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Associations with Corneal Hysteresis in a Population Cohort

Results from 96 010 UK Biobank Participants

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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: Corneal hysteresis (mmHg).

Results: The mean CH was 10.6 mmHg (10.4 mmHg in male and 10.8 mmHg in female participants). After adjusting for covariables, CH was significantly negatively associated with male sex, age, black ethnicity, self-reported glaucoma, diastolic blood pressure, and height. Corneal hysteresis 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 10.1 mmHg (odds ratio, 0.86; 95% confidence interval, 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.

Conclusions: 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 10.1 mmHg. Corneal hysteresis may serve as a biomarker aiding glaucoma case detection. *Ophthalmology 2019;■:1−11 Crown Copyright © 2019 Published by Elsevier Inc. on behalf of the American Academy of Ophthalmology*

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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, because one particular high-risk group (African Americans) typically has 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 provide valuable information related to the presence, progression, and response to therapy of glaucoma.[8,9] Corneal hysteresis can be measured simultaneously with IOP using noncontact 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

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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 on the basis of 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 years 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) that 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 described.[18] Visual acuity was measured using a bespoke computerized logarithm of the minimum angle of resolution acuity measure conforming to British Standard BS4274-1968,[19] with left eye following right eye. Autorefraction was performed with the RC5000 Auto Refkeratometer (Tomey, Tokyo, Japan). After measuring visual acuity and refraction, CH and Goldmann-correlated IOP (IOPg) were measured with the Reichert Ocular Response Analyzer (ORA, Reichert, Inc., Depew, NY) according to a predetermined protocol (available at 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, Hoofddorp, 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, Birmingham, 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 status was collected in the verbal interview or 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 as follows:

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 who 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. Intraocular pressure–lowering medication status was dichotomized to user and nonuser 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 years or older than 69 years of age were excluded on the basis of the UK Biobank eligibility criteria. Extreme values (lowest 0.5% and highest 0.5%) of CH and IOPg may represent measurement errors and were excluded. We excluded participants with a

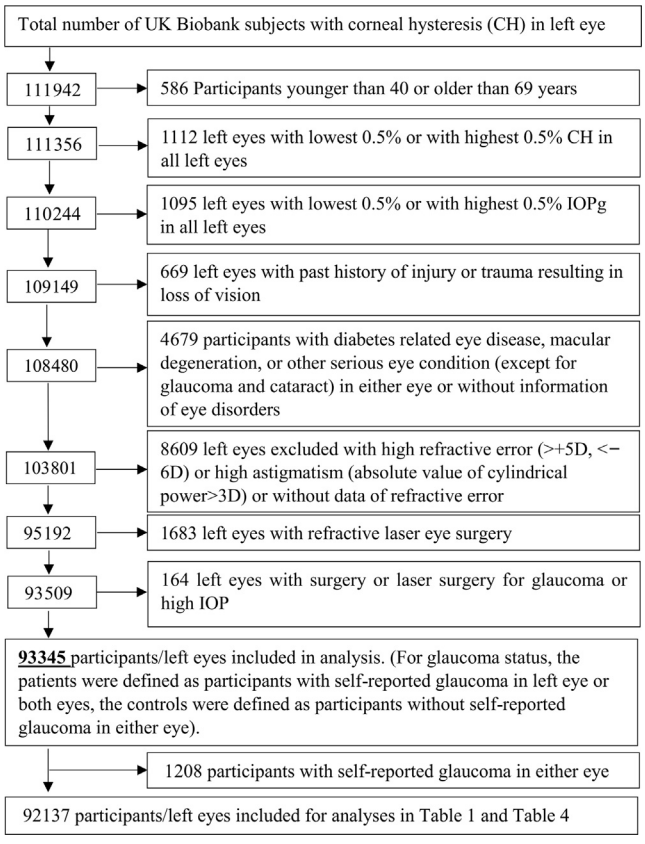

Figure 1. Flowchart showing participants included for analysis. CH = corneal hysteresis; D = diopter; IOPg = Goldmann-correlated intraocular pressure.

Table 1. Distribution of Corneal Hysteresis (mmHg) Stratified by Age, Gender, and Ethnicity in 92 137 Left Eyes without Self-Reported Glaucoma*

	40–44 Yrs	45–49 Yrs	50–54 Yrs	55–59 Yrs	60–64 Yrs	65–69 Yrs	P†	Total
Female								
White	11.3±1.9 (4127)	11.2±1.8 (5600)	11.0±1.8 (6877)	10.9±1.9 (8099)	10.7±1.8 (11 768)	10.5±1.8 (8449)	1.82×10^{-174}	10.8±1.8 (44 920)
Asian	10.7±1.8 (315)	10.7±1.7 (292)	10.7±1.8 (323)	10.2±1.7 (295)	10.6±1.7 (287)	10.2±1.8 (167)	2.62×10^{-4}	10.5±1.8 (1679)
Black	9.8±1.8 (364)	9.8±1.8 (482)	9.8±1.8 (434)	9.7±1.8 (243)	9.6±2.0 (204)	9.8±2.1 (152)	0.88	9.8±1.9 (1879)
Chinese	10.9±2.1 (39)	11.1±2.1 (47)	10.9±1.5 (43)	10.6±1.9 (58)	10.8±2.1 (39)	10.6±1.7 (24)	0.80	10.8±1.9 (250)
Mixed	10.8±1.8 (104)	10.4±1.8 (125)	10.6±1.6 (108)	10.8±1.8 (78)	10.7±1.8 (56)	10.2±1.7 (48)	0.24	10.6±1.8 (519)
Others	10.4±1.8 (147)	10.6±1.7 (177)	10.6±2.0 (173)	10.4±1.7 (147)	10.1±1.8 (140)	10.0±1.6 (75)	0.05	10.4±1.8 (859)
P‡	1.36×10^{-52}	3.91×10^{-58}	5.58×10^{-40}	2.47×10^{-26}	7.71×10^{-17}	1.52×10^{-6}	–	1.28×10^{-150}
Total§	11.1±1.9 (5125)	11.0±1.9 (6756)	10.9±1.9 (7999)	10.8±1.9 (8953)	10.7±1.8 (12 545)	10.5±1.8 (8952)	1.03×10^{-122}	10.8±1.9 (50 330)
Male								
White	10.8±1.9 (3484)	10.7±1.9 (4393)	10.6±1.9 (5125)	10.5±1.8 (6243)	10.3±1.9 (9897)	10.1±1.9 (8328)	9.35×10^{-123}	10.4±1.9 (37 470)
Asian	10.4±1.9 (388)	10.3±1.8 (321)	10.4±1.8 (276)	10.3±1.8 (294)	10.0±1.9 (254)	9.9±1.8 (244)	0.001	10.2±1.8 (1777)
Black	9.7±2.0 (292)	9.4±1.8 (319)	9.4±1.7 (232)	9.4±2.0 (193)	9.2±1.7 (129)	9.2±2.0 (122)	0.08	9.4±1.9 (1287)
Chinese	11.4±1.3 (17)	10.9±2.4 (25)	10.6±2.0 (24)	10.7±2.4 (27)	11.0±2.0 (27)	10.2±1.7 (20)	0.53	10.8±2.1 (140)
Mixed	10.6±2.1 (66)	10.6±2.0 (86)	10.1±1.8 (49)	10.1±1.9 (36)	10.4±1.7 (37)	9.7±1.5 (33)	0.11	10.3±1.9 (307)
Others	10.2±1.7 (128)	10.2±1.8 (110)	10.1±2.0 (87)	10.5±1.7 (92)	10.1±1.7 (71)	10.1±2.0 (62)	0.78	10.2±1.8 (550)
P‡	3.94×10^{-25}	3.51×10^{-35}	5.55×10^{-19}	1.71×10^{-11}	2.77×10^{-10}	1.74×10^{-7}	–	2.90×10^{-79}
Total§	10.7±1.9 (4404)	10.6±1.9 (5296)	10.5±1.9 (5829)	10.4±1.8 (6919)	10.3±1.9 (10 491)	10.1±1.9 (8868)	3.40×10^{-96}	10.4±1.9 (41 807)
P‖	1.87×10^{-23}	9.29×10^{-29}	1.30×10^{-34}	2.54×10^{-39}	1.04×10^{-61}	3.01×10^{-36}	–	9.42×10^{-228}
All§	10.9±1.9 (9529)	10.8±1.9 (12 052)	10.8±1.9 (13 828)	10.6±1.9 (15 872)	10.5±1.9 (23 036)	10.3±1.8 (17 820)	6.70×10^{-234}	10.6±1.9 (92 137)

*Participants with self-reported glaucoma in either eye were excluded. Data in format, mean ± SD mmHg (n of included eyes).
†*P* value of 1-way analysis of variance of the means between different age groups.
‡*P* value of 1-way analysis of variance of the means between participants with different ethnicities.
§Ethnicity was unclear for 500 participants (224 female and 276 male), with mean CH of 10.3±1.9 mmHg (10.4±1.9 mmHg in female participants and 10.2±1.9 mmHg in male participants).
‖*P* value of 1-way analysis of variance of the means between women and men from the same age groups.

Table 2. Linear Regression with Corneal Hysteresis as the Dependent Variable in 93 345 Left Eyes

	Univariable		Multivariable (n = 91 765)	
Corneal Hysteresis	*Coefficient (β) (95% CI)*	P	*Coefficient (β) (95% CI)*	P
Age/10 yrs	−0.26 (−0.27 to −0.24)	7.19×10^{-252}	−0.33 (−0.35 to −0.32)	$<10^{-300}$
Gender (Ref. = female)	−0.40 (−0.43 to −0.38)	1.42×10^{-233}	−0.19 (−0.23 to −0.16)	2.07×10^{-27}
Ethnicity (Ref. = white)		5.77×10^{-221}		
Asian	−0.28 (−0.34 to −0.22)	5.37×10^{-19}	−0.46 (−0.53 to −0.40)	2.08×10^{-45}
Black	−1.03 (−1.10 to −0.96)	7.51×10^{-205}	−1.22 (−1.29 to −1.15)	1.03×10^{-260}
Chinese	0.14 (−0.05 to 0.34)	0.14	−0.02 (−0.22 to 0.17)	0.80
Mixed	−0.15 (−0.27 to −0.03)	0.02	−0.39 (−0.51 to −0.26)	8.63×10^{-10}
Others	−0.33 (−0.43 to −0.24)	4.27×10^{-12}	−0.60 (−0.70 to −0.50)	3.52×10^{-34}
DBP/10 mmHg	−0.12 (−0.13 to −0.11)	5.67×10^{-81}	−0.08 (−0.09 to −0.06)	1.29×10^{-33}
SBP/10 mmHg	−0.08 (−0.09 to −0.07)	9.71×10^{-124}	–	–
Height/10 cm	−0.19 (−0.20 to −0.17)	3.18×10^{-173}	−0.16 (−0.18 to −0.14)	4.71×10^{-61}
Eyesight/logMAR	0.00 (−0.06 to 0.06)	0.98	–	–
Refractive error/D	0.02 (0.01–0.02)	2.55×10^{-8}	0.03 (0.03–0.04)	3.06×10^{-26}
IOPg/mmHg	0.02 (0.02–0.03)	2.82×10^{-38}	0.03 (0.03–0.04)	2.32×10^{-67}
Smoking (Ref. = Never smoker)		4.04×10^{-99}		
Current smoker	0.46 (0.42–0.50)	3.34×10^{-100}	0.42 (0.38–0.46)	1.22×10^{-84}
Former smoker	0.05 (0.03–0.08)	1.05×10^{-4}	0.10 (0.07–0.12)	7.71×10^{-13}
Alcohol intake frequency (Ref. = never drinker)		0.26		
Occasional drinker	0.04 (−0.01 to 0.09)	0.15	–	–
Monthly or more, less often than every week	0.06 (0.01–0.12)	0.03	–	–
Weekly or more, less often than daily	0.05 (0.00–0.09)	0.048	–	–
Daily or almost daily	0.04 (−0.01 to 0.08)	0.15	–	–
Self-reported glaucoma	−0.70 (−0.82 to −0.57)	1.29×10^{-26}	−0.52 (−0.64 to −0.39)	1.13×10^{-15}
Diabetes	0.13 (0.07–0.19)	3.50×10^{-5}	0.28 (0.22–0.34)	1.25×10^{-20}
Townsend Index	0.01 (0.01–0.01)	6.34×10^{-7}	0.01 (0.01–0.02)	7.82×10^{-8}

CI = confidence interval; D = diopter; DBP = diastolic blood pressure; IOPg = Goldmann–correlated intraocular pressure; logMAR = logarithm of the minimum angle of resolution; SBP = systolic blood pressure.

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 or refractive error, with high refractive errors (spherical equivalent >+5 diopters [D] or <−6 D), high astigmatism (absolute value of cylindrical power >3 D), 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, 1208 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 diopters (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 points found on the LOWESS curve were used as nodes for piecewise analysis.
2. Piecewise logistic regression for self-reported glaucoma and CH was performed in 3 models after adjusting for covariables.
3. The joint distribution of the proportion of self-reported glaucoma, CH, and IOPg was displayed using a 3-dimensional bar chart.

We then applied linear regression to evaluate the relationships between CH and 16 systemic diseases after adjusting for covariables.

The 3-dimensional bar chart was plotted using Excel for Office 365 (Microsoft Corp, Redmond, WA). All other analyses were performed and plots generated using STATA/SE-15 (StataCorp LLC, College Station, TX).

Results

All analyses were performed using left eye data in this study. A total of 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% confidence interval [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

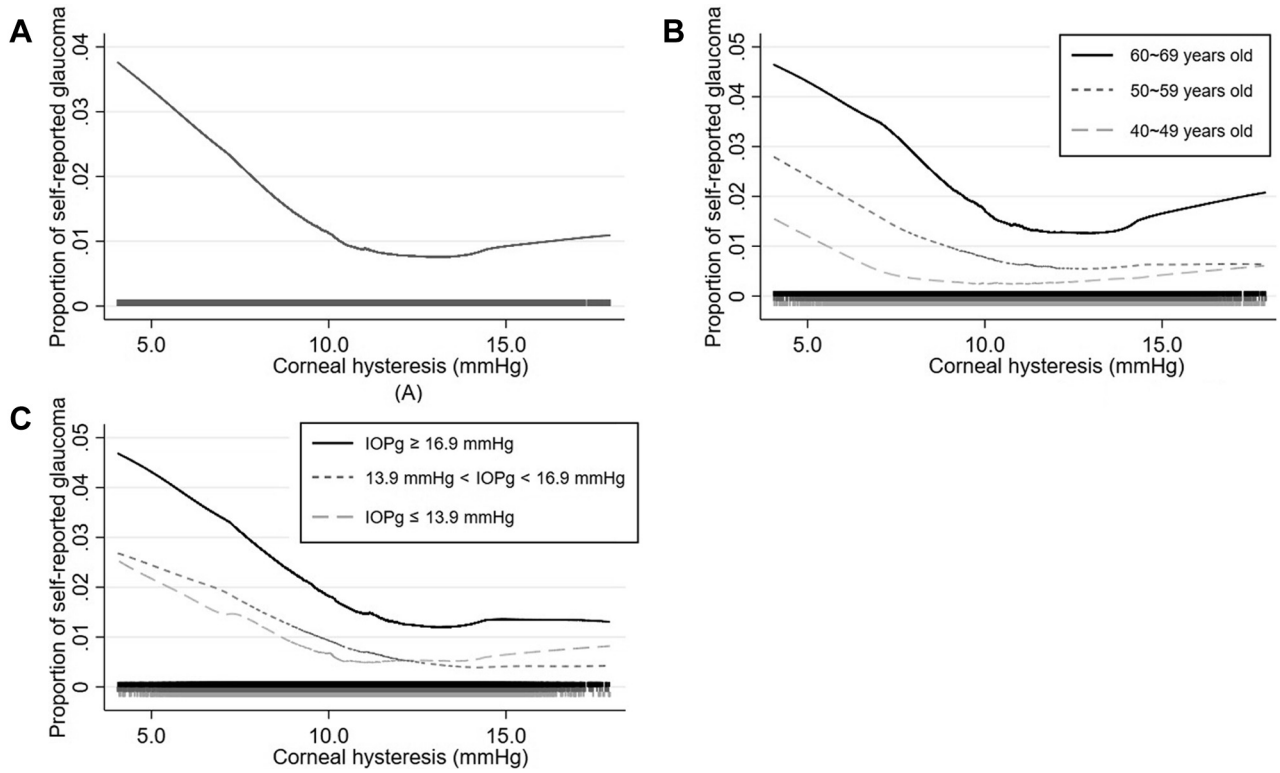

Figure 2. Locally weighted scatterplot smoothing (LOWESS) of self-reported glaucoma and corneal hysteresis (CH), **(A)** unstratified, **(B)** stratified by age, and **(C)** stratified according to the tertiles of Goldmann-correlated intraocular pressure (IOPg).

summarized in Table 1. A significant difference in CH was found between participants with different ethnicities ($P < 0.001$). The CH values were lower in black participants (9.62±1.87 mmHg, 95% CI, 9.56−9.69 mmHg) compared with white participants (10.66±1.87 mmHg, 95% CI, 10.65−10.67 mmHg). The CH was significantly greater in female participants (10.79±1.86 mmHg, 95% CI, 10.77−10.80 mmHg) compared with male participants (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%

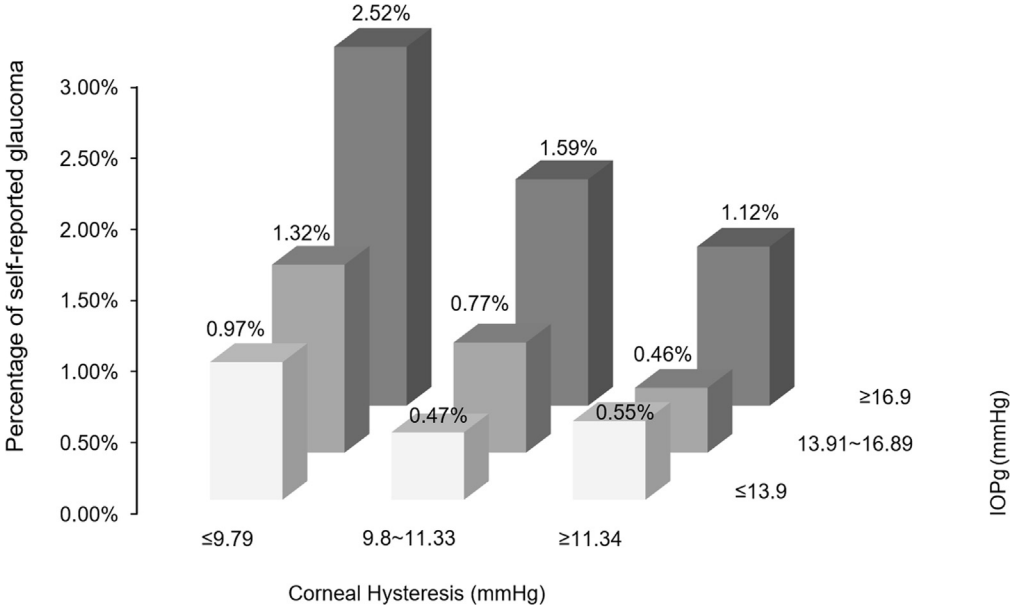

Figure 3. Three-dimensional bar charts showing the percentage of self-reported glaucoma stratified according to tertiles of corneal hysteresis (CH) and Goldmann-correlated intraocular pressure (IOPg).

Table 3. Logistic Regression for Self−Reported Glaucoma

	Model I (n = 92 637)†		Model II (n = 92 637)*		Model III (n = 91 013)‡	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
CH/mmHg						
≤10.1	0.78 (0.73−0.82)	6.44×10^{-19}	0.82 (0.78−0.87)	2.20×10^{-12}	0.86 (0.79−0.94)	4.96×10^{-4}
>10.1	0.99 (0.93−1.05)	0.70	0.94 (0.88−1.00)	0.06	1.01 (0.94−1.09)	0.76
IOPg/mmHg	–	–	1.14 (1.11−1.16)	3.05×10^{-40}	1.13 (1.11−1.16)	1.61×10^{-21}

CI = confidence interval; IOPg = Goldmann−correlated intraocular pressure; OR = odds ratio.
*Adjusting for age, sex, and ethnicity.
†Adjusting for age, sex, ethnicity, and IOPg.
‡Adjusting for age, sex, ethnicity, IOPg, currently intraocular pressure−lowering medication (s) using (Ref. = not), diastolic blood pressure, height, visual acuity, refractive error, smoking status, alcohol drinking frequency, diabetes status, and Townsend deprivation index.

CI, 10.87−10.95 mmHg for those aged 40 to 44 years compared with 10.30±1.84 mmHg, 95% CI, 10.27−10.32 mmHg for those aged 65 to 69 years, $P < 0.001$).

The associations of CH were analyzed with linear regression models as shown in Table 2. Corneal hysteresis 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 those with self-reported diabetes (0.28 mmHg, $P = 1.25\times10^{-20}$). Corneal hysteresis 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 those with self-reported glaucoma (−0.52 mmHg, $P = 1.13\times10^{-15}$).

Figures 2 and 3 and Table 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 10 mmHg, the proportion of self-reported glaucoma increased markedly when CH decreased. However, with increases in CH above 10 mmHg, the proportion of self-reported glaucoma remained relatively stable at approximately 1%. The LOWESS curve shapes were similar in analyses stratified by age (Fig 2B) and IOPg (Fig 2C), with sharp increases in the proportions of self-reported glaucoma at CH values less than approximately 10 mmHg.

Piecewise logistic regressions were performed with a node set at 10.1 mmHg (Table 3). As shown in the Supplementary Material (available at www.aaojournal.org), 10.1 mmHg was the smallest node that self-reported glaucoma and CH were significantly associated when CH was less than the node, whereas there was no association between self-reported glaucoma and CH when CH was greater than the node in all 3 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 odds ratio (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 3 models (Table 3).

The relationship among self-reported glaucoma, CH, and IOPg is displayed using a 3-dimensional bar chart (Fig 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 immunologic/systemic disorders (Table 4). Only systemic lupus erythematosus (SLE) was significantly associated with CH after correction for multiple testing ($P < 0.003125$, Bonferroni-corrected threshold). Corneal hysteresis 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.

Corneal hysteresis 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 epidemiologic study showed a marked reduction in the incidence of keratoconus among 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

Table 4. Linear Regressions for Corneal Hysteresis and Self–Reported Disorders of the Thyroid Gland, Pituitary Gland, or Other Immunologic/Systemic Disorders*

	Model 1†		Model 2†		Model 3†		
Corneal Hysteresis	*Coefficient (β)*	P	*Coefficient (β)*	P	*Coefficient (β)*	P	**Prevalence‡**
Thyroid disorders							
Hyperthyroidism/thyrotoxicosis/Grave's disease	−0.02 (−0.16 to 0.12)	0.74	−0.02 (−0.16 to 0.12)	0.75	−0.04 (−0.18 to 0.10)	0.61	1.05% (0.94%)
Hypothyroidism/myxedema	0.02 (−0.04 to 0.07)	0.57	0.02 (−0.03 to 0.08)	0.43	0.02 (−0.03 to 0.08)	0.42	6.46% (6.50%)
Thyroid goiter	−0.22 (−0.43 to −0.01)	0.04§	−0.22 (−0.43 to −0.02)	0.04§	−0.19 (−0.39 to 0.02)	0.07	0.13% (0.40%)
Thyroiditis	0.20 (−0.26 to 0.66)	0.40	0.20 (−0.26 to 0.66)	0.39	0.21 (−0.24 to 0.67)	0.36	0.07% (0.09%)
Disorders of pituitary gland							
Acromegaly	1.09 (0.12–2.06)	0.03§	1.11 (0.15–2.07)	0.02§	1.22 (0.21–2.22)	0.02§	0.02% (0.02%)
Hypopituitarism	−0.25 (−0.82 to 0.32)	0.40	−0.26 (−0.83 to 0.31)	0.38	−0.24 (−0.80 to 0.33)	0.42	0.05% (0.06%)
Hyperprolactinemia	−0.06 (−0.87 to 0.75)	0.89	−0.03 (−0.87 to 0.81)	0.95	−0.03 (−0.84 to 0.78)	0.95	0.02% (0.02%)
Pituitary adenoma/tumor	−0.09 (−0.51 to 0.34)	0.69	−0.07 (−0.49 to 0.35)	0.74	−0.02 (−0.44 to 0.39)	0.92	0.09% (0.10%)
Immunological/systemic disorders							
SLE	0.64 (0.31–0.96)	0.0001‖	0.64 (0.32–0.97)	0.0001‖	0.55 (0.24 to 0.86)	0.0006‖	0.17% (0.16%)
Sjögren's syndrome/sicca syndrome	0.10 (−0.29 to 0.48)	0.63	0.11 (−0.28 to 0.50)	0.58	0.13 (−0.26 to 0.52)	0.51	0.13% (0.11%)
Rheumatoid arthritis	0.11 (−0.01 to 0.24)	0.07	0.12 (0.00–0.24)	0.06	0.08 (−0.04 to 0.20)	0.20	1.51% (1.25%)
Vasculitis	0.04 (−0.19 to 0.27)	0.72	0.05 (−0.18 to 0.27)	0.68	0.07 (−0.16 to 0.30)	0.56	0.37% (0.39%)
Dermatopolymyositis	−0.24 (−1.02 to 0.54)	0.54	−0.25 (−1.02 to 0.52)	0.52	−0.26 (−1.05 to 0.52)	0.51	0.03% (0.02%)
Scleroderma/systemic sclerosis	0.04 (−0.62 to 0.71)	0.90	0.03 (−0.63 to 0.70)	0.92	0.07 (−0.55 to 0.70)	0.82	0.04% (0.03%)
Psoriasis	0.10 (−0.03 to 0.22)	0.12	0.10 (−0.03 to 0.22)	0.13	0.07 (−0.06 to 0.19)	0.28	1.49% (1.32%)
Sarcoidosis	−0.29 (−0.56 to −0.01)	0.04§	−0.27 (−0.55 to 0.01)	0.06	−0.18 (−0.46 to 0.11)	0.22	0.27% (0.26%)

SLE = systemic lupus erythematosus.
*Participants with self–reported glaucoma in either eye were excluded.
†Model I, adjusted for age, sex and ethnicity; Model II, adjusted for age, sex, ethnicity and Goldmann-correlated intraocular pressure (IOPg); Model III, adjusted for age, sex, ethnicity, IOPg, height, diastolic blood pressure, visual acuity, smoking status, refractive error, diabetes status, and Townsend deprivation index.
‡Prevalence % = Proportion using all UK Biobank participants with available data (n = 375 064). (%) = Proportion within the sample with available data after data cleaning (n = 69 973).
§$P < 0.05$.
‖$P < 0.003125$ (Bonferroni-corrected threshold for multiple testing).

found no significant association between alcohol consumption and CH.

Our findings in Figures 2 and 3, and Table 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 10.1 mmHg, the rate of self-reported glaucoma remained relatively stable with further increases in CH. Medeiros et al[38] reported that lower CH with values below 10 mmHg was a risk factor for glaucoma progression.

Measurement of CH 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. Corneal hysteresis 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] Figures 2C and 3 and Table 3 show that CH and IOPg could be analyzed together in clinical settings to evaluate glaucoma risk, because 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 that reported CH was lower in patients with SLE.[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 by Ozkok et al;[13] however, our results were 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 among patients with diabetes as previously reported,[60,61] which is supported by the former findings that having diabetes decreased the odds of having more severe keratoconus.[62] The increased cross-linking of corneal collagen[63] in diabetes may contribute to the higher CH. However, 2 small sample studies[64,65] reported no significant change of CH after cross-linking operation in keratoconus. Another possible mechanism is the morphologic[66] and functional alteration[67] of corneal endothelium in diabetic patients, leading to abnormal hydration and increased thickness of cornea,[66,67] which is associated with higher CH.

Study Strengths and Limitations

The 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 statuses were self-reported by participants, which can result in misclassification error.[68] The UK Biobank has a low response rate of 5.5%, which limits external validity. With respect to glaucoma, there will be an under-ascertainment of disease because approximately 50% of cases may not have been diagnosed.[68] Meanwhile, participants with ocular hypertension, suspected glaucoma, or cataracts may report a diagnosis of glaucoma. The potential impact of these errors is unknown. We excluded participants with a history of surgery or laser for glaucoma or ocular hypertension. A potential confounding variable in the reported association between CH and glaucoma is the use of IOP-lowering medications, which may significantly alter corneal biomechanical properties.[9,69,70] The binary variable of current, regular IOP-lowering medication use versus no use in this study may oversimplify the effects of different medications on corneal biomechanics. Corneal hysteresis and IOPg in this study were measured together using the same instrument and adjusting one for the other makes interpretation difficult. Despite this, we found a weak correlation between them *(Pearson correlation coefficient, rho* $= 0.045$) in the sample after data cleaning. Investigation into the association between CH and diseases including glaucoma, SLE, and diabetes is scarce, and we anticipate that future research will build on our findings.

In conclusion, our study offers CH reference values for future research and clinical practice. We also report associations between CH and age, sex, ethnicity, smoking status, refractive error, self-reported glaucoma, diabetes, and SLE, which may be important when interpreting CH. Corneal hysteresis measurement may play a role in clinical practice for glaucoma and other ocular and systemic conditions.

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No animal subjects were used in this study.

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Abbreviations and Acronyms:

CCT = central corneal thickness; **CH** = corneal hysteresis; **CI** = confidence interval; **D** = diopters; **IOP** = intraocular pressure; **IOPg** = Goldmann-correlated intraocular pressure; **LOWESS** = locally weighted scatterplot smoothing; **OR** = odds ratio; **SLE** = systemic lupus erythematosus.

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