Risk Factors Associated with the Incidence of Open-Angle Glaucoma: The Visual Impairment Project

Anhchuong Le, Bickol N. Mukesh, Catherine A. McCarty, and Hugh R. Taylor

PURPOSE. To assess the relationship between potential risk factors and the development of open-angle glaucoma (OAG) in Australian residents aged 40 and or more years.

METHODS. A total of 3271 participants were recruited at baseline from nine urban areas through cluster random sampling and subjected to comprehensive standardized interviews and ophthalmic examination, both at baseline and at 5-year follow-up. The participation rate at follow-up was 85% of the surviving baseline cohort. OAG was diagnosed with definite, probable, or possible certainty by a consensus panel of six ophthalmologists. Potential risk factors identified at baseline included various sociodemographic, anthropometric, dietary, familial, medical, and ocular characteristics of the participants. Risk factor analyses were performed for development of at least possible OAG (possible, probable, and definite OAG) and then at least probable OAG (probable and definite OAG) to represent a higher level of certainty. Univariate and multivariate analyses were performed.

RESULTS. Increased age and increased intraocular pressure (IOP) were associated with increased risk of development of OAG, according to multivariate analyses. A family history of glaucoma (relative risk [RR] = 2.1, 95% confidence interval [CI] = 1.05–4.2), the presence of age-related macular degeneration (RR = 2.2, 95% CI = 1.2–3.9), the presence of pseudoexfoliation (RR = 9.4, 95% CI = 2.6–34.4), and a cup-disc ratio (CDR) greater than 0.7 (RR = 7.9, 95% CI = 4.4–14.1) were associated with greater risk of development of at least possible OAG. Having ever taken a-blockers (RR = 4.8, 95% CI = 1.2–18.8), the presence of pseudoexfoliation (RR = 11.2, 95% CI = 2.0–63.5), and a CDR higher than 0.7 (RR = 11.0, 95% CI = 4.6–26.8) also indicated significant risk of development of at least probable OAG.

CONCLUSIONS. Certain nonmodifiable risk factors may be used to identify high-risk individuals, and increased IOP remains an important modifiable risk factor for OAG. However, more prospective studies on risk factors are required to clarify further the etiological picture of OAG. (Invest Ophthalmol Vis Sci. 2003;44:3783–3789) DOI:10.1167/iovs.03-0077

Glucoma is one of the leading causes of blindness worldwide and open-angle glaucoma (OAG) is the most common form of glaucoma in the Western world. OAG is a neurodegenerative condition that is multifactorial in origin.

Increased intraocular pressure (IOP) remains an important primary and prognostic risk factor for OAG, but other IOP-independent risk factors may be involved in the pathogenesis and progression of OAG.

Consideration of other IOP-independent risk factors have led to speculation that optic nerve fiber sensitivity to damage and its tolerance to presenting IOP, even in a normal range, may be the major concept in the pathogenesis of OAG. A clear understanding of risk factors would also promote greater public and medical awareness for prevention and early recognition of this insidious disease. In addition, the decision to treat and the complete management of OAG require consideration of all potential risk factors, which may provide the possibility of halting progression of glaucomatous field damage, despite IOP normalization. Indeed, any elimination of modifiable risk factors could be viewed as part of the neuroprotective strategy with which to tackle this neurodegenerative disease.

However, there is still inconclusive evidence regarding many proposed risk factors, and, for the most part, assessment of risk factors has been based on retrospective or cross-sectional studies. The purpose of this study was to add significantly to the current body of evidence by providing a collective report on associations of various potential risk factors with the development of OAG, in the context of a well-designed, population-based prospective follow-up study.

METHODS

The detailed methods used in the Visual Impairment Project (VIP) have been published previously. The VIP baseline examination was conducted from 1992 to 1994. Residents aged 40 or more years who had resided in the district address for at least 6 months were recruited by door-to-door survey from nine randomly selected adjacent pairs of census collection districts within metropolitan Melbourne. The 3271 residents who participated were representative of the Victorian and Australian population. All attended the standardized eye examination and interview at locally established test centers. Information regarding sociodemographic, anthropometric, dietary, familial, medical, and ocular characteristics, including sunlight exposure was obtained. Interviewers were used for non-English-speaking participants, and home visits were conducted when participants were unable to attend the local examination center.

A standardized 5-year follow-up examination and an interview were conducted from 1997 to 1999. All available participants from the baseline study were invited to take part. To promote participation, every effort was made to ensure the same examination site or the one closest to that used in the baseline study. Nonparticipants in the follow-up study were those who moved overseas or interstate, those who refused to participate, and those who died before the commencement of the 5-year follow-up. Those who died were confirmed through...
Glaucoma was assessed by a consensus panel of six ophthalmologists, two of whom were glaucoma specialists. Participants who had IOP greater than 21 mm Hg, possible glaucomatous visual field defect (nasal step >5 dB in three adjacent points or >10 dB in two adjacent points, any bundle-type defect, or any enlarged blind spot), or CDR higher than 0.7 or who reported a history of glaucoma were considered to have suspected glaucoma and their examination records and repeated measurements were taken if results were greater than 21 mm Hg or unreliable. Persistent measurements of greater than 21 mm Hg were combined with the Goldmann applanation tonometer, and this measurement was considered final.

A standardized slit lamp biomicroscopic examination was performed by experienced ophthalmic research fellows. The participant’s anterior chamber depth was examined before instillation of dilation drops—that is, 1 drop of tropicamide (0.5%) followed in 5 minutes by 1 drop of phenylephrine hydrochloride (10%). A 90-D convex lens was used for general fundus examination, and the vertical cup-disc ratio (CDR) was measured. Indirect ophthalmoscopy was conducted with a 28-D lens on eyes with suspected peripheral retinal abnormalities. Paired color fundal photographs were taken with a retinal camera (TRC FET; Topcon, Paramus, NJ) and subsequently assessed through stereo viewers. Other structures of the eye were also examined and recorded systematically as part of the complete ophthalmic examination.

Glaucoma was diagnosed on an ascending scale of possible, probable, or definite glaucoma, or abnormal due to other causes. Visual fields were then classified into one of five categories. Finally case notes of the participants, which included the participant’s full medical history and IOP measurements were provided to the examiners, and an overall classification of the participant was made. Each examiner made this assessment independently for each selected participant. For those participants in whom the classification by any observer varied by more than two steps, adjudication by the six examiners was conducted until consensus was reached. The same process was used for baseline and follow-up assessment. The rate of agreement using this method has been outlined.

Risk factor analysis was performed for the development of at least possible OAG (probable, possible, and definite OAG) and at least probable OAG (probable and definite OAG) separately. These represent OAG diagnoses based on two different levels of certainty, which reflects levels of strictness in diagnosing OAG. Analysis of definite OAG alone was not performed because of the limited number of participants who experienced development of the disease. However, using at least probable OAG as the outcome is a reasonable predictor for definite OAG alone, because our 5-year follow-up data showed that in 50% of the participants with probable OAG at baseline, the disease progressed to definite OAG.

Participants in whom at least possible OAG developed were compared with participants who remained free of any OAG. Therefore participants with a diagnosis of possible OAG at baseline and in whom possible or definite OAG had not developed at follow-up were excluded from the analyses. Participants diagnosed with at least probable OAG at baseline and participants with secondary and AC were also excluded from the analyses.

All potential risk variables that were assessed were initially independently selected and have been summarized in Table 1. The initial value of the factors at baseline was used as the important predictor of glaucoma. Cardiovascular medications were grouped into β-blockers, α-blockers, angiotensin-converting enzyme inhibitors, thiazide diuretics, loop diuretics, calcium channel blockers, and peripheral vasodilators. Information on medications was obtained from the interview at the test centers, and participants were recontacted when possible for further clarification. Duration was determined for all dietary supplements, medications, and medical illnesses. Pack-years of smoking, total years of smoking, and number of years since cessation of smoking were explored, in addition to cigarette smoking status (never, current, or past). The number of standard alcohol drinks was also considered in

<table>
<thead>
<tr>
<th>Table 1. Potential Risk Factors for Open-Angle Glaucoma</th>
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<tr>
<td>Sociodemographic</td>
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<tr>
<td>Age</td>
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<tr>
<td>Gender</td>
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<td>Country of birth</td>
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<td>Occupation</td>
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<td>Private health insurance status</td>
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<td>Behavioral</td>
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<td>Cigarette smoking</td>
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<td>Alcohol intake</td>
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<tr>
<td>Weight</td>
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<td>Body mass index</td>
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<td>Dietary</td>
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<td>Regular vitamin intake</td>
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<td>Vitamin C intake</td>
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<td>Zinc intake</td>
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<td>Retinol intake</td>
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<td>Family history of glaucoma</td>
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<td>Diabetes</td>
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<td>Cardiovascular disease</td>
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<td>Cardiovascular medications</td>
</tr>
<tr>
<td>Corticosteroid</td>
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<tr>
<td>Aspirin/NSAIDs</td>
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<tr>
<td>Oral contraceptive pill</td>
</tr>
<tr>
<td>HRT</td>
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<tr>
<td>Ocular</td>
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<tr>
<td>Iris color</td>
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<tr>
<td>Intraocular pressure</td>
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<tr>
<td>Cup-disc ratio</td>
</tr>
<tr>
<td>Refractive status</td>
</tr>
<tr>
<td>Previous cataract surgery</td>
</tr>
<tr>
<td>Age-related macular degeneration</td>
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<tr>
<td>Previous eye injury</td>
</tr>
<tr>
<td>Pseudoxulubation</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>Sunlight exposure</td>
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<tr>
<td>Early menarche</td>
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<tr>
<td>Early menopause</td>
</tr>
</tbody>
</table>

HRT, hormone replacement therapy; NSAIDs, nonsteroidal anti-inflammatory drugs.
addition to alcohol status (never, current, or past). The model used to quantify lifetime ocular exposure to UV-B has been described, annual ocular sun exposure was calculated by taking the logarithm of lifetime exposure divided by the age of the participant.

Interview data were entered directly into a database (Paradox; Borland International, Scotts Valley, CA), and clinical data were entered twice. All data entry had internal consistency checks. A computer was used for statistical analysis (SAS statistical software, ver. 6.10; SAS Institute Inc, Cary, NC). The χ² or Fisher exact test was performed for categorical variables, and the Mantel-Haenszel test was used for ordinal variables and the t-test for continuous variables. Age-adjusted relative risks with 95% confidence intervals were also presented. Risk variables with statistical significance of less than 0.10 were included in multivariate modeling. Multivariate analysis was performed using backward multiple logistic regression.

RESULTS

There were 3271 participants examined in the baseline study, 231 of whom died before the 5-year follow-up examination and 446 of whom migrated from Victoria, lost contact, or refused to attend the follow-up examination. Therefore, 2594 participants (85% of the surviving cohort) attended the follow-up. Of these, 105 participants who had incomplete data on IOP, CDR, and visual fields, either at baseline or at follow-up, and 52 participants who received a diagnosis of probable or definite OAG at baseline were excluded from the analyses. After all exclusions, 2415 participants were at risk for development of OAG, which represents 93% of those who participated in the follow-up examination (Fig. 1). Those who did not participate in the follow-up study were more likely to be older (P < 0.01), male (P = 0.01), or of Greek or Italian background (P < 0.01) and to have visual acuity of less than 6/12 (P < 0.01), IOP greater than 21 mm Hg (P < 0.01), and a CDR higher than 0.7 (P < 0.01).

The mean age of the participants at baseline was 58.7 ± 11.4 years (SD; range, 40–98) and 54% were women. The mean duration between baseline and follow-up examinations was 4.5 ± 0.64 years (range, 4–7 years). At the 5-year follow-up examination, there were 12 participants with definite diagnosis of OAG, 15 participants with probable OAG, and 39 participants with definite OAG (Fig. 1). The overall incidence of at least possible OAG was 2.7% (95% confidence interval [CI] = 1.8–3.7), and that of at least probable OAG was 1.1% (95% CI = 0.8–1.4).17

Significant age-adjusted risk factors for development of at least possible OAG were past cigarette smokers, family history of glaucoma, the presence of age-related macular degeneration (AMD), the presence of pseudoexfoliation, and a baseline CDR higher than 0.7 (Table 2). The variables significantly associated with development of at least probable OAG after adjustment for age were past cigarette smokers, having ever taken α-blockers, the presence of pseudoexfoliation, and a baseline CDR higher than 0.7 (Table 3).

The mean baseline IOP of participants who had at least possible OAG or at least probable OAG was marginally (1.2–1.5 mm Hg) but significantly higher (P < 0.05) than that of those who remained free of OAG (Tables 2, 3). This remained significant when adjusted for age (Tables 2, 3). The overall mean IOP at baseline was 15.1 ± 3.1 mm Hg (SD), and 2.5% of participants had IOP greater than 21 mm Hg. However, having an IOP higher than 21 mm Hg was not significantly associated in univariate analyses with increased risk. Only 6.1% of participants who had at least possible OAG and 7.4% of those who had at least probable OAG had a baseline IOP of greater than 21 mm Hg. Comparison between the handheld and Goldmann applanation tonometers used in the VIP has been presented, and it showed no statistically significant difference between the two methods.
After multivariate analyses, the factors significantly associated with the development of at least possible OAG were increased age, increased IOP, having a family history of glaucoma, the presence of pseudoexfoliation, the presence of AMD, and a baseline CDR higher than 0.7. The factors significantly associated with development of at least possible OAG were increased age, increased IOP, having a family history of glaucoma, and a baseline CDR higher than 0.7. The factors significantly associated with the development of at least possible OAG were smoking status, past history of glaucoma, past cataract surgery, and pseudoexfoliation.

### DISCUSSION

The present study follows on from the report on the 5-year incidence of OAG from the VIP. Despite all that is known about OAG and its causing blindness worldwide, the epidemiology of OAG is still not well understood. At present, the VIP, the Barbados Incidence Eye Study, the Dalby Sweden (incidence) Study, and the Tierp Sweden (incidence) Glaucoma Survey have reported incidence rates through prospective population-based surveys and the Collaborative Glaucoma Study through a prospective clinic-based survey. However, potential risk factors have predominantly been evaluated through prevalence data. Prospective data provide better evidence on which to base inferences on causation, because of ascertainment of temporality, which is one of the major causative criteria and has always been an inherent problem in studying a disease with low incidence.

The present study showed that there was a significant risk of OAG after 60 years of age and the risk increased with each subsequent decade of life. A similar age-related trend was shown in the Barbados Incidence Eye Study and numerous prevalence studies, but not in the Dalby Sweden Study. Increased age may reflect the cumulative effects of some other factors that cause the aging optic nerve head to be more vulnerable to IOP, even of normal range. The present study also showed that development of OAG was not gender related. The Barbados Incidence Eye Study had shown a higher incidence in men, whereas the Dalby Sweden Study showed a higher incidence in women. This inconsistency was reflected in previous prevalence studies.

The pressure theory of OAG is supported by the fact that IOP has been found consistently to be associated with the development of OAG.

### Table 2. Univariate Risk Factors for Development of at Least Possible OAG

<table>
<thead>
<tr>
<th>Risk Variables</th>
<th>Glaucoma*</th>
<th>No Glaucoma*</th>
<th>Crude RR (95% CI)</th>
<th>Age-Adjusted RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at baseline (n = 2415)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40–49</td>
<td>3/66 (4.6)</td>
<td>639/2549 (27.2)</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>50–59</td>
<td>12/66 (18.2)</td>
<td>770/2549 (32.8)</td>
<td>3.3 (0.95, 11.8)</td>
<td></td>
</tr>
<tr>
<td>60–69</td>
<td>26/66 (39.4)</td>
<td>609/2549 (25.9)</td>
<td>9.1 (2.7, 30.2)</td>
<td></td>
</tr>
<tr>
<td>70–79</td>
<td>17/66 (25.8)</td>
<td>270/2549 (11.5)</td>
<td>15.4 (3.9, 46.2)</td>
<td></td>
</tr>
<tr>
<td>80+</td>
<td>8/66 (12.1)</td>
<td>65/2549 (2.7)</td>
<td>26.6 (6.9, 103)</td>
<td></td>
</tr>
<tr>
<td>Smoking status (n = 2412)</td>
<td></td>
<td></td>
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<tr>
<td>Never</td>
<td>24/66 (36.4)</td>
<td>1153/2546 (49.2)</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>10/66 (15.2)</td>
<td>398/2546 (17.0)</td>
<td>1.2 (0.57, 2.5)</td>
<td>1.4 (0.66, 3.0)</td>
</tr>
<tr>
<td>Past</td>
<td>32/66 (48.5)</td>
<td>795/2546 (33.9)</td>
<td>1.9 (1.1, 3.3)</td>
<td>1.7 (1.01, 3.0)</td>
</tr>
<tr>
<td>Family history (n = 2385)</td>
<td>12/66 (18.2)</td>
<td>203/2549 (8.8)</td>
<td>2.3 (1.2, 4.3)</td>
<td>2.3 (1.2, 4.5)</td>
</tr>
<tr>
<td>AMD present (n = 2387)</td>
<td>22/66 (33.3)</td>
<td>528/2541 (14.1)</td>
<td>3.0 (1.8, 5.0)</td>
<td>2.0 (1.1, 3.4)</td>
</tr>
<tr>
<td>Pseudoexfoliation present (n = 2384)</td>
<td>4/63 (6.4)</td>
<td>11/2341 (0.5)</td>
<td>14.2 (5.8, 34.8)</td>
<td>7.9 (2.7, 22.7)</td>
</tr>
<tr>
<td>Previous cataract surgery (n = 2396)</td>
<td>5/66 (7.6)</td>
<td>50/2330 (2.2)</td>
<td>3.7 (1.5, 9.1)</td>
<td>1.6 (0.56, 4.7)</td>
</tr>
<tr>
<td>CDR more than 0.7 (n = 2386)</td>
<td>24/66 (36.4)</td>
<td>129/2540 (5.6)</td>
<td>9.7 (6.2, 15.1)</td>
<td>8.6 (5.3, 15.8)</td>
</tr>
<tr>
<td>IOP (mean mm) Hg ± SD</td>
<td>(16.5 ± 3.3)</td>
<td>(15.1 ± 3.1)</td>
<td>1.1 (1.04, 1.2)</td>
<td>1.1 (1.05, 1.2)</td>
</tr>
</tbody>
</table>

* Data are number with each risk factor, with the total number in the glaucoma and no-glaucoma groups and the percentage of the total group in parentheses.

### Table 3. Univariate Risk Factors for Development of at Least Probable OAG

<table>
<thead>
<tr>
<th>Risk Variables</th>
<th>Glaucoma*</th>
<th>No Glaucoma*</th>
<th>Crude RR (95% CI)</th>
<th>Age-Adjusted RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at baseline (n = 2376)</td>
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<tr>
<td>40–49</td>
<td>1/27 (3.7)</td>
<td>639/2549 (27.2)</td>
<td>1.0</td>
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<tr>
<td>50–59</td>
<td>3/27 (11.1)</td>
<td>770/2549 (32.8)</td>
<td>2.5 (0.26, 24.0)</td>
<td></td>
</tr>
<tr>
<td>60–69</td>
<td>1/27 (40.7)</td>
<td>609/2549 (25.9)</td>
<td>11.5 (1.5, 88.7)</td>
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<tr>
<td>70–79</td>
<td>8/27 (29.6)</td>
<td>270/2549 (11.5)</td>
<td>19.0 (2.4, 152)</td>
<td></td>
</tr>
<tr>
<td>80+</td>
<td>4/27 (14.8)</td>
<td>64/2549 (2.7)</td>
<td>39.9 (4.4, 362)</td>
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<tr>
<td>Smoking status (n = 2373)</td>
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</tr>
<tr>
<td>Never</td>
<td>8/27 (29.6)</td>
<td>1153/2546 (49.2)</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>4/27 (14.8)</td>
<td>398/2546 (17.0)</td>
<td>1.5 (0.43, 4.8)</td>
<td>1.8 (0.52, 5.9)</td>
</tr>
<tr>
<td>Past</td>
<td>15/27 (55.6)</td>
<td>795/2546 (33.9)</td>
<td>2.7 (1.1, 6.4)</td>
<td>2.5 (1.03, 5.9)</td>
</tr>
<tr>
<td>Family history (n = 2346)</td>
<td>3/27 (11.1)</td>
<td>203/2539 (8.8)</td>
<td>1.3 (0.39, 4.4)</td>
<td>1.3 (0.40, 4.5)</td>
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<tr>
<td>α-Blocker use (n = 2369)</td>
<td>3/27 (11.1)</td>
<td>48/2342 (2.1)</td>
<td>6.0 (2.0, 17.7)</td>
<td>3.5 (1.04, 11.9)</td>
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<tr>
<td>AMD present (n = 2348)</td>
<td>8/27 (29.6)</td>
<td>328/2521 (14.1)</td>
<td>2.6 (1.1, 5.7)</td>
<td>1.5 (0.64, 3.3)</td>
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<tr>
<td>Pseudoexfoliation present (n = 2346)</td>
<td>2/25 (8.0)</td>
<td>11/2312 (0.47)</td>
<td>18.3 (5.9, 56.5)</td>
<td>9.5 (2.4, 36.9)</td>
</tr>
<tr>
<td>Previous cataract surgery (n = 2357)</td>
<td>3/27 (11.1)</td>
<td>50/2330 (2.2)</td>
<td>5.7 (1.9, 17.0)</td>
<td>2.5 (0.51, 11.9)</td>
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<td>CDR more than 0.7 (n = 2347)</td>
<td>11/27 (40.7)</td>
<td>129/2320 (5.6)</td>
<td>11.7 (6.2, 21.9)</td>
<td>10.1 (5.1, 19.8)</td>
</tr>
<tr>
<td>IOP (mean mm) Hg ± SD</td>
<td>(16.5 ± 3.4)</td>
<td>(15.1 ± 3.1)</td>
<td>1.1 (1.03, 1.2)</td>
<td>1.1 (1.04, 1.2)</td>
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</table>

* Data are described in Table 2.
The vasogenic theory of OAG proposes that hemodynamic factors—such as increased IOP and hypotension—are associated with optic nerve head ischemia, which is a hallmark of OAG. However, the relationship between IOP and OAG is complex, and the role of hemodynamic factors remains controversial.

### Table 4. Multivariate Risk Factors for Development of OAG

<table>
<thead>
<tr>
<th>Risk Variables</th>
<th>At Least Possible OAG RR (95% CI)</th>
<th>At Least Probable OAG RR (95% CI)</th>
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</thead>
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<tr>
<td>Age at baseline</td>
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<tr>
<td>40–49</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>50–59</td>
<td>2.6 (0.74–9.4)</td>
<td>2.0 (0.21–19.5)</td>
</tr>
<tr>
<td>60–69</td>
<td>7.0 (2.1–23.8)</td>
<td>8.4 (1.1–66.6)</td>
</tr>
<tr>
<td>70–79</td>
<td>8.3 (2.3–29.9)</td>
<td>12.2 (1.5–103)</td>
</tr>
<tr>
<td>80+</td>
<td>10.0 (2.2–46.0)</td>
<td>8.6 (0.63–116)</td>
</tr>
<tr>
<td>Family history</td>
<td>2.1 (1.03–4.2)</td>
<td>1.1 (0.29–4.0)</td>
</tr>
<tr>
<td>α-Blocker use</td>
<td>1.7 (0.45–6.1)</td>
<td>4.8 (1.2–18.8)</td>
</tr>
<tr>
<td>Pseudoexfoliation</td>
<td>9.4 (2.6–34.4)</td>
<td>11.2 (2.0–63.5)</td>
</tr>
<tr>
<td>AMD present</td>
<td>2.2 (1.2–3.9)</td>
<td>1.7 (0.67–4.2)</td>
</tr>
<tr>
<td>IOP (mm Hg)</td>
<td>1.1 (1.03–1.2)</td>
<td>1.1 (1.04–1.2)</td>
</tr>
<tr>
<td>CDR more than 0.7</td>
<td>7.9 (4.4–14.1)</td>
<td>11.0 (4.6–26.8)</td>
</tr>
</tbody>
</table>

OAG. However, there is considerable individual variability in the level of pressure that is necessary to cause damage. In this study, there was no significant risk obtained for IOP greater than 21 mm Hg but there was a significant risk with increasing IOP. Only 0.1% of those in whom at least possible OAG developed had baseline IOP greater than 21 mm Hg, which differed from the Barbados Incidence Eye Study (52.2%) and the Tierp Sweden Glaucoma Survey (61.5%).

Previous prevalence studies revealed 25% to 70% with IOP of more than 21 mm Hg. Such a large variation may be due to differences in IOP distribution among the various study populations and the substantial overlap within normal and OAG populations. The results in this study could also be influenced by the lower participation rate among those with IOP greater than 21 mm Hg. However, it highlights the arbitrary nature of distinguishing high- and low-tension glaucoma based on a certain IOP cutoff level, although these entities seem to exist morphologically and clinically.

The high risk of OAG associated with a preexisting CDR higher than 0.7 was consistent with the Barbados Incidence Eye Study. The prevalence study in the Baltimore Eye Survey also reported larger cups and discs in the black population, which had a higher prevalence of OAG. A high CDR may indicate abnormal variation in the organization of optic nerve head connective tissue, which has been shown to have some heritability and racial influence, suggesting that some individuals are born with high CDRs. However there is subjectivity involved in CDR measurements, and detection bias could occur by including it as a marker for diagnosis of OAG. Also an increased CDR could be considered part of the causal pathway toward clinically evident OAG, rather than an independent risk factor.

This study showed approximately double the risk for development of at least possible OAG in individuals who reported a family history of glaucoma. No other incidence data are available to confirm this finding, but previous prevalence and case-control studies have supported this association. However, as outlined in the Baltimore Eye Study, participants with previously diagnosed glaucoma tend to have greater awareness of family history.

The lower positive association in population-based studies compared with clinic-based studies is due to less recall bias, which is further expected in this study, because it is also a prospective study. There was no distinction between family members in this study, but siblings have consistently been shown to have higher association with OAG. Further characterization of hereditary factors lie in genetic studies, which recently linked several genes to adult-onset OAG.

The vasogenic theory of OAG proposes that hemodynamic alterations may directly cause ischemic damage to the optic nerve head or act in concert with presenting IOP. In this study, having ever taken α-blockers was shown to be a significant risk factor for development of at least probable OAG after multivariate adjustment. The result could have been spurious because of the small number of participants who had ever taken α-blockers. The specific reasons for the use of α-blockers was not obtained, but all participants who had ever taken α-blockers also reported a history of hypertension. The medication was used more by women (59%). Catecholamine receptors in the retina have been documented and α-adrenoceptor agonists such as brimonidine have recently been shown to be neuroprotective in rat experimental models of the optic nerve. However, whether α-blockers have any hemodynamic influence on the optic nerve head remains to be elucidated, given that no other antihypertensive medications were a significant risk.

Other cardiovascular-related factors—in particular, smoking, cardiovascular disease, hypertension, and diabetes—failed to show any risk for OAG. The null result for smoking was similar to many other cross-sectional and retrospective surveys. A weak correlation between smoking and increased IOP has been shown, suggesting smoking may alternatively have an indirect relationship with glaucoma. A recent case-control study showed cardiovascular disease to be associated more with the senile sclerotic subgroup of glaucomatous disc appearance, but an association with OAG in general has not yet been demonstrated.

In contrast, systolic or diastolic hypertension has been shown to be associated with OAG in several studies, but not in others. It may be that perfusion pressure (systolic or diastolic blood pressure minus IOP) or hypotension are more appropriate variables for assessing optic nerve head ischemia, and both have been shown to be associated with OAG.

There is also no consensus as to the association between diabetes and OAG and those studies that have revealed an association may have inherent selection bias, because individuals with previously diagnosed glaucoma were more likely to know whether they have diabetes. Pseudoexfoliation of the lens capsule was shown to have 9 and 11 times the risk of development of at least possible OAG and at least probable OAG, respectively. Similar results have been reported in the Tierp Sweden Eye (incidence) Survey (RR = 9.8) and the Blue Mountains Eye (prevalence) Study (odds ratio [OR] = 5.0). The mechanism could be due to elevated IOP caused by exfoliation material obstructing the trabecular meshwork, but its level of risk was unaffected when adjusted for IOP. However, the result could be spurious, due to the low number of pseudoexfoliation cases, and studies in Australian aborigines showed that pseudoexfoliation is not always associated with an increased risk of glaucoma.

This study also showed that AMD may be a risk factor for at least possible OAG, although a prevalence study of AMD showed no association with OAG. Both diseases, however, may have a common vascular pathogenesis.

The present study is valuable from several perspectives. Although chance could play a role in some of the significant associations, given the multiple comparisons performed, this study has deliberately chosen all relevant potential risk factors based on previous studies and has analyzed all factors within the one study. This allows more complete multivariate adjustments, reflecting the heterogeneity of etiology and clinical manifestation of OAG. Also the results in this study can be generalized to the Victorian and Australian population, and the study has provided prospective data with a high follow-up participation rate (85% of the surviving cohort), in which the risk of a given factor can be directly measured. However, there are certain limitations in this study, including having no data at intervening time points, and given that the VIP has shown that...
visual impairment increases mortality, an underestimate of the incidence rate could arise. Also the small number of participants in whom OAG developed and the small number of participants exposed to certain risk factors analyzed could affect the stability of risk estimates due to wide confidence limits.

In conclusion, this study has provided greater evidence to support certain risk factors for the development of OAG. However, we still should be cautious when interpreting the results unless further prospective epidemiologic studies on risk factors and physiological studies on pathomechanisms lend greater support and physiological correlation.

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References


