Diabetes, Fasting Glucose, and the Risk of Glaucoma

A Meta-analysis

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Topic: We performed a systematic review to summarize the association of diabetes and blood glucose levels with glaucoma, intraocular pressure (IOP), and ocular hypertension in the general population.

Clinical Relevance: Diabetes has been proposed as a risk factor for glaucoma, but epidemiologic studies have been inconsistent, and the association is still controversial. Furthermore, no systematic reviews evaluated other metabolic abnormalities, such as the metabolic syndrome, with the risk of glaucoma.

Methods: We identified the studies by searching the PubMed and EMBASE databases. We used inverse-variance weighted random-effects models to summarize relative risks across studies.

Results: We identified 47 studies including 2 981 342 individuals from 16 countries. The quality of evidence generally was higher in the cohort compared with case-control or cross-sectional studies. The pooled relative risk for glaucoma comparing patients with diabetes with those without diabetes was 1.48 (95% confidence interval [CI], 1.29–1.71), with significant heterogeneity across studies ($I^2 = 82.3\%$; $P < 0.001$). The risk of glaucoma increased by 5% (95% CI, 1%–9%) for each year since diabetes diagnosis. The pooled average difference in IOP comparing patients with diabetes with those without diabetes was 0.18 mmHg (95% CI, 0.09–0.27; $I^2 = 73.2\%$), whereas the pooled average increase in IOP associated with an increase in 10 mg/dl in fasting glucose was 0.09 mmHg (95% CI, 0.05–0.12; $I^2 = 34.8\%$).

Conclusions: Diabetes, diabetes duration, and fasting glucose levels were associated with a significantly increased risk of glaucoma, and diabetes and fasting glucose levels were associated with slightly higher IOP. *Ophthalmology 2015;122:72-78 © 2015 by the American Academy of Ophthalmology.*

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Glaucoma, the most common cause of irreversible blindness worldwide, represents a major public health problem.[1] The number of glaucoma patients in the United States is expected to increase from 2.7 million in 2010 to 6.3 million in 2050.[2] Elevated intraocular pressure (IOP) or ocular hypertension (OHT) is the only well-established modifiable risk factor for primary open-angle glaucoma (POAG), the most common form of glaucoma. Thus, there is considerable interest in identifying potentially modifiable risk factors for glaucoma to develop interventions that may reduce the incidence or improve the prognosis of the disease.

Diabetes mellitus has been suggested to causes microvascular damage and vascular dysregulation of the retina and the optic disc, increasing the susceptibility of the optic nerve head to damage in glaucoma.[3–5] Diabetes also may result in elevated IOP and increased risk of POAG by disrupting the trabecular meshwork function.[6] Diabetes has been proposed as a risk factor for elevated IOP and POAG, but epidemiologic studies of the association between diabetes mellitus and glaucoma have been inconsistent,[7–10] and the association is still controversial.

A meta-analysis published in 2004 evaluated the available literature on the association between diabetes mellitus and glaucoma.[11] This meta-analysis was based on 12 cross-sectional or case-control studies published before 2002. Several studies, including 6 longitudinal studies published in the past 10 years, have never been appraised systematically. Furthermore, there are no systematic reviews evaluating other metabolic abnormalities, such as the metabolic syndrome, with the risk of glaucoma. Our objective thus was to conduct a comprehensive and updated systematic review and meta-analysis to summarize the association between diabetes, diabetes duration, metabolic syndrome, and glucose levels with the risk of glaucoma and with IOP levels in the general population.

Methods

Search Strategy and Study Selection

Our systematic review and meta-analysis was reported according to the Meta-analysis of Observational Studies in Epidemiology guidelines.[12] The protocol for the systematic review was registered in the International Database of Prospectively Registered

Systematic Reviews (no. CRD42013005989). We searched MEDLINE and EMBASE to identify relevant studies. The search items were based on established terminology using MESH and EMBASE extensive search terms when possible. Keywords included *diabetes mellitus, diabetes, metabolic syndrome, hyperglycemia, insulin resistance, hyperinsulinism, blood glucose, hemoglobin A1c, blood sugar, pancreas islet disease, intraocular pressure, intraocular tension, eye pressure, eye internal pressure, intraorbital pressure, ocular pressure, ocular tension, intraocular hypertension, intraocular tension,* and *glaucoma.* The terms *diabetes* and *glaucoma* are general key terms that cover their subtypes in MEDLINE and EMBASE database searches and details are included in Appendix A (available at www.aaojournal.org). We also manually reviewed the reference lists from retrieved articles and identified additional relevant studies. The databases were searched for reports published through May 2013 with no language restrictions.

We aimed to identify all studies reporting an association between diabetes, metabolic syndrome, or glucose levels with glaucoma, IOP levels, or OHT in adults 18 years of age or older. The exclusion criteria were: (1) no original research (reviews, commentaries, editorials, or letters); (2) case reports or case series; (3) studies not conducted in humans or adults; (4) studies conducted in population samples comprising only patients with diabetes, metabolic syndrome, glaucoma, or OHT at baseline; (5) studies not reporting glaucoma, IOP, or OHT as outcomes; (6) studies not using diabetes, metabolic syndrome, blood glucose, or hemoglobin A1c as exposures; (7) studies mainly investigating drug effects or metabolism; or (8) studies conducted in population samples comprising only patients with specific conditions (e.g., hemodialysis, eye surgery) that limit their generalizability to general population samples. Because age is a strong risk factor for glaucoma and for diabetes development, we further excluded studies that did not adjust for age in the design or the analysis.

The study end points were POAG, IOP, and OHT. For studies that did not report POAG separately from other types of glaucoma, we used results for open-angle glaucoma or glaucoma as end points. If more than 1 published article reported on the same association within a study population, we selected the most recent publication or the publication with the longest follow-up. Studies reporting only correlation coefficients or point estimates of other measures of association without standard errors or any other estimates of statistical variability were included in the systematic review, but were excluded from the quantitative meta-analysis.

Data Extraction and Quality Assessment

Two authors (D.Z. and M.K.) independently reviewed all search results to identify eligible studies and abstracted data from selected articles. Discrepancies between reviewers were resolved by consensus or adjudication by the third reviewer (E.G.). The following data were extracted from each study: publication year, country where the study was performed, study period, study size, gender and age of study participants, measure and range of exposure, methods for identification of type 2 diabetes, variables adjusted for in the analysis, and reported measures of association with corresponding standard errors or 95% CIs. We assessed study quality using the methods described by Sanderson et al[13] and Viswanathan et al.[14] We examined the methods for selecting study participants, the criteria for defining exposures and outcomes, the

risk of bias associated with different designs, the methods used to control for confounding, and potential conflicts of interest (Appendix B, available at www.aaojournal.org).

Statistical Analysis

We conducted a separate meta-analysis for each combination of exposure (diabetes, diabetes duration, metabolic syndrome, and glucose levels) and outcome (glaucoma, IOP, and OHT) using random-effects meta-analyses to combine study-specific measures of association. For binary outcomes (glaucoma and OHT), the measures of association abstracted (odds ratios, incidence risk ratios, and hazard ratios) were combined together and referred to as relative risk (RR). We estimated the pooled average difference in IOP in millimeters of mercury comparing patients with and without diabetes and comparing patients with and without metabolic syndrome, as well as the pooled average difference in IOP associated with an increase in 10 mg/dl of serum glucose. Finally, we estimated the increase in glaucoma risk associated with a 1-year increase in diabetes duration compared with no diabetes by using a random-effects dose-response meta-analysis.[15,16]

When a study reported several models for a given end point, we used the measure of association with the greatest degree of control for potential confounders. For studies reporting results separately by subgroup (e.g., reporting results separately by men and women, diabetes with treatment and without treatment in one study), we pooled results across subgroups for each study first. For studies reporting standardized regression coefficients (e.g., the change of outcome with 1-standard deviation increase in exposure), we used the standard deviations reported for that population to recalculate unstandardized regression coefficients (the change of outcome with 1 unit increase in exposure).

Between-study heterogeneity was quantified using the I^2 statistic. We also conducted sensitivity analyses omitting 1 study at a time to assess whether results were markedly affected by any single study. Publication bias was evaluated by funnel plots and by Egger's tests.[17] To examine potential sources of heterogeneity by study type (case-control, cross-sectional, longitudinal), location (Europe, America, Asia, other), year of publication (<2000, ≥2000), and exposure and outcome definitions, we used meta-regression models with restricted maximum likelihood estimation of between-study variance. Meta-analyses were conducted with Stata software version 12 (STATA Corp, College Station, TX).

Results

We identified 47 studies, including 2 981 342 individuals from 16 countries (Fig 1 and Table 1, available at www.aaojournal.org). Sixteen studies were performed in North America, 15 in Asia, 11 in Europe, 2 in Australia, 1 in Africa, 1 in the Middle East, and 1 in the West Indies (Table 2, available at www.aaojournal.org). Thirty-two studies were cross-sectional, 9 were case-control, and 6 were longitudinal. Twenty-nine studies reported on the association between diabetes and glaucoma, 5 on diabetes duration and glaucoma, 2 on hemoglobin A1c and glaucoma, 1 on metabolic syndrome, glucose levels and glaucoma, 11 on diabetes and IOP levels, 6 on glucose and IOP levels, 6 on diabetes and OHT, and 1 on glucose and OHT. The definitions of the exposures and outcomes and the factors used for adjustment in each study are summarized in Tables 3 and 4 (available at www.aaojournal.org).

As described in Appendix B (available at www.aaojournal.org), the quality of the evidence generally was good in longitudinal cohort studies, but fair or poor in case-control and cross-sectional studies.

The prevalence of glaucoma ranged from 1.5% to 8.1%, and the prevalence of OHT ranged from 1.1% to 10.9% across studies. Among 29 studies that used glaucoma as outcome, 10 studies used characteristics of the optic disc, anterior chamber angle, optic nerve damage, or visual field changes as diagnostic criteria; 10 studies also considered IOP as an additional criteria; 4 studies used medical records, medication prescription records, or medical database data; and 5 studies used self-reports. Among 17 studies using IOP levels as outcome, 7 measured IOP using Goldmann applanation tonometers and 10 measured IOP using noncontact tonometers.

Glaucoma

The pooled RR for glaucoma comparing patients with diabetes with those without diabetes was 1.48 (95% CI, 1.29−1.71), with significant heterogeneity across studies ($I^2 = 82.3\%$; $P < 0.001$; Fig 2). The estimates from cross-sectional, case-control, and longitudinal studies were similar (RR, 1.58, 1.44, and 1.37,

respectively). The results also were similar by country, method for ascertainment of diabetes, criteria for defining glaucoma, and year of publication. However, the pooled RR for studies using exclusively POAG as outcome was 1.23 (95% CI, 1.04−1.45), whereas the RR for studies using open-angle glaucoma or glaucoma as outcome was 1.71 (95% CI, 1.44−2.03). The pooled RRs obtained after omitting 1 study at a time ranged from 1.43 to 1.52. Egger's test for publication bias was statistically significant ($P < 0.001$), and funnel plots suggested that small studies were reporting stronger associations compared with larger studies, although large studies also reported positive associations.

Among 5 studies with dose-response data on the association of diabetes duration with glaucoma, the risk of glaucoma increased by 5% (95% CI, 1%−9%) for each year since diabetes diagnosis (Fig 3). In one study reporting the association between metabolic syndrome and POAG,[18] the RR for POAG comparing participants with 2 or more metabolic syndrome components compared with those with 1 or fewer components was 0.52 (95% CI, 0.37−0.73). One cross-sectional study reported the association between impaired blood glucose and POAG[19] with an RR of 1.2 (95% CI, 0.8−1.8).

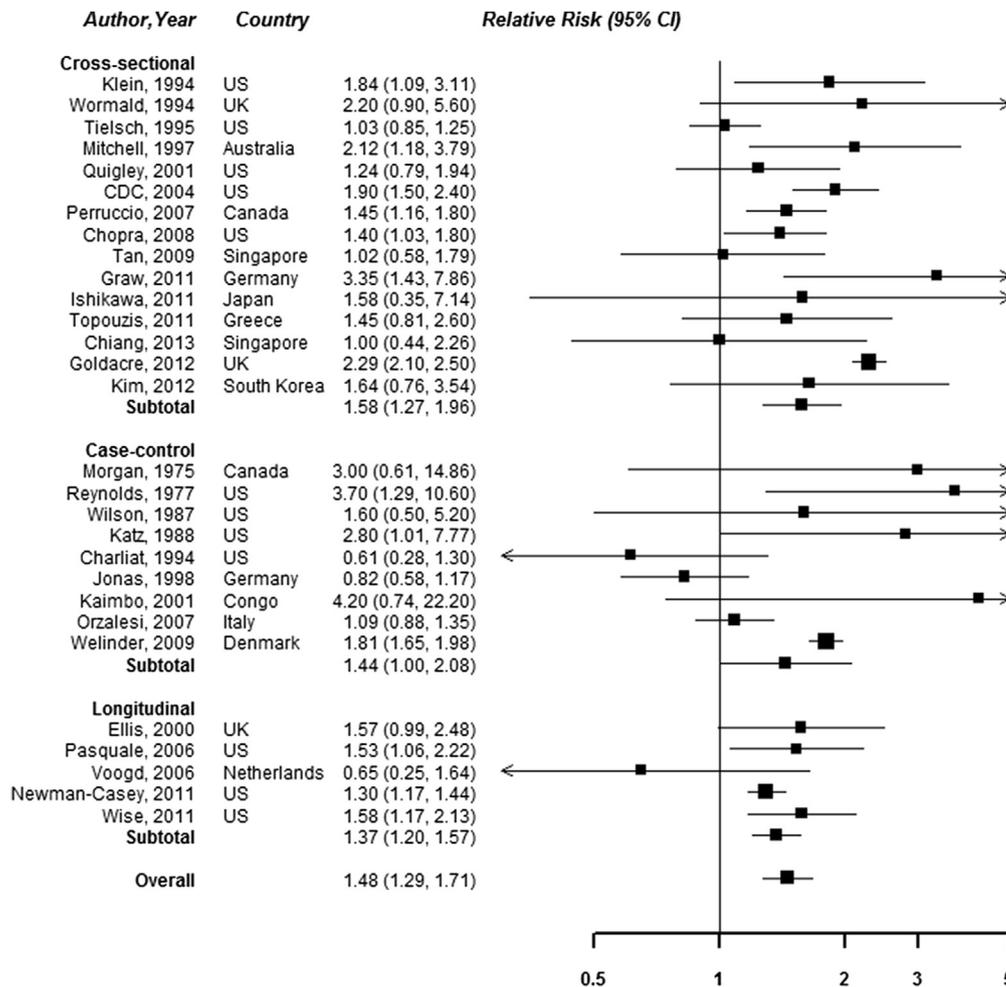| Author, Year	Country	Relative Risk (95% CI)
Cross-sectional		
Klein, 1994	US	1.84 (1.09, 3.11)
Wormald, 1994	UK	2.20 (0.90, 5.60)
Tielsch, 1995	US	1.03 (0.85, 1.25)
Mitchell, 1997	Australia	2.12 (1.18, 3.79)
Quigley, 2001	US	1.24 (0.79, 1.94)
CDC, 2004	US	1.90 (1.50, 2.40)
Perruccio, 2007	Canada	1.45 (1.16, 1.80)
Chopra, 2008	US	1.40 (1.03, 1.80)
Tan, 2009	Singapore	1.02 (0.58, 1.79)
Graw, 2011	Germany	3.35 (1.43, 7.86)
Ishikawa, 2011	Japan	1.58 (0.35, 7.14)
Topouzis, 2011	Greece	1.45 (0.81, 2.60)
Chiang, 2013	Singapore	1.00 (0.44, 2.26)
Goldacre, 2012	UK	2.29 (2.10, 2.50)
Kim, 2012	South Korea	1.64 (0.76, 3.54)
Subtotal		1.58 (1.27, 1.96)
Case-control		
Morgan, 1975	Canada	3.00 (0.61, 14.86)
Reynolds, 1977	US	3.70 (1.29, 10.60)
Wilson, 1987	US	1.60 (0.50, 5.20)
Katz, 1988	US	2.80 (1.01, 7.77)
Charliat, 1994	US	0.61 (0.28, 1.30)
Jonas, 1998	Germany	0.82 (0.58, 1.17)
Kaimbo, 2001	Congo	4.20 (0.74, 22.20)
Orzalesi, 2007	Italy	1.09 (0.88, 1.35)
Welinder, 2009	Denmark	1.81 (1.65, 1.98)
Subtotal		1.44 (1.00, 2.08)
Longitudinal		
Ellis, 2000	UK	1.57 (0.99, 2.48)
Pasquale, 2006	US	1.53 (1.06, 2.22)
Voogd, 2006	Netherlands	0.65 (0.25, 1.64)
Newman-Casey, 2011	US	1.30 (1.17, 1.44)
Wise, 2011	US	1.58 (1.17, 2.13)
Subtotal		1.37 (1.20, 1.57)
Overall		1.48 (1.29, 1.71)

Figure 2. Graph showing the relative risk for glaucoma comparing patients with diabetes with those without diabetes. The size of the box representing the point estimate for each study in the forest plot is proportional to the contributing weight of that study estimate to the summary estimate. Horizontal lines represent 95% confidence intervals (CI). UK = United Kingdom; US = United States.
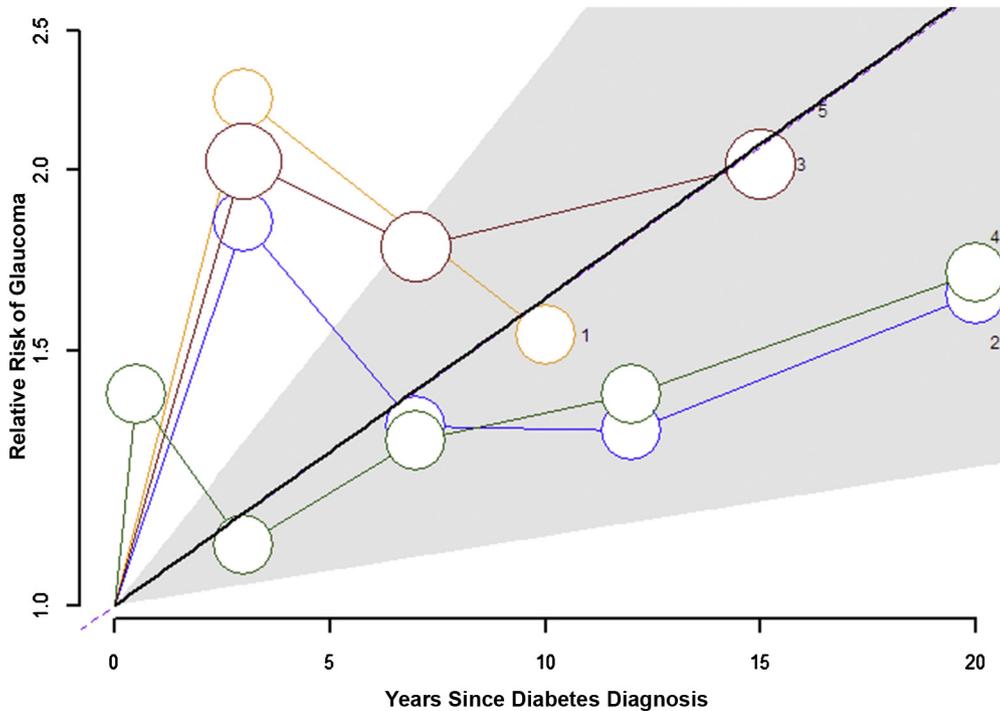
Figure 3. Graph showing the relative risk for glaucoma with increasing duration of diabetes in a dose-response meta-analysis. Circle areas are inversely proportional to the variance of the log relative risks. The pooled linear risk trend (thick solid line) and its 95% confidence band (shaded region) were obtained using a random-effects dose-response meta-analysis. The individual studies were Pasquale et al (2006),[33] Wise et al (2011),[36] Welinder et al (2009),[37] Chopra et al (2008),[19] and Chiang et al (2013).[38]

Intraocular Pressure

The pooled average difference in IOP comparing patients with diabetes with those without diabetes was 0.18 mmHg (95% CI, 0.09–0.27), with substantial heterogeneity ($I^2 = 72.3\%$; Fig 4). The pooled estimates were not statistically different by study design, country, method for ascertainment of diabetes, method of IOP measurement, and year of publication (<2000, ≥2000). The pooled average differences in IOP comparing participants with diabetes with those without diabetes obtained after omitting 1 study at a time ranged from 0.14 to 0.34 mmHg. Although Egger's test for publication bias was not significant, funnel plots suggested that small studies were reporting stronger associations compared with larger studies. Two additional studies reported regression coefficients without measures of variability and could not be incorporated in the pooled analysis. A study in Taiwan reported higher IOP levels among participants with diabetes compared with those without diabetes (regression coefficient, 0.12 mmHg; $P < 0.001$), whereas a study in Turkey reported lower IOP levels among participants with diabetes compared with those without diabetes (regression coefficient, −0.13; $P < 0.001$).[20,21]

The pooled average increase in IOP associated with an increase in 10 mg/dl in fasting glucose was 0.09 mmHg (95% CI, 0.05–0.12; $I^2 = 34.8\%$; Fig 5, available at www.aaojournal.org). The estimates ranged from 0.08 to 0.09 mmHg after omitting 1 study at a time. Egger's test for publication bias was significant ($P = 0.01$), with small studies reporting stronger associations compared with larger studies.
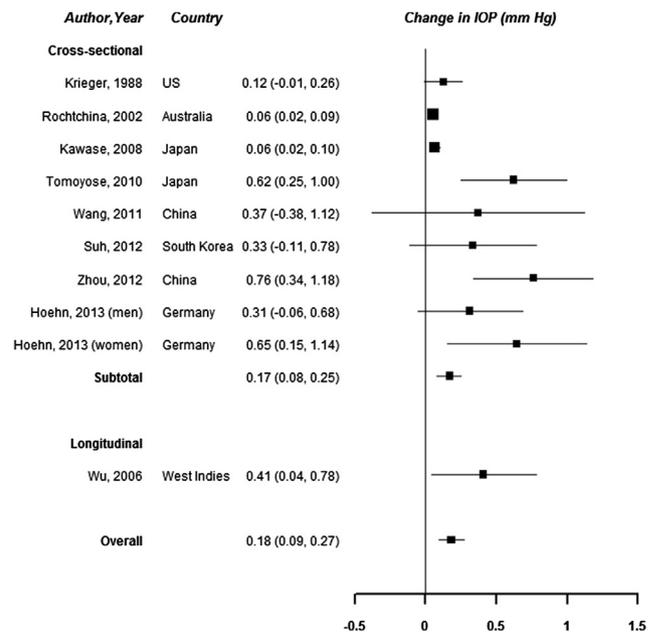

Figure 4. Graph showing the difference in intraocular pressure comparing patients with diabetes with those without diabetes. The size of the box representing the point estimate for each study in the forest plot is proportional to the contributing weight of that study estimate to the summary estimate. Horizontal lines represent 95% confidence intervals (CI). US = United States.

Ocular Hypertension

One case-control study, 4 cross-sectional studies, and 1 longitudinal study reported data on the association between diabetes and OHT (Fig 6, available at www.aaojournal.org). The pooled RR for OHT comparing participants with diabetes with those without diabetes was 1.52 (95% CI, 1.11−2.09; $I^2 = 53.1\%$). The RR estimates were lower in case-control studies compared with cross-sectional studies or longitudinal studies (0.14, 1.69, and 1.38, respectively), but the results did not vary by year of publication, country, IOP threshold to determine OHT, or diabetes definition criteria. After omitting 1 study at a time, the pooled RRs varied from 1.37 to 1.62. Finally, one study reported data on the association between impaired fasting glucose (defined as ≥100 mg/dl) and OHT (RR, 2.12; 95% CI, 1.30−3.45).[22]

Discussion

In this systematic review and meta-analysis, we found that diabetes was associated with an increased risk of glaucoma, OHT, and increased level of IOP. Importantly, the association was also evident in longitudinal studies, which are less subject to bias than cross-sectional or case-control studies. We also identified positive associations between diabetes duration and the risk of glaucoma and a weak association between fasting glucose levels and increased IOP levels. Finally, we identified a relative lack of research on the association between glucose biomarkers, prediabetes, and metabolic syndrome with glaucoma. Given the high prevalence of these metabolic abnormalities, future studies should target this area of research to understand fully the implications of altered glucose metabolism on glaucoma risk.

The mechanisms relating diabetes to increased IOP are unclear. Increased IOP in diabetes may be the result of hyperglycemia, which may induce an osmotic gradient that draws excess aqueous humor into the anterior chamber[23] and to autonomic dysfunction. Hyperglycemia also may increase IOP by interrupting the trabecular meshwork function.[6] In addition, diabetes may increase corneal stiffness and central corneal thickness, which may raise IOP readings artificially.[24−26] However, the association between diabetes and IOP was weak, suggesting that the association between diabetes and glaucoma in part may be independent of raised IOP. This is also supported by the fact that the association between diabetes and glaucoma in our meta-analysis was similar in studies that used IOP as criteria for defining glaucoma compared with those that did not use IOP.

Vascular mechanisms have been implicated to explain the increased risk of glaucoma in patients with diabetes regardless of IOP levels. Diabetes causes microvascular damage and may affect vascular autoregulation of the retina and optic nerve.[3,19,27] Vascular damage can reduce blood flow and impair oxygen diffusion. Endothelial cell injury and dysfunction can reduce the autoregulatory capacity to protect against fluctuations of IOP and blood pressure,[28−31] which could lead to relative hypoxia and to damage of the optic nerve head and of the retinal nerve fiber layer.[26] Furthermore, vascular changes in diabetes may increase the susceptibility of the retina to additional stress related to

POAG or IOP elevation.[5] In addition to vascular changes, diabetes impairs physiological glial and neuronal function in the retina, which may increase the susceptibility of retinal ganglion cells to glaucomatous damage.[4]

We also found that longer duration of diabetes was associated with higher risk of glaucoma. This robust association was consistent across cross-sectional, case-control, and longitudinal studies and was independent of age, race, gender, and other confounders controlled in the original studies. A longer duration of diabetes could impose prolonged damage to the glial and neuronal functions, leading to higher glaucoma risk. This finding further supports the need for patients with longer duration of diabetes to adhere to optimal glaucoma screening examinations and management.

Because diabetes is a known risk factor for a variety of ocular diseases besides glaucoma, patients with diabetes are more likely to receive eye examinations. This may result in an overestimation of the association between diabetes and glaucoma, because the higher prevalence of glaucoma in patients with diabetes may be a reflection of more frequent ophthalmologic visits. In addition, it is also possible that retinal disease from diabetic retinopathy could lead to visual field defects and could result in overdiagnosis of glaucoma in these studies. Indeed, the Beaver Dam Eye Study reported that the proportion of participants who had seen an ophthalmologist in the 2 years before enrollment was significantly higher in patients with diabetes compared with those without it.[32] Similarly, 22% of incident cases of glaucoma or OHT detected in diabetic patients in a retrospective cohort study were attributable to contact with medical services for diabetes screening.[10] However, other studies suggest that selection or information biases were unlikely to explain the association between diabetes and glaucoma. In the Nurses' Health Study, a longitudinal cohort study, participants with diabetes reported the same number of eye examinations on serial occasions as those without diabetes, and the prospective association between diabetes and glaucoma was unchanged when adjusting for factors that predicted more thorough eye examinations.[33] Also, in the Blue Mountains Eye Study, most previously diagnosed cases of glaucoma had been diagnosed before the diagnosis of diabetes,[7] indicating that the positive association between diabetes and risk of glaucoma cannot be explained completely by surveillance bias.

Several limitations need to be considered in the interpretation of our findings. First, there was substantial heterogeneity in the methods and quality of the original studies, and the methods used to ascertain exposure and outcomes varied widely across studies, likely contributing to the high degree of heterogeneity in the results. For instance, in our meta-regression analysis, studies using noncontact tonometers showed stronger associations between diabetes and IOP compared with studies using Goldmann applanation tonometers, the gold standard for measuring IOP. Second, there was also heterogeneity in the covariates adjusted for in each study. We attempted to limit the influence of uncontrolled confounders on this meta-analysis by excluding studies that did not adjust for age. However, some studies still may be affected by uncontrolled or residual confounding by factors such as ethnicity or central corneal thickness (CCT). For example, we found that studies that adjusted for CCT showed

stronger associations between diabetes and IOP compared with studies that did not adjust for CCT ($P < 0.001$). We used a random effects meta-analysis technique to obtain a pooled estimate of studies in the presence of significant residual heterogeneity. Although the random effects methods take into account between study variability, unknown factors may affect the association between diabetes and glaucoma end points and may limit the generalizability of our findings. Reassuringly, the findings of the meta-analysis were consistent in early studies, which tended to show more methodologic limitations, and in more recent studies. Similarly, sensitivity analyses found that the results were consistent across study designs, location, and exposure and across outcome assessments and definitions. This consistency adds weight to the internal validity of our findings. Future research should focus on longitudinal cohort studies with objective measurements of diabetes, IOP, and POAG; appropriate masking of diabetic status; and control of surveillance bias by having similar ophthalmologic testing for diabetic and nondiabetic participants and proper adjustment of potential confounders such as CCT.

Another concern was the lack of evidence of the effect modification by types of diabetes. The association between diabetes and the glaucomatous process may be different in type 1 diabetes, in which lack of insulin production leads to increased blood glucose, compared with type 2 diabetes, in which insulin resistance is the primary underlying mechanism. However, detailed information on the type of diabetes was not available in the original studies. In our meta-analysis, we found that patients with diabetes treated with insulin had a higher risk for glaucoma compared with patients with diabetes not treated with insulin,[9,34–36] but we could not identify whether insulin was used in the context of type 1 or type 2 diabetes. Future studies should characterize the implications of the different types of diabetes on glaucoma risk.

Strengths of this meta-analysis included the large sample of studies combined, the evaluation of multiple diabetes-related exposures and glaucoma-related outcomes, and the inclusion of prospective studies, which provide natural estimates of incidence and temporal trends and can establish the temporal sequence required for causal inference.

In conclusion, we found that diabetes, diabetes duration, and fasting glucose levels were associated with a significantly increased risk of POAG and that diabetes and fasting glucose levels were associated with increased levels of IOP. As a consequence, the importance of glaucoma screening in patients with diabetes, particularly those with long-standing disease, should be underlined and could be considered when these patients are receiving routine diabetic eye screening.

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Footnotes and Financial Disclosures

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Abbreviations and Acronyms:
CCT = central corneal thickness; **CI** = confidence interval; **IOP** = intraocular pressure; **OHT** = ocular hypertension; **POAG** = primary open-angle glaucoma; **RR** = relative risk.

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