-unit increase, unless specified otherwise. Combined IOP metrics PC1 is an
813 unitless variable, which combines fluctuation unrelated IOP metrics (baseline IOP,
814 peak IOP, mean IOP, supine IOP, peak phasing IOP) through Principal Component

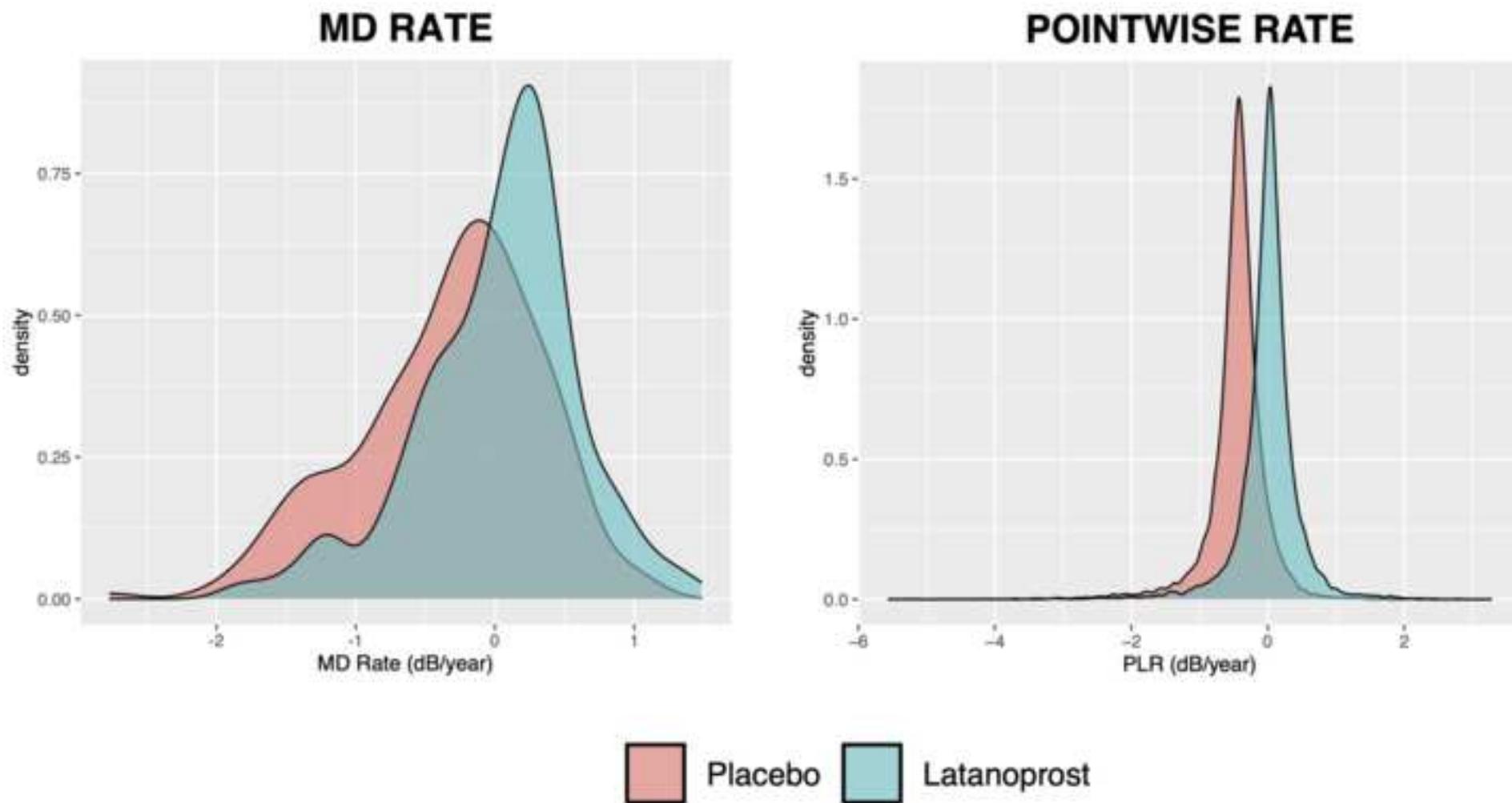
815 Analysis. CCT: central corneal thickness; CH: corneal hysteresis; IOP: intraocular
816 pressure; OPA: ocular pulse amplitude; PC1: principal component 1; PLR: pointwise
817 linear rates.

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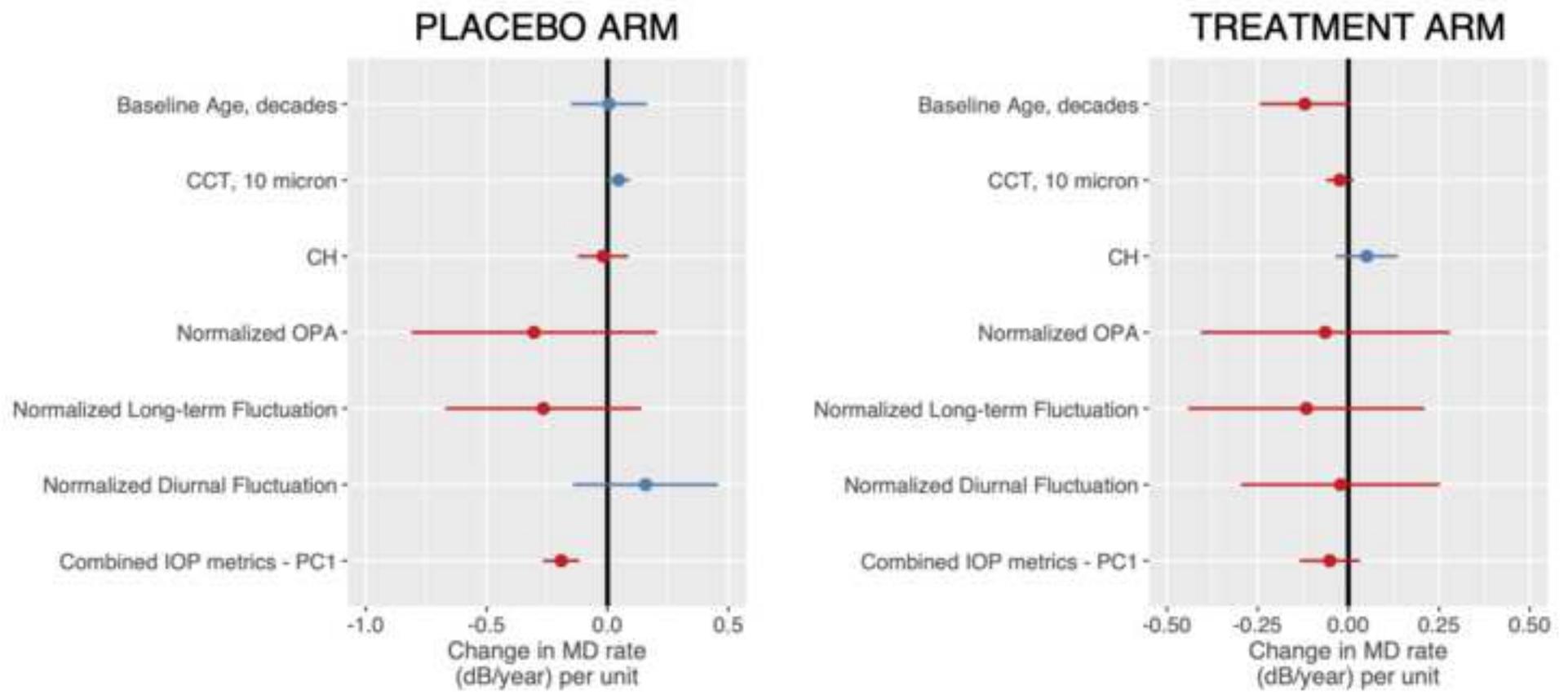
819 **Figure 9.** Forest plots for factors associated with the pointwise rates of progression
820 of the five fastest locations in the placebo (**left panel**) and treatment (**right panel**)
821 group. Dots and bars indicate point estimates and 95% confidence intervals,
822 respectively. Estimates are intended for 1-unit increase, unless specified otherwise.
823 Combined IOP metrics PC1 is an unitless variable, which combines fluctuation
824 unrelated IOP metrics (baseline IOP, peak IOP, mean IOP, supine IOP, peak
825 phasing IOP) through Principal Component Analysis. CCT: central corneal thickness;
826 CH: corneal hysteresis; IOP: intraocular pressure; OPA: ocular pulse amplitude;
827 PC1: principal component 1; PLR: pointwise linear rates.

Figure 5

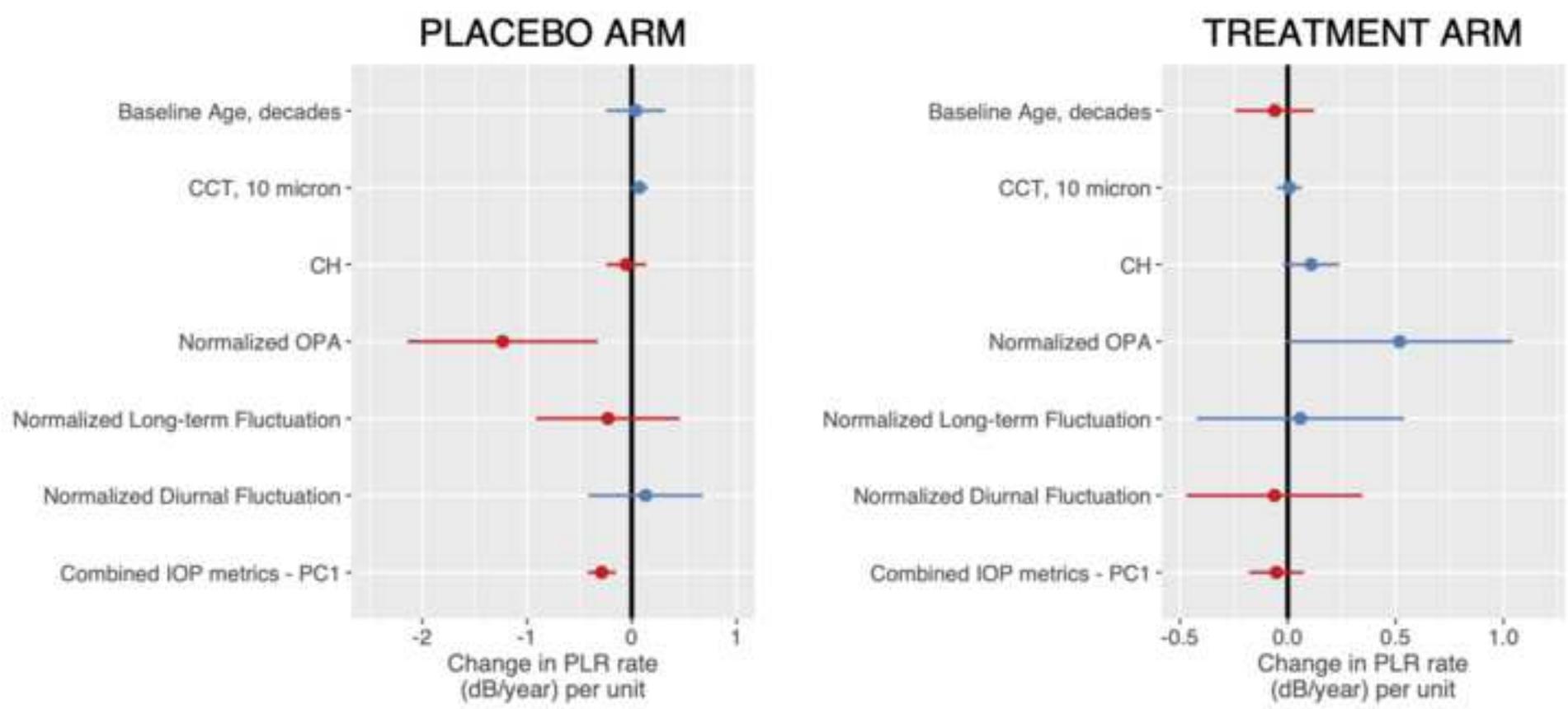




MD RATE



PLR – ALL LOCATIONS



PLR – 5 FASTEST LOCATIONS

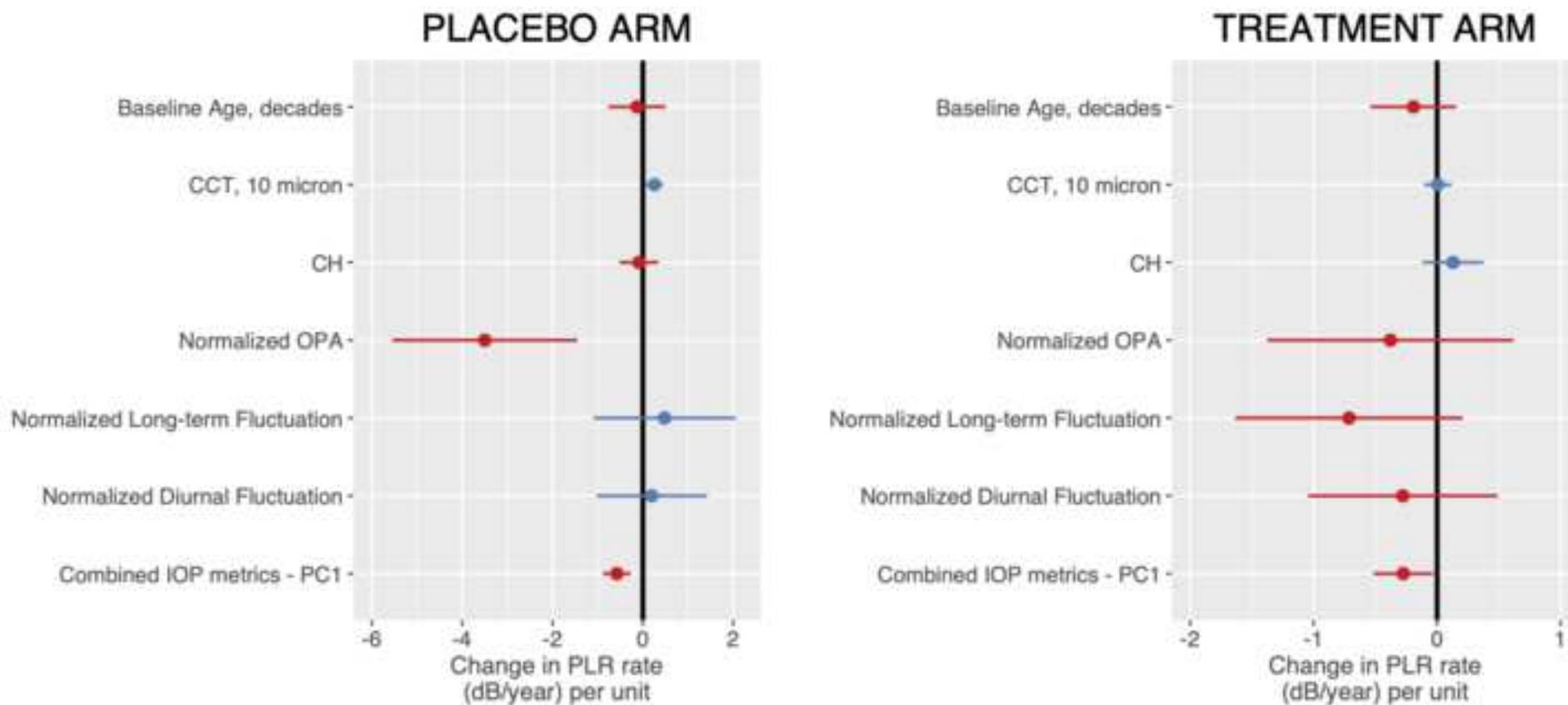
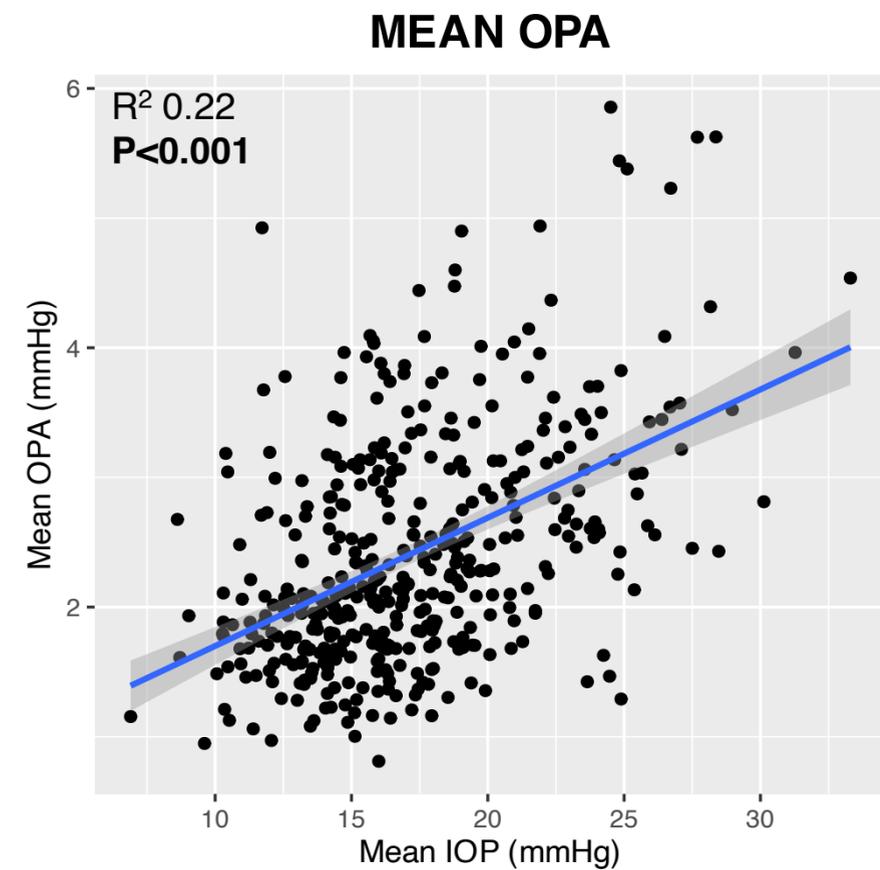
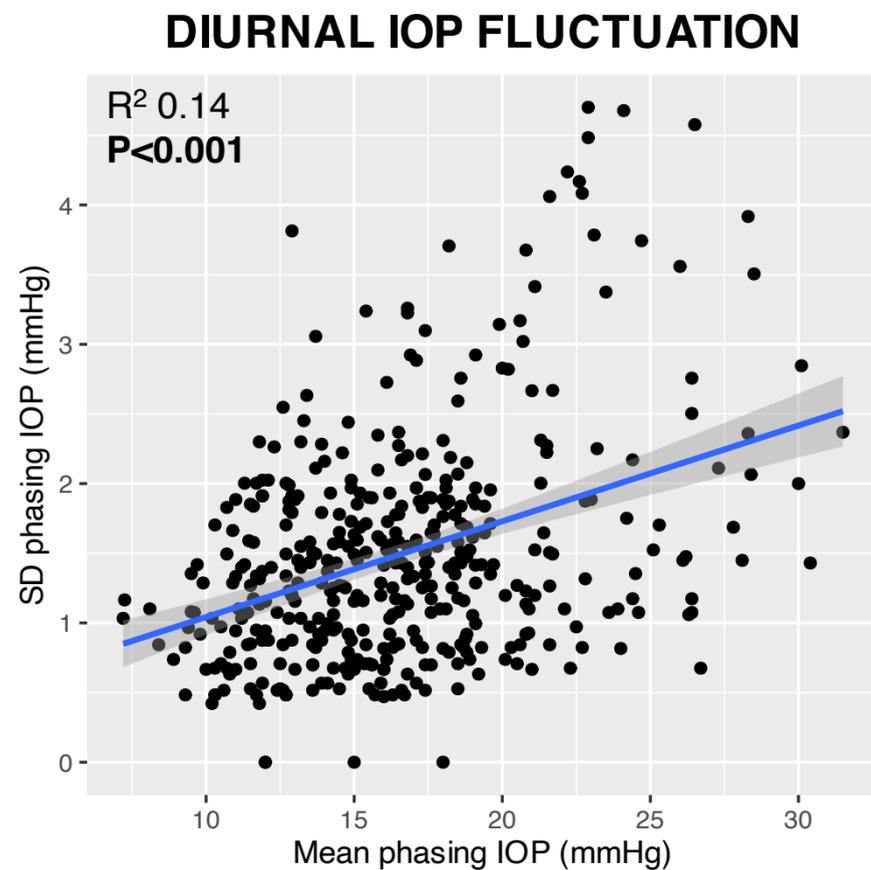
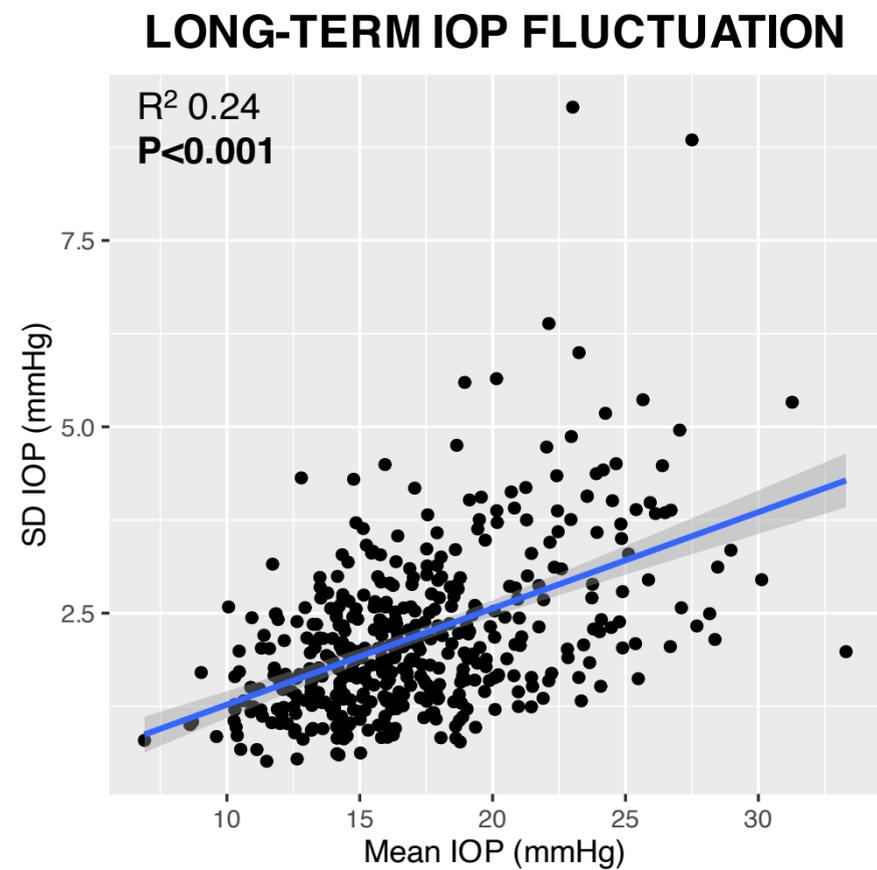


Table 1. Baseline demographic and clinical characteristics of the study population		
Variable	Placebo Cohort	Treatment Cohort
No. Eyes/Patients	213/213	217/217
Age, years, mean (\pm SD)	66.5 (\pm 10.3)	65.1 (\pm 10.4)
Sex, male/female	105/108	119/98
Eye, right / left	92/121	80/137
Ethnicity		
White	193 (90.6%)	197 (90.8%)
Black	11 (5.2%)	7 (3.2%)
Asian	5 (2.3%)	9 (4.2%)
Other	1 (0.5%)	2 (0.9%)
Unknown	3 (1.4%)	2 (0.9%)
Baseline IOP, mmHg, mean (\pm SD)	19.5 (16.0 to 22.8)	19.3 (16.5 to 22.0)
Baseline MD, dB, median (IQR)	-3.4 (-2.0 to -5.6)	-3.4 (-2.1 to -5.4)
CCT, micron, mean (\pm SD)	544 (\pm 34)	539 (\pm 34)
CCT: central corneal thickness, IOP: intraocular pressure; IQR: interquartile range; MD: mean deviation; SD: standard deviation.		

UNNORMALIZED



NORMALIZED

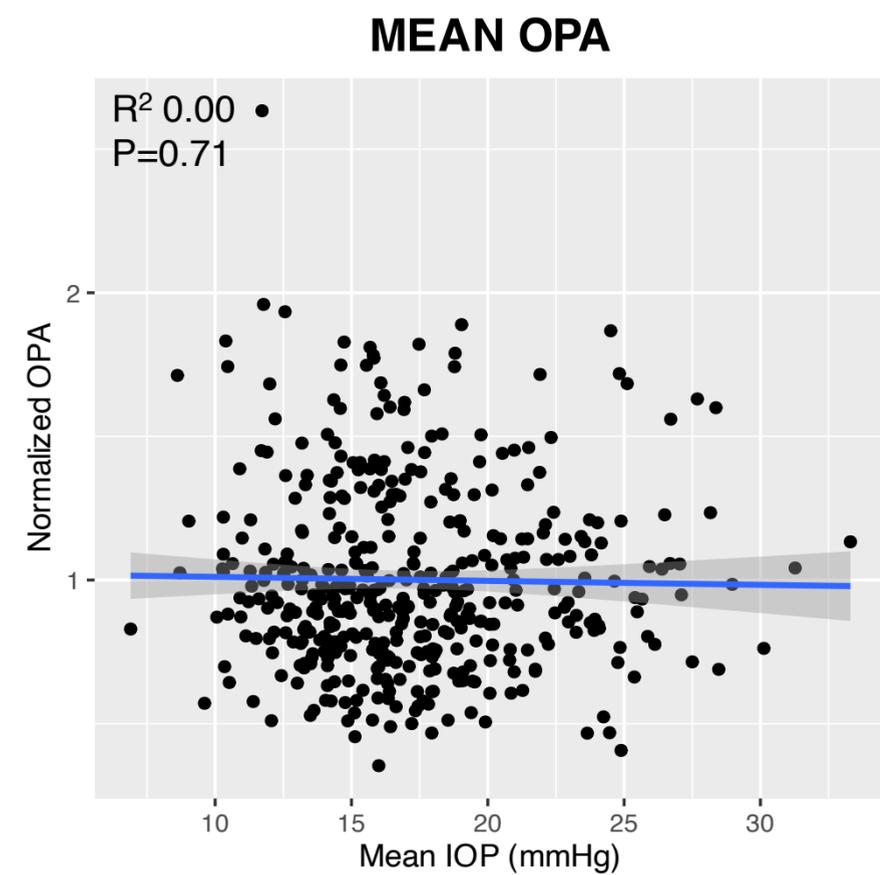
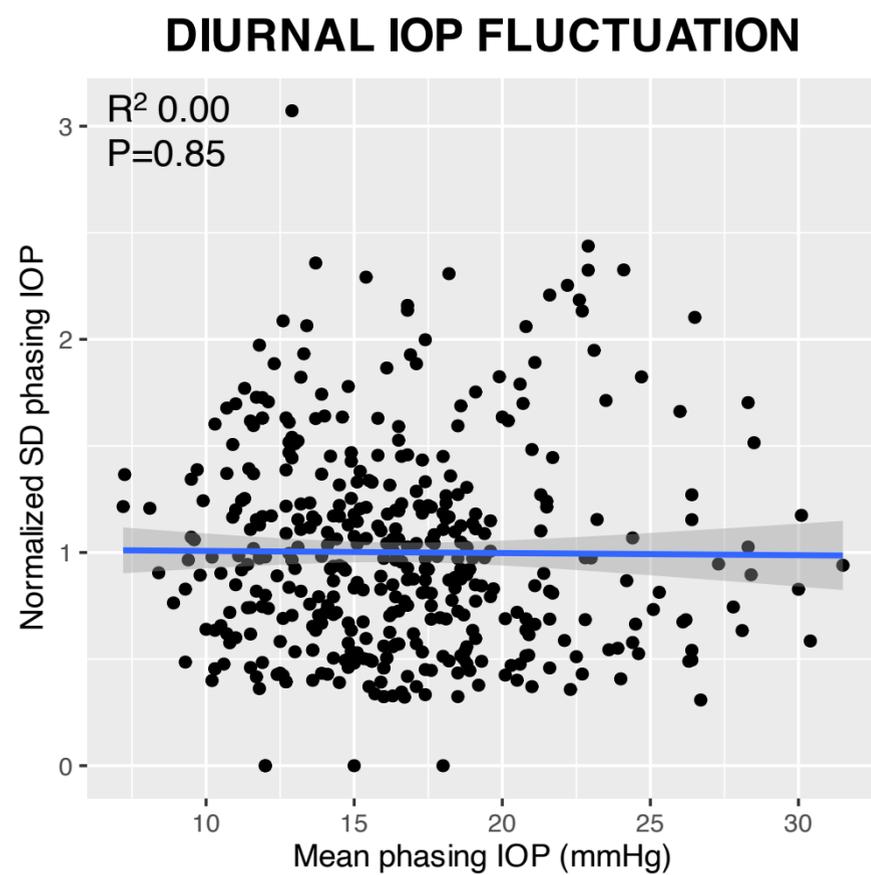
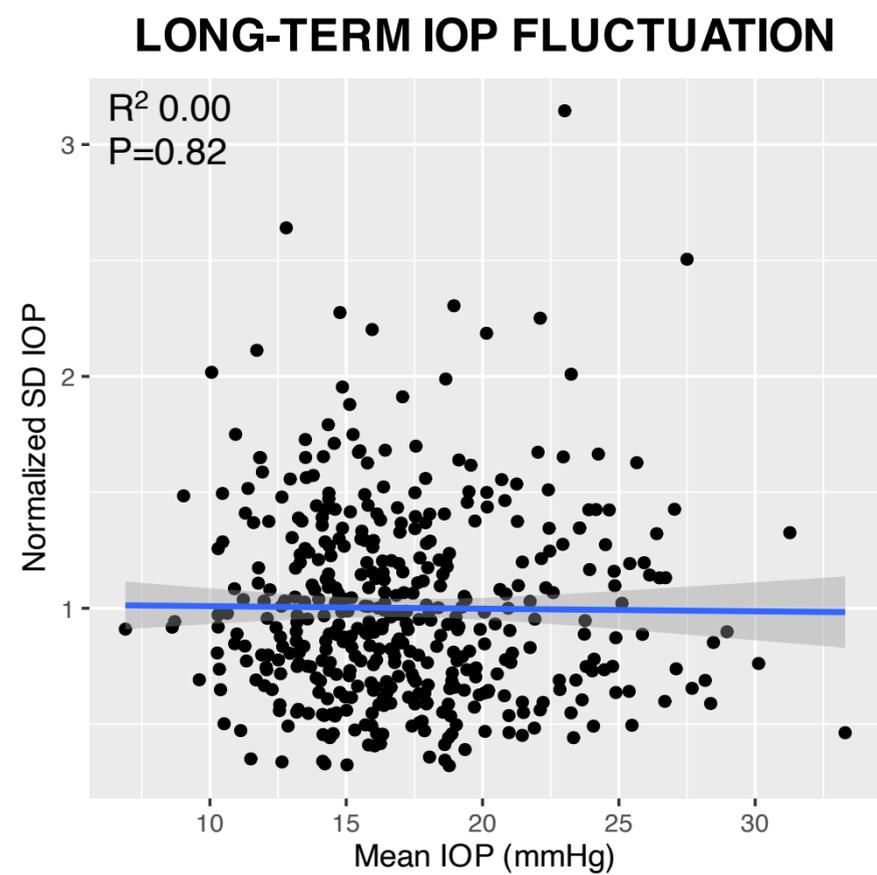
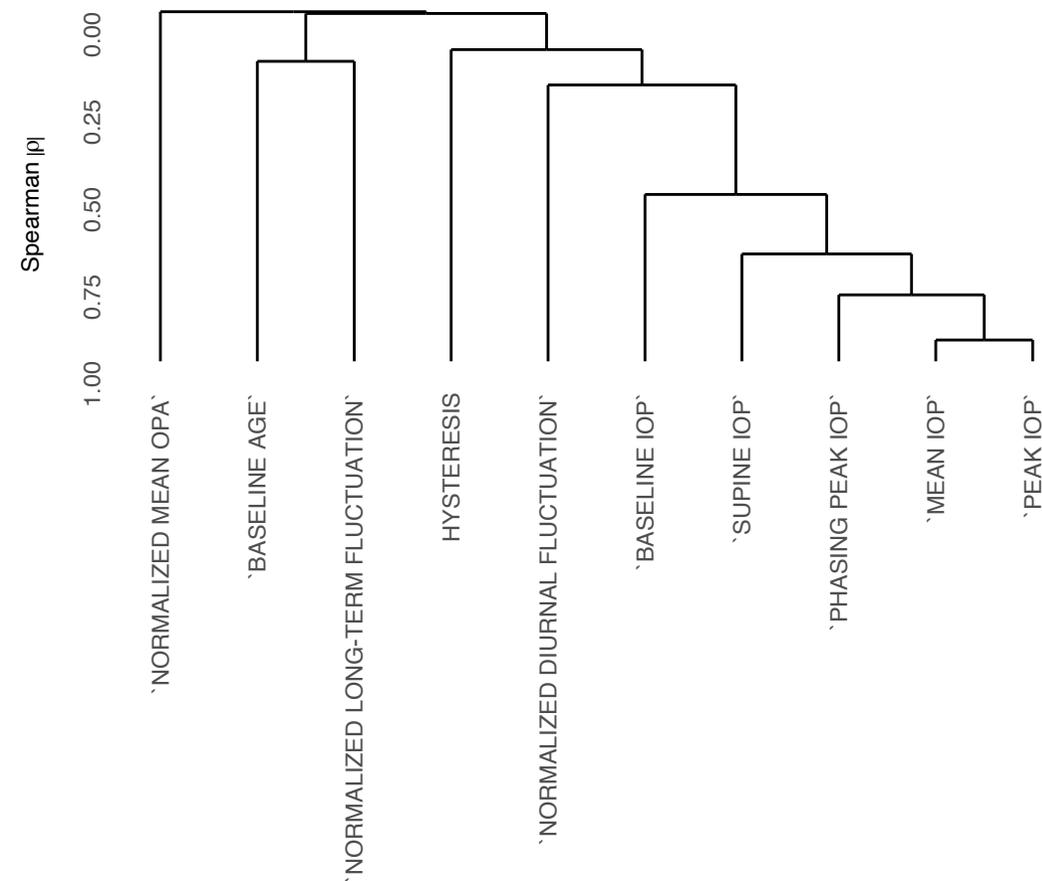


Figure S1. Bivariate plots showing the relationship between mean IOPs and the various unnormalized (**top row**) and normalized (**bottom row**) IOP fluctuation metrics. Blue lines and grey shadow represent regression lines and 95% confidence intervals, respectively. IOP: intraocular pressure; OPA: ocular pulse amplitude; SD: standard deviation.

Figure S2

COVARIATES CORRELATIONS ORIGINAL VARIABLES



COVARIATES CORRELATIONS PCA

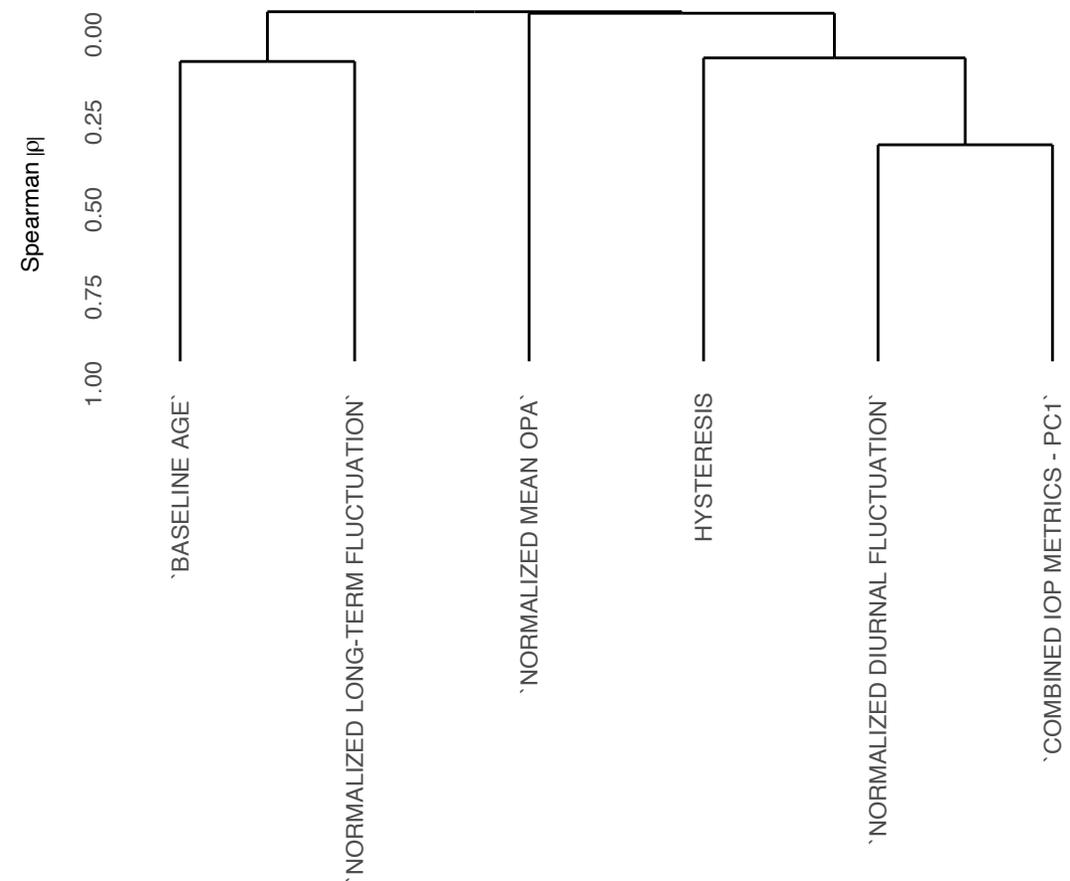
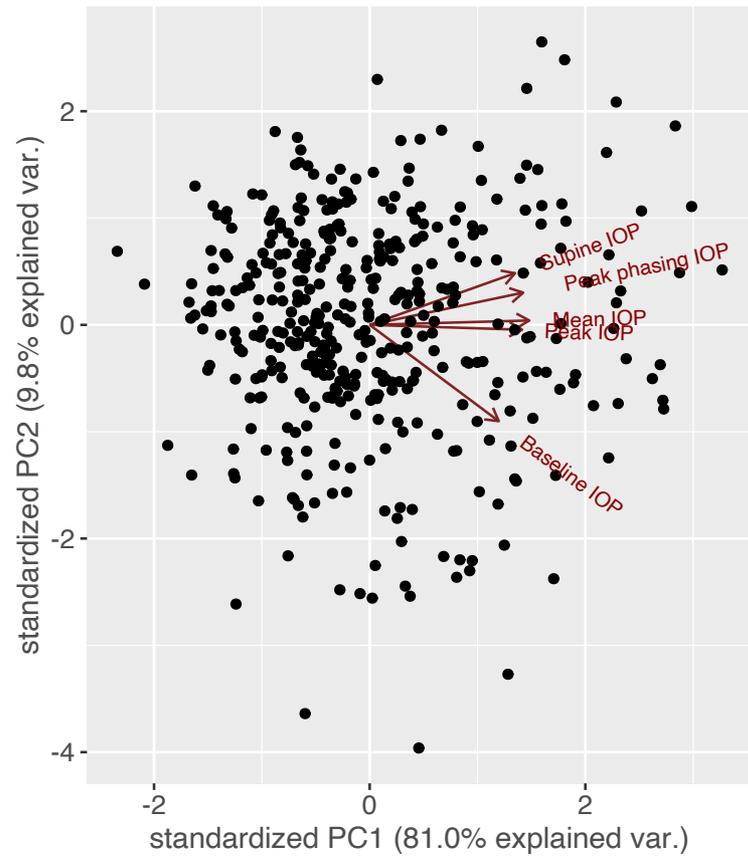


Figure S2. Hierarchical cluster analysis of covariates based on the absolute value of Spearman's correlation coefficient for original variables (**left panel**) and after combining baseline IOP, peak IOP, mean IOP, supine IOP, peak phasing IOP into a combined IOP metric through PCA (**right panel**). IOP: intraocular pressure; OPA: ocular pulse amplitude; PCA: principal component analysis; PC1: principal component 1.

PCA BIPLLOT



PCA SCREE PLOT

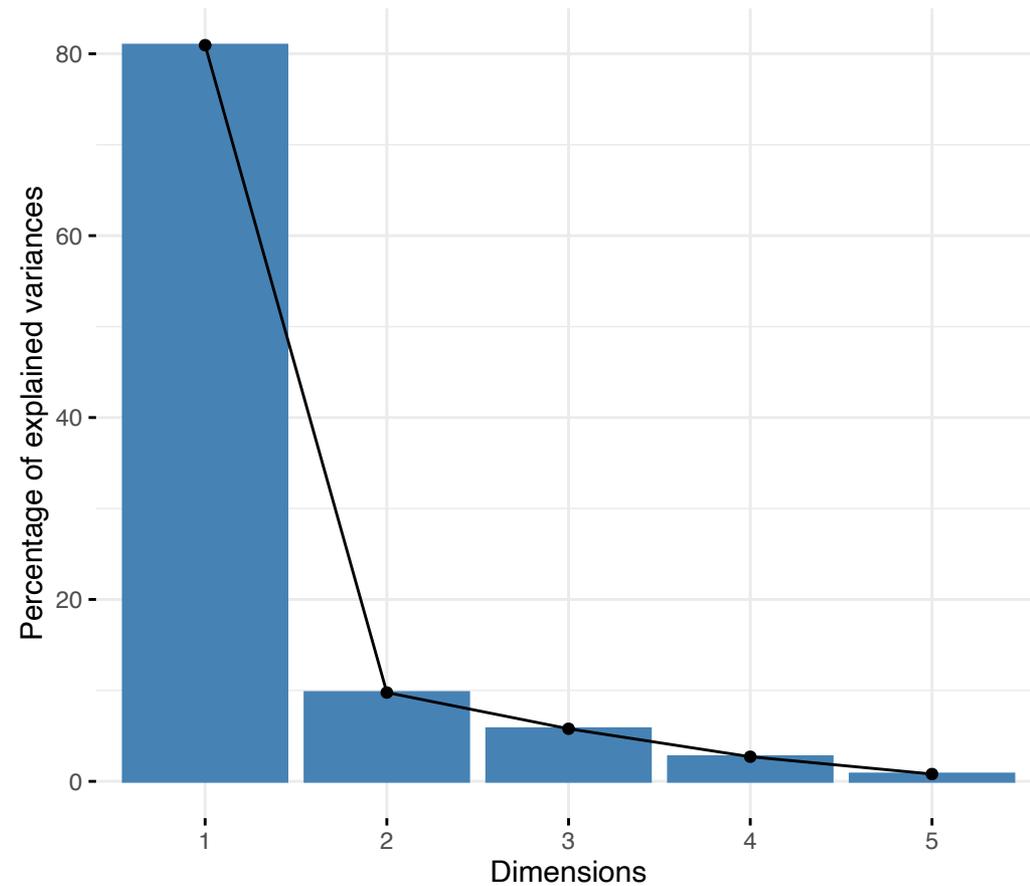
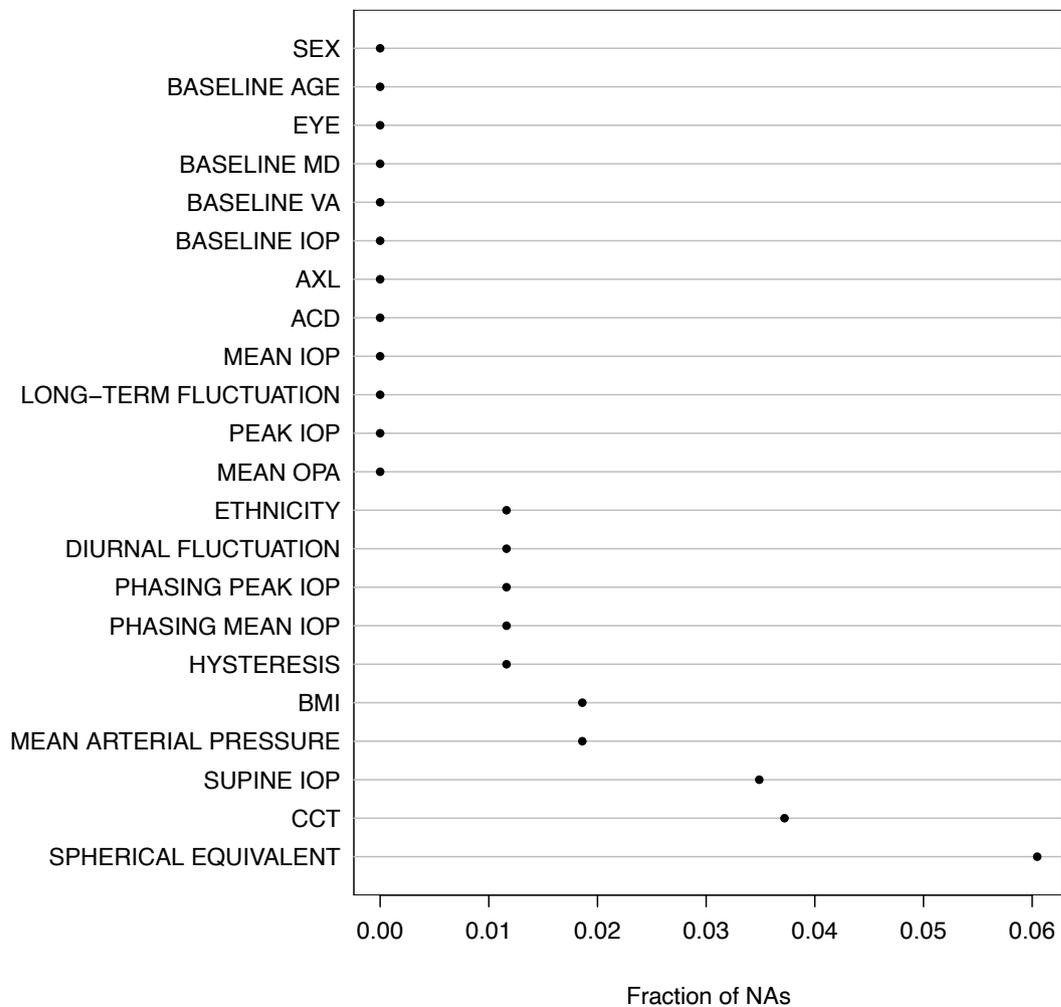


Figure S3. Principal component analysis (PCA) Biplot (**left panel**) and scree plot (**right panel**). IOP: intraocular pressure; PC1: principal component 1; PC2: principal component 2.

Figure S4

Proportion of Missing Data



Patterns of Missing Data

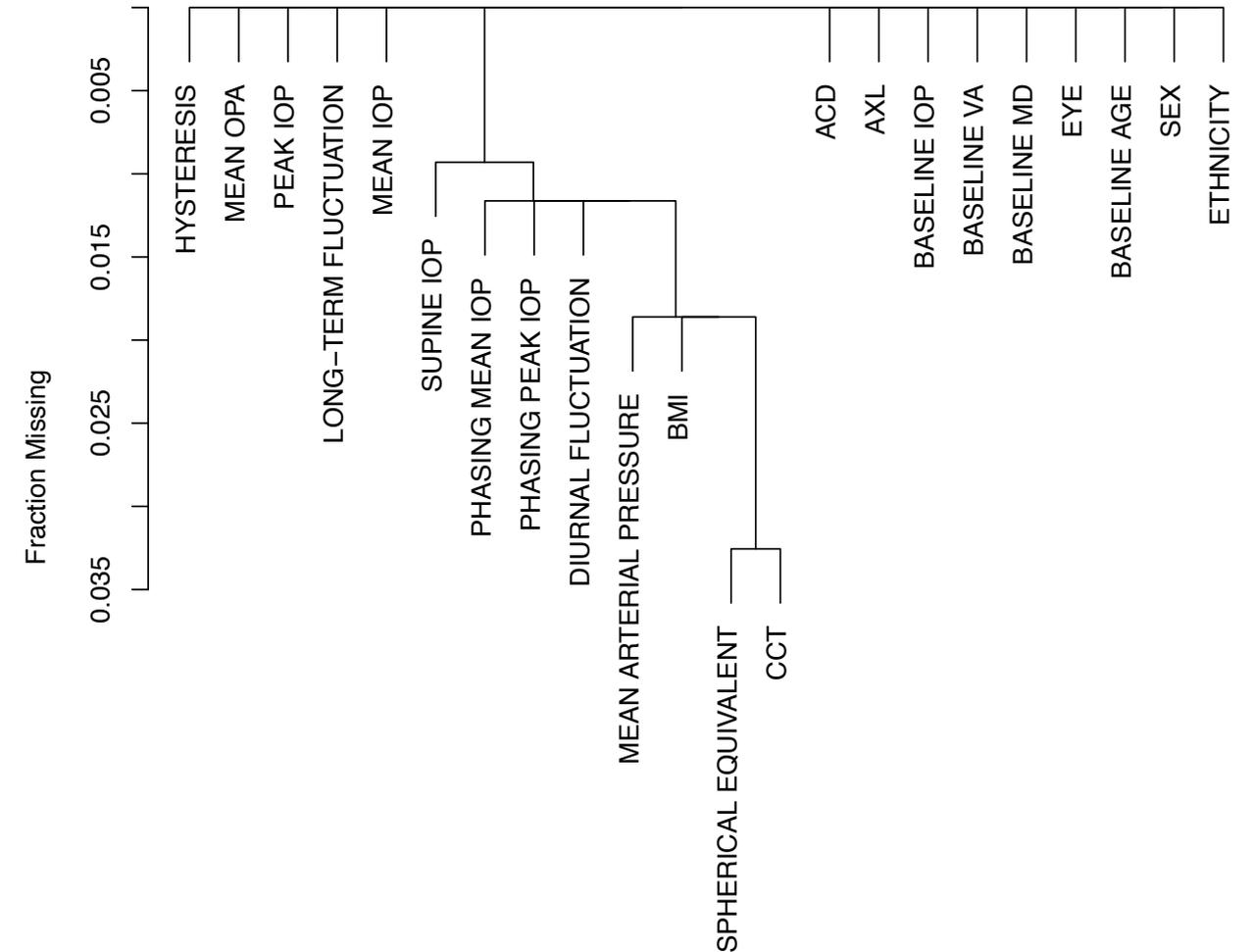


Figure S4. Fraction of missing data for each variable (**left panel**) and hierarchical cluster analysis of missingness combinations (**right panel**). ACD: anterior chamber depth; AXL: axial length; BMI: body mass index; CCT: central corneal thickness; IOP: intraocular pressure; MD: mean deviation; OPA: ocular pulse amplitude; VA: visual acuity.

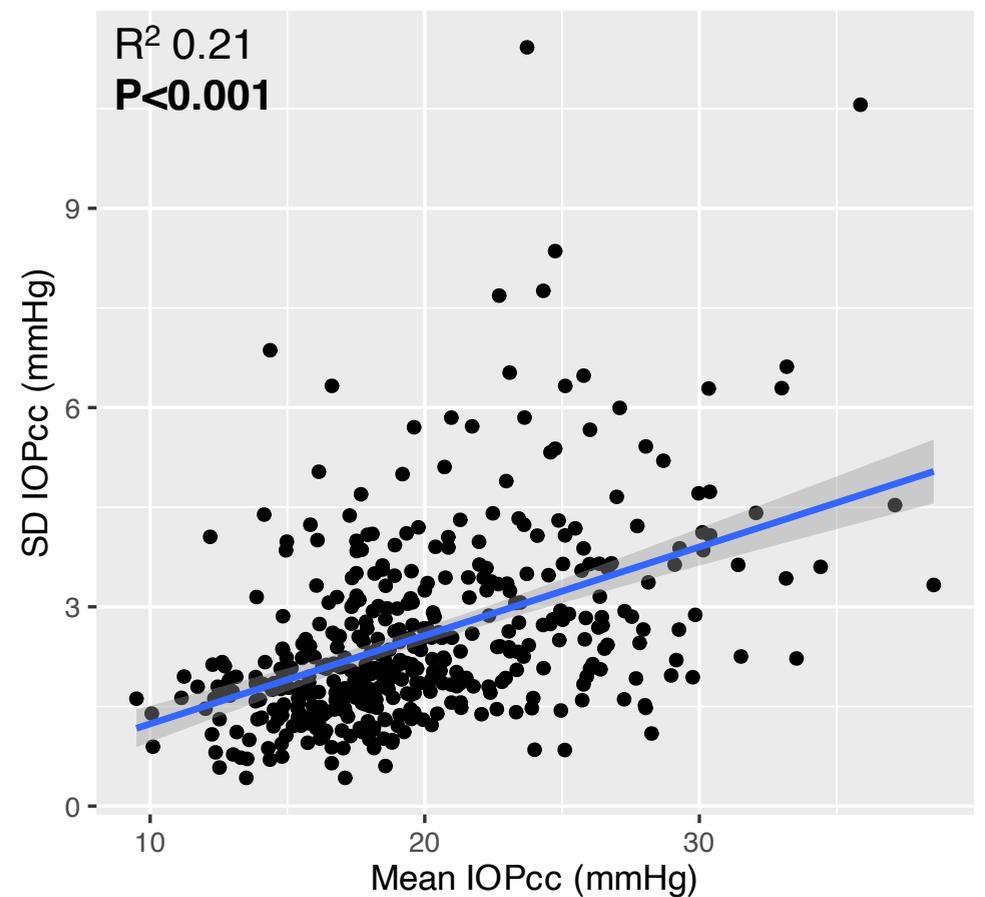
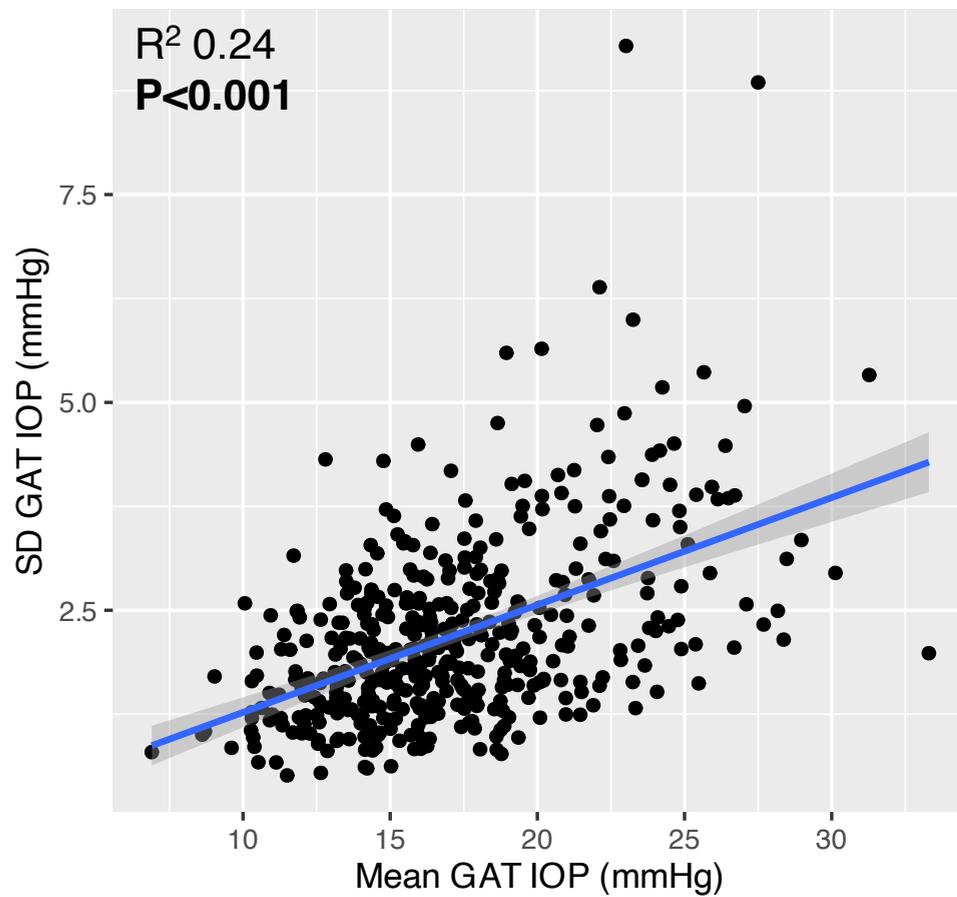
GAT IOP

ORA IOP_{cc}

LONG-TERM GAT IOP FLUCTUATION

LONG-TERM IOP_{cc} FLUCTUATION

UNNORMALIZED



LONG-TERM GAT IOP FLUCTUATION

LONG-TERM IOP_{cc} FLUCTUATION

NORMALIZED

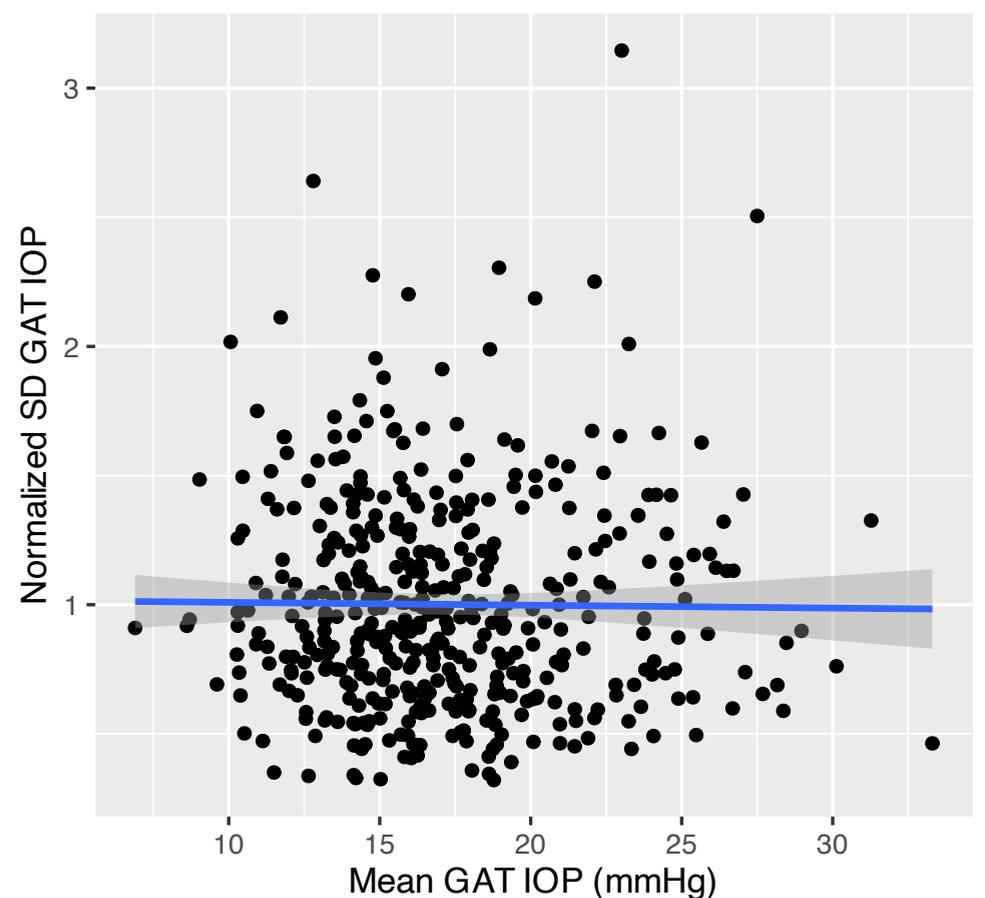
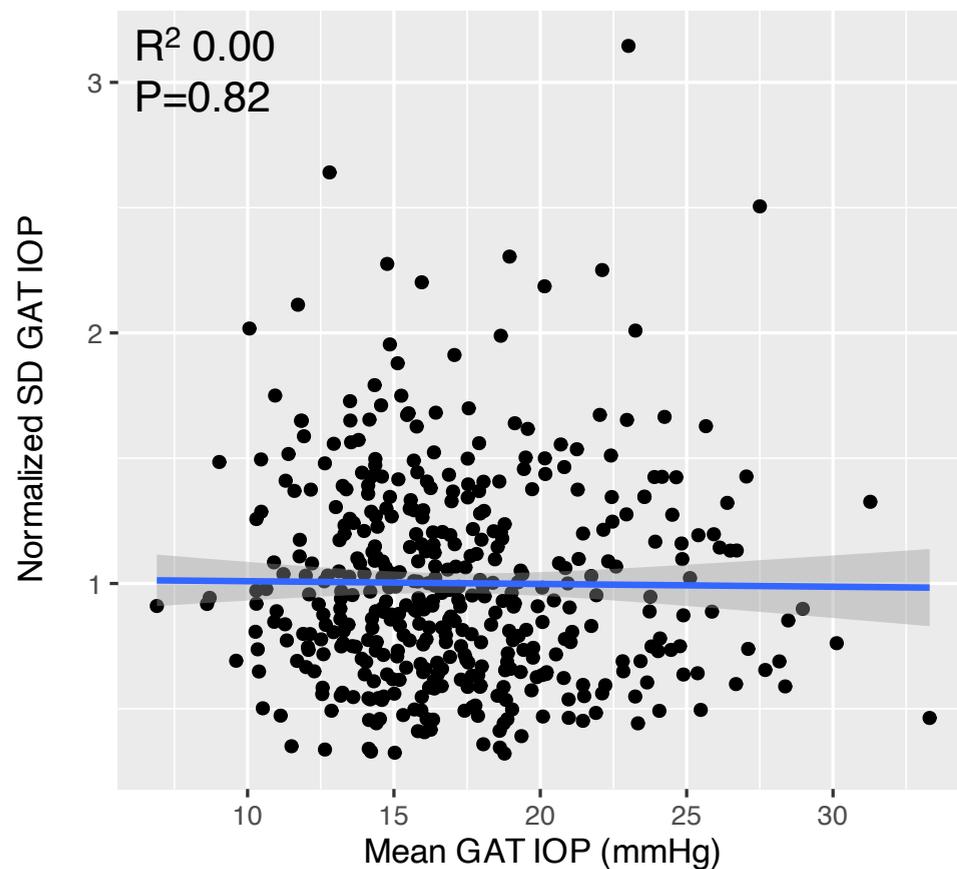
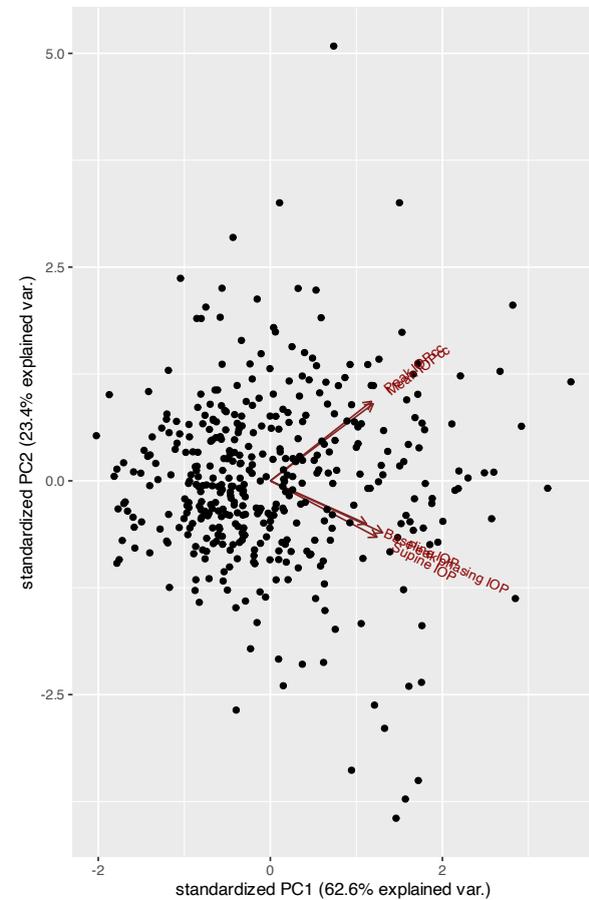


Figure S10. Bivariate plots showing the relationship between mean IOP and long-term IOP fluctuation as measured with GAT (**left column**) and ORA (**right column**). Blue lines and grey shadow represent regression lines and 95% confidence intervals, respectively. GAT: Goldmann applanation tonometer; IOP: intraocular pressure; IOP_{cc}: corneal-compensated IOP; ORA: ocular response analyzer; SD: standard deviation.

PCA BIPLLOT



PCA SCREE PLOT

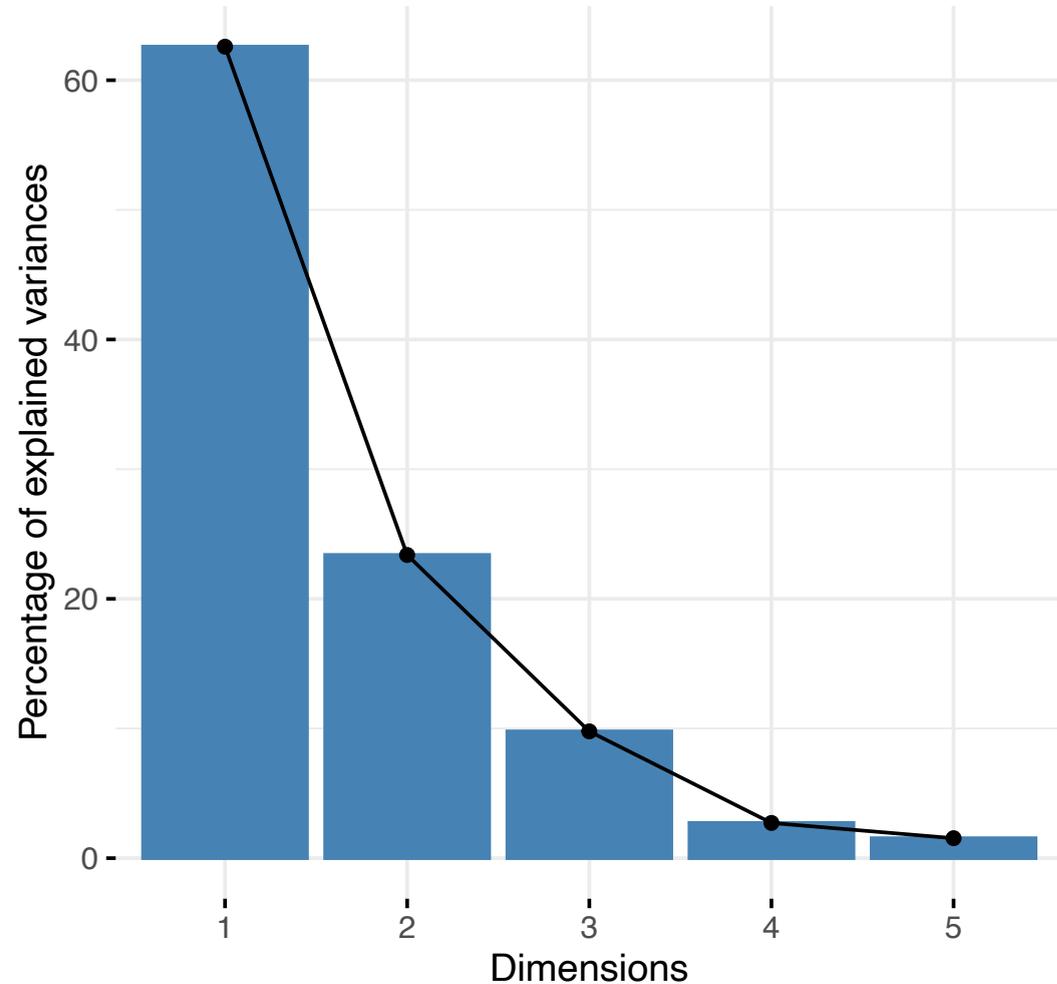


Figure S11. Principal component analysis (PCA) biplot (**left panel**) and scree plot (**right panel**) using IOPcc values to estimate mean and peak IOP. IOP: intraocular pressure; IOPcc: corneal-compensated IOP; PC1: principal component 1; PC2: principal component 2.

MD RATE

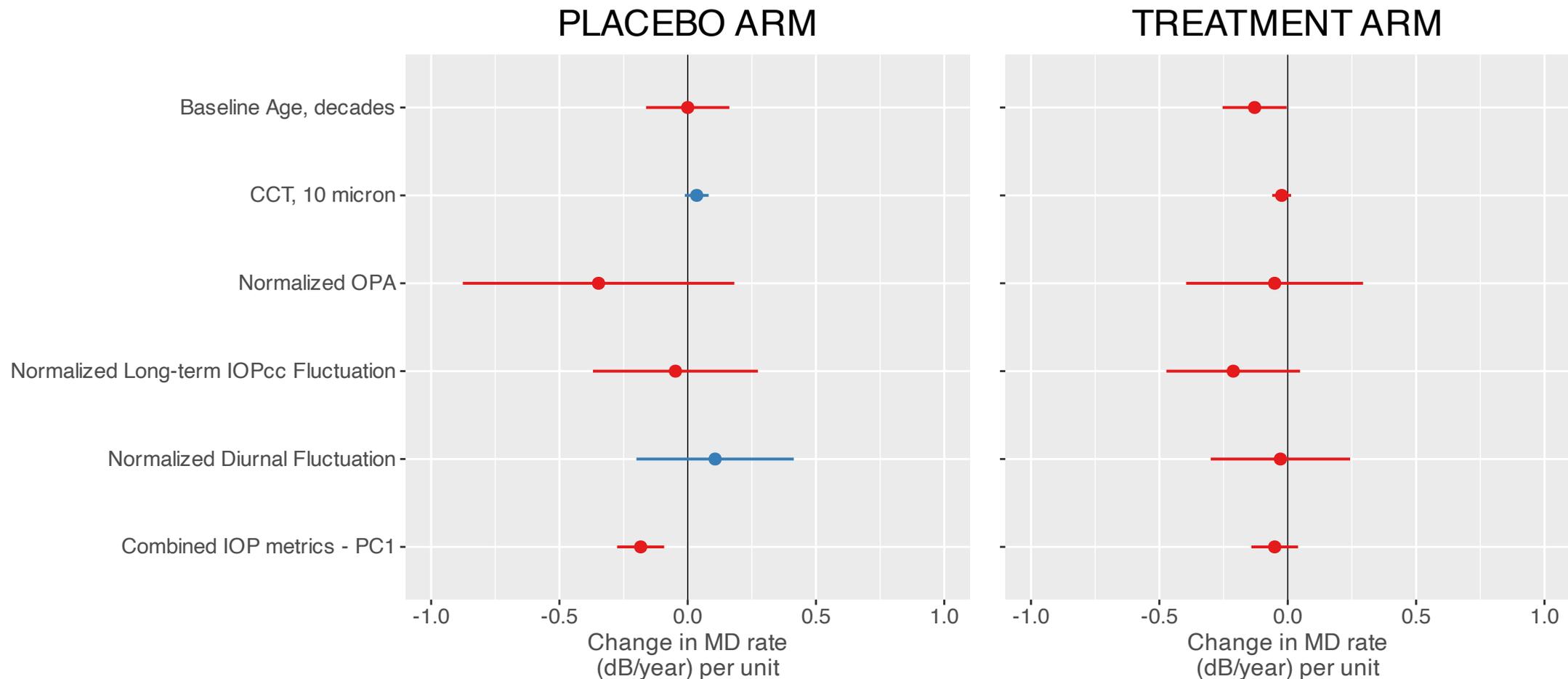


Figure S12. Forest plots for factors associated with the MD rates of progression in the placebo (**left panel**) and treatment (**right panel**) group. Mean IOP, peak IOP and normalized LTF fluctuation were calculated from corneal compensated IOP as measured with the Ocular Response Analyzer (Reichert, Inc, Buffalo, NY). Dots and bars indicate point estimates and 95% confidence intervals, respectively. Estimates are intended for 1-unit increase, unless specified otherwise. CCT: central corneal thickness; IOP: intraocular pressure; IOPcc: corneal-compensated IOP; MD: mean deviation; OPA: ocular pulse amplitude; PC1: principal component 1

PLR – ALL LOCATIONS

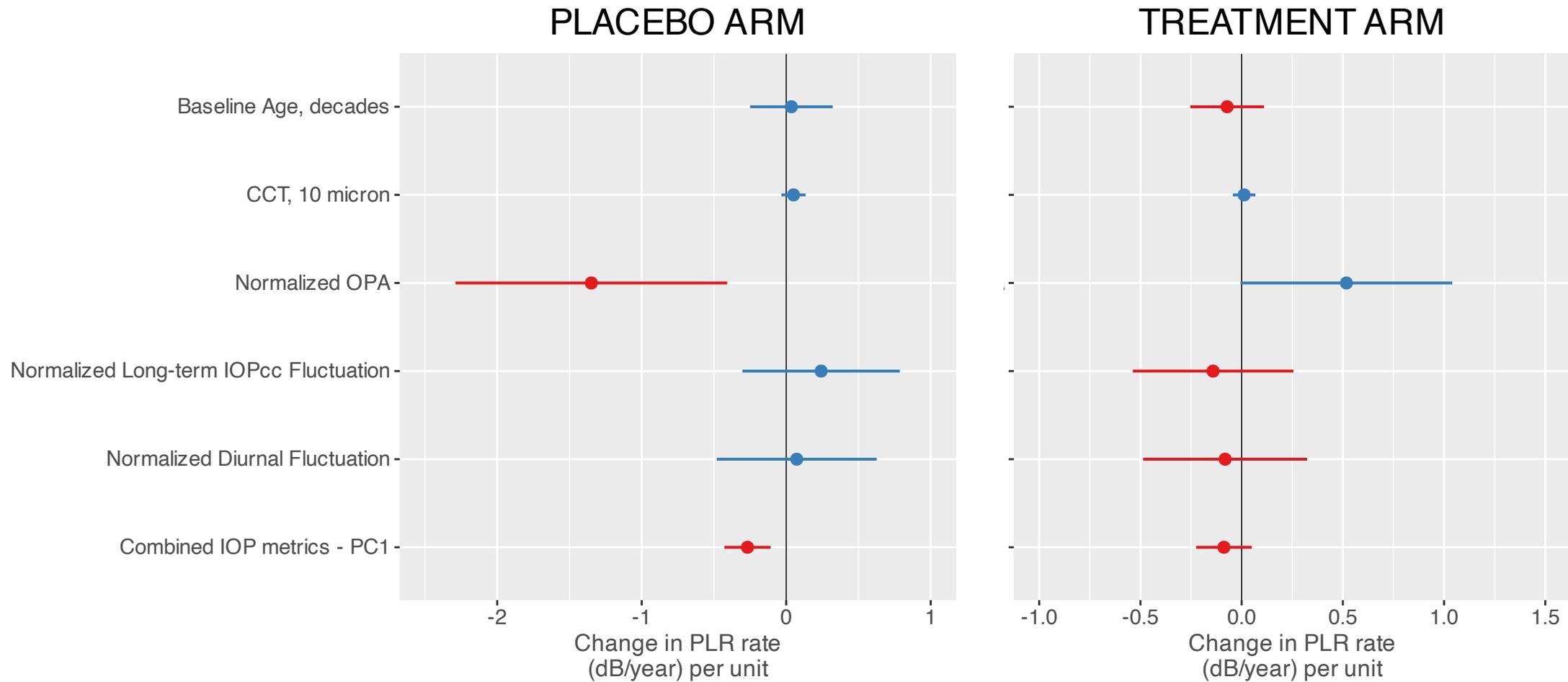


Figure S13. Forest plots for factors associated with the pointwise rates of progression in the placebo (**left panel**) and treatment (**right panel**) group. Mean IOP, peak IOP and normalized LTF fluctuation were calculated from corneal compensated IOP as measured with the Ocular Response Analyzer (Reichert, Inc, Buffalo, NY). Dots and bars indicate point estimates and 95% confidence intervals, respectively. Estimates are intended for 1-unit increase, unless specified otherwise. CCT: central corneal thickness; IOP: intraocular pressure; IOPcc: corneal-compensated IOP; MD: mean deviation; OPA: ocular pulse amplitude; PC1: principal component 1

PLR – 5 FASTEST LOCATIONS

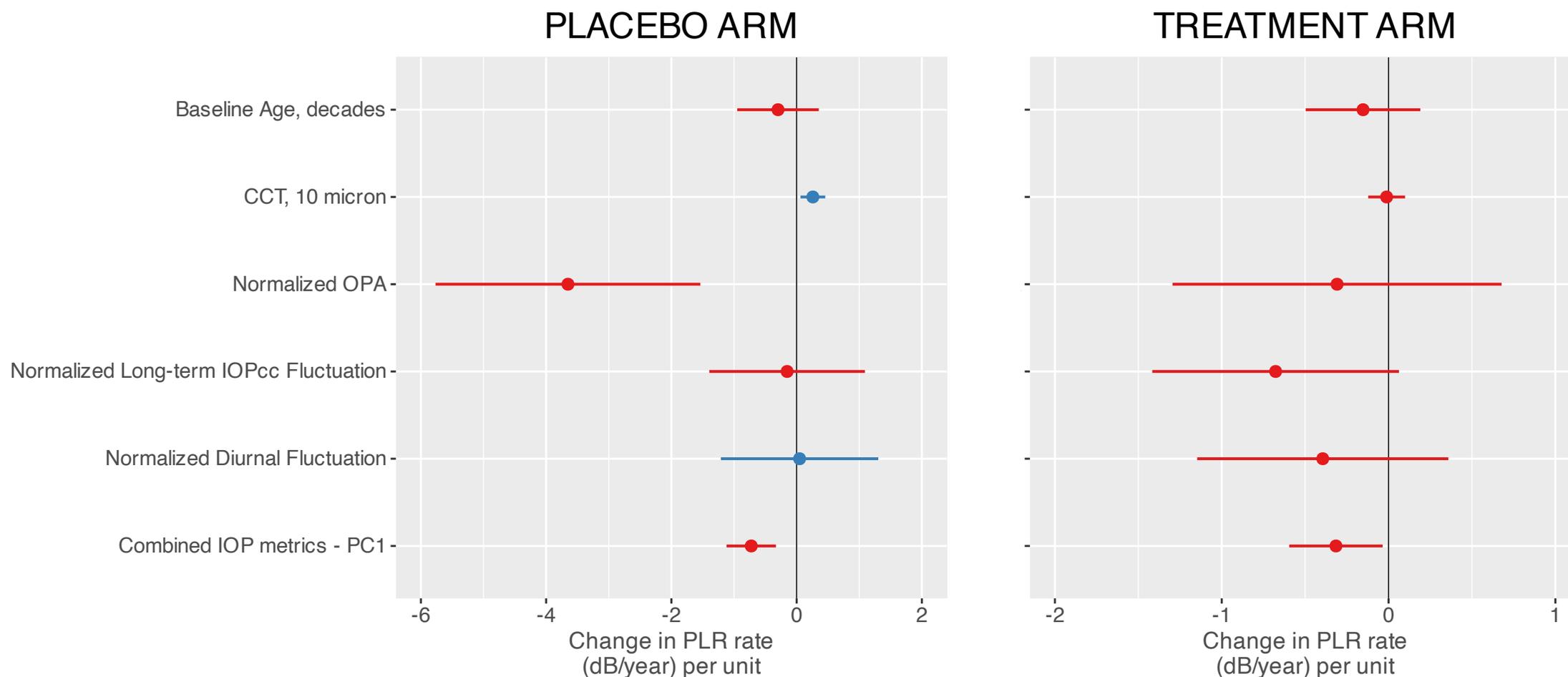


Figure S14. Forest plots for factors associated with the pointwise rates of progression of the fastest five locations in the placebo (**left panel**) and treatment (**right panel**) group. Mean IOP, peak IOP and normalized LTF fluctuation were calculated from corneal compensated IOP as measured with the Ocular Response Analyzer (Reichert, Inc, Buffalo, NY). Dots and bars indicate point estimates and 95% confidence intervals, respectively. Estimates are intended for 1-unit increase, unless specified otherwise. CCT: central corneal thickness; IOP: intraocular pressure; IOPcc: corneal-compensated IOP; MD: mean deviation; OPA: ocular pulse amplitude; PC1: principal component 1

DIURNAL IOP FLUCTUATION

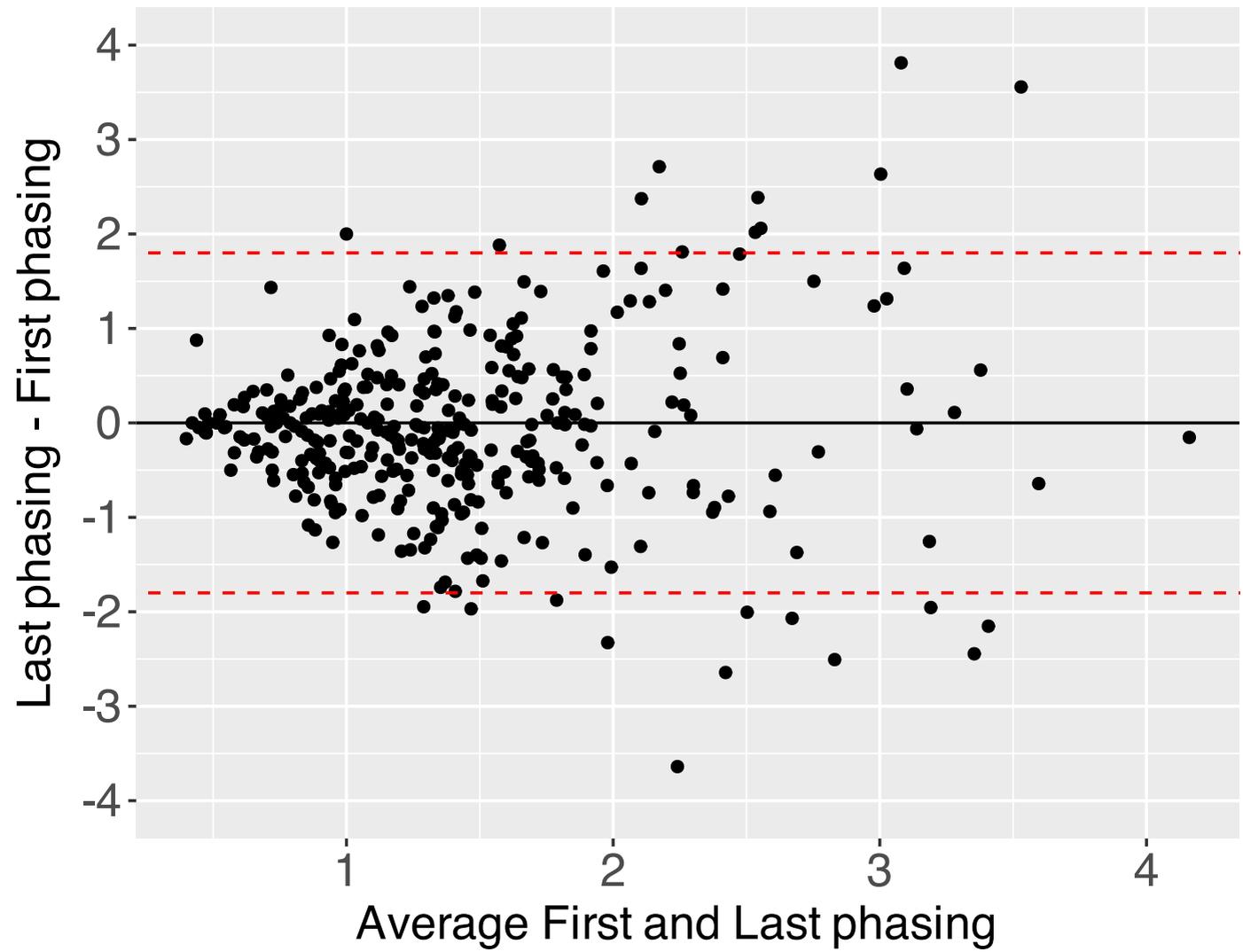


Figure S15. Bland-Altman plots of agreement for diurnal IOP fluctuation calculated from the IOP phasing performed at the first and last post-randomization visits. Black solid line and red dashed lines indicate the no difference lines. and 95% limits of agreements, respectively.

Figure S16

DIURNAL SD IOP DIFFERENCES BETWEEN LAST AND FIRST PHASING

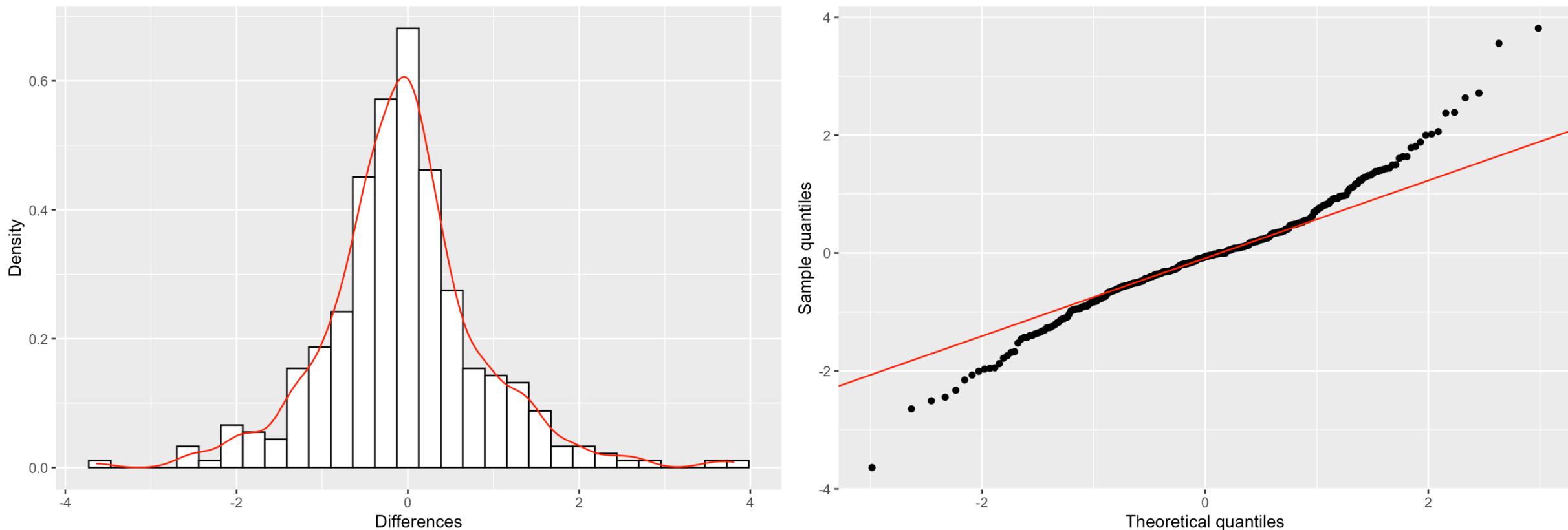


Figure S16. Frequency histogram (**left panel**) and quantile-quantile plot (**right panel**) for the difference in IOP fluctuation values calculated from IOP phasings performed at the last and first post-randomization visits.

Table S2. Univariable analysis for factors associated with the MD rate of progression				
	PLACEBO		TREATMENT	
Variable	Est (SE)	p-value	Est (SE)	p-value
Baseline Age, decades	-0.01 (0.08)	0.89	-0.08 (0.06)	0.18
CCT, per 10 μm	0.02 (0.02)	0.34	-0.02 (0.02)	0.35
CH	0.05 (0.05)	0.34	0.05 (0.04)	0.25
Baseline IOP	-0.06 (0.02)	<0.001	0.00 (0.01)	0.77
Mean IOP	-0.08 (0.02)	<0.001	-0.03 (0.02)	0.18
Peak IOP	-0.07 (0.01)	<0.001	-0.02 (0.01)	0.10
Peak Phasing IOP	-0.05 (0.02)	<0.001	-0.02 (0.02)	0.14
Supine IOP	-0.06 (0.01)	<0.001	-0.01 (0.02)	0.49
OPA	-0.32 (0.09)	<0.001	-0.04 (0.08)	0.62
Long-term Fluctuation	-0.27 (0.07)	<0.001	-0.12 (0.06)	0.047
Diurnal Fluctuation	-0.11 (0.09)	0.23	-0.09 (0.09)	0.35
Normalized OPA	-0.42 (0.26)	0.11	0.02 (0.18)	0.90
Normalized long-term Fluctuation	-0.28 (0.20)	0.17	-0.16 (0.15)	0.30
Normalized diurnal Fluctuation	0.05 (0.15)	0.77	-0.01 (0.13)	0.91
Estimates are intended for 1-unit increase unless specified otherwise. CCT: central corneal thickness; CH: corneal hysteresis; IOP: intraocular pressure; OPA: ocular pulse amplitude; SE: standard error.				

Table S3. Multivariable analysis for factors associated with the MD rate of progression				
	PLACEBO		TREATMENT	
Variable	Est (SE)	p-value	Est (SE)	p-value
Baseline Age, decades	0.01 (0.08)	0.95	-0.12 (0.06)	0.06
CCT, per 10 μm	0.05 (0.02)	0.06	-0.02 (0.02)	0.23
CH	-0.02 (0.05)	0.73	0.05 (0.04)	0.25
Normalized OPA	-0.30 (0.26)	0.24	-0.06 (0.18)	0.72
Normalized long-term Fluctuation	-0.27 (0.21)	0.20	-0.12 (0.17)	0.49
Normalized diurnal Fluctuation	0.16 (0.15)	0.31	-0.02 (0.14)	0.88
Combined IOP metrics – PC1	-0.19 (0.04)	<0.001	-0.05 (0.04)	0.23
<p>Estimates are intended for 1-unit increase. Combined IOP metrics PC1 is an unitless variables, combining fluctuation unrelated IOP metrics (baseline IOP, peak IOP, mean IOP, supine IOP, peak phasing IOP) through Principal Component Analysis. CCT: central corneal thickness; CH: corneal hysteresis; IOP: intraocular pressure; PC1: principal component 1; SE: standard error.</p>				

Table S4. Multivariable analysis for factors associated with the MD rate of progression				
	PLACEBO		TREATMENT	
Variable	Est (SE)	p-value	Est (SE)	p-value
Baseline Age, decades	0.02 (0.08)	0.85	-0.13 (0.06)	0.037
CCT, per 10 μm	0.05 (0.02)	0.056	-0.03 (0.02)	0.19
CH	-0.02 (0.05)	0.73	0.04 (0.04)	0.32
OPA	-0.15 (0.10)	0.11	-0.05 (0.08)	0.54
Long-term Fluctuation	-0.12 (0.09)	0.17	-0.12 (0.08)	0.11
Diurnal Fluctuation	0.09 (0.10)	0.35	-0.06 (0.11)	0.61
Combined IOP metrics – PC1	-0.14 (0.05)	0.005	0.00 (0.05)	0.95
<p>Estimates are intended for 1-unit increase. Combined IOP metrics PC1 is a unitless variable, combining fluctuation unrelated IOP metrics (baseline IOP, peak IOP, mean IOP, supine IOP, peak phasing IOP) through Principal Component Analysis.</p> <p>CCT: central corneal thickness; CH: corneal hysteresis; IOP: intraocular pressure; OPA: ocular pulse amplitude; PC1: principal component 1; SE: standard error.</p>				

Table S5. Univariable analysis for factors associated with the pointwise rate of progression				
	PLACEBO		TREATMENT	
Variable	Est (SE)	p-value	Est (SE)	p-value
Baseline Age, decades	-0.04 (0.14)	0.78	-0.04 (0.09)	0.67
CCT, per 10 μm	0.03 (0.04)	0.50	0.01 (0.03)	0.84
CH	0.07 (0.09)	0.49	0.10 (0.06)	0.12
Baseline IOP	-0.09 (0.03)	0.003	0.00 (0.02)	0.87
Mean IOP	-0.13 (0.03)	<0.001	-0.03 (0.03)	0.36
Peak IOP	-0.11 (0.03)	<0.001	-0.02 (0.02)	0.30
Peak IOP Phasing	-0.09 (0.03)	<0.001	-0.02 (0.03)	0.32
Supine IOP	-0.10 (0.03)	<0.001	0.00 (0.02)	0.86
OPA	-0.65 (0.15)	<0.001	0.11 (0.11)	0.32
Long-term Fluctuation	-0.34 (0.13)	0.008	-0.12 (0.08)	0.16
Diurnal Fluctuation	-0.22 (0.15)	0.14	-0.08 (0.13)	0.53
Normalized OPA	-1.36 (0.48)	0.005	0.48 (0.26)	0.07
Normalized Long-term Fluctuation	-0.36 (0.35)	0.32	-0.12 (0.22)	0.58
Normalized Diurnal Fluctuation	-0.02 (0.29)	0.93	-0.01 (0.20)	0.97
Estimates are intended for 1-unit increase, unless specified otherwise. CCT: central corneal thickness; CH: corneal hysteresis; IOP: intraocular pressure; OPA: Ocular Pulse Amplitude; SE: standard error.				

Table S6. Multivariable analysis for factors associated with the pointwise rate of progression				
	PLACEBO		TREATMENT	
Variable	Est (SE)	p-value	Est (SE)	p-value
Baseline Age, decades	0.04 (0.14)	0.79	-0.06 (0.09)	0.52
CCT, per 10 μm	0.07 (0.04)	0.11	0.01 (0.03)	0.81
CH	-0.05 (0.10)	0.59	0.11 (0.07)	0.11
Normalized OPA	-1.23 (0.46)	0.009	0.52 (0.27)	0.055
Normalized Long-term Fluctuation	-0.23 (0.35)	0.52	0.06 (0.25)	0.81
Normalized Diurnal Fluctuation	0.13 (0.28)	0.63	-0.06 (0.21)	0.77
Combined IOP metrics – PC1	-0.29 (0.07)	<0.001	-0.05 (0.06)	0.42
<p>Estimates are intended for 1-unit increase unless specified otherwise. Combined IOP metrics PC1 is an unitless variable, combining fluctuation unrelated IOP metrics (baseline IOP, peak IOP, mean IOP, supine IOP, peak phasing IOP) through Principal Component Analysis.</p> <p>CCT: central corneal thickness; CH: corneal hysteresis; IOP: intraocular pressure; OPA: ocular pulse amplitude; PC1: principal component 1; SE: standard error.</p>				

Table S7. Multivariable analysis for factors associated with the pointwise rate of progression				
	PLACEBO		TREATMENT	
Variable	Est (SE)	p-value	Est (SE)	p-value
Baseline Age, decades	0.05 (0.14)	0.74	-0.07 (0.09)	0.44
CCT, per 10 μm	0.07 (0.04)	0.13	0.01 (0.03)	0.84
CH	-0.05 (0.10)	0.60	0.10 (0.07)	0.15
OPA	-0.47 (0.17)	0.008	0.18 (0.12)	0.14
Long-term Fluctuation	-0.09 (0.14)	0.54	-0.06 (0.11)	0.60
Diurnal Fluctuation	0.03 (0.16)	0.87	-0.09 (0.14)	0.55
Combined IOP metrics – PC1	-0.17 (0.09)	0.06	-0.05 (0.08)	0.50

Estimates are intended for 1-unit increase unless specified otherwise. Combined IOP metrics PC1 is an unitless variable, combining fluctuation unrelated IOP metrics (baseline IOP, peak IOP, mean IOP, supine IOP, peak phasing IOP) through Principal Component Analysis.

CCT: central corneal thickness; CH: corneal hysteresis; IOP: intraocular pressure; OPA: ocular pulse amplitude; PC1: principal component 1; SE: standard error.

Table S8. Univariable analysis for factors associated with the rate of fastest five locations				
	PLACEBO		TREATMENT	
Variable	Est (SE)	p-value	Est (SE)	p-value
Baseline Age, decades	-0.42 (0.33)	0.19	-0.16 (0.17)	0.37
CCT, per 10 μm	0.15 (0.10)	0.11	0.01 (0.05)	0.88
CH	0.25 (0.22)	0.26	0.15 (0.12)	0.24
Baseline IOP	-0.21 (0.07)	0.003	-0.07 (0.04)	0.06
Mean IOP	-0.27 (0.07)	<0.001	-0.09 (0.05)	0.09
Peak IOP	-0.19 (0.06)	0.002	-0.07 (0.04)	0.07
Peak IOP Phasing	-0.20 (0.06)	0.002	-0.08 (0.05)	0.12
Supine IOP	-0.21 (0.06)	<0.001	-0.01 (0.05)	0.80
OPA	-1.67 (0.34)	<0.001	-0.24 (0.28)	0.28
Long-term Fluctuation	-0.49 (0.30)	0.11	-0.46 (0.17)	0.006
Diurnal Fluctuation	-0.56 (0.34)	0.10	-0.33 (0.26)	0.20
Normalized OPA	-3.95 (1.10)	<0.001	-0.19 (0.52)	0.71
Normalized Long-term Fluctuation	0.23 (0.83)	0.79	-0.81 (0.44)	0.06
Normalized Diurnal Fluctuation	-0.15 (0.65)	0.82	-0.19 (0.40)	0.63
Estimates are intended for 1-unit increase, unless specified otherwise. CCT: central corneal thickness; CH: corneal hysteresis; IOP: intraocular pressure; OPA: Ocular Pulse Amplitude; SE: standard error.				

Table S9. Multivariable analysis for factors associated with the rate of fastest five locations				
	PLACEBO		TREATMENT	
Variable	Est (SE)	p-value	Est (SE)	p-value
Baseline Age, decades	-0.13 (0.33)	0.69	-0.19 (0.18)	0.28
CCT, per 10 μm	0.26 (0.10)	0.010	0.01 (0.06)	0.93
CH	-0.09 (0.22)	0.69	0.13 (0.13)	0.31
Normalized OPA	-3.50 (1.04)	0.001	-0.38 (0.51)	0.46
Normalized Long-term Fluctuation	0.48 (0.80)	0.55	-0.71 (0.47)	0.13
Normalized Diurnal Fluctuation	0.20 (0.62)	0.75	-0.28 (0.39)	0.48
Combined IOP metrics – PC1	-0.58 (0.16)	<0.001	-0.27 (0.12)	0.028
<p>Estimates are intended for 1-unit increase unless specified otherwise. Combined IOP metrics PC1 is an unitless variable, combining fluctuation unrelated IOP metrics (baseline IOP, peak IOP, mean IOP, supine IOP, peak phasing IOP) through Principal Component Analysis.</p> <p>CCT: central corneal thickness; CH: corneal hysteresis; IOP: intraocular pressure; OPA: ocular pulse amplitude; PC1: principal component 1; SE: standard error.</p>				

Table S10. Multivariable analysis for factors associated with the rate of fastest five locations				
	PLACEBO		TREATMENT	
Variable	Est (SE)	p-value	Est (SE)	p-value
Baseline Age, decades	-0.14 (0.32)	0.66	-0.24 (0.18)	0.18
CCT, per 10 μm	0.24 (0.10)	0.016	0.01 (0.06)	0.91
CH	-0.09 (0.22)	0.66	0.11 (0.13)	0.40
OPA	-1.36 (0.39)	<0.001	-0.19 (0.23)	0.40
Long-term Fluctuation	0.12 (0.33)	0.73	-0.47 (0.22)	0.032
Diurnal Fluctuation	-0.06 (0.36)	0.87	-0.33 (0.27)	0.22
Combined IOP metrics – PC1	-0.32 (0.21)	0.13	-0.06 (0.15)	0.71
<p>Estimates are intended for 1-unit increase unless specified otherwise. Combined IOP metrics PC1 is an unitless variable, combining fluctuation unrelated IOP metrics (baseline IOP, peak IOP, mean IOP, supine IOP, peak phasing IOP) through Principal Component Analysis.</p> <p>CCT: central corneal thickness; CH: corneal hysteresis; IOP: intraocular pressure; OPA: ocular pulse amplitude; PC1: principal component 1; SE: standard error.</p>				

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TITLE OF ARTICLE: **Intraocular pressure fluctuation and rates of visual field progression in primary open-angle**

glaucoma: an exploratory analysis from the United Kingdom Glaucoma Treatment Study (UKGTS)

AUTHORS: Alessandro Rabiolo, Giovanni Montesano, David P Crabb, David F Garway-Heath

AUTHOR NAME	RESEARCH DESIGN	DATA ACQUISITION AND/OR RESEARCH EXECUTION	DATA ANALYSIS AND/OR INTERPRETATION	MANUSCRIPT PREPARATION
Alessandro Rabiolo	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
Giovanni Montesano	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
David P Crabb	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
David F Garway-Heath	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
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OTHER CONTRIBUTIONS:

United Kingdom Glaucoma Treatment Study investigators

David F. Garway-Heath MD, David P. Crabb PhD, Catey Bunce DSc, Gerassimos Lascaratos MSc, Francesca Amalfitano BSc, Nitin Anand MD, Augusto Azuara-Blanco PhD, Rupert R. Bourne MD, David C. Broadway MD, Ian A. Cunliffe FRCOphth, Jeremy P. Diamond PhD, Scott G. Fraser MD, Tuan A. Ho MSc, Prof Keith R. Martin DM, Andrew I. McNaught MD, Anil Negi MD, Krishna Patel MSc, Richard A. Russell PhD, Ameet Shah MRCOphth, Paul G. Spry PhD, Katsuyoshi Suzuki PhD, Edward T. White BSc, Richard P. Wormald FRCOphth, Wen Xing MSc, Thierry G. Zeyen PhD