Associations with corneal hysteresis in a population cohort: Results from 96,010 UK Biobank participants

Bing Zhang [1], Yusrah Shweikh [2], Anthony P Khawaja [2], John Gallacher [1], Sarah Bauermeister [1], Paul J Foster [2] on behalf of the UKBiobank Eye and Vision Consortium

Running head: Associations with corneal hysteresis in UK Biobank

Abbreviations/Acronyms

CCT, central corneal thickness

CH, corneal hysteresis

CI, confidence interval

IOPg, Goldmann-correlated intraocular pressure

LOWESS, locally weighted scatterplot smoothing

OR, odds ratio

SLE, systemic lupus erythematosus

Author affiliations:

[1] Department of Psychiatry, University of Oxford, Oxford, UK

[2] NIHR Biomedical Research Centre, Moorfields Eye Hospital NHS Foundation Trust and UCL Institute of Ophthalmology, London, United Kingdom; Moorfields Eye Hospital, 162 City Road, London EC1V 2PD; UCL Institute of Ophthalmology, 11-43 Bath Street, London, EC1V 9EL

Corresponding author:
Prof Paul J Foster
Address: UCL Institute of Ophthalmology, 11-43 Bath Street, London, EC1V 9EL
Email: p.foster@ucl.ac.uk
Telephone: 07971 663189

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FURTHER DETAILS

Authors' Contributions:

PJF, JG & BZ contributed to the conception and design of the study.
BZ performed data analysis.
All authors contributed to data interpretation.
All authors reviewed the results, read and critically revised the manuscript. All authors approved the final manuscript.

Declaration of interest:

PJF reports personal fees from Allergan, Carl Zeiss, Google/DeepMind and Santen, a grant from Alcon, outside the submitted work;
APK, BZ, JG, SB, YS declare no competing interests.

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Ethical approval: The North West Multi-centre Research Ethics Committee approved the study (reference no., 06/MRE08/65), in accordance with the tenets of the Declaration of Helsinki. Detailed information about the study is available at the UK Biobank web site (www.ukbiobank.ac.uk)

Abstract

Purpose: To describe the distribution of corneal hysteresis (CH) in a large cohort and explore its associated factors and possible clinical applications.

Design: Cross-sectional study within the UK Biobank, a large cohort study in the United Kingdom.

Participants: We analyzed CH data from 93,345 eligible participants in the UK Biobank cohort, aged 40 to 69 years.

Methods: All analyses were performed using left eye data. Linear regression models were used to evaluate associations between CH and demographic, lifestyle, ocular and systemic variables. Piecewise logistic regression models were used to explore the relationship between self-reported glaucoma and CH.

Main outcome measures: CH (mmHg).

Results: The mean CH was 10.6 mmHg (10.4 mmHg in males and 10.8 mmHg in females). After adjusting for covariables, CH was significantly negatively associated with male sex, age, Black ethnicity, self-reported glaucoma, diastolic blood pressure and height. CH was significantly positively associated with smoking, hyperopia, diabetes, systemic lupus erythematosus (SLE), greater deprivation (Townsend index) and Goldmann-correlated intraocular pressure (IOPg). Self-reported glaucoma and CH were significantly associated when CH was less than 10.1mmHg (OR 0.86, 95%CI 0.79-0.94 per mmHg CH increase) after adjusting for covariables. When CH exceeded 10.1 mmHg, there was no significant association between CH and self-reported glaucoma.

Conclusion: In our analyses, CH was significantly associated with factors including age, sex and ethnicity which should be taken into account when interpreting CH values. In our cohort, lower CH was significantly associated with a higher prevalence of self-reported glaucoma when CH was less

than 10.1mmHg. CH may serve as a biomarker aiding glaucoma case detection.

It is well recognized that variation in central corneal thickness (CCT) influences the accuracy of intraocular pressure (IOP) measurements[1-3]. It has also been hypothesized that CCT independently influences the risk of glaucoma, with thin CCT evidenced in those at highest risk[4]. However, this view is not universally accepted, as one particular high-risk group (African Americans) typically have thinner CCT than people of European heritage[5]. A plausible alternative explanation is that thin CCT is a biomarker for race, and identifies those at highest risk, attributable to other ocular or systemic factors.

Corneal hysteresis (CH) offers an alternative index of corneal biomechanical characteristics to CCT and reflects the viscoelastic damping effect of corneal tissues, defined as the difference in air pulse pressure between inward and outward applanation forces[6,7]. Recent evidence indicates CH can also provide valuable information related to the presence, progression and response to therapy of glaucoma[8,9]. CH can be measured simultaneously with IOP using non-contact tonometry with augmented functionality. Differences in CH have been reported not only in glaucoma but also in many systemic diseases including thyroid eye disease[10], rheumatoid arthritis[11], psoriasis[12], acromegaly[13] and myotonic dystrophy[14], which suggests CH may play a clinical role in fields other than ophthalmology. Previous studies on CH are limited by small sample sizes[15,16]. The distribution of CH and its associations with demographic, ocular and systemic variables remain to be accurately determined and confirmed in a large sample.

The UK Biobank is one of the largest prospective population cohort studies in the world. In this study, we aimed to report the distribution of CH by age, sex and ethnicity, and explore its associations including the relationship between CH and self-reported glaucoma. We also tested the association between CH and 16 self-reported diseases selected based on existing literature[10-13].

Methods

Study population

The UK Biobank is a multisite community-based cohort study with 502,544 participants. All UK residents aged 40 to 69 who registered with the National Health Service and lived within 25 miles of any of the 22 assessment centers were invited to join the study. The initial visit assessments took place between 2006 and 2010. Eye assessments were carried out from 2009 in 6 recruitment centers (5 in England and 1 in Wales) which enrolled 133,953 participants. The UK Biobank study was approved by the North West Multi-centre Research Ethics Committee (Reference No. 06/MRE08/65) and adhered to the tenets of the Declaration of Helsinki. Written consent was obtained from every participant. More detailed information and protocols for UK Biobank are available online (http://www.ukbiobank.ac.uk/).

Ethnicity was self-reported by participants and selected from White, Asian, Black, Chinese, mixed and other ethnic backgrounds. Socioeconomic status was derived using the Townsend deprivation index estimated using residence postcodes. This represents an indicative measure of economic deprivation in an area and higher scores indicate worse socioeconomic status[17].

Measurements

Cohort characteristics and ophthalmic measures have been previous described[18]. Visual acuity was measured using a bespoke computerized logMAR acuity measure conforming to British Standard BS4274-1968[19], with left eye following right eye. Autorefraction was performed with the RC5000 Auto Refkeratometer (Tomey, Japan). After measuring visual acuity and refraction, CH and Goldmann-correlated IOP (IOPg) were measured with the Reichert Ocular Response Analyser (ORA, Reichert, Inc. USA) according to a predetermined protocol (available online

http://biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id=100236). Participants who had any eye surgery within the preceding 4 weeks were excluded from tests. The measurements were performed first in the right eye and taken only once in each eye. If participants blinked during the test a further measurement was attempted.

Blood pressure was measured with an automatic blood pressure monitor, HEM-70151T (Omron, The Netherlands). Two measurements were performed for each participant and the average was used for analysis if the values of both were available. Height was measured with the Seca 202 instrument (Seca, UK).

Medical History

All diseases were self-reported by participants via verbal interviews conducted by trained nurses or via touchscreen questionnaires. Self-reported eye disorder(s) status was collected in the verbal interview or was selected by participants from a list of eye disorders in response to the question "Has a doctor told you that you have any of the following problems with your eyes?". The list of eye disorders was:

1. Diabetes related eye disease
2. Glaucoma
3. Injury or trauma resulting in loss of vision
4. Cataract
5. Macular degeneration
6. Other serious eye condition
7. None of the above
8. Prefer not to answer

9. Do not know

Smoking and alcohol consumption were self-reported via touchscreen questionnaires. Smoking status was trichotomized for the purpose of analysis to current smokers, ex-smokers and those that have never smoked. Alcohol consumption was pentachotomized to daily/almost daily, weekly or more often, monthly or more often, occasional and never. The use of IOP lowering medications was recorded by trained interviewers. Only currently and regularly used ones were recorded. IOP lowering medication status was dichotomized to user and non-user for analysis.

More detailed information about all variables is available online (http://biobank.ctsu.ox.ac.uk/crystal/index.cgi).

Eligibility criteria

All participants who had available ORA data (CH and IOPg) in the left eye were used for this analysis. Participants who met any exclusion criteria in Figure 1 were excluded from the analyses. 0.5% of participants who were younger than 40 or older than 69 years were excluded based on the UK Biobank eligibility criteria. Extreme values (lowest 0.5% and highest 0.5%) of CH and IOPg may represent measurement errors and were therefore excluded. We excluded participants with a history of eye injury in their left eye, diabetes related eye disease, macular degeneration or other serious eye conditions (except for glaucoma and cataract) in either eye. Left eyes without data on ocular comorbidities and/or refractive error, and/or with high refractive errors (spherical equivalent >+5D or <-6D) and/or high astigmatism (absolute value of cylindrical power >3D) and/or a history of refractive surgery were excluded. Participants with a history of surgery or laser for glaucoma or ocular hypertension were also excluded. Of the 93,345 left eyes remained in analysis, 1,208 eyes with self-reported glaucoma were excluded for analyses of CH distribution.

Statistical analysis

All analyses were performed using left eye data which were captured after right eye data as specified in the study protocol. This may mean left eye data are less prone to artefact, such as blinking, in our cohort[20]. We included refractive error in analyses as the spherical equivalent in dioptres (D, sphere power+1/2 cylinder power). For glaucoma status, controls were defined as participants without self-reported glaucoma in either eye.

A descriptive analysis of CH in left eyes stratified by age, sex and ethnicity was conducted after excluding all participants with self-reported glaucoma. One-way analysis of variance was performed to compare means of CH by age, sex and ethnicity.

Associations between CH and other demographic, ocular and systemic factors and self-reported glaucoma were evaluated with univariable linear regression and all factors with $p<0.05$ in univariable analysis were also analyzed with multivariable linear regression.

We analyzed the relationship between self-reported glaucoma and CH using the following steps:

1) Locally weighted scatterplot smoothing (LOWESS)[21], a method usually used to visualize the structure of data[22], was used to explore the relationship between self-reported glaucoma and corneal hysteresis. The turning point(s) found on the LOWESS curve was used as node(s) for piecewise analysis.
2) Piecewise logistic regression for self-reported glaucoma and CH was performed in three models after adjusting for covariables.
3) The joint distribution of the proportion of self-reported glaucoma, CH and IOPg was displayed using a 3D bar chart.

We then applied linear regression to evaluate the relationships between CH and 16 systemic diseases

after adjusting for covariables.

The 3D bar chart was plotted using Excel for Office 365 (MicrosoftCorp, CA, USA). All other analyses were performed and plots generated using STATA/SE-15 (StataCorp LLC, TX, USA).

Results

All analyses were performed using left eye data in this study. 111,942 UK Biobank participants had available CH values for left eyes. After data cleaning as shown in Figure 1, the mean CH was 10.60 ±1.88 mmHg (95% CI 10.59-10.62 mmHg) in the 92,137 eyes without self-reported glaucoma. The distribution of mean CH stratified by age, sex and ethnicity is summarized in Table 1. A significant difference in CH was found between participants with different ethnicities (p<0.001). CH values were lower in Black people (9.62±1.87 mmHg, 95% CI 9.56-9.69 mmHg) compared to White participants (10.66±1.87 mmHg, 95% CI 10.65-10.67 mmHg). CH was significantly greater in females (10.79±1.86 mmHg, 95% CI 10.77-10.80 mmHg) compared to males (10.39±1.88 mmHg, 95% CI 10.37-10.40 mmHg, p<0.001). Overall, CH was also significantly higher in younger people across the whole age spectrum enrolled (mean 10.91±1.91mmHg, 95% CI 10.87−10.95mmHg for those aged 40-44 compared to 10.30±1.84mmHg, 95% CI 10.27−10.32mmHg for those aged 65-69, p<0.001).

The associations of CH were analyzed with linear regression models as shown in Table 2. CH was significantly associated with all included factors except for visual acuity and alcohol intake frequency. In the multivariable linear regression model after adjusting for covariates, CH was significantly higher in women (0.19 mmHg, $p=2.07\times10^{-27}$), smokers (reference: never smoked; 0.10 mmHg former smokers, $p=7.71\times10^{-13}$; 0.42 mmHg current smokers, $p=1.22\times10^{-84}$), participants with a higher Townsend deprivation index (0.01 mmHg/Unit, $p=7.82\times10^{-8}$) and self-

reported diabetes (0.28 mmHg, $p=1.25\times10^{-20}$). CH was significantly lower in older participants (-0.33 mmHg/10 years, $p<10^{-300}$), Black participants (reference: white; -1.22 mmHg, $p=1.03\times10^{-260}$), Asian participants (reference: white; -0.46 mmHg, $p=2.08\times10^{-45}$), participants with higher blood pressure (-0.08 mmHg/10 mmHg diastolic blood pressure, $p=1.29\times10^{-33}$), greater height (-0.16 mmHg/10 cm, $p=4.71\times10^{-61}$), greater myopia (0.03 mmHg/D, $p=3.06\times10^{-26}$) and in those with self-reported glaucoma (-0.52 mmHg, $p=1.13\times10^{-15}$).

Figure 2, Table 3 and Figure 3 show the relationship between self-reported glaucoma and CH. Overall, lower CH was associated with a higher proportion of self-reported glaucoma. As shown in Figure 2A, when CH was less than approximately 10mmHg, the proportion of self-reported glaucoma increased markedly when CH decreased. However, with increases in CH above 10mmHg the proportion of self-reported glaucoma remained relatively stable at around 1%. The LOWESS curve shapes were similar in analyses stratified by age (Figure 2B) and IOPg (Figure 2C), with sharp rises in the proportions of self-reported glaucoma at CH values less than approximately 10mmHg.

Piecewise logistic regressions were performed with a node set at 10.1mmHg (Table 3). As shown in the online supplementary material, 10.1 mmHg was the smallest node that self-reported glaucoma and CH were significantly associated when CH was less than the node while there was no association between self-reported glaucoma and CH when CH was greater than the node in all three models. When CH was less than 10.1 mmHg, higher CH was a protective factor for self-reported glaucoma. A 1 mmHg increase in CH was associated with an OR of 0.78 (95% CI 0.73-0.82, $p<0.001$) after adjusting for age, sex and ethnicity in Model I, an OR of 0.82 (95% CI 0.78-0.87, $p<0.001$) in Model II (Model I with further adjusting for IOPg) and an OR of 0.86 (95% CI 0.79-0.94, $p<0.001$) in Model III (the maximally adjusted model). When CH exceeded 10.1 mmHg it was

not associated with self-reported glaucoma in all three models (Table 3).

The relationship between self-reported glaucoma, CH and IOPg is displayed using a 3D bar chart (Figure 3). In keeping with the analyses reported in Figure 2C and Table 3, the proportion of self-reported glaucoma was highest in participants with high IOPg and low CH, and lowest in the participants whose IOPg was not high and CH was not low.

We analyzed associations between CH and 16 self-reported disorders of the thyroid gland, pituitary gland and other immunological/systemic disorders (Table 4). Only systemic lupus erythematosus (SLE) was significantly associated with CH following correction for multiple testing (p<0.003125, Bonferroni-corrected threshold). CH was significantly higher in participants with self-reported SLE (0.55, 95% CI 0.24-0.86 mmHg in the fully adjusted model).

Discussion

In this large UK cohort, we have described mean CH stratified by age, sex and ethnicity (Table 1). We found that CH was significantly lower in Black participants and in older age groups, which is consistent with previously published findings[15,23]. Past studies indicate that CH and CCT are positively associated[24-26] and CCT is negatively associated with darker skin pigmentation[27]. One explanation for the variation in CH by ethnicity may be differences mediated by changes in CCT. Conversely, previous publications revealed no significant association between CCT and age[7,28,29], suggesting an independent association between lower CH and older age.

CH was significantly higher in smokers in our cohort (both current and former smokers). A previous, smaller study had suggested this but results were inconclusive[30]. The mechanisms underlying the relationship between smoking and corneal changes are unknown[31,32] and the association between smoking and corneal ectatic disorders is controversial[33,34]. An epidemiological study showed a

marked reduction in the incidence of keratoconus amongst smokers[34], implying altered corneal biomechanics. This is supported by experimental evidence of collagen crosslinking by formaldehyde, a constituent of cigarette smoke, with resulting increased resistance to collagenases[34]. Smoking has also been reported to damage the tear film[35,36] and possibly the corneal endothelium[37], which may influence CCT and CH measurements. We found no significant association between alcohol consumption and CH.

Our findings in Figure 2, Table 3 and Figure 3 suggest that CH may be useful in glaucoma risk stratification in clinical practice. Figure 2 and Table 3 indicate that a CH value of 10.1 mmHg could play a role as cutoff point in clinical practice to evaluate a patient's risk of glaucoma. When CH is less than 10.1mmHg, lower CH may be associated with a higher risk of glaucoma (OR 1.16, 95% CI 1.07-1.26 per mmHg CH decrease in the fully adjusted model). When CH was greater than 10.1mmHg, the rate of self-reported glaucoma remained relatively stable with further increases in CH. Medeiros et al reported that lower CH with values below 10mmHg was a risk factor for glaucoma progression[38].

CH measurement demonstrates good repeatability[39] and there are no significant diurnal fluctuations [26,40], making CH measurement a potentially attractive addition to current glaucoma risk stratification methods. CH has been shown to be lower in different types of glaucoma including open angle glaucoma, angle closure glaucoma, normal tension glaucoma, pseudoexfoliative glaucoma and congenital glaucoma[41-46]. Lower CH is also positively associated with visual field progression[8,38]. Some studies have found a positive association between CH and glaucoma-related changes in optic disc morphology[47-49] whereas others found no such relationship[50-52]. Unlike CH, IOP and CCT measurements are limited by significant diurnal variation[26,40,53-55]. Figure 2C, Table 3 and Figure 3

show that CH and IOPg could be analyzed together in clinical settings to evaluate glaucoma risk, as the risk of self-reported glaucoma was highest in participants with low CH and high IOPg, and lowest in participants whose IOPg was not high and CH was not low.

In analyses for associations between CH and self-reported disorders shown in Table 4, only SLE was significantly associated with CH at $p<0.003$ (Bonferroni-corrected threshold for multiple testing). We found that CH was significantly higher in participants with SLE, which is contradictory to the result in a case-control study which reported CH was lower in SLE patients[56]. Lower CH has also been reported in thyroid eye disease[10], however we did not find an association between CH and thyroid disorders. We also did not find associations between CH and rheumatoid arthritis or psoriasis as previously published[11,12]. Participants with acromegaly in our cohort had higher CH values (at $p<0.05$), in agreement with findings from Ozkok and colleagues[13], however our result was not significant after correction for multiple testing Former studies have yielded variable results when evaluating CH in diabetes[57-60]. Our study shows higher CH amongst patients with diabetes as previously reported[60,61], which is supported by the former findings that having diabetes decreased odds of having more severe keratoconus[62]. The increased cross-linking of corneal collagen[63] in diabetes may contribute to the higher CH. However, two small sample studies[64,65] reported no significant change of CH after cross-linking operation in keratoconus. Another possible mechanism is the morphological[66] and functional alteration[67] of corneal endothelium in diabetes patients, leading to abnormal hydration and increased thickness of cornea[66,67], which is associated with higher CH.

The very large sample size and standardized techniques are major strengths of our study, allowing us to detect and quantify small effects. However, the study is limited by the fact that all disease

244 statuses were self-reported by participants which can result in misclassification error[68]. UK Biobank
245 has a low response rate of 5.5% which limits external validity. With respect to glaucoma, there will
246 be an under-ascertainment of disease since approximately 50% of cases may not have been
247 diagnosed[68]. Meanwhile participants with ocular hypertension, suspected glaucoma or cataracts may
248 report a diagnosis of glaucoma. The potential impact of these errors is unknown. We excluded
249 participants with a past history of surgery or laser for glaucoma or ocular hypertension. A potential
250 confounding variable in the reported association between CH and glaucoma is the use of IOP
251 lowering medications, which may significantly alter corneal biomechanical properties[9,69,70]. The
252 binary variable of current, regular IOP lowering medication use versus no use in this study may
253 oversimplify the effects of different medications on corneal biomechanics. CH and IOPg in this
254 study were measured together using the same instrument and adjusting one for the other makes
255 interpretation difficult. Despite this, we found weak correlation between them (ρ=0.045) in the
256 sample after data cleaning. Investigation into the association between CH and diseases including
257 glaucoma, SLE and diabetes is scarce and we anticipate that future research will build on our
258 findings.
259 Our study offers CH reference values for future research and clinical practice. We also report
260 associations between CH and age, sex, ethnicity, smoking status, refractive error, self-reported
261 glaucoma, diabetes and SLE, which may be important when interpreting CH. CH measurement may
262 play a role in clinical practice for glaucoma and other ocular and systemic conditions.
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264 **References**

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UK Biobank Eye and Vision Consortium membership

UK Biobank Eye & Vision Consortium: The UK Biobank Eye & Vision Consortium members are Tariq Aslam, PhD, Manchester University, Sarah A. Barman, PhD, Kingston University, Jenny H. Barrett, PhD, University of Leeds, Paul Bishop, PhD, Manchester University, Peter Blows, BSc, NIHR Biomedical Research Centre, Catey Bunce, DSc, King's College London, Roxana O. Carare, PhD, University of Southampton, Usha Chakravarthy, FRCOphth, Queens University Belfast, Michelle Chan, FRCOphth, NIHR Biomedical Research Centre, Sharon Y.L. Chua, PhD, NIHR Biomedical Research Centre, David P. Crabb, PhD, UCL, Philippa M. Cumberland, MSc, UCL Great Ormond Street Institute of Child Health, Alexander Day, PhD, NIHR Biomedical Research Centre, Parul Desai, PhD, NIHR Biomedical Research Centre, Bal Dhillon, FRCOphth, University of Edinburgh, Andrew D. Dick, FRCOphth, University of Bristol, Cathy Egan, FRCOphth, NIHR Biomedical Research Centre, Sarah Ennis, PhD, University of Southampton, Paul Foster, PhD, NIHR Biomedical Research Centre, Marcus Fruttiger, PhD, NIHR Biomedical Research Centre, John E.J. Gallacher, PhD, University of Oxford, David F. GARWAY-HEATH FRCOphth- NIHR Biomedical Research Centre, Jane Gibson, PhD, University of Southampton, Dan Gore, FRCOphth, NIHR Biomedical Research Centre, Jeremy A. Guggenheim, PhD, Cardiff University, Chris J. Hammond, FRCOphth, King's College London, Alison Hardcastle, PhD, NIHR Biomedical Research Centre, Simon P. Harding, MD, University of Liverpool, Ruth E. Hogg, PhD, Queens University Belfast, Pirro Hysi, PhD, King's College London, Pearse A. Keane,MD, NIHR Biomedical Research Centre, Sir Peng T. Khaw, PhD, NIHR Biomedical Research Centre, Anthony P. Khawaja, DPhil, NIHR Biomedical Research Centre, Gerassimos Lascaratos, PhD, NIHR Biomedical Research Centre, Andrew J. Lotery, MD, University of Southampton, TomMacgillivray, PhD, University of Edinburgh, Sarah Mackie, PhD, University of Leeds, Keith Martin, FRCOphth, University of

Cambridge, Michelle McGaughey, Queen’s University Belfast, BernadetteMcGuinness, PhD, Queen’s University Belfast, Gareth J. McKay, PhD, Queen's University Belfast, Martin McKibbin, FRCOphth, Leeds Teaching HospitalsNHS Trust, Danny Mitry, PhD, NIHR Biomedical Research Centre, Tony Moore, FRCOphth, NIHR Biomedical Research Centre, James E. Morgan, DPhil, Cardiff University, Zaynah A. Muthy, BSc, NIHR Biomedical Research Centre, Eoin O’Sullivan, MD, King's College Hospital NHS Foundation Trust, Chris G. Owen, PhD, University of London, Praveen Patel, FRCOphth, NIHR Biomedical Research Centre, Euan Paterson, BSc, Queens University Belfast, Tunde Peto, PhD, Queen's University Belfast, Axel Petzold, PhD, UCL, Jugnoo S. Rahi, PhD, UCL Great Ormond Street Institute of Child Health, Alicja R. Rudnikca, PhD, University of London, Jay Self, PhD, University of Southampton, Sobha Sivaprasad, FRCOphth, NIHR Biomedical Research Centre, David Steel, FRCOphth, Newcastle University, Irene Stratton, MSc, Gloucestershire HospitalsNHS Foundation Trust, Nicholas Strouthidis, PhD, NIHR Biomedical Research Centre, Cathie Sudlow, DPhil, University of Edinburgh, Dhanes Thomas, FRCOphth, NIHR Biomedical Research Centre, Emanuele Trucco, PhD, University of Dundee, Adnan Tufail, FRCOphth, NIHR Biomedical Research Centre, Veronique Vitart, PhD, University of Edinburgh, Stephen A. Vernon, DM, Nottingham University HospitalsNHS Trust, Ananth C. Viswanathan, FRCOphth, NIHR Biomedical Research Centre, Cathy Williams, PhD, University of Bristol, Katie Williams, PhD, King's College London, Jayne V. Woodside, MRCOphth, PhD, Queen's University Belfast, Max M. Yates, PhD, University of East Anglia, Jennifer Yip, PhD, University of Cambridge, and Yalin Zheng, PhD, University of Liverpool.

Figure 1: Flow chart showing participants included for analysis.(CH, corneal hysteresis; D, dioptre; IOPg, Goldmann-correlated intraocular pressure)

Figure 2: Locally weighted scatterplot smoothing (LOWESS) of self-reported glaucoma and corneal hysteresis, (A) unstratified (B) stratified by age (C) stratified according to the tertiles of IOPg. (IOPg, Goldmann-correlated intraocular pressure)

Figure 3:3D bar charts showing the percentage of self-reported glaucoma stratified according to tertiles of corneal hysteresis and IOPg. (IOPg, Goldmann-correlated intraocular pressure)