

# Diabetes and risk of glaucoma: systematic review and a Meta-analysis of prospective cohort studies

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## Abstract

• **AIM:** To quantify the association between diabetes and glaucoma using Meta-analysis.

• **METHODS:** PubMed and Embase were searched using medical subject headings and key words related to diabetes and glaucoma. The inclusion criteria were: 1) the study design was a prospective cohort study; 2) the exposure of interest was diabetes; 3) the outcome of interest was primary open angle glaucoma (POAG); 4) risk ratios (RR) and the corresponding 95% confidence interval (CI). Data were pooled using fixed effects models to take into account heterogeneity between studies. Seven prospective studies were selected. Diabetes increased the incidence of glaucoma by 36% (OR=1.36, 95% CI=1.25-1.50). There was no evidence of statistical heterogeneity ( $I^2=0$ ,  $P=0.53$ ) or publication bias (the funnel plot did not identify obvious asymmetry).

• **RESULTS:** Seven prospective cohort studies were incorporated in this Meta-analysis. The pooled RR of the association between POAG and diabetes based on the risk estimates of the seven cohort studies was 1.36 (95%CI=1.24-1.50), with no significant heterogeneity across studies ( $I^2=0$ ;  $P=0.526$ ). The sensitivity analysis yielded a range of RRs from 1.34 (95%CI=1.22-1.48) to 1.40 (95%CI=1.18-1.67).

• **CONCLUSION:** Diabetes is associated with a significantly increased risk of glaucoma.

• **KEYWORDS:** primary open angle glaucoma; diabetes; prospective studies

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## INTRODUCTION

Glaucoma is a progressive optic disease that is mainly caused by high pressure in the eyes and is characterized by gradual death of retinal ganglion cells (RGC)<sup>[1]</sup>. This eye disease, which is a leading cause of irreversible blindness worldwide, has generated a major public health problem<sup>[2]</sup>. Primary open angle glaucoma (POAG) is the most common type of glaucoma in diabetic individuals, with nearly 70 million affected worldwide<sup>[3]</sup>. Therefore, potential risk factors for POAG need to be identified so that interventions to reduce its incidence can be developed.

So far, the pathogenesis of POAG is still not well understood. Some researches postulated damage to the microvasculature network and/or reduced nutritional supply to the RGC axons due to interference of blood regulation in the optic nerve head area<sup>[4-5]</sup>. This nutritional deficiency may lead to degeneration of RGCs and initiate glaucomatous impairment. Therefore, any vascular-related systemic disease, such as diabetes, which directly or indirectly disrupts nutritional supply to RGCs, may result in development of POAG.

Diabetes had been deemed as a risk factor for POAG by some reports, however, epidemiologic studies of the relationship between diabetes and POAG are still controversial. Two previous Meta-analyzes found a statistically significant association between diabetes and glaucoma<sup>[6-7]</sup>. However, most of the studies included in those Meta-analyzes were cross sectional or case control, which were prone to more biases than prospective studies. With recent accumulation of evidence, this review aimed to evaluate the association of diabetes with POAG by performing a Meta-analysis of prospective cohort studies.

## MATERIALS AND METHODS

**Search Strategy** This systematic review and Meta-analysis was reported following the guideline of Meta-analysis of Observational Studies in Epidemiology. The protocol of this systematic review was registered in the PROSPERO (No. CRD42016053714). PubMed and Embase database were searched up to November 2016 for relevant studies that tested the association between diabetes and glaucoma. The following search terms were used: 1) diabetes mellitus, diabetes, glycaemia, risk factors; 2) glaucoma, glaucomas; 3) cohort studies, prospective studies, cohort and prospective. There will be no language restrictions. In addition, we manually searched

the reference lists from key articles and identified additional relevant studies.

**Study Selection** Our purpose was to identify all studies reporting an association between diabetes and glaucoma. We first conducted an initial screening of abstracts and titles. Then a second screening based on full-text review was followed. Studies were included in this Meta-analysis if they met the following criteria: 1) the study design was a prospective cohort study; 2) the exposure of interest was diabetes; 3) the outcome of interest was POAG; and 4) risk ratio (RR) or odds ratio (OR) and the corresponding 95% confidence interval (CI) (or data to calculate them) were reported. If more than one identified articles reported on the same study population, we selected the study with the longest follow-up or the most recent study.

**Data Extraction** Two authors (Chen XW and Zhao YX) separately reviewed all searched articles to determine eligible studies and extracted data from selected results. Any disagreements were resolved by discussion. Data extraction was performed by using a standardized data-collection form. Information was extracted as follows: the first author's last name; publication year; country location; characteristics of study population (age, number of participants); number of POAG; methods for identification of diabetes; RR (or OR) from the most fully adjusted models for the diabetes compared with the non-diabetes and its corresponding 95% CI; and statistical adjustments for confounding factors.

**Quality Assessment** The study quality was assessed by the Newcastle-Ottawa Scale, which is a star system that comprised eight items to evaluate a study based on three broad perspectives, including selection, comparability, and outcome categories. A study can be awarded a maximum of one star for each numbered item within the selection and outcome categories and a maximum of two stars for each item in the comparability category. A score of five or higher indicated that the study had high quality. A score of four or lower indicated that the study had low quality. Two authors independently scored each included study and any disagreement was resolved by discussion.

**Statistical Analyses** The statistical analyses were based on estimates extracted from prospective studies. Thus, RRs and its 95% CI were used as the common measure of association across studies, and were pooled within a Meta-analysis using the random effects model, which were used for studies with considerable heterogeneity, or the fixed effects model, which were used for studies with low heterogeneity. The hazard ratios (HR) and OR were directly considered as RR for the incidence rate of glaucoma was low.

The homogeneity of RRs across studies was identified by using the  $Q$  statistic (significance level at  $P < 0.1$ ). Furthermore, the value of  $I^2$  statistic, which was a quantitative measure of

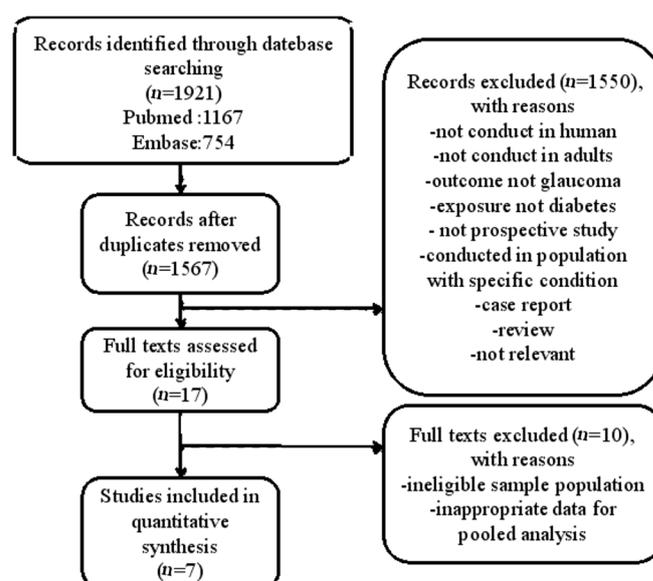


Figure 1 Flow chart of study selection.

homogeneity across studies, was calculated to provide a better interpretation of inconsistency across the included studies. The values of  $I^2 > 75\%$ ,  $< 75\%$ ,  $< 50\%$ , and  $< 25\%$  represent considerable, substantial, moderate, and low heterogeneity, respectively.

A sensitivity analysis was performed to investigate the influence of a single study on the overall RR by omitting one study in each turn. Potential publication bias was qualitatively assessed by funnel plots and quantitatively assessed by Egger's regression test, the latter would not be conducted if the included studies  $< 10$  cases. The Meta-analysis was performed using the Stata version 12.0 software statistical analysis.

## RESULTS

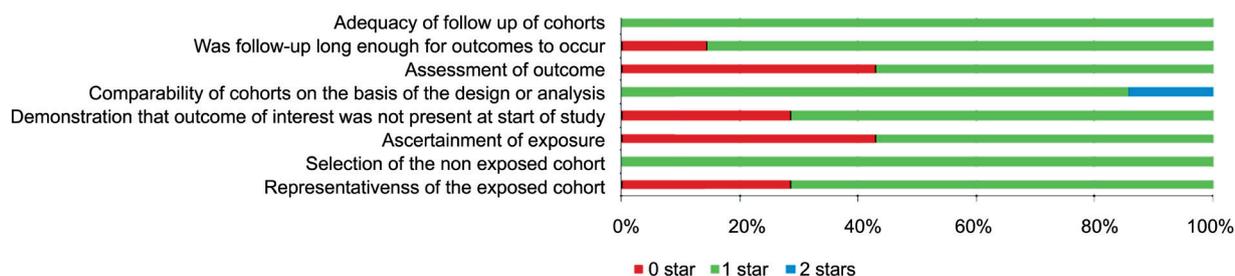
**Literature Search** We initially obtained a total of 1921 citations (1167 from PubMed and 754 from Embase). Of these, we excluded 354 publications because these were duplicate reports and 1550 publications because these were reviews, case reports, outcome or exposure studies not relevant to our analysis, conducted in a population with specific condition, or not prospective studies. After full text review of the remaining 17 papers, we selected 7 papers that were considered for analysis<sup>[8-14]</sup>. The main reasons for exclusion were inappropriate data for pooled analysis or ineligible sample population. The flowchart of study selection is shown in Figure 1.

**Study Characteristics** Table 1 provides an overview of key characteristic of the eligible studies. The included studies were published between 2000 and 2014. The studies varied in size between 3222 and 2 182 315 subjects, with an overall sample size across the studies of 2 445 203. The mean length of follow-up in prospective studies ranged from 2 to 20y. Two studies adjusted for age only and five studies controlled a set of normal risk factors for glaucoma, such as gender, age, diabetes, smoking, myopia and so on. Additionally, only one study adjusted for intraocular pressure (IOP).

## Relationship between diabetes and glaucoma

**Table 1** key characteristics of the eligible studies

Author, year	Characteristics of population	Follow up (a)	Adjusted covariates	Assessment of exposure	Main findings
Ellis <i>et al</i> , 2000	Aged ≥40a, n=1752 residents of Tayside, 44 cases of glaucoma	2	Age	Medical diagnosis	No significant association (RR=1.57, 95% CI 0.99-2.48)
De Voogd <i>et al</i> , 2006	aged ≥55a, n=3837 living in Rotterdam, 87 cases of glaucoma	6.5	Age, gender, follow-up time, IOP, IOP lowering treatment, BMI and hypertension	Non-fasting glucose tolerance test	No significant association (RR=0.65, 95% CI 0.25-1.64)
Pasquale <i>et al</i> , 2006	Aged ≥40a, n=43732 registered nurses, 429 cases of glaucoma	20	Age	Medical record review	Significant association (RR=1.53, 95% CI 1.06-2.22)
Leske <i>et al</i> , 2008	Aged ≥40a, n=3222 African descents, 125 cases of glaucoma	9	Age and gender	No description	No significant association (OR=1.20, 95% CI 0.70-1.80, P=0.49)
Newman-casey <i>et al</i> , 2011	Aged ≥40a, n=2182315 participants, 55090 cases of glaucoma	6	Age, sex, race, education level, household net worth <i>etc</i>	No description	Significant association (HR=1.35, 95% CI 1.21-1.50)
Wise <i>et al</i> , 2011	Aged ≥21a, n=32570 African-American woman, 365 cases of glaucoma	12	Age, questionnaire cycle, education cigarette smoking, current alcohol consumption, hypertension <i>etc</i>	Self-reported	Significant association (RR=1.58, 95% CI 1.17-2.13)
Vijaya <i>et al</i> , 2014	Aged ≥40a, n=4316 indian, 129 cases of glaucoma	6	Age, gender and habitation type	Detailed medical history	No significant association (OR=1.07, 95% CI 0.62-1.82)



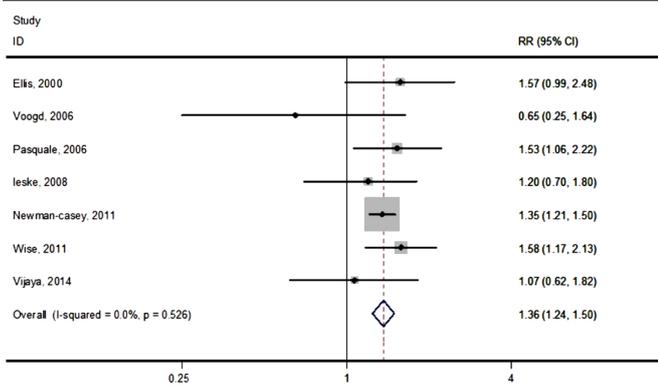
**Figure 2** Methodological quality of included studies using the NOS tool.

**Quality Assessment** The process of quality assessment of the included studies is shown in Figure 2. For the items “selection of the non-exposed cohort” and “adequacy of follow-up of cohorts,” all included studies were awarded a maximum star. For the items “ascertainment of exposure” and “assessment of outcome,” only four studies were awarded one star. In general, one study was scored only 4 stars<sup>[14]</sup>, whereas each of the other six studies was scored at least 5 stars (5, 6, 7, 7, 8, and 9 stars). **Synthesis of Results and Meta-analysis** The pooled RR of the association between POAG and diabetes based on the risk estimates of the seven cohort studies was 1.36 (95% CI: 1.24-1.50), with no significant heterogeneity across studies ( $I^2=0$ ;  $P=0.526$ ). These results were showed in Figure 3. Of these 7 included studies, 3 studies found a statistically significant association between diabetes and glaucoma and 4 studies found not. The sensitivity analysis, which investigated the influence of a single study on the overall risk estimate by omitting one study at each turn, yielded a range of RRs from 1.34 (95%CI:1.22-1.48) to 1.40 (95%CI:1.18-1.67). This suggested that exclusion of any single study did not obviously alter the overall combined RR (Figure 4).

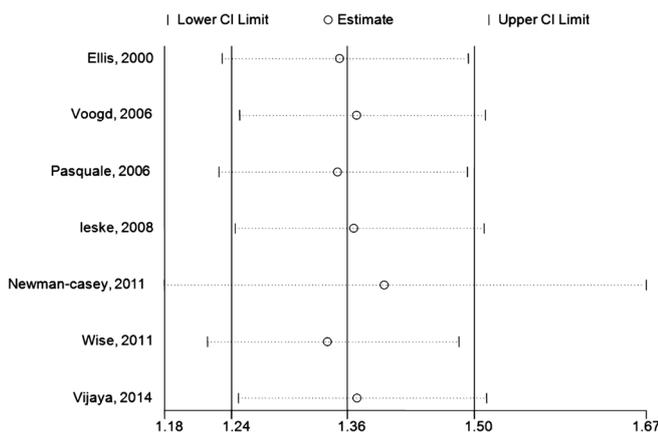
**Publication Bias** Visual inspection of the funnel plot did not identify obvious asymmetry. The Egger test for funnel plot asymmetry was not performed for that the power of this test was too low to distinguish chance from real asymmetry when the Meta-analysis included less than 10 studies (Figure 5).

## DISCUSSION

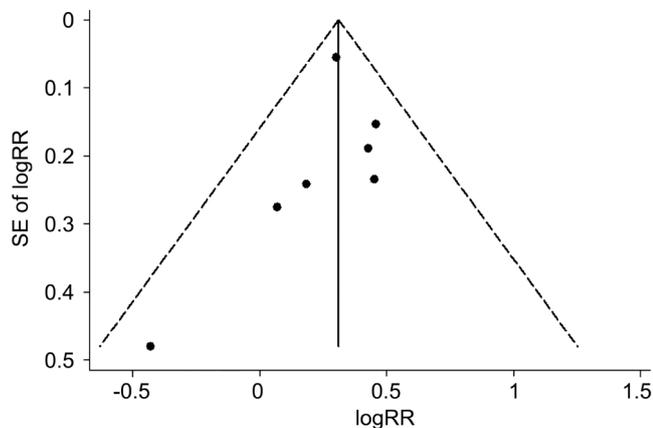
Diabetes mellitus had been proposed as a risk factor for POAG, but epidemiologic studies on the association between diabetes and glaucoma were still controversial. Although some articles reported a positive association between diabetes and glaucoma<sup>[11,15-18]</sup>, some others believed that the higher prevalence of glaucoma in individuals with diabetes was caused by the more frequent ophthalmologic visits among diabetes patients<sup>[13,19]</sup>. Two previous Meta-analyses reported a positive association between POAG and diabetes<sup>[6-7]</sup>. However, the publication biases reported in those systematic reviews were significant and a large number of nil association studies were not incorporated in them<sup>[20-21]</sup>. Moreover, several cohort studies that had accumulated in recent years were likewise not included<sup>[8-9]</sup>. Therefore, the direction and magnitude of pooled estimates in these reviews should be interpreted with caution.



**Figure 3 Forest plot of prospective cohort studies examining diabetes and risk of glaucoma.**



**Figure 4 Sensitivity analysis of exclusion each single study.**



**Figure 5 Funnel plot of diabetes and risk of glaucoma incidence.**

To better ascertain the association between diabetes and POAG, a more robust Meta-analysis should be conducted.

In this paper, we aimed to quantify the risk for development of glaucoma in individuals with diabetes by performing a Meta-analysis of prospective cohort studies. The results of this review revealed that the incidence of glaucoma markedly increased by 36% (RR=1.36, 95%CI:1.25-1.50) in patients with diabetes compared with individuals with no diabetes. In addition, the overall combined RRs were not obviously altered by the exclusion of any single study in the sensitivity analysis. Furthermore, we discovered that there was little heterogeneity in the methods and quality of the original studies and the publication bias assessed by the funnel plot in this review

was not significant. To sum up, all these findings provided strong evidence that there was a definitive association between diabetes mellitus and POAG.

The mechanisms relating diabetes to POAG were unclear. Several hypotheses on biological links between diabetes mellitus and glaucoma had been proposed. First, it was postulated that diabetes would lead to impairment of microcirculation and vascular autoregulation<sup>[22-24]</sup>. These vascular injuries would reduce blood flow to the retina and optic nerve<sup>[25-26]</sup>, resulting in reduced nutrient and oxygen supply to the RGC axons and increased expression of hypoxia-inducible factor-1 in the retinal cells in response to elevated IOP. Ultimately these were likely to induce the degeneration of the RGCs and initiation of glaucomatous impairment. Second, there was a large amount of evidence that the hyperglycemia and lipid anomalies induced by diabetes could increase the risk of neuronal injury<sup>[4,27]</sup>, indicating that the RGCs were more likely to be killed in the patients with diabetes. Third, the hyperglycemia of aqueous humor in the eyes of diabetes patients would stimulate the synthesis and accumulation of fibronectin in the trabecular meshwork to promote depletion of trabecular meshwork cells, which could impair the outflow system of the aqueous humor and finally result in POAG<sup>[28-29]</sup>.

A major strength of this systematic review was that it was based on prospective cohort studies, which minimized the possibility of selection and recall biases that had always been the limitation of case control and cross sectional studies. Another strength of this Meta-analysis was that all but one of the included studies were scored as high quality, suggesting that there was little methodological heterogeneity among the included studies. This point was supported by the results of quantitative homogeneity assessment in this review ( $I^2=0$ ,  $P>0.1$ ). Finally, this Meta-analysis had a larger sample size in the cohort studies as compared with two previous reviews, revealing that the statistical power provided in this study was more precise and reliable than the former Meta-analyses.

The limitations of this Meta-analysis should be acknowledged when interpreting the findings. First, the presence of residual confounders was always the concern of prospective cohort studies. Although age, which was an important potential confounding factor<sup>[30]</sup>, was controlled in all included studies, several other important potential confounding factors were not sufficiently considered. For instance, IOP, which could affect the relationship between diabetes and POAG, was not adjusted in all but one of the selected studies. Therefore, the exclusion of likelihood factors that may be responsible for the link between diabetes and glaucoma would weaken the validity of this Meta-analysis. Second, there was considerable difference among original studies with regard to population characteristics, follow-up years, and diagnosis confirmations.

These discrepancies would underestimate the reliability of statistical results in the review. Third, the association between glaucoma and type 1 diabetes may be different from that between glaucoma and type 2 diabetes. Unfortunately, the type of diabetes in the included studies was not detailedly described. This would limit the generalizability of our findings. Finally, the quantitative assessment of publication bias was not performed in this review for the inadequate included studies. Although visual inspection of the funnel plot of the present Meta-analysis did not identify any obvious asymmetry, indicating that there was no significant publication bias in this review, the absence of the quantitative measurement of publication bias would make the results in this review less convincing.

In conclusion, the current Meta-analysis of prospective cohort studies provided strong evidence in support of significant positive association between diabetes and POAG. Yet the actual influence of important confounding factors, such as IOP, central corneal thickness and so on, was not comprehensively investigated in this review. Further prospective studies were warranted to clarify the role of other important confounding factors in the diabetes and glaucoma association.

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**Conflicts of Interest:** Zhao YX, None; Chen XW, None.

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