The Association of Primary Open-angle Glaucoma With Mortality

A Meta-analysis of Observational Studies

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Objective: To conduct a meta-analysis to estimate the relationship between primary open-angle glaucoma (POAG) and mortality.

Methods: A systematic search of the PubMed, Embase, and Web of Science databases yielded 9 cohort studies with relative risk (RR) estimates for all-cause mortality. The studies were critically reviewed by an expert in the field. The data were extracted and analyzed in a pooled analysis by the random-effects model. Meta-regression to assess for heterogeneity by several covariates and subgroup analysis on cardiovascular mortality were performed.

Results: A significant risk was not detected in the final pooled analysis (RR, 1.13; 95% confidence interval [CI], 0.97-1.31) for all-cause mortality. A meta-regression across mean follow-up time, age, and sex was not significant. A meta-regression across diabetes status in 3 of the 9 studies did not demonstrate significant results ($P = .94$). Subgroup analysis on cardiovascular mortality from 4 of the 9 studies was marginally significant (RR, 1.20; 95% CI, 1.00-1.43; $P = .05$), but insignificant after removal of a study in which POAG was ascertained by self and proxy report (RR, 1.12; 95% CI, 0.87-1.46).

Conclusion: This meta-analysis does not demonstrate an association between POAG and all-cause or cardiovascular mortality.

Arch Ophthalmol. 2009;127(2):204-210

Primary open-angle glaucoma (POAG) is a multifactorial, chronic, progressive disease that results in damaged structural integrity of the optic nerve and diminished visual function. The exact etiology of POAG remains unknown, and it is unclear whether POAG is an ocular process in the context of a diseased host predisposed to a shortened life span. Understanding the relationship between POAG and mortality is critical, with an estimated 44.7 million people affected worldwide by the year 2010. If true mortality rates in patients with POAG differ from those of the general population, this information may provide insight into the underlying disease etiology.

It is difficult to infer the relationship between POAG and mortality based on an analysis of known determinants of mortality in middle-aged adults. Primary open-angle glaucoma may not produce excess mortality simply because the disease prevalence increases dramatically with age. Mean arterial pressure as well as other blood pressure indices are risk factors for all-cause mortality, yet lower blood pressure in the context of higher intraocular pressure (IOP) resulting in low perfusion pressure is a strong risk factor for POAG. Obesity is associated with cardiovascular mortality, and several studies show a positive correlation between body mass index (calculated as weight in kilograms divided by height in meters squared) and IOP, however, the association between body mass index and POAG may be null or inverse in nature. Finally, diabetes mellitus, a risk factor for cardiovascular and all-cause mortality, is positively associated with POAG in some, but not all, studies.

A limitation in studies assessing POAG and mortality is the small number of POAG cases. Epidemiologic studies with a limited number of participants may lack sufficient study power to detect a small to moderate relationship between POAG and mortality. Furthermore, studies may have variable accounting of important covariates that affect mortality. The primary aim of this study is to conduct a meta-analysis to estimate the relationship between POAG and mortality and to evaluate for sources of heterogeneity.
METHODS

LITERATURE SEARCH

Two independent reviewers (M.A. and S.A.) completed a systematic search of the PubMed, Embase, and Web of Science databases without date restrictions for articles related to mortality in patients with POAG. A combination of text words and Medical Subject Headings of the National Library of Medicine or subject headings was used in the database search. The terms included were glaucoma, glaucoma open angle, primary open angle glaucoma, hazard rate, mortality, and survival.

The titles of all articles were read and the relevant abstracts evaluated. The bibliographies were cross-referenced, and pertinent papers were extracted in this manner. Authors were contacted for supplemental information. Manual searches for articles found electronically and/or referenced, but not available online, were completed at the institutional library. The electronic and hand searches were completed in March 2008.

SELECTION CRITERIA AND DATA EXTRACTION

Studies were included if they (1) reported POAG or IOP status, (2) excluded secondary glaucoma, (3) reported all-cause mortality relative risks (RR) with 95% confidence intervals (CI), (4) included a control group, and (5) were written in English. Study quality was assessed using the suggested framework from Egger et al.35 The variables examined included adequate explanation of study sampling and diagnostic criteria for POAG, outcome results for a high proportion of the population, and appropriate statistical adjustment of the outcome. In the primary analysis, the definition of POAG included diagnosis based on optic nerve and/or visual field criteria from standardized examinations as well as cases diagnosed by elevated IOP measurements or based on self and proxy report of glaucoma. However, not all patients with elevated IOP develop POAG, and not all POAG patients have high IOP. Similarly, self and family reporting may not be a reliable estimate of glaucoma, has a potential for recall bias, and may lead to overreporting and/or underreporting. To account for the reservations associated with the latter definitions, we performed a secondary analysis excluding these studies.36,37

We excluded 2 studies that were not published in English.38,39 Their abstracts were not available for review, and we could not determine if they met the inclusion criteria. We excluded studies that were limited to nongeneralizable patients, including a study of mortality in blind40 and in diabetic41 patients with POAG. Finally, because exfoliation syndrome is thought to be of different genetic etiology42-44 and possibly associated with excess morbidity,45 we eliminated one study with an overrepresentation of exfoliation syndrome.46

Reviewers independently extracted the following information from included articles: (1) names of the first author and publication date, (2) methods of POAG and mortality assessment, (3) mean follow-up time, (4) total number of patients with glaucoma, (5) mean age and sex distribution, (6) the maximally- and minimally-adjusted risk estimates, (7) confounders considered in the final analysis, and (8) distribution of systemic and ophthalmic comorbidities such as diabetes, if reported. Two studies offered multiple definitions of POAG.37,54 In the Rotterdam Study,48 we used cases in the definite category because this highly specific definition is least likely to affect RR data.48 In the National Health Interview Survey,37 estimates from the glaucoma group without visual impairment were used because visual impairment may be an independent predictor of mortality.40 An expert in the field (L.P.) reviewed the studies to resolve inconsistencies in the extracted data.

STATISTICAL ANALYSIS

We used the Q test to evaluate study heterogeneity and the I² statistic to estimate the proportion of total variability of the pooled estimate due to between-study variation.31 We calculated pooled estimates with a random-effects model that accounted for variability between study populations.31 The fully-adjusted risk ratios from studies were used in the pooled analyses. We included 2 studies that assessed IOP and self- or proxy-reported POAG in the primary analysis but excluded them in secondary analysis.36,37 We performed a meta-regression to assess heterogeneity in length of follow-up and sex, age, and diabetes status across studies. In a subgroup analysis we assessed the relationship between POAG and cardiovascular mortality using 4 studies in which such data were available.37,52-54 A sensitivity analysis was performed to assess the robustness of the pooled estimates of all-cause and cardiovascular mortality. We used the Begg funnel plot and Egger publication bias plot to detect publication bias. The statistical software used was STATA version 9 (StataCorp LP, College Station, Texas), and the significance level was set to P < .05.

RESULTS

The search revealed 844 articles, 792 of which were excluded after first-pass review of titles because they were not relevant to the subject of POAG and mortality. Forty of the remaining 52 articles did not meet inclusion criteria after review of the abstracts. Four of the 40 articles related to glaucoma and mortality used population life tables for comparison and thus did not meet the inclusion criteria of a control group.35-39 Articles that met the a priori inclusion criteria (n = 12) were further evaluated. Three articles were excluded and 9 included in the final analysis (Figure 1).

Figure 1. Search and study selection process.
STUDY CHARACTERISTICS

The characteristics of included studies are outlined in Table 1 and Table 2. One study was a population-based, annual, cross-sectional study, while the others were prospective cohorts. The mean time to follow-up ranged from 4.5 to 16 years. Collectively, the sample size was 146,848, with 28,11 classified as having POAG. While studies varied on their exact criteria for POAG, most were independent of IOP measurement. Many studies included presence of glaucomatous visual field defects and assessment of the optic disc in their definition of POAG.

Mortality was assessed using multiple sources (Table 1), but one study did not detail the tools used to assess mortality outcomes. Several studies reported crude mortality analysis (not shown). Univariate analyses and age- and sex-adjusted analyses showed significant mortality risk among patients with POAG in some studies. These results, with the exception of those in the National Health Interview Survey, became insignificant in multivariate analyses. All studies adjusted for age and sex in the final analysis but differed in the additional covariates adjusted for. A detailed list of confounders adjusted for is outlined in Table 1.

Several studies listed estimates for mortality by cardiovascular disease, cancer, or stroke. Stratified analysis demonstrated increased cardiovascular mortality risk in patients previously diagnosed with glaucoma, but not in those who were newly diagnosed. There was an insignificant increase in cardiovascular mortality for the POAG group as a whole. Table 3 lists the relative risks for cardiovascular mortality and POAG used in the subgroup analysis. In the

Table 1. Characteristic of Included Studies

<table>
<thead>
<tr>
<th>Source, y</th>
<th>Details of Glaucoma Assessment</th>
<th>Details of Outcome Measurement</th>
<th>Adjusted Covariates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hiller R, et al, 1999</td>
<td>3 Measurements of IOP, history of glaucoma treatment</td>
<td>Contact family members and physicians, death registers, hospital surveillance</td>
<td>Age, sex, HTN, DM, cigarette smoking, BMI</td>
</tr>
<tr>
<td>McCarty C, et al, 2001</td>
<td>IOP, VFD, optic disc appearance</td>
<td>NDI, contact references</td>
<td>Age, sex, cigarette smoking, HTN, arthritis, best-corrected visual acuity &lt;6/12</td>
</tr>
<tr>
<td>Borger P, et al, 2003</td>
<td>Glaucomatous optic neuropathy, VFD</td>
<td>Municipal registry, medical records</td>
<td>Age, sex, DM, HTN, cigarette smoking, history of CVD, BMI, cholesterol level, atherosclerosis</td>
</tr>
<tr>
<td>Lee D, et al, 2003</td>
<td>Self or proxy report</td>
<td>NDI</td>
<td>Age, sex, race, marital status, education level, reported health status</td>
</tr>
<tr>
<td>Grodum K, et al, 2004</td>
<td>VFD</td>
<td>Centrally administered register</td>
<td>Age, sex, DM, cigarette smoking, BMI, education, history of cancer, ratio of total to HDL cholesterol level, pulse rate, CVD, sedentary lifestyle, proteinuria, SBP</td>
</tr>
<tr>
<td>Knudtson M, et al, 2006</td>
<td>VFD, cup-disc ratio, cup-disc asymmetry</td>
<td>Local newspapers, telephone contact, department of health and family services, NDI</td>
<td>Age, sex, HTN, DM, cigarette smoking, CVD, history of cancer, history of stroke, alcohol use</td>
</tr>
<tr>
<td>Lee A, et al, 2006</td>
<td>VFD, cup-disc ratio, cup-disc asymmetry</td>
<td>NDI, telephone contact</td>
<td>Age, sex, education</td>
</tr>
<tr>
<td>Xu L, et al, 2008</td>
<td>Optic disc appearance, open anterior chamber angle</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Wu S, et al, 2008</td>
<td>VFD, optic disc appearance</td>
<td>Ministry of Health</td>
<td>Age, sex, DM, HTN, history of CVD, stroke, IOP, IOP-lowering treatment</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CVD, cardiovascular disease; DM, diabetes mellitus; HDL, high-density lipoprotein; HTN, hypertension; IOP, intraocular pressure; NA, not available; NDI, National Death Index; SBP, systolic blood pressure; VFD, visual field defect.

Table 2. Results of Included Studies

<table>
<thead>
<tr>
<th>Source, y</th>
<th>Mean Follow-up</th>
<th>Details of Glaucoma Participants</th>
<th>All-Cause Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Time, y</td>
<td>Cases, No.</td>
<td>Mean Age, y</td>
</tr>
<tr>
<td>Hiller R, et al, 1999</td>
<td>16</td>
<td>79</td>
<td>60.9a</td>
</tr>
<tr>
<td>McCarty C, et al, 2001</td>
<td>4.5</td>
<td>120</td>
<td>59a</td>
</tr>
<tr>
<td>Borger P, et al, 2003</td>
<td>7</td>
<td>44</td>
<td>72.3</td>
</tr>
<tr>
<td>Lee D, et al, 2003</td>
<td>7</td>
<td>1289</td>
<td>NA</td>
</tr>
<tr>
<td>Grodum K, et al, 2004</td>
<td>7.75</td>
<td>402</td>
<td>69.4</td>
</tr>
<tr>
<td>Knudtson M, et al, 2006</td>
<td>13.2</td>
<td>198</td>
<td>64.7</td>
</tr>
<tr>
<td>Lee A, et al, 2006</td>
<td>9</td>
<td>108</td>
<td>75.9</td>
</tr>
<tr>
<td>Xu L, et al, 2008</td>
<td>5</td>
<td>96</td>
<td>55.9a</td>
</tr>
<tr>
<td>Wu S, et al, 2008</td>
<td>9</td>
<td>300</td>
<td>58.6a</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; NA, not available; RR, relative risk. Values taken from total population. Multivariate adjusted.

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There was no relationship between POAG and all-cause mortality in the primary pooled analysis (RR, 1.13; 95% CI, 0.97-1.31). A forest plot summarizing the results of the component studies and combined estimate is provided in Figure 2. Only 7 studies with physician diagnosis of POAG were included in secondary analysis (Figure 3). This estimated a smaller insignificant risk (RR, 1.02; 95% CI, 0.90-1.16). A Q test for heterogeneity was significant in the primary analysis (P = .04), but insignificant for the secondary analysis (P = .41). The I² statistic failed to show significant heterogeneity in both primary and secondary analyses.

A meta-regression conducted to assess heterogeneity across mean follow-up time, age, or sex was not statistically significant (data not shown). A meta-regression across diabetes status failed to demonstrate significant results (P = .94). Subgroup analysis on cardiovascular mortality estimated a marginally significant increased risk with a RR of 1.20 (95% CI, 1.00-1.43; P = .05). This estimate was attenuated in a sensitivity analysis, removing the study with patients with self- or proxy-reported glaucoma (RR, 1.12; 95% CI, 0.87-1.46). Forest plots of the subgroup analyses are provided in Figure 4 and Figure 5.

The Begg test failed to demonstrate publication bias. Furthermore, the Egger plot and the Begg funnel plot (Figure 6) failed to show significant signs of publication bias with no signs of asymmetry.

**COMMENT**

In this systematic literature review, we did not find an association between POAG and risk of all-cause mortality. All studies (with the exception of the National Health Interview Survey17) that contributed to the pooled estimate of the relationship between POAG and all-cause mortality reported insignificant results. Four of the 9 studies with moderate weighting described fairly tight CIs around the estimate of the effect and probably had the biggest influence on the combined result.35-37 Three studies that had broad CIs for the estimate of the effect carried less weight than the other studies.58,59,61
In our analysis, meta-regression did not detect heterogeneity by age, sex, or follow-up time, although we were likely limited by the effective range of each covariate. Studies tended to be similar in the distribution of these factors. Many studies did not report the distribution of participants by ethnicity, limiting inclusion of this attribute in the meta-regression. The Barbados Eye Study was conducted in a population predominately of African descent,\(^5\) while the Beaver Dam Eye Study\(^3\) comprised mostly white persons of European descent. The Beijing Eye Study\(^6\) included Asian participants from rural communities in the south of Beijing. Ethnicity could introduce variability when pooling study estimates. Nonetheless, we failed to find significant heterogeneity in the secondary analysis. A meta-regression on the 3 studies with information regarding diabetes status in the glaucoma population did not demonstrate any heterogeneity. Caution must be exercised in interpreting a meta-regression on such a small sample because it may fail to provide sufficient power in analysis.

The relationship between POAG and cardiovascular mortality is of particular interest. In the Blue Mountains Eye Study,\(^5\) the authors found an increased risk of cardiovascular mortality in patients previously diagnosed with POAG. This risk was primarily seen in patients with POAG who were taking timolol. In the Barbados Eye Study,\(^3\) the authors also found a positive association between mortality and previously-treated POAG that was not statistically significant (P = .07). This relationship became stronger among subjects treated with timolol (P = .04). In our study, a pooled analysis demonstrated a marginally statistically significant association between POAG and cardiovascular mortality. Not surprisingly, this result was attenuated and insignificant when the largest study published by Lee et al (National Health Interview Survey)\(^7\) was excluded. Our analysis was limited to few studies, and issues of reporting bias in the National Health Interview Survey should be considered during interpretation. Also, even if a positive relation between POAG and cardiovascular mortality exists, one must consider that this relationship may be owing to the side effects of glaucoma medications (as suggested in the Blue Mountains Eye Study\(^5\)) and the adverse effects of systemic medications used to treat cardiovascular disease.

Given the paucity of research in POAG incidence, incident estimates are typically derived from prevalence data.\(^5\)\(^,\)\(^6\) Deriving incidence estimates from prevalence data are based on the assumption that mortality in patients with POAG is similar to that in the general population. Our study supports this assumption.

This study is useful because prior epidemiologic research in this area had little power to reject the null hypothesis of no association between POAG and mortality. A limitation in the meta-analysis of observational studies is that residual sources of bias or confounding in the original studies may exist in the pooled analysis. In the pooled analysis, the fully-adjusted estimates were aggregated to account for known confounders such as age and sex. Although several studies sampled from predominantly ethnically uniform populations,\(^3\)\(^,\)\(^5\)\(^,\)\(^6\) only 1 of the remaining studies adjusted for ethnicity, an important risk factor for POAG,\(^6\)\(^,\)\(^9\) in the multivariate analysis.\(^3\) Furthermore, the studies included in the pooled estimate of the relationship between POAG and mortality did not completely account for blood pressure, body mass index, and diabetes mellitus status, attributes known to independently influence mortality (Table 1).\(^3\)\(^,\)\(^4\)\(^,\)\(^9\)\(^,\)\(^10\)\(^,\)\(^19\)\(^,\)\(^22\)

Disease misclassification is another potential source of bias that may alter the relationship between POAG and mortality. Inconsistent diagnostic criteria may have underestimated or overestimated the sample size of patients with POAG. Evidence suggests that subtle changes in diagnostic standards affect the estimated prevalence of POAG.\(^6\) It is difficult to estimate the direction and magnitude of this bias in our pooled analysis. In the secondary analysis, all studies used qualitative and/or quantitative criteria for glaucoma diagnosis. Qualitative measures such as pathological thinning of the neuroretinal rim introduce the potential of interreviewer variability. Quantitative measures such as the assessment of cup-to-disc ratio, may introduce misclassification by arbitrary cutoff points for the categorization of abnormal or normal. There is no reason to assume that any source of misclassification would be differential across those who died or survived. If the misclassification is truly nondifferential, then

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Figure 5. Forest plot for sensitivity analysis of cardiovascular mortality. Excluding the National Health Survey, the relative risks with 95% confidence intervals for each study and pooled analysis are depicted on a logarithmic scale. The size of each square is proportional to the study’s weight. The lateral points of the diamond provide the confidence interval for the combined estimate.

Figure 6. Begg funnel plot assessing for publication bias in the primary analysis. The relative risks and standard errors are on a logarithmic scale and presented with pseudo-95% confidence intervals.

Barbados Eye Study\(^\)\(^5\)\(^4\) or the adverse effects of systemic medications used to treat cardiovascular disease.

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the effect estimates of individual studies are likely to be attenuated toward the null. Several studies described the use of physician panels to determine diagnosis or the use of consecutive test results, potentially limiting this source of misclassification. 36,59-61

We did not find any signs of publication bias. We found limited heterogeneity in primary analysis that was no longer observable in secondary analysis. Interstudy variability could potentially introduce heterogeneity and limit the effectiveness of pooled analysis to estimate associations. Although there was no uniform diagnostic criterion for glaucoma across aggregated studies, there was overlap in diagnostic criteria, including both quantitative and qualitative measures. All of the studies included were published in 1990s and later, and the design and analysis characteristics were similar across studies.

Our meta-analysis did not demonstrate an association between POAG and all-cause mortality. Although we did not find an association in a subgroup analysis of cardiovascular mortality, this study highlights the importance of evaluating specific causes of mortality. These data do not support the notion that POAG is a disease consisting of a sick eye in a body predisposed to excess mortality. This review, however, does not exclude the possibility that POAG is part of an underlying systemic process with subtle manifestations that do not necessarily lead to premature death.

Submitted for Publication: June 9, 2008; final revision received October 2, 2008; accepted October 20, 2008.

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Author Contributions: Ms M. Akbari had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Financial Disclosure: None reported.

Additional Contributions: Harry A. Quigley, MD, A. Edward Maumenee Professor, Ophthalmology, Wilmer Institute, Johns Hopkins University School of Medicine; and Michael D. Knudson, Department of Ophthalmology and Visual Sciences, University of Wisconsin School of Medicine and Public Health (grant EY06594 from the National Institutes of Health).

REFERENCES