Relationship between Diabetic Retinopathy and Primary Open-Angle Glaucoma: A Systematic Review and Meta-Analysis

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**Keywords**

Diabetic retinopathy · Primary open-angle glaucoma · Systematic review · Meta-analysis

**Abstract**

**Background:** Pathophysiological overlaps exist between diabetes and primary open-angle glaucoma (POAG) and presence of diabetes increases the risk of POAG. Considering that diabetic retinopathy (DR) is an ocular complication of diabetes, one could speculate that DR as a severity measure may associate with or even predict POAG. Given that POAG is asymptomatic in early stages, an association to DR may prove clinically important and facilitate an earlier diagnosis of POAG. **Objectives:** The aim of the study was to investigate if DR is associated with and predictive of POAG. **Method:** We systematically searched 11 literature databases on May 12, 2021. We screened a total of 1,535 records and found six studies eligible for qualitative and quantitative analysis. Two independent authors reviewed the studies, extracted data, and evaluated risk of bias within individual studies. Studies were reviewed qualitatively, and meta-analyses were made based on the odds ratios (ORs) with 95% confidence intervals (CI) of the association between DR and POAG using the random-effects model. Subgroup analyses were made on the association between subtypes of DR and POAG. **Results:** Six studies (two longitudinal and four cross-sectional) were eligible for review with a total of 255,614 patients with diabetes, of which 20,483 patients had any degree of DR and 5,258 had POAG. All studies were based on patients with type 2 diabetes except one with both type 1 and type 2 patients. Any DR was not associated with POAG (OR 1.17; 95% CI: 0.58–2.35; \(p = 0.65\)). Further stratification revealed that neither cross-sectional (OR 1.00; 95% CI: 0.56–1.81, \(p = 0.99\)) nor longitudinal studies (OR 1.47; 95% CI: 0.57–3.78, \(p = 0.43\)) demonstrated an association between DR and POAG. **Conclusions:** We did not find convincing evidence of an association between DR and prevalent or incident POAG.

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**Introduction**

The global prevalence of diabetes was estimated to 476 million people in 2017 and is expected to increase to 571 million people in year 2025 [1]. Diabetic retinopathy (DR) is the most prevalent microvascular complication in diabetes [2, 3] and one of the primary causes of vision loss.
globally in the working age population [4]. DR presents with no symptoms in the early stages and can even remain without symptoms in selected cases with advanced stage of DR. Fundus screening of patients with diabetes allows timely identification of patients with sight-threatening DR and is important to prevent vision loss [5].

The World Health Organization has identified glaucoma as the second leading cause of blindness globally, with primary open-angle glaucoma (POAG) being the most common type [6]. POAG is a progressive optic neuropathy with characteristic changes in the optic nerve head, and it is often asymptomatic in earlier stages [7].

Diabetic retinopathy is a well-established risk factor for neovascular glaucoma [8], but some pathophysiological similarities between DR and POAG, such as retinal neurodegeneration or impairment of vascular supply to the optic nerve head [9], could also indicate that DR may associate with or even predict POAG. Given that POAG is asymptomatic in early stages, early identification and commencement of treatment is important. An association between DR and POAG may prove clinically important if glaucoma case-detection is included in future DR screening protocols. Our aim of this study was to systematically review the literature and conduct meta-analysis to determine if DR is associated with and predictive of POAG.

**Methods**

**Study Design**

This study was a systematic review and meta-analysis designed according to the considerations and items of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) and Meta-Analysis of Observational Studies in Epidemiology (MOOSE) [10, 11]. Conducting systematic reviews do not require institutional review board approval according to Danish law.

Our protocol was registered a priori in the PROSPERO database the May 13, 2021 (registration ID CRD42021254694). The PRISMA guidelines checklist is available as online supplementary File 1 (for all online suppl. material, see www.karger.com/doi/10.1159/000523940).

**Eligibility Criteria**

Studies were considered on the condition that they fulfilled following criteria:

- **Population**: Human adults with diabetes. No restrictions were made on demographics, diabetes type, approach to diagnosis, or diagnostic criteria; details of such aspects were extracted for the review.
- **Exposure**: Studies that evaluated presence of diabetic retinopathy (DR). No restrictions were made on the method of diagnosis or definition of DR; details of such aspects were extracted for the review.

- **Outcomes**: Presence and incidence of primary open-angle glaucoma (POAG). No restrictions were made on the approach to diagnose or to define POAG; details of such aspects were extracted for the review. In case glaucoma data were reported without data on subtypes, such data were included, unless there was reason to believe that reported type of glaucoma in study was not constituted by a majority (>50%) of POAG.
- **Study types**: We included studies with observational original data in either the entirety or subsample of the study data, and such observational data could be based on a longitudinal or cross-sectional design. We did not restrict based on whether the studies were population- or clinic-based, or if the studies were prospective or retrospective. We did not restrict studies based on geography or published journal. Relevant conference abstracts were considered eligible. We did not include studies without original data or case reports. We only included studies presented in English.

**Information Sources and Search Strategy**

We searched the databases the Cochrane Central, EMBASE, PubMed, and the entire Web of Science database collection (Web of Science Core Collection, BIOSIS Previews, Current Contents Connect, Data Citation Index, Derwent Innovations Index, KCI-Korean Journal Database, Russian Science Citation Index, and SciELO Citation Index). All databases were searched on May 12, 2021 with database specific details outlined in online supplementary File 2.

**Study Selection, Data Collection, and Risk of Bias Assessment**

One author (M.K.) examined all titles and abstracts to remove duplicates and obviously irrelevant reports using EndNote (Clarivate, Philadelphia, PA, USA). Remaining references were retrieved in full text for evaluation of eligibility. The author group discussed these papers until consensus. References listed in full text studies were reviewed for other potentially eligible studies. Two authors (M.K. and Y.S.) independently extracted data from each study regarding study and participant characteristics, details of study methods, and specific study results using extraction forms. We used the Agency for Healthcare Research and Quality checklist for cross-sectional studies [12] with relevant items (Question 1–4 and Question 6–7) for the risk of bias assessment of the studies (shown in online suppl. file 3). Extracted data and risk of bias analysis were compared and differences were discussed until a consensus, otherwise a third author (J.G. or A.V.) was involved for final decision.

**Outcomes Measures, Data Synthesis, and Data Analysis**

All studies were qualitatively reviewed in text and in tables. Our primary outcome measure was if DR is associated with and predictive of OAG in patients with diabetes. Unit of analysis was data per patient. Meta-analysis was performed with MetaXL 5.3 (EpiGear International, Sunrise Beach, QLD, Australia) for Microsoft Excel 2013 (Microsoft, Redmont, WA, USA). We followed the recommendations of the Cochrane Handbook for all analytical aspects of the meta-analysis [13]. The random-effects model was used. Summary estimate outcome was odds ratio (OR) with 95% confidence intervals (CI). Heterogeneity across studies was assessed using Cochrane’s Q and I² [14]. Funnel plots were used to evaluate the risk of bias across studies [15]. Sensitivity analyses were made by excluding each study in turn and repeating the analyses to evaluate
the robustness of the found results. Subgroup analyses were planned for diabetes subtype (type 1 diabetes vs. type 2 diabetes), DR stage (non-proliferative diabetic retinopathy [NPDR] vs. proliferative diabetic retinopathy [PDR]), and study design (cross-sectional vs. longitudinal data). *p* values below 0.05 were considered statistically significant.

Results

Study Selection

The literature search identified 1,535 records. Four records were known a priori and were also included. After removing duplicates and obviously irrelevant records (i.e., records that were clearly irrelevant based on title and abstract review), 69 records were deemed eligible for evaluation in full text. From the reference lists of these 69 records, we identified further 13 study titles that were eligible for evaluation in full text and therefore retrieved in full-text for further evaluation. Thus, from 82 full text records evaluated in full text, we found six studies to be eligible according to our eligibility criteria, and these studies were included for the qualitative and quantitative analysis (that is the systematic review and the meta-analysis, respectively). The study selection process is outlined in detail in Figure 1.
**Table 1.** Characteristics of studies included in the review

| Reference          | Country      | Sample source   | Study design            | Study population                                                                                           | Patients with diabetes | Age and gender | Diabetes duration | HbA1c level | Patients with any DR | Patients with NPDR | Patients with PDR | Patients with POAG |
|--------------------|--------------|-----------------|-------------------------|-----------------------------------------------------------------------------------------------------------|------------------------|-----------------|-------------------|--------------|----------------------|--------------------|------------------|------------------|------------------|
| Behera et al. [16] | India        | Clinic-based    | Cross-sectional        | Multicenter study from 14 eye care facilities. Patients had a history of type 2 diabetes and results were included from the patients’ first eye exam | 11,182                | 58±11 years       | Unclear         | Unclear     | 3,611                | N/A                | N/A              | 228              |
| Dharmadhikari et al. [17] | India | Clinic-based    | Cross-sectional        | Single-center study of patients with type 2 diabetes. Patients with secondary glaucoma were excluded       | 841                    | 54±11 years       | 30% 5–9 years, the rest <5 years | Unclear     | 231                  | 124                | 107*             | 66               |
| Gangwani et al. [18] | China        | Population-based | Cross-sectional        | Patients with type 2 diabetes who had never undergone examination by an ophthalmologist before            | 2,182                  | Unclear          | Unclear         | Unclear     | 470                  | 372                | 98†              | 36‡              |
| Horwitz et al. [19] | Denmark      | Population-based | Longitudinal, retrospective | Nationwide registry of claimed prescriptions for diabetes and POAG                                      | 238,671                | Mean 59 (range 1–110) years | Unclear, but patients were followed for median 15.66 years | Unclear     | 14,535               | N/A                | N/A              | 5,332            |
| Klein et al. [20]  | USA          | Population-based | Longitudinal, prospective | Patients with diabetes identified through primary care physicians. Study populations were: (1) patients aged <30 years with insulin-demanding diabetes and (2) patients with any diabetes aged ≥30 years. Patients with rubecosis were excluded | 2,366                  | Young population: 28±12 years 49% females Older population: 65±11 years 55% females | Young population: 14±10 years Older population: 11±8 years | Unclear     | 1,029                | 833                | 196              | 110              |
| Satici et al. [21] | Turkey       | Clinic-based    | Cross-sectional        | Single-center study of consecutive adult patients with type 2 diabetes                                   | 1,184                  | 66% females       | Unclear         | Unclear     | 607                  | 485§               | 122              | 97               |

DR, diabetic retinopathy; NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; POAG, primary open-angle glaucoma; USA, United States of America. * Study reported sight-threatening DR without further definition. † Study reported sight-threatening DR, which was defined as either diabetic maculopathy, pre-PDR, or PDR. § Data includes normal-tension glaucoma. ‡ Study reported background DR andpre-proliferative DR, which was pooled into NPDR for this table.
Study and Participant Characteristics

Five studies were reported as full-text reports [16–20] and one was a conference abstract [21]. Studies were cross-sectional (n = 3) [16, 17, 21], prospective longitudinal (n = 1) [20], and retrospective longitudinal (n = 1) [18] in design. Three studies were clinic-based studies [16, 17, 21] and three studies were population-based studies [18–20]. Study populations were from India (n = 2) [16, 17], China (n = 1) [18], Denmark (n = 1) [19], Turkey (n = 1) [21], and the USA of America (n = 1) [20]. Study characteristics are summarized in detail in Table 1.

Diagnosis and definition of diabetes were only specified in three studies [16, 17, 19]. Here, diabetes was diagnosed based on blood glucose level (fasting or random glucose, or HbA1c) or the patient being medicated for glycemic control. A comprehensive eye examination using at least slit-lamp biomicroscopy, intraocular pressure measurement, and gonioscopy was described in four studies [16–18, 20]. The definition and stratification of DR were described in three studies with largely uniform definitions [18, 20, 21]. Horwitz et al. [19] relied on registry-based data regarding any DR. The definition of POAG was described in detail in four studies [16–19]. Details of these diagnostic methods and definitions and summarized in Table 2.

Results of Individual Studies

Behera et al. [16] estimated the proportion of people with type 2 diabetes and glaucoma in a multicenter study with participants from 14 centers. Outcome measures were not reported according to glaucoma subtypes, but the majority of the glaucoma cases had POAG [16]. Neither DR nor DR severity was statistically significantly associated with glaucoma [16]. Dharmadhikari et al. [17] estimated the magnitude and determinants of glaucoma among individuals with type 2 diabetes in a single-center study. Outcome measures were not reported according to glaucoma subtypes, but the majority of the glaucoma cases had POAG [17]. Presence of DR was not statistically significantly associated with glaucoma, but interestingly, the authors reported a statistically significant association between diabetes duration and glaucoma [17]. Gangwani et al. [18] collected data from a DR eye screening program to investigate potential association between DR and glaucoma. Outcome measures were not reported according to glaucoma subtypes, but the majority of the glaucoma cases had either POAG or normal-tension glaucoma [18]. Here, DR was not a statistically significant associated with glaucoma even after adjustment for age and sex. Horwitz et al. [19] retrospectively reviewed nationwide registry data from Denmark for claimed prescriptions for anti-diabetic and anti-glaucomatous medication, as well as ICD-10 based coding, for any DR. Considering the anti-glaucomatous medication approach, we consider the vast majority of these glaucoma cases to represent POAG. Based on a median follow-up time of 15.9 years, the authors reported that any DR was associated with later development of POAG (hazard ratio 1.40, 95% CI 1.24–1.55). Klein et al. [20] determined the incidence of self-reported glaucoma in patients with diabetes. Patients who reported presence of glaucoma or taking medication for glaucoma were clinically examined for rubeosis, narrow-angle glaucoma, or secondary glaucoma, and such cases were excluded [20]. Therefore, the glaucoma cases were considered to consist of a majority of POAG. The authors reported a 10-year incidence of glaucoma of 3.7% and 6.9% in their younger-onset (i.e., type 1 diabetes) and older-onset (i.e., type 2 diabetes) study group, respectively [20]. The younger-onset study group had a statistically significant trend of increased incidence of glaucoma with increased severity of DR, which was not present in the older-onset study group [20]. Satici et al. [21] recruited consecutive patients with type 2 diabetes to investigate the relationship between POAG with the presence and the severity of DR. Here, the authors reported a statistically significant correlation between the severity of DR and POAG [21].

Risk of Bias within Studies

Risk of bias within studies revealed that studies were generally clear in defining the source and eligibility criteria of participants. Time period of study completion was clearly stated in five studies. Quality assurance (i.e., description of any assessments undertaken for quality assurance of outcome measures) was only reported in two studies. Consecutive recruitment of participants was clearly stated in three studies. The two studies with participant exclusion from analysis both clearly explained the rationale. The risk of bias evaluation within studies is summarized in Table 3.

Meta-Analyses of Any DR as a Risk Factor for POAG

Six studies of 255,614 patients with diabetes provided data eligible for the quantitative analyses [16–21]. Of these, 20,483 had any DR and 5,258 had POAG. Summary estimate of any DR as associated with POAG was OR 1.17 (95% CI: 0.58–2.35, p = 0.65) (Fig. 2). Heterogeneity estimates suggested an important degree of heterogeneity across data (Cochran’s Q = 183.6, I² = 97%, p < 0.01) (Fig. 2); however, these estimates should be inter-
Table 2. Methods of diagnoses and definitions used in studies included in the review

| Reference          | Diagnosis and definition of diabetes                      | Eye exam                                                                 | Definition of diabetic retinopathy                        | Definition of glaucoma                                      |
|--------------------|----------------------------------------------------------|---------------------------------------------------------------------------|------------------------------------------------------------|------------------------------------------------------------|
| Behera et al. [16] | Fasting glucose level of >126 mg/dL, and 2-h post-load glucose and random glucose of >200 mg/dL and HbA1c >6.5% | IOP measurement, slit-lamp exam including optic nerve head exam, gonioscopy, and where necessary also humphrey VF | Not specified                                               | IOP >21 mm Hg on applanation tonometry, optic disc changes, neuroretinal thinning, CDR >0.5, nerve fiber layer splinter hemorrhage at disc margin, and corroborating VF changes were the basis for glaucoma diagnosis. Based on findings and underlying etiology, cases were further stratified into primary or secondary glaucoma, and OAG or NAG |
| Dharmadhikari et al. [17] | Fasting glucose level of >7 mmol/L (>125 mg/dL) or the patient being medicated for glycemic control | Refraction and visual acuity. Slit-lamp exam including optic nerve head exam. IOP measurement using Goldmann applanation tonometer. Humphrey 30-2 VF. Gonioscopy with a 4-mirror lens | Not specified                                               | Two or more of following findings: (1) CDR >0.5, (2) focal notch in the neuroretinal rim, (3) thinning and pallor of the neuroretinal rim, (4) hemorrhage on the optic disc, (5) peripapillary atrophy, (6) VF defects correlated with optic disc changes, and (7) mean deviation >6 dB and pattern standard deviation >3 dB on perimetry, (8) IOP >21 mm Hg |
| Gangwani et al. [18] | Not specified                                             | Visual acuity, slit-lamp exam including optic nerve head exam, central corneal thickness, gonioscopy, fundus photographs, OCT, and humphrey 24-2 VF | Grading was made according to the English National Screening Programme classification. The authors report data based on any DR and a subgroup of sight threatening DR defined as any presence of maculopathy, pre-PDR, or PDR | CDR ≥0.6, glaucomatous defects on VF exam, or retinal nerve fiber layer thinning. Glaucoma types were defined as primary NAG (glaucomatous optic neuropathy and peripheral anterior synechia or appositional closure), primary OAG (glaucomatous optic neuropathy without appositional closure), and normal-tension glaucoma (glaucomatous optic neuropathy, open angle, and IOP ≤21 mm Hg) |
| Horwitz et al. [19] | Individuals aged 40–100 years who were prescribed antidiabetic medications | Not performed (registry-based study)                                      | Any DR was identified using ICD-10 diagnoses: DH36, DH368, DH360H, DH360J, DH360K, DH368D, DH368D1, and DH368D2 | Glaucoma was defined as at least 2 prescriptions <90 days for ≥1 anti-glaucomatous medication type (β-blockers, prostaglandin analogues, α2-adrenergic agonists, parasympathomimetic drugs, carbon anhydrase inhibitors, fixed combination drugs) |
| Klein et al. [20] | Not specified                                             | Refraction and visual acuity. Slit-lamp exam, IOP using Goldmann applanation tonometer, fundus photographs in ETDRS protocol | Eyes were grouped into one of four categories of DR: no DR, mild NPDR, moderate NPDR, and PDR | Not specified |
| Satici et al. [21] | Not specified                                             | Not specified                                                             | Eyes were categorized into no DR, “background” DR, pre-PDR, PDR, and macular edema | Not specified |

CDR, cup-disc-ratio; DR, diabetic retinopathy; ETDRS, early treatment diabetic retinopathy study; ICD-10, International Classification of Diseases 10th revision; IOP, intraocular pressure; NAG, narrow-angle glaucoma; NPDR, non-proliferative diabetic retinopathy; OAG, open-angle glaucoma; OCT, optical coherence tomography; PDR, proliferative diabetic retinopathy; VF, visual field.
Table 3. Risk of bias within individual studies included in the review

| Reference            | Defines source | Eligibility criteria | Time period | Consecutive recruitment | Quality assurance | Explains exclusions |
|----------------------|----------------|----------------------|-------------|-------------------------|------------------|--------------------|
| Behera et al. [16]   | Yes            | Yes                  | No          | No                      | Yes              | No exclusions      |
| Dharmadhikari et al. [17] | Yes            | Yes                  | Yes         | No                      | No               | No exclusions      |
| Gangwani et al. [18] | Yes            | Yes                  | Yes         | Yes                     | Unclear          | Yes                |
| Horwitz et al. [19]  | Yes            | Yes                  | Yes         | Yes                     | No               | Yes                |
| Klein et al. [20]    | Yes            | Yes                  | Yes         | Yes                     | No               | Yes                |
| Satici et al. [21]   | Yes            | Yes                  | No          | Yes                     | No               | No exclusions      |

Studies are assessed on relevant items from the Agency for Healthcare Research and Quality checklist: Defines source, defines the source of information; Eligibility criteria, lists the inclusion and the exclusion criteria or refers to any previous publications; Time period, indicates the time period used for identifying the participants; Consecutive recruitment, indicates if participants were recruited consecutively; Quality assurance, describes any assessments undertaken for quality assurance; Explains exclusions, explains any patient exclusions made from the analyses.

Fig. 2. Forest plot of the meta-analysis of any diabetic retinopathy as a risk factor for POAG in patients with diabetes. The summary estimate is stated in OR.

Subgroup Meta-Analyses of DR as a Risk Factor for POAG

The low number of available studies limited possibilities for data stratification and conduction of a priori planned subgroup analyses. Details and limitations of these analyses are summarized below, and results are summarized in Table 4. Overall, heterogeneity estimates suggested an important degree of heterogeneity across data (Table 4); however, these estimates should be interpreted with caution due to the small number of studies available in each subgroup analysis.

Subgroup Meta-Analysis Based on Diabetes Subtypes

Only Klein et al. [20] reported data that to a certain extent could be assumed to represent patients with type 1 diabetes. Klein et al. [20] found that increased severity of DR was associated with later development of glaucoma in younger insulin-demanding patients with diabetes (assumed to represent patients with type 1 diabetes). Our analyses of this subgroup of patients with type 1 diabetes found that any DR was associated with POAG at a level close to statistical significance (OR 2.78, 95% CI: 0.96–8.08, p = 0.06). Klein et al. [20] also reported data on older patients with any diabetes (with or without insulin-demanding diabetes). Similarly, Horwitz et al. [19] reported data on older patients in any antidiabetic medication (with or without insulin-demanding diabetes) [20]. For a more accurate estimate amongst patients with type 2 diabetes, we looked at the summary estimates after excluding Klein et al. [20] and Horwitz et al. [19] from the analyses. Here, the summary estimate was OR 1.00 (95% CI: 0.56–1.81, p = 0.99).
Subgroup Meta-Analysis Based on DR Subtypes

Four studies reported data that allowed subgroup analyses based on DR subtypes according to our stratification of reported data into either NPDR or PDR [17, 18, 20, 21]. Summary estimate of NPDR and PDR in association with POAG was OR 1.02 (95% CI: 0.63–1.63, \( p = 0.95 \)) and OR 1.42 (95% CI: 0.58–3.45, \( p = 0.44 \)), respectively.

Subgroup Meta-Analysis Based on Study Designs

Klein et al. [20] and Horwitz et al. [19] evaluated the risk of DR prior to development of POAG in a longitudinal design, and a meta-analysis of this subgroup lead to a summary estimate of OR 1.47 (95% CI: 0.57–3.78, \( p = 0.43 \)). Remaining four studies were cross-sectional of design [16–18, 21] and a meta-analysis of these lead to a summary estimate of OR 1.00 (95% CI: 0.56–1.81, \( p = 0.99 \)).

Discussion

In this systematic review and meta-analysis of six studies with a total of 255,614 patients with diabetes, we did not find that presence of any DR was associated to POAG. Further, when exploring DR subtypes, we found that neither NPDR nor PDR was statistically significant associated with POAG. In contrast, the scientific literature has sufficiently documented that diabetes is a risk factor for POAG [22, 23]. In a systematic review and meta-analysis of 13 studies, Zhou et al. [23] reported a pooled OR of 1.35 (95% CI: 1.06–1.74), i.e., a statistically significant higher risk among patients with diabetes for development of POAG. Hence, although diabetes can be considered a risk factor for POAG, presence of DR or the severity of DR do not appear to be a further associated with POAG.

In our systematic search, we identified a number of interesting studies that did not meet the inclusion criteria. Abikoye et al. [24] found that glaucomatous diabetic eyes were almost three times more likely to develop DR compared to non-glaucomatous diabetic eyes. Griffith and Goldberg [25] reported that patients with POAG and diabetes had higher prevalence of DR compared to patients with other glaucoma subtypes. Williams et al. [26] reported that patients with POAG had less severe DR than among non-glaucomatous controls and suggested a suppressive effect of glaucoma on DR. These studies underscore that our knowledge on the potential relationship between DR and POAG remains limited and call for further studies to understand the pathology and mechanisms of DR and POAG.

Important limitations of our study need to be acknowledged when interpreting our results. Six studies on 255,614 patients with diabetes may appear as a critical number for analysis but considering that 93% of these individuals are from one of the studies and the generally low number of DR and POAG among patients with diabetes, we actually consider this meta-analysis to be small in size and one should interpret our summary estimates with caution. Further, different approaches in defining patients with diabetes may introduce a certain heterogeneity across studies. One important aspect of this is that some cases of type 2 diabetes can be treated with lifestyle

Table 4. Summary of subgroup meta-analyses on diabetic retinopathy as a risk factor for POAG

| Subgroup analysis                                                                 | Studies,  \( N \) | Patients,  \( N \) | OR  | 95% CI          | \( p \) value | Cochran’s \( Q \) | \( I^2 \)  | \( p \) value for heterogeneity |
|-----------------------------------------------------------------------------------|-------------------|-------------------|-----|----------------|--------------|-----------------|---------|-------------------------------|
| Any DR associated with POAG across diabetes subtypes                               |                   |                   |     |                |              |                 |         |                               |
| In type 1 diabetes                                                                | 1                 | 789               | 2.78| 0.96–8.08      | 0.06         | –               | –       | –                             |
| In type 2 diabetes                                                                | 4                 | 15,389            | 1.00| 0.56–1.81      | 0.99         | 19.2            | 84.4    | <0.01                         |
| Different types of DR associated with POAG                                        |                   |                   |     |                |              |                 |         |                               |
| NPDR                                                                              | 4                 | 1,815             | 1.02| 0.63–1.63      | 0.95         | 7.1             | 57.9    | 0.07                          |
| PDR                                                                               | 4                 | 522               | 1.42| 0.58–3.45      | 0.44         | 14.4            | 79.2    | <0.01                         |
| Any DR associated with and predictive of POAG across study designs                 |                   |                   |     |                |              |                 |         |                               |
| Longitudinal                                                                     | 2                 | 240,348           | 1.47| 0.57–3.78      | 0.43         | 22.0            | 95.5    | <0.01                         |
| Cross-sectional                                                                   | 4                 | 15,389            | 1.00| 0.56–1.81      | 0.99         | 19.3            | 84.4    | <0.01                         |

95% CI, 95% confidence interval; DR, diabetic retinopathy; NPDR, non-proliferative diabetic retinopathy; POAG, primary open-angle glaucoma; PDR, proliferative diabetic retinopathy; OR, odds ratio.
interventions or there may be cases with poor medication compliance. These cases may be missed by Horwitz et al. [19], where identification of patients is partly based on antidiabetic medication and partly based on International Classification of Diseases 10th revision (ICD-10) diagnoses. As ICD-10 is only used in a hospital setting, the patients with DR are selected and the diagnostic accuracy low. Additionally, Horwitz et al. [19] identify glaucoma cases through antidiabetic medication use, though evidence shows that the compliance among POAG patients is low [27]. Similar bias exists for patients, who do miss or do not show up for DR grading or cases of undiagnosed glaucoma.

Finally, cross-sectional data are unable to provide much insight into causally and temporal relationship between DR and POAG. Ideally, better designed and larger longitudinal studies are needed for more conclusive insight.

Statement of Ethics

An ethics statement is not applicable because this study is based exclusively on published literature.

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Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

J.G. and A.H.V. conceived the initial idea; M.K., J.G., A.H.V., and Y.S. developed the protocol; M.K., J.G., A.H.V., and Y.S. were involved in study selection, data extraction, risk of bias assessment, and data analysis and synthesis; M.K. and Y.S. drafted the manuscript; M.K., J.G., A.H.V., and Y.S. revised and finalized the manuscript.

Data Availability Statement

All data have been extracted from published literature and referenced appropriately so that others can access same data.
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