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

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Abstract:	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. Design. Randomized, double-masked, placebo-controlled multicenter trial. Participants: Participants with ≥5 VFs (213 placebo, 217 treatment). 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. Main Outcome Measures. Associations between IOP fluctuation metrics and rates of MD and five fastest test locations. 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. 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.
Suggested Reviewers:	
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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 OPHTHA-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
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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

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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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ABSTRACT

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.

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

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

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.

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

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.

Conclusions. There is no evidence to support that either diurnal ~~and~~ 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.

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

INTRODUCTION

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

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

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

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

METHODS

Study Population and Procedures

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

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

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

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

IOP Metrics

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

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

- Baseline pretreatment IOP, defined as the average of the IOP readings obtained in the two pre-randomization visits.
- Mean IOP, defined as the average of all post-randomization IOP readings.
- Peak IOP, defined as the highest IOP reading of all post-randomization IOP readings.
- Supine IOP, defined as the Perkins applanation tonometry IOP readings measured at the first post-randomization visit.
- Phasing peak IOP, defined as the highest IOP reading of the diurnal phasing performed at the first post-randomization visit.
- Diurnal IOP fluctuation, defined as the SD of IOP measurements obtained from the diurnal IOP phasing performed at the first post-randomization visit. Diurnal IOP fluctuation was also calculated using the IOP measurements from the last post-randomization visit.
- Long-term IOP fluctuation, defined as the SD of post-randomization IOP readings.

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

Statistical Analysis

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

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

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

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

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

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

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

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

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

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

RESULTS

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

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

Global MD rate

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

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

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

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

Pointwise Rates

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

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

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

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

DISCUSSION

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

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

these two variables. IOP fluctuation is known to be positively correlated with mean IOP. In a retrospective study performed on non-human primates of experimental glaucoma, Gardiner and colleagues[10] used the coefficient of variation (SD IOP divided by mean IOP) to remove the relationship between these two variables. In our cohort, the coefficient of variation reversed the association with mean IOP values, leading to a negative relationship between IOP fluctuation and mean IOP. The explanation for this is likely that there are two components of variability (measurement error and true IOP fluctuation), one of which (true fluctuation) is related to mean IOP and the other (measurement error) is not.[14] Dividing the measurement error by the mean IOP induces the negative association. The method of normalization used in our study likely respects both the increased fluctuations at higher mean IOP and constant measurement errors. Fourth, IOP-related metrics tend to be highly correlated because they are related to the same original quantity. Modeling highly correlated variables may lead to a statistical issue called multicollinearity. In the presence of multicollinearity, regression models may become inefficient with loss of statistical power, greater computation inaccuracy, unstable estimates, and high variance.[15] Various methods have been proposed to deal with multicollinearity. One or more highly collinear covariates may be omitted from the regression model, which may cause information loss. Ridge regression, a form of penalized linear regression, is another popular method to handle multicollinearity; however, it produces biased estimates and is better suited for predictive rather than explanatory models.[16] In our study, we addressed the issue of multicollinearity with PCA, which creates a new set of orthogonal linear combinations of the original variables (PCs), by definition perfectly uncorrelated to each other.[17] In this study, we used PCA to obtain a maximally informative combined metric of IOP control. Fifth,

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

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

development. Other studies found contrasting results, showing a positive association between long-term IOP fluctuation and VF progression. In a post-hoc analysis of the Advanced Glaucoma Intervention Study (AGIS), Nouri-Mahdavi and colleagues[9] found that long-term IOP fluctuation was an independent risk factor for glaucoma progression, while mean IOP was not. The results of this study were criticized because the authors analyzed the entire available follow-up, including time points after treatment escalation. Further intervention, either in the form of trabeculectomy or laser trabeculoplasty as per AGIS protocol, might have been itself a cause of clinician-induced increased fluctuation in patients at high risk of progression. In a subsequent post-hoc analysis of the AGIS, Caprioli and Coleman[8] investigated the relationship between long-term IOP fluctuation and VF progression, excluding those patients having multiple interventions; they found that long-term IOP fluctuations was significantly associated with VF progression in patients with low mean IOP, but not in those with high IOP. A post-hoc analysis from the Collaborative Initial Glaucoma Treatment Study (CIGTS)[6] examined the role of various IOP parameters on VF progression and found that long-term IOP fluctuation and peak IOP were associated with VF progression, while mean IOP was not.

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

randomizing patients to either pilocarpine or argon laser trabeculoplasty, Bergea et al.[20] investigated the relationship between visual field progression and different IOP variables, and they found that both mean IOP and diurnal IOP fluctuation were associated with visual field progression. That study, however, had several limitations, including the small sample size (76 eyes), high proportion of pseudoexfoliation glaucoma (72%), and the use of range IOP as a measure of fluctuation, which is vulnerable to outlier and highly related to peak IOP. A retrospective study by Matlach and colleagues[21] assessed the impact of long-term and diurnal-nocturnal IOP fluctuation on glaucoma progression in a cohort of 120 glaucoma patients randomly selected from a tertiary referral center; they found that diurnal-nocturnal IOP fluctuation was associated with glaucoma progression, while long-term IOP fluctuation and mean IOP were not. A retrospective study by Kim et al.[22] found similar results in a cohort of NTG patients, with higher diurnal IOP fluctuations and disc hemorrhages being associated with higher hazard of visual field progression. Both these studies are limited by their retrospective nature, making them vulnerable to potential confounders and selection bias. Also, these studies did not employ any statistical method to mitigate multicollinearity.

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

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

damage. So, high OPA might be a surrogate for hypertensive vascular damage, and previous studies[37, 38] have shown that high blood pressure may be a risk factors for primary open-angle glaucoma.

Our study confirms the importance of elevated IOP on glaucoma progression. PC1, which combined information from various IOP parameters (i.e., mean IOP, peak IOP, baseline IOP, peak phasing IOP, and supine IOP), was consistently associated with the rate of visual field progression in the placebo group. On the other hand, such a relationship was significant in the treatment group only for the rates of the fastest five visual field locations, but not for global rates of change. The progression rate of the treatment arm was extremely slow during the trial duration, and the signal from a few progressing locations may be obscured by the overall stability of most test locations. Comparative studies[39, 40] have shown that pointwise methods (especially those considering only locations with significant deterioration) have higher sensitivity and require less time to detect progression than those based on global indices or all test locations. Our study does not provide any information on which IOP metric is the most important for disease progression; this is arduous to tackle because of the intimate relationship among these variables. De Moraes and colleagues[2] evaluated the effect of mean IOP, peak IOP, and SD IOP in a large retrospective cohort of glaucoma patients under clinical care; they found that all these variables were associated with disease progression in the univariable analysis, but only peak IOP was significantly associated with VF progression in the multivariable model. However, mean IOP and peak IOP are highly correlated, and a multivariable model containing both variables would likely suffer from multicollinearity. Treatment modifications highly influence mean IOP and SD IOP in

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

We also investigated the impact of non-IOP and other ocular factors on glaucomatous progression rates, including age, CCT, and corneal hysteresis. The evidence for role of CCT as a risk factor for glaucoma progression is often misunderstood. A thinner cornea causes artifacts in applanation tonometry, with underestimation of the true IOP.[41] Alternatively, corneal thickness may serve as a biomarker of the biomechanical properties of the lamina cribrosa and peripapillary sclera, providing insights into the vulnerability of the optic nerve to increased IOP.[42] An experimental study by Wells and colleagues[43] investigated whether CCT was associated with optic disc compliance after inducing acute IOP rise and found no significant association, indicating that CCT may not reflect ocular biomechanics. In our cohort, thinner CCT was associated with faster progression rates in some multivariable models (which included IOP metrics), while it did not show significance in any of the univariable models. This suggests that CCT alone is not directly associated with glaucoma progression: rather, it becomes statistically significant when measured IOP is included in the model due to the effect of CCT on measured IOP. Other studies, including the Early Manifest Glaucoma Treatment (EMGT)[44] and the Los Angeles Latino Eye Study (LALES),[45] found similar finding, associating thin CCT with conversion to glaucoma and incident glaucoma in multivariable models, but not in univariable models. Khawaja and Jansonius[46] performed a simulation study that mimicked datasets similar to the LALES and Ocular Hypertensive Treatment Study so that IOP, but not CCT, was not associated with glaucoma risk. Consistent with our findings and those from other studies, they found that CCT was not associated with the risk of glaucoma in the univariable model, but a spurious

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

Although previous studies[47-49] have shown a relationship between corneal hysteresis and visual field progression rates, we were not able to confirm such association in our cohort. In any given eye, corneal hysteresis is inversely related to IOP. Therefore, low corneal hysteresis may reflect high IOP, which is an established risk factors for faster glaucoma progression. Also, corneal hysteresis is directly related to corneal stiffness and thickness. Hence, IOP might have underestimated in patients with low corneal hysteresis, with consequent undertreatment leading to faster progression.

Many studies have reported an association between older age and faster progression rates.[1, 44, 50, 51] In our study, older age was associated with faster MD (but not pointwise) progression rates in the latanoprost group but not in the placebo group. Ageing causes the lamina cribrosa to become stiffer and less compliant, potentially reducing its ability and that of peripapillary sclera to comply with IOP changes. Girard and colleagues[35] investigated the age-related biomechanical differences in monkey posterior sclera and found that older animals had higher tensile stress secondary to IOP elevation than younger ones. As tensile stress increased non-linearly with IOP rise, the impact of ageing should theoretically be more pronounced in patients with higher mean IOP; however, we found that older age was associated with worse progression rates in the treatment arm, which had lower mean IOP than the placebo arm. This finding is in agreement with a large retrospective cohort study by De Moraes and colleagues[2], reporting that older age was independently associated with glaucomatous VF progression only in patients with lower mean IOP. Similar findings were found in the JAMDIG study, a large

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

This study has limitations. This was a planned secondary analysis based on the UKGTS dataset and the number of subjects and the duration of follow-up may not provide enough statistical power to identify a meaningful relationship between IOP fluctuation and visual field progression, especially in the treatment arm, where progression rates were extremely slow over the study period. The study cohort included treatment-naïve primary open-glaucoma patients, mainly of European descent and with early glaucomatous damage. Some authors[11] have hypothesized that the effect of IOP fluctuation on the rates of visual progression might vary as a function of disease stage, mean IOP, glaucoma subtype, ethnicity, and treatment modality (medical vs surgical intervention); hence, the results of this study may be not entirely generalizable to other populations. Nevertheless, the results of this study are in agreement with those from the EMGT analysis.[5] The diurnal IOP fluctuation calculation was based on five measurements obtained during the morning and afternoon, and this study provides only IOP snapshots across the day and no information on IOP fluctuation outside office hours. Although we used clinically relevant definitions of IOP fluctuation, these measurements may not adequately characterize short-term IOP variability. Diurnal phasing has been shown to be poorly reproducible, indicating that single-day IOP measurements may not be sufficient to accurately assess short-term fluctuations.[52-55] Our findings are consistent with existing literature in this field. A comparison between the two available diurnal IOP curves revealed that the 95% limits of agreement were around 4 mmHg, aligning closely with the most pronounced fluctuation extremes observed in this dataset

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

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

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Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used chatGPT3.5 in order to improve readability and language of the manuscript. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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FIGURE LEGENDS

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

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

Figure 7. Forest plots for factors associated with the MD rates of progression in the placebo **(left panel)** and treatment **(right panel)** group. Dots and bars indicate point estimates and 95% confidence intervals, respectively. Estimates are intended for 1-unit increase, unless specified otherwise. Combined IOP metrics PC1 is an unitless variable, which combines 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; MD: mean deviation; OPA: ocular pulse amplitude; PC1: principal component 1.

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

816 Analysis. CCT: central corneal thickness; CH: corneal hysteresis; IOP: intraocular
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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
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Relationship between intraocular pressure fluctuation and visual field progression rates in the United Kingdom Glaucoma Treatment Study

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ABSTRACT

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.

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

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

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.

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

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.

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.

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

INTRODUCTION

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

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

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

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

METHODS

Study Population and Procedures

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

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

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

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

IOP Metrics

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

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

- Baseline pretreatment IOP, defined as the average of the IOP readings obtained in the two pre-randomization visits.
- Mean IOP, defined as the average of all post-randomization IOP readings.
- Peak IOP, defined as the highest IOP reading of all post-randomization IOP readings.
- Supine IOP, defined as the Perkins applanation tonometry IOP readings measured at the first post-randomization visit.
- Phasing peak IOP, defined as the highest IOP reading of the diurnal phasing performed at the first post-randomization visit.
- Diurnal IOP fluctuation, defined as the SD of IOP measurements obtained from the diurnal IOP phasing performed at the first post-randomization visit. Diurnal IOP fluctuation was also calculated using the IOP measurements from the last post-randomization visit.
- Long-term IOP fluctuation, defined as the SD of post-randomization IOP readings.

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

Statistical Analysis

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

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

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

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

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

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

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

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

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

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

RESULTS

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

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

Global MD rate

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

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

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

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

Pointwise Rates

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

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

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

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

DISCUSSION

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

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

these two variables. IOP fluctuation is known to be positively correlated with mean IOP. In a retrospective study performed on non-human primates of experimental glaucoma, Gardiner and colleagues[10] used the coefficient of variation (SD IOP divided by mean IOP) to remove the relationship between these two variables. In our cohort, the coefficient of variation reversed the association with mean IOP values, leading to a negative relationship between IOP fluctuation and mean IOP. The explanation for this is likely that there are two components of variability (measurement error and true IOP fluctuation), one of which (true fluctuation) is related to mean IOP and the other (measurement error) is not.[14] Dividing the measurement error by the mean IOP induces the negative association. The method of normalization used in our study likely respects both the increased fluctuations at higher mean IOP and constant measurement errors. Fourth, IOP-related metrics tend to be highly correlated because they are related to the same original quantity. Modeling highly correlated variables may lead to a statistical issue called multicollinearity. In the presence of multicollinearity, regression models may become inefficient with loss of statistical power, greater computation inaccuracy, unstable estimates, and high variance.[15] Various methods have been proposed to deal with multicollinearity. One or more highly collinear covariates may be omitted from the regression model, which may cause information loss. Ridge regression, a form of penalized linear regression, is another popular method to handle multicollinearity; however, it produces biased estimates and is better suited for predictive rather than explanatory models.[16] In our study, we addressed the issue of multicollinearity with PCA, which creates a new set of orthogonal linear combinations of the original variables (PCs), by definition perfectly uncorrelated to each other.[17] In this study, we used PCA to obtain a maximally informative combined metric of IOP control. Fifth,

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

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

development. Other studies found contrasting results, showing a positive association between long-term IOP fluctuation and VF progression. In a post-hoc analysis of the Advanced Glaucoma Intervention Study (AGIS), Nouri-Mahdavi and colleagues[9] found that long-term IOP fluctuation was an independent risk factor for glaucoma progression, while mean IOP was not. The results of this study were criticized because the authors analyzed the entire available follow-up, including time points after treatment escalation. Further intervention, either in the form of trabeculectomy or laser trabeculoplasty as per AGIS protocol, might have been itself a cause of clinician-induced increased fluctuation in patients at high risk of progression. In a subsequent post-hoc analysis of the AGIS, Caprioli and Coleman[8] investigated the relationship between long-term IOP fluctuation and VF progression, excluding those patients having multiple interventions; they found that long-term IOP fluctuations was significantly associated with VF progression in patients with low mean IOP, but not in those with high IOP. A post-hoc analysis from the Collaborative Initial Glaucoma Treatment Study (CIGTS)[6] examined the role of various IOP parameters on VF progression and found that long-term IOP fluctuation and peak IOP were associated with VF progression, while mean IOP was not.

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

randomizing patients to either pilocarpine or argon laser trabeculoplasty, Bergea et al.[20] investigated the relationship between visual field progression and different IOP variables, and they found that both mean IOP and diurnal IOP fluctuation were associated with visual field progression. That study, however, had several limitations, including the small sample size (76 eyes), high proportion of pseudoexfoliation glaucoma (72%), and the use of range IOP as a measure of fluctuation, which is vulnerable to outlier and highly related to peak IOP. A retrospective study by Matlach and colleagues[21] assessed the impact of long-term and diurnal-nocturnal IOP fluctuation on glaucoma progression in a cohort of 120 glaucoma patients randomly selected from a tertiary referral center; they found that diurnal-nocturnal IOP fluctuation was associated with glaucoma progression, while long-term IOP fluctuation and mean IOP were not. A retrospective study by Kim et al.[22] found similar results in a cohort of NTG patients, with higher diurnal IOP fluctuations and disc hemorrhages being associated with higher hazard of visual field progression. Both these studies are limited by their retrospective nature, making them vulnerable to potential confounders and selection bias. Also, these studies did not employ any statistical method to mitigate multicollinearity.

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

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

damage. So, high OPA might be a surrogate for hypertensive vascular damage, and previous studies[37, 38] have shown that high blood pressure may be a risk factors for primary open-angle glaucoma.

Our study confirms the importance of elevated IOP on glaucoma progression. PC1, which combined information from various IOP parameters (i.e., mean IOP, peak IOP, baseline IOP, peak phasing IOP, and supine IOP), was consistently associated with the rate of visual field progression in the placebo group. On the other hand, such a relationship was significant in the treatment group only for the rates of the fastest five visual field locations, but not for global rates of change. The progression rate of the treatment arm was extremely slow during the trial duration, and the signal from a few progressing locations may be obscured by the overall stability of most test locations. Comparative studies[39, 40] have shown that pointwise methods (especially those considering only locations with significant deterioration) have higher sensitivity and require less time to detect progression than those based on global indices or all test locations. Our study does not provide any information on which IOP metric is the most important for disease progression; this is arduous to tackle because of the intimate relationship among these variables. De Moraes and colleagues[2] evaluated the effect of mean IOP, peak IOP, and SD IOP in a large retrospective cohort of glaucoma patients under clinical care; they found that all these variables were associated with disease progression in the univariable analysis, but only peak IOP was significantly associated with VF progression in the multivariable model. However, mean IOP and peak IOP are highly correlated, and a multivariable model containing both variables would likely suffer from multicollinearity. Treatment modifications highly influence mean IOP and SD IOP in

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

We also investigated the impact of non-IOP and other ocular factors on glaucomatous progression rates, including age, CCT, and corneal hysteresis. The evidence for role of CCT as a risk factor for glaucoma progression is often misunderstood. A thinner cornea causes artifacts in applanation tonometry, with underestimation of the true IOP.[41] Alternatively, corneal thickness may serve as a biomarker of the biomechanical properties of the lamina cribrosa and peripapillary sclera, providing insights into the vulnerability of the optic nerve to increased IOP.[42] An experimental study by Wells and colleagues[43] investigated whether CCT was associated with optic disc compliance after inducing acute IOP rise and found no significant association, indicating that CCT may not reflect ocular biomechanics. In our cohort, thinner CCT was associated with faster progression rates in some multivariable models (which included IOP metrics), while it did not show significance in any of the univariable models. This suggests that CCT alone is not directly associated with glaucoma progression: rather, it becomes statistically significant when measured IOP is included in the model due to the effect of CCT on measured IOP. Other studies, including the Early Manifest Glaucoma Treatment (EMGT)[44] and the Los Angeles Latino Eye Study (LALES),[45] found similar finding, associating thin CCT with conversion to glaucoma and incident glaucoma in multivariable models, but not in univariable models. Khawaja and Jansonius[46] performed a simulation study that mimicked datasets similar to the LALES and Ocular Hypertensive Treatment Study so that IOP, but not CCT, was not associated with glaucoma risk. Consistent with our findings and those from other studies, they found that CCT was not associated with the risk of glaucoma in the univariable model, but a spurious

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

Although previous studies[47-49] have shown a relationship between corneal hysteresis and visual field progression rates, we were not able to confirm such association in our cohort. In any given eye, corneal hysteresis is inversely related to IOP. Therefore, low corneal hysteresis may reflect high IOP, which is an established risk factors for faster glaucoma progression. Also, corneal hysteresis is directly related to corneal stiffness and thickness. Hence, IOP might have underestimated in patients with low corneal hysteresis, with consequent undertreatment leading to faster progression.

Many studies have reported an association between older age and faster progression rates.[1, 44, 50, 51] In our study, older age was associated with faster MD (but not pointwise) progression rates in the latanoprost group but not in the placebo group. Ageing causes the lamina cribrosa to become stiffer and less compliant, potentially reducing its ability and that of peripapillary sclera to comply with IOP changes. Girard and colleagues[35] investigated the age-related biomechanical differences in monkey posterior sclera and found that older animals had higher tensile stress secondary to IOP elevation than younger ones. As tensile stress increased non-linearly with IOP rise, the impact of ageing should theoretically be more pronounced in patients with higher mean IOP; however, we found that older age was associated with worse progression rates in the treatment arm, which had lower mean IOP than the placebo arm. This finding is in agreement with a large retrospective cohort study by De Moraes and colleagues[2], reporting that older age was independently associated with glaucomatous VF progression only in patients with lower mean IOP. Similar findings were found in the JAMDIG study, a large

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

This study has limitations. This was a planned secondary analysis based on the UKGTS dataset and the number of subjects and the duration of follow-up may not provide enough statistical power to identify a meaningful relationship between IOP fluctuation and visual field progression, especially in the treatment arm, where progression rates were extremely slow over the study period. The study cohort included treatment-naïve primary open-glaucoma patients, mainly of European descent and with early glaucomatous damage. Some authors[11] have hypothesized that the effect of IOP fluctuation on the rates of visual progression might vary as a function of disease stage, mean IOP, glaucoma subtype, ethnicity, and treatment modality (medical vs surgical intervention); hence, the results of this study may be not entirely generalizable to other populations. Nevertheless, the results of this study are in agreement with those from the EMGT analysis.[5] The diurnal IOP fluctuation calculation was based on five measurements obtained during the morning and afternoon, and this study provides only IOP snapshots across the day and no information on IOP fluctuation outside office hours. Although we used clinically relevant definitions of IOP fluctuation, these measurements may not adequately characterize short-term IOP variability. Diurnal phasing has been shown to be poorly reproducible, indicating that single-day IOP measurements may not be sufficient to accurately assess short-term fluctuations.[52-55] Our findings are consistent with existing literature in this field. A comparison between the two available diurnal IOP curves revealed that the 95% limits of agreement were around 4 mmHg, aligning closely with the most pronounced fluctuation extremes observed in this dataset

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

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. Other aspects of IOP, such as mean IOP and peak IOP, may be more informative. Higher OPA may be an independent factor for faster glaucoma progression.

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Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used chatGPT3.5 in order to improve readability and language of the manuscript. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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FIGURE LEGENDS

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

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

Figure 7. Forest plots for factors associated with the MD rates of progression in the placebo **(left panel)** and treatment **(right panel)** group. Dots and bars indicate point estimates and 95% confidence intervals, respectively. Estimates are intended for 1-unit increase, unless specified otherwise. Combined IOP metrics PC1 is an unitless variable, which combines 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; MD: mean deviation; OPA: ocular pulse amplitude; PC1: principal component 1.

Figure 8. Forest plots for factors associated with the pointwise rates of progression in the placebo **(left panel)** and treatment **(right panel)** group. Dots and bars indicate point estimates and 95% confidence intervals, respectively. Estimates are intended for 1-unit increase, unless specified otherwise. Combined IOP metrics PC1 is an unitless variable, which combines 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; PLR: pointwise linear rates.

Figure 9. Forest plots for factors associated with the pointwise rates of progression of the five fastest locations in the placebo **(left panel)** and treatment **(right panel)** group. Dots and bars indicate point estimates and 95% confidence intervals, respectively. Estimates are intended for 1-unit increase, unless specified otherwise. Combined IOP metrics PC1 is an unitless variable, which combines 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; PLR: pointwise linear rates.

Figure 5

Click here to access/download;Figure;Figure 5.tiff

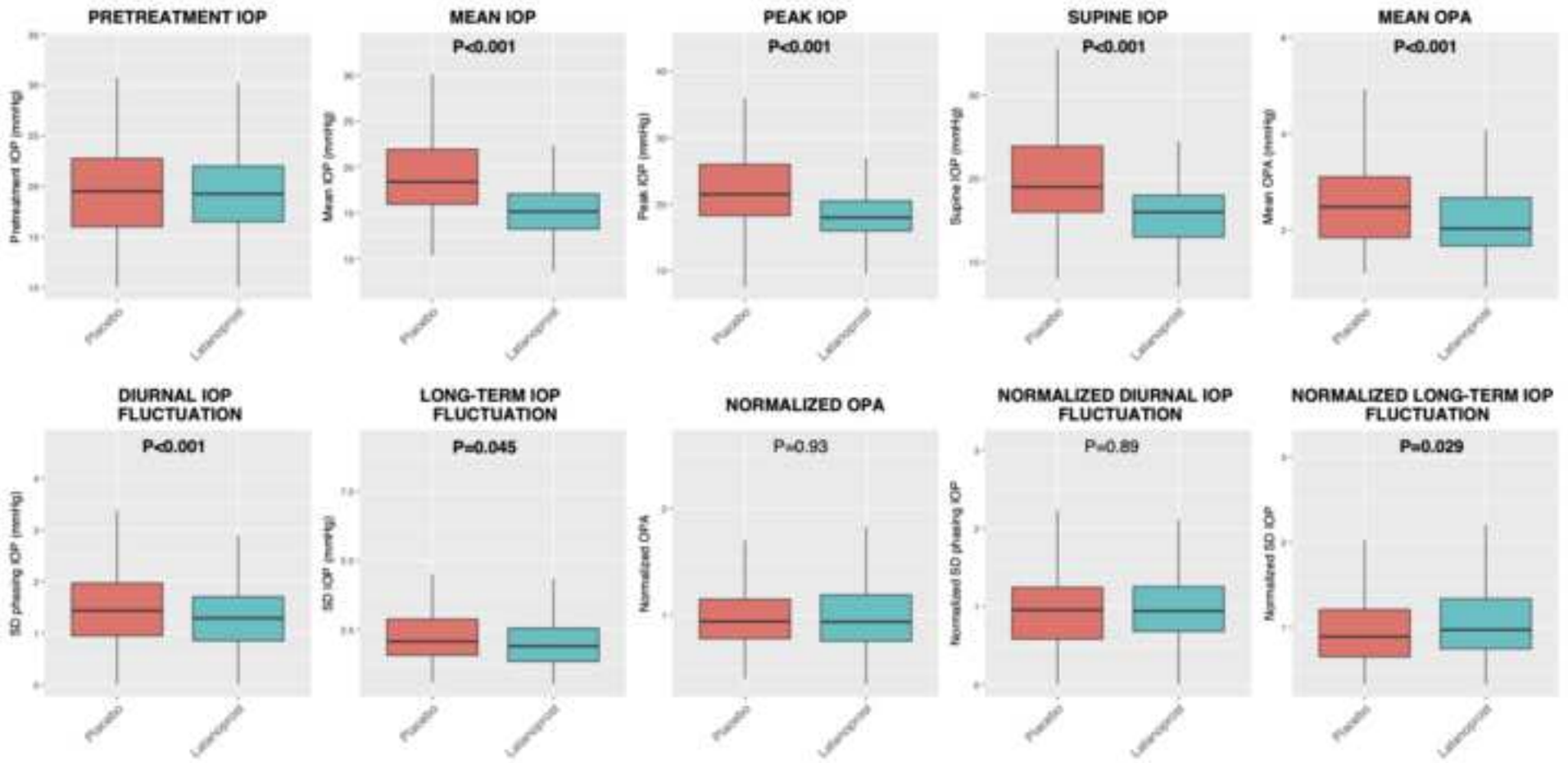


Figure 6

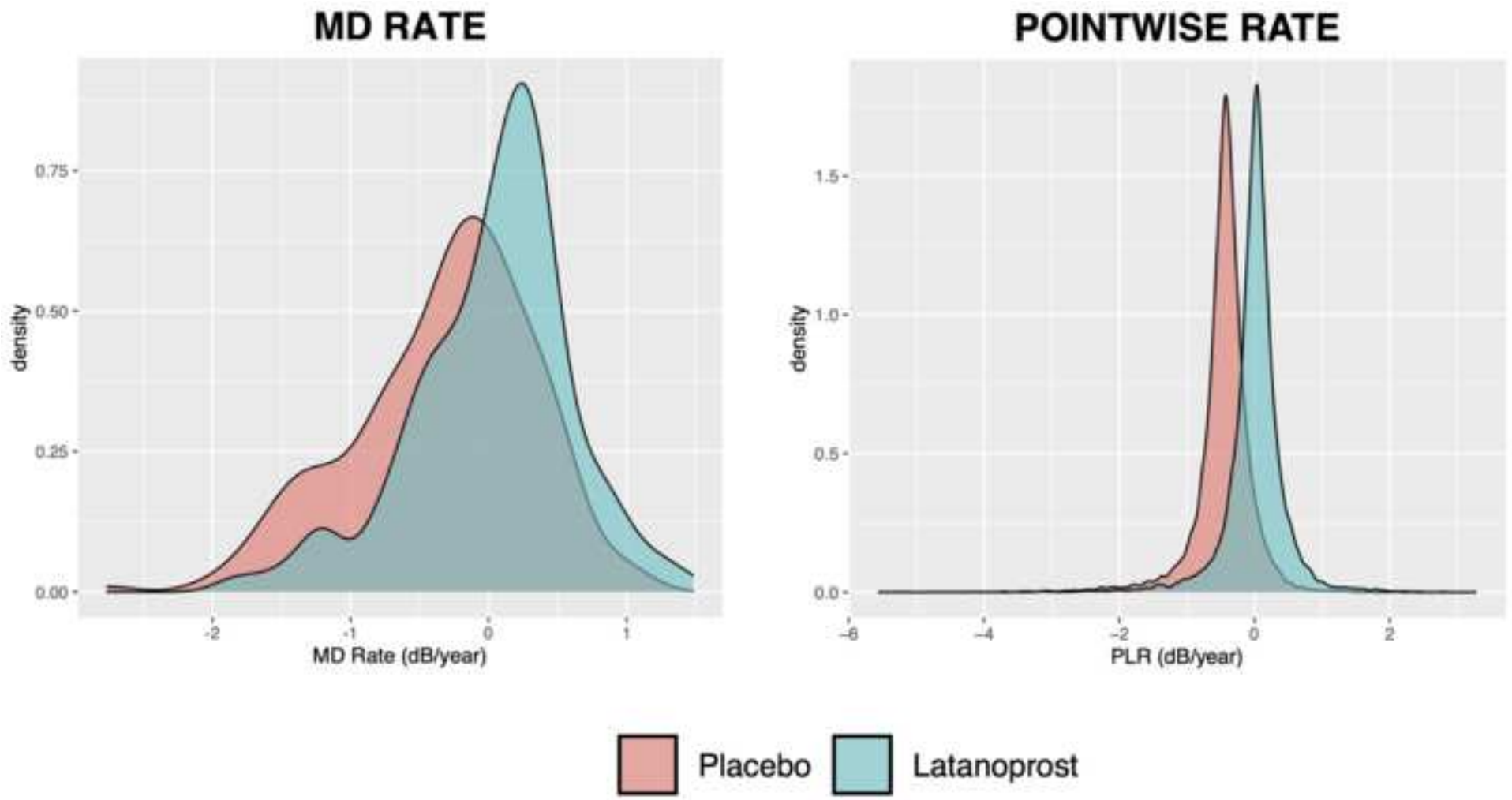


Figure 7

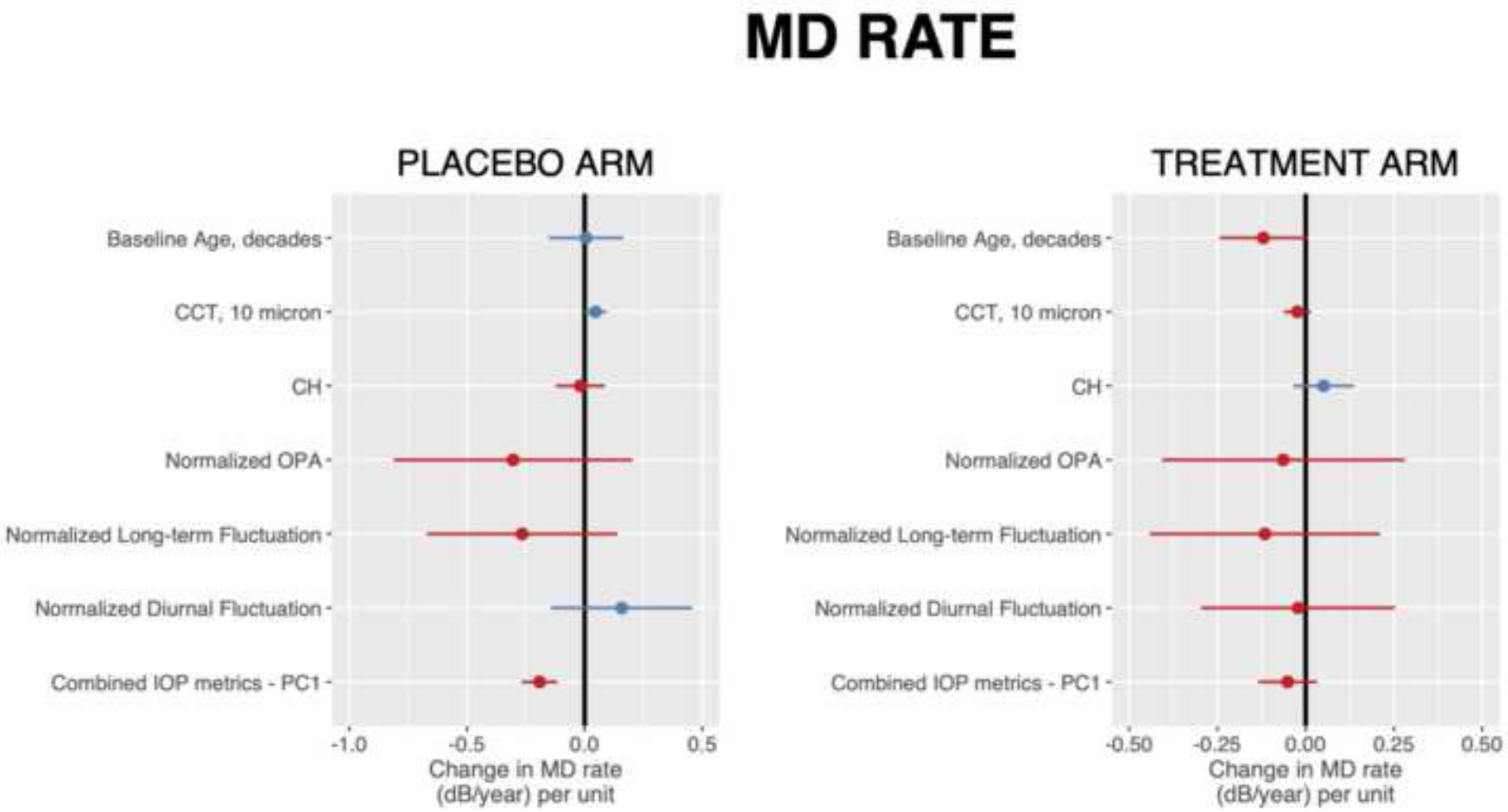


Figure 8

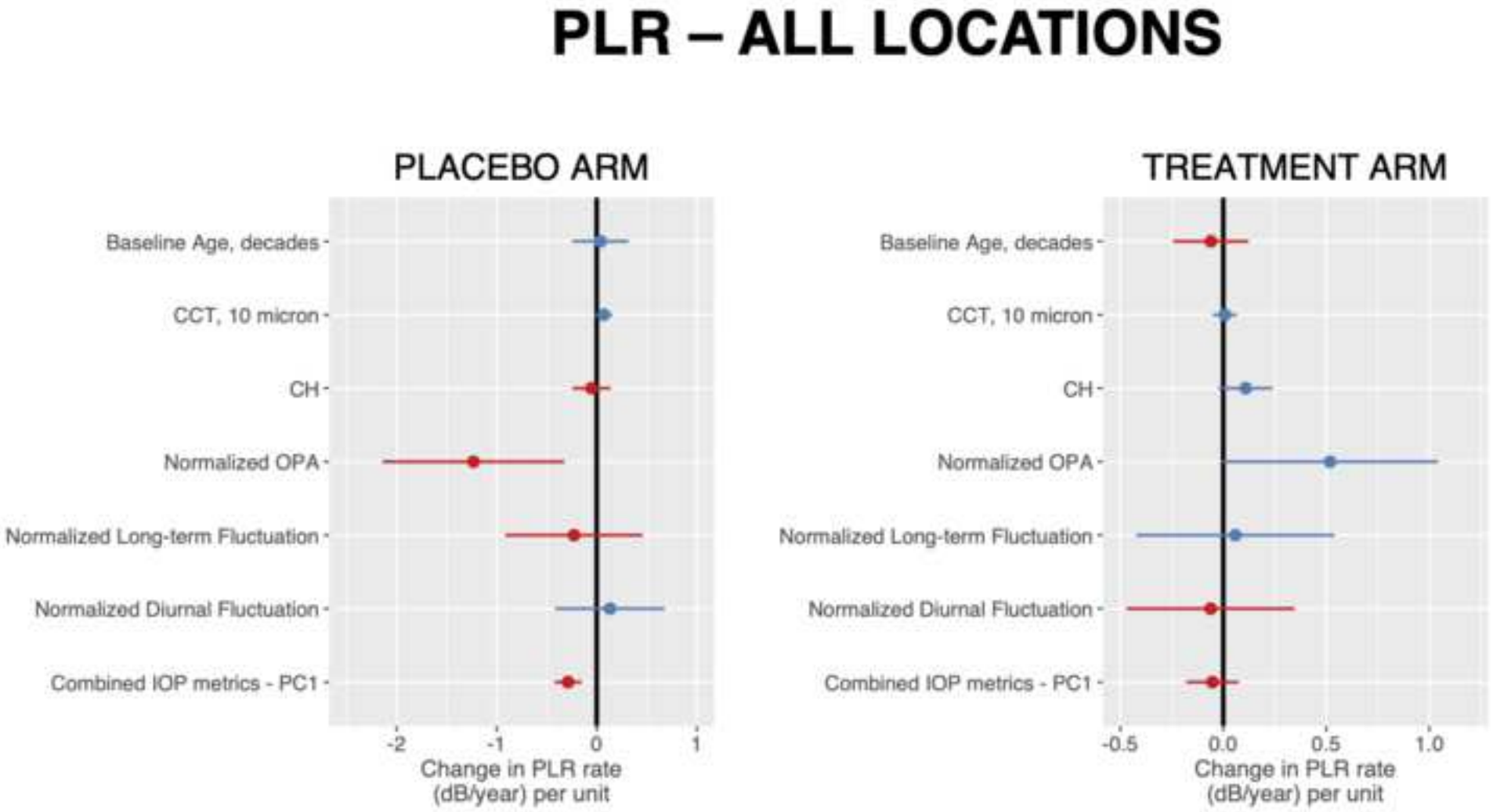


Figure 9

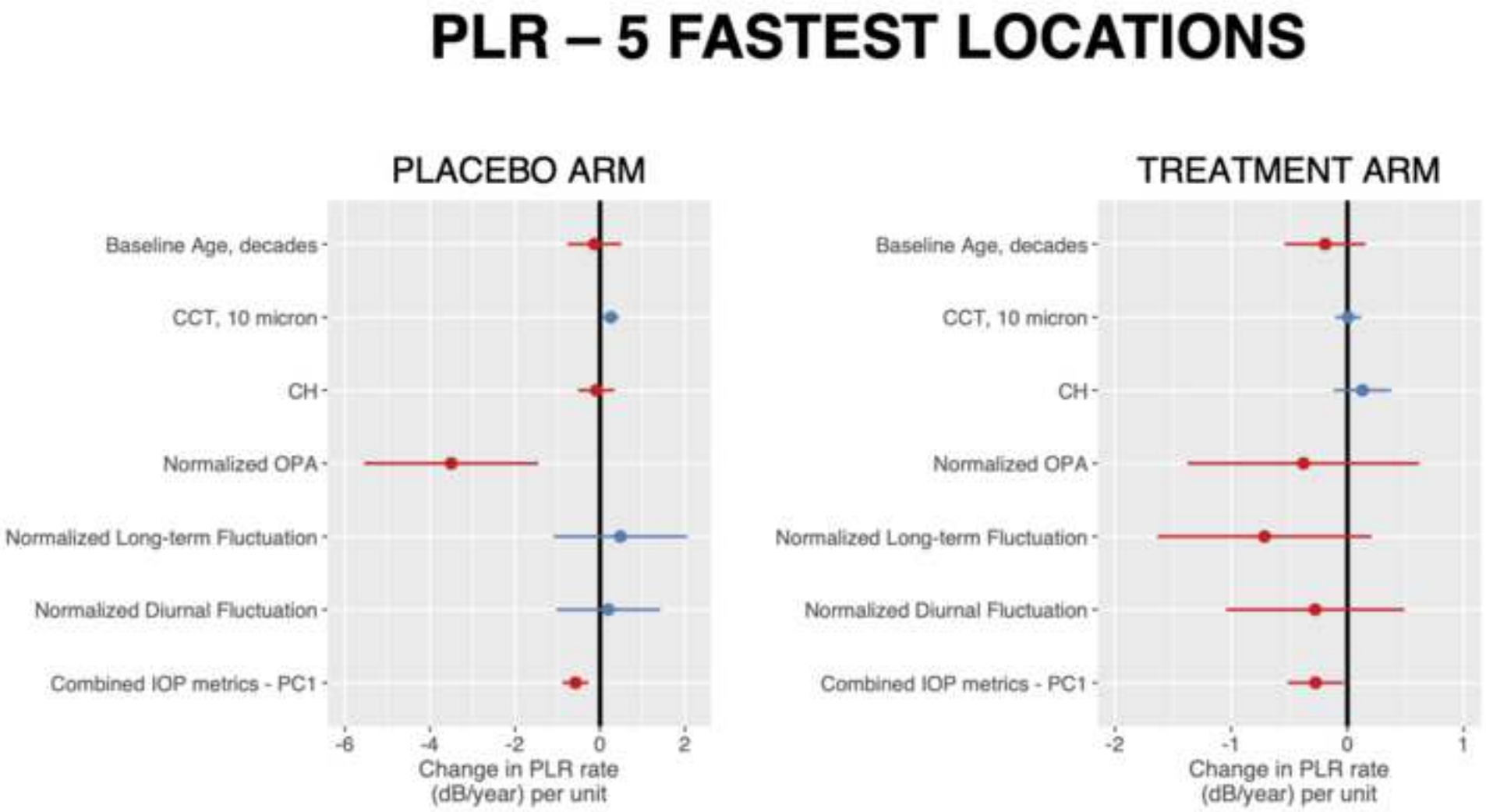


Table 1. Baseline demographic and clinical characteristics of the study population

Variable	Placebo Cohort	Treatment Cohort
No. Eyes/Patients	213/213	217/217
Age, years, mean (±SD)	66.5 (±10.3)	65.1 (±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 (±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 (±SD)	544 (±34)	539 (±34)

CCT: central corneal thickness, IOP: intraocular pressure; IQR: interquartile range; MD: mean deviation; SD: standard deviation.

Figure S1

UNNORMALIZED

NORMALIZED

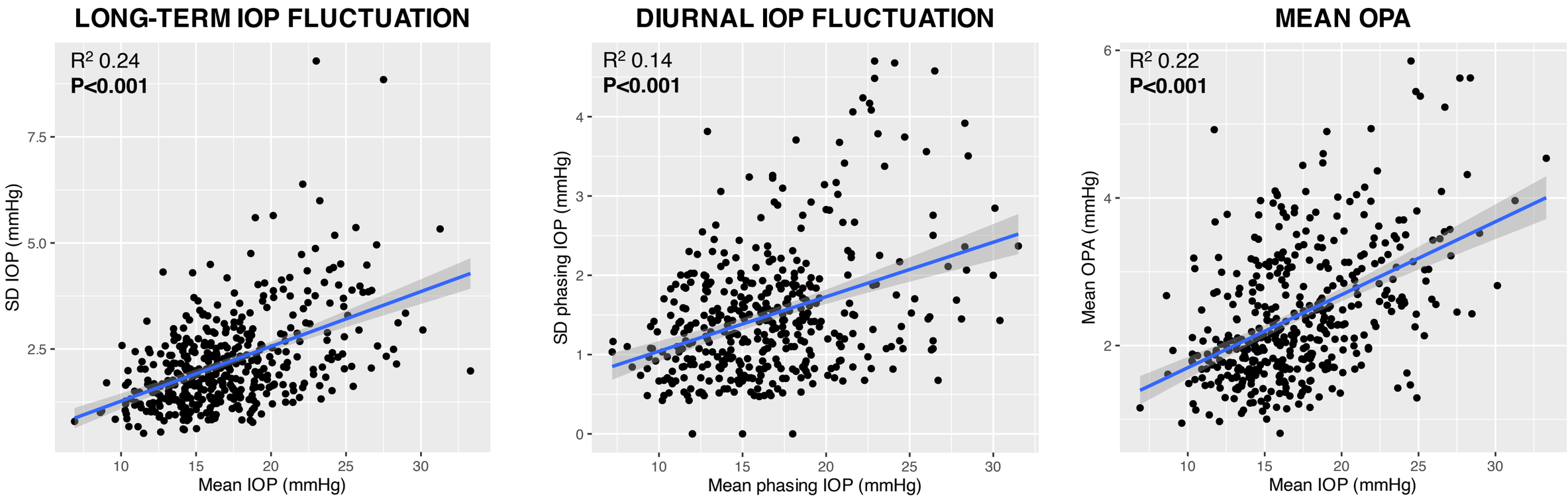


Figure S1. Bivariate plots showing the relationship between mean IOPs and the various unnormalized **(top row)** and normalized **(bottom row)** IOP fluctuation metrics. Blue lines and grey shadow represent regression lines and 95% confidence intervals, respectively. IOP: intraocular pressure; OPA: ocular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

Figure S2

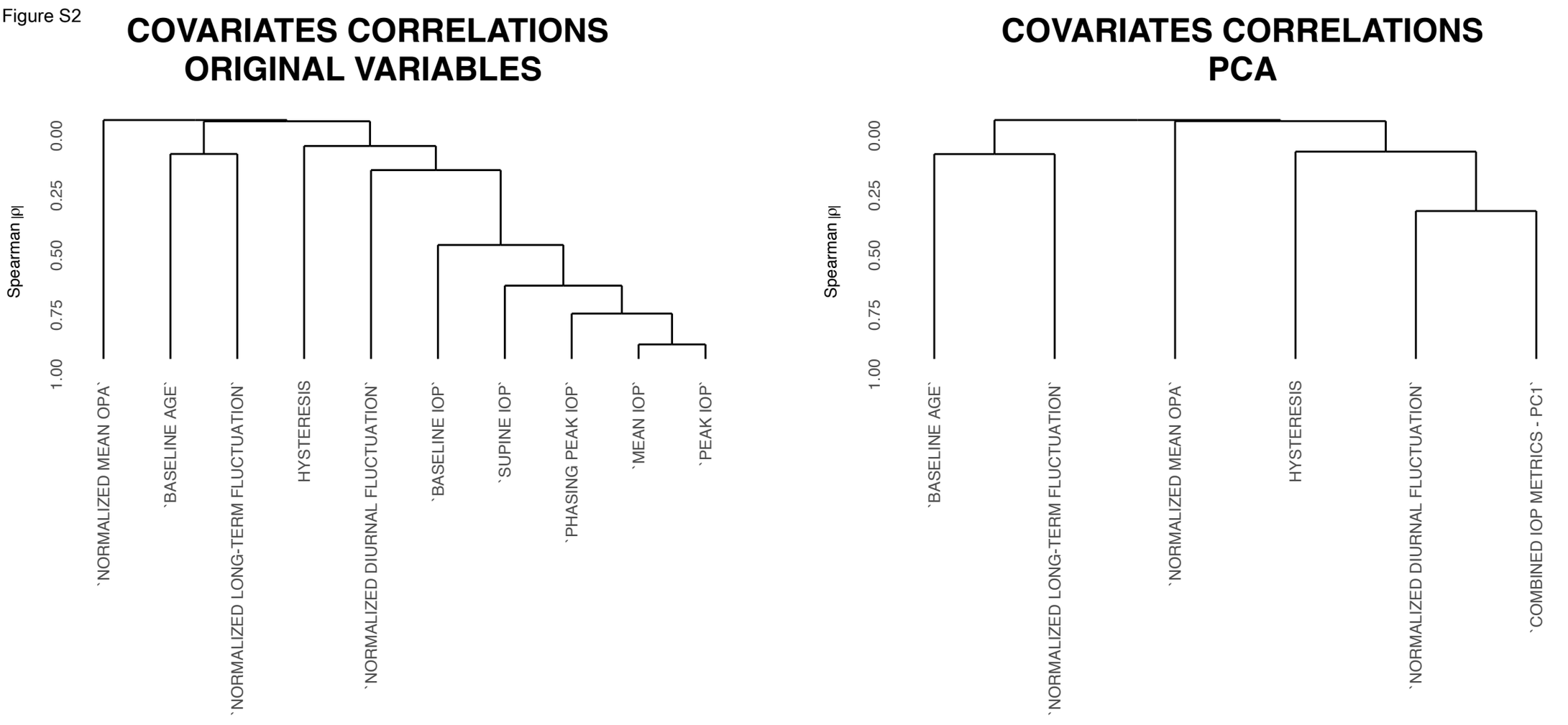


Figure S2. Hierarchical cluster analysis of covariates based on the absolute value of Spearman's correlation coefficient for original variables **(left panel)** and after combining baseline IOP, peak IOP, mean IOP, supine IOP, peak phasing IOP into a combined IOP metric through PCA **(right panel)**.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

Figure S3

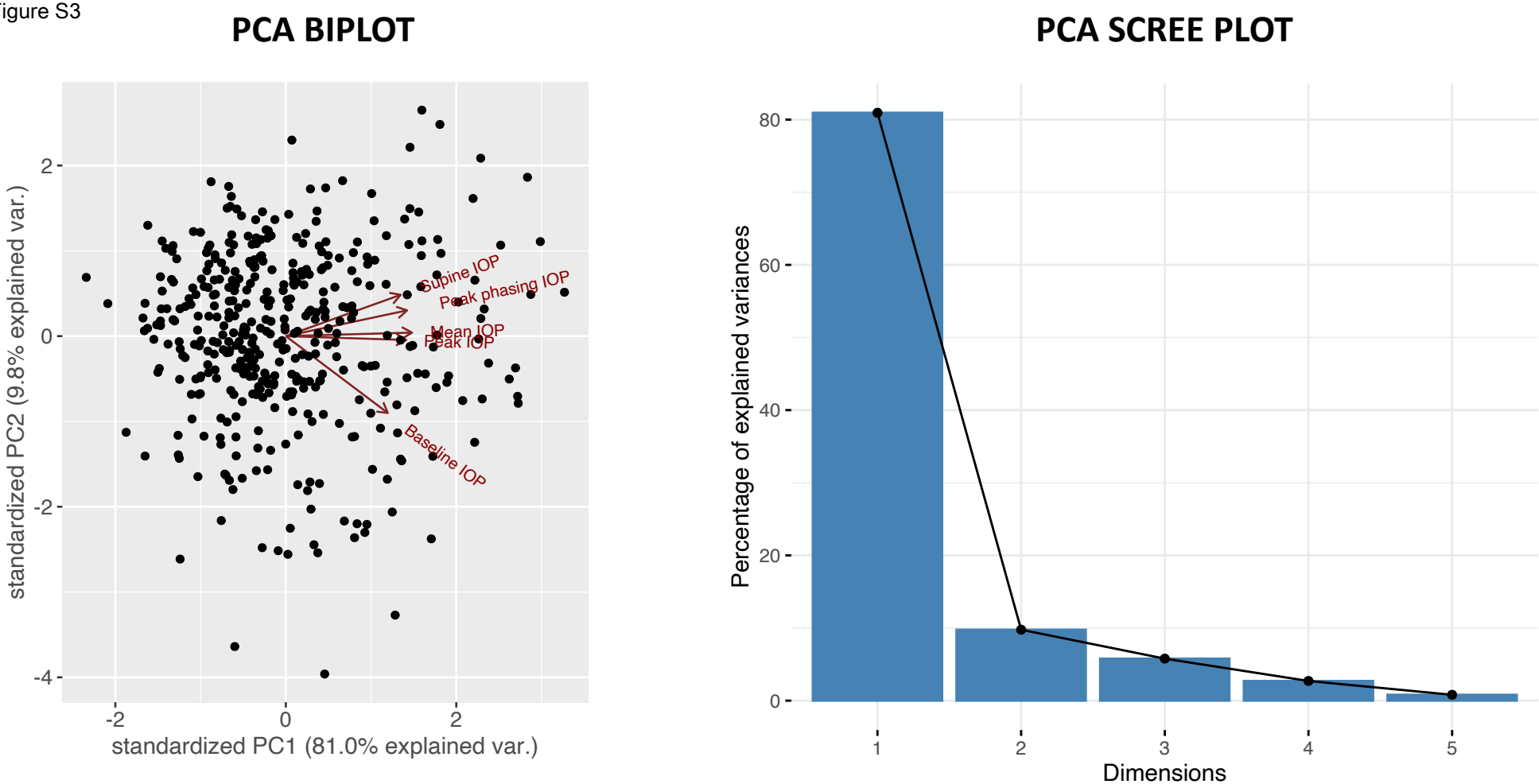


Figure S3. Principal component analysis (PCA) Biplot **(left panel)** and scree plot **(right panel)**. IOP: intraocular pressure; PC1: principal component 1; PC2: principal component 2.

Figure S4

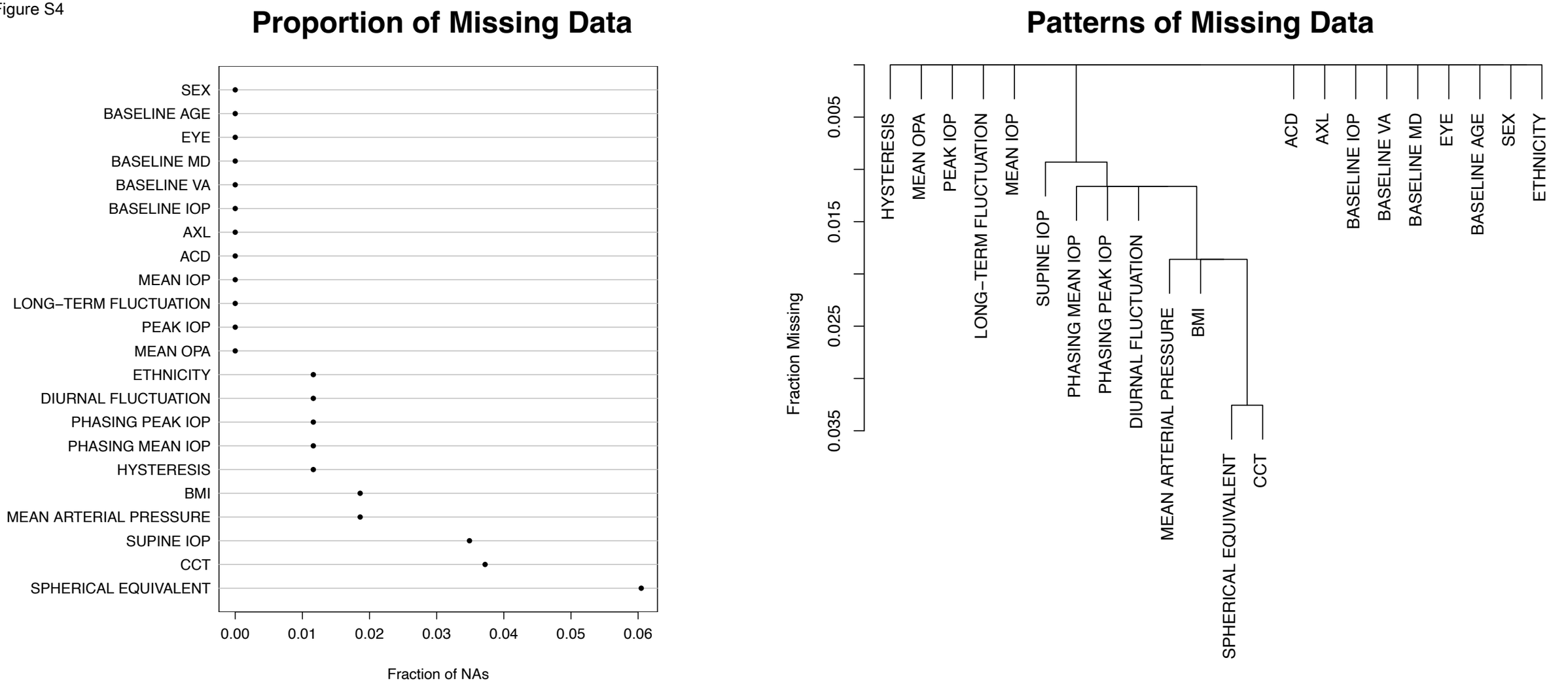


Figure S4. Fraction of missing data for each variable **(left panel)** and hierarchical cluster analysis of missingness combinations **(right panel)**. ACD: anterior chamber depth; AXL: axial length; BMI: body mass index; CCT: central corneal thickness; IOP: intraocular pressure; MD: mean deviation;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

Figure S10

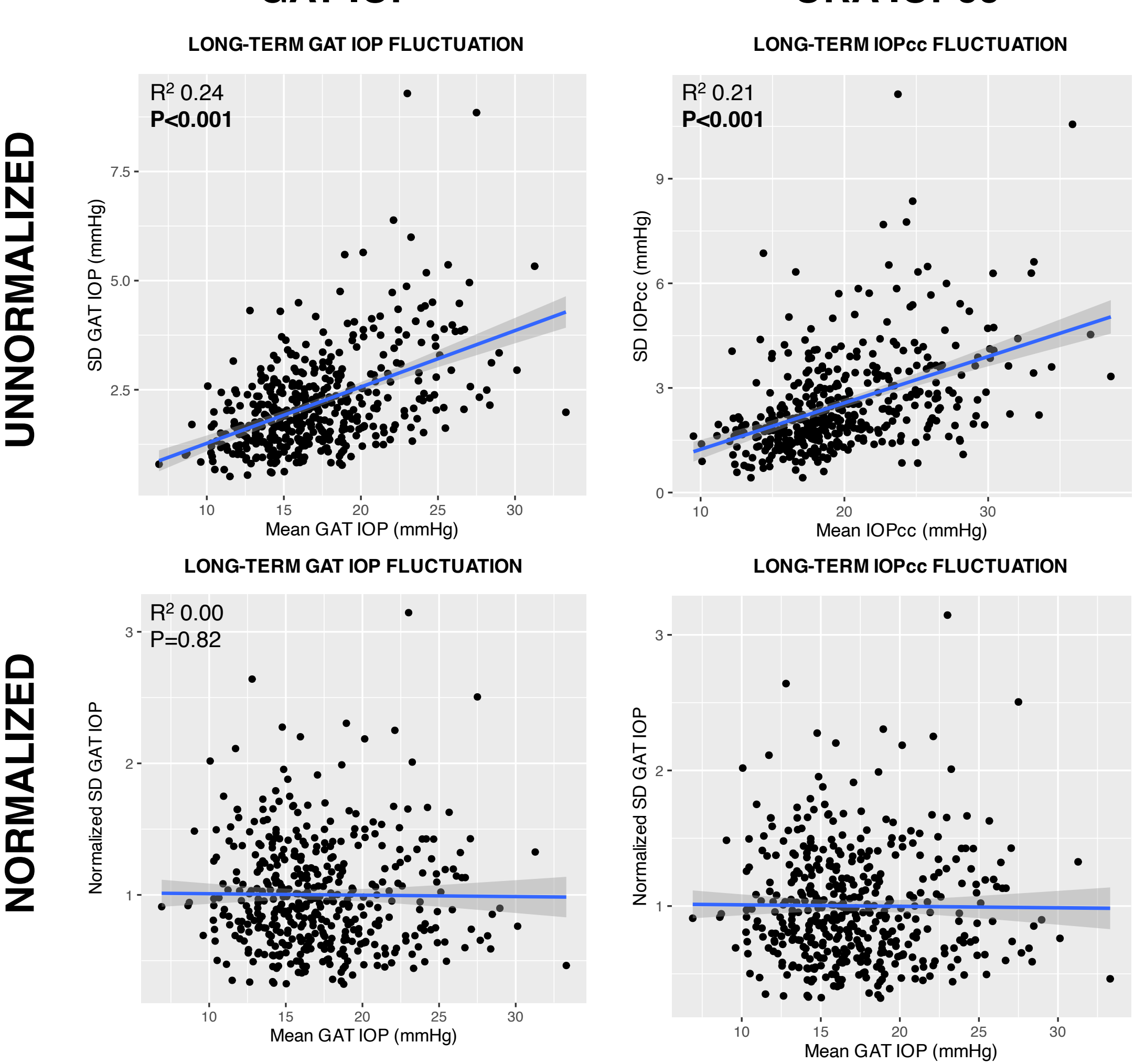


Figure S10. Bivariate plots showing the relationship between mean IOP and long-term IOP fluctuation as measured with GAT **(left column)** and ORA **(right column).** Blue lines and grey shadow represent regression lines and 95% confidence intervals, respectively. GAT: Goldmann applanation tonometer;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

Figure S11

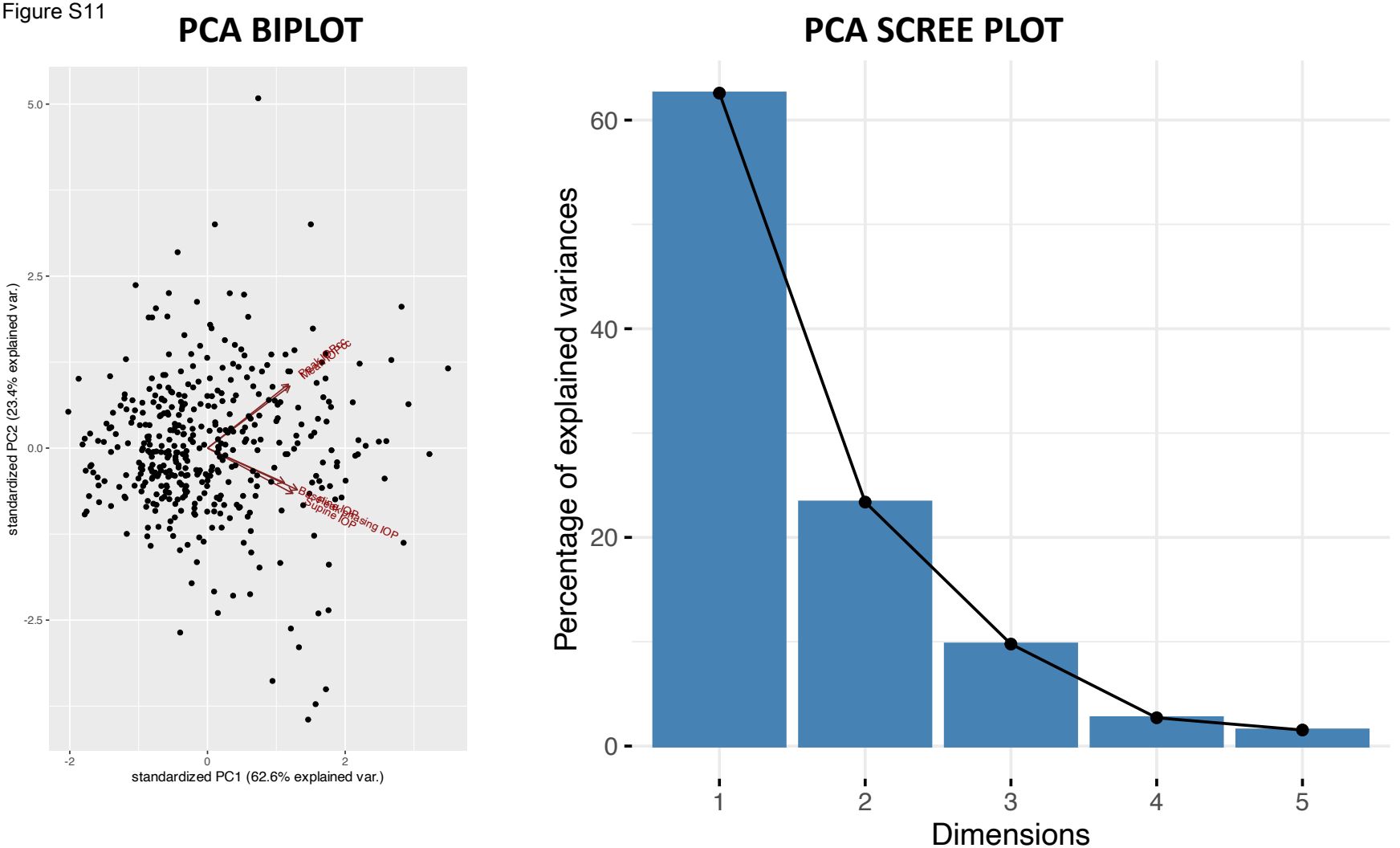


Figure S11. Principal component analysis (PCA) biplot **(left panel)** and scree plot **(right panel)** using IOPcc values to estimate mean and peak IOP. IOP: intraocular pressure; IOPcc: corneal-compensated IOP; PC1: principal component 1; PC2: principal component 2.

Figure S12

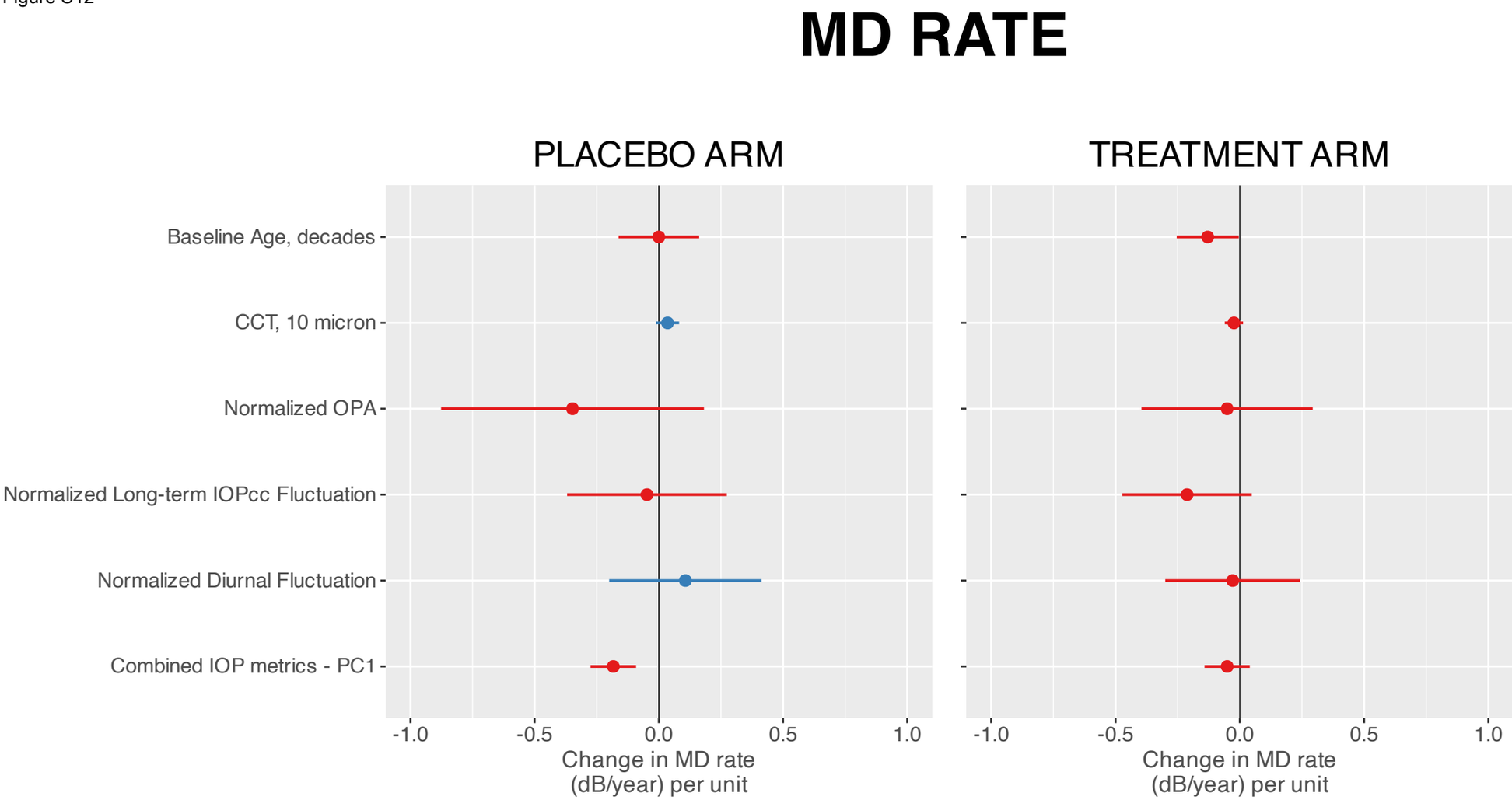


Figure S12. Forest plots for factors associated with the MD rates of progression in the placebo **(left panel)** and treatment **(right panel)** group. Mean IOP, peak IOP and normalized LTF fluctuation were calculated from corneal compensated IOP as measured with the Ocular Response Analyzer (Reichert, 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

Figure S13

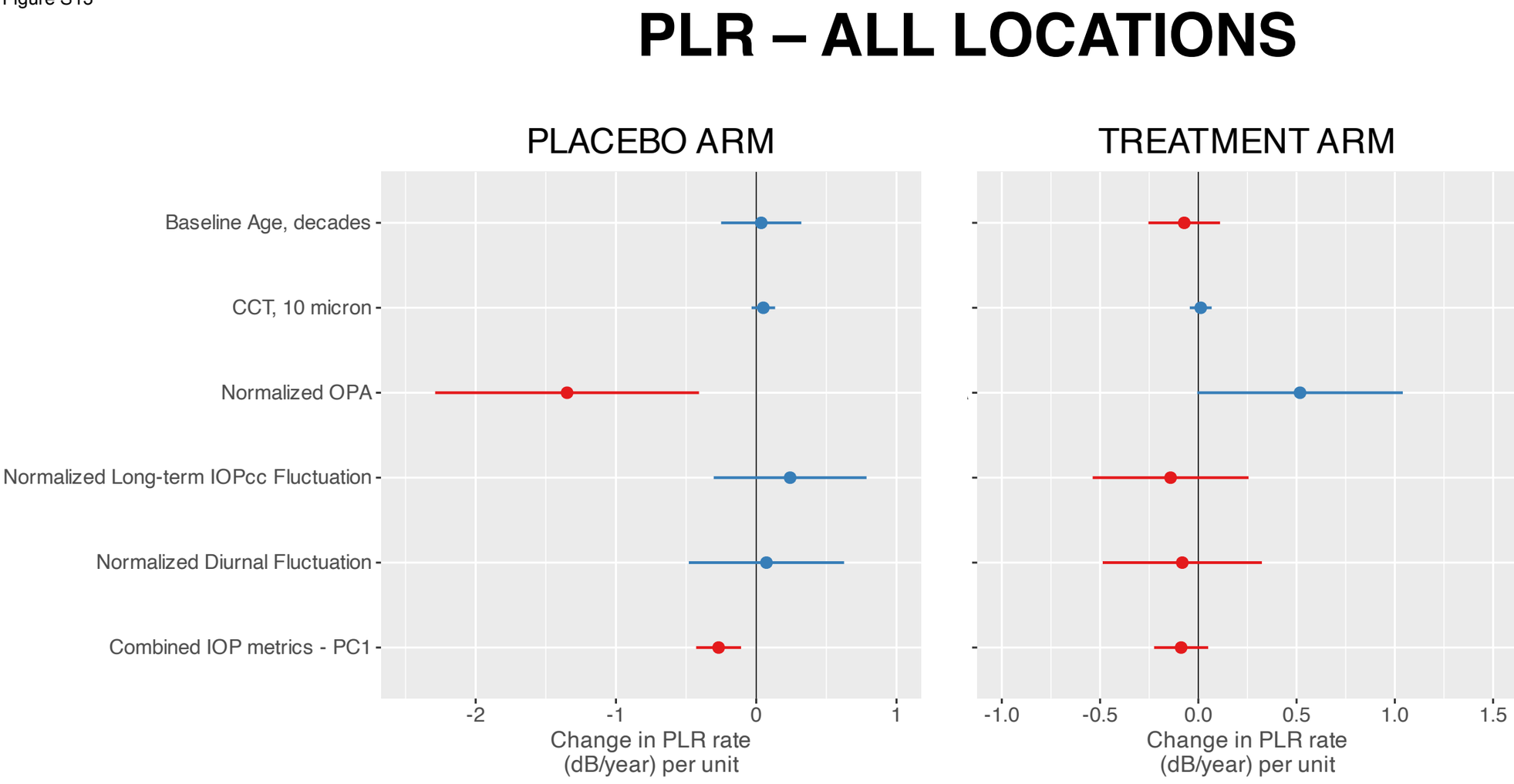


Figure S13. Forest plots for factors associated with the pointwise rates of progression in the placebo **(left panel)** and treatment **(right panel)** group. Mean IOP, peak IOP and normalized LTF fluctuation were calculated from corneal compensated IOP as measured with the Ocular Response Analyzer (Reichert, 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

Figure S14

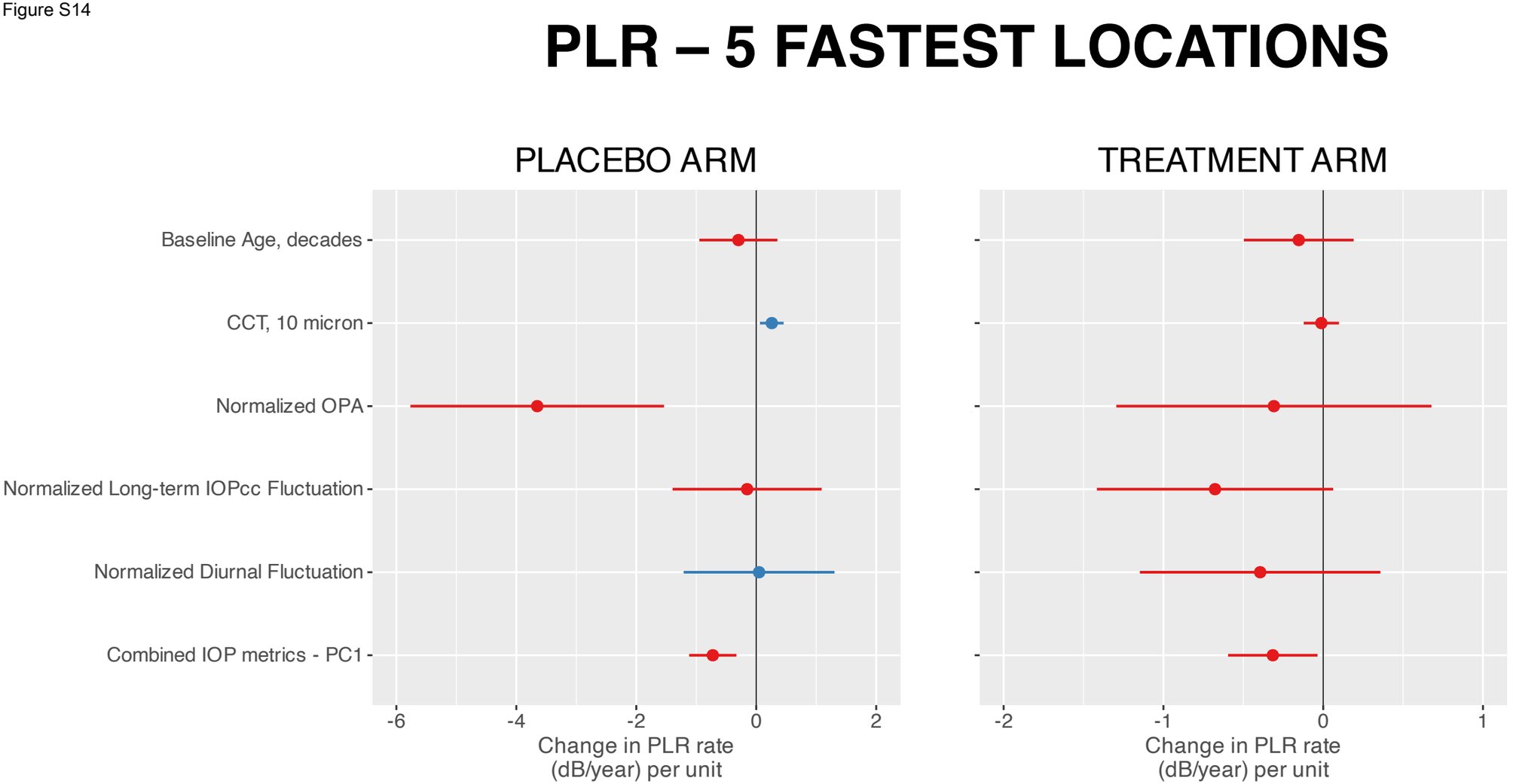


Figure S14. Forest plots for factors associated with the pointwise rates of progression of the fastest five locations in the placebo **(left panel)** and treatment **(right panel)** group. Mean IOP, peak IOP and normalized LTF fluctuation were calculated from corneal compensated IOP as measured with 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

Figure S15

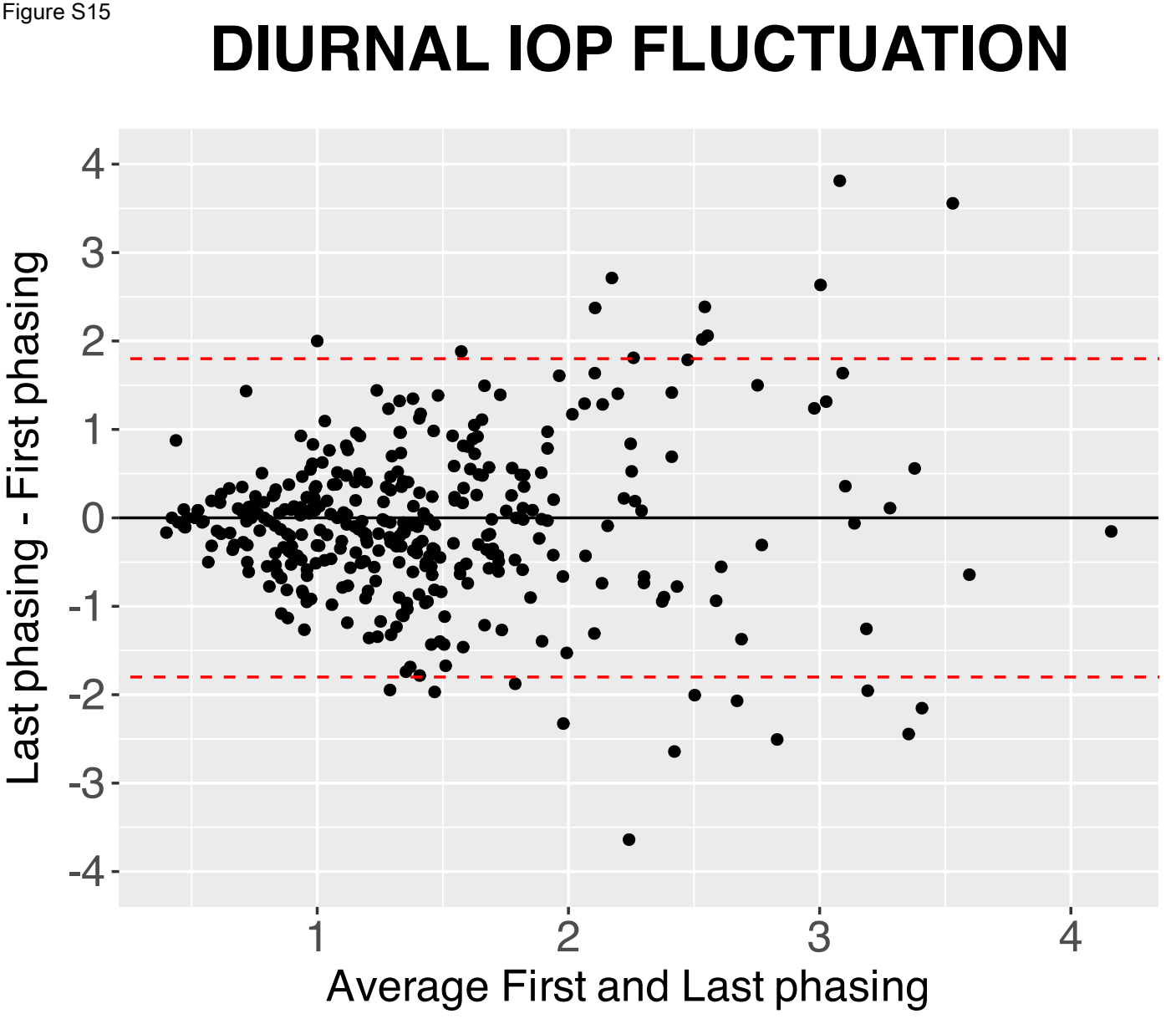
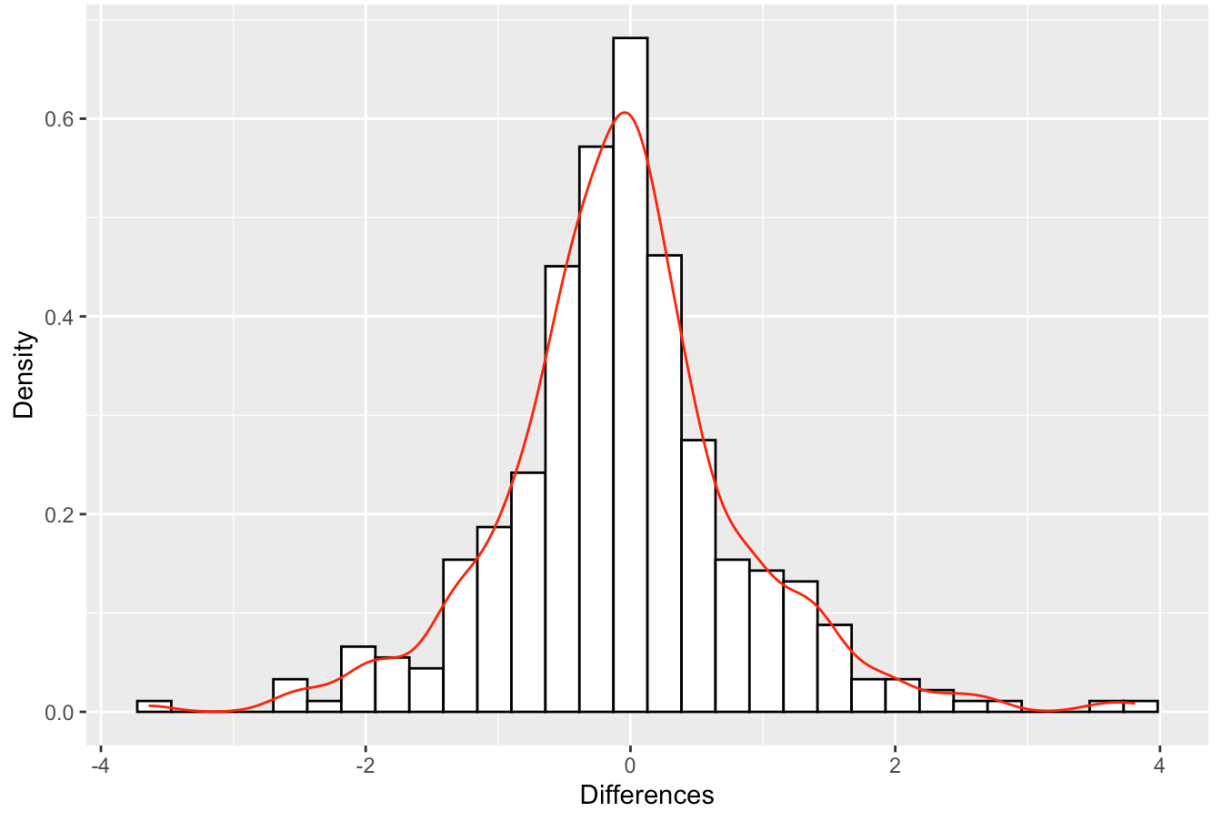


Figure S15. Bland-Altman plots of agreement for diurnal IOP fluctuation calculated from the IOP phasing performed at the first and last post-randomization visits. Black solid line and red dashed lines indicate the no difference lines. and 95% limits of agreements, respectively.

Figure S16

DIURNAL SD IOP DIFFERENCES BETWEEN LAST AND FIRST PHASING



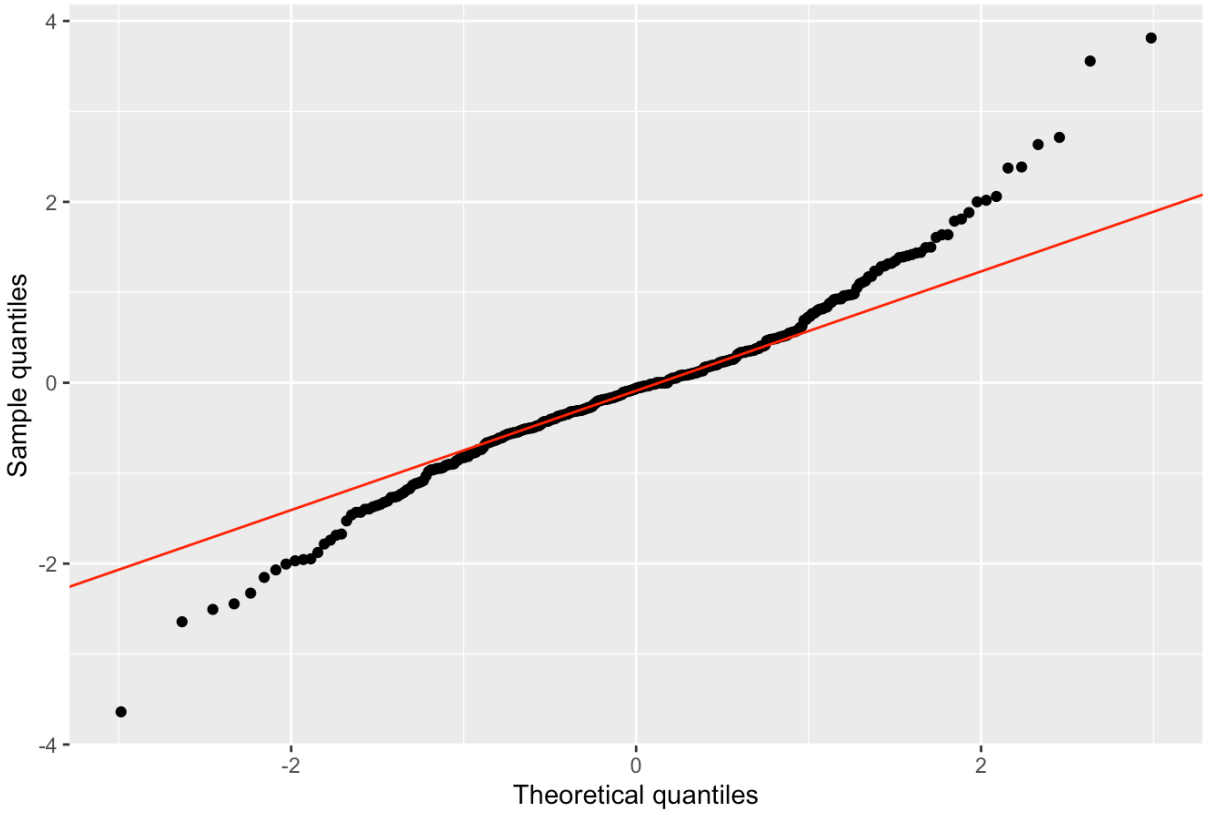


Figure S16. Frequency histogram **(left panel)** and quantile-quantile plot **(right panel)** for the difference in IOP fluctuation values calculated from IOP phasings performed at the last and first post-randomization visits.

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
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.				

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
Estimates are intended for 1-unit increase. 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 S5

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

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 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**

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 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
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.				

ICMJE FORM

Date: 10/4/2023

Your Name: David Crabb

Manuscript Title: 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)

US-based Author (if yes, you must fill out Open Payment section below): NO

Manuscript Number (if known): Click or tap here to enter text.

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9	Participation on a Data Safety Monitoring Board or Advisory Board	☒ **None**	
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12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	☒ **None**	
13	Other financial or non-financial interests	☐ **None**	
		Santen	Non-remunerative
		Medisoft	Non-remunerative

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If no, please briefly explain discrepancy: Click or tap here to enter text.

ICMJE FORM

Date: 10/4/2023

Your Name: David F Garway-Heath

Manuscript Title: 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)

US-based Author (if yes, you must fill out Open Payment section below): NO

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<table><tr><td>Moorfields Eye Hospital NHS Foundation Trust</td><td>UKGTS trial sponsor</td></tr><tr><td>Pfizer</td><td>Unrestricted investigator-initiated research grant</td></tr><tr><td>UK's NIHR Biomedical Research Centre at Moorfields Eye Hospital NHS Foundation Trust</td><td>Supplementary Funding</td></tr><tr><td>UCL Institute of Ophthalmology, London, UK</td><td>Supplementary Funding</td></tr><tr><td>Heidelberg Engineering</td><td>Equipment loan</td></tr><tr><td>Carl Zeiss Meditec</td><td>Equipment loan</td></tr><tr><td>Optovue</td><td>Equipment loan</td></tr></table></td></tr>
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ICMJE FORM

Date: 9/22/2023

Your Name: Giovanni Montesano

Manuscript Title: 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)

US-based Author (if yes, you must fill out Open Payment section below): NO

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Date: 9/23/2023

Your Name: Alessandro Rabiolo

Manuscript Title: 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)

US-based Author (if yes, you must fill out Open Payment section below): NO

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6	Payment for expert testimony	☒ **None**	
7	Support for attending meetings and/or travel	☐ **None**	
		Bausch + Lomb	Flight, hotel reservation, and congress fee for ARVO 2023 meeting
		Thea farma spa	Flight and hotel reservation for the 2023 Moorfields International Glaucoma Symposium
		Visufarma spa	Hotel reservation and congress fee for the the Associazione per lo Studio del Glaucoma (AISG) 2023 annual meeting
8	Patents planned, issued or pending	☒ **None**	
9	Participation on a Data Safety Monitoring Board or Advisory Board	☒ **None**	

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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	☒	☒	☒	☒
Giovanni Montesano	☐	☐	☒	☒
David P Crabb	☐	☐	☐	☒
David F Garway-Heath	☒	☒	☒	☒
	☐	☐	☐	☐
	☐	☐	☐	☐
	☐	☐	☐	☐
	☐	☐	☐	☐

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