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Comparison of Associations with Different Macular Inner Retinal Thickness Parameters in a Large Cohort

The UK Biobank

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Purpose: To describe and compare associations with macular retinal nerve fiber layer (mRNFL), ganglion cell complex (GCC), and ganglion cell–inner plexiform layer (GCIPL) thicknesses in a large cohort.

Design: Cross-sectional study.

Participants: We included 42 044 participants in the UK Biobank. The mean age was 56 years.

Methods: Spectral-domain OCT macular images were segmented and analyzed. Corneal-compensated intraocular pressure (IOPcc) was measured with the Ocular Response Analyzer (Reichert, Corp., Buffalo, NY). Multivariable linear regression was used to examine associations with mean mRNFL, GCC, and GCIPL thicknesses. Factors examined were age, sex, ethnicity, height, body mass index (BMI), smoking status, alcohol intake, Townsend deprivation index, education level, diabetes status, spherical equivalent, and IOPcc.

Main Outcome Measures: Thicknesses of mRNFL, GCC, and GCIPL.

Results: We identified several novel independent associations with thinner inner retinal thickness. Thinner inner retina was associated with alcohol intake (most significant for GCIPL: −0.46 μm for daily or almost daily intake compared with special occasion only or never [95% confidence interval (CI), 0.61–0.30]; $P = 1.1\times10^{-8}$), greater social deprivation (most significant for GCIPL: −0.28 μm for most deprived quartile compared with least deprived quartile [95% CI, −0.42 to −0.14]; $P = 6.6\times10^{-5}$), lower educational attainment (most significant for mRNFL: −0.36 μm for less than O level compared with degree level [95% CI, −0.45 to 0.26]; $P = 2.3\times10^{-14}$), and nonwhite ethnicity (most significant for mRNFL comparing blacks with whites: −1.65 μm [95% CI, −1.86 to −1.43]; $P = 2.4\times10^{-50}$). Corneal-compensated intraocular pressure was associated most significantly with GCIPL (−0.04 μm/mmHg [95% CI, −0.05 to −0.03]; $P = 4.0\times10^{-10}$) and was not associated significantly with mRNFL (0.00 μm/mmHg [95% CI, −0.01 to 0.01]; $P = 0.77$). The variables examined explained a greater proportion of the variance of GCIPL (11%) than GCC (6%) or mRNFL (7%).

Conclusions: The novel associations we identified may be important to consider when using inner retinal parameters as a diagnostic tool. Associations generally were strongest with GCIPL, particularly for IOP. This suggests that GCIPL may be the superior inner retinal biomarker for macular pathophysiologic processes and especially for glaucoma. *Ophthalmology 2019;■:1–10 © 2019 by the American Academy of Ophthalmology*

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Damage to macular retinal ganglion cells occurs early in glaucoma,[1] and spectral-domain (SD) OCT measurements of the inner retina at the macula have been shown to be useful for detecting glaucoma.[2,3] Different commercially available SD OCT devices report different segments of inner retinal macular thickness; commonly reported segments are the ganglion cell complex (GCC; macular retinal nerve fiber layer [mRNFL] + ganglion cell layer [GCL] + inner plexiform layer [IPL]) and the ganglion cell–inner plexiform layer (GCIPL; GCL + IPL). Both GCC and GCIPL thickness have been reported to be comparable with circumpapillary retinal nerve fiber layer (cRNFL) thickness at diagnosing glaucoma.[4,5] Macular GCC and GCIPL measurements have been shown to be helpful in the detection of glaucoma progression[6,7] and may be superior to cRNFL measurements at detecting progression in severe disease.[8–10] A meta-analysis reports similar accuracy of GCC and GCIPL measurements for glaucoma diagnosis,[11]

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which is in agreement with studies that conducted head-to-head comparisons of GCC and GCIPL diagnostic accuracy within the same study participants.[12–14]

Understanding epidemiologic associations with macular inner retinal measurements is important to help define normal ranges in population subgroups and may shed light on pathophysiologic mechanisms underlying glaucoma. Comparing strengths of associations among mRNFL, GCC, and GCIPL measurements may provide insight into their relative potential as biomarkers. Using data from a very large adult cohort, the UK Biobank, we aimed to describe and compare basic demographic, socioeconomic, anthropometric, lifestyle, and ocular associations with mRNFL, GCC, and GCIPL.

Methods

UK Biobank

The UK Biobank is a very large multisite cohort study established by the Medical Research Council, Department of Health, Wellcome Trust medical charity, Scottish Government, and Northwest Regional Development Agency. Detailed study protocols are available online (http://www.ukbiobank.ac.uk/resources/ and http://biobank.ctsu.ox.ac.uk/crystal/docs.cgi). A baseline questionnaire, physical measurements, and biological samples were undertaken in 22 assessment centers across the United Kingdom between 2006 and 2010. All United Kingdom residents 40 to 69 years of age who were registered with the National Health Service and living up to 25 miles from a study center were invited to participate. The study was conducted with the approval of the North-West Research Ethics Committee (reference, 06/MRE08/65), in accordance with the principles of the Declaration of Helsinki, and all participants gave written informed consent. This research has been conducted using the UK Biobank Resource under application number 2112.

Participants completed a touch-screen self-administered questionnaire and underwent physical examination at a baseline assessment. Table 1 summarizes the ascertainment of the baseline assessment variables used in the current study. Body mass index (BMI) was calculated as weight in kilograms per height in square meters. We selected these variables a priori to examine the basic descriptive epidemiologic features of inner retinal morphologic characteristics, including demographic, socioeconomic, anthropometric, and basic lifestyle factors. We additionally examined diabetes status as a potentially important confounder, given that diabetes is relatively common and has known retinal sequalae.

Ophthalmic Assessment

Ophthalmic assessment was not part of the original baseline assessment and was introduced as an enhancement in 2009 for 6 assessment centers that are spread across the United Kingdom (Liverpool and Sheffield in North England, Birmingham in the Midlands, Swansea in Wales, and Croydon and Hounslow in greater London). Spectral-domain OCT imaging of both eyes was performed using the Topcon 3D OCT-1000 Mark II (Topcon, Inc., Tokyo, Japan) in a dark room without pupil dilation using the 3-dimensional 6×6-mm^2 macular volume scan mode (512 A scans per B scan; 128 horizontal B scans in a raster pattern). The right eye was imaged first. Version 1.6.1.1 of the Topcon Advanced Boundary Segmentation (TABS) algorithm was used to delineate the inner and outer retinal surfaces.[15] Quality control to exclude images of poor quality was described in detail previously.[16] We excluded scans with an image quality score (signal strength) less than 45. Additionally, several segmentation indicators were calculated that also identified poor scan quality or segmentation failures; we excluded the poorest 20% of images for each of these indicators. The inner limiting membrane indicator was a measure of the minimum localized edge strength around the inner limiting membrane boundary across the entire scan; this is useful for identifying blinks, scans that contain regions of severe signal fading, and segmentation errors. The validity count indicator is used to identify scans with a significant degree of clipping in the OCT scan's z-axis dimension. The motion indicators use both the nerve fiber layer and the full retinal thicknesses, from which Pearson correlations and absolute differences between the thickness data from each set of consecutive B-scans are calculated. The lowest correlation and the highest absolute difference in a scan serve as the resulting indicator scores and identify blinks, eye motion artifacts, and segmentation failures. The image quality score and the aforementioned indicators usually are highly correlated. We used average thickness parameters derived from the macula 6 grid. Participant-level mRNFL, GCC, and GCIPL thicknesses (in micrometers) were calculated as the mean of right and left eye values for each participant with good-quality images available for both eyes. If data were available only for 1 eye, we considered that value for the participant.

Participant intraocular pressure (IOP; in millimeters of mercury) was measured once for each eye using the Ocular Response Analyzer (ORA; Reichert, Corp., Buffalo, NY). Participants who reported eye surgery within the previous 4 weeks or participants reporting an eye infection were precluded from having IOP measured. The ORA is a noncontact tonometer that measures the force required to flatten the cornea using a jet of air. Unlike conventional noncontact tonometry, the ORA measures 2 pressures: first, when the cornea flattens on inward motion, and second, when the cornea is flattened on outward motion. The average of these 2 pressures has been calibrated to derive a Goldmann-correlated IOP (IOPg), and the difference between these 2 pressures has been shown to be related to the biomechanical properties of the cornea.[17] A linear combination of these 2 pressures has been developed to derive a corneal-compensated IOP (IOPcc).[18] We used IOPcc for our primary analyses because it is thought to provide the most accurate assessment of true IOP and to be least affected by corneal properties.[19] To handle extreme values of IOP, we excluded the top and bottom 0.5% of IOP measurements. We excluded participants with a history of laser or surgery for glaucoma, eye injury, corneal graft surgery, or refractive laser surgery because these participants are likely to have IOP that has been altered from physiologic levels. For patients using IOP-lowering medication (n = 1151), we imputed pretreatment IOP by dividing by 0.7 based on the mean IOP reduction achieved by medication.[20] This approach has been used successfully in genome-wide association studies of IOP.[21,22] Additionally, in sensitivity analyses, we used IOPg with imputed pretreatment IOP and also IOPg and IOPcc after exclusion of participants using IOP-lowering medication. Refractive status of both eyes was measured by autorefraction (Tomey RC5000; Erlangen-Tennenlohe). Spherical equivalent was calculated as the sphere + 0.5 × cylinder. We excluded participant eyes with high refractive error (<−6 diopters [D] or >+6 D). We calculated participant-level IOP and spherical equivalent as the mean of right and left eye values if data were available for both or as either the right or left eye value if data were available for only 1 eye.

Table 1. Baseline Assessment Details for Variables Analyzed in the Current Study

Variable	Assessment Details
Touch-screen self-administered questionnaire	
Ethnicity	Response options included: white (English/Irish or other white background), Asian or British Asian (Indian/Pakistani/Bangladeshi or other Asian background), black or black British (Caribbean, African, or other black background), Chinese, mixed (white and black Caribbean or African, white and Asian, or other mixed background), or other ethnic group (not defined).
Smoking status	Determined by response to "Do you smoke tobacco now?" and "In the past, how often have you smoked tobacco?"
Alcohol intake	Determined by response to "About how often do you drink alcohol?" (options: daily or almost daily, 3 or 4 times a week, once or twice weekly; 1 to 3 times monthly; special occasions only; never).
Townsend deprivation index	Determined according to participant post code at recruitment and the corresponding output area from the preceding national census. The index was calculated based on the output area's employment status, home and car ownership, and household condition; the higher and more positive the index, the more deprived an area.
Education level	Determined by response to "Which of the following qualifications do you have (you can select more than one)?" (options: college or university degree; A levels/AS levels or equivalent; O levels/GCSEs or equivalent; CSEs or equivalent; NVQ or HND or HNC or equivalent; other professional qualifications, e.g., nursing, teaching; none of the above). For analyses, qualifications lower than "O level/GCSEs or equivalent" were considered together as "less than O level."
Diabetes status	Determined as those who answered yes to "Has a doctor ever told you that you have diabetes?"
Physical measures	
Weight	BV-418 MA body composition analyzer (Tanita, Arlington Heights, IL)
Height	Seca 202 height measure (Seca, Birmingham, United Kingdom)

A level = Advanced level; AS level = Advanced subsidiary level; CSE = Certificate of Secondary Education; GCSE = General Certificate of Secondary Education; HNC = Higher National Certificate; HND = Higher National Diploma; NVQ = National Vocational Qualification.

Statistical Analyses

Demographic, systemic, and ocular characteristics for included participants were described, stratified by sex. Comparisons between men and women for each of the variables were made using the independent sample *t* test for continuous variables and the chi-square test for categorical variables. We first examined crude associations with mRNFL, GCC, and GCIPL thicknesses using univariable linear regression. Variables significantly associated with any of mRNFL, GCC, or GCIPL thicknesses at a $P < 0.01$ level then were considered together in a multivariable linear regression model for each of mRNFL, GCC, and GCIPL thickness. Given that weight and BMI are correlated highly, we considered only 1 of the parameters in multivariable analyses; we selected BMI based on stronger univariable associations. Similarly, given that IOPg and IOPcc are correlated highly, we considered only 1 of the parameters in multivariable analyses; IOPcc was selected on the basis that it better reflects true physiologic IOP.[19] To determine whether the associations we identified were driven primarily by participants with established glaucoma, we carried out the same multivariable analyses after exclusion of participants with self-reported (touch-screen questionnaire) or hospital admission coded (International Classification of Disease, Tenth Edition) glaucoma, and excluding any participants using IOP-lowering medication (n = 41 449 after exclusion of 595 participants). We also conducted sensitivity analyses for the associations of mRNFL, GCC, and GCIPL thicknesses with IOP for primary analyses included IOP measurements that were imputed for pretreatment levels in participants using glaucoma medication. First, rather than imputing pretreatment IOP, we conducted analyses using current IOP, even if the patient was using IOP-lowering medication, and additional analyses excluding participants using IOP-lowering medication. Second, we conducted further analyses using IOPg rather than IOPcc. To examine how much of mRNFL, GCC, and GCIPL thickness variances are explained by the factors we examined, we calculated R^2 statistics for the multivariate regression models. Stata software version 15.1 (StataCorp LP, College Station, TX) was used for all statistical analyses.

Results

In total, SD OCT images from 67 310 UK Biobank participants were available at the time of this analysis. After image segmentation and quality control, 45 815 participants with mRNFL, GCC, and GCIPL thickness measurements remained. Complete data were available for all exposure (age, sex, ethnicity, weight, height, BMI, smoking status, alcohol intake, deprivation score, diabetes status, education level, spherical equivalent, IOP) and retinal thickness variables for 42 044 participants; all analyses were conducted using these participants. The mean age of included participants was 56 years and 53% were women. Table 2 summarizes mean mRNFL, GCC, and GCIPL thicknesses as well as demographic, systemic, and ocular factors for included participants.

Univariable associations with mRNFL, GCC, and GCIPL thicknesses are shown in Table 3. Significant associations were found with at least 1 of mRNFL, GCC, and GCIPL thicknesses for all examined variables except for height, which was not associated significantly with any thickness parameter (all $P > 0.30$; Table 3). Therefore, height was not carried forward for the multivariable analyses. Both weight and BMI were associated significantly with all 3 thickness parameters; given their collinearity, only BMI was carried forward for multivariable analyses, as described in Methods. Both IOPg and IOPcc were associated significantly with GCC and GCIPL thicknesses (both $P < 0.001$) but not with mRNFL thickness (both $P \geq 0.12$). Given the collinearity between IOPg and IOPcc, only IOPcc was carried forward for multivariate analyses, as detailed in "Methods."

Multivariable associations with mRNFL, GCC, and GCIPL thicknesses are shown in Table 4. Age was associated strongly with a thinner mRNFL, GCC, and GCIPL; the association appeared stronger for GCC and GCIPL thickness than for mRNFL thickness. Related to the strength of association and the very large sample size, the *P* values for associations with age were extremely small; for GCC and GCIPL thickness, the *P* values were smaller than can be handled by most modern statistical software ($P < 10^{-300}$). Men had significantly thinner mRNFL and GCC than women (both $P \leq 7.1 \times 10^{-23}$) and thinner GCIPL

Table 2. Demographic, Systemic, and Ocular Characteristics for Included Participants (n = 42 044)

Characteristic	Data
Age, mean (SD)	56.4 (8.1)
Gender, no. (%)	
Female	22 332 (53)
Male	19 712 (47)
Ethnicity, no. (%)	
White	38 509 (92)
Asian	1163 (3)
Black	1234 (3)
Other/mixed	1138 (3)
Weight (kg), mean (SD)	78.1 (15.3)
Height (cm), mean (SD)	169.0 (9.2)
Body mass index (kg/m^2), mean (SD)	27.3 (4.4)
Smoking status, no. (%)	
Never	23 052 (55)
Previous	14 869 (35)
Current	4123 (10)
Alcohol intake	
Never or special occasion only	8237 (20)
1–3 times per month	4771 (11)
1–2 times per week	10 557 (25)
3–4 times per week	9610 (23)
Daily or almost daily	8869 (21)
Townsend deprivation index, no. (%)	
Least deprived quartile	10 721 (25)
Second quartile	10 748 (26)
Third quartile	10 487 (25)
Most deprived quartile	10 088 (24)
Education level, no. (%)	
Less than O level	13 215 (31)
O level	8919 (21)
A Level	5007 (12)
Degree	14 903 (35)
Diabetes (self-report), no. (%)	
No	39 955 (95)
Yes	2089 (5)
Spherical equivalent (diopters), mean (SD)	0.001 (1.9)
IOPg (mmHg), mean (SD)	15.66 (3.59)
IOPcc (mmHg), mean (SD)	15.83 (3.60)
mRNFL (μm), mean (SD)	28.91 (3.83)
GCC (μm), mean (SD)	104.15 (7.56)
GCIPL (μm), mean (SD)	75.24 (5.19)

GCC = ganglion cell complex; GCIPL = ganglion cell–inner plexiform layer; IOPcc = corneal-compensated intraocular pressure; IOPg = Goldmann-correlated intraocular pressure; mRNFL = macular retinal nerve fiber layer; SD = standard deviation.

of borderline significance ($P = 0.042$). Asian and black participants showed thinner mRNFL, GCC, and GCIPL than white participants. Participants with higher BMI had thinner mRNFL, GCC, and GCIPL (all $P \leq 1.5\times10^{-8}$). Daily or almost daily alcohol intake was associated with thinner mRNFL, GCC, and GCIPL when compared with participants who drank least (never or special occasions only). There was no significant difference in thickness parameters for participants reporting less frequent alcohol intake (Table 4). Participants in the most deprived quartile of the Townsend deprivation index had significantly thinner GCC and GCIPL (both $P \leq 1.2\times10^{-4}$) than participants in the least deprived quartile; the difference was borderline significant only for mRNFL thickness ($P = 0.012$). There was evidence of progressively thicker mRNFL, GCC, and GCIPL with higher educational attainment (Table 4). Participants with self-reported diabetes had thinner mRNFL, GCC, and GCIPL (all $P < 0.003$). There were very strong and highly significant associations between thickness parameters and spherical equivalent, and these were in different directions for mRNFL compared with GCC and GCIPL. A more myopic refraction was associated with a thicker mRNFL ($P = 1.1\times10^{-251}$) but a thinner GCC ($P = 1.2\times10^{-93}$) and GCIPL ($P < 10^{-300}$). Corneal-compensated IOP was not associated with mRNFL but was associated negatively with both GCC ($P = 5.8\times10^{-5}$) and GCIPL ($P = 4.0\times10^{-10}$) thickness. Of the 3 multivariable models, the R^2 was greatest for the GCIPL model, indicating that the explanatory variables we assessed explained more of the variance of GCIPL thickness (11%) than mRNFL (7%) or GCC (6%) thickness (Table 4). The same multivariable analyses also were conducted after exclusion of participants using glaucoma medication, self-reported glaucoma, or both or hospital International Classification of Disease, Tenth Edition, coded glaucoma (Table S1, available at www.aaojournal.org). Associations were very similar for all variables apart from IOP, for which the associations were less significant. There was no longer a significant association between IOP and GCC, and the association between IOP and GCIPL was less significant ($P = 3.9\times10^{-5}$).

We also conducted sensitivity analyses for the associations between IOP and inner retinal thickness measures, as described in Methods. Results were similar when we examined IOPg instead of IOPcc (Table 5). Also, results were similar if we either excluded participants using IOP-lowering medication or used current treated IOP, rather than imputing the pretreatment IOP (Table 5). For all analyses, IOP was not associated with mRNFL and was associated more significantly with GCIPL than GCC. Again, the model R^2 value was greatest for the GCIPL models (Table 5).

Discussion

Our study is the largest to date examining the epidemiologic features of macular inner retinal anatomic characteristics, to the best of our knowledge. We confirmed previously reported associations with age, sex, BMI, diabetes, and refractive error and identified multiple novel associations with thinner inner retina at the macula, including nonwhite ethnicity, frequent alcohol intake, greater social deprivation, lower educational attainment, and higher IOP. Our study also examines how epidemiologic associations vary between different inner retinal parameters, namely mRNFL, GCC, and GCIPL thickness.

Older age was associated strongly with thinner inner retinal thickness, in agreement with previous studies.[23–26] This association was apparent for all 3 inner retinal parameters but was strongest and most significant for GCC and GCIPL thickness. Although it is not possible to infer a causal effect of inner retinal thinning because of aging from a cross-sectional study, it is unlikely an association this strong is the result of a cohort effect. Comparing the age coefficients (Table 4) with the mean thickness values in our study (Table 2) derives a yearly percentage decline in thickness of 0.14% for mRNFL, 0.18% for GCC, and 0.20% for GCIPL; this is also in keeping with previous studies.[23–26]

We found men to have thinner macular inner retinas, and this was most apparent for mRNFL. Thinner GCIPL in men was reported previously in a multiethnic volunteer study of 282 healthy participants.[23] Other studies found no

Table 3. Univariable Associations with Average Macular Retinal Nerve Fiber Layer, Ganglion Cell Complex, and Ganglion Cell–Inner Plexiform Layer Thicknesses

	Macular Retinal Nerve Fiber Layer Thickness (μm)		Ganglion Cell Complex Thickness (μm)		Ganglion Cell–Inner Plexiform Layer Thickness (μm)	
	β Coefficient (95% Confidence Interval)	P *Value*	*β Coefficient (95% Confidence Interval)*	P *Value*	*β Coefficient (95% Confidence Interval)*	P *Value*
Age (per decade)	−0.57 (−0.61 to −0.52)	**<0.001**	−1.73 (−1.82 to −1.64)	**<0.001**	−1.17 (−1.22 to −1.10)	**<0.001**
Gender						
Female	Reference		Reference		Reference	
Male	−0.70 (−0.77 to −0.63)	**<0.001**	−1.00 (−1.14 to −0.85)	**<0.001**	−0.30 (−0.39 to −0.19)	**<0.001**
Ethnicity						
White	Reference		Reference		Reference	
Asian	−0.75 (−0.97 to −0.53)	**<0.001**	−1.28 (−1.72 to −0.84)	**<0.001**	−0.53 (−0.83 to −0.22)	**0.001**
Black	−1.46 (−1.68 to −1.24)	**<0.001**	−1.20 (−1.62 to −0.77)	**<0.001**	0.27 (−0.03–0.55)	0.08
Other/mixed	−0.21 (−0.43, 0.01)	0.07	0.64 (0.19–1.08)	0.005	0.84 (0.53–1.14)	**<0.001**
Weight (per 10 kg)	−0.12 (−0.14 to −0.09)	**<0.001**	−0.21 (−0.25 to −0.15)	**<0.001**	−0.08 (−0.11 to −0.05)	**<0.001**
Height (per 10 cm)	0.02 (−0.02, 0.05)	0.37	0.04 (−0.03 to 0.11)	0.30	0.02 (−0.03 to 0.07)	0.40
Body mass index (per 5 kg/m^2)	−0.26 (−0.30 to −0.22)	**<0.001**	−0.46 (−0.53 to −0.37)	**<0.001**	−0.19 (−0.25 to −0.13)	**<0.001**
Smoking status						
Never	Reference		Reference		Reference	
Previous	−0.22 (−0.29 to −0.13)	**<0.001**	−0.45 (−0.60 to −0.29)	**<0.001**	−0.24 (−0.34 to −0.13)	**<0.001**
Current	−0.28 (−0.40 to −0.15)	**<0.001**	0.04 (−0.21 to 0.29)	0.75	0.32 (0.14–0.49)	**<0.001**
Alcohol intake						
Never or special occasion only	Reference		Reference		Reference	
1–3 times per month	0.26 (0.12–0.39)	**<0.001**	0.42 (0.15–0.69)	0.002	0.16 (−0.02 to 0.34)	0.09
1–2 times per week	0.24 (0.12–0.34)	**<0.001**	0.40 (0.18–0.61)	**<0.001**	0.16 (0.01–0.31)	0.032
3–4 times per week	0.16 (0.04–0.27)	0.005	0.07 (−0.15 to 0.29)	0.54	−0.09 (−0.24 to 0.06)	0.25
Daily or almost daily	−0.02 (−0.13 to 0.09)	0.68	−0.62 (−0.84 to −0.39)	**<0.001**	−0.60 (−0.75 to −0.44)	**<0.001**
Townsend deprivation index						
Least deprived quartile	Reference		Reference		Reference	
Second quartile	−0.06 (−0.16 to 0.04)	0.27	−0.03 (−0.23 to 0.17)	0.76	0.03 (−0.11 to 0.16)	0.71
Third quartile	−0.08 (−0.18 to 0.02)	0.12	−0.10 (−0.30 to 0.10)	0.32	−0.02 (−0.16 to 0.11)	0.76
Most deprived quartile	−0.20 (−0.30 to −0.09)	**<0.001**	−0.19 (−0.39 to 0.01)	0.07	0.02 (−0.12 to 0.15)	0.83
Test of trend	−0.06 (−0.09 to −0.03)	**<0.001**	−0.06 (−0.12 to 0.00)	0.06	0.00 (−0.04 to 0.04)	0.99
Education level						
Less than O level	Reference		Reference		Reference	
O level	0.47 (0.37–0.57)	**<0.001**	0.69 (0.48–0.89)	**<0.001**	0.22 (0.08–0.35)	0.002
A Level	0.85 (0.72–0.96)	**<0.001**	1.11 (0.86–1.35)	**<0.001**	0.26 (0.09–0.42)	0.003
Degree	0.83 (0.74–0.92)	**<0.001**	0.99 (0.81–1.16)	**<0.001**	0.16 (0.03–0.28)	0.010
Diabetes status						
No	Reference		Reference		Reference	
Yes	−0.95 (−1.12 to −0.78)	**<0.001**	−1.92 (−2.25 to −1.59)	**<0.001**	−0.97 (−1.19 to −0.74)	**<0.001**
Spherical equivalent (diopters)	−0.40 (−0.41 to −0.38)	**<0.001**	0.20 (0.16–0.23)	**<0.001**	0.60 (0.57–0.62)	**<0.001**
IOPg (mmHg)	−0.01 (−0.01 to 0.00)	0.15	−0.11 (−0.12 to −0.08)	**<0.001**	−0.10 (−0.11 to −0.08)	**<0.001**
IOPcc (mmHg)	−0.01 (−0.01 to 0.00)	0.12	−0.11 (−0.13 to −0.09)	**<0.001**	−0.10 (−0.11 to −0.09)	**<0.001**

IOPcc = corneal-compensated intraocular pressure; IOPg = Goldmann-correlated intraocular pressure.
Results are from linear regression models (n = 42 044). *P* values less than 0.0020 appear in boldface and represent significance at a Bonferroni-corrected threshold for 25 statistical tests.

significant association between inner retinal thickness and sex,[24,26] and 1 study from a subset of the Singapore Chinese Eye Study found women to have thinner inner retinas.[25] Although it is possible that the relationship between sex and macular inner retinal thickness varies between populations, it is more likely that the variation in results is stochastic because of the smaller sample sizes and resultant statistical power of previous studies. Our finding of a thinner inner retina in men may be aligned with the greater susceptibility to glaucoma reported in men.[27]

Higher BMI was associated with thinner inner retina, in agreement with a study of British twins that reported thinner GCC with higher BMI.[24] We observed the association with similar strength for mRNFL, GCC, and GCIPL thicknesses, suggesting the association is not related specifically to retinal ganglion cells. Also in agreement with this is the previously reported association of higher BMI with thinner macular total retina thickness in the UK Biobank.[16]

We observed thinner inner retinas in participants with diabetes; this association was more significant for mRNFL thickness than for GCC or GCIPL thickness. This is in agreement with small case-control studies that have reported thinner inner retinas in participants with diabetes compared with controls[28–30] and has led to the hypothesis that diabetic peripheral neuropathy and inner retinal thinning may share common biological pathways.[31] Interestingly, laser

Table 4. Multivariate Associations with Average Macular Retinal Nerve Fiber Layer, Ganglion Cell Complex, and Ganglion Cell–Inner Plexiform Layer Thicknesses

	Macular Retinal Nerve Fiber Layer Thickness (μm)		Ganglion Cell Complex Thickness (μm)		Ganglion Cell–Inner Plexiform Layer Thickness (μm)	
	β Coefficient (95% Confidence Interval)	P *Value*	*β Coefficient (95% Confidence Interval)*	P *Value*	*β Coefficient (95% Confidence Interval)*	P *Value*
Age (per decade)	−0.43 (−0.47 to −0.38)	**5.5×10^{-70}**	−1.90 (−1.99 to −1.80)	**$<1 \times 10^{-300}$**	−1.51 (−1.58 to −1.45)	**$<1 \times 10^{-300}$**
Gender						
Female	Reference		Reference		Reference	
Male	−0.66 (−0.73 to −0.58)	**1.8×10^{-68}**	−0.73 (−0.88 to −0.59)	**7.1×10^{-23}**	−0.10 (−0.20 to 0.00)	0.042
Ethnicity						
White	Reference		Reference		Reference	
Asian	−0.97 (−1.19 to −0.75)	**9.9×10^{-18}**	−1.98 (−2.42 to −1.54)	**1.2×10^{-18}**	−1.09 (−1.38 to −0.79)	**3.9×10^{-13}**
Black	−1.65 (−1.86 to −1.43)	**2.4×10^{-50}**	−1.95 (−2.38 to −1.52)	**5.7×10^{-19}**	−0.38 (−0.67 to −0.10)	0.009
Other/mixed	−0.48 (−0.70 to −0.26)	**2.1×10^{-5}**	−0.12 (−0.56 to 0.32)	0.58	0.39 (0.10–0.68)	0.009
Body mass index (per 5 kg/m^2)	−0.12 (−0.16 to −0.08)	**1.5×10^{-8}**	−0.29 (−0.37 to −0.21)	**5.9×10^{-12}**	−0.18 (−0.24 to −0.13)	**1.1×10^{-10}**
Smoking status						
Never	Reference		Reference		Reference	
Previous	0.02 (−0.06 to 0.10)	0.65	0.02 (−0.14 to 0.18)	0.80	0.00 (−0.10 to 0.10)	0.99
Current	−0.06 (−0.18 to 0.07)	0.37	−0.07 (−0.32 to 0.18)	0.57	−0.01 (−0.18 to 0.15)	0.89
Alcohol intake						
Never or special occasion only	Reference		Reference		Reference	
1–3 times per month	0.02 (−0.11 to 0.16)	0.72	0.08 (−0.19 to 0.34)	0.57	0.07 (−0.11 to 0.24)	0.45
1–2 time per week	0.04 (−0.07 to 0.15)	0.43	0.07 (−0.15 to 0.29)	0.53	0.04 (−0.11 to 0.18)	0.60
3–4 times per week	−0.09 (−0.21 to 0.02)	0.11	−0.24 (−0.47 to −0.02)	0.036	−0.14 (−0.29 to 0.02)	0.08
Daily or almost daily	−0.19 (−0.31 to −0.07)	**0.002**	−0.63 (−0.87 to −0.40)	**1.4×10^{-7}**	−0.46 (−0.61 to −0.30)	**1.1×10^{-8}**
Townsend deprivation index						
Least deprived quartile	Reference		Reference		Reference	
Second quartile	−0.02 (−0.12 to 0.08)	0.69	−0.02 (−0.22 to 0.18)	0.84	0.00 (−0.14 to 0.13)	0.95
Third quartile	−0.12 (−0.22 to −0.02)	0.019	−0.25 (−0.44 to −0.05)	0.016	−0.13 (−0.26 to 0.00)	0.06
Most deprived quartile	−0.13 (−0.24 to −0.03)	0.012	−0.41 (−0.61 to −0.20)	**1.2×10^{-4}**	−0.28 (−0.42 to −0.14)	**6.6×10^{-5}**
Education level						
Less than O level	Reference		Reference		Reference	
O level	0.15 (0.05–0.25)	0.004	0.30 (0.10–0.50)	0.003	0.16 (0.02–0.29)	0.022
A Level	0.35 (0.22–0.47)	**3.3×10^{-8}**	0.61 (0.37–0.86)	**8.4×10^{-7}**	0.26 (0.09–0.42)	**0.002**
Degree	0.36 (0.26–0.45)	**2.3×10^{-14}**	0.65 (0.47–0.83)	**1.7×10^{-12}**	0.30 (0.18–0.42)	**8.4×10^{-7}**
Diabetes status						
No	Reference		Reference		Reference	
Yes	−0.54 (−0.71 to −0.38)	**1.5×10^{-10}**	−0.83 (−1.16 to −0.50)	**8.5×10^{-7}**	−0.34 (−0.56 to −0.12)	0.003
Spherical equivalent (diopters)	−0.33 (−0.35 to −0.31)	**1.1×10^{-251}**	0.40 (0.36–0.43)	**1.2×10^{-93}**	0.73 (0.71–0.76)	**$<1 \times 10^{-300}$**
IOPcc (mmHg)	0.00 (−0.01–0.01)	0.77	−0.03 (−0.05 to −0.01)	**5.8×10^{-5}**	−0.04 (−0.05 to −0.03)	**4.0×10^{-10}**
Model R^2 value	6.7%		5.6%		11.2%	

IOPcc = corneal–compensated intraocular pressure.
Results are presented for 3 multivariate models with all explanatory variables presented together in the same model (n = 42 044 for each model). *P* values less than 0.0024 appear in boldface and represent significance at a Bonferroni-corrected threshold for 21 statistical tests.

treatment for proliferative diabetic retinopathy without macular edema has been shown to cause an increase in GCIPL thickness.[32]

We observed very strong associations of spherical equivalent with inner retinal thickness, and strikingly, the associations were in a different direction for mRNFL than for GCC and GCIPL. Our finding of thinner GCC and GCIPL with increasing myopia is in agreement with previous reports.[23–26] Our finding of a thicker mRNFL with increasing myopia is novel, to the best of our knowledge. Analyzing the relationship between refractive error and retinal thickness is extremely difficult because of the issue of magnification effects, which cannot be accounted for accurately. The grid within which the SD OCT measurements are made will cover different absolute amounts of the macula depending on the refractive status of the eye. Because of this, the foveal pit will take up a different proportion of the grid simply as a result of refractive error-induced magnification effects. In longer, myopic eyes, the grid will cover a larger proportion of the macula than in shorter, emmetropic eyes. This will result in the thickest parts of the inner retina proportionally covering less of the grid in myopic eyes, potentially explaining the thinner GCC and GCIPL. Additionally, the foveal pit will make up proportionally less of the imaged and analyzed grid in myopic eyes than emmetropic eyes. If the foveal pit affects the

Table 5. Associations of Intraocular Pressure with Average Macular Retinal Nerve Fiber Layer, Ganglion Cell Complex, and Ganglion Cell–Inner Plexiform Layer Thicknesses

	Macular Retinal Nerve Fiber Layer Thickness (μm)			Ganglion Cell Complex Thickness (μm)			Ganglion Cell–Inner Plexiform Layer Thickness (μm)		
	β Coefficient (95% *Confidence Interval*)	P *Value*	R^2 *Value* (%)	*β Coefficient* (95% *Confidence Interval*)	P *Value*	R^2 *Value* (%)	*β Coefficient* (95% *Confidence Interval*)	P *Value*	R^2 *Value* (%)
IOP imputed if using IOP-lowering medication (n = 42 044)									
IOPg (mmHg)	−0.01 (−0.02 to 0.00)	0.042	5.6	−0.07 (−0.09 to −0.05)	**7.8×10^{-13}**	4.8	−0.06 (−0.08 to −0.05)	**2.7×10^{-20}**	10.8
IOPcc (mmHg)	0.00 (−0.01 to 0.01)	0.55	5.6	−0.05 (−0.07 to −0.03)	**1.4×10^{-6}**	4.8	−0.05 (−0.06 to −0.03)	**1.1×10^{-11}**	10.8
Current IOP analyzed regardless of IOP-lowering medication (n = 42 044)									
IOPg (mmHg)	0.00 (−0.01 to 0.01)	0.56	5.6	−0.06 (−0.08 to −0.04)	**3.5×10^{-8}**	4.8	−0.05 (−0.07 to −0.04)	**4.4×10^{-15}**	10.8
IOPcc (mmHg)	0.01 (−0.01 to 0.02)	0.31	5.6	−0.03 (−0.05 to −0.01)	**0.003**	4.7	−0.04 (−0.05 to −0.02)	**1.4×10^{-7}**	10.8
Excluded if using IOP-lowering medication (n = 41 770)									
IOPg (mmHg)	0.00 (−0.01 to 0.01)	0.72	5.6	−0.05 (−0.07 to −0.03)	**1.6×10^{-7}**	4.7	−0.05 (−0.07 to −0.04)	**2.8×10^{-14}**	10.7
IOPcc (mmHg)	0.01 (0.00–0.02)	0.15	5.6	−0.03 (−0.05 to −0.01)	0.012	4.6	−0.03 (−0.05 to −0.02)	**1.2×10^{-6}**	10.6

IOPcc = corneal-compensated intraocular pressure; IOPg = Goldmann-correlated intraocular pressure.
Results are from linear regression models adjusted for age, gender, and spherical equivalent. Six different associations with intraocular pressure are presented: either IOPg or IOPcc and 3 methods for handling intraocular pressure values for patients taking intraocular pressure-lowering treatment (including participants taking intraocular pressure-lowering medication and imputing pretreatment intraocular pressure, including participants taking intraocular pressure-lowering medication and using current intraocular pressure rather than imputing intraocular pressure, and excluding participants using intraocular pressure-lowering medications [see "Methods"]). *P* values less than 0.008 appear in boldface and represent significance at a Bonferroni-corrected threshold for 6 statistical tests.

retinal nerve fiber layer more than the GCC or GCIPL, then this may explain why the retinal nerve fiber layer is thicker in SD OCT images of myopic eyes. With the current data in our study, we do not believe it is possible to determine true differences in inner retinal thickness by refractive error because we were unable to distinguish the contribution as a result of magnification.

We identified several novel associations with inner retinal thickness parameters. Asian and black participants had thinner mRNFL, GCC, and GCIPL than white participants. Although this in part may reflect a greater susceptibility to glaucomatous processes in nonwhite people, as suggested from epidemiologic data,[27] this more likely reflects ethnically determined differences in baseline retinal anatomic features. This highlights the importance of taking ethnicity into account when defining normal ranges for diagnostic tests for glaucoma.

Frequent alcohol intake was associated with thinner mRNFL, GCC, and GCIPL compared with rare or no alcohol intake. This is in agreement with a study examining cRNFL (i.e., circumpapillary rather than macular measures)[33]; Lamparter et al[33] reported thinner cRNFL in participants of the Gutenberg Health Study whose alcohol intake was high according to World Health Organization guidelines (≥10 g/day for women; ≥20 g/day for men). Our findings support the assertion that retinal nerve fiber layer thinning may occur as a result of chronic alcohol intake and in a dose-dependent manner.[33] It is not possible to determine from our study what mechanisms may be underlying the association with alcohol. Potential mechanisms may include direct effects of alcohol on retinal ganglion cells or indirect effects via dehydration.

We found participants who were more socially deprived to have thinner inner retinas, particularly for GCC and GCIPL measurements. This is consistent with the previously reported association of social deprivation with self-reported glaucoma in the UK Biobank.[34] We also found less educated participants to have thinner mRNFL, GCC, and GCIPL. This is consistent with a scanning laser ophthalmoscopy study of cRNFL in participants of another, independent United Kingdom cohort of older adults.[35] Interestingly, the association of a thicker GCC and GCIPL in more educated participants is strong enough to outweigh the expected thinner GCC and GCIPL we may expect to see given the association between education and myopia,[36] even in unadjusted analyses (Table 3). From our cross-sectional study, it is not possible to know if less educated participants demonstrated thinner inner retinas at baseline, or whether this is something that developed over time as a result of lack of education. Another study of UK Biobank participants reported that baseline mRNFL predicted future cognitive decline.[37] If inner retinal thickness is associated causally with cognitive health, this may explain the relationship with education that we observed with more cognitively able people with thicker inner retinas being more likely to pursue education for longer periods.

Typically, in epidemiologic studies, if a significant association is not found, it may be the case that a true association does not exist or that the study was underpowered to

detect a true association. With the huge sample size in our study, it is unlikely that a biologically meaningful association will not be identified if it truly exists. Strong associations in our study (e.g., age and spherical equivalent) were so statistically significant that the *P* value was so small such that the statistical software could not distinguish it from 0 ($P < 10^{-300}$). We did not find associations between inner retinal thickness and height or smoking status. Given the statistical power, our study provides good evidence for no true association between inner retinal thickness and height or smoking. The lack of association with smoking suggests that inflammatory mechanisms do not have a prominent role in pathophysiologic processes underlying variation in inner retinal thickness.

The effect sizes for the associations we report are modest in magnitude but important when considered in the context of the standard deviation of the retinal thickness parameters and when compared with the association with age (a well-established important association of inner retinal thickness that is corrected for in diagnostic tests). For example, the thinner mRNFL observed in men had a magnitude of 17% of the standard deviation of mRNFL and is equivalent to the magnitude of thinner mRNFL observed in participants who were 15 years older. Similarly, the thinner GCC seen in black compared with white participants had a magnitude of 26% of the standard deviation of GCC, equivalent to being 10 years older. Collectively, the predictor variables we examined explained a considerable proportion of the total variance of inner retinal thickness: 6.7% for mRNFL, 5.6% for GCC, and 11.2% for GCIPL (Table 4).

We found higher IOP to be associated with a thinner GCC and GCIPL. If we consider glaucoma as a complex disease with multiple underlying causes and with a phenotypic spectrum from normal to severe disease, it is likely that variation in inner retinal anatomic features in a population may be reflecting the preclinical disease spectrum and may be secondary to these causes. Therefore, determinants of inner retinal thickness variation also may be determinants of the glaucomatous process. On this basis, we would expect to see an association between IOP and inner retinal thickness, given the strength of IOP as a risk factor for glaucoma.[38] The association with IOP in our study was most significant for GCIPL, potentially suggesting GCIPL as a superior biomarker for glaucomatous processes. We found no significant association between IOP and mRNFL, potentially suggesting mRNFL to be a less effective biomarker for glaucomatous processes. This is in contrast to the well-established role of cRNFL as a biomarker in the management of glaucoma.[39] Our data suggest that, at the macula, variation in mRNFL within a population may be more influenced by factors other than glaucomatous processes.

Overall, the predictor variables we examined explained twice more of the variance of GCIPL than of either GCC or mRNFL. This suggests that GCIPL is better reflecting the biological processes that these variables contribute to and therefore may be a superior biomarker for pathophysiologic processes influencing retinal ganglion cell health in general.

The major strength of our study is the very large sample size, which afforded sufficient power to determine definitively which factors were or were not associated with inner retinal thickness. Limitations of our study include the reliance on automated segmentation of the retina. Although we applied strict quality control criteria and manually checked a proportion of scans,[16] it was not feasible to check all scans manually for accurate segmentation. Additionally, it was not possible to segment reliably the boundary between the ganglion cell layer and inner plexiform layer, meaning we could not examine these layers individually. Another limitation of the UK Biobank is that it is a volunteer cohort, and participants are likely healthier than the general population. Furthermore, our quality control process excluded participants, and this also could lead to selection bias. This may limit the generalizability of our results, although it seems unlikely that that directions of association with inner retinal thickness would be differential by selection.

In summary, we present a very large epidemiologic study of inner retinal anatomic characteristics. We identified novel associations with thinner inner retina, including non-European ethnicity, frequent alcohol intake, greater social deprivation, and lower educational attainment. These associations were statistically independent from each other and warrant further investigation to help determine if they are causal and what the underlying mechanisms may be. Stronger associations were seen with GCIPL compared with mRNFL or GCC, particularly for IOP, suggesting that GCIPL may be a superior biomarker for macular pathophysiologic processes and especially for glaucoma.

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Abbreviations and Acronyms:
BMI = body mass index; **cRNFL** = circumpapillary retinal nerve fiber layer; **D** = diopter; **GCC** = ganglion cell complex; **GCIPL** = ganglion cell–inner plexiform layer; **IOP** = intraocular pressure; **IOPcc** = corneal-compensated intraocular pressure; **IOPg** = Goldmann-correlated intraocular pressure; **mRNFL** = macular retinal nerve fiber layer; **ORA** = Ocular Response Analyzer; **SD** = spectral-domain; **TABS** = Topcon Advanced Boundary Segmentation.

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