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A Polygenic Risk Score Predicts Intraocular Pressure Readings Outside Office Hours and Early Morning Spikes as Measured by Home Tonometry

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Purpose: Intraocular pressure (IOP) elevations may occur in early morning or outside office hours and can be missed during routine in-clinic IOP measurements. Such fluctuations or peaks likely contribute to glaucoma progression. We sought to investigate the relationship between an IOP polygenic risk score (PRS) and short-term IOP profile.

Design: Cross-sectional study.

Participants: Four hundred seventy-three eyes from 239 participants with suspected or established primary open-angle glaucoma sampled from 4 outpatient clinics in Australia between August 2016 and December 2019.

Methods: Participants underwent Icare HOME (Icare Oy, Vanda, Finland) tonometer measurements to record IOP 4 times daily for 5 days. Unreliable measurements were excluded. A minimum of 2 days with at least 3 reliable measurements were required. We used a validated IOP PRS derived from 146 IOP-associated variants in a linear regression model adjusted for central corneal thickness and age.

Main Outcome Measures: Highest recorded early morning IOP and mean IOP within and outside office hours. Early morning IOP spikes were defined by a higher early morning IOP than the maximum in-office hours IOP.

Results: Reliable measurements were obtained from 334 eyes of 176 participants (mean age, 64 ± 9 years). Eyes in the highest IOP PRS quintile showed an early morning IOP increase of 4.3 mmHg (95% confidence interval [CI], 1.4−7.3; $P = 0.005$) and mean increase in IOP outside office hours of 2.7 mmHg (95% CI, 0.61−4.7; $P = 0.013$) than the lowest quintile, which were significant independently after accounting for a recent in-clinic IOP measured by Goldmann applanation tonometry. Eyes in the highest PRS quintile were 5.4-fold more likely to show early morning IOP spikes than the lowest quintile (odds ratio 95% CI, 1.3−23.6; $P = 0.023$).

Conclusions: A validated IOP PRS was associated with higher early morning IOP and mean IOP outside office hours. These findings support a role for genetic risk prediction of susceptibility to elevated IOP that may not be apparent during in-clinic hours, requiring more detailed clinical phenotyping using home tonometry, the results of which may guide additional interventions to improve IOP control. *Ophthalmology Glaucoma 2021;4:411-420 © 2020 by the American Academy of Ophthalmology*

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Because intraocular pressure (IOP) remains the only modifiable risk factor in glaucoma, IOP-lowering therapies form the basis of current evidence-based glaucoma treatment.[1] Intraocular pressure monitoring is a key component of the management algorithm, but traditionally has relied on relatively scarce data obtained during office hours. These isolated IOP measurements fail to capture the dynamic IOP fluctuation occurring over the 24-hour period.[2,3] Jonas et al[3] reported that any single IOP measurement has only a 25% probability of capturing the peak of a diurnal IOP curve.[3] Similarly, Fogagnolo et al[4] reported that IOP measurements during office hours identified peak, mean, and IOP fluctuation in only 20% of glaucoma patients.

Unrecognized IOP spikes may contribute to glaucomatous neurodegeneration.[5] The phenomenon of circadian IOP fluctuation has garnered growing interest in recent years, with the expectation that treatment of currently unmeasured

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IOP fluctuations could be integrated into the future glaucoma treatment paradigm.[6] Ambulatory rebound tonometry using devices such as the Icare HOME (Icare Oy, Vanda, Finland) can provide accurate and comparable measurements of IOP compared with Goldmann applanation tonometry (GAT), the gold standard of clinical IOP measurement.[7,8]

Because primary open-angle glaucoma (POAG) is an asymptomatic disease in the early stages and often remains undiagnosed in the community, additional screening tools are required to facilitate early diagnosis and risk stratification.[9] Intraocular pressure is a highly heritable trait (estimated heritability, approximately 60%),[10] and recent genome-wide association studies (GWAS) have identified more than 100 common genetic variants associated with elevated IOP.[11,12] An IOP polygenic risk score (PRS) is a quantitative measure of an individual's burden of IOP-associated genetic risk variants and is calculated as the weighted sum of their IOP-associated variants.[13] A high IOP PRS has been demonstrated to correlate with risk of POAG diagnosis and glaucoma disease parameters, including the highest long-term pretreatment IOP, higher rates of medical and surgical intervention, and a higher total number of family members affected by glaucoma.[11,14] Whether this IOP PRS also correlates with circadian IOP parameters that may be relevant to glaucoma disease progression currently is unknown.

Given the poor correlation of isolated IOP measurements during office hours with peak diurnal IOP,[5] we tested the hypothesis that the IOP PRS could provide useful predictive information about IOP measurements outside of office hours. This study investigated the association between genetic markers of high IOP and circadian IOP measurements through correlation of a validated IOP PRS and ambulatory IOP data measured using the Icare HOME tonometer in glaucoma suspects and early glaucoma patients sampled from an outpatient setting.

Methods

Study Participants

Participants with diagnosed POAG or optic nerve head changes suspicious for early glaucoma based on a disc damage likelihood scale score of 1 or more[15] were recruited from 4 practices across Australia and drawn from the Progression Risk of Glaucoma: Relevant SNPs [single nucleotide polymorphisms] with Significant Association study. Patients with angle closure on gonioscopy, secondary causes of elevated IOP, or other ophthalmic conditions causing reduced visual acuity were excluded. For this study, only participants with European ancestry were included to maximize the applicability of the current model of the PRS. This study adhered to the tenets of the Declaration of Helsinki and followed the National Health and Medical Research Council statement of ethical conduct in research involving humans. Informed written consent was obtained from all participants, and the study was approved by the Southern Adelaide Clinical and the Macquarie University Human Research Ethics Committees.

Intraocular Pressure Measurements

Each participant attended a training session conducted by a trained instructor (M.S.A., T.A., A.M.S., or A.Q.). Participants were required to be able to position the Icare HOME tonometer appropriately and to demonstrate competence in independently generating at least 2 reliable measurements. Participants were instructed to measure the IOP of both eyes 4 times daily. The stipulated timings for IOP measurements were early morning, midday, late afternoon, and late evening. Each measurement was to be performed seated and concurrently for each eye. We instructed the participants to do this for 5 consecutive days.

The Icare HOME was connected to a computer, and data were exported. Measurements labelled as "Rejected" by the device's quality score were discarded as per manufacturer recommendations. Intraocular pressure measurements were evaluated systematically to minimize measurement errors and artefacts. Intraocular pressure measurements of more than 50 mmHg or less than 5 mmHg were excluded because such extreme measurements were more likely to be artefactual as a result of decentered measurements. To exclude unreliable measurements further, we grouped IOP measurements repeated within a 10-minute period into clusters. Such clustered measurements were the result of the participants repeating the IOP measurement process (observed in 54% of the eyes) and could contribute to skewed means and variance if not controlled for. Clusters with a wide IOP range ($\geq$5 mmHg) suggesting poor reliability were excluded. In an effort to minimize the effect of repeated measurements on summary parameters, only the second IOP measurement within each cluster was included in analyses, and other repeat measurements were discarded. To generate reliable summary parameters, especially when stratified by office hours, we included only eyes that completed a minimum of 2 days with at least 3 IOP measurements per day after the aforementioned exclusions.

Mean and maximum IOP of all measurements were determined for each eye over the duration of the study. The mean IOP also was calculated for measurements made during office hours (between 9:00 AM and 5:00 PM) and outside office hours (between 5:00 PM and 9:00 AM) for each eye over all days for the duration of the study. Highest-recorded early morning pressures were defined as the maximum IOP recorded between 5:00 AM and 9:00 AM at any day corresponding with the morning IOP elevation observed in glaucomatous eyes.[3,5] To assess the correlation between IOP PRS and IOP fluctuation, we defined 2 parameters: absolute IOP range and standard deviation (SD) of all IOP measurements. Absolute IOP range was defined as the difference between the maximum and the minimum IOP recorded across all the days for a given eye over the course of the study (Fig 1).

Polygenic Risk Score

A weighted PRS was generated for each patient using a set of IOP-associated single nucleotide polymorphisms (SNPs).[11] The method of calculating this PRS has been described previously.[14] Briefly, each variant was weighted on a per-allele basis by its estimated effect size on IOP and then summed, using summary statistics from a meta-analysis of IOP GWAS.[11] Variants associated with corneal-compensated IOP as measured by noncontact tonometry (Ocular Response Analyzer) in UK Biobank participants (n = 103 914)[16] were identified and were meta-analyzed with IOP GWAS results from the International Glaucoma Genetics Consortium (n = 29 578). To maximize the likelihood that SNPs used in the PRS were associated with IOP, we included only 146 statistically independent SNPs meeting genome-wide significance (P value threshold at 5×10^{-8} and linkage disequilibrium clumping at $R^2 = 0.1$).[14] We also used a recently reported, more comprehensive multitrait glaucoma PRS for comparison.[17] This weighted score comprises 2673 uncorrelated SNPs that were associated with glaucoma (at $P < 0.001$ threshold) using a multitrait analysis of the GWAS approach. The variants were discovered by combined analysis of GWAS of glaucoma (case control) and its 2 key endophenotypes: IOP and vertical cup-to-disc ratio (adjusted to

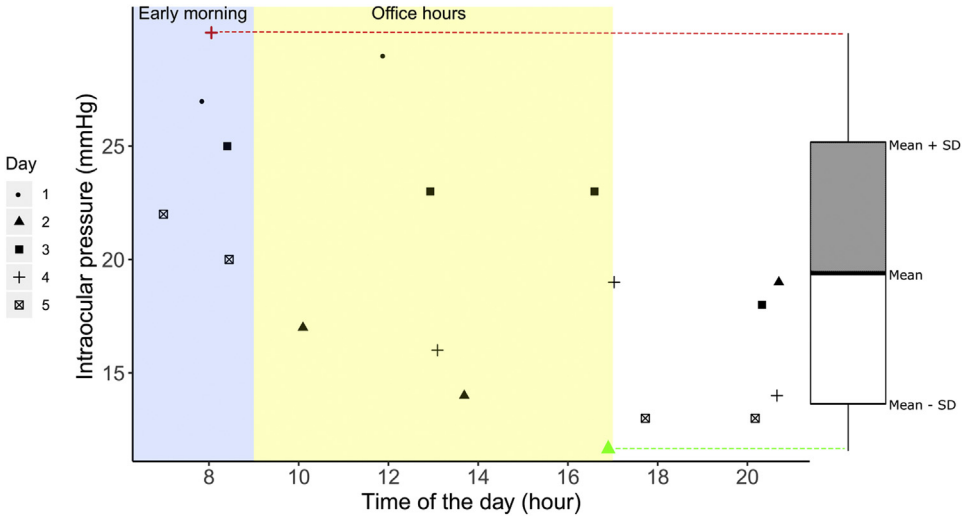

Figure 1. An example of the home tonometry measurement output for an eye after quality control. Each dot represents an intraocular pressure (IOP) measurement obtained at a particular time over 5 days. The shapes indicate the day the measurement was obtained. Office hours (9:00 AM–5:00 PM) and early morning (5:00 AM–9:00 AM) are highlighted. The unshaded region and the early morning represent the period outside office hours (5:00 PM–5:00 AM). The box plot represents the mean and standard deviation (SD) of the IOP measurements, with the grey area representing IOP fluctuation (1 SD). The absolute IOP range is shown as the difference between the maximum (red cross) and the minimum (green triangle) IOP recorded.

disc diameter). No sample overlap existed between the discovery and study cohorts.[17] As such, this multitrait glaucoma PRS included glaucoma risk alleles not related to IOP, rather than being solely focused on IOP. Genotyping of the Progression Risk of Glaucoma: Relevant SNPs with Significant Association cohort was performed in several phases using either Illumina Omni1M, OmniExpress, or HumanCoreExome arrays (Illumina) as described previously.[11]

Statistical Analysis

All eligible eyes of each participant were included in the study. Mixed-effects linear regression modeling with a random intercept for each patient to account for the intereye correlation was used to investigate the relationship between IOP PRS and home tonometry IOP parameters.[18,19] We used central corneal thickness (CCT) as a covariate in all analyses because of its well-established influence on IOP measurements made using rebound tonometry (Fig S1, available at www.ophthalmologyglaucoma.org).[7,8] The IOP PRS was used as a continuous variable in the regression analyses. Additionally, for clinical interpretation, we stratified the cohort into 3 risk groups based on the quintile distribution of the IOP PRS relative to a control population: the lowest 20% of the sample PRS was considered low risk, the middle 60% was considered intermediate risk, and the highest 20% was considered high risk.[14] The control population included 17 642 genotyped individuals from the population-based QSkin cohort, a cohort of randomly sampled individuals 40 to 69 years of age from Queensland, Australia.[20] In such intergroup comparisons, binomial generalized mixed-effect linear regression models were used, which accounted for the intereye correlation. The R^2 (coefficient of determination) of the linear model was used to assess the variance of the dependant variable explained by the model and was calculated for the mixed-effects model using the fixed-effects terms only as described by Nakagawa et al.[21] All analyses were performed using R software version 4.0.2 (R Foundation for Statistical Computing). The significance level (α value) was set at 0.05 for 2-tailed hypothesis testing. P values for the multiple regression models were adjusted using the Benjamini and Hochberg false-discovery rate.[22,23]

Results

Baseline Data

Ambulatory IOP data were collected from August 2016 until December 2019 from a total of 473 eyes of 239 participants trained in the use of the Icare HOME tonometer who had genotyping data available. The same tonometer model and participant training protocol were used throughout the study period. No correlation was found between recruitment date and mean IOP and fluctuation. The main exclusion criterion was participants not completing sufficient measurements (i.e., having fewer than 2 days with at least 3 measurements; 129 eyes [27%]), which excluded 61 patients who had no other eligible eyes. After assessing the quality of the data, 336 eyes from 177 patients met the study inclusion criteria. One participant with 2 eligible eyes was excluded for being related to another participant to avoid inflating genetic association results. Thus, 334 eyes were used in the analyses (Fig 2). Participants had a mean of 3 reliable measurements per day. The clinical and demographic characteristics of the study participants are summarized in Table 1. Age was correlated negatively to maximum IOP (including the highest recorded early morning IOP) and IOP fluctuation ($P = 0.031$ and $P = 0.006$). These associations were modest (Pearson's correlation coefficient, −0.10 to −0.20), although they persisted after adjustment for gender, CCT, and the number of topical glaucoma medications. Thus, we included age as a covariate in regression analyses.[24] Gender was not correlated significantly with any home tonometry parameters.

Home Tonometry Parameters

Increasing IOP PRS correlated strongly with higher mean and maximum IOP measurements across all periods (Table 2). The magnitude of effect of this association was greatest for the highest-recorded IOP in the early morning. Participants stratified within the highest IOP PRS quintile showed a highest-recorded IOP

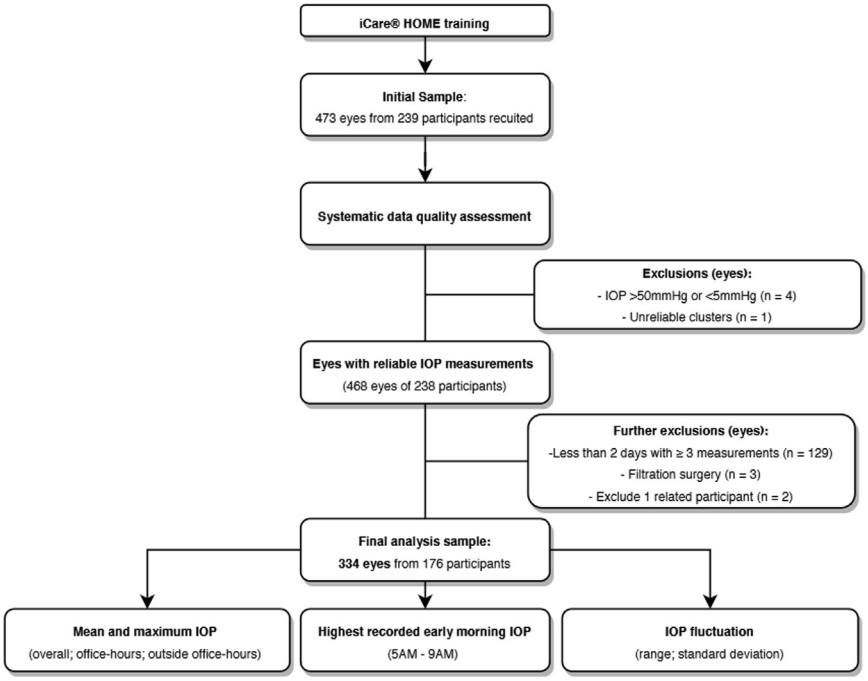

Figure 2. Flowchart showing study design. IOP = intraocular pressure.

increase in the early morning of 4.3 mmHg (95% confidence interval [CI], 1.4−7.3 mmHg; $P = 0.005$; Fig 3A) compared with the lowest-risk quintile. The mean IOP outside office hours was 2.7 mmHg higher in the highest IOP PRS quintile relative to the lowest-risk quintile (95% CI, 0.61−4.7 mmHg; $P = 0.013$; Fig 3B). Similarly, the mean IOP inside office hours was higher by 2.9 mmHg (95% CI, 0.72−5.1 mmHg; $P = 0.011$; Fig 3C). The IOP PRS accounted for 14% of the variance in the mean diurnal IOP and 19% of the highest recorded early morning IOP, with adjustment for CCT and age. A model inclusive of the IOP PRS was significantly better compared with a model using CCT and age alone in predicting the overall mean IOP and the highest recorded early morning IOP (additional R^2 of 7% and 9%, respectively; $P < 0.001$).

We then investigated the proportion of patients who had elevated home tonometry IOP that can be identified by the IOP PRS. An eye was deemed to have an elevated home tonometry IOP if the mean IOP (stratified by office hours) was higher than the cohort mean. Similarly, the highest recorded early morning IOP for each eye was compared with the cohort mean to identify the proportion of eyes with a relatively higher early morning IOP. More than half of the eyes in the high-risk PRS quintile group (56%; n = 55 eyes) showed an elevated highest-recorded early morning IOP compared with 37% in the intermediate-risk group (n = 65 eyes; $P = 0.021$) and 15% in the low-risk group (n = 4 eyes; $P = 0.003$; Fig 4). Similar results were apparent for the mean IOP measured inside or outside office hours, whereby the IOP PRS identified more than twice the proportion of eyes in the high-risk group with elevated mean IOPs inside or outside office hours compared with the low-risk group (Fig 4).

The IOP PRS identified individuals who showed IOP spikes in the early morning hours that were not otherwise detected during in-office hours. Those with early morning IOP spikes were defined as those having an early morning IOP higher than the highest recorded IOP during office hours, which was observed in 87 eyes (26%). When stratified in accordance with the IOP PRS, 36% of eyes in the highest PRS quintile (n = 99 eyes) showed early morning IOP spikes, compared with 27% of intermediate-quintile risk (n = 48) and 11% of low-quintile risk groups (n = 3; $P = 0.019$, linear regression). Participants in the highest IOP PRS quintile were 5.4-fold more likely to show early morning IOP spikes compared with the lowest-risk quintile (odds ratio 95% CI, 1.3−23.6; $P = 0.023$).

The IOP PRS correlated with IOP fluctuations as defined by the SD of all IOP measurements and IOP range ($P = 0.009$ and $P = 0.008$, respectively, linear regression). However, measurement of short-term fluctuation using variance is confounded strongly by maximum IOP measurements (Pearson's correlation coefficient, 0.82; $P < 0.001$). Thus, when the maximum recorded IOP was included in the model, the IOP PRS, CCT, and age were not associated significantly with IOP fluctuation as measured by either the SD or the absolute range.

Topical glaucoma medications are expected to change the circadian IOP profile.[25] We performed a sensitivity analysis using eyes that were not receiving topical glaucoma medications at the time of home tonometry measurements. The IOP PRS remained associated with all the variables reported in Table 2 (Table S1, available at www.ophthalmologyglaucoma.org). In the medication-free subgroup, the highest IOP PRS quintile showed a higher highest-recorded early morning IOP by 4.7 mmHg (95% CI, 1.2−8.3; $P = 0.012$) and mean IOP outside office hours by 2.4 mmHg (95% CI, 0.66−6.1 mmHg; $P = 0.019$) than the low-risk quintile. We also performed a sensitivity analysis including a binary covariate for whether an eye has perimetric glaucoma, which did not change the results significantly (data not shown).

Additionally, we performed a sensitivity analysis using the complete dataset (n = 466 eyes, after excluding 1 related participant and 5 eyes with outlier IOP measurements; Fig 2). The results

Table 1. Clinical Cohort Characteristics Stratified by Intraocular Pressure Polygenic Risk Score

Characteristic	Low Risk	Intermediate Risk	High Risk	*P* Value
No. of eyes/participants	33	194	107	—
Male gender, no. (%)	15 (46)	104 (54)	51 (48)	0.49
Age, years	65.1 (8.9)	63.7 (9.1)	64.4 (10.0)	0.64
Central corneal thickness, μm	550 (46)	551 (34)	546 (33)	0.51
Vertical cup-to-disc ratio	0.68 (0.11)	0.70 (0.12)	0.70 (0.13)	0.69
Eyes receiving topical glaucoma medications, no. (%)	16 (49)	83 (43)	54 (51)	0.42
Visual field mean deviation, dB	−0.81 (2.1)	−0.84 (2.3)	−1.28 (2.6)	0.27

— = not applicable.
Data are presented as mean (standard deviation) unless otherwise indicated. *P* values were obtained using Kruskal-Wallis rank-sum test.

of this analysis largely were consistent with our primary findings, albeit with a slightly lower statistical goodness of fit (Fig S2, available at www.ophthalmologyglaucoma.org). This indicates that our findings withstand any potentially unreliable measurements or measurement periods of shorter duration.

Usefulness of the Polygenic Risk Score in Addition to the In-Clinic Intraocular Pressure Measurements

It was reported previously that IOP measurements obtained during office hours characterize circadian IOP parameters in some, but not all, individuals with glaucoma.[4] We investigated the added usefulness of the IOP PRS in predicting home tonometry parameters by including the clinician-measured GAT IOP performed during the Icare Home training visit in a multivariate model. Only participants who performed home tonometry within 30 days of the last recorded in-clinic GAT measurement were included (n = 277 eyes [83%]).

After accounting for the most recent in-clinic GAT IOP, CCT, and age, the IOP PRS remained associated significantly with the highest-recorded IOP in the early morning, with an increase of 3.6 mmHg in the high IOP PRS quintile (95% CI, 0.72−6.5; P = 0.017) relative to the lowest. The IOP PRS remained associated with the mean IOP outside office hours and the mean IOP during office hours (P = 0.010 and P = 0.001, respectively, linear regression using continuous PRS) after adjustment for GAT IOP, CCT, and age. Inclusion of clinician-measured GAT IOP improved the variance explained in mean IOP to 31%. A model inclusive of the IOP PRS performed better than that with a recent GAT IOP, CCT, and age alone (additional R^2 of 4%; P = 0.005). The relative contribution (using R^2) of the IOP PRS and GAT IOP in models

Table 2. Summary of the Home Tonometry Intraocular Pressure Parameters Stratified by the Intraocular Pressure Polygenic Risk Score Groups

Circadian Intraocular Pressure Parameter (mmHg)	Low Risk (n = 33)	Intermediate Risk (n=194)	High Risk (n = 107)	*P* Value*
Highest recorded early morning IOP†				<0.001
Mean (SD)	15.2 (3.5)	17.3 (5.0)	20.2 (7.2)	
Range	9.0−22.0	6.0−33.0	10.0−46.0	
Mean IOP				<0.001
Mean (SD)	13.5 (2.9)	14.6 (3.8)	16.3 (5.0)	
Range	9.0−20.9	7.3−24.4	8.2−33.4	
Maximum IOP				0.001
Mean (SD)	19.3 (4.8)	21.1 (6.5)	22.5 (7.2)	
Range	11.0−36.0	11.0−50.0	10.0−47.0	
Mean IOP during office hours				<0.001
Mean (SD)	14.3 (3.4)	15.3 (4.0)	17.2 (5.5)	
Range	9.5−22.8	6.5−25.8	8.5−33.5	
Mean IOP outside office hours				0.002
Mean (SD)	13.0 (2.5)	14.1 (4.0)	15.7 (4.9)	
Range	8.6−19.0	6.5−28.8	7.7−33.3	
Absolute IOP range				0.009
Mean (SD)	11.1 (4.4)	11.9 (6.0)	12.6 (5.8)	
Range	5.0−26.0	3.0−42.0	3.0−35.0	
IOP fluctuation (standard deviation)				0.008
Mean (SD)	3.3 (1.3)	3.4 (1.5)	3.7 (1.7)	
Range	1.3−6.9	1.2−10.4	1.2−9.2	

IOP = intraocular pressure; SD = standard deviation.
*Mixed-effect linear regression model using the IOP polygenic risk score as a continuous score as the predicting variable and the circadian IOP parameters as the outcome variable while adjusting for age and central corneal thickness, and adjusted for multiple testing using a false-discovery rate.
†Early morning IOP data were available for 301 eyes (90%).

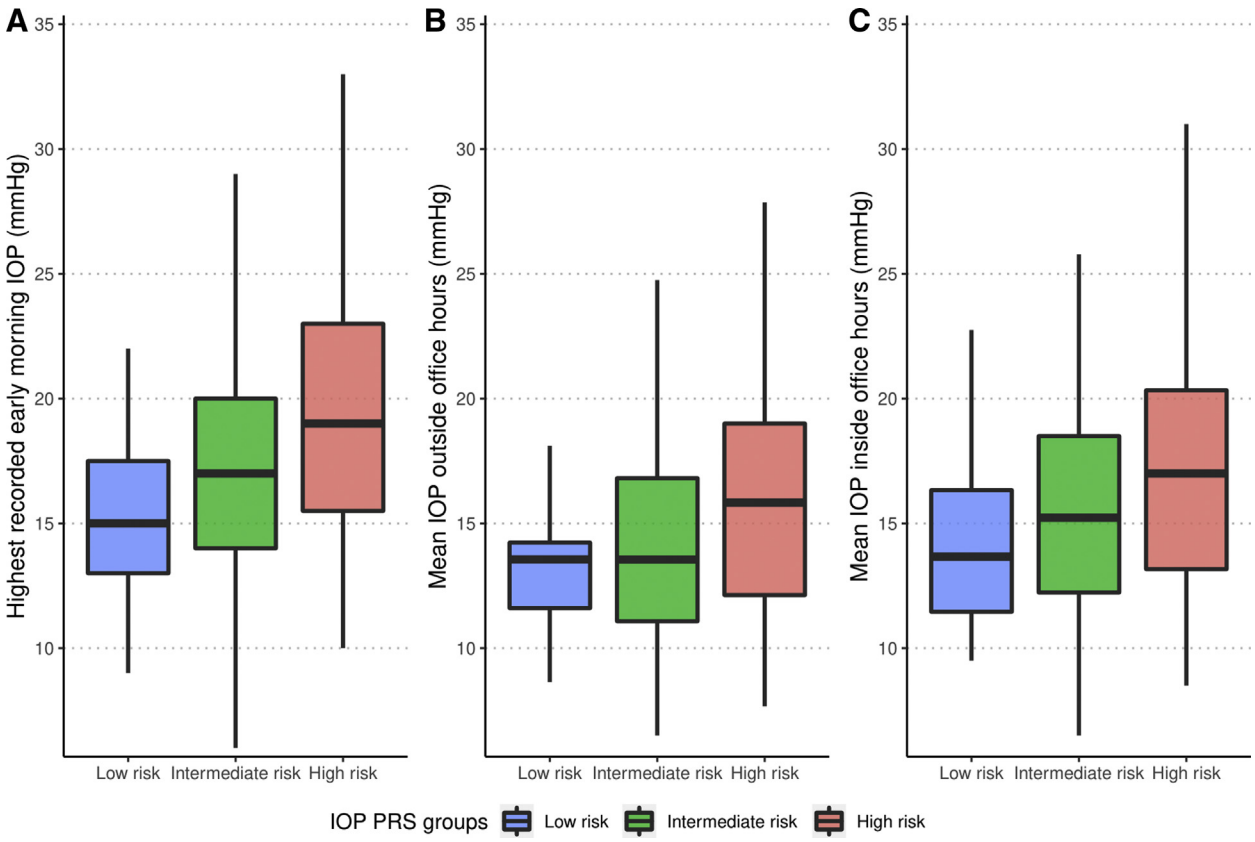

Figure 3. Box-and-whisker plots showing a comparison of home tonometry intraocular pressure (IOP) profile stratified by the IOP polygenic risk score (PRS): (**A**) highest recorded early morning (5:00 AM–9:00 AM) intraocular pressure (IOP), (**B**) mean IOP outside office hours (5:00 PM–9:00 AM), and (**C**) mean IOP inside office hours (9:00 AM–5:00 PM) among 3 groups of IOP-derived genetic risk scores ($P \leq 0.001$ for trend using linear mixed-effect model adjusting for age and central corneal thickness). The box plot represents the median and the first and third quartiles.

predicting home tonometry parameters is summarized in Table S2 (available at www.ophthalmologyglaucoma.org).

Comparison with a Multitrait Glaucoma Polygenic Risk Score

We compared the performance of the IOP PRS with that of a recently reported, more comprehensive multitrait glaucoma PRS that, in addition to IOP, includes variants associated with vertical cup-to-disc ratio and glaucoma diagnosis.[17] The IOP-only PRS was associated more strongly with circadian IOP parameters than the multitrait glaucoma PRS (Fig 5). For instance, for each 1-SD higher IOP PRS, an associated increase of 1.74 mmHg (SD, 0.40 mmHg) in highest-recorded early morning IOP was found ($P < 0.001$) compared with 0.95 mmHg (SD, 0.41 mmHg) for the multitrait glaucoma PRS ($P = 0.043$). The IOP PRS explained more variance of the mean IOP measured during the entire study compared with the multitrait glaucoma PRS (13.5% vs. 9.9%, respectively). Although the PRS is not aimed to be diagnostic or to replace clinical examination, but rather, is intended to be used as a risk stratification tool, these results show that the IOP-only PRS infers more meaningful stratification of the diurnal IOP profile than the multitrait glaucoma PRS. Thus, a trait-specific PRS may provide additional usefulness in risk stratification compared with a multitrait or a case-control PRS.

Discussion

Herein, we demonstrated an association between a PRS for IOP and circadian IOP parameters, as measured with the Icare HOME tonometer, in a cohort of established POAG or open-angle glaucoma suspect patients. These observations suggest that the same genetic variants associated with IOP measured during office hours in the normal population are implicated in parameters of IOP lability, including outside office hours IOP, early-morning highest IOP, and early morning IOP spiking. Furthermore, after accounting for the most recent in-clinic IOP measured by GAT (current standard of care), the IOP PRS was associated independently and most strongly with higher early-morning IOP, as well as a higher mean IOP both during and outside office hours. These findings support a role for the IOP PRS not only in stratifying population-based glaucoma risk,[11] but also in predicting circadian IOP parameters in glaucoma patients.

Genetic variants associated with IOP explain part of the IOP variation observed in the population. Khawaja et al[12] reported that a set of IOP-associated SNPs explained 17% of IOP variance in the European Prospective Investigation into Cancer (EPIC)-Norfolk cohort and 9% of variance in the UK Biobank cohort. Both of these studies used cross-

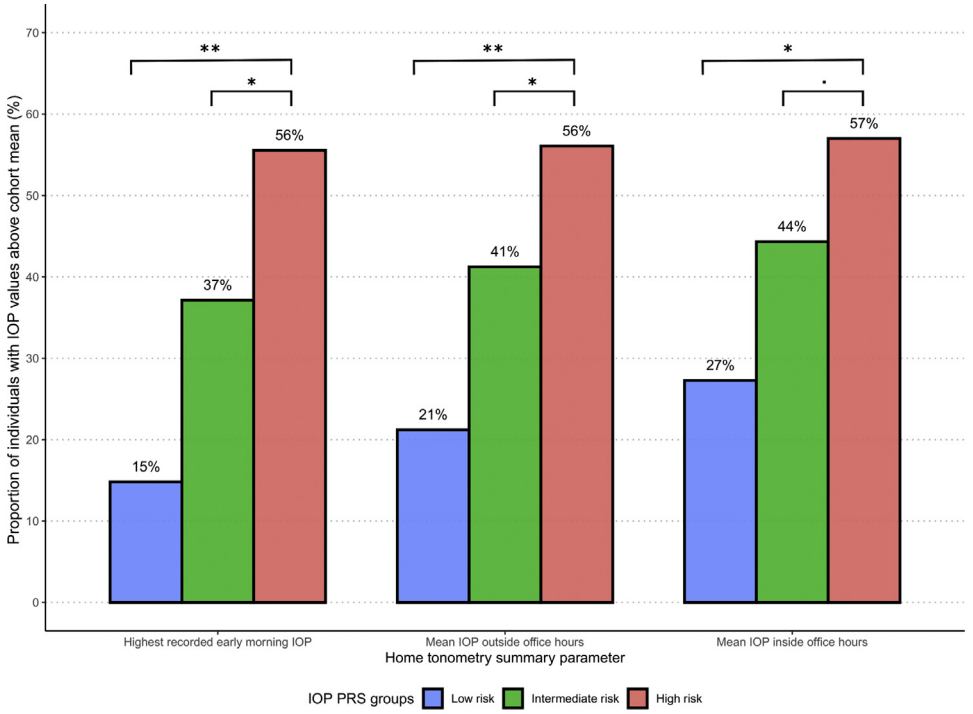

Figure 4. Bar graph summarizing the proportion of individuals within each intraocular pressure (IOP) polygenic risk score (PRS) category who have an elevated home tonometry parameter in reference to the cohort mean. Statistical comparison is made using binomial mixed-effect regression among the high-risk, intermediate-risk, and low-risk groups. Risk groups were based on the IOP PRS quintiles with reference to a control population. $P < 0.1$ (not significant); $^{*}P < 0.05$; and $^{**}P < 0.01$.

sectional point-in-time IOP measurements. In the EPIC-Norfolk cohort, 3 repeat IOP measurements were recorded (using the measurement with the best signal in the variance analysis), whereas only 1 measurement was obtained in the UK Biobank cohort; the EPIC-Norfolk cohort were older than the UK Biobank sample. Both studies used noncontact tonometry (Ocular Response Analyser) to measure corneal-compensated IOP, which is influenced less by corneal properties than applanation and rebound methods.[26] In this study, we report that a model inclusive of IOP PRS explained 14% of the variance in the short-term mean diurnal IOP and 19% of the highest recorded early morning IOP after adjustment for CCT and age.

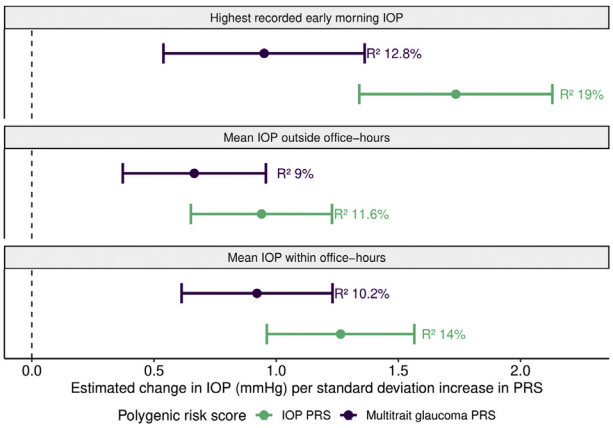

Figure 5. Graph showing the relative performance of the intraocular pressure (IOP) polygenic risk score (PRS) and a multitrait glaucoma PRS in predicting home tonometry IOP profile. The dots represent the estimated mean change in IOP per 1-standard deviation increase in PRS (scaled β coefficients) in a linear model using the home tonometry parameters as outcomes. The error bars represent standard errors of the estimate. The variance explained (R^2) by each PRS model also is displayed. All models were adjusted for central corneal thickness and age.

Because IOP is a heritable polygenic trait in the healthy population, a PRS is an effective method of measuring the contribution of common genetic variants to IOP. Polygenic risk score can be calculated readily before the onset of a disease, and thus has the advantage of risk stratifying patients before the confirmed onset of glaucoma. The IOP PRS infers a significant risk of glaucoma developing, which previously was quantified as a 5.6-fold increase in risk from the lowest decile of risk to the highest in a case-control cohort and is predictive of disease phenotype in those diagnosed with glaucoma.[11,14] This study provides further evidence for the usefulness of an IOP PRS in glaucoma by predicting higher peak, mean, highest early morning, and outside office hours mean IOPs. Previous evidence showed that optic nerve head insult caused by unrecognized IOP spikes—such as those occurring early morning and outside office hours—may contribute to glaucomatous neurodegeneration,[5] highlighting further the clinical usefulness of genetic markers in stratifying patients at high risk of IOP fluctuation and glaucoma progression. Interestingly, although combining multiple

traits (such as vertical cup-to-disc ratio and glaucoma status) to generate a more comprehensive glaucoma PRS significantly improves glaucoma risk and phenotype stratification (15-fold increase in risk from the lowest decile of risk to the highest in a case-control cohort),[11] the IOP PRS provided a comparatively better association with outside office hours and early morning IOP profiling. This highlights the clinical usefulness of a trait-specific PRS in addition to a comprehensive disease risk PRS, depending on the desired prediction and use of the PRS data.

Diurnal change and fluctuation in IOP previously were reported in glaucomatous eyes.[5,27,28] Liu et al[5] reported an early morning IOP increase in glaucomatous eyes that was not seen in control participants. Additional IOP measurements obtained during office hours may offer clinical usefulness in the management of glaucoma. Asrani et al[27] reported that short-term IOP fluctuation was an independent risk factor for glaucoma progression. Similarly, diurnal IOP parameters and 24-hour IOP fluctuation measured by a contact lens sensor recently were reported to be associated with glaucoma progression.[29,30] Barkana et al[31] reported that in a study of 32 patients with progressive glaucoma not attributable to IOP measurement obtained during office hours, most (69%) showed a higher peak and fluctuation in IOP outside office hours that informed a treatment change in 19 patients (59%). Finally, we recently reported that treatment with selective laser trabeculoplasty immediately reduces the diurnal IOP mean and fluctuations, correlating these parameters to treatment response.[28] Our study supports that genetic risk stratification using a PRS of common variants associated with IOP provides insight into individuals' diurnal IOP changes and fluctuations. Nonetheless, larger prospective studies of the clinical usefulness of 24-hour IOP profiles are needed before routine clinical use of these data.

This study has several strengths and some limitations. We enrolled patients from 4 clinics across 2 states in Australia with a relatively large sample size encompassing early glaucoma patients and glaucoma suspect patients. We sampled the larger Progression Risk of Glaucoma: Relevant SNPs with Significant Association cohort, who have a well-characterized phenotype in the early open-angle glaucoma spectrum. We also undertook a systematic and objective approach to exclude unreliable measurements. The IOP PRS has been generated from the largest IOP GWAS meta-analysis using corneal-compensated IOP measurements from the UK Biobank and the International Glaucoma Genetics Consortium. This PRS also was validated previously in glaucoma risk stratification and phenotyping in large cohorts.[11,14]

Our results are limited to patients with established or suspected open-angle glaucoma only, and further studies are needed of other types of glaucoma or of individuals with ocular hypertension. Although the Icare HOME tonometer provides valid ambulatory IOP measurements, it does not provide continuous IOP monitoring, which may be better suited to assess IOP fluctuations. Furthermore, we did not study nocturnal IOP, which has been reported to be elevated in glaucoma.[2] Frequent and reliable measurements also are operator dependent, although we have used a systematic method to train patients and to exclude unreliable outcomes. Other confounding factors include posture, fluid intake, and systemic blood pressure, although these factors are not expected to correlate with the IOP PRS. Rebound tonometry is affected significantly by CCT; thus, we used CCT as a covariate in all our analyses.[7,8] Intraocular pressure-lowering treatments will affect IOP measurements and fluctuations significantly and will confound our analysis in comparison with treatment-naïve newly diagnosed patients. It is encouraging that we found consistent positive associations between the PRS and several home tonometry parameters despite this. We performed a sensitivity analysis in topical glaucoma medication-naïve eyes that supports our primary findings. Finally, PRSs perform best in the ethnicities from which they were derived; therefore, our results require cross-ancestry validation in populations of non-European ancestry ethnicities. Replication in additional cohorts also is needed.

In conclusion, we report that an IOP PRS was effective in risk stratifying glaucomatous eyes and providing insight into their diurnal IOP profile. Genetic risk profiling using a PRS is not intended to replace clinical assessment or to be used as a diagnostic tool.[17,32] Rather, PRS allows clinically valuable, personalized risk stratification through incorporation of the individual's predetermined genetic disease risk. In the setting of home tonometry, an IOP PRS is informative of measurements obtained outside office hours and IOP spikes in the early hours of the morning. These measurements are not readily available to clinicians in the course of routine glaucoma care. Thus, an IOP PRS may have added usefulness in risk profiling patients for these specific disease features. Further research is needed on the practical implementation strategies of PRS in glaucoma care.

Footnotes and Disclosures

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No animal subjects were included in this study.

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Data collection: Qassim, Mullany, Awadalla, Hassall, Nguyen, Kolovos, Schulz, Han, Gharahkhani, Galanopoulos, Agar, Healey, Hewitt, Landers, Casson, Graham, MacGregor, Souzeau, Siggs, Craig

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Abbreviations and Acronyms:
CCT = central corneal thickness; **CI** = confidence interval; **GAT** = Goldmann applanation tonometry; **GWAS** = genome-wide association study; **IOP** = intraocular pressure; **LD** = linkage disequilibrium; **MD** = mean deviation; **OR** = odds ratio; **POAG** = primary open-angle glaucoma; **PRS** = polygenic risk score; **SD** = standard deviation; **SNP** = single nucleotide polymorphism.

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Diurnal IOP, Genetic risk prediction, Glaucoma, Home tonometry, iCare HOME, Intraocular pressure, Polygenic risk score.

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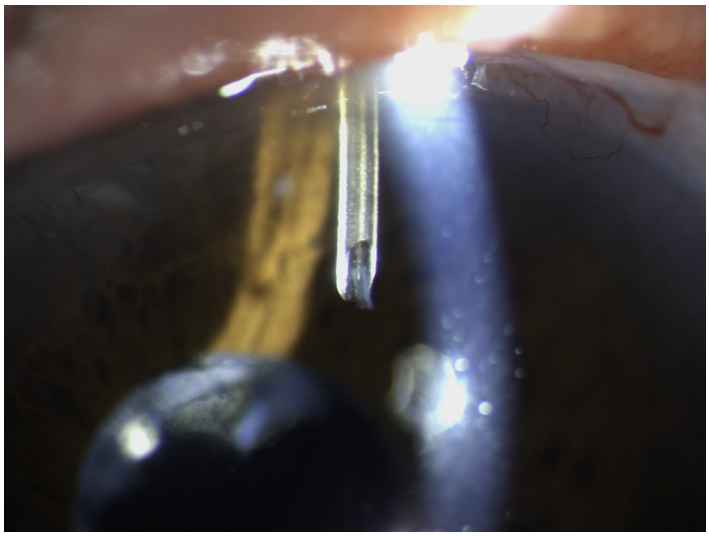
Pictures & Perspectives



An Unexpected Cork

Yttrium-aluminum-garnet (YAG)-capsulotomy is a relatively frequent ophthalmological procedure, rarely associated with complications. Fragments of the ruptured capsule are rarely a cause of concern other than the occasional initial floater. A 91-year-old man had undergone a Preserflo microshunt implantation 2 months before the laser capsulotomy, which included a widening of a clinically significant anterior capsular phimosis. Although the procedure was uneventful, the patient had an intraocular pressure (IOP) spike the following week (from 12 to 32 mmHg), with slit-lamp observation showing a clogging of the device with capsular fragments. While this was easily solved by a YAG-laser targeting the obstructing tissue, restoring IOP to 12 mmHg, physicians should be aware of the possibility of anterior segment fragments occluding a working fistula (Magnified version of Fig 1 is available online at www.ophthalmologyglaucoma.org).

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