Genetic and Environmental Factors Associated With the Ganglion Cell Complex in a Healthy Aging British Cohort

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IMPORTANTANCE Measurement of ganglion cell complex (GCC) thickness may be more sensitive than current methods for glaucoma diagnosis and research. However, little is known about the factors influencing GCC thickness in the general population.

OBJECTIVES To investigate the heritability of and factors associated with GCC thickness in a healthy aging population.

DESIGN, SETTING, AND PARTICIPANTS A cross-sectional twin study was conducted from August 27, 2014, to March 31, 2016, among 1657 participants of white British ancestry from the TwinsUK study cohort without ocular pathologic conditions. Heritability analyses were conducted in 1432 twins (426 monozygous and 290 dizygous pairs). Association analyses were performed using univariable and multivariable stepwise linear regression models, taking family structure into account. Heritability analyses were conducted using maximum likelihood structural equation twin modeling.

MAIN OUTCOMES AND MEASURES Parameters measured included GCC thickness, autorefraction, intraocular pressure, blood pressure, body mass index, and cholesterol, creatinine, glucose, insulin, triglycerides, and urea levels. Estimated glomerular filtration rate was calculated using the Modification of Diet in Renal Disease formula.

RESULTS Among the 1657 participants (mean [SD] age, 56.0 [15.3] years; 89.5% women and 10.5% men), the mean [SD] inner GCC thickness was 96.0 [7.6] μm (95% CI, 95.1-96.2). In multivariable modeling, the mean inner GCC thickness was associated with advancing age (β, -0.14; P < .001), increased body mass index (β, -0.15; P = .001), spherical equivalent (β, 0.70; P < .001), and higher estimated glomerular filtration rate (β, 0.03; P = .02). A 1-U increase in age or body mass index was associated with a 0.14-μm and 0.15-μm decrease in GCC thickness, respectively (P < .001), while a 1-U increase in spherical equivalent or estimated glomerular filtration rate was associated with a 0.70-μm (P < .001) and 0.03-μm (P = .02) increase in GCC thickness, respectively. Ganglion cell complex thickness was not associated with sex, intraocular pressure, or diabetes. Age-adjusted GCC thickness was highly heritable, with additive genetic effects explaining 81% (95% CI, 78%-84%) of phenotypic variance and individual environmental factors explaining the remaining 19% (95% CI, 16%-22%).

CONCLUSIONS AND RELEVANCE Ganglion cell complex thickness appears to be highly heritable and further genetic analysis may help identify new biological pathways for glaucoma. The results suggest it may be important to account for age, body mass index, refractive error, and sex when using GCC thickness as a diagnostic tool. Replication of their results is required, as is further research to explain the association between renal function and GCC thickness.
Glaucoma is the second leading cause of blindness worldwide, affecting up to 3% of the global population older than 40 years, and is forecasted to affect 79.6 million people worldwide by 2020.1,2 Glaucoma comprises a group of optic neuropathies characterized by progressive, irreversible visual field loss. Impaired retrograde neurotrophic transport causes dysfunction of retinal ganglion cells and, ultimately, apoptosis with axonal atrophy.3-5 As loss of retinal ganglion cells is not visible on ophthalmoscopy, glaucoma is traditionally detected using optic nerve examination and visual field tests. These tests have low sensitivity, are prone to interobserver variation, and detect changes that occur relatively late in the disease process, leading to a diagnostic delay of up to 10 years.6-9 The advent of spectral domain-optical coherence tomography (SD-OCT) has afforded the opportunity to acquire noninvasive in vivo high-resolution segmentation of the inner retinal layers.10-12 Since the macula contains up to 50% of retinal ganglion cells, it is very sensitive to early glaucomatous damage.13 Spectral domain-optical coherence tomography measurements of the macular ganglion cell complex (GCC) thickness, comprising the ganglion cell layer, the inner plexiform layer, and the retinal nerve fiber layer (RNFL), correlate closely with histologic data.14 Various studies have investigated the diagnostic ability and validity of SD-OCT parameters, concluding that both GCC and peripapillary RNFL thickness have high sensitivity, specificity, and positive predictive value for disease.15-27 It is well established that older age and higher intraocular pressure (IOP) are risk factors for primary open-angle glaucoma (POAG).28 It also has been suggested that factors such as vascular dysregulation29-32 and diabetes33 may play an important role in the development of POAG. In addition, family history is known to contribute to the risk of developing POAG28 and genetic variants have been identified that play a role in POAG and its endophenotypes.34,35 The extent to which any of these factors may influence GCC thickness in a healthy population is unclear. We undertook a cross-sectional observational study to explore the systemic and ophthalmic factors influencing GCC thickness in a healthy population of European ancestry. In particular, we focused on parameters that might be associated with microvascular damage, such as blood pressure, diabetes, and renal function. To investigate to what extent genetic factors influence GCC thickness, we used a twin model design to perform a heritability study.

Methods

Participants
All monozygous and dizygous twin pairs were volunteers in the TwinsUK study, an unselected population-based twin cohort representative of the broader population in terms of disease-associated and lifestyle characteristics.36 We assessed 1753 individuals for eligibility and included those of European ancestry and who were 18 years or older and excluded 39 not of European ancestry, 33 with treated glaucoma, 4 with ocular hypertension, 7 with other pathologic conditions affecting the retina, 12 with poor-quality SD-OCT images, and 1 with incorrect data. Zygosity was determined by a standardized questionnaire and confirmed using genome-wide genotyping of single-nucleotide polymorphisms or short tandem repeats in some monozygous twin pairs for whom genome-wide data were not available. The study was approved by the Guy’s and St. Thomas’ ethics committee and all the participants provided written informed consent in accordance with the Declaration of Helsinki.37

Clinical Examination
Data were collected between August 27, 2014, and March 31, 2016. Each participant completed a questionnaire to elicit any previous ophthalmic history. Nonophthalmic parameters were assessed, including height, weight, blood pressure, and standard blood markers relevant to microvascular disease (ie, levels of cholesterol, creatinine, glucose, insulin, triglycerides, and urea). Estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease formula.38 Ophthalmic examination on both eyes included autorefraction, pachymetry, and noncontact measurement of IOP (Visionix120; The Luneau Technology Group). Spherical equivalent (SpHk) was calculated using the standard formula of sphere + (cylinder/2). Fundus photography and SD-OCT, including mapping of GCC thickness, were performed (iVue SD-OCT; Optovue).18,19,39-41 Scans were reviewed by an ophthalmologist (E.B.) and poor-quality scans (n = 59, confirmed by K.M.W.) were excluded from the final analyses. As there was a high correlation between left and right eyes for all measurements (Pearson correlation coefficient, >0.7), we used the mean of the 2 eyes when both eyes were available.

Statistical Analysis
Differences between monozygous and dizygous twins, or between any other group (eg, participants with hypertension or diabetes vs controls), were compared using 2-sample, 2-tailed t tests or z tests, assuming equal variance. Associations were assessed between GCC thickness and the following 14 factors: age, sex, body mass index (BMI; calculated as weight in kilograms divided by height in meters squared), diabetes status, blood pressure (systolic and diastolic), 2 ophthalmic parameters (SpHk and IOP), and 6 blood markers (levels of cholesterol, creatinine, glucose, insulin, triglycerides, and urea).
Univariable linear regression analyses were performed, followed by a multivariable linear regression model for factors with an association significant at \( P < .05 \) in the univariable model. Independent variables were identified using stepwise backward procedure with a threshold for removal set at \( P < .05 \). Variables that, in the multivariable model, would survive Bonferroni correction for multiple testing (\( P < .004; 0.05 \) divided by 14, where 14 is the number of independent variables tested), were considered associated with GCC thickness. Mean arterial pressure and eGFR are not independent variables, as they are calculated from these variables, so they do not affect the Bonferroni correction threshold. In all regression models, family structure was taken into account.

All analyses, except for the heritability, were carried out using STATA, version 14, statistical package (StataCorp). Heritability analyses were performed using maximum likelihood structural equation twin modeling implemented in the OpenMx package in R (http://openmx.psyc.virginia.edu). We compared the phenotypic variance between monozygous and dizygous twins to estimate the extent to which GCC thickness was a result of additive or dominant genetic effects and common or unique environmental factors. The goodness of fit of the full and reduced additive, common, and unique (ACE) or additive, dominant, and unique (ADE) models was compared with the observed data and the best-fitting model was selected. Before the heritability analysis, GCC thickness was adjusted with the observed data and the best-fitting model was selected. Independent variable were identified using stepwise backward procedure with a threshold for removal set at \( P < .05 \).

### Results

Data on GCC thickness were acquired from 3235 eyes of 1657 predominantly female (89.5%) participants, whose demographic and clinical characteristics are presented in Table 1. We excluded 39 individuals of non-European ancestry, 44 with ocular pathologic conditions, and 13 for other reasons. The individuals who were excluded for ocular pathologic conditions or other reasons were a mean of 14.3 years older than the remaining participants, who were a mean (SD) age of 56.0 (15.3) years (range, 18-90 years). Monozygous twins were on average younger than the dizygous twins (54 vs 59 years) and had thicker mean GCC (96.4 vs 95.3 μm; \( P < .01 \)). Monozygous and dizygous twins also had different mean (SD) values for the following parameters: BMI (25.6 [0.16] vs 26.5 [0.21]), SphE (–0.21 [0.08] vs 0.15 [0.10] diopeters), systolic blood pressure (126.3 [0.58] vs 128.9 [0.66] mm Hg), and serum cholesterol level (206.95 [1.54] vs 212.36 [1.54] mg/dL [to convert to millimoles per liter, multiply by 0.0259]). In multivariable stepwise regression analyses. On univariable analysis, the mean GCC was thinner with advancing age (β [SE], –0.12 [0.02]; \( P < .001 \)), increased BMI (β [SE], –0.19 [0.04]; \( P < .001 \)), and higher systolic (β [SE], –0.06 [0.01]; \( P < .001 \)) and diastolic blood pressures (β [SE], –0.06 [0.02]; \( P = .003 \)). The association with systolic and diastolic blood pressure survived adjustment for hypertension status (β [SE], –0.05 [0.01]; \( P < .001 \)).

### Table 1. Demographic and Clinical Characteristics of the Study Population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>56.0 (15.3)</td>
</tr>
<tr>
<td>Height, mean (SD), m</td>
<td>Women 1.6 (0.1)</td>
</tr>
<tr>
<td></td>
<td>Men 1.7 (0.1)</td>
</tr>
<tr>
<td>Weight, mean (SD), kg</td>
<td>Women 68.6 (13.2)</td>
</tr>
<tr>
<td></td>
<td>Men 82.6 (16.4)</td>
</tr>
<tr>
<td>Body mass index, mean (SD)*</td>
<td>26.2 (5.1)</td>
</tr>
<tr>
<td></td>
<td>Women 26.1 (4.9)</td>
</tr>
<tr>
<td></td>
<td>Men 27.3 (4.5)</td>
</tr>
<tr>
<td>Blood pressure, mean (SD), mm Hg</td>
<td>Systolic 127.3 (17.4)</td>
</tr>
<tr>
<td></td>
<td>Diastolic 75.8 (10.6)</td>
</tr>
<tr>
<td>Female sex, No. (%)</td>
<td>1483 (89.5)</td>
</tr>
<tr>
<td>Diabetes, No. (%)</td>
<td>190 (11.5)</td>
</tr>
<tr>
<td>Hypertension, No. (%)</td>
<td>290 (17.5)</td>
</tr>
<tr>
<td>Receiving antihypertensive treatment, No. (%)</td>
<td>213 (12.9)</td>
</tr>
<tr>
<td>IOP, mean (SD), mm Hg</td>
<td>Women 13.3 (2.6)</td>
</tr>
<tr>
<td></td>
<td>Men 1.6 (0.1)</td>
</tr>
<tr>
<td>SphE, mean (SD), diopters</td>
<td>–0.1 (2.4)</td>
</tr>
<tr>
<td>CCT, mean (SD), μm</td>
<td>536.2 (35.6)</td>
</tr>
<tr>
<td>Total cholesterol, mean (SD), mg/dL</td>
<td>208.5 (42.5)</td>
</tr>
<tr>
<td>Creatinine, mean (SD), mg/dL</td>
<td>0.83 (0.15)</td>
</tr>
<tr>
<td>Glucose, mean (SD), mg/dL</td>
<td>86.5 (10.8)</td>
</tr>
<tr>
<td>Insulin, mean (SD), μIU/mL</td>
<td>49.1 (32.2)</td>
</tr>
<tr>
<td>Total triglycerides, mean (SD), mg/dL</td>
<td>88.5 (53.1)</td>
</tr>
<tr>
<td>Urea, mean (SD), mg/dL</td>
<td>32.43 (6.6)</td>
</tr>
</tbody>
</table>

* Calculated as weight in kilograms divided by height in meters squared.

Abbreviations: CCT, central corneal thickness; IOP, intraocular pressure; SphE, spherical equivalent.

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of age, hypertension, and diabetes status (β, 0.03; P < .001). Higher eGFR was associated with a thicker GCC, independent of age, hypertension, and diabetes status (β, 0.03; P = .02).

Finally, we calculated the heritability of GCC thickness in 1432 twins (426 monozygous and 290 dizygous pairs), as 225 individuals had their twin missing. We found the best-fitting model to be the additive genetic and unique environment (AE) model, in which 81% (95% CI, 78%-84%) of variance in age-adjusted GCC thickness was explained by additive genetic factors and the remaining 19% (95% CI, 16%-22%) by unique environmental factors.

Discussion

Many cross-sectional and longitudinal studies have investigated the effects of age, sex, race/ethnicity, IOP, and axial length on RNFL thickness. 47-54 As GCC incorporates RNFL, the 2 variables are correlated (Pearson correlation coefficient, 0.76 in this sample) and likely share risk factors. However, we set out to examine the associations in a large population-based epidemiologic study of GCC thickness in healthy European individuals and found it to be strongly and independently associated with age, BMI, SphE, and eGFR. Except for eGFR, all the other parameters survived correction for multiple testing.

With respect to age, our results are similar to those previously found for RNFL. 55-57 We found, cross-sectionally, a thinner GCC with older age (a mean decrease of 0.14 μm per year). The effect we found is comparable with that found by Zhang et al54 in 92 controls (0.17 μm per year) in the Advanced Imaging for Glaucoma Study. In contrast, the association between RNFL and BMI is more variable. Morbid obesity had a significant influence on RNFL, retinal ganglion cells, and choroidal thickness in 1 study, 58 while others suggest that BMI plays a role in RNFL thickness only in men59 or not at all. 60 The UK Biobank study found a significant negative association between macular thickness and both BMI and male sex, 56 which is in keeping with our study findings of a reduction in GCC thickness of 0.15 μm per 1-U increase in BMI. Owing to the small number of male participants in this study, we were underpowered to detect sex effects; however, the direction of effect was the same in the 2 groups (β, -0.19 and P < .001 for women; β, -0.28 and P = .20 for men).

Studies of RNFL thickness from the European Prospective Investigation Into Cancer and Nutrition (EPIC)-Norfolk and UK Biobank cohorts found RNFL and macular thickness to be thinner in men than in women. 55,56 Wang et al60 found no sex differences in the mean thickness of GCC and ganglion cells and the inner plexiform layer in a Chinese cohort. However, while Mwanza et al61 did not find a difference between the sexes for mean thickness of ganglion cells and the inner plexiform layer (P = .36), they did find that male sex was associated with GCC thickness in multivariate analysis with RNFL thickness, age, and axial length (β, -1.62; P = .005). We did not observe a difference in mean (SD) GCC thickness between the 174 men (95.7 [7.98] μm) and 1483 women (96.1 [7.45] μm; P = .69) in our study.

Of the ophthalmic parameters, GCC thickness was associated only with SphE, with more myopic eyes having a thinner GCC and a mean increase in thickness of 0.70 μm per 1 diopter increase in SphE. Previous studies have proposed that longer axial length is associated with thinner RNFL. 62-64 However, Khawaja et al65 using scanning laser polarimetry in the EPIC-Norfolk study, found that longer axial length appeared to be associated with a thicker RNFL. There is some controversy as to the possible magnification effects of the eye with increasing ametropia, which is not routinely corrected for by SD-OCT software. 55,65,66 Some studies using SD-OCT have found that this association reversed once ocular magnification was mathematically corrected. 65,67 Patel et al66 demonstrated that, on results of SD-OCT, increasing myopia was associated with increased central macular thickness but a decrease in the other macular subfield thicknesses, resulting in an overall positive association with refractive error. Optical coherence tomography also has been shown to be more repeatable and sensitive than glaucoma diagnoses by scanning laser polarimetry at detecting glaucoma in cases of high myopia. 60,68-72 Irrespective of whether the effect is physiological or owing to optics, we propose that future studies of GCC

Table 2. Univariable and Multivariable Linear Regression Analysis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>β (SE) Univariable</th>
<th>P Value Univariable</th>
<th>β (SE) Multivariable</th>
<th>P Value Multivariable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>-0.12 (0.02)</td>
<td>&lt;.001</td>
<td>-0.14 (0.02)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Sex</td>
<td>0.31 (0.77)</td>
<td>.69</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body mass index</td>
<td>-0.19 (0.04)</td>
<td>&lt;.001</td>
<td>-0.15 (0.04)</td>
<td>.001</td>
</tr>
<tr>
<td>Blood pressure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>-0.06 (0.01)</td>
<td>&lt;.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diastolic</td>
<td>-0.06 (0.02)</td>
<td>.003</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>-0.91 (0.47)</td>
<td>.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spherical equivalent</td>
<td>0.45 (0.09)</td>
<td>&lt;.001</td>
<td>0.70 (0.09)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Intraocular pressure</td>
<td>0.05 (0.08)</td>
<td>.51</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>-0.01 (0.01)</td>
<td>.27</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine</td>
<td>-2.69 (1.28)</td>
<td>.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose</td>
<td>-0.27 (0.03)</td>
<td>.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td>-0.02 (0.01)</td>
<td>.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total triglycerides</td>
<td>-0.01 (0.004)</td>
<td>.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urea</td>
<td>-3.42 (0.90)</td>
<td>&lt;.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

0.70 [0.09]; P < .001, and increased BMI (β [SE], -0.15 [0.04]; P = .001) only; these associations would survive correction for multiple testing (Bonferroni threshold, P ≤ .004).

Given the possible connection between GCC thickness and both blood pressure42-44 and kidney function,45 we explored associated parameters even though they did not survive the multivariable analysis. We first examined if mean arterial pressure, which is considered to be a better marker of organ perfusion,46 was associated with GCC thickness. The mean arterial pressure in our study was a mean (SD) of 92.9 (12.1) mm Hg. Similar to systolic and diastolic blood pressure, mean arterial pressure was associated with GCC thickness, irrespective of hypertension status (β, -0.06; P < .001), but not when adjusted for age (β, -0.03; P = .13). Next, we looked at whether GCC thickness was associated with the eGFR. In our study, the mean (SD) eGFR was 82.5 (19.6) mL/min/1.73m². Higher eGFR was associated with a thicker GCC, independent of age, hypertension, and diabetes status (β, 0.03; P = .02).

Discussion

Many cross-sectional and longitudinal studies have investigated the effects of age, sex, race/ethnicity, IOP, and axial length on RNFL thickness. 47-54 As GCC incorporates RNFL, the 2 variables are correlated (Pearson correlation coefficient, 0.76 in this sample) and likely share risk factors. However, we set out to examine the associations in a large population-based epidemiologic study of GCC thickness in healthy European individuals and found it to be strongly and independently associated with age, BMI, SphE, and eGFR. Except for eGFR, all the other parameters survived correction for multiple testing.

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should consider adjusting for SphE or axial length, given their strong association with GCC thickness.

Although IOP is a known risk factor for POAG, we were not able to identify an association between IOP and GCC thickness in our study. However, this is in agreement with the findings from RNFL association studies, such as the EPIC-Norfolk, UK Biobank, and Advanced Imaging for Glaucoma Study groups.54-56 It is possible that our exclusion of individuals taking IOP-lowering medication diminished the association with GCC thickness, although we excluded only 37 individuals on this criterion. Furthermore, there is increasing evidence for the role of the association between IOP and intracranial pressure, known as the translaminar pressure difference, in the pathophysiologic cause of glaucoma.73,74 It may be that the IOP does not damage retinal ganglion cell axons at the lamina cribrosa until it reaches a given threshold, which would, in part, further explain the pathophysiologic cause of normal-tension glaucoma.

Vascular dysregulation has been proposed to play an important role in POAG29-32 and several recent studies have suggested that systemic hypertension is associated with RNFL and GCC thinning, which may represent an important consideration when using retinal SD-OCT measurements as a diagnostic tool.42-44 Therefore, in this study, we explored the association between GCC thickness and blood pressure (systolic, diastolic, and mean arterial pressure). We did find GCC to be thinner in individuals with hypertension (94.3 μm) vs those with normal blood pressure (96.3 μm; P < .001), and an increase in any of the blood pressure parameters was associated with GCC thickness in univariable analyses. However, this association was small (β, -0.06 μm) and not independent from the effect of age.

Similarly, some studies have shown diabetes to have an early neurodegenerative effect on the retina, causing neuronal dysfunction, leading to thinning of both the RNFL and GCC, with associated functional visual deficits.75-82 Chhablani et al79 showed that inner retinal thinning was present in patients with type 2 diabetes, even before signs of retinopathy were visible, while Salvi et al80 showed a significant association of GCC thinning in patients with diabetic polyneuropathy but not in those with retinopathy. We did not find an association between a diagnosis of diabetes and GCC thickness, nor with fasting serum glucose and insulin levels. The participants in the TwinsUK study cohort are generally healthy, so we may be underpowered to detect effects specific to hypertension or diabetes, although our study did include 290 and 190 participants with these respective diagnoses.

Finally, we found eGFR to be associated with mean GCC thickness. The association survived correction for the effects of age, diabetes, and hypertension, accounting for a 0.03-μm change in GCC thickness per 1-U change in eGFR. This finding suggests that there may be an association between renal function and retinal neuropathy. Srivastav et al83 found an association between increased serum urea and creatinine levels and decreased RNFL thickness in patients with diabetes, while Shim et al84 recently demonstrated that low eGFR levels are independently associated with POAG. However, there is a paucity of data regarding this potential association in the absence of diabetes. One study, by Demir et al,45 evaluated the RNFL thickness in patients with chronic renal failure without diabetes, concluding that it was significantly thinner than normal. Our data are consistent with this notion, but further investigation is required to elucidate the underlying association. It is accepted that the kidneys and retina share common developmental pathways and structural similarities, such as the vascular configuration and type IV collagen basement-membrane composition.85 Therefore, if renal function correlates with retinal neuronal anatomy in a healthy population, it may become a factor to consider in the interpretation of GCC thickness as a diagnostic parameter.

This is the first study, to our knowledge, that explores the heritability of GCC thickness. We found GCC thickness to be highly heritable, with additive genetic effects accounting for 81% of variance, while unique environmental effects explained the remaining 19% of variance. This finding is comparable with the heritability estimates for central retinal thickness (90%) and RNFL thickness (between 48% and 82%).86-88 It would be interesting to explore whether any of the known genetic risk factors for POAG and its other endophenotypes also influence GCC thickness. Alleles in SIX1-SIX6 (GenBank: 6495 and 4990, respectively) have been associated with POAG genome-wide association studies, and with a decrease in global and sectoral RNFL thickness in individuals of European and Asian descent.89-91

Limitations
This study contains some limitations. First, the TwinsUK study cohort is predominantly females of European ancestry, limiting our ability to draw conclusions as to the effect of sex or race/ethnicity on GCC thickness. As this is a cross-sectional study, we cannot draw any conclusions on causation and, as an observational study, we are potentially susceptible to residual confounding and missing data. As we relied on self-reported ocular and systemic disease, as well as drug history, we may be liable to misspecification of variables. Our novel findings require replication.

Conclusions
Ganglion cell complex thickness is a highly heritable trait. We identified an association between SD-OCT–derived GCC thickness measurements and age, refractive error, BMI, and eGFR in a healthy, aging, predominantly female cohort of European descent. The associations between SphE, BMI, and age are strong and therefore adjustment is likely to be relevant if GCC thickness were to be used as a clinical parameter. Future studies of GCC and its association with glaucoma or neurologic disease should take these associations into account. We did not find GCC thickness to be independently associated with sex, diabetes, blood pressure, or IOP. Further studies are required to establish the precise association between renal function and inner retinal structures and to investigate the genetic factors underlying GCC thickness.
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REFERENCES


