# Diabetes mellitus and risk of open-angle glaucoma-A population-based follow-up study

Virtanen, Aapo

2023-03

Virtanen , A , Haukka , J , Loukovaara , S & Harju , M 2023 , ' Diabetes mellitus and risk of open-angle glaucoma-A population-based follow-up study ' , Acta Ophthalmologica , vol. 101 , no. 2 , pp. 160-169 . https://doi.org/10.1111/aos.15240

http://hdl.handle.net/10138/355505
https://doi.org/10.1111/aos.15240

Received: 1 February 2022 | Accepted: 14 August 2022

DOI: 10.1111/aos.15240

Acta Ophthalmologica

ORIGINAL ARTICLE

# Diabetes mellitus and risk of open-angle glaucoma—A population-based follow-up study

**Aapo Virtanen**[1,2] | **Jari Haukka**[2] | **Sirpa Loukovaara**[1,2] | **Mika Harju**[1,2]

[1]Department of Ophthalmology, Helsinki University Central Hospital Head and Neck Center, Helsinki, Finland

[2]Faculty of Medicine, University of Helsinki, Helsinki, Finland

**Correspondence**
Aapo Virtanen, Department of Ophthalmology, Helsinki University Central Hospital Head and Neck Center. P.O.BOX 220, 00029 HUS, Helsinki, Finland.
Email: aapo.virtanen@helsinki.fi

**Funding information**
Glaukooma Tukisäätiö Lux, Grant/Award Number: 202100010; Silmäsäätiö, Grant/Award Number: 20200014; Suomen Silmälääkäriyhdistyksen

## Abstract

**Purpose:** The aim of this study was to investigate the association of diabetes mellitus (DM) and risk of open-angle glaucoma (OAG).

**Methods:** This population-based historic cohort consisted of individuals at age ≥ 40 years with DM treatment initiated 2001–2010 and a reference population matched by age, gender and hospital district. Incidence of OAG was compared between individuals with DM and their matched non-diabetic reference pairs. New glaucoma cases were identified from medication reimbursement certificates and hospital billing records. Incidence rate ratios (IRR) were analysed with Poisson regression models adjusted for age, sex, hospital district, socioeconomic status, systemic medications and chronic diseases. We analysed the sensitivity of the results with adapted input variables and performed a competing events analysis.

**Results:** Of the 244 100 study subjects meeting inclusion criteria, 2721 (1.1%) developed OAG. Follow-up spanned from 2001 to 2017. DM was associated with a modestly reduced incidence of OAG when adjusted for confounding factors (IRR 0.92, CI 0.85–0.99).

**Conclusions:** In our longitudinal population-based study, we found a modest decrease in the risk of OAG for individuals with DM.

**KEYWORDS**
cohort, diabetes, epidemiology, glaucoma, longitudinal, population-based, real-world data

## 1 | INTRODUCTION

Glaucoma is a group of diseases of the optic nerve fibres, presenting with optic nerve cupping, often elevated intraocular pressure (IOP), progressive loss of visual field and other anatomically classifying findings. At present, the pathophysiology of glaucoma is held as an intertwining process of neurodegeneration and vasculopathy (Song et al., 2016). Globally, glaucoma accounted for 4.5 million cases of moderate to severe visual impairment and 3.2 cases of bilateral blindness in 2020 predominantly affecting people with high age and weaker socioeconomic status (Flaxman et al., 2017; Wang et al., 2019). Elevated IOP, older age, family history and ethnicity are known risk factors for glaucoma (Stein et al., 2021). Additionally, an intricate network of genetics, systemic diseases, medications, behavioural and environmental factors appear to contribute to the development glaucoma (Lee et al., 2019; Wang et al., 2018; Wu et al., 2020). Diabetes mellitus (DM) may influence the pathophysiology of glaucoma through changes in vascular, neural and connective tissues but the exact mechanisms and their clinical ramifications are not fully understood (AGIS Investigators, 2002; Choi & Kook, 2015; Hou et al., 2018; Lee et al., 2014). Better understanding the role of DM in the development and progression of glaucoma can help in individualizing screening and in developing novel therapeutic approaches.

Four cohort studies have identified DM as a risk factor for higher glaucoma prevalence (Chopra et al., 2008; Dielemans et al., 1996; Klein et al., 1994; Mitchell et al., 1997). Two longitudinal studies investigating the incidence, as opposed to prevalence, of OAG have reported higher risk for individuals with DM in

cohorts of female nurses (Pasquale et al., 2006) and African Americans (Wise et al., 2011). Additionally, one study in a diverse population of US nationwide health plan beneficiaries found the risk of OAG to be compounded by concurrent DM and arterial hypertension (Newman-Casey et al., 2011). However, other population-based studies have found no association between DM and OAG prevalence (Tan et al., 2009; Tielsch et al., 1995),or incidence (de Voogd et al., 2006; Ellis et al., 2000; Le et al., 2003; Leske et al., 2008). Three meta-analyses have been conducted to clarify the complex association between glaucoma and DM. Two of them concluded a higher OAG prevalence associated with DM (Bonovas et al., 2004; Zhou et al., 2014), unlike the most recent meta-analysis of seven population-based studies, that established no association between DM and glaucoma (Grzybowski et al., 2020). Despite being widely studied, the association between DM and glaucoma remains controversial.

The main objective of this study was to investigate the association between DM and glaucoma by examining the incidence of glaucoma measured by approved drug reimbursement claims or billed procedures for glaucoma during a 17-year follow-up period in a large Finnish population.

## 2 | METHODS

### 2.1 | Cohort

The original CARING cohort ($n$ = 398 708) contained 199 354 subjects with DM and an equivalent reference population matched by age, sex and hospital district. Subjects with DM were identified based on dispensed insulin or oral antidiabetic prescriptions and medication reimbursement claims (Niskanen et al., 2020). We formed a study population by excluding individuals with follow-up starting before 2001 or younger than 40 years at baseline (Figure 1). Individuals with prevalent glaucoma at baseline were excluded based on pre-existing medication reimbursement claims ($n$ = 15 476), hospital visits for glaucoma ($n$ = 450) or previous glaucoma surgery ($n$ = 86). In the case of exclusion, we excluded the corresponding matched pair. The study period spanned from 1 January 2001 to 31 December 2017. Follow-up started on the date of the first diabetes medication prescription or randomization to reference population and ended on the endpoint event of glaucoma diagnosis or censoring by death or end of the study period.

Incident glaucoma was defined as a new accepted medication reimbursement claim, hospital visit, laser or surgical treatment with the diagnosis of glaucoma. In Finland medication, reimbursement for chronic glaucoma during the study period 2001–2017 was conditional on either the IOP measuring over 30 mmHg or meeting two of the following criteria: (1) detectable excavation of the optic cup or defect in the nerve fibre layer, (2) visual field defect or (3) IOP over 21 mmHg in repeated measurements (personal communication with Social Insurance Institute, SII, administrator). Data on medication prescriptions and reimbursements were obtained from the SII, which is a governmental agency providing national public health insurance to all Finnish residents (Kela 16/522/2012). Glaucoma reimbursement certificates were assigned an ICD-10 code at SII with 3-digit accuracy precluding classification into different subtypes of open-angle glaucoma (OAG). We used only OAG (H40.1) as an endpoint in the analysis. We excluded other than OAG ($n$ = 271): angle closure glaucoma (73), glaucoma induced by medication (9), ocular inflammation (4), other ocular diseases (135) or trauma (11) and glaucoma of unspecified cause (39). Data on glaucoma-related hospital visits, laser treatments and surgical procedures were obtained from the Institute of Health and Welfare. We used the following glaucoma procedures in ascertainment of prevalent glaucoma when forming the cohort and as endpoints for incident glaucoma presented with corresponding NOMESCO codes ('NOMESCO Classification of Surgical Procedures (NCSP), version 1.16', 2011): argon laser trabeculoplasty (CHD00), selective laser trabeculoplasty (CHD05), trabeculectomy (CHD10), trabeculectomy with iridectomy (CHD15), implantation of glaucoma drainage device (CHD50), deep sclerectomy (CHD60), deep sclerectomy with collagen implant (CHD65) and trans-scleral cyclophotocoagulation (CHF05). Statistics Finland provided data on mortality and socioeconomic status. We identified systemic medications at baseline by dispensed prescriptions and comorbidities by granted special medication reimbursements. We obtained data on malignant neoplastic disease other than non-melanotic skin cancers from the Finnish Cancer Registry (THL/264/5.05.00/2012).

### 2.2 | Statistical analysis

We carried out a multivariate Poisson regression analysis on the population at risk ($n$ = 244 100) reporting incidence rate ratios (IRR) of OAG with 95% confidence intervals (CI) comparing subjects with and without DM. The models were adjusted for age, sex, hospital district, socioeconomic status, chronic diseases verified by permanent reimbursement approvals and systemic medications. Individuals with at least three dispensed prescriptions during 1 year before the start of follow-up were defined as users of a pharmaceutical. Drug classes included in the univariate model were angiotensin agents, beta-blockers, calcium channel antagonists, diuretics, statins, selective serotonin reuptake inhibitors (SSRI), tricyclic antidepressants, systemic corticosteroids, memantine and other drugs for Alzheimer's disease. For the final adjusted multivariate model, we selected drugs that showed associations with OAG incidence in the univariate model or that have reported associations with both DM and OAG. A Kaplan–Meier curve was plotted to visualize glaucoma incidences over time in the DM and reference groups (Figure 2). The endpoints indicating incident glaucoma were defined as new medication reimbursement decision or new glaucoma treatment by laser or surgery.

Additionally, we fitted a Fine–Gray model for competing risks using OAG and death as competing events

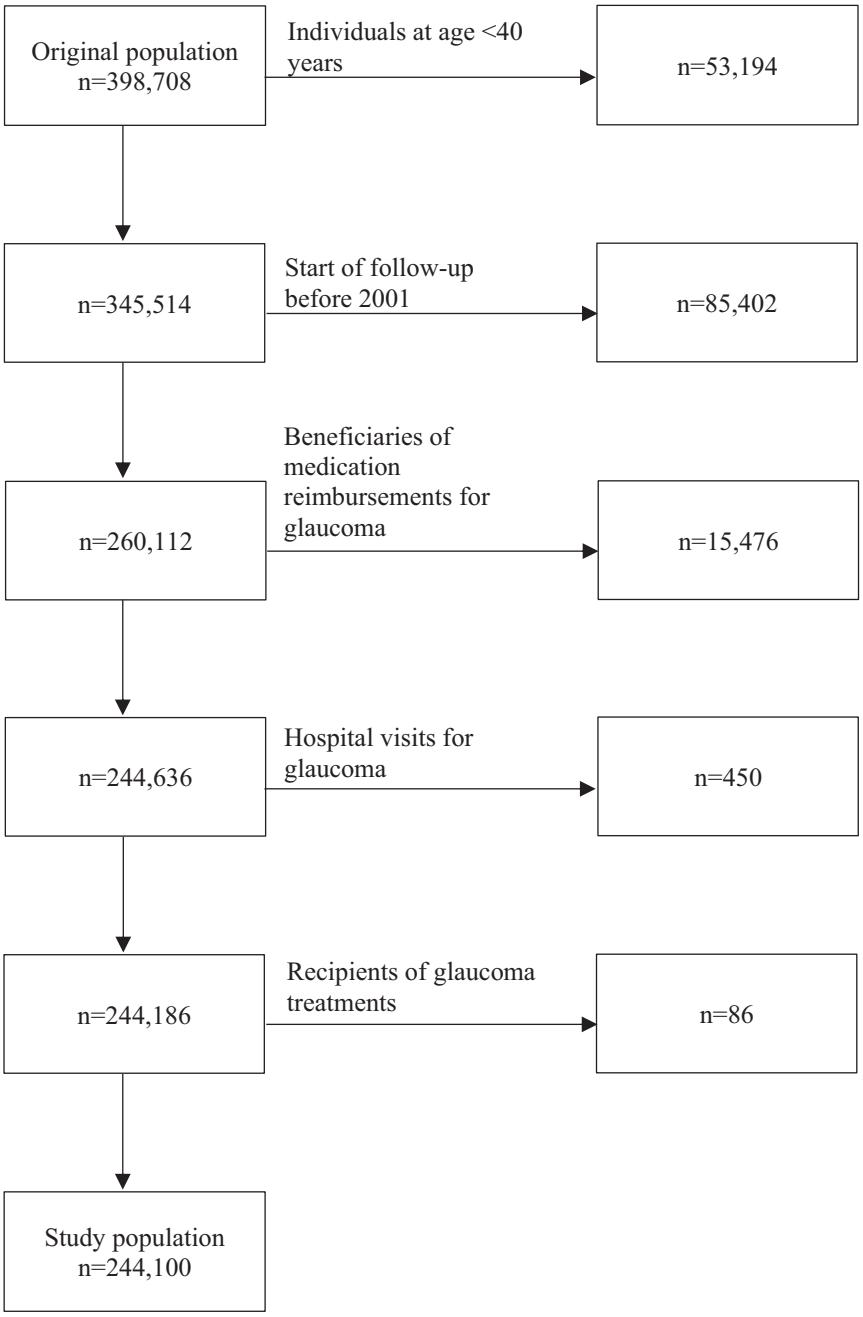


**FIGURE 1** Flowchart of the study population formation

with DM, sex and age as explanatory variables (Fine & Gray, 1999). We carried out a sensitivity analysis to test whether changes in the input variables altered the results. We used R language for all statistical calculations (R Core Team, 2019).

## 2.3 | Ethics considerations

We obtained approval from the Ethics Committee of Faculty of Medicine, University of Helsinki, 17 January 2012 (Ref 02/2012). Approvals to extend the original study plan and research group were granted by register holders SII (Kela 29/522/2019), and the Institution for Health and Welfare (THL/486/5.05.00/2019) and (THL/3157/14.02.00/2020). All data are pseudonymized and handled under confidentiality agreements.

# 3 | RESULTS

There were 122 050 individuals with diabetes aged 40 or more years in the cohort with DM onset between 1 January 2001 and 31 December 2010 and their matched reference pairs. The mean (SD) age at the start of follow-up was 62.5 years (11.4), and 45% ($n$ = 54 587) were female subjects. During a 17-year study period, 2.40 million person-years were cumulated. Mean follow-up time was 9.8 years (Table 1).

Altogether, 2721 new cases of OAG were diagnosed during the study period. OAG was identified based on medication reimbursement data in 2229 cases and hospital billing data in 492 cases. Out of these, 1248 were diagnosed in the DM group in 1.16 million person-years of follow-up (rate 1.08, CI 1.02–1.14/ 1000 person-years), while 1473 incident cases occurred in the non-diabetic

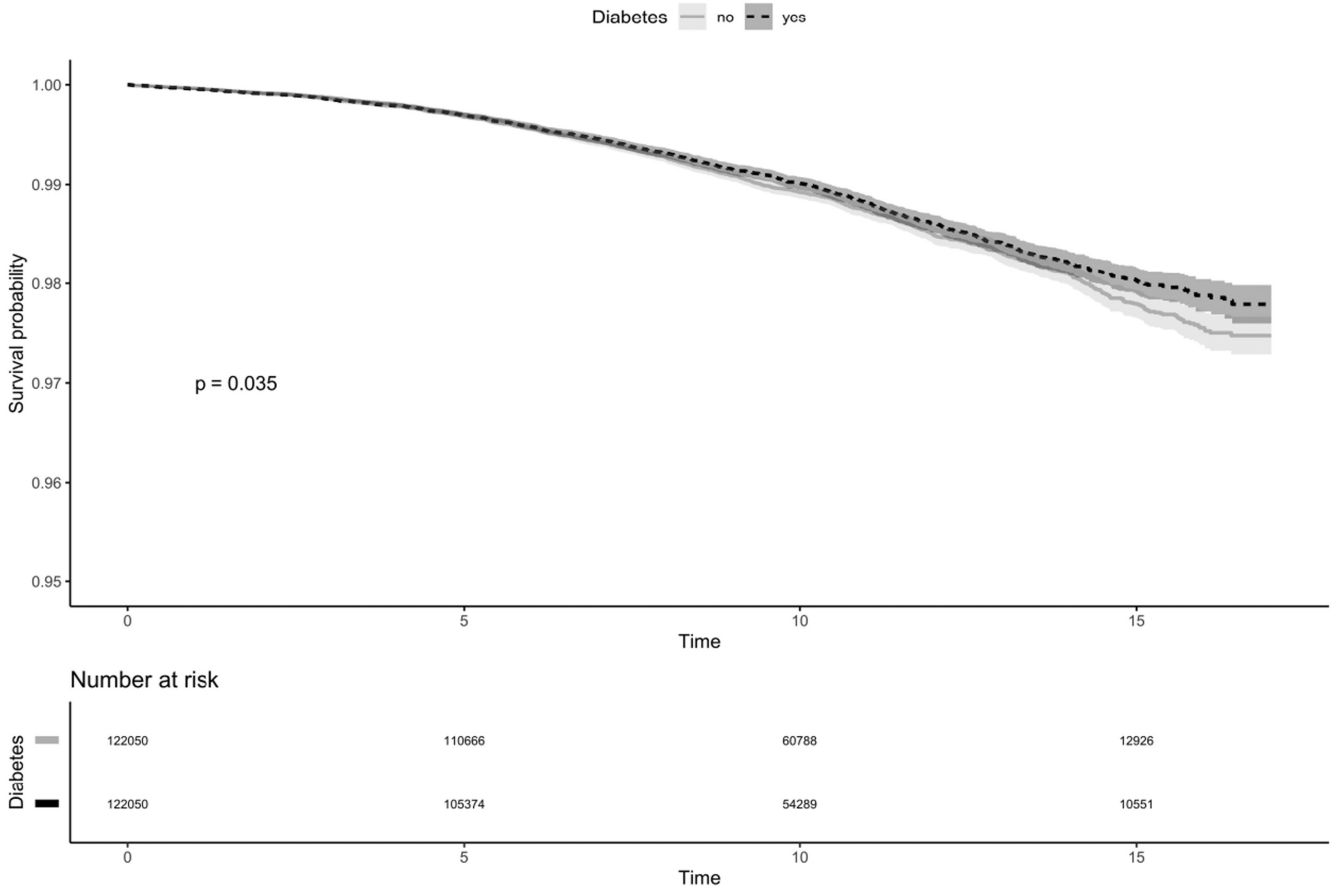


**FIGURE 2** Survival curve of open-angle glaucoma incidence. Kaplan-Meier survival probability curve showing the incidence of open-angle glaucoma cases over the 17-year follow-up time. The solid gray line represents individuals with diabetes and the black dashed line represents a reference population matched by age, sex, and region. The table below the graph shows the number of individuals still at risk of developing glaucoma in each group at the beginning, 5 years, 10 years, and 15 years of follow-up

reference population in 1.24 million person-years (rate 1.19, CI 1.13–1.26), the resulting rate ratio 0.90 (CI 0.84–0.97) indicating a lower glaucoma incidence associated with DM (Table 2).

Diabetes was associated with a lower incidence of OAG when adjusted for age, sex, hospital district and socioeconomic status only (IRR 0.91, CI 0.84–0.98). Similar results followed when adjusted for use of systemic medications potentially associated with altered glaucoma incidence (IRR 0.91, CI 0.85–0.99). Accounting for a set of chronic systemic diseases for which medication reimbursements were documented no association between OAG and DM was detected (IRR 0.92, CI 0.86–1.00). Finally, when adding all variables into a single multivariate model, a modestly reduced OAG incidence among diabetic subjects remained (IRR 0.92, CI 0.85–0.99) (Table 3).

Female sex (IRR 1.22, CI 1.13–1.33) and older age (1-year increment) were associated with a higher incidence for OAG (IRR 1.03, CI 1.03–1.04). Incidence was highest in the age groups of 70- to 80-year-olds (rate 1.90, CI 1.79–2.01) and over 80-year-olds (1.93, CI 1.78–2.10), over 5 times the incidence compared with the 50- to 60-year-olds (0.37, CI 0.32–0.43) (Table 2).

Medication use was higher in the DM group across all studied drug classes except for dementia medications (Table 1). As secondary findings, we identified a lower OAG incidence associated with beta-blocker use (IRR 0.88, CI 0.80–0.98). Accordingly, there was a lower OAG incidence associated with chronic coronary heart disease (IRR 0.73, IRR 0.63–0.84) and chronic cardiac insufficiency (IRR 0.61, CI 0.44–0.84), both common indications for beta-blockers. Among the hypertension drugs, the use of diuretics was associated with lower (IRR 0.79, CI 0.69–0.91) but angiotensin agents with higher incidence of OAG (IRR 1.17, CI 1.05–1.30). SSRI medication was found to be associated with lower incidence of OAG (IRR 0.79, CI 0.65–0.96), while tricyclic antidepressants showed no association. The use of systemic statin therapy was associated with a higher incidence of OAG (IRR 1.38, CI 1.25–1.52).

## 3.1 | Sensitivity analysis

We tested the sensitivity of our findings against possible confounders with additional analyses. Results of the Fine–Gray competing causes model showed that the lower glaucoma incidence among diabetic subjects was not due to higher mortality with hazard ratios (HR) for OAG (0.85, CI 0.78–0.92) and death (1.54, CI 1.51–1.56) in the diabetic population. When we tested the interaction of beta-blockers and diabetes, we found that beta-blockers' effect on the risk of glaucoma was not altered by DM status. Similarly, there was no interaction between chronic hypertension and diabetes in terms of glaucoma risk. To test the possible impact of treatment of retinal vascular diseases on the incidence of glaucoma, we repeated our

**TABLE 1** Basic characteristics of the study population

| | Diabetes mellitus | | |
|---|---|---|---|
| | No | Yes | All |
| ***n*** | **122 050** | **122 050** | **244 100** |
| Age, mean (SD) | 62.5 (11.4) | 62.5 (11.4) | 62.5 (11.4) |
| Female (%) | 54 597 (44.7) | 54 597 (44.7) | 109 194 (44.7) |
| Socioeconomic group (%) | | | |
| Upper-level employees | 11 180 (9.2) | 7941 (6.5) | 19 121 (7.8) |
| Self-employed | 8109 (6.6) | 7082 (5.8) | 15 191 (6.2) |
| Lower-level employees | 16 162 (13.2) | 13 908 (11.4) | 30 070 (12.3) |
| Manual workers | 17 691 (14.5) | 17 651 (14.5) | 35 342 (14.5) |
| Students | 642 (0.5) | 717 (0.6) | 1359 (0.6) |
| Pensioners | 57 893 (47.4) | 62 910 (51.5) | 120 803 (49.5) |
| Others | 10 373 (8.5) | 11 841 (9.7) | 22 214 (9.1) |
| Systemic medication | | | |
| Angiotensin agents | 12 899 (10.6) | 23 498 (19.3) | 36 397 (14.9) |
| Beta-blockers | 20 106 (16.5) | 37 301 (30.6) | 57 407 (23.5) |
| Calcium channel blockers | 9410 (7.7) | 16 897 (13.8) | 26 307 (10.8) |
| Diuretics | 7853 (6.4) | 17 622 (14.4) | 25 475 (10.4) |
| Medication for Alzheimer's other than memantine | 952 (0.8) | 726 (0.6) | 1678 (0.7) |
| Memantine | 254 (0.2) | 227 (0.2) | 481 (0.2) |
| Metformin | 0 (0.0) | 69 837 (57.2) | 69 837 (28.6) |
| SSRI | 3668 (3.0) | 5704 (4.7) | 9372 (3.8) |
| Statin | 16 467 (13.5) | 27 131 (22.2) | 43 598 (17.9) |
| Comorbidities | | | |
| Arrhythmias | 2238 (1.8) | 3228 (2.6) | 5466 (2.2) |
| Cancer | 3764 (3.1) | 5404 (4.4) | 9168 (3.8) |
| Cardiac insufficiency | 2232 (1.8) | 4401 (3.6) | 6633 (2.7) |
| Coronary heart disease | 9474 (7.8) | 14 134 (11.6) | 23 608 (9.7) |
| Hypertension | 21 731 (17.8) | 40 164 (32.9) | 61 895 (25.4) |
| Inflammatory bowel disease | 765 (0.6) | 886 (0.7) | 1651 (0.7) |
| Parkinson's disease | 839 (0.7) | 617 (0.5) | 1456 (0.6) |
| Severe psychotic and other severe mental disorders | 3230 (2.6) | 5693 (4.7) | 8923 (3.7) |
| Thyroid insufficiency | 2974 (2.4) | 3815 (3.1) | 6789 (2.8) |

Abbreviations: SD, standard deviation, SSRI, selective serotonin reuptake inhibitors.

analysis excluding all subjects that had received retinal photocoagulation or intravitreal injections 5 years prior to the start of follow-up. This exclusion did not change the findings. We also tested the possibility of a detection bias related to previous cataract surgery finding no difference in the risk estimates.

## 4 | DISCUSSION

In this population-based historic cohort study, DM was associated with a marginally lower incidence of OAG compared with a matched non-diabetic reference population. The role of diabetes in glaucoma pathogenesis has long been a disputed topic. According to cross-sectional studies and subsequent meta-analyses, diabetes appeared to be associated with up to 1.5-fold increased risk of OAG (Bonovas et al., 2004; Zhou et al., 2014). Later on, with more longitudinal studies being published, this relationship appears less evident, with a range of follow-up studies either establishing a higher OAG incidence (Newman-Casey et al., 2011; Pasquale et al., 2006; Wise et al., 2011), or no association with DM (de Voogd et al., 2006; Ellis et al., 2000; Le et al., 2003; Leske et al., 2007). Recent evidence brings into question whether DM truly is as a risk factor for OAG.

The longitudinal study setting of this study has advantages over a cross-sectional design because the order of exposure and outcome events are known, and incidence of events can be measured over time in a population at risk that has been cleared of prevalent cases. Known temporal relationship of exposures and events makes inference of causation more reliable. Prevalence data are prone to selection bias and reverse causation as evidenced by a reported positive association between DM and OAG, if OAG was diagnosed before study recruitment (Tielsch et al., 1995). This implies that individuals with glaucoma were likely to know their DM status

**TABLE 2** Incidence rates of open-angle glaucoma with 95% confidence intervals and incidence rate ratios based on univariate analysis

| | Group | Person-years/1000 | OAG (*n*) | Rate | 95% CI | | IRR | 95% CI | |
|---|---|---|---|---|---|---|---|---|---|
| Diabetes mellitus | No | 1235 | 1473 | 1.19 | 1.13 | 1.26 | Reference | | |
| | Yes | 1161 | 1248 | 1.08 | 1.02 | 1.14 | 0.90 | 0.84 | 0.97 |
| Sex | | | | | | | | | |
| Male | | 1321 | 1263 | 0.96 | 0.90 | 1.01 | Reference | | |
| Female | | 1075 | 1458 | 1.36 | 1.29 | 1.43 | 1.42 | 1.32 | 1.53 |
| Age at OAG diagnosis | | | | | | | | | |
| (40, 50) | | 149 | 21 | 0.14 | 0.09 | 0.22 | Reference | | |
| (50, 60) | | 540 | 201 | 0.37 | 0.32 | 0.43 | 2.65 | 1.69 | 4.15 |
| (60, 70) | | 814 | 795 | 0.98 | 0.91 | 1.05 | 6.94 | 4.50 | 10.71 |
| (70, 80) | | 578 | 1098 | 1.90 | 1.79 | 2.01 | 13.50 | 8.77 | 20.79 |
| (80, Inf) | | 313 | 606 | 1.93 | 1.78 | 2.10 | 13.76 | 8.90 | 21.25 |
| Socioeconomic status | | | | | | | | | |
| Upper-level employees | | 207 | 196 | 0.95 | 0.82 | 1.09 | Reference | | |
| Self-employed | | 166 | 118 | 0.71 | 0.59 | 0.85 | 0.75 | 0.60 | 0.94 |
| Lower-level employees | | 325 | 336 | 1.03 | 0.93 | 1.15 | 1.09 | 0.92 | 1.30 |
| Manual workers | | 381 | 250 | 0.66 | 0.58 | 0.74 | 0.69 | 0.57 | 0.83 |
| Students | | 14 | 13 | 0.90 | 0.48 | 1.54 | 0.95 | 0.54 | 1.66 |
| Pensioners | | 1075 | 1614 | 1.50 | 1.43 | 1.58 | 1.59 | 1.37 | 1.84 |
| Others | | 226 | 194 | 0.86 | 0.74 | 0.99 | 0.90 | 0.74 | 1.10 |
| Medication | | | | | | | | | |
| Angiotensin agents | No | 2070 | 2269 | 1.10 | 1.05 | 1.14 | Reference | | |
| | Yes | 326 | 452 | 1.39 | 1.26 | 1.52 | 1.27 | 1.15 | 1.40 |
| Beta-blockers | No | 1875 | 2102 | 1.12 | 1.07 | 1.17 | Reference | | |
| | Yes | 521 | 619 | 1.19 | 1.10 | 1.29 | 1.06 | 0.97 | 1.16 |
| Calcium channel blockers | No | 2154 | 2397 | 1.11 | 1.07 | 1.16 | Reference | | |
| | Yes | 241 | 324 | 1.34 | 1.20 | 1.50 | 1.21 | 1.08 | 1.36 |
| Diuretics | No | 2188 | 2474 | 1.13 | 1.09 | 1.18 | Reference | | |
| | Yes | 207 | 247 | 1.19 | 1.05 | 1.35 | 1.05 | 0.92 | 1.20 |
| Statins | No | 1993 | 2093 | 1.05 | 1.01 | 1.10 | Reference | | |
| | Yes | 403 | 628 | 1.56 | 1.44 | 1.69 | 1.48 | 1.36 | 1.62 |
| SSRI | No | 2310 | 2650 | 1.15 | 1.10 | 1.19 | Reference | | |
| | Yes | 85 | 71 | 0.83 | 0.65 | 1.05 | 0.73 | 0.57 | 0.92 |
| Tricyclic antidepressants | No | 2370 | 2697 | 1.14 | 1.10 | 1.18 | Reference | | |
| | Yes | 25 | 24 | 0.96 | 0.61 | 1.42 | 0.84 | 0.56 | 1.26 |
| Systemic corticosteroids | No | 2366 | 2686 | 1.14 | 1.09 | 1.18 | Reference | | |
| | Yes | 30 | 35 | 1.18 | 0.82 | 1.64 | 1.04 | 0.74 | 1.45 |
| Medication for Alzheimer's other than memantine | No | 2387 | 2715 | 1.14 | 1.10 | 1.18 | Reference | | |
| | Yes | 9 | 6 | 0.68 | 0.25 | 1.49 | 0.60 | 0.27 | 1.34 |
| Memantine | No | 2393 | 2720 | 1.14 | 1.09 | 1.18 | Reference | | |
| | Yes | 2 | 1 | 0.46 | 0.01 | 2.54 | 0.40 | 0.06 | 2.85 |
| Metformin | No | 1753 | 1949 | 1.11 | 1.06 | 1.16 | Reference | | |
| | Yes | 643 | 772 | 1.20 | 1.12 | 1.29 | 1.08 | 0.99 | 1.17 |
| Comorbidities | | | | | | | | | |
| Arrhythmias | No | 2351 | 2671 | 1.14 | 1.09 | 1.18 | Reference | | |
| | Yes | 45 | 50 | 1.12 | 0.83 | 1.48 | 0.99 | 0.75 | 1.30 |
| Cancer | No | 2331 | 2634 | 1.13 | 1.09 | 1.17 | Reference | | |
| | Yes | 64 | 87 | 1.35 | 1.08 | 1.67 | 1.20 | 0.97 | 1.48 |
| Cardiac insufficiency | No | 2349 | 2680 | 1.14 | 1.10 | 1.19 | Reference | | |
| | Yes | 47 | 41 | 0.88 | 0.63 | 1.19 | 0.77 | 0.56 | 1.05 |

(Continues)

**TABLE 2** (Continued)

| | Group | Person-years/1000 | OAG (*n*) | Rate | 95% CI | | IRR | 95% CI | |
|---|---|---|---|---|---|---|---|---|---|
| Coronary heart disease | No | 2191 | 2490 | 1.14 | 1.09 | 1.18 | Reference | | |
| | Yes | 204 | 231 | 1.13 | 0.99 | 1.29 | 1.00 | 0.87 | 1.14 |
| Hypertension | No | 1806 | 1984 | 1.10 | 1.05 | 1.15 | Reference | | |
| | Yes | 590 | 737 | 1.25 | 1.16 | 1.34 | 1.14 | 1.05 | 1.24 |
| Inflammatory bowel disease | No | 2379 | 2701 | 1.14 | 1.09 | 1.18 | Reference | | |
| | Yes | 16 | 20 | 1.24 | 0.76 | 1.92 | 1.09 | 0.70 | 1.70 |
| Parkinson's disease | No | 2385 | 2713 | 1.14 | 1.10 | 1.18 | Reference | | |
| | Yes | 10 | 8 | 0.78 | 0.34 | 1.54 | 0.69 | 0.34 | 1.37 |
| Severe psychotic and other severe mental disorders | No | 2313 | 2651 | 1.15 | 1.10 | 1.19 | Reference | | |
| | Yes | 83 | 70 | 0.85 | 0.66 | 1.07 | 0.74 | 0.58 | 0.94 |
| Thyroid insufficiency | No | 2330 | 2628 | 1.13 | 1.09 | 1.17 | Reference | | |
| | Yes | 66 | 93 | 1.42 | 1.14 | 1.74 | 1.26 | 1.02 | 1.54 |

Abbreviations: CI, confidence interval; IRR, incidence rate ratio; OAG, open-angle glaucoma; SSRI, selective serotonin reuptake inhibitors.

due to broader medical interventions. The Rotterdam Eye Study found a higher OAG prevalence associated with DM, odds ratio 3.11 (95% CI 1.12–8.66) (Dielemans et al., 1996), while a longitudinal study following on from the same cohort showed no association between glaucoma incidence and DM, relative risk 0.65 (95% CI 0.25–1.64) (de Voogd et al., 2006). Different interpretations of risk can be inferred from the same study cohort depending on the study design.

The large cohort size and long follow-up time are other major advantages of this study. The 17-year study period fairs well relative to previous longitudinal studies with follow-up times ranging from 2 to 20 years. In addition, the large number of matched DM and reference subjects yielded cumulated person-years for both exposure groups unmatched by other population-based cohort studies adding to the statistical power of our observation.

We applied specific methods to limit bias. We controlled confounding from systemic diseases, medications and sociodemographic factors by including of a wide set of variables in the multivariate analysis. By focusing on new incident glaucoma cases, we limited selection bias, a common issue in prevalence studies. To test for survival bias, we treated death as a competing event using the Fine–Gray model. The association between DM and glaucoma did not change in the competing events model signifying that higher mortality in DM does not explain the lower OAG incidence. To assess misclassification bias of macular diseases with visual field defects mimicking glaucoma, we carried out a sensitivity analysis excluding all patients that received retinal photocoagulation or vitreous injections. This should have ruled out retinal vascular complications that are more common in the diabetic population. Similarly, the higher prevalence of cataract in association with diabetes may lead to higher detection of glaucoma in conjunction with perioperative eye examinations (Prokofyeva et al., 2013). To rule out bias attributable to cataract surgery, we tested the sensitivity of our results by excluding subjects with past cataract surgery. Lower OAG incidence in the DM group remained regardless of previous macular treatments or cataract surgery. This strengthens the main finding as OAG was diagnosed less frequently in individuals with DM regardless of presumably more frequent eye examinations. Given the targeted visual health screening in DM, it is necessary to address the concern of detection bias when comparing glaucoma incidences. We could not control our findings against number of visits to ophthalmic services. However, the relatively steady glaucoma incidence curve after DM diagnosis indicates little effect from fundus screening measures on detected glaucoma (Figure 2).

There are certain limitations in identifying glaucoma rates from administrative medication data that may lead to over or under detection of incident glaucoma. According to one study, up to 30% of topical glaucoma medications may be prescribed for ocular hypertension rendering electronic definition of glaucoma based on dispensed prescriptions sometimes unreliable (Ellis et al., 2000). Fortunately, each glaucoma reimbursement claim is subject to rigorous clinical and administrative scrutiny. Therefore, we assert that the Finnish nationwide medical insurance register provides a solid source for identifying beneficiaries with definitive glaucoma.

Medication reimbursement by SII, one definition for incident glaucoma used in our study, requires an application process including an ophthalmologist's certificate adhering to clinical criteria as described in the methods section. This definition of glaucoma may be skewed towards cases with high IOP; cases with low IOP need to meet additional criteria, while those with high IOP are more likely to be referred for glaucoma examination. In fact, a prediction model based on a Swedish cohort found that most subjects with glaucoma (57%) had IOP 21 mmHg or less (Oskarsdottir et al., 2019). The incidence observed in our study, 1.19/1000 person-years in the DM group and 1.08 in the reference group, is below the incidence observed in a Finnish nationwide health survey with 2.2 new self-reported glaucoma cases per 1000 person-years (Purola et al., 2021). In the Rotterdam Eye Study cohort, the overall incidence rate of definitive

**TABLE 3** Incidence rate ratios of open-angle glaucoma with 95% confidence intervals based on Poisson regression adjusted for diabetes, sex, age, socioeconomic status, medication, comorbidities and hospital district (not shown)

| | IRR | 95% CI | |
|---|---|---|---|
| **Diabetes mellitus** | **0.92** | **0.85** | **0.99** |
| Female | 1.22 | 1.13 | 1.33 |
| Age | 1.03 | 1.03 | 1.04 |
| Socioeconomic status | | | |
| Upper-level employees | Reference | | |
| Self-employed | 0.77 | 0.61 | 0.97 |
| Lower-level employees | 1.06 | 0.89 | 1.27 |
| Manual workers | 0.73 | 0.60 | 0.88 |
| Students | 1.04 | 0.59 | 1.82 |
| Pensioners | 0.97 | 0.82 | 1.15 |
| Other | 0.88 | 0.72 | 1.08 |
| Medication | | | |
| Angiotensin agents | 1.17 | 1.05 | 1.30 |
| Beta-blockers | 0.88 | 0.80 | 0.98 |
| Calcium channel blockers | 1.02 | 0.90 | 1.15 |
| Diuretics | 0.79 | 0.69 | 0.91 |
| Statins | 1.38 | 1.25 | 1.52 |
| SSRI | 0.75 | 0.59 | 0.95 |
| Tricyclic antidepressants | 0.86 | 0.57 | 1.29 |
| Systemic corticosteroids | 0.92 | 0.66 | 1.28 |
| Comorbidities | | | |
| Arrhythmias | 0.92 | 0.69 | 1.22 |
| Cancer | 1.00 | 0.81 | 1.24 |
| Cardiac insufficiency | 0.61 | 0.44 | 0.84 |
| Coronary heart disease | 0.73 | 0.63 | 0.84 |
| Hypertension | 1.00 | 0.91 | 1.10 |
| Inflammatory bowel disease | 1.22 | 0.82 | 1.98 |
| Parkinson's disease | 0.56 | 0.28 | 1.13 |
| Severe psychotic and other severe mental disorders | 0.82 | 0.65 | 1.05 |
| Thyroid insufficiency | 1.05 | 0.86 | 1.30 |

Abbreviations: CI, confidence interval; IRR, incidence rate ratio; OAG, open-angle glaucoma; SSRI, selective serotonin reuptake inhibitors.

and probable OAG was 3.5 per 1000 person-years over a mean follow-up time of 6.5 years (de Voogd et al., 2005). In the same cohort, the incidence of glaucomatous visual field loss was 2.9 per 1000 person-years (Czudowska et al., 2010). These higher incidences compared with our real-world data may reflect the detection of otherwise undiagnosed OAG by screening within the Rotterdam Eye Study protocol. The age-specific OAG incidences in our study have a steeper increase towards older age compared with the Rotterdam Eye Study cohort (Table 2). In our study, the difference in OAG incidence from 50–60-year-olds to 70–80-year-olds was fivefold, while in the Rotterdam Study, the difference was less than double from 2.8 in 55–60-year-olds to 4.8 in 70–74-year-olds and 5.2 in 75–79-year-olds (de Voogd et al., 2005). These differences in OAG incidences by age may indicate an earlier diagnosis due to screening. Based on the above comparison, we believe our definition of glaucoma did not overestimate glaucoma incidences and that the criteria reasonably avoided inclusion of glaucoma suspects or ocular hypertension as definitive glaucoma.

The definitions of DM and glaucoma differ across previously published studies contributing to some variation in their results. Broadly utilized sources have been healthcare registers, self-reporting through questionnaires, or clinical examinations complemented with ocular imaging, visual field tests, blood samples and other physiological measurements. Unlike survey studies, we were unable to incorporate self-reported behavioural data, for example smoking, alcohol consumption, physical activity, body mass index or family history of glaucoma. There was no clinical assessment of study subjects or their medical files to obtain IOP readings and type of tonometry, visual field data, slit-lamp examination findings or other detailed information for the purpose of this study.

Due to the nature of the register data, we could not discern between primary open-angle, normal-tension and pseudoexfoliation glaucoma as distinct endpoints or report their relative incidences. In a recent Finnish population-based cohort study, investigating glaucoma prevalence in 45- to 49-year-olds, 30 (89%) of 33 definitive glaucoma cases were normal-tension glaucoma (Karvonen et al., 2019). In another Finnish cohort of people over 70 years of age, half of the prevalent OAG cases represented primary and another half pseudoexfoliation glaucoma (Hirvelä et al., 1994). In a Swedish population-based study, pseudoexfoliation glaucoma represented 8% of all open-angle glaucoma cases (Leske et al., 1999). Because we could not discern between glaucoma reimbursement decisions that were based on IOP or neuropathy criteria, it is possible the glaucoma criteria identified the effects of diabetic-induced corneal stiffening on tonometry measurements rather than glaucomatous optic neuropathy (Wang et al., 2020). Nonetheless, this was not reflected as higher OAG detection in DM based on our results.

Diabetes mellitus may influence biological processes linked with the pathogenesis and progression of glaucoma in ways that are difficult to fully control for in register studies. Type 2 DM has been associated with a slower rate of retinal nerve fibre layer thinning (Hou et al., 2018), with medications and other health care interventions targeted at DM presenting one possible explanation to this finding. Metformin, an oral antidiabetic agent, protected against retinal cell injury in an experimental study on diabetic mice (Kim et al., 2017). In a US cohort study, metformin was associated with a dose-dependent reduction in risk of developing OAG (Lin et al., 2015). As a limitation, we could not identify drug selection patterns for treating comorbidities and cardiovascular risks specific to DM that may differ from that of the population in general. Some of these drug classes may modulate the pathophysiology and risk of glaucoma. We aimed to control for confounding by medication in our adjusted model by including clinically relevant drug classes.

The findings of this study can be interpreted in the context of recent advances in the care of DM in Finland. The mortality of Finnish DM patients has

decreased over the past two decades driven by falling cardiovascular mortality (Niskanen et al., 2020). We can assume this to be due to a publicly funded healthcare system, early detection of DM and a holistic treatment approach aimed at the full spectrum of metabolic syndrome and diabetic complications. As components of metabolic syndrome may have a compounding risk on developing OAG (Newman-Casey et al., 2011), it is plausible that a well-rounded diabetes treatment regimen can attenuate the risk of diseases with vascular pathophysiology, including glaucoma. Such intermediary effects linked to DM could explain the lower OAG incidence associated with DM in our study as the impact of DM on OAG may vary by population and management of other vascular conditions. Large longitudinal studies with comparable case definitions for OAG and DM followed by meta-analysis would help further in determining the relationship between DM and risk of developing OAG. In conclusion, DM was associated with a modestly lower OAG incidence in this population-based longitudinal study.

## FUNDING INFORMATION

This study was financially supported by A.V.: Eye Foundation Research Grant (20200014), Glaucoma Support Foundation Lux (202100010), Finnish Ophthalmology Association Research Grant. The funding organizations had no role in the design or conduct of this research

## ORCID

*Aapo Virtanen* https://orcid.org/0000-0003-2916-4183
*Jari Haukka* https://orcid.org/0000-0003-1450-6208
*Sirpa Loukovaara* https://orcid.org/0000-0002-2506-3900
*Mika Harju* https://orcid.org/0000-0003-0103-1581

## REFERENCES

AGIS Investigators. (2002) The advanced glaucoma intervention study (AGIS): 12. Baseline risk factors for sustained loss of visual field and visual acuity in patients with advanced glaucoma. *American Journal of Ophthalmology*, 134, 499–512.

Bonovas, S., Peponis, V. & Filioussi, K. (2004) Diabetes mellitus as a risk factor for primary open-angle glaucoma: a meta-analysis. *Diabetic Medicine*, 21, 609–614.

Choi, J. & Kook, M.S. (2015) Systemic and ocular hemodynamic risk factors in glaucoma. *BioMed Research International*, 2015, 141905.

Chopra, V., Varma, R., Francis, B.A., Wu, J., Torres, M., Azen, S.P. et al. (2008) Type 2 diabetes mellitus and the risk of open-angle glaucoma the Los Angeles Latino eye study. *Ophthalmology*, 115, 227–232.e1.

Czudowska, M.A., Ramdas, W.D., Wolfs, R.C.W., Hofman, A., De Jong, P.T.V.M., Vingerling, J.R. et al. (2010) Incidence of glaucomatous visual field loss: a ten-year follow-up from the Rotterdam study. *Ophthalmology*, 117, 1705–1712.

de Voogd, S., Ikram, M.K., Wolfs, R.C.W., Jansonius, N.M., Hofman, A. & de Jong, P.T.V.M. (2005) Incidence of open-angle glaucoma in a general elderly population. *Ophthalmology*, 112, 1487–1493.

de Voogd, S., Ikram, M.K., Wolfs, R.C.W., Jansonius, N.M., Witteman, J.C.M., Hofman, A. et al. (2006) Is diabetes mellitus a risk factor for open-angle glaucoma? The Rotterdam study. *Ophthalmology*, 113, 1827–1831.

Dielemans, I., de Jong, P.T., Stolk, R., Vingerling, J.R., Grobbee, D.E. & Hofman, A. (1996) Primary open-angle glaucoma, intraocular pressure, and diabetes mellitus in the general elderly population. The Rotterdam study. *Ophthalmology*, 103, 1271–1275.

Ellis, J.D., Evans, J.M., Ruta, D.A., Baines, P.S., Leese, G., MacDonald, T.M. et al. (2000) Glaucoma incidence in an unselected cohort of diabetic patients: is diabetes mellitus a risk factor for glaucoma? DARTS/MEMO collaboration. Diabetes audit and research in Tayside study. Medicines monitoring unit. *British Journal of Ophthalmology*, 84, 1218–1224.

Fine, J.P. & Gray, R.J. (1999) A proportional hazards model for the subdistribution of a competing risk. *Journal of the American Statistical Association*, 94, 496–509.

Flaxman, S.R., Bourne, R.R.A., Resnikoff, S., Ackland, P., Braithwaite, T., Cicinelli, M.V. et al. (2017) Global causes of blindness and distance vision impairment 1990-2020: a systematic review and meta-analysis. *The Lancet Global Health*, 5, e1221–e1234.

Grzybowski, A., Och, M., Kanclerz, P., Leffler, C. & Moraes, C.G.D. (2020) Primary open angle glaucoma and vascular risk factors: a review of population based studies from 1990 to 2019. *Journal of Clinical Medicine*, 9, 761–778.

Hirvelä, H., Tuulonen, A. & Laatikainen, L. (1994) Intraocular pressure and prevalence of glaucoma in elderly people in Finland: a population-based study. *International Ophthalmology*, 18, 299–307.

Hou, H., Shoji, T., Zangwill, L.M., Moghimi, S., Saunders, L.J., Hasenstab, K. et al. (2018) Progression of primary open-angle glaucoma in diabetic and nondiabetic patients. *American Journal of Ophthalmology*, 189, 1–9.

Karvonen, E., Stoor, K., Luodonpää, M., Hägg, P., Kuoppala, J., Lintonen, T. et al. (2019) Prevalence of glaucoma in the northern Finland birth cohort eye study. *Acta Ophthalmologica*, 97, 200–207.

Kim, Y.S., Kim, M., Choi, M.Y., Lee, D.H., Roh, G.S., Kim, H.J. et al. (2017) Metformin protects against retinal cell death in diabetic mice. *Biochemical and Biophysical Research Communications*, 492, 397–403.

Klein, B.E., Klein, R. & Jensen, S.C. (1994) Open-angle glaucoma and older-onset diabetes. The Beaver Dam eye study. *Ophthalmology*, 101, 1173–1177.

Le, A., Mukesh, B.N., McCarty, C.A. & Taylor, H.R. (2003) Risk factors associated with the incidence of open-angle glaucoma: the visual impairment project. *Investigative Ophthalmology & Visual Science*, 44, 3783–3789.

Lee, E., Harris, A., Siesky, B., Schaab, T., McIntyre, N., Tobe, L.A. et al. (2014) The influence of retinal blood flow on open-angle glaucoma in patients with and without diabetes. *European Journal of Ophthalmology*, 24, 542–549.

Lee, M.J., Wang, J., Friedman, D.S., Boland, M.V., De Moraes, C.G. & Ramulu, P.Y. (2019) Greater physical activity is associated with slower visual field loss in glaucoma. *Ophthalmology*, 126, 958–964.

Leske, M.C., Heijl, A., Hyman, L. & Bengtsson, B. (1999) Early manifest glaucoma trial: design and baseline data. *Ophthalmology*, 106, 2144–2153.

Leske, M.C., Heijl, A., Hyman, L., Bengtsson, B., Dong, L., Yang, Z. et al. (2007) Predictors of long-term progression in the early manifest glaucoma trial. *Ophthalmology*, 114, 1965–1972.

Leske, M.C., Wu, S.-Y., Hennis, A., Honkanen, R., Nemesure, B. & BESs Study Group. (2008) Risk factors for incident open-angle glaucoma: the Barbados eye studies. *Ophthalmology*, 115, 85–93.

Lin, H.-C., Stein, J.D., Nan, B., Childers, D., Newman-Casey, P.A., Thompson, D.A. et al. (2015) Association of Geroprotective Effects of metformin and risk of open-angle glaucoma in persons with diabetes mellitus. *JAMA Ophthalmology*, 133, 915–923.

Mitchell, P., Smith, W., Chey, T. & Healey, P.R. (1997) Open-angle glaucoma and diabetes: the Blue Mountains eye study, Australia. *Ophthalmology*, 104, 712–718.

Newman-Casey, P.A., Talwar, N., Nan, B., Musch, D.C. & Stein, J.D. (2011) The relationship between components of metabolic syndrome and open-angle glaucoma. *Ophthalmology*, 118, 1318–1326.

Niskanen, L., Partonen, T., Auvinen, A. & Haukka, J. (2020) Trends and predictors in all-cause and cause-specific mortality in diabetic and reference populations during 21 years of follow-up. *Journal of Epidemiology and Community Health*, 74(11), 950–956.

NOMESCO Classification of Surgical Procedures (NCSP), version 1.16 (2011): Nordic Centre for Classifications in Health Care

WHO Collaborating Centre for the Family of International Classifications in the Nordic Countries Norwegian Directorate of Health.

Oskarsdottir, S.E., Heijl, A. & Bengtsson, B. (2019) Predicting undetected glaucoma according to age and IOP: a prediction model developed from a primarily European-derived population. *Acta Ophthalmologica*, 97, 422–426.

Pasquale, L.R., Kang, J.H., Manson, J.E., Willett, W.C., Rosner, B.A. & Hankinson, S.E. (2006) Prospective study of type 2 diabetes mellitus and risk of primary open-angle glaucoma in women. *Ophthalmology*, 113, 1081–1086.

Prokofyeva, E., Wegener, A. & Zrenner, E. (2013) Cataract prevalence and prevention in Europe: A literature review. *Acta Ophthalmologica*, 91, 395–405.

Purola, P.K.M., Nättinen, J.E., Ojamo, M.U.I., Koskinen, S.V.P., Rissanen, H.A., Sainio, P.R.J. et al. (2021) Prevalence and 11-year incidence of common eye diseases and their relation to health-related quality of life, mental health, and visual impairment. *Quality of Life Research*, 30, 2311–2327.

R Core Team. (2019) *R: a language and environment for statistical computing*. Vienna, Austria: R Foundation for Statistical Computing.

Song, B.J., Aiello, L.P. & Pasquale, L.R. (2016) Presence and risk factors for glaucoma in patients with diabetes. *Current Diabetes Reports*, 16, 124.

Stein, J.D., Khawaja, A.P. & Weizer, J.S. (2021) Glaucoma in adults—screening, diagnosis, and management: a review. *JAMA*, 325, 164.

Tan, G.S., Wong, T.Y., Fong, C.-W., Aung, T. & Singapore Malay Eye Study. (2009) Diabetes, metabolic abnormalities, and glaucoma. *Archives of Ophthalmology*, 127, 1354–1361.

Tielsch, J.M., Katz, J., Quigley, H.A., Javitt, J.C. & Sommer, A. (1995) Diabetes, intraocular pressure, and primary open-angle glaucoma in the Baltimore eye survey. *Ophthalmology*, 102, 48–53.

Wang, W., He, M., Li, Z. & Huang, W. (2019) Epidemiological variations and trends in health burden of glaucoma worldwide. *Acta Ophthalmologica*, 97, e349–e355.

Wang, H.-W., Sun, P., Chen, Y., Jiang, L.-P., Wu, H.-P., Zhang, W. et al. (2018) Research progress on human genes involved in the pathogenesis of glaucoma (review). *Molecular Medicine Reports*, 18, 656–674.

Wang, X., Xu, G., Wang, W., Wang, J., Chen, L., He, M. et al. (2020) Changes in corneal biomechanics in patients with diabetes mellitus: a systematic review and meta-analysis. *Acta Diabetologica*, 57, 973–981.

Wise, L.A., Rosenberg, L., Radin, R.G., Mattox, C., Yang, E.B., Palmer, J.R. et al. (2011) A prospective study of diabetes, lifestyle factors, and glaucoma among African-American women. *Annals of Epidemiology*, 21, 430–439.

Wu, A., Khawaja, A.P., Pasquale, L.R. & Stein, J.D. (2020) A review of systemic medications that may modulate the risk of glaucoma. *Eye (London, England)*, 34, 12–28.

Zhou, M., Wang, W., Huang, W. & Zhang, X. (2014) Diabetes mellitus as a risk factor for open-angle glaucoma: A systematic review and meta-analysis. *PLoS One*, 9, e102972.

**How to cite this article:** Virtanen, A., Haukka, J., Loukovaara, S. & Harju, M. (2023) Diabetes mellitus and risk of open-angle glaucoma—A population-based follow-up study. *Acta Ophthalmologica*, 101, 160–169. Available from: https://doi.org/10.1111/aos.15240