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**Citation:** Zhang, B., Shweikh, Y., Khawaja, A. P., Gallacher, J., Bauermeister, S., Foster, P. J., UKBiobank Eye and Vision Consortium & Crabb, D. P. (2019). Associations with Corneal Hysteresis in a Population Cohort: Results from 96010 UK Biobank Participants. *Ophthalmology*, 126(11), pp. 1500-1510. doi: 10.1016/j.ophtha.2019.06.029

This is the accepted version of the paper.

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**Permanent repository link:** <https://openaccess.city.ac.uk/id/eprint/26977/>

**Link to published version:** <https://doi.org/10.1016/j.ophtha.2019.06.029>

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

**Bing Zhang<sup>1</sup>, Yusrah Shweikh<sup>2</sup>, Anthony P Khawaja<sup>2</sup>, John Gallacher<sup>1</sup>, Sarah Bauermeister<sup>1</sup>, Paul J Foster<sup>2</sup> on behalf of the UKBiobank Eye and Vision Consortium**

Financial Support: None

Conflict of Interest: None

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:**

<sup>1</sup> Department of Psychiatry, University of Oxford, Oxford, UK

<sup>2</sup> 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](mailto:p.foster@ucl.ac.uk)

Telephone: 07971 663189

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**Word count: 3152**

## **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 (to be copied from ICMJE form once completed):**

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.

## **Acknowledgements & Funding**

### **Funding**

The UK Biobank Eye and Vision Consortium is supported by grants from The NIHR Biomedical Research Centre at Moorfields Eye Hospital NHS Foundation Trust and UCL Institute of Ophthalmology, the Alcon Research Institute, Moorfields Eye Charity, and the International Glaucoma Association (UK).

No funders had a direct role in the collection, management, analysis, or interpretation of the data; preparation, review, or approval of the manuscript; nor in the decision to submit the manuscript for publication.

### **Acknowledgements**

PJF received support from the Richard Desmond Charitable Trust, via Fight for Sight, London. APK is supported by a Moorfields Eye Charity Career Development Fellowship. PJF & APK received salary support from the NIHR BRC at Moorfields Eye Hospital. These authors acknowledge a proportion of our financial support from the UK Department of Health through an award made by the National Institute for Health Research to Moorfields Eye Hospital NHS Foundation Trust and UCL Institute of Ophthalmology for a Biomedical Research Centre for Ophthalmology.

**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](http://www.ukbiobank.ac.uk))

1 **Abstract**

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

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

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

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

11 **Main outcome measures:** CH (mmHg).

12 **Results:** The mean CH was 10.6 mmHg (10.4 mmHg in males and 10.8 mmHg in females). After  
13 adjusting for covariables, CH was significantly negatively associated with male sex, age, Black  
14 ethnicity, self-reported glaucoma, diastolic blood pressure and height. CH was significantly  
15 positively associated with smoking, hyperopia, diabetes, systemic lupus erythematosus (SLE),  
16 greater deprivation (Townsend index) and Goldmann-correlated intraocular pressure (IOPg). Self-  
17 reported glaucoma and CH were significantly associated when CH was less than 10.1mmHg (OR  
18 0.86, 95%CI 0.79-0.94 per mmHg CH increase) after adjusting for covariables. When CH exceeded  
19 10.1 mmHg, there was no significant association between CH and self-reported glaucoma.

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

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

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

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

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

46 **Methods**

47 **Study population**

48 The UK Biobank is a multisite community-based cohort study with 502,544 participants. All UK  
49 residents aged 40 to 69 who registered with the National Health Service and lived within 25 miles  
50 of any of the 22 assessment centers were invited to join the study. The initial visit assessments took  
51 place between 2006 and 2010. Eye assessments were carried out from 2009 in 6 recruitment centers  
52 (5 in England and 1 in Wales) which enrolled 133,953 participants. The UK Biobank study was  
53 approved by the North West Multi-centre Research Ethics Committee (Reference No. 06/MRE08/65)  
54 and adhered to the tenets of the Declaration of Helsinki. Written consent was obtained from every  
55 participant. More detailed information and protocols for UK Biobank are available online  
56 (<http://www.ukbiobank.ac.uk/>).

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

61 **Measurements**

62 Cohort characteristics and ophthalmic measures have been previously described<sup>18</sup>. Visual acuity was  
63 measured using a bespoke computerized logMAR acuity measure conforming to British Standard  
64 BS4274-1968<sup>19</sup>, with left eye following right eye. Autorefractometry was performed with the RC5000  
65 Auto Refractometer (Tomey, Japan). After measuring visual acuity and refraction, CH and  
66 Goldmann-correlated IOP (IOPg) were measured with the Reichert Ocular Response Analyser  
67 (ORA, Reichert, Inc. USA) according to a predetermined protocol (available online

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

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

#### 76 **Medical History**

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

- 82 1. Diabetes related eye disease
- 83 2. Glaucoma
- 84 3. Injury or trauma resulting in loss of vision
- 85 4. Cataract
- 86 5. Macular degeneration
- 87 6. Other serious eye condition
- 88 7. None of the above
- 89 8. Prefer not to answer

90 9. Do not know

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

97 More detailed information about all variables is available online

98 (<http://biobank.ctsu.ox.ac.uk/crystal/index.cgi>).

99 **Eligibility criteria**

100 All participants who had available ORA data (CH and IOPg) in the left eye were used for this  
101 analysis. Participants who met any exclusion criteria in Figure 1 were excluded from the analyses.  
102 0.5% of participants who were younger than 40 or older than 69 years were excluded based on the  
103 UK Biobank eligibility criteria. Extreme values (lowest 0.5% and highest 0.5%) of CH and IOPg  
104 may represent measurement errors and were therefore excluded. We excluded participants with a  
105 history of eye injury in their left eye, diabetes related eye disease, macular degeneration or other  
106 serious eye conditions (except for glaucoma and cataract) in either eye. Left eyes without data on  
107 ocular comorbidities and/or refractive error, and/or with high refractive errors (spherical  
108 equivalent  $>+5D$  or  $<-6D$ ) and/or high astigmatism (absolute value of cylindrical power  $>3D$ ) and/or  
109 a history of refractive surgery were excluded. Participants with a history of surgery or laser for  
110 glaucoma or ocular hypertension were also excluded. Of the 93,345 left eyes remained in analysis,  
111 1,208 eyes with self-reported glaucoma were excluded for analyses of CH distribution.

112 **Statistical analysis**

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

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

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

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

125 1) Locally weighted scatterplot smoothing (LOWESS)<sup>21</sup>, a method usually used to visualize  
126 the structure of data<sup>22</sup>, was used to explore the relationship between self-reported glaucoma  
127 and corneal hysteresis. The turning point(s) found on the LOWESS curve was used as  
128 node(s) for piecewise analysis.

129 2) Piecewise logistic regression for self-reported glaucoma and CH was performed in three  
130 models after adjusting for covariables.

131 3) The joint distribution of the proportion of self-reported glaucoma, CH and IOPg was  
132 displayed using a 3D bar chart.

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

134 after adjusting for covariables.

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

## 137 **Results**

138 All analyses were performed using left eye data in this study. 111,942 UK Biobank participants had  
139 available CH values for left eyes. After data cleaning as shown in Figure 1, the mean CH was 10.60  
140  $\pm 1.88$  mmHg (95% CI 10.59-10.62 mmHg) in the 92,137 eyes without self-reported glaucoma.

141 The distribution of mean CH stratified by age, sex and ethnicity is summarized in Table 1. A  
142 significant difference in CH was found between participants with different ethnicities ( $p < 0.001$ ).

143 CH values were lower in Black people ( $9.62 \pm 1.87$  mmHg, 95% CI 9.56-9.69 mmHg) compared to  
144 White participants ( $10.66 \pm 1.87$  mmHg, 95% CI 10.65-10.67 mmHg). CH was significantly greater  
145 in females ( $10.79 \pm 1.86$  mmHg, 95% CI 10.77-10.80 mmHg) compared to males ( $10.39 \pm 1.88$   
146 mmHg, 95% CI 10.37-10.40 mmHg,  $p < 0.001$ ). Overall, CH was also significantly higher in younger  
147 people across the whole age spectrum enrolled (mean  $10.91 \pm 1.91$  mmHg, 95% CI 10.87-  
148  $10.95$  mmHg for those aged 40-44 compared to  $10.30 \pm 1.84$  mmHg, 95% CI 10.27-10.32 mmHg for  
149 those aged 65-69,  $p < 0.001$ ).

150 The associations of CH were analyzed with linear regression models as shown in Table 2. CH was  
151 significantly associated with all included factors except for visual acuity and alcohol intake  
152 frequency. In the multivariable linear regression model after adjusting for covariates, CH was  
153 significantly higher in women ( $0.193$  mmHg,  $p = 2.07 \times 10^{-27}$ ), smokers (reference: never smoked;  
154  $0.095$  mmHg former smokers,  $p = 7.71 \times 10^{-13}$ ;  $0.419$  mmHg current smokers,  $p = 1.22 \times 10^{-84}$ ),  
155 participants with a higher Townsend deprivation index ( $0.012$  mmHg/Unit,  $p = 7.82 \times 10^{-8}$ ) and self-

156 reported diabetes ( $0.283 \text{ mmHg}$ ,  $p=1.25 \times 10^{-20}$ ). CH was significantly lower in older participants  
157 ( $-0.033 \text{ mmHg/year}$ ,  $p=0$ ), Black participants (reference: white;  $-1.219 \text{ mmHg}$ ,  $p=1.03 \times 10^{-260}$ ),  
158 Asian participants (reference: white;  $-0.461 \text{ mmHg}$ ,  $p=2.08 \times 10^{-45}$ ), participants with higher blood  
159 pressure ( $-0.0076 \text{ mmHg/1mmHg diastolic blood pressure}$ ,  $p=1.29 \times 10^{-33}$ ), greater height ( $-0.016$   
160  $\text{mmHg/cm}$ ,  $p=4.71 \times 10^{-61}$ ), greater myopia ( $0.034 \text{ mmHg/D}$ ,  $p=3.06 \times 10^{-26}$ ) and in those with self-  
161 reported glaucoma ( $-0.516 \text{ mmHg}$ ,  $p=1.13 \times 10^{-15}$ ).

162 Figure 2, Table 3 and Figure 3 show the relationship between self-reported glaucoma and CH.  
163 Overall, lower CH was associated with a higher proportion of self-reported glaucoma. As shown in  
164 Figure 2A, when CH was less than approximately  $10 \text{ mmHg}$ , the proportion of self-reported  
165 glaucoma increased markedly when CH decreased. However, with increases in CH above  $10 \text{ mmHg}$   
166 the proportion of self-reported glaucoma remained relatively stable at around 1%. The LOWESS  
167 curve shapes were similar in analyses stratified by age (Figure 2B) and IOPg (Figure 2C), with sharp  
168 rises in the proportions of self-reported glaucoma at CH values less than approximately  $10 \text{ mmHg}$ .  
169 Piecewise logistic regressions were performed with a node set at  $10.1 \text{ mmHg}$  (Table 3). As shown in  
170 the online supplementary material,  $10.1 \text{ mmHg}$  was the smallest node that self-reported glaucoma  
171 and CH were significantly associated when CH was less than the node while there was no  
172 association between self-reported glaucoma and CH when CH was greater than the  $10.1 \text{ mmHg}$   
173 node in all three models. When CH was less than  $10.1 \text{ mmHg}$ , higher CH was a protective factor  
174 for self-reported glaucoma. A  $1 \text{ mmHg}$  increase in CH was associated with an OR of  $0.78$  (95% CI  
175  $0.73-0.82$ ,  $p<0.001$ ) after adjusting for age, sex and ethnicity in Model I, an OR of  $0.82$  (95% CI  
176  $0.78-0.87$ ,  $p<0.001$ ) in Model II (Model I with further adjusting for IOPg) and an OR of  $0.86$  (95%  
177 CI  $0.79-0.94$ ,  $p<0.001$ ) in Model III (the maximally adjusted model). When CH exceeded  $10.1$

178 mmHg it was not associated with self-reported glaucoma in all three models (Table 3).  
179 The relationship between self-reported glaucoma, CH and IOPg is displayed using a 3D bar chart  
180 (Figure 3). In keeping with the analyses reported in Figure 2C and Table 3, the proportion of self-  
181 reported glaucoma was highest in participants with high IOPg and low CH, and lowest in the  
182 participants whose IOPg was not high and CH was not low.  
183 We analyzed associations between CH and 16 self-reported disorders of the thyroid gland, pituitary  
184 gland and other immunological/systemic disorders (Table 4). Only systemic lupus erythematosus  
185 (SLE) was significantly associated with CH following correction for multiple testing ( $p < 0.003125$ ,  
186 Bonferroni-corrected threshold). CH was significantly higher in participants with self-reported  
187 SLE (0.549, 95% CI 0.237-0.862 mmHg in the fully adjusted model).

## 188 **Discussion**

189 In this large UK cohort, we have described mean CH stratified by age, sex and ethnicity (Table 1).  
190 We found that CH was significantly lower in Black participants and in older age groups, which is  
191 consistent with previously published findings<sup>15,23</sup>. Past studies indicate that CH and CCT are  
192 positively associated<sup>24-26</sup> and CCT is negatively associated with darker skin pigmentation<sup>27</sup>. One  
193 explanation for the variation in CH by ethnicity may be differences mediated by changes in CCT.  
194 Conversely, previous publications revealed no significant association between CCT and age<sup>7,28,29</sup>,  
195 suggesting an independent association between lower CH and older age.  
196 CH was significantly higher in smokers in our cohort (both current and former smokers). A previous,  
197 smaller study had suggested this but results were inconclusive<sup>30</sup>. The mechanisms underlying the  
198 relationship between smoking and corneal changes are unknown<sup>31,32</sup> and the association between  
199 smoking and corneal ectatic disorders is controversial<sup>33,34</sup>. An epidemiological study showed a

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

206 Our findings in Figure 2, Table 3 and Figure 3 suggest that CH may be useful in glaucoma risk  
207 stratification in clinical practice. Figure 2 and Table 3 indicate that a CH value of 10.1 mmHg could  
208 play a role as cutoff point in clinical practice to evaluate a patient's risk of glaucoma. When CH is  
209 less than 10.1mmHg, lower CH may be associated with a higher risk of glaucoma (OR 1.16, 95%  
210 CI 1.07-1.26 per mmHg CH decrease in the fully adjusted model). When CH was greater than  
211 10.1mmHg, the rate of self-reported glaucoma remained relatively stable with further increases in  
212 CH. Medeiros et al reported that lower CH with values below 10mmHg was a risk factor for  
213 glaucoma progression<sup>38</sup>.

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

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

225 In analyses for associations between CH and self-reported disorders shown in Table 4, only SLE  
226 was significantly associated with CH at  $p < 0.003$  (Bonferroni-corrected threshold for multiple  
227 testing). We found that CH was significantly higher in participants with SLE, which is contradictory  
228 to the result in a case-control study which reported CH was lower in SLE patients<sup>56</sup>. Lower CH has  
229 also been reported in thyroid eye disease<sup>10</sup>, however we did not find an association between CH and  
230 thyroid disorders. We also did not find associations between CH and rheumatoid arthritis or psoriasis  
231 as previously published<sup>11,12</sup>. Participants with acromegaly in our cohort had higher CH values (at  
232  $p < 0.05$ ), in agreement with findings from Ozkok and colleagues<sup>13</sup>, however our result was not  
233 significant after correction for multiple testing. Our study also shows higher CH amongst patients  
234 with diabetes as previously reported<sup>57,58</sup>. Former studies have yielded variable results when  
235 evaluating CH in diabetes<sup>58-61</sup>.

236 The very large sample size and standardized techniques are major strengths of our study, allowing  
237 us to detect and quantify small effects. However, the study is limited by the fact that all disease  
238 statuses were self-reported by participants which can result in misclassification error<sup>62</sup>. UK Biobank  
239 has a low response rate of 5.5% which limits external validity. With respect to glaucoma, there will  
240 be an under-ascertainment of disease since approximately 50% of cases may not have been  
241 diagnosed<sup>62</sup>. Meanwhile participants with ocular hypertension, suspected glaucoma or cataracts may  
242 report a diagnosis of glaucoma. The potential impact of these errors is unknown. We excluded  
243 participants with a past history of surgery or laser for glaucoma or ocular hypertension. A potential

244 confounding variable in the reported association between CH and glaucoma is the use of IOP  
245 lowering medications, which may significantly alter corneal biomechanical properties<sup>9,63,64</sup>. The  
246 binary variable of current, regular IOP lowering medication use versus no use in this study may  
247 oversimplify the effects of different medications on corneal biomechanics. CH and IOPg in this  
248 study were measured together using the same instrument and adjusting one for the other makes  
249 interpretation difficult. Despite this, we found weak correlation between them ( $\rho=0.045$ ) in the  
250 sample after data cleaning. Investigation into the association between CH and diseases including  
251 glaucoma, SLE and diabetes is scarce and we anticipate that future research will build on our  
252 findings.

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

257

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419 **UK Biobank Eye and Vision Consortium membership**

420 UK Biobank Eye & Vision Consortium: The UK Biobank Eye & Vision Consortium members are Tariq  
421 Aslam, PhD, Manchester University, Sarah A. Barman, PhD, Kingston University, Jenny H. Barrett, PhD,  
422 University of Leeds, Paul Bishop, PhD, Manchester University, Peter Blows, BSc, NIHR Biomedical  
423 Research Centre, Catey Bunce, DSc, King's College London, Roxana O. Carare, PhD, University of  
424 Southampton, Usha Chakravarthy, FRCOphth, Queens University Belfast, Michelle Chan, FRCOphth,  
425 NIHR Biomedical Research Centre, Sharon Y.L. Chua, PhD, NIHR Biomedical Research Centre, David  
426 P. Crabb, PhD, UCL, Philippa M. Cumberland, MSc, UCL Great Ormond Street Institute of Child Health,  
427 Alexander Day, PhD, NIHR Biomedical Research Centre, Parul Desai, PhD, NIHR Biomedical Research  
428 Centre, Bal Dhillon, FRCOphth, University of Edinburgh, Andrew D. Dick, FRCOphth, University of  
429 Bristol, Cathy Egan, FRCOphth, NIHR Biomedical Research Centre, Sarah Ennis, PhD, University of  
430 Southampton, Paul Foster, PhD, NIHR Biomedical Research Centre, Marcus Fruttiger, PhD, NIHR  
431 Biomedical Research Centre, John E.J. Gallacher, PhD, University of Oxford, David F. GARWAY-  
432 HEATH FRCOphth- NIHR Biomedical Research Centre, Jane Gibson, PhD, University of Southampton,  
433 Dan Gore, FRCOphth, NIHR Biomedical Research Centre, Jeremy A. Guggenheim, PhD, Cardiff

434 University, Chris J. Hammond, FRCOphth, King's College London, Alison Hardcastle, PhD, NIHR  
435 Biomedical Research Centre, Simon P. Harding, MD, University of Liverpool, Ruth E. Hogg, PhD,  
436 Queens University Belfast, Pirro Hysi, PhD, King's College London, Pearse A. Keane, MD, NIHR  
437 Biomedical Research Centre, Sir Peng T. Khaw, PhD, NIHR Biomedical Research Centre, Anthony P.  
438 Khawaja, DPhil, NIHR Biomedical Research Centre, Gerassimos Lascaratos, PhD, NIHR Biomedical  
439 Research Centre, Andrew J. Lotery, MD, University of Southampton, Tom Macgillivray, PhD, University  
440 of Edinburgh, Sarah Mackie, PhD, University of Leeds, Keith Martin, FRCOphth, University of  
441 Cambridge, Michelle McGaughey, Queen's University Belfast, Bernadette McGuinness, PhD, Queen's  
442 University Belfast, Gareth J. McKay, PhD, Queen's University Belfast, Martin McKibbin, FRCOphth,  
443 Leeds Teaching Hospitals NHS Trust, Danny Mitry, PhD, NIHR Biomedical Research Centre, Tony  
444 Moore, FRCOphth, NIHR Biomedical Research Centre, James E. Morgan, DPhil, Cardiff University,  
445 Zaynah A. Muthy, BSc, NIHR Biomedical Research Centre, Eoin O'Sullivan, MD, King's College  
446 Hospital NHS Foundation Trust, Chris G. Owen, PhD, University of London, Praveen Patel, FRCOphth,  
447 NIHR Biomedical Research Centre, Euan Paterson, BSc, Queens University Belfast, Tunde Peto, PhD,  
448 Queen's University Belfast, Axel Petzold, PhD, UCL, Jugnoo S. Rahi, PhD, UCL Great Ormond Street  
449 Institute of Child Health, Alicja R. Rudnikca, PhD, University of London, Jay Self, PhD, University of  
450 Southampton, Sobha Sivaprasad, FRCOphth, NIHR Biomedical Research Centre, David Steel,  
451 FRCOphth, Newcastle University, Irene Stratton, MSc, Gloucestershire Hospitals NHS Foundation Trust,  
452 Nicholas Strouthidis, PhD, NIHR Biomedical Research Centre, Cathie Sudlow, DPhil, University of  
453 Edinburgh, Dhanes Thomas, FRCOphth, NIHR Biomedical Research Centre, Emanuele Trucco, PhD,  
454 University of Dundee, Adnan Tufail, FRCOphth, NIHR Biomedical Research Centre, Veronique Vitart,  
455 PhD, University of Edinburgh, Stephen A. Vernon, DM, Nottingham University Hospitals NHS Trust,

456 Ananth C. Viswanathan, FRCOphth, NIHR Biomedical Research Centre, Cathy Williams, PhD,  
457 University of Bristol, Katie Williams, PhD, King's College London, Jayne V. Woodside, MRCOphth,  
458 PhD, Queen's University Belfast, Max M. Yates, PhD, University of East Anglia, Jennifer Yip, PhD,  
459 University of Cambridge, and Yalin Zheng, PhD, University of Liverpool.

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