Risk factors for previously undiagnosed primary open-angle glaucoma: the EPIC-Norfolk Eye Study

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ABSTRACT

Background and aim Undiagnosed glaucoma is an invisible but important public health issue. At least half of glaucoma cases are estimated to be undiagnosed in western countries. The aim of this study is to examine risk factors for previously undiagnosed primary open-angle glaucoma (POAG).

Design Cross-sectional study within the European Prospective Investigation of Cancer-Norfolk Eye Study, a large-scale cohort study in the UK.

Participants 314 study participants with POAG in either eye.

Methods Logistic regression was used to examine associations with previously undiagnosed POAG compared with previously diagnosed POAG. The factors examined included sociodemographic, ocular, physical and economic factors that could be barriers to eye care access.

Results 217 participants had previously diagnosed POAG and 107 participants were newly diagnosed with POAG during the study. After adjusting for covariables, the factors significantly associated with previously undiagnosed POAG were: a lower pretreatment intraocular pressure (IOP) (OR 0.71/mm Hg, 95% CI 0.63 to 0.80, p<0.0001), and to have reported no problems in their eyesight (OR 0.03, 95% CI 0.01 to 0.10, p<0.0001).

Conclusions The risk factors for previously undiagnosed POAG identified in this study highlight the over-reliance on IOP level in glaucoma screening and the risk of missing glaucoma among lower IOP cases. It also suggests a role in improving glaucoma awareness in the community.

INTRODUCTION

Undiagnosed glaucoma is an invisible yet sizeable public health issue. Eye surveys conducted in developed western countries have consistently shown that at least half of glaucoma cases are previously undiagnosed.1,2 Published studies have described the clinical features and risk factors of undiagnosed glaucoma compared with previously known cases,3,4 which include lower education attainment,3 not having seen an ophthalmologist in the prior year4,5 or seeing an optometrist rather than an ophthalmologist.3,4 There are also reasons to suspect that the clinical features and severity of glaucoma may differ between previously diagnosed and patients with undiagnosed glaucoma. The features shown to be significant for undiagnosed glaucoma are: smaller vertical cup to disc ratio, a negative family history of glaucoma,5 presence of visual field detect,5 lower mean baseline intraocular pressure (IOP) and baseline hyperopia.6 The aim of this study was to examine the associations with previously undiagnosed primary open-angle glaucoma (POAG) in the European Prospective Investigation of Cancer (EPIC)-Norfolk Eye Study, a large British community cohort, focusing on the potential roles of ocular features, physical factors and social barriers to eye care access in undiagnosed POAG.

METHODS

Study design

The EPIC study is a pan-European multi-cohort study, designed to investigate the lifestyle determinants of cancer risks. The EPIC-Norfolk cohort was established in the city of Norwich and the surrounding rural and urban areas, in the eastern English county of Norfolk, between 1993 and 1997.6 A total of 30 445 men and women aged 40–79 years were recruited at a baseline survey from the databases of 35 general practices. The predominant ethnicity of the cohort was white, and included individuals across the range of socioeconomic status and educational achievements. The EPIC-Norfolk Eye Study was carried out between 2004 and 2011 when ophthalmic data were collected from 8623 participants.7

Detailed descriptions of the study design7 and glaucoma diagnosis8 of the EPIC-Norfolk Eye Study have been reported previously. In brief, all subjects were examined systematically in a screening test, which included tonometry (ORA; Reichert Corporation, Philadelphia, USA), optic nerve head assessment (fundus photos and Heidelberg Retina Tomograph II) and peripapillary nerve fibre layer assessment with scanning laser polarimetry (GDx-VCC, Zeiss, Dublin, California, USA). A 24-2 central threshold visual field test (Humphrey 750i Visual Field Analyzer, Carl Zeiss Meditech, Welwyn Garden City, UK) was performed in participants with abnormal findings suspicious of glaucoma on HRT or GDx-VCC, and in 1 out of 10 subjects with normal findings. Subjects with abnormal findings who met a set of predefined criteria designed to detect glaucoma were referred to the Eye Department of the Norfolk and Norwich University Hospital for a definitive eye examination by a consultant ophthalmologist with a specialist interest in glaucoma (DCB). Full details of these criteria were published previously.7 Glaucoma was defined as the presence of structural optic disc abnormalities and visual field loss, with no other explanations for the disc and field appearances. POAG is defined as
glaucoma in the presence of open anterior angles with no known secondary causes. The differentiation of high tension glaucoma (HTG) and normal tension glaucoma (NTG) was based on IOP level before glaucoma treatment commenced. HTG was defined as untreated IOP >24 mm Hg on one occasion, or >21 mm Hg on at least two separate occasions or on diurnal IOP phasing. NTG was defined as untreated IOP ≤21 mm Hg on at least two separate occasions or on diurnal IOP phasing. An individual participant’s glaucoma diagnosis was defined by taking the clinically more serious diagnosis of either eye, in the following hierarchy (most serious to least serious): glaucoma, glaucoma suspect, ocular hypertension, narrow angle spectrum (primary angle closure, primary angle closure suspect and narrow angles) and normal. Self-reported data including family history of glaucoma, contact lens or glasses wear, eyesight problem and health status were all collected from a self-administered questionnaire.

Statistical analysis

Logistic regression was used to analyse the risk factors for previously undiagnosed POAG, with the dependent variable coded as 0=subjects with known POAG and 1=subjects with previously undiagnosed POAG. Factors that were significant (p<0.05) in the univariable analysis were included in the multivariable model in a stepwise backward model, and removed if p>0.05. The factors examined (box 1) included socioeconomic, demographic and systemic factors, as well as ocular factors that could affect a subject’s likelihood of seeking eye care, such as presence of low visual acuity, previous cataract surgery, self-reported eyesight problems, high refractive error or wearing glasses/contact lens. Physical and economic factors that could present a barrier to eye care access, such as financial difficulty, physical frailty and poor health status were also included. Cup/disc ratio (CDR) and CDR asymmetry were multiplied by 10 in the regression models to allow the OR to be analysed per 0.1 increase in CDR. For ocular factors, the worse value of the two eyes were used for visual acuity, axial length (longer value) and central corneal thickness (lower value). For IOP, CDR and visual field mean deviation, the value of the OAG eye was used; if both eyes had OAG then the worse value was used. All statistical analyses were performed using STATA (Stata/SE V.13.1).

Pretreatment IOP and its imputation

To allow unbiased comparison of IOP levels between the two groups, the pretreatment IOP was used for participants who have had pressure-lowering treatment. Pretreatment IOP is defined as the highest IOP (Goldmann applanation tonometry) documented in the patient’s hospital records before any IOP-lowering treatment (drops or surgery) was instigated. For those who have had IOP-lowering treatment but the pretreatment IOP was unavailable, the pretreatment IOP was imputed. Imputed IOP was not used in the diagnosis of NTG and HTG, which was made based on measured untreated IOP.

Among the 314 POAG participants in the study, 213 HTG and 100 NTG eyes were on pressure-lowering treatment, defined as being on pressure-lowering medication and/or having undergone glaucoma surgery. In 114 HTG eyes and 42 NTG eyes the pretreatment IOP was available. Due to the high proportion of missing values (missing at random), they were imputed using multiple imputation by linear regression. The predictors were age, sex and OAG type (NTG vs HTG), and 100 iterations were imputed.

RESULTS

Out of the 8623 participants in the EPIC-Norfolk Eye Study, 363 participants were diagnosed with glaucoma in either eye; 314 of them had POAG. Among the 314 POAG subjects, 160 of them had HTG and 154 had NTG; 207 (65.9%) were known cases, diagnosed before the start of the study and 107 (34.1%) were previously undiagnosed. The mean age of the 314 participants was 74.2 years (range 49–90 years) and 45% were women. Table 1 summarises the characteristics of the participants. Table 2 shows the univariable logistic regression results comparing known POAG to previously undiagnosed POAG cases (0=known POAG, 1=previously undiagnosed POAG). The factors associated with previously undiagnosed POAG in the univariable regression were: younger age, being currently employed, having NTG rather than HTG, lower pretreatment IOP, smaller CDR, visual field mean deviation, negative family history of glaucoma, reporting no problems with eyesight, being phakic rather than pseudophakic in either eye and higher absolute refractive error.

In the final multivariable model (table 3), subjects with previously undiagnosed POAG compared with those with a known diagnosis were more likely to have: a lower pretreatment IOP (OR 0.71/mm Hg, 95%CI 0.63 to 0.80, p<0.0001), and to have reported no problems with their eyesight (OR 0.03, 95%CI 0.01 to 0.69, p<0.0001). The type of glaucoma was strongly associated with the pretreatment IOP, with the IOP being significantly lower among NTG than HTG patients (OR 0.63/mm Hg, 95%CI 0.55 to 0.72, p<0.0001).
Factors removed from the model in order were: age (p=0.52), being currently employed (p=0.60), visual fields mean deviation (p=0.40), pseudophakia in either eye (p=0.76), absolute refractive error (p=0.13), family history (p=0.10), CDR (p=0.12) and glaucoma type (p=0.09).

**DISCUSSION**

Among the social, economic, systemic and ocular factors examined, the two factors associated with undiagnosed POAG in the community were lower pretreatment IOP and the participants reporting no eyesight problems. The first points to an over-reliance on IOP level to exclude glaucoma in the community, leading to patients with lower IOP to be missed. The National Institute for Health and Clinical Excellence guidelines in the UK recommend a referral to the Hospital Eye Service if IOP is greater than 24 mm Hg in the absence of other risk factors, as ocular hypertension on its own may warrant treatment. Nevertheless, IOP has been shown to be an ineffective tool for glaucoma case finding in the EPIC-Norfolk Eye Study, and no single IOP level provides both high sensitivity and specificity in glaucoma diagnosis. This study demonstrates that it is easy for eye care providers to be reassured by an IOP level <24 mm Hg, while other features of glaucoma are missed. It must be stressed therefore that among patients with non-elevated IOP, care should be taken to examine the optic disc carefully and with supportive disc imaging and visual field testing to improve the chances of identifying suspicious disc features.

**Table 1** Characteristics of the previously known versus previously undiagnosed primary open angle glaucoma participants

| Characteristics | Previously diagnosed | Previously undiagnosed |
|-----------------|----------------------|------------------------|
| n               | 207                  | 107                    |
| Age, years      | 72.8 (67.0 to 78.4)  | 75.4 (70.3 to 81.0)    |
| Sex             | Male 52.2%           | 61.7%                  |
|                 | Female 47.8%         | 38.3%                  |
| Social class    | Professional/managerial 48.3% | 33.3% |
|                 | Skilled (manual/non-manual) 41.6% | 25.7% |
|                 | Semi-skilled/unskilled 10.1% | 21.0% |
| Education       | No qualifications 30.4% | 29.9% |
|                 | O levels 7.3%        | 10.3%                  |
|                 | A levels 48.8%       | 48.6%                  |
|                 | Degree 13.5%         | 11.2%                  |
| Currently employed? | No 89.3%         | 79.8%                  |
|                 | Yes 10.7%            | 20.2%                  |
| How often do you not have enough money for basics? | Never 63.9% | 65.7% |
|                 | Seldom/sometimes 36.1% | 34.3% |
| POAG type       | HTG 69.1%            | 15.9%                  |
|                 | NTG 30.9%            | 84.1%                  |
| IOPg (mm Hg)    | 16.8 (16.7 to 18.2)  | 19.0 (17.6 to 19.4)    |
| Pretreatment IOP (mm Hg) | 26.7 (25.9 to 27.5) | 18.3 (17.6 to 19.1) |
| Axial length (mm) | 23.9 (23.2 to 25.1) | 23.9 (23.1 to 24.8) |
| LogMAR visual acuity (n=286) | 0.20 (0.16 to 0.24) | 0.08 (0.0 to 0.26) |
| Disc photo CDR (n=249) | 0.55 (0.54 to 0.57) | 0.50 (0.48 to 0.53) |
| CDR asymmetry (n=210) | 0.06 (0.02 to 0.11) | 0.07 (0.04 to 0.11) |
| Visual field mean deviation | −4.79 (−7.72 to 5.57) | −3.40 (−4.63 to −3.31) |
| Central corneal thickness (μm) | 535 (532 to 543) | 544 (536 to 551) |
| Family history of glaucoma (n=269) | No 64.0% | 77.7% |
|                 | Yes 36.0%            | 22.3%                  |
| Wears glasses/contact lenses? (n=308) | No 2.5% | 0.96% |
|                 | Yes 97.6%            | 99.0%                  |
| Do you have any problems with eyesight? (n=298) | No 11.5% | 75.5% |
|                 | Yes 88.5%            | 24.5%                  |
| Pseudophakic in either eye (n=314) | No 62.3% | 85.1% |
|                 | Yes 37.7%            | 15.0%                  |
| Absolute refractive error (Dioptres) (n=309) | 1.81 (0.75 to 2.63) | 1.25 (0.63 to 2.25) |
| Systolic BP (mm Hg) (n=314) | 137.5 (135.5 to 140.0) | 140 (135.8 to 141.8) |
| Diastolic BP (mm Hg) (n=314) | 76.5 (76.0 to 79.6) | 79.0 (76.4 to 80.4) |
| BMI (kg/m^2) (n=313) | 26.0 (26.0 to 27.0) | 26.6 (26.1 to 27.6) |
| Diabetes | No 97.1% | 98.1% |
|                 | Yes 2.9%             | 1.9%                   |
| Self-reported health status (n=312) | Excellent/very good 37.4% | 33.0% |
|                 | Good 44.2%           | 47.2%                  |
|                 | Fair 16.5%           | 15.1%                  |
|                 | Poor 1.9%            | 4.7%                   |

Median (95% CI) shown for continuous variables.

*Unimputed data for pretreatment IOP.

BMI, body mass index; BP, blood pressure; HTG, high tension glaucoma; IOPg, Goldmann-correlated intraocular pressure; NTG, normal tension glaucoma.
In this study, other features of severity of glaucoma such as vertical CDR and visual field mean deviation were not associated with missed OAG cases. It could be because CDR does not adequately capture features of a glaucomatous disc, and visual fields may not be done routinely at the optician. Even with advanced field defects, many patients with glaucoma are asymptomatic, so field defects will not necessarily provide a reason to visit the optician.

Several factors were examined that could reflect a participant’s access or likelihood to seek eye care. An important limitation of the methodology is that specific questions about the participants’ history of visits to eye care professionals were not collected prospectively, and asking the questions retrospectively would be prone to recall bias and significant inaccuracies. Hence, there was the need to use proxy factors, such as absolute refractive error, glasses use, being pseudophakic and self-reported visual problems, which require careful interpretation. The strongest

### Table 2  Univariable logistic regression of previously diagnosed versus previously undiagnosed primary open angle glaucoma (0=diagnosed 1=undiagnosed)

| Characteristics                      | OR (95% CI) | P value |
|--------------------------------------|-------------|---------|
| Age, years                           | 0.96 (0.93 to 0.99) | 0.008   |
| Sex                                  |             |         |
| Male                                 | 1.00        |         |
| Female                               | 0.68 (0.42 to 1.09) | 0.15    |
| Social class                         |             |         |
| Professional/managerial              | 1.00        |         |
| Skilled (manual/non-manual)          | 0.57 (0.33 to 0.98) | 0.04    |
| Semi-skilled/unskilled               | 1.84 (0.93 to 3.63) | 0.08    |
| Education                            |             |         |
| No qualifications                    | 1.00        |         |
| O levels                             | 1.44 (0.59 to 3.50) | 0.42    |
| A levels                             | 1.01 (0.59 to 1.74) | 0.96    |
| Degree                               | 0.84 (0.38 to 1.88) | 0.68    |
| Currently employed?                  |             |         |
| No                                   | 1.00        |         |
| Yes                                  | 2.12 (1.10 to 4.06) | 0.02    |
| How often do you not have enough money for basics? |             |         |
| Never                                | 1.00        |         |
| Seldom/sometimes                     | 0.93 (0.56 to 1.54) | 0.77    |
| POAG type                            |             |         |
| HTG                                  | 1.00        |         |
| NTG                                  | 11.8 (6.52 to 21.5) | <0.0001 |
| IOPg (mm Hg)                         | 1.04 (0.99 to 1.09) | 0.08    |
| Pretreatment IOP (mm Hg) *           | 0.75 (0.69 to 0.82) | <0.0001 |
| Axial length (mm)                    | 1.12 (0.94 to 1.34) | 0.21    |
| LogMAR visual acuity                 | 0.86 (0.39 to 1.69) | 0.70    |
| Disc photo CDR ×10                   | 0.69 (0.55 to 0.87) | 0.02    |
| CDR asymmetry ×10                    | 0.74 (0.48 to 1.15) | 0.19    |
| Visual field (MD)                    | 1.14 (1.06 to 1.22) | p<0.0001 |
| Central corneal thickness (μm)       | 1.01 (0.99 to 1.01) | 0.1     |
| Family history of glaucoma           |             |         |
| No                                   | 1.00        |         |
| Yes                                  | 0.51 (0.29 to 0.91) | 0.02    |
| Wears glasses/contact lenses?        |             |         |
| No                                   | 1.00        |         |
| Yes                                  | 2.59 (0.30 to 22.4) | 0.39    |
| Do you have any problems with eyesight? |             |         |
| No                                   | 1.00        |         |
| Yes                                  | 0.04 (0.02 to 0.08) | <0.0001 |
| Pseudophakic in either eye           |             |         |
| No                                   | 1.00        |         |
| Yes                                  | 0.29 (0.16 to 0.53) | <0.0001 |
| Absolute refractive error (Dioptres) |             |         |
| No                                   | 1.00        |         |
| Yes                                  | 1.16 (1.01 to 1.33) | 0.03    |
| Systolic BP (mm Hg)                  | 1.00 (0.99 to 1.02) | 0.60    |
| Diastolic BP (mm Hg)                 | 1.01 (0.99 to 1.04) | 0.32    |
| BMI (kg/m²)                          | 1.02 (0.96 to 1.08) | 0.50    |
| Diabetes                             |             |         |
| No                                   | 1.00        |         |
| Yes                                  | 0.64 (0.13 to 3.22) | 0.59    |
| Self-reported health status           |             |         |
| Excellent/Very good                  | 1.00        |         |
| Good                                 | 1.21 (0.71 to 2.05) | 0.48    |
| Fair                                 | 1.04 (0.51 to 2.12) | 0.93    |
| Poor                                 | 2.75 (0.70 to 10.9) | 0.15    |

*Imputed data.
CDR, cup/disc ratio; HTG, high tension glaucoma; IOP, intraocular pressure; NTG, normal tension glaucoma; POAG, primary open angle glaucoma.

### Table 3  Multivariable regression of previously diagnosed versus previously undiagnosed primary open angle glaucoma (0=diagnosed 1=undiagnosed)

| Characteristics                      | OR (95% CI) | P value |
|--------------------------------------|-------------|---------|
| Pretreatment IOP (mm Hg) *           | 0.71 (0.63 to 0.80) | <0.0001 |
| Do you have any problems with eyesight? |             |         |
| No                                   | 1.00        | <0.0001 |
| Yes                                  | 0.03 (0.01 to 0.69) | <0.0001 |

*Imputed data.
IOP, intraocular pressure.
factor associated with undiagnosed POAG was answering no to the question ‘do you have problems with your eyesight’, while worse acuity of either eye was not related. A possible interpretation of this finding is that it was the self-perception of good eyesight, and by implication, a lesser likelihood to visit an optometrist, rather than actual visual function, that led the POAG to be undiagnosed. Nevertheless, the participants with existing glaucoma might have perceived their eyesight as being worse than those with undiagnosed glaucoma as a recall bias, as they had a known eye condition, or the use of eyedrops or having had eye surgery diminished their visual function. Wearing glasses or contact lenses was not a significant factor, most likely because 97% of the cohort wore glasses, and it was not effective in discriminating those with previously diagnosed and undiagnosed POAG.

Published studies have explored the question whether visits to eye care professionals is important in facilitating the discovery of glaucoma. The Thessaloniki Study found that previously undiagnosed patients were more likely to not have seen an eye doctor in the past year. Similarly, both the Barbados Eye Study and the Melbourne Visual Impairment Project reported that previously undiagnosed patients sought eye care less frequently in the past year, with the source of eye care more likely to be an optometrist rather than an ophthalmologist. 

However, these findings are potentially confounded by the fact that patients with diagnosed glaucoma would already be under the care of an ophthalmologist, so a prospective study is required to adequately answer that question.

Currently in the UK, POAG is diagnosed by opportunistic case finding, relying on patients presenting to an optometrist for an eye test, and referral made to the Hospital Eye Service under the suspicion of glaucoma. The Thessaloniki Study found that previously undiagnosed patients were more likely to not have seen an eye doctor in the past year. Similarly, both the Barbados Eye Study and the Melbourne Visual Impairment Project reported that previously undiagnosed patients sought eye care less frequently in the past year, with the source of eye care more likely to be an optometrist rather than an ophthalmologist. However, these findings are potentially confounded by the fact that patients with diagnosed glaucoma would already be under the care of an ophthalmologist, so a prospective study is required to adequately answer that question.

In conclusion, the most important healthcare implication from this analysis is to avoid being falsely reassured by a lower level of IOP in glaucoma case finding. There is also a suggestion that raising public awareness of glaucoma and encouraging regular eye tests at the optician can help reduce undiagnosed glaucoma.

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Contributors MPYC designed and performed the analysis and drafted the manuscript. AKJ and LY contributed to data collection and interpretation. DCH, PJF and K-TK contributed to the design of the EPIC-Norfolk Eye Study and DCH and PJF contributed to data collection and interpretation. RL contributed to data management. SH contributed to the running of the EPIC-Norfolk Eye Study. TP contributed to disc photo grading in the EPIC-Norfolk Eye Study.

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