

Is Diabetes Mellitus a Risk Factor for Open-Angle Glaucoma?

The Rotterdam Study

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Purpose: To investigate whether diabetes mellitus is a risk factor for open-angle glaucoma (OAG).

Design: Prospective population-based cohort study.

Participants: Participants ages ≥ 55 years from the Rotterdam Study, The Netherlands.

Methods: Participants at risk for incident OAG (iOAG) underwent at baseline (1990–1993) and follow-up (1997–1999) the same ophthalmic examination including intraocular pressure (IOP) measurement, visual field testing, and simultaneous stereo optic disc photography. At baseline, diabetes mellitus was defined as the use of antidiabetic medication and/or a random or postload glucose value ≥ 11.1 mmol/l. The diagnosis of OAG was made with an algorithm based on optic disc measures and visual fields, independent of the IOP.

Main Outcome Measure: Incident OAG.

Results: In total, 3837 participants without OAG at baseline were reexamined. After a mean follow-up time of 6.5 years, iOAG developed in 87 persons. The relative risk of iOAG associated with baseline diabetes was 0.82 (0.33–2.05). After adjustment for age, gender, follow-up time, IOP, IOP-lowering treatment, body mass index, and systemic hypertension, the relative risk of iOAG was 0.65 (0.25–1.64).

Conclusions: In this prospective population-based study, diabetes mellitus was not a risk factor for OAG. *Ophthalmology* 2006;113:1827–1831 © 2006 by the American Academy of Ophthalmology.

Open-angle glaucoma (OAG) may be characterized as glaucomatous optic neuropathy (GON) possibly with glaucomatous visual field loss (GVFL), after exclusion of angle-closure and secondary glaucoma. It is a progressive disease that has substantial impact on the daily functioning of people. Because of aging populations, the burden of OAG is predicted to increase.¹ Among risk factors, such as elevated intraocular pressure (IOP), age, race, myopia, positive family history, and pseudoexfoliation syndrome, only IOP can be effectively modulated.² Another possible risk factor that

can be influenced is diabetes mellitus. Some studies have found an association between diabetes and prevalent OAG in a general population,^{3–5} although others have not.^{6–10}

There are 2 longitudinal studies on the relation between prevalent diabetes and incident OAG (iOAG). One study in Scotland measuring the association from prescription and morbidity record databases did not show a significant difference in incidence of OAG between persons with and without diabetes,¹¹ nor did a large population-based study

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Table 1. Abbreviations and Definitions Used in This Article

Glaucomatous optic neuropathy (GON)		
Possible GON	With ImageNet*	VCDR \geq 0.7 or asymmetry between both eyes \geq 0.2 or minimal neural rim width $<$ 0.10
	With ophthalmoscopy*	VCDR \geq 0.7 or asymmetry between both eyes \geq 0.2
Probable GON	With ImageNet	VCDR \geq 0.8 or asymmetry between both eyes \geq 0.3 or minimal neural rim width $<$ 0.05
	With ophthalmoscopy	VCDR \geq 0.9 or asymmetry between both eyes \geq 0.3
Glaucomatous visual field loss (GVFL)	Visual field loss compatible with glaucoma (thus excluding hemianopia, quadrantanopia, and an isolated central defect) after exclusion of all possible causes, after a (neuro)ophthalmic examination. No optic disc criteria or IOP data were used for diagnosing GVFL.	
Intraocular pressure (IOP)	The median of 3 Goldmann applanation measurements. [†]	
Open-angle glaucoma (OAG)		
Possible OAG	Presence of possible GON in absence of GVFL.	
Probable OAG	Presence of probable GON in absence of GVFL or presence of GVFL in absence of any GON.	
Definite OAG	Presence of possible or probable GON and GVFL.	
Incident open-angle glaucoma (iOAG)	From no or possible OAG at baseline to probable or definite OAG at follow-up.	
Ocular hypertension (OH)	Presence of IOP $>$ 21 mmHg without therapy, or \leq 21 mmHg with therapy, in the presence of a normal disc and visual field.	

VCDR = vertical cup-to-disc ratio.

*Ophthalmoscopic data were used in case no (reliable) ImageNet data were available.

[†]Based on Dielemans et al.¹⁸

from Melbourne.¹² We prospectively studied associations between baseline diabetes mellitus and iOAG in a general elderly, white population.

Materials and Methods

Study Population

The ophthalmic part of the Rotterdam Study, a prospective population-based cohort study of residents aged \geq 55 years (99% white) living in a district of Rotterdam has been described previously (response rate: 78%).^{13,14} Home interviews and ophthalmic examinations were conducted after the appropriate medical ethics committees approved the study protocol and all participants gave written informed consent, according to the Declaration of Helsinki. After the baseline examination in 1990 to 1993, the first follow-up examination focusing on iOAG was performed in 1997 to 1999.

Assessment of Diabetes Mellitus and Covariates

During home interviews, current medicine use was assessed. Non-fasting serum blood samples were collected at baseline. Participants without known diabetes underwent also a nonfasting glucose tolerance test (85% of the total population).¹⁵ Diabetes mellitus at baseline was defined as the use of antidiabetic medication and/or a random or postload glucose value \geq 11.1 mmol/l.^{16,17}

Body mass index was calculated as weight/height² (kg/m²). We defined systemic hypertension as systolic blood pressure \geq 160 mmHg and/or diastolic blood pressure \geq 100 mmHg and/or use of blood pressure-lowering medication with hypertension as indication.

Assessment of Open-Angle Glaucoma

The ophthalmic examination included Goldmann applanation tonometry,¹⁸ automated suprathreshold visual field screening of both eyes of each participant, followed by ophthalmoscopy and stereoscopic fundus photography in pharmacological mydriasis. The procedures were the same at baseline and at follow-up.^{19,20}

The diagnosis of OAG was made with an algorithm based on the presence of GON and GVFL, and could only be made in persons who had at least in one and the same eye an open anterior chamber angle and no history or sign of angle-closure or secondary glaucoma. For GON evaluation, simultaneous stereo color transparencies were digitized and analyzed with a semiautomated image analyzer (ImageNet, Topcon Optical Company, Tokyo, Japan).^{13,20} If the transparencies were absent or of poor quality, ophthalmoscopic estimates were used. The definitions of possible and probable GON are given in Table 1.¹³ Participants with repeatedly abnormal or unreliable visual field screening tests underwent Goldmann perimetry on both eyes by 1 of 2 experienced full-time perimetrists according to a fixed protocol with standardized isopters. The perimetrists took into account only the result of the last performed suprathreshold test. Visual field loss, compatible with OAG (thus excluding hemianopia, quadrantanopia, or isolated central defect) and not explained by other (neuro)ophthalmic causes, was defined as GVFL.¹⁹ The definitions of definite OAG, probable OAG, possible OAG, and ocular hypertension (OH) are given in Table 1.¹³ Incident OAG was defined as no or possible OAG in either eye at baseline and probable or definite OAG in at least one eye at follow-up.²⁰ Excluded from this incidence definition were persons with possible GON at baseline and probable GON at follow-up as the only change, because a tiny increase in 1 of the GON criteria could lead to a change in this classification. Additionally, we wanted to be as confident as possible that we actually analyzed cases with iOAG for risk analyses.

Data Analysis

At baseline, 6780 participants underwent an ophthalmologic examination. After excluding persons with prevalent definite or probable OAG (n = 221) and persons without information on diabetes at baseline (n = 27), 6532 participants formed the cohort at risk for developing iOAG.

We used univariate analyses of covariance to compare baseline characteristics of participants and nonparticipants in the follow-up examination, adjusted for age and gender when appropriate. Logistic regression analyses were used to calculate odds ratios, which can be interpreted as relative risks. In further analyses we adjusted for age, gender, follow-up time, IOP, IOP-lowering treatment,

Table 2. Baseline Characteristics of Persons at Risk for Incident Open-Angle Glaucoma (OAG)

Status at Follow-up	Participated (n = 3837)	Refused (n = 1462)	P Value	Deceased (n = 1233)	P Value
Age \pm SD (yrs)	65.7 \pm 6.9	71.2 \pm 8.7	<0.001	77.3 \pm 9.1	<0.001
Gender (% female)	60.3	67.1	<0.001	48.4	<0.001
Diabetes mellitus (%)	7.9	10.0	0.03	18.6	<0.001
Vertical cup-to-disc ratio*	0.52	0.50	<0.001	0.49	<0.001
Possible OAG (%)	8.1	7.1	0.08	7.0	0.11
Intraocular pressure \pm SD, mmHg [†]	15.0 \pm 3.1	15.2 \pm 3.4	0.15	14.8 \pm 3.4	0.10
Intraocular pressure–lowering treatment (%)	2.1	2.6	0.31	1.4	0.18
Systemic hypertension (%)	31.1	36.6	<0.001	40.8	<0.001
Body mass index \pm SD (kg/m ²)	26.3 \pm 3.5	26.6 \pm 3.9	0.06	25.8 \pm 3.9	<0.001

SD = standard deviation.

All values are adjusted for age and gender when appropriate. *P* values are based on comparisons with participants.

*Measured as maximum vertical cup-to-disc ratio in any eye.

[†]Only presented here for persons without intraocular pressure–lowering treatment. Measured as highest intraocular pressure in any eye.

body mass index, and systemic hypertension, with corresponding 95% confidence intervals (CI). Stratified analyses were performed on age and OH. All analyses were performed with SPSS for Windows v.11 (SPSS Inc., 2001, Chicago, IL).

Results

After a mean follow-up time of 6.5 years (range, 5.0–9.4), 3837 persons at risk for iOAG participated in the follow-up examination. Of the nonparticipants, 46% (n = 1233) died and 54% (n = 1462) refused or were unable to attend the follow-up examination. Table 2 presents baseline characteristics of the study population. The nonparticipants were on average older, more often female, and more often had diabetes or systemic hypertension. Table 3 shows that baseline OAG characteristics for persons with diabetes did not differ between participants and those who refused to participate.

Incident OAG developed in 82 of 3573 persons without and in 5 of 264 persons with diabetes. Persons with diabetes at baseline had a relative risk of iOAG of 0.82 (95% CI, 0.33–2.05) compared to persons without diabetes (Table 4). After adjustment for confounders this relative risk was 0.65 (95% CI, 0.25–1.64). We found no differences in relative risks between participants aged 55 to 75 years and persons aged \geq 75 years.

We also examined the risk of OAG persons who developed diabetes during follow-up. At the follow-up examination, 256 persons were diagnosed with incident diabetes, 5 of whom also had iOAG. After exclusion of these 256 persons, the risk estimates remained similar. We performed an analysis in which we added the 256 persons to the baseline group with diabetes, based on the assumption that diabetes was subclinically present at baseline but

not yet detectable. This did not show different risk estimates compared to the presented results.

Because some other studies have investigated the association between diabetes and iOAG or GVFL in persons with OH,^{21–23} we stratified our cohort in a group without and a group with OH. Table 5 shows a nonsignificant increased risk of iOAG in diabetic persons with OH, with large CIs because of the small number of cases per stratum.

Among the participants at follow-up, 3.0% of those with diabetes mellitus received IOP-lowering treatment at baseline compared to 1.7% of those without diabetes mellitus. This difference in participants with IOP lowering treatment at baseline was not significant after adjusting for age and gender (*P* = 0.20). We also performed an analysis in which persons who started IOP-lowering treatment during follow-up (n = 148) were excluded. The relative risk did not change much: 0.69 (95% CI, 0.24–1.98, fully adjusted model).

Discussion

In this study, no association between diabetes mellitus and iOAG was detected. This was in line with 2 other prospective studies^{11,12} but in contrast with a recent meta-analysis²⁴ performed on 5 case-control and 7 cross-sectional studies. Of the cross-sectional studies, only 3 showed significant associations between diabetes and OAG, and 1 of these 3 with the highest odds ratio was ours, which, after reanalysis, no longer showed an association (see below).⁴ There is variation in the diagnostic criteria for diabetes, such as

Table 3. Baseline Ophthalmic Characteristics of Persons with Diabetes Mellitus at Baseline

Status at Follow-up	Participated (n = 264)	Refused (n = 155)	P Value	Deceased (n = 258)	P Value
Vertical cup-to-disc ratio*	0.51	0.49	0.26	0.48	0.18
Intraocular pressure (mmHg) [†]	16.0	15.7	0.43	15.2	0.02
Intraocular pressure–lowering treatment (%)	3.6	3.2	0.83	2.6	0.56
Possible open-angle glaucoma (%)	9.9	9.3	0.74	6.9	0.12

All values are adjusted for age and gender when appropriate. *P* values are based on comparisons with participants.

*Measured as maximum vertical cup-to-disc ratio in any eye.

[†]Only presented here for persons without intraocular pressure–lowering treatment. Measured as maximum intraocular pressure in any eye.

Table 4. Relative Risks of Incident Open-Angle Glaucoma (OAG) in Persons with and without Prevalent Diabetes Mellitus

	Prevalent Diabetes Mellitus	
	No	Yes
Number of persons at risk	3573	264
Number of incident OAG cases	82	5
Relative risk (95% confidence interval)*		
Model 1	0.82 (0.33–2.05)	
Model 2	0.72 (0.29–1.80)	
Model 3	0.65 (0.25–1.64)	

*Model 1 = unadjusted; model 2 = adjusted for age, gender, and follow-up time; model 3 = adjusted for age, gender, follow-up time, intraocular pressure, intraocular pressure-lowering treatment, body mass index, and systemic hypertension.

medication use, fasting, nonfasting or postload blood glucose levels, or self-reported diabetes; additionally, the definitions of OAG varied widely across these studies.^{3,5,6,11,12} Given these different definitions and the fact that in the meta-analysis²⁴ 2 studies that did not find a relationship were excluded,^{7,8} we consider it more likely that diabetes is not a risk factor for OAG.

The Ocular Hypertension Treatment Study found a protective effect of diabetes among persons with OH.²³ Two more OH studies did not find an association.^{21,22} Differences in definitions or study designs again play a role here. For example, in the Ocular Hypertension Treatment Study, persons with diabetic retinopathy were excluded from the cohort.

Halfway through collection of our baseline data we presented a relative risk of 3.11 (95% CI, 1.12–8.66) of prevalent OAG in participants with diabetes.⁴ We changed, however, between the first and final analyses of the baseline cohort,^{4,13} our definition of OAG. When we recalculated the relative risk at baseline for the whole cohort using our current OAG definitions, the risk dropped to a nonsignifi-

cant 1.40 (95% CI, 0.96–2.03), adjusted for age, gender, and body mass index.

Selection bias, in the form of selective nonresponse, could distort the results. The nonparticipants indeed had significantly more often diabetes than the participants at baseline, and this could affect the extrapolation of our findings to the general population. However, nonresponse to the follow-up examination seemed to be related only to their diabetes and not to their risk of iOAG, as is shown in Table 3.

The number of deaths that occurred during follow-up in this elderly cohort could also lead to selection bias. If persons who died between baseline and follow-up developed OAG more often than those who survived, this would have biased the results toward the null value. However, there are 2 studies showing that people who have OAG are not at an increased risk of death, making survival bias as an explanation for our negative findings less likely.^{25,26}

Another potential selection bias could have been that, in The Netherlands, patients with diabetes more often visit their ophthalmologist to check for retinopathy than persons without diabetes and might therefore be more often diagnosed with OH or beginning OAG. This could have led to fewer iOAG cases, had they received more IOP-lowering treatment.²⁷ The difference between diabetic and nondiabetic participants with regard to IOP lowering treatment at baseline seemed not to be significant in our study (see Results). Therefore, we do not think that this explains our results.

Strengths of this study are the population-based and prospective design, relatively large size of the cohort, collection of perimetric and other data necessary for the OAG diagnosis in all participants, and the transparent diagnostic criteria for diabetes and OAG. In studies where data are taken from existing patient files (and thus not all participants are screened for OAG), selection bias could have occurred.¹¹ The sample size in this study was quite large. However, because of the low incidence of OAG, not many cases of iOAG were found and the power to demonstrate small differences was lacking. That is why probable and

Table 5. Relative Risks of Incident Open-Angle Glaucoma (OAG) in Persons with and without Prevalent Diabetes Mellitus Stratified with Regard to Ocular Hypertension

	Prevalent Ocular Hypertension			
	No		Yes	
	Prevalent Diabetes Mellitus		Prevalent Diabetes Mellitus	
	No	Yes	No	Yes
Number of persons at risk	3423	238	76	13
Number of incident OAG cases	68	3	3	2
Relative risk (95% confidence interval)*				
Model 1	0.63 (0.20–2.02)		4.42 (0.66–29.53)	
Model 2	0.58 (0.18–1.85)		4.23 (0.52–34.21)	
Model 3	0.62 (0.19–2.01)		4.83 (0.47–49.59)	

Persons with intraocular pressure-lowering treatment at baseline were excluded from these analyses.

*Model 1 = unadjusted; model 2 = adjusted for age, gender, and follow-up time; model 3 = adjusted for age, gender, follow-up time, body mass index, and systemic hypertension.

definite OAG in iOAG were combined. When we based our analyses on only the 29 definite iOAG cases, the relative risk of iOAG in diabetic persons was 1.04 (95% CI, 0.30–3.66, fully adjusted model).

The wide CIs of these estimates hamper interpretation of the results. However, if there is any effect of diabetes, then it will be small, and protection is at least as likely as a negative influence. The rather low incidence of OAG stresses the necessity to make OAG definitions and diagnoses worldwide more comparable so that, in the future, studies can more reliably be pooled for a meta-analysis to improve these estimates.

In conclusion, this study does not confirm that diabetes mellitus is a risk factor for iOAG.

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