Direct and Indirect Associations Between Diabetes and Intraocular Pressure: The Singapore Epidemiology of Eye Diseases Study

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PURPOSE. The association between diabetes and IOP is controversial; diabetes is associated with thicker central corneal thickness (CCT), and thicker CCT is associated with higher IOP. We therefore aimed to clarify the diabetes–IOP association, considering CCT as a potential mediator.

METHODS. We included 8636 participants from the Singapore Epidemiology of Eye Diseases (SEED) Study. Associations of diabetes, serum glucose, or HbA1c with IOP were assessed using regressions models, with adjustments for potential confounding factors. Regression-based mediation (path) analyses were further performed to evaluate the indirect effects of diabetes on IOP through the mediator (CCT), in addition to the direct effect of diabetes on IOP.

RESULTS. Of the 8636 participants, 2524 (29.23%) had diabetes. Diabetes, higher serum glucose, or HbA1c levels were all associated with higher IOP (all $P < 0.01$). The effect of diabetes on IOP was partially and minimally mediated through CCT; the proportion of mediating effect of CCT was 11.09% of the total effect of diabetes on IOP. Axial length and spherical equivalent were not mediating variables in the diabetes–IOP association. Findings were consistent across three ethnicity groups.

CONCLUSIONS. Diabetes or higher long-term hyperglycemia was associated with higher IOP. CCT contributed a small proportion of mediating effect to the total effect of diabetes on IOP. We conclude that high IOP observed in diabetes is mainly due to the direct association of diabetes and IOP, and this finding may have pathophysiologic significance with respect to the risk of glaucoma among persons with diabetes.

Keywords: diabetes, intraocular pressure, direct and indirect association, glaucoma

Diabetes commonly leads to complications in the eyes.[1-3] The association between diabetes and IOP has been documented in many studies,[4-9] although such an association was not entirely consistent in all studies.[10-13] Diabetes has also been associated with greater central corneal thickness (CCT).[14,15] Greater CCT may lead to an "overestimation" of the true IOP.[16-18] It remains unclear whether the diabetes–IOP association is mediated via thicker CCT among persons with diabetes. We hypothesize that thicker CCT in persons with diabetes partially explains the association between diabetes and IOP.

In addition to CCT, several possible indirect pathways, such as short axial length (AL) or myopic or hyperopic shifting in spherical equivalent (SE) refractive power, could also explain partly the diabetes–IOP association. Diabetes may affect AL and SE.[19-21] Lens thickness can be influenced by fluctuation of glucose levels in diabetes; increased aldose reductase activity

and sugar alcohol sorbitol levels in the lens can cause the lens to swell and change its refractive power.[22] Some studies documented that induced hyperglycemia had led to changes in refraction, and either myopic[23-25] or hyperopic shift[26-29] had been reported in patients with diabetes. However, there was a study reporting no changes in refractive properties during acute hyperglycemia.[30] There were studies documenting short AL associated with diabetes[23] and diabetic retinopathy.[20]

The overall aim of this study was twofold: first, to confirm the putative association between diabetes and IOP in a large multiethnic Asian sample of Malay, Indian, and Chinese participants; and second, to determine whether the association between diabetes and IOP was mediated primarily or partly through CCT or other potential mediating factors.

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METHODS

Study Population

The Singapore Epidemiology of Eye Diseases Study (SEED) is a population-based study, comprising three major ethnic groups in Singapore: Malay, Indian, and Chinese, separately conducted as Malay (the Singapore Malay Eye Study, 2004 to 2006), Indian (the Singapore Indian Eye Study, 2007 to 2009), and Chinese (the Singapore Chinese Eye Study, 2009 to 2011). The detailed methodology of the SEED study was published previously.[31,32] The sampling frame consisted of Malay, Indian, and Chinese subjects 40 to 80 years of age living in 15 residential districts across the southwestern part of Singapore. From an initial list names provided by the Ministry of Home Affairs, an age-stratified random sampling procedure was used to select 5600 names of each ethnic group (1400 people from each decade of aged ranging from 40 to 80 years). Of these, 3280 Malay (response rate 78.7%), 3400 Indian (75.6%), and 3353 Chinese (72.8%) participated in the study, respectively. The overall response rate for SEED was 75.6%. The SEED study was approved by the SingHealth Centralized Institutional Review Board and adhered to the tenets of the Declaration of Helsinki. Signed informed consent was obtained from all participants.

Ocular Examination

All subjects recruited in the SEED study underwent a standardized ocular examination at the Singapore Eye Research Institute.[31,32] Goldmann applanation tonometry (Haag-Streit, Koeniz, Switzerland) was used to measure IOP before pupil dilation. One reading was taken from each eye. If the reading was greater than 21 mm Hg, then a repeat reading was taken, and the mean of the two readings was used. Fundus examination included the evaluation of the optic disc with a 78-diopter (D) lens at 16× magnification with a measuring graticule during dilated ophthalmoscopy for the calculation of the vertical cup-disc ratio (VCDR). Standard automated perimetry (24-2 Swedish Interactive Thresholding Algorithm, Humphrey Visual Field Analyzer II; Carl Zeiss Meditec, Inc., Dublin, CA, USA) was also performed on glaucoma suspects. Glaucoma suspects were defined based on any of the following: (1) IOP >21 mm Hg, (2) VCDR >0.6 or VCDR asymmetry >0.2, (3) signs consistent with pseudoexfoliation or pigment dispersion syndrome, (4) narrow angles (posterior trabecular meshwork visible <180° during static gonioscopy), (5) peripheral anterior synechiae of the trabecular meshwork, (6) other findings consistent with secondary glaucoma, and (7) known history of glaucoma. Glaucoma was diagnosed according to International Society for Geographical and Epidemiologic Ophthalmology criteria. Auto refraction, keratometry, and corneal curvature were measured using an auto refractor (Canon RK-5 Auto Ref-Keratometer; Canon, Inc., Ltd., Tokyo, Japan). SE was calculated as the spherical power in diopter plus half of the negative cylinder power. AL was measured using noncontact partial coherence interferometry (IOLMaster V3.01; Carl Zeiss Meditec AG, Jena, Germany). CCT was measured from each eye using an ultrasound pachymeter (Advent; Mentor O&O, Inc., Norwell, MA, USA). The mean of five measurements of each parameter was used in analysis.

Systemic Measurements

An interviewer-administered questionnaire was used to collect demographic data,[31] lifestyle risk factors (e.g., smoking, education), medical history (e.g., history of diabetes or hypertension), ocular history (e.g., cataract surgery, previous refractive surgery, glaucoma surgery, or history of glaucoma), and medication use from all participants. Ethnicity was determined by the Singapore census and indicated on the National Registration Identity Card of Singapore citizens and permanent residents.[31,32] Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured using a digital automatic blood pressure monitor (Dinamap model Pro Series DP110X-RW, 100V2; GE Medical Systems Information Technologies, Inc., Milwaukee, WI, USA) following the protocol used in the Multi-Ethnic Study of Atherosclerosis,[33] after participants were seated for at least 5 minutes. Blood pressures were measured twice, at 5 minutes apart. A third measurement was taken if previous the SBP readings differed by more than 10 mm Hg or the DBP differed by more than 5 mm Hg. Mean arterial blood pressure (MABP) was calculated as [(2 × DBP) +SBP]/3. Body mass index (BMI) was calculated as body weight in kilograms divided by body height in squared meters. Blood samples were collected from study participants for serum glucose, serum glycosylated hemoglobin (HbA1c), serum cholesterol levels, and serum creatinine levels by biochemistry analysis. Nonfasting serum glucose level was measured using Beckman Coulter AU5800 (Beckman Coulter, Inc., Indianapolis, IN, USA). HbA1c level was measured using Roche Cobas c502 (Roche Diagnostics GmbH, Mannheim, Germany). All biochemistry tests were performed at the Division of Pathology, Singapore General Hospital, on the same day as the blood samples were collected.

Diabetes was defined as if any of the following criterions was met: nonfasting (random) glucose levels ≥200 mg/dL (11.1 mmol/L), a self-reported use of diabetic medication, physician diagnosis of diabetes, or serum HbA1c ≥6.5%.[1]

Statistical Analyses

Statistical analysis was performed using Stata Version 14.0 (StataCorp LP, College Station, TX, USA). We used data from one eye per subject in analysis, and when data from both eyes were available, we used the right eye. The comparisons of characteristics of persons, or eyes of persons with and without diabetes, were performed using χ^2 tests and t-tests for categorical and continuous data, respectively. Mediation analysis (also termed path analysis) was carried out to access the direct association between diabetes and IOP and their indirect effect through potential mediating variables (termed mediators).

In the first stage of analysis, multiple linear regression analysis was conducted to evaluate relationship between diabetes and IOP after adjusting for age, sex, ethnicity, MABP, smoking status, and BMI. The effect estimates of diabetes on IOP without taking into account any mediating variable were termed "total effects" (Fig., panel A).

In the second stage of analysis, associations between diabetes and potential mediating variable (CCT, AL, or SE), and associations between potential mediating variables and IOP, were assessed using multiple linear regression models, to screen for potential mediators for the diabetes–IOP association. Potential mediators must be independently associated with diabetes as well as independently associated with IOP and have plausible mechanism(s) underlying its mediating effect on the association. P value for significance was set at <0.05. Models were initially adjusted for age, sex, and ethnicity, and then further adjusted for MABP, smoking status, BMI, and additionally AL in the model assessing the association between IOP and CCT.

In the third stage of analysis, we performed regression-based mediation analyses (Fig., panel B) to evaluate the direct effect of exposure factor (diabetes primarily, and serum glucose and HbA1c as alternative exposure factor in supplement analyses) on the outcome (IOP), and the indirect effect
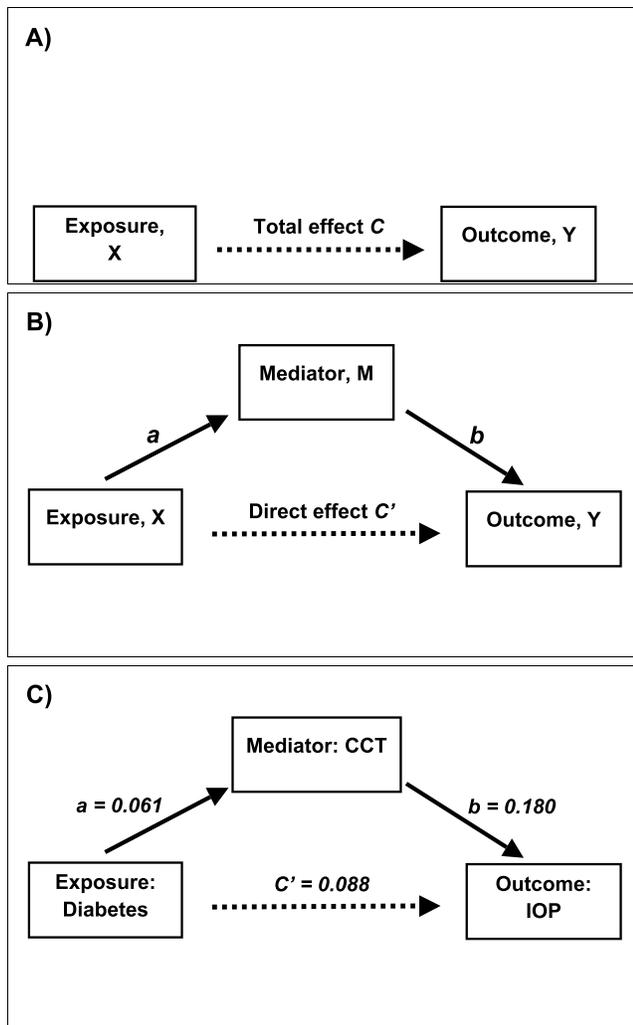
FIGURE. (A) Illustrations of the regression modeling of total, direct, and indirect effect in a mediation framework. The effect estimate of exposure X on outcome Y without taking into account mediator M is known as the total effect (denoted as coefficient c). (**B**) The effect estimate of X on Y while controlling for M is known as the direct effect (denoted as coefficient c'). The indirect effect of X on Y is quantified by multiplication between standardized coefficient a and standardized coefficient b. Proportion of mediated (*PM*) effect by the intermediate variable is calculated as the ratio of indirect effect to total effect ($\frac{a*b}{(a*b)+c'}$). (**C**) Path analysis shows the direct and indirect associations of diabetes (X) with IOP (Y) through CCT (M). The direct effect (C') between diabetes and IOP is $\beta' = 0.088$; the indirect effect ($a*b$) of diabetes with IOP via CCT is $\beta' = (0.061 \times 0.180) = 0.011$. Proportion of mediated (*PM*) effect through CCT was 11.09%.

via mediating variables such as CCT or other potential mediators identified at the second stage of analysis. Partial coefficients (β) derived from path regression analysis were used to estimate the magnitude of direct and indirect effects of the diabetes–IOP association. These partial coefficients are standardized regression coefficients, indicating the magnitude of change in the outcome (dependent) variable per unit change in the exposure (independent) variable. For instance, the indirect association of diabetes (exposure factor) with IOP (outcome) is the product of the association between diabetes and CCT (mediator) and the association between CCT and IOP. The total association of diabetes with IOP (Fig., panel A: Total effect) is the sum of the direct and indirect associations. Proportion of mediating effect (*PM*) by the mediator was

calculated as the ratio of the indirect effect to the total effect (Fig., panel B).[34]

RESULTS

Of the 10,033 participants (3280 Malay, 3400 Indian, and 3353 Chinese), we excluded 448 subjects with missing diabetes information; 39 with previous refractive surgery, 265 with previous glaucoma surgery or on antiglaucoma medication, and 645 with previous cataract surgery, corneal edema, or corneal dystrophy. This left 8636 subjects for analysis, comprising of 2971 Malay, 2879 Indian, and 2786 Chinese.

The participants' demographics and ocular characteristics by diabetes status are shown in Table 1. The mean age was 57.7 ± 9.85 years. Of the 8636 subjects, 4276 (49.5%) were male, and 2524 (29.2%) had diabetes. Compared to participants without diabetes, those with diabetes were older and more likely to be Indian, past smokers, and have a lower education level, higher SBP or MABP, higher BMI, higher serum cholesterol levels, higher serum creatinine levels, and higher serum glucose and HbA1c levels. Furthermore, participants with diabetes had poorer best-corrected visual acuity, higher mean IOP, and shorter AL in the study (primarily right) eyes. Of note, there was no significant difference in the CCT between the participants with and without diabetes in crude analysis (the unadjusted mean CCT was 545.05 ± 33.61 vs. 544.56 ± 33.96 μm, $P = 0.542$), whereas the IOP in participants with diabetes (15.92 ± 3.24 mm Hg) was higher than those without (14.86 ± 3.16 mm Hg, $P < 0.001$). The observation of higher IOP in those with diabetes was consistent across both males (0.55 ± 0.12 mm Hg higher, $P < 0.001$) and females (0.83 ± 0.11 mm Hg higher, $P < 0.001$).

In the multiple linear regression model adjusted for age, sex, ethnicity, MABP, smoking status, and BMI, diabetes was significantly associated with higher IOP level ($\beta = 0.69$; 95% confidence interval [CI]: 0.53, 0.84; Table 2). Mediating variables were identified based on multiple linear regression findings shown in Tables 2 and 3. After adjusting for age, sex, ethnicity, MABP, smoking status, and BMI, diabetes was significantly associated with thicker CCT ($\beta = 4.59$; 95% CI: 2.91, 6.29) and shorter AL ($\beta = -0.11$; 95% CI: −0.17, −0.05), but not associated with SE ($\beta = -0.04$; 95% CI: −0.15, 0.08). After adjusting for age, sex, ethnicity, MABP, smoking status, and BMI, thicker CCT ($\beta = 0.02$; 95% CI: 0.02, 0.02) and lower SE ($\beta = -0.06$; 95% CI: −0.09, −0.03) were independently associated with higher IOP, whereas AL was not associated with IOP ($\beta = -0.03$; 95% CI: −0.09, 0.03; Table 3).

Based on the above analyses, only CCT was identified as a potential mediating variable to be included in the mediation analysis for the diabetes–IOP association, as it was associated with both diabetes (Table 2) and IOP (Table 3). Neither SE (which was not associated with diabetes, $P = 0.515$) nor AL (which was not associated with IOP, $P = 0.318$) was a mediator.

Table 4 showed that the direct association between diabetes and IOP was $\beta' = 0.088$ (95% CI: 0.067, 0.110) and the indirect association via CCT was $\beta' = 0.011$ (95% CI: 0.007, 0.015). We found that, although both direct and indirect associations were statistically significant, the proportion of mediating effect through CCT was small (*PM* = 11.09%). Similar associations were evident in the three subgroups by ethnicity.

Findings of additional pathway analyses of hyperglycemia–IOP associations were shown in Table 5. After adjusting for the same potential confounders, higher serum glucose or HbA1c levels were significantly associated with higher IOP. These associations were observed in all participants, as well as among those with diabetes (all $P < 0.05$ for total effects). The indirect effects of serum glucose or HbA1c on IOP via CCT were also

TABLE 1. Participants' Demographics and Clinical and Ocular Characteristics

Characteristics	Total (n = 8636)		Diabetes (n = 2524)		No Diabetes (n = 6112)		P Value*
	Mean/Frequency	SD/%	Mean/Frequency	SD/%	Mean/Frequency	SD/%	
Demographic and systemic factors							
Age, y	57.70	9.85	60.45	9.59	56.57	9.74	<0.001
Sex, male	4276	49.51	1280	50.71	2996	49.02	0.152
Ethnicity							
Malay	2971	34.40	949	37.60	2022	33.08	<0.001
Indian	2879	33.34	1114	44.14	1765	28.88	
Chinese	2786	32.26	461	18.26	2325	38.04	
Education level							
Primary or lower	5102	59.17	1719	68.35	3383	55.40	<0.001
Secondary or above	3520	40.83	796	31.65	2724	44.60	
Smoking status							
Never	5969	69.20	1734	68.84	4235	69.35	<0.001
Current smoker	1434	16.62	357	14.17	1077	17.64	
Past smoker	1223	14.18	428	16.99	795	13.01	
SBP, mm Hg	139.4	21.90	145.38	22.24	136.91	21.27	<0.001
DBP, mm Hg	78.68	10.53	78.87	10.60	78.60	10.50	0.273
MABP, mm Hg	98.91	12.90	101.04	12.93	98.04	12.79	<0.001
BMI, kg/m^2	25.49	4.69	26.99	4.84	24.87	4.52	<0.001
Total cholesterol, mmol/L	5.46	1.12	5.24	1.26	5.55	1.05	<0.001
Serum creatinine, mg/dL	0.92	0.48	0.98	0.62	0.89	0.41	<0.001
Serum glucose, mmol/L	6.77	3.41	9.93	4.84	5.50	1.13	<0.001
Serum HbA1c, %	6.31	1.33	7.77	1.70	5.72	0.35	<0.001
Ocular factors							
Best-corrected visual acuity, logMAR	0.13	0.32	0.18	0.38	0.11	0.29	<0.001
SE, D	−0.31	2.37	−0.09	2.26	−0.39	2.41	<0.001
Corneal curvature, mm	7.64	0.26	7.62	0.26	7.65	0.26	<0.001
IOP, mmHg	15.17	3.22	15.92	3.24	14.86	3.16	<0.001
CCT, μm	544.70	33.86	545.05	33.61	544.56	33.96	0.542
Axial length, mm	23.64	1.21	23.47	1.10	23.71	1.24	<0.001

MABP was calculated as [(2 × DBP) + SBP]/3. Data presented are mean (SD) or frequency (%), where appropriate.

* P value was based on χ^2 or t-test where appropriate.

statistically significant in all participants, as well as among those with diabetes. In participants with diabetes, the proportions of indirect effect mediated through CCT were 21.57% and 17.31%, respectively, for the glucose-IOP and

TABLE 2. Associations of Diabetes with IOP and Potential Intermediate Variables Assessed Using Multiple Linear Regression Analysis

Diabetes as the Exposure Variable With the Following Factors as Respective Outcomes	Model 1 β (95% CI)	Model 2 β (95% CI)
Men		
Diabetes, yes	0.61 (0.39,0.82)*	0.55 (0.32,0.78)*
Women		
Diabetes, yes	1.04 (0.83, 1.25)*	0.83 (0.62, 1.04)*
IOP	0.83 (0.68, 0.98)*	0.69 (0.53, 0.84)*
CCT	5.23 (3.62, 6.83)*	4.59 (2.91, 6.29)*
AL	−0.09 (−0.15, −0.03)†	−0.11 (−0.17, −0.05)*
SE	−0.02 (−0.14, 0.09)	−0.04 (−0.15, 0.08)

β represents adjusted difference in potential mediating variables between persons with and without diabetes (reference group). Model 1: adjusted for age, sex, and ethnicity. Model 2: β for AL and SE was adjusted for age, sex, ethnicity, MABP, smoking status, and BMI, whereas β for IOP and CCT was additionally adjusted for AL.

* P < 0.01.

† P < 0.05.

HbA1c-IOP associations. In participants without diabetes, there was no association between serum glucose and IOP. Although higher HbA1c was associated with higher IOP (β′ = 0.035; 95% CI: 0.009, 0.060), the indirect effect via CCT was not significant for the HbA1c–IOP association in persons with diabetes.

DISCUSSION

In this large, multiethnic, Asian population, we confirmed the associations of diabetes, or higher glycemic levels, with higher IOP. Second, although greater CCT in diabetes contributed significantly to higher IOP, the indirect contribution of CCT to the diabetes–IOP association was small (11.09% of the total association between diabetes and IOP). Third, in all participants or in those with diabetes, higher nonfasting serum glucose or HbA1c levels were significantly associated with higher IOP; and the indirect effect of CCT contributing to these associations was significant but small (20% or less) in proportions of the total association. In participants without diabetes, the HbA1c-IOP association was not mediated through CCT. Our findings suggest that higher IOP associated with diabetes is not primarily mediated through thicker CCT. Therefore, diabetes and poorer long-term glycemic control may potentially place one at a greater risk of glaucoma through non–CC-related mechanisms.

Previous studies had shown inconsistent results between diabetes (or poorer glycemic control) and IOP. The Rotterdam

TABLE 3. Associations of Potential Intermediate Variables With IOP Assessed Using Multiple Linear Regression Analysis

IOP as Outcome	Model 1 β (95% CI)	Model 2 β (95% CI)
CCT, per um thicker	0.02 (0.02, 0.02)*	0.02 (0.02, 0.02)*
AL, per mm longer	−0.01 (−0.07, 0.04)	−0.03 (−0.09, 0.03)
SE, per diopter higher	−0.06 (−0.09, −0.03)*	−0.06 (−0.09, −0.03)*

β represents adjusted change in IOP per unit change in the respective potential mediating variables. Model 1: adjusted for age, sex, and ethnicity. Model 2: β for AL and SE was adjusted for age, sex, ethnicity, MABP, smoking status, and BMI, whereas β for CCT was additionally adjusted for AL.

* $P < 0.001$.

Study and the Blue Mountains Eye Study[4,5] documented the association between diabetes and elevated IOP. However, other studies,[10,12,13] where diabetes was defined by a self-reported history, showed that diabetes was not associated with higher IOP. The present study supported the association between diabetes and higher IOP. Interestingly, we also found that even in those without diabetes, higher HbA1c levels were associated with higher IOP.

It is postulated that hyperglycemia may lead to the accumulation of sorbitol in the cornea, and due to osmotic forces, sorbitol may result in the influx of water from the aqueous into the cornea.[35,36] CCT is known to affect IOP measurement. Applanation tonometry estimates IOP via measuring the force required to flatten cornea area. Therefore, a thinner cornea may lead to underestimation and a thicker cornea overestimation of the true IOP.[16-18] In this present study, we found that diabetes and poorer glycemic control have predominately direct associations with higher IOP and only minimal indirect associations through thicker CCT. These findings reassure that high IOP among diabetes is not an overestimate due to thicker CCT.

Genetics studies have showed that the FNC3B gene is associated with both CCT and IOP,[37-39] with IOP-associated single nucleotide polymorphisms (SNPs) (rs6445055, rs7635832) and CCT-associated SNPs (rs4894535) all located within the same gene. We further found that there is high linkage disequilibrium (LD) between the two pairs of IOP- and CCT-associated SNPs ($D' = 1.0$; $R^2 = 0.99$ for rs6445055, rs4894535 and $D' = 1.0$; $R^2 = 0.961$ for rs7635832, rs4894535). As these two pairs of SNPs are highly correlated and often coinherited, this could lead to potential collider bias when conditioning on CCT as a mediator. Previously findings have found the effect size of the mentioned SNPs to be relatively small ($\beta_{rs6445055} = -0.121$, $\beta_{rs4894535} = -0.10$, and $\beta_{rs7635832} = -0.22$, all reported βs are unstandardized).

We further conducted a sensitivity analysis to assess how our results could be affected by this collider bias imposed by the associated SNPs among the subset of participants with genetic data available. Our results showed that the impact of this bias imposed is small as results obtained from model controlling for the genetic variants were not drastically different from the model without. Therefore, we conclude that the existence of collider bias imposed by genetic variants does not invalidate our findings.

The exact physiologic mechanism that underlies the association between diabetes and higher IOP is not clear. Our finding that HbA1c levels were associated with IOP irrespective of diabetes status implies that long-term hyperglycemia may induce changes that increase IOP. This could be related to the accumulation of advanced glycation end (AGE) products.[40] AGE products in turn promote cellular senescence and induce apoptosis of human trabecular meshwork cells. With dysfunction of the trabecular meshwork, IOP may increase. Another postulation is the effects of TGF-β. TGF-β was found to be elevated in the aqueous humor and trabecular meshwork of eyes with diabetes or glaucoma.[41] In animal studies, human TGF-β2 was found to reduce outflow of the aqueous and elevate IOP in rodent eyes.[42]

Strengths of our study include a large-sample population from three ethnic groups with high participation rates (response rate, 75.6%) and a comprehensive and standardized assessment of systemic and ocular parameters, which allowed for adjustment of multiple potential confounders. Limitations of this study are threefold. First, our cross-sectional study design limits inferences of causality, and the association direction (from diabetes to higher IOP) was established based on content knowledge with plausible mechanisms. Second, we were unable to examine the contribution of other factors (e.g., ocular concentrations of AGE products, TGF-β, or lens thickness) that may underlie the association between diabetes and higher IOP. Third, it may have the possible existence of collider biases imposed on the direct effect by unknown and unmeasured genetic variants correlated with both CCT and IOP. Based on current GWAS findings, only gene FNDC3B has been reported to be associated with both CCT and IOP, from which we concluded that the extent of imposed bias is small. However, there might still exist other unknown genes and SNPs correlated with both CCT and IOP yet to be discovered for which we cannot assess their bias impact.

In summary, we confirmed that diabetes or high HbA1c levels are associated with increased IOP. The observed association of diabetes or hyperglycemia with IOP was minimally through the effects of diabetes on CCT and the influence of CCT on IOP measurement. The high IOP level observed in persons with diabetes is not predominantly an overestimation of IOP due to thicker CCT in diabetes, and therefore may increase the risk of glaucoma among persons with diabetes.

TABLE 4. Direct and Indirect Effects of Diabetes on IOP Through CCT: Findings From Path Analysis, Stratified by Ethnicity

Effect	Overall β'	95% CI	PM (%)	Chinese β'	95% CI	PM (%)	Indian β'	95% CI	PM (%)	Malay β'	95% CI	PM (%)
Total effect	0.099	(0.078, 0.121)*		0.116	(0.078, 0.154)*		0.111	(0.073, 0.148)*		0.078	(0.040, 0.116)*	
Direct effect	0.088	(0.067, 0.110)*		0.107	(0.070, 0.144)*		0.101	(0.063, 0.138)*		0.066	(0.028, 0.103)†	
Indirect effect	0.011	(0.007, 0.015)*	11.09	0.009	(0.001, 0.016)†	7.43	0.010	(0.004, 0.016)†	9.20	0.013	(0.004, 0.021)†	16.13

β' represents standardized β coefficients (direct, indirect, and total effect estimates) derived from regression-based path analysis, adjusted for age, sex, ethnicity, MABP, axial length, smoking status, and BMI. All effect sizes were significant ($P < 0.05$).

* $P < 0.001$.
† $P < 0.05$.

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TABLE 5. Direct and Indirect Effects of Random Glucose or HbA1c on IOP Through CCT, Findings From Path Analysis, Stratified by Diabetes Status

Effect	Overall			Diabetes			No Diabetes‡	
	β'	95% CI	PM (%)	β'	95% CI	PM (%)	β'	95% CI
Random serum glucose								
Total effect	0.075	(0.054, 0.096)*		0.051	(0.011, 0.092)†		0.016	(−0.009, 0.042)
Direct effect	0.065	(0.044, 0.085)*		0.041	(0.001, 0.080)†		0.016	(−0.009, 0.041)
Indirect effect	0.010	(0.006, 0.015)*	13.33	0.011	(0.003, 0.019)**	21.57	0.000	(−0.004, 0.005)
HbA1c								
Total effect	0.085	(0.064, 0.106)*		0.052	(0.011, 0.093)†		0.035	(0.009, 0.060)†
Direct effect	0.075	(0.054, 0.096)*		0.043	(0.003, 0.083)†		0.033	(0.008, 0.058)†
Indirect effect	0.010	(0.006, 0.015)*	11.76	0.009	(0.001, 0.017)†	17.31	0.001	(−0.003, 0.006)

β' represents standardized β coefficients (for direct, indirect, and total effect estimates) derived from regression-based path analysis, adjusted for age, sex, ethnicity, MABP, axial length, smoking status, and BMI. The PM by CCT was calculated as the ratio of the indirect effect to the total effect.
* $P < 0.001$.
† $P < 0.05$.
‡ The indirect effect was not significant in persons without diabetes; hence, PM is not applicable and not presented for this group.

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