Genetic Correlations Between Diabetes and Glaucoma: An Analysis of Continuous and Dichotomous Phenotypes

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• PURPOSE: A genetic correlation is the proportion of phenotypic variance between traits that is shared on a genetic basis. Here we explore genetic correlations between diabetes- and glaucoma-related traits.

• DESIGN: Cross-sectional study.

• METHODS: We assembled genome-wide association study summary statistics from European-derived participants regarding diabetes-related traits like fasting blood sugar (FBS) and type 2 diabetes (T2D) and glaucoma-related traits (intraocular pressure [IOP], central corneal thickness [CCT], corneal hysteresis [CH], corneal resistance factor [CRF], cup-to-disc ratio [CDR], and primary open-angle glaucoma [POAG]). We included data from the National Eye Institute Glaucoma Human Genetics Collaboration Heritable Overall Operational Database, the UK Biobank, and the International Glaucoma Genetics Consortium. We calculated genetic correlation (r_g) between traits using linkage disequilibrium score regression. We also calculated genetic correlations between IOP, CCT, and select diabetes-related traits based on individual level phenotype data in 2 Northern European population-based samples using pedigree information and Sequential Oligogenic Linkage Analysis Routines.

• RESULTS: Overall, there was little r_g between diabetes- and glaucoma-related traits. Specifically, we found a nonsignificant negative correlation between T2D and POAG ($r_g = -0.14$; $P = .16$). Using Sequential Oligogenic Linkage Analysis Routines, the genetic correlations between measured IOP, CCT, FBS, fasting insulin, and hemoglobin A1c were null. In contrast, genetic correlations between IOP and POAG ($r_g \geq 0.45$; $P \leq 3.0 \times 10^{-4}$) and between CDR and POAG were high ($r_g = 0.57$; $P = 2.8 \times 10^{-10}$). However, genetic correlations between corneal properties (CCT, CRF, and CH) and POAG were low (r_g range -0.18 to 0.11) and nonsignificant ($P \geq .07$).

• CONCLUSION: These analyses suggest that there is limited genetic correlation between diabetes- and

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CLARIFYING THE RELATIONSHIP BETWEEN DIABETES mellitus and primary open-angle glaucoma (POAG) could help prioritize glaucoma detection efforts and focus glaucoma drug discovery. Studies show that patients with diabetes have higher intraocular pressure (IOP) than patients without diabetes and that increased fasting blood sugar (FBS) is associated with higher IOP.[1–6] However, the link between diabetes and IOP is complex because diabetes alters corneal hysteresis (CH) and corneal resistance factor (CRF), possibly confounding the true correlation between diabetes and IOP.[7,8] The Ocular Response Analyzer (ORA) noncontact tonometer generates both a Goldmann-correlated IOP (IOPg) and a cornea-compensated IOP (IOPcc), with the latter adjusting for corneal biomechanical properties. Among 110,573 participants in the UK Biobank where IOP was measured with the ORA noncontact tonometer, self-reported diabetes was associated with higher IOPg but there was no significant difference in IOPcc between subjects with and without diabetes in multivariate analysis.[9] A meta-analysis of seven prospective cohort studies also shows that type 2 diabetes (T2D) is associated with an increased risk of POAG[10]; however, this meta-analysis is not consistent with a study finding that POAG patients with T2D and no diabetic retinopathy had significantly slower rates of retinal nerve fiber layer thinning compared to POAG patients without T2D.[11]

Several other correlations between diabetes-related traits and IOP are notable. For example, there was a positive association between postprandial glucose level and IOP in patients with and without diabetes.[12,13] Among nonobese individuals,[14] there was a positive relationship between insulin resistance and IOP.[15] Serum diabetes-related biomarkers positively associated with IOP include hemoglobin A1c (HbA1c),[16] high-density lipoprotein (HDL), and triglyceride (TG).[2] Several studies also showed a positive correlation between body mass index (BMI), a continuous trait positively linked to T2D,[17–19] and IOP.[4,20] Currently, it is unclear if any of these diabetes-related traits translate into increased vulnerability to POAG.

Genetic analyses offer powerful tools to analyze relationships between various traits without confounding by reverse causality, measurement artifact, or detection bias. One such tool is linkage disequilibrium (LD) score regression, which estimates the genetic correlation (r_g) between traits using genome-wide association study (GWAS) summary statistics.[21,22] For example, Pickrell and associates[23] reported strong genetic correlations between each of the following continuous diabetes-related traits and T2D using LD score regression: FBS, TG, low-density lipoprotein (LDL), HDL, and BMI. For glaucoma-related traits, a strong genetic correlation between IOP measured with Goldmann applanation tonometry and POAG was reported using GWAS summary data from 2 large European-derived consortia.[24] Using LD score regression in a Japanese population, Shiga and associates[25] found a positive genetic correlation between T2D and POAG ($r_g = 0.27$; $P = 2.00 \times 10^{-4}$) but Kinai and associates[26] found no significant correlations between various quantitative diabetes traits and POAG in the same population. Another approach is to form panels of genome-wide significant markers for a trait and test them in relation to another trait of interest. In a multiethnic U.S. population (N = 69,685), 39 genome-wide significant diabetes alleles were not collectively associated with POAG (n = 3554 cases) after adjustment for T2D.[27]

A repository of existing GWAS summary statistics and an atlas of genetic cross-correlations can be found at LD Hub.[28] Given the preponderance of epidemiologic evidence linking diabetes and glaucoma, we tested the hypothesis that there would be genetic correlations between diabetes- and glaucoma-related traits. First, we used LD score regression to explore the relations between quantitative glaucoma-related traits (IOP measured using various techniques in the International Glaucoma Genetics Consortium [IGGC], as well as IOPcc and IOPg—both measured with the ORA in the UK BioBank study, central corneal thickness [CCT], CH, CRF, cup-to-disc ratio [CDR], and POAG) using existing GWAS summary statistics. Next, we performed LD score regression to assess the genetic correlation between diabetes-related traits (2-hour glucose, FBS, HbA1c, fasting insulin [FI], BMI, TG, LDL, HDL, and T2D) and glaucoma-related traits. Finally, we compared our estimates of genetic correlations between selected diabetes quantitative traits and glaucoma quantitative traits to values derived from directly measured traits leveraging pedigree information in 2 Northern European island cohorts.

METHODS

THE INSTITUTIONAL REVIEW BOARD OF PARTNERS HEALTHcare prospectively approved the genetic correlation analyses described in this work. The Icahn School of Medicine Institutional Review Board has a reliance agreement with Partners to conduct this research. These analyses represent a retrospective study of publicly available summary genotype data. The island cohort studies described below were approved by the Scotland National Health Study.

• **ASSEMBLY OF GENOME-WIDE ASSOCIATION STUDY SUMMARY STATISTICS:** We assembled publicly available GWAS summary statistics and outlined the traits, sample sizes, population characteristics, and trait heritability based on GWAS data for relevant studies in Table 1.[29–38] The

GWAS summary data were accessed at http://jass.pasteur.fr/selectPhenotypes.html and http://ldsc.broadinstitute.org. We used the European-derived subgroups of these studies. Details such as study demographics, detailed phenotype collection methods, adjustments for covariates, the genotyping platforms used and number of single nucleotide polymorphisms (SNPs) that passed quality control can be found in references listed in Table 1. The trait heritability based on classic twin studies and family studies and the methodology for determining these traits can also be found by referring to the appropriate references in Table 1. Heritability based on classic twin and family studies was high overall and upward of 0.95 for CCT[39] (Table 1). As expected, calculations of heritability for these traits based on summary GWAS data were lower than values estimated from classic twin studies. Several hypotheses for the source of this "missing heritability" have been proposed in the genetics literature.[40] In the studies of quantitative diabetes traits, efforts were taken to exclude patients with known diabetes. The studies of blood lipids and BMI contains patients with and without dyslipidemia—there was no concerted effort to exclude patients with diabetes. In the studies of IOP measured in various ways, studies of CDR and in the studies of corneal biophysical properties, <1.5% of subjects were undergoing treatment for glaucoma.

• **GENETIC CORRELATION BETWEEN TRAITS ANALYSES:** The methodology for estimating genetic correlation between traits using high throughput allelic markers has been previously described[21] and appears in the Appendix. We provide an overview of the method here. The genetic correlation r_g measures the covariance between the genetic components of 2 traits scaled by their respective heritabilities. It ranges between −1 and 1, although occasional out-of-bounds estimates arise because of estimation error.[41,42] Negative r_g between trait pairs means that alleles that are positively associated with phenotype 1 are negatively associated phenotype 2. Positive r_g between trait pairs means that there are common alleles positively associated between both traits. An absolute value of $r_g \geq 0.5$ can be considered strong, while an absolute $r_g \leq 0.12$ can be regarded as weak. P values $< 6.9 \times 10^{-4}$ associated with r_g were considered as significant to correct for the multiple comparisons made (9 diabetes traits × 8 glaucoma traits). Power calculations[41] for all possible bivariate analyses are provided in Supplemental Table 1.

• **THE ORKNEY AND SHETLANDIC COHORTS: PEDIGREES WITH MEASURED IOP, CCT, AND SERUM DIABETES-RELATED BIOMARKERS:** The Orkney Complex Disease Study (ORCADES) is a family-based cross-sectional study that seeks to identify genetic factors influencing cardiovascular and other disease risk in the isolated archipelago of the Orkney Isles in northern Scotland.[43] In total, 2078 participants 16-100 years of age were recruited between 2005 and 2011, most having 3 or 4 grandparents from Orkney, the remainder with 2 Orcadian grandparents.

The Viking Health Study (VIKING) is a family-based cross-sectional study that aims to identify genetic factors influencing cardiovascular and other disease risk in the population isolate of the Shetland Islands in northern Scotland. In total, 2105 participants were recruited between 2013 and 2015, each having ≥3 grandparents from Shetland.

Genetic diversity in both the ORCADES and VIKING populations is less than mainland Scotland, consistent with high levels of endogamy historically.[44] In both cohorts, FBS samples were collected and many health-related phenotypes, including IOP and CCT as well as environmental exposures were measured. Specifically, serum glucose, FI, and HbA1c were measured. CCT was measured using an ultrasound pachymeter (Heidelberg Engineering; Heidelberg, Germany). IOP was measured with a tonopen (Reichert Technologies; Buffalo, New York, USA).

• **GENETIC CORRELATIONS IN THE ORKNEY AND SHETLANDIC COHORTS:** We used Sequential Oligogenic Linkage Analysis Routines to decompose phenotypic covariances for IOP, CCT, and diabetes-related serum biomarkers from our island cohorts into environmental, phenotypic, and genetic components using pedigree data. We used measures averaged between both eyes of a participant. We excluded measures from eyes with a history of surgery that might affect CCT or IOP measurements and from participants with keratoconus. HbA1c values from individuals with diabetes or FBS >7 mmol/L were also excluded. IOPs were not adjusted for CCT or transformed but were adjusted for age and sex. CCT, adjusted for age and sex, underwent z score transformation while FBS, HbA1c, and FI underwent rank transformation, with FI undergoing natural log transformation first. All serum diabetes biomarkers were further adjusted for sex, age, age^2, and BMI. P values < .0042 were considered significant to correct for the multiple comparisons made (2 glaucoma traits × 3 diabetes traits × 2 cohorts).

RESULTS

GENETIC CORRELATION BETWEEN THE VARIOUS glaucoma-related quantitative traits and POAG revealed significant trends (Table 2). There was a positive genetic association between IOP measured in the IGGC and POAG as previously reported ($r_g = 0.45$; standard error [SE] = 0.12; $P = 3.0 \times 10^{-4}$).[24] Similarly there were strong positive genetic correlations between IOPcc and POAG ($r_g = 0.50$; SE = 0.09; $P = 5.5 \times 10^{-8}$) and between IOPg and POAG ($r_g = 0.60$; SE = 0.15; $P = 4.3 \times 10^{-5}$). None of the corneal features (CCT, CH, or CRF)

TABLE 1. Summary of Genome-Wide Association Studies Used in this Analysis

Trait	Description of Trait	Sample Size, n (Study PMID)	Population Characteristics	Heritability or Heritability Range[a] (Study PMID[s])	Heritability Explained by GWAS Data (SE)[b]
FBS	Fasting blood sugar	133,010 (22885924)	Individuals with physician diagnosis of diabetes were excluded	0.38-0.52 (10064092, 10207722, and 11723071)	0.03 (0.01)
2HRG	Glucose level 2 h after oral glucose challenge adjusted for BMI	15,234 (20081857)	Individuals with a diagnosis of diabetes, using diabetic medication and/or fasting glucose ≥7 mM were excluded	0.4 (12898014)	0.10 (0.03)
FI	Fasting insulin	108,557 (22885924)	See 2HRG	0.36 (17956454)	0.03 (0.01)[c]
HbA1c	Serum hemoglobin A1c levels	46,368 (20858683)	See 2HRG	0.47-0.59 (11872688 and 16934002)	0.06 (0.01)
LDL	Serum LDL	95,454[d] (20686565)	Patients with and without dyslipidemia; there was no systematic attempt to exclude subjects with diabetes	0.21-0.44 (18165655)	0.12 (0.02)
HDL	Serum HDL	99,900[d] (20686565)	See LDL	0.27-0.48 (18165655)	0.14 (0.02)
TG	Serum triglyceride	96,598[d] (20686565)	See LDL	0.37 (11309690)	0.14 (0.02)
BMI	Calculated based on measured or self-reported weight and height	339,224[d] (25673413)	Includes patients with and without diabetes	0.47-0.89 (22645519)	0.13 (0.01)
T2D	T2D[e]	34,840 cases; 114,981 control subjects (22885922)	T2D	0.72 (26678054)	0.05 (0.01)
IOP	IOP measured in various ways in the IGGC[f]	29,578 (28073927)	Mostly patients without glaucoma	0.55 (20851442)	0.13 (0.02)
IOPcc	Corneal compensated IOP for the OD measured with the Reichert tonometer in the UKBB[g]	76,630 (29785010)	Mostly patients without glaucoma	NA	0.15 (0.01)[h]
IOPg	IOP Goldmann-correlated for the OD measured with the Reichert tonometer in the UKBB[g]	76,630 (29785010)	Mostly patients without glaucoma measured with the Reichert tonometer	NA	0.19 (0.02)[h]
CCT	CCT measured with a pachymeter as the mean of both eyes	17,803 (29760442)	Patients without eye disease	0.68-0.95 (19556215, 19420341, and 16186354)	0.34 (0.04)
CH	CH of the OD measured with Reichert tonometer in the UKBB[g]	76,630 (29785010)	Mostly patients without glaucoma	NA	0.20 (0.01)[h]
CRF	CRF of the OD measured with Reichert tonometer in the UKBB[g]	76,630 (29785010)	Mostly patients without glaucoma measured with Reichert tonometer	NA	0.25 (0.02)[h]
CDR	Vertical CDR ratio measured various ways in the IGGC[i]	23,899 (28073927)	Mostly patients without glaucoma	0.48-0.62 (15939473, 20237253, 14691154, and 19458335)	0.31 (0.04)
POAG	Primary optic nerve degeneration across IOP values in NEIGHBORHOOD	3853 cases; 33,480 control subjects (26752265)	POAG	0.70 (28783162)	0.13 (0.03)

showed significant genetic correlation with CDR ($P \geq .13$) or POAG ($P \geq .07$). Interestingly, while CCT showed strong positive genetic correlations with IOPg ($r_g = 0.58$; SE = 0.07; $P = 1.8 \times 10^{-15}$) and IOPg ($r_g = 0.48$; SE = 0.07; $P = 3.7 \times 10^{-12}$), it did not show significant genetic correlation with IOPcc ($r_g = 0.07$; SE = 0.05; $P = .21$). Furthermore, there was also a strong positive genetic correlation between CDR and POAG ($r_g = 0.57$; SE = 0.09; $P = 2.8 \times 10^{-10}$). IOPcc showed a positive genetic correlation with CDR ($r_g = 0.16$; SE = 0.05; $P = 9.3 \times 10^{-4}$) that was not significant after correcting for multiple comparisons. We found strong genetic correlations between IOP measured in various ways in the IGGC as well as between IOPg with the following corneal biophysical traits: CCT, CH, and CRF (range of $r_g = 0.31$-0.81; $P \leq 3.2 \times 10^{-7}$).

Next, we examined the genetic correlations between BMI, blood lipid traits, and glaucoma-related traits (Table 3) as well as the genetic correlations between diabetes- and glaucoma-related traits (Table 4). Overall, these results were null after correction for multiple comparisons. Notably, there were nonsignificant inverse genetic correlations between HbA1c and POAG ($r_g = -0.31$; SE = 0.14; $P = .02$) and between T2D and POAG ($r_g = -0.14$; SE = 0.10; $P = .16$).

The ORCADES and VIKING cohorts offered an opportunity to assess the phenotypic correlations between measured glaucoma-related traits and measured serum biomarkers related to diabetes as well as genotypic correlations based on pedigree information, as opposed to genetic biomarkers (Supplemental Tables 2 and 3). Consistent with classic twin studies,[39] the heritability of CCT was high (range 0.78-0.85). Heritability for IOP was 0.13-0.14 in ORCADES and 0.25 in the VIKING study. Phenotypic correlations were low (<6%) between CCT or IOP and measured diabetes-related serum biomarkers. We found no statistically significant genetic or environmental correlations between diabetes- and glaucoma-related traits after correction for multiple testing in both cohorts (Supplemental Tables 2 and 3). In the VIKING cohort, there was a strong genetic correlation between IOP and CCT ($r_g = 0.45$; $P = 9.7 \times 10^{-6}$). In both cohorts, a modest phenotypic correlation (r_p) between IOP and CCT was observed ($r_p = 0.16$; $P = 7.8 \times 10^{-8}$ in ORCADES; $r_p = 0.26$; $P = 3.3 \times 10^{-25}$ in the VIKING study).

DISCUSSION

USING A GENOME-WIDE GENETIC CORRELATION approach, we found no significant relationship between diabetes- and glaucoma-related traits after adjustment for multiple comparisons. These null results must be assessed in context of the power of this study to find significant associations. A consensus estimate of "good" power is based

BMI = body mass index; CCT = central corneal thickness; CDR = cup-to-disc ratio; CH = corneal hysteresis; CRF = corneal resistance factor; GWAS = genome-wide association study; HDL = high-density lipoprotein; IGGC = International Glaucoma Genetics Consortium; IOP = intraocular pressure measured in various ways in the IGGC; IOPcc = corneal-compensated IOP; IOPg = Goldmann-correlated IOP; LDL = low-density lipoprotein; NA = not available; OD = oculus dexter; POAG = primary open-angle glaucoma; PMID = PubMed unique identifier; SE = standard error; T2D = Type 2 diabetes; UKBB = UK Biobank.

[a]Heritability of a trait is the proportion of trait variance attributable to genetic factors. Estimates for heritability values provided here are based on classic twin or family studies except for POAG. The latter is based on pedigree analysis of insurance claim data using the generic term "glaucoma."

[b]Heritability calculated from genome-wide association study data is the proportion of the heritability that is explained by variants that were genotyped. The formula for estimating heritability can be found in the Appendix. All heritability estimates are on the observed scale except for POAG and T2D. Heritability of the latter traits were based on the liability scale assuming a population prevalence of 2% and 5% for POAG and T2D, respectively.

[c]SE was rounded up to 0.01.

[d]Sample size for each of these traits in this study.

[e]Details regarding how T2D was ascertained are provide in the Appendix.

[f]For the 1.4% of participants who were on medical therapy for glaucoma, the measured IOP value was multiplied by 1.3. Patients with a history of laser trabeculoplasty and incisional glaucoma surgery were excluded from analysis.

[g]For the 1.5% of participants who were on medical therapy for glaucoma, the measured IOP value was multiplied by 1.3. Patients with a history of any laser trabeculoplasty, any incisional glaucoma surgery, any eye surgery within the previous 4 weeks, active ocular infection, eye injury, corneal graft surgery, or refractive laser surgery were excluded.

[h]We used inverse rank normalized transformed genome-wide association study summary data for the calculation of heritability for these traits. Raw genome-wide association study data yielded materially similar results (data not shown).

[i]1.4% of participants were on medical therapy for glaucoma. Patients with a history of any laser trabeculoplasty and any incisional glaucoma surgery were excluded.

TABLE 2. Genetic Correlations (Standard Error) Among Glaucoma-Related Traits

	IOPcc	IOPg	CCT	CH	CRF	CDR	POAG
IOP	0.81 (0.07), $P = \mathbf{3.8 \times 10^{-34}}$	1.10 (0.13), $P = \mathbf{2.0 \times 10^{-17}}$	0.58 (0.07), $P = \mathbf{1.8 \times 10^{-15}}$	0.39 (0.06), $P = \mathbf{5.0 \times 10^{-10}}$	0.81 (0.06), $P = \mathbf{2.9 \times 10^{-38}}$	0.08 (0.07), $P = .29$	0.45 (0.12), $P = \mathbf{3.0 \times 10^{-4}}$
IOPcc	—	0.77 (0.02), $P \sim 0$	0.07 (0.05), $P = .21$	−0.32 (0.04), $P = \mathbf{1.1 \times 10^{-19}}$	0.16 (0.04), $P = \mathbf{7.8 \times 10^{-6}}$	0.16 (0.05), $\mathbf{P = 9.3 \times 10^{-4}}$	0.50 (0.09), $P = \mathbf{5.5 \times 10^{-8}}$
IOPg	—	—	0.48 (0.07), $P = \mathbf{3.7 \times 10^{-12}}$	0.30 (0.06), $P = \mathbf{3.2 \times 10^{-7}}$	0.71 (0.03), $P \sim 0$	0.07 (0.08), $P = 0.39$	0.60 (0.15), $P = \mathbf{4.3 \times 10^{-5}}$
CCT	—	—	—	0.64 (0.06), $P = 3.0 \times 10^{-24}$	0.71 (0.06), $P = \mathbf{8.7 \times 10^{-36}}$	0.08 (0.06), $P = .13$	−0.18 (0.10), $P = .07$
CH	—	—	—	—	0.88 (0.01), $P \sim 0$	−0.07 (0.05), $P = .19$	−0.14 (0.08), $P = .07$
CRF	—	—	—	—	—	0.02 (0.05), $P = .66$	0.11 (0.07), $P = .13$
CDR	—	—	—	—	—	—	0.57 (0.09), $P = \mathbf{2.8 \times 10^{-10}}$

CCT = central corneal thickness; CDR = cup disc ratio; CH = corneal hysteresis; CRF = corneal resistance factor; IOP = intraocular pressure measured with various tonometers in the International Glaucoma Genetics Consortium; IOPcc = corneal-compensated intraocular pressure, as determined in the UK Biobank study; IOPg = Goldmann-correlated intraocular pressure as determined in the UK Biobank study; POAG = primary open angle glaucoma.

Note: Tables 2, 3, and 4, use inverse rank normalized transformed genome-wide association study summary data for the oculus dexter for IOPcc, IOPg, CH, and CRF. For CCT we used raw genome-wide association study summary data based on the mean of both eyes.

P values corrected for multiple comparisons ($<6.9 \times 10^{-4}$) are in bold; *P* values $<1 \times 10^{-100}$ were regarded as ~0.

on the square root of the product of the heritability and sample size for the traits having a value >4500.[41] The power was considered to be "good" or better for 47 of 56 bivariate analyses between quantitative diabetes- and quantitative glaucoma-related traits (Supplemental Table 1). There was 1 nominal positive association between IOP measured in the IGGC and FBS with subpar power ($r_g = 0.23$; $P = .0075$; power product = 3917) but more adequately powered associations between IOPg and FBS and IOPcc and FBS were definitely null ($P \geq .47$; power product ≥ 6772; Table 4 and Supplemental Table 1). T2D did not show any significant genetic correlations with any of the 7 quantitative glaucoma-related traits ($P \geq .16$) and for all of these bivariate analyses there was at least "good" power to observe such an association (power product ≥ 4800; Supplemental Table 3). POAG and T2D are categorical traits and the analysis for genetic correlation between them was slightly underpowered (power product = 3957); yet the result was in the inverse direction ($r_g = -0.14$) and not significant ($P = .16$). Our findings using GWAS statistics were consistent with individual level data from 2 population pedigrees and do not support a genetic relationship between diabetes and glaucoma.

Our result showing a nonsignificant inverse genetic correlation between T2D and POAG runs contrary to the significant positive correlation between these quantitative traits in a Japanese population.[25] The numbers of cases in the genome-wide datasets were comparable between the Asian and our European sample so power differences were unlikely, but there could be differences in genetic structure between these groups that account for these differences. For example, *LOXL1* was found to be a genome-wide marker for POAG in Japanese subjects,[25] but to date *LOXL1* markers are not associated with POAG in European-derived whites.[45] Using the same Japanese population, Kinai and associates[26] did not find significant genetic correlations between diabetes quantitative traits (HDL, LDL, TG, blood sugar, and HbA1c) and glaucoma, a finding consistent with our results. In addition, in a U.S.-based multiethnic population, a panel of genome-wide genetic biomarkers for T2D were not associated with POAG.[27]

Several diabetes quantitative traits are positively related to IOP in epidemiologic studies[1–6]; we find no genetic correlations between these quantitative diabetes traits and IOP. Overall, while CCT is increased in patients with diabetes based on several studies,[46–48] this corneal feature only partially mediated IOP variation in a study from Singapore.[6] While CCT is a static biophysical parameter, CH and CRF are dynamic biomechanical properties that are also affected by diabetes control.[49,50] Overall, accounting for CCT, CH, and CRF may not completely explain how the diabetic process leads to increased IOP as measured by Goldman applanation tonometry. Nonetheless, the large UK BioBank study suggests that there is no relationship between self-reported diabetes

TABLE 3. Genetic Correlations (Standard Error) Among Body Mass Index, Blood Lipid Traits, and Glaucoma-Related Traits

	BMI	LDL	HDL	TG
IOP	0.07 (0.04), $P = .099$	0.14 (0.08), $P = .059$	0.03 (0.08), $P = .72$	0.01 (0.05), $P = .83$
IOPcc	−0.02 (0.03), $P = .60$	0.06 (0.05), $P = .16$	0.06 (0.05), $P = .22$	−0.01 (0.04), $P = .81$
IOPg	0.02 (0.04), $P = .67$	0.07 (0.05), $P = .16$	0.01 (0.06), $P = .84$	0.00 (0.05), $P = .97$
CCT	0.03 (0.04), $P = .37$	0.00 (0.07), $P = .99$	0.07 (0.06), $P = .24$	−0.07 (0.05), $P = .21$
CH	0.03 (0.03), $P = .18$	0.01 (0.05), $P = .84$	−0.02 (0.04), $P = .65$	0.07 (0.03), $P = .05$
CRF	0.03 (0.02), $P = .21$	0.04 (0.04), $P = .38$	0.00 (0.04), $P = .94$	0.06 (0.03), $P = .05$
CDR	0.00 (0.03), $P = .92$	0.02 (0.05), $P = .75$	0.04 (0.05), $P = .42$	−0.02 (0.04), $P = .64$
POAG	−0.04 (0.05), $P = .41$	0.04 (0.09), $P = .64$	0.16 (0.08), $P = .06$	−0.06 (0.07), $P = .44$

BMI = body mass index; CCT = central corneal thickness; CDR = cup disc ratio; CH = corneal hysteresis; CRF = corneal resistance factor; HDL = high-density lipoprotein; IOP = intraocular pressure measured with various tonometers in the International Glaucoma Genetics Consortium; IOPcc = corneal-compensated intraocular pressure, as determined in the UK Biobank study; IOPg = Goldmann-correlated intraocular pressure as determined in the UK Biobank study; LDL = low-density lipoprotein; POAG = primary open-angle glaucoma; TG = triglyceride.

Note: Tables 2, 3, and 4, use inverse rank normalized transformed genome-wide association study summary data for the oculus dexter for IOPcc, IOPg, CH, and CRF. For CCT we used raw genome-wide association study summary data based on the mean of both eyes.

TABLE 4. Genetic Correlations (Standard Error) Between Diabetes-Related Traits and Glaucoma-Related Traits

	FBS	2HG	FI	HbA1c	T2D
IOP	0.23 (0.09), $P = 7.5 \times 10^{-3}$	0.17 (0.16), $P = .29$	0.17 (0.10), $P = .09$	0.10 (0.10), $P = .31$	0.08 (0.07), $P = .30$
IOPcc	0.02 (0.06), $P = .71$	−0.01 (0.09), $P = .90$	0.02 (0.08), $P = .83$	−0.01 (0.07), $P = .84$	0.00 (0.05), $P = .98$
IOPg	0.06 (0.08), $P = .47$	0.11 (0.12), $P = .36$	0.02 (0.09), $P = .84$	−0.03 (0.08), $P = .71$	−0.03 (0.07), $P = .62$
CCT	0.04 (0.07), $P = .58$	0.11 (0.13), $P = .38$	−0.04 (0.08), $P = .63$	0.11 (0.08), $P = .13$	0.05 (0.06), $P = .41$
CH	0.03 (0.06), $P = .58$	0.14 (0.09), $P = .12$	0.10 (0.06), $P = .13$	0.03 (0.06), $P = .60$	0.05 (0.04), $P = .24$
CRF	0.05 (0.06), $P = .45$	0.13 (0.09), $P = .14$	0.11 (0.06), $P = .07$	0.04 (0.05), $P = .50$	0.06 (0.04), $P = .16$
CDR	0.06 (0.06), $P = .39$	0.11 (0.10), $P = .28$	−0.02 (0.09), $P = .79$	−0.07 (0.08), $P = .37$	0.07 (0.07), $P = .26$
POAG	−0.02 (0.12), $P = .87$	0.04 (0.16), $P = .81$	0.00 (0.13), $P = .99$	−0.31 (0.14), $P = .02$	−0.14 (0.10), $P = .16$

2HG = 2-h glucose; CCT = central corneal thickness; CDR = cup-to-disc ratio; CH = corneal hysteresis; CRF = corneal resistance factor; FBS = fasting blood sugar; FI = fasting insulin; HbA1c = hemoglobin A1c; IOP = intraocular pressure measured with various tonometers in the International Glaucoma Genetics Consortium; IOPcc = corneal-compensated intraocular pressure measured in the UK Biobank study; IOPg = Goldmann-correlated intraocular pressure measured in the UK Biobank; POAG = primary open-angle glaucoma; T2D = type 2 diabetes.

Note: Tables 2, 3, and 4, use inverse rank normalized transformed genome-wide association study summary data for the oculus dexter for IOPcc, IOPg, CH, and CRF. For CCT we used raw genome-wide association study summary data based on the mean of both eyes.

and cornea-compensated IOP.[9] Of course, both epidemiologic[51] and genetic correlation analysis[24] strongly link IOP to POAG risk, and our study affirms the latter regardless of how IOP is measured. Yet the genetic correlations between any corneal phenotype (CCT, CRF, and CH) and POAG are not significant. Furthermore, while genetic correlations between IOP measured in the IGGC and corneal phenotypes and between IOPg and corneal phenotypes are all high, there was no correlation between IOPcc and CCT. Overall, these data suggest that from a genetic perspective CCT, CH and CRF quantify features unrelated to POAG, although they may be related to POAG phenotypically.

The epidemiologic association between diabetes and glaucoma is somewhat more controversial, but most studies indicate a positive association between the 2 conditions.[52] Our genetic correlation study, which is relatively free of bias related to reverse causation or disease detection, indicates a nonsignificant inverse genetic correlation between T2D and POAG. Furthermore, genetic correlations between IOP and T2D and between CDR and T2D are also null despite adequate power (power product ≥ 4800; Supplemental Table 1). Notably, we found strong genetic correlations between CDR and POAG despite only modest power (power product = 4400; Supplemental Table 1) and modest but nonsignificant correlations between CDR and IOP, suggesting that, from a genetic perspective, T2D genetic markers are largely not shared with POAG in European populations. These genetic findings may not be applicable to people of other ancestry but do seem adequately powered to address our study question and call for more prospective study of the relationship between diabetes and POAG using a population that is free of disease at

baseline and that is systematically monitored for both conditions.

Several longitudinal studies found a modest positive association between measured BMI and IOP,[53–55] while epidemiologic studies of the relation between BMI and incident POAG had mixed results.[56,57] In addition, some studies suggest that components of the metabolic syndrome are associated with open-angle glaucoma[58] but this association may vary by BMI status.[59] BMI is a readily obtainable phenotype with the largest summary GWAS dataset available among the traits we studied.[33] There is strong genetic correlation between BMI and T2D ($r_g = 0.35$; SE = 0.04; $P = 4.0 \times 10^{-15}$; Supplemental Table 4) but no significant correlation between BMI and any of the glaucoma-related traits ($P \geq .099$; Table 3). These findings suggest that if BMI or metabolic syndrome plays a role in POAG pathogenesis, they may do so through intermediary effects on the glaucomatous process that are not measured in this study.

While these results do not support genetic correlations between diabetes and glaucoma, there are several nongenetic explanations that can be advanced in support of a positive relation between diabetes and glaucoma. For example, it is possible that hyperglycemia leads to the accumulation of advanced glycation end products[60] and fibronectin production[61] in the trabecular meshwork leading to increased IOP in patients with T2D. Several reports indicate that experimental diabetes exacerbates IOP-induced optic damage[62-64]; however, there is contrary evidence that hyperglycemia was neuroprotective in a rodent model of glaucoma.[65] Finally, there is an anecdotal report of a rhesus monkey with spontaneous diabetes, elevated IOP, diabetic retinopathy, and glaucoma.[66]

This study has strengths and weaknesses. Strengths include the use of LD score regression, a novel unbiased approach, to assess correlations between many traits where strong positive associations are suspected, such as IOP and POAG,[24] and others where there is controversy, such as T2D and POAG.[25,26] Furthermore, our genetic correlation analysis between diabetes and glaucoma was extensive as we considered 9 diabetes- and 8 glaucoma-related traits. We included some studies where the genetic architecture for continuous traits were ascertained in populations where the prevalence of the respective related diseases (T2D and POAG) was minimized. Such approaches allow for the unbiased detection of novel physiologic loci that might be disease-related as well as cross-correlated with another disease. The absence of major genetic correlations between diabetes- and glaucoma-related traits is corroborated by pedigree data obtained in 2 cohorts. In addition, we leveraged the largest available samples of genetic data on diabetes- and glaucoma-related traits that were largely adequately powered. The cross-correlations within diabetes traits and within glaucoma traits produced expected results. For example, we estimated a strong inverse relation between HDL and T2D ($r_g = -0.40$; SE = 0.06; $P = 4.2 \times 10^{-11}$; Supplemental Table 4) and a strong positive genetic correlation between IOP measured in various ways and POAG, as previously reported.[24] Weaknesses include the fact that the study was limited to European populations, although some, but not all, data from Japan are consistent with our findings.[26] Second, the absence of a statistically significant genetic correlation does not rule out that a minority of genes are truly shared between diabetes- and glaucoma-related traits.

In summary, we found no genetic correlations between comprehensive sets of diabetes- and glaucoma-related traits. These findings were supported in analyses from 2 island-based cohorts designed to estimate genetic, environmental, and phenotypic correlations in directly measured traits that is informed by pedigree data. T2D and related quantitative traits also do not share significant genome-wide SNP heritability with POAG or its related traits. It is therefore reasonable to consider nongenetic factors, including those that affect the biomechanical properties of the cornea and perhaps even the optic nerve, as mediating the epidemiologic associations between diabetes and elevated IOP or POAG. These findings have important implications for our understanding of POAG.

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Drs Khawaja, MacGregor, and Pasquale contributed equally.

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THE ORKNEY COMPLEX DISEASE STUDY

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VIKING STUDY

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