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ABSTRACT

Objectives

To report the distribution of intraocular pressure (IOP) by age and sex, and the frequency of glaucoma in the EPIC-Norfolk cohort.

Design

A community-based cross-sectional observational study.

Setting

The city of Norwich and the surrounding rural and urban areas.

Participants

8623 participants aged 48-92 years recruited from the community who underwent ocular examination to identify glaucoma.

Main outcome measures

The frequency and characteristics of glaucoma in the cohort, IOP distribution, and the sensitivity and specificity of IOP in diagnosing glaucoma.

Results

A total of 363 participants (4.2%) had glaucoma in either eye, 86.5% of whom had primary open angle glaucoma (POAG). 607 subjects (7.0%) were glaucoma suspects, and 863 (10.0%) were ocular hypertensives. 66.6% of glaucoma cases had been previously diagnosed. The cohort's mean IOP was 16.3mmHg (95% CI 16.2-16.3mmHg, SD 3.6mmHg), and 65% of POAG cases had IOP less than the ocular hypertension threshold of 21mmHg. No one IOP level provided adequately high sensitivity and specificity for glaucoma diagnosis.

Conclusions

In this British community, glaucoma, suspected glaucoma and ocular hypertension represent a large number of potential referrals to the hospital eye service. The use of IOP for glaucoma case-finding is probably not viable.

INTRODUCTION

Glaucoma is the leading cause of irreversible blindness in the world[1] and the second most common cause of registered blindness in England and Wales.[2] It comprises a group of ocular diseases of progressive damage of the optic nerve, with characteristic structural optic disc changes and visual field defects.[3] Glaucoma and suspect glaucoma combined account for the sixth largest share of NHS outpatient attendances in England, after general medical examination, breast cancer, schizophrenia, prostate cancer and joint pain. [4] The most common type of glaucoma among white populations is primary open angle glaucoma (POAG); primary angle closure glaucoma (PACG), which results from occlusion of aqueous humour outflow, is more common among Asians;[5] secondary glaucoma results from a diverse range of ocular and systemic conditions. Elevated intraocular pressure (IOP) is the major modifiable risk factor for POAG, [6 7 8] but around 50% of glaucoma cases present with IOP below 21mmHg, the threshold defined as ocular hypertension, which was raised IOP without any evidence of glaucoma. [9] The EPIC-Norfolk Eye Study, initiated in 2004, is the most recent large-scale eye survey in the UK. The aim of this study was to report the frequency and characteristics of glaucoma and IOP distribution of the study participants.

METHODS

The European Prospective Investigation of Cancer (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 1993-1997.[10] 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 2004-2011 when ophthalmic data were collected from 8,623 participants.[11] The work was carried out with the approval of the East Norfolk & Waverney NHS Research Governance Committee (2005EC07L) and the Norfolk Research Ethics Committee (05/Q0101/191), in accordance with the principles of the Declaration of Helsinki.

The first 443 sequential participants had IOP measured with a non-contact tonometer (AT555, Reichert Corporation, Philadelphia, USA), and the remaining participants had three IOP measurements for each eye made with the Ocular Response Analyzer non-contact analyzer (ORA; Reichert Corporation, Philadelphia, USA) using software version 3.01. The ORA flattens the cornea with a jet of air and uses an electro-optical system to measure the

air pressures at which the cornea flattens both inwards and outwards. The average of the two ORA pressure values are calibrated linearly against the Goldmann applanation tonometer (GAT) to provide a Goldmann-equivalent IOP measurement (IOPg, mmHg).[12] A systematic review showed that among 12 studies that directly compared the agreement of IOPg and GAT, the mean difference between the two (IOPg-GAT) is 1.5mmHg (95% predictived interval -0.6 to 3.7mmHg). [13]

The glaucoma status of the subjects was determined from the systematic examination of all subjects, which included visual acuity, tonometry, optic nerve head assessment (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 Ltd, Welwyn Garden City, UK) was performed in those participants with abnormal findings 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 & Norwich University Hospital for a definitive eye examination by a consultant ophthalmologist with a specialist interest in glaucoma (DCB). A detailed description of the study design has been published previously.[11] Glaucoma was defined as the presence of characteristic structural optic disc abnormalities and visual field loss, with no other explanations for the disc and field appearances. The differentiation of high tension and normal tension glaucoma was based on IOP level before glaucoma treatment commenced. Glaucoma suspect was defined as the presence of early or minor glaucomatous disc features, associated with a normal visual field or the absence of visual field data. Ocular hypertension was defined as IOP>21mmHg with no features of glaucoma in the optic disc or visual field. Specific quantitative methods and principles for diagnosis of POAG and suspected POAG observed the International Society of Geographical and Epidemiological Ophthalmology (ISGEO) diagnostic principles.[3] A further refinement process was in place to limit false positives or false negatives by reviewing all examination findings and history of a high-risk subset of subjects by another consultant glaucoma ophthalmologist (PJF). A summary diagram for the flow of participants through the study and the glaucoma diagnostic process is in Appendix I. Glaucoma diagnosis per person was determined by taking the clinically more serious diagnosis of either eye, in the following hierarchy (most serious to least serious): glaucoma, glaucoma suspect, ocular hypertension (IOP>21mmHg), narrow angle spectrum (primary angle closure, primary angle closure suspect and narrow angles), and normal.

Statistical Analysis

IOP reported for the cohort was the mean of left and right eyes' mean IOP, using the ORA IOPg or the AT555 NCT values. Sensitivities and specificities of IOP for glaucoma detection in Figure 4 and Table 6 were derived from the ability of various IOP thresholds to differentiate between subjects with all cause glaucoma in either eye, and subjects with no glaucoma in either eye. The reporting of this study conformed to the STROBE statement.[14] All statistical analyses were performed using STATA (Stata/SE 13.1, StataCorp, College Station, Texas).

RESULTS

There were 8,623 participants in the EPIC-Norfolk Eye Study, their mean age was 68.7 years (range 48-92 years), and 55% were female. Compared to the population estimates for Norfolk and for the UK, the study population was older, and had a decreasing proportion of women with age, which is opposite to the Norfolk and UK population's trend of an increasing proportion of women with age (Figure 1). The study population comprised of 99.4% Caucasians, while Norfolk and the UK had 96.5% and 87.2% Caucasians respectively.[15]

Table 1 and 2 show the glaucoma diagnosis by eye and by person. A total of 363 participants (4.2%, 95% CI 3.8-4.6%) had glaucoma in either eye, 315 had POAG (3.6% (95% CI 3.3-4.0%), 607 (7.0%) were glaucoma suspects, 863 (10.0%) were ocular hypertensives (untreated IOP>21mmHg), 54 (0.6%) had narrow angle spectrum. Twenty-three participants (0.3%) had no recorded diagnosis, as they declined or were unable to undergo definitive eye examination after failing the screening tests. The majority of people with glaucoma had POAG (86.5%), with an equal proportion of high pressure and normal pressure glaucoma. Out of the 523 glaucoma eyes, formal visual field assessment was not feasible in 28 due to poor vision. Most of these participants had secondary glaucoma which was diagnosed by advanced disc cupping and uncontrolled IOP.

Among the glaucoma cases, 242 (66.6%) were previously known, and 66.3% of POAG cases were previously known. The glaucoma prevalence in the study population increased with age, and was higher among men than women (Table 4).

Table 1. Glaucoma diagnosis per eye

Glaucoma diagnosis	Right eye n	Right eye %	Left eye n	Left eye %
Normal	7091	82.2	7061	81.9
Primary open angle glaucoma	236	2.7	231	2.7
High tension glaucoma	121	1.4	121	1.4
Normal tension glaucoma	115	1.3	109	1.3
Primary angle closure glaucoma	20	0.2	17	0.2
Secondary glaucoma	9	0.1	11	0.1
Subtotal with glaucoma	265	3.1	258	3.0
Suspect OAG	444	5.2	443	5.1
OHT & Suspect OAG	67	0.8	67	0.8
Suspect ACG	27	0.3	28	0.3
Secondary OHT / OAG suspect	2	0.0	4	0.1
Subtotal glaucoma suspects	540	6.3	542	6.3
OHT	641	7.4	670	7.8
PAC	27	0.3	32	0.4
Narrow angles	36	0.4	34	0.4
Not recorded	23	0.3	26	0.3
Total	8623	100	8623	100

OAG open angle glaucoma; ACG angel closure glaucoma; OHT ocular hypertension; PAC primary angle closure

Table 2. Glaucoma diagnosis per person

Diagnosis	n	%
Normal	6,713	77.9
Glaucoma	363	4.2
Glaucoma suspect	607	7.0
Ocular hypertension	863	10.0
Narrow angle spectrum	54	0.6
Unrecorded	23	0.3
Total	8623	100

* More serious diagnosis of either eye used, in the following hierarchy (most serious to least serious) - glaucoma, glaucoma suspect, ocular hypertension, narrow angles spectrum (primary angle closure, primary angle closure suspect), normal, diagnosis not recorded

Table 3. Glaucoma type per person

Diagnosis	n	%
Primary open angle glaucoma	314	86.5
High tension glaucoma	157	43.3
Normal tension glaucoma	157	43.3
Primary angle closure glaucoma	29	8.0
Secondary glaucoma	20	5.5
Total (all glaucoma)	363	100

Table 4. Glaucoma per person by age and sex

	All Cause glaucoma				Primary open angle glaucoma			
	Men		Women		Men		Women	
Age (yrs)	n	% of age group	n	% of age group	n	% of age group	n	% of age group
<55	1	0.8	1	0.5	1	0.8	1	0.5
55-60	4	1.5	5	1.0	4	1.5	5	1.0
60-65	20	2.3	19	1.5	16	1.8	15	1.2
65-70	34	4.3	22	2.2	27	3.4	21	2.1
70-75	50	6.6	42	5.0	44	5.8	31	3.7
75-80	43	7.2	30	4.9	39	6.6	26	4.3
80+	48	11.2	44	10.8	44	10.5	41	10.1
Total	200	5.2	163	3.4	175	4.5	140	3.0

8,401 subjects had IOP measured (7,958 with ORA, 443 with AT555 NCT), 243 of them used ocular hypotensive eyedrops in either eye. Figure 2 shows the distribution of mean IOP of both eyes, which followed an approximately Gaussian distribution, with a right skew and an exaggerated peak. The cohort mean IOP was 16.3mmHg (95%CI 16.2-16.3mmHg, SD 3.6mmHg). Table 5 shows the cohort's IOP distribution by age and sex. The mean IOP for glaucomatous eyes was 16.7mmHg (95%CI 17.1-18.1mmHg, range 4.0-45.6mHg), and the percentage of eyes with glaucoma increases with IOP (Figure 3).

Table 6 and figure 4 show the sensitivity and specificity of glaucoma detection at different IOP thresholds. Overall, sensitivity for glaucoma detection was poor at all IOP levels shown, regardless of the additional refining parameters of age and sex, and there was no one single IOP level that afforded both high sensitivity and specificity.

Table 5. Intraocular pressure* distribution by age and sex in the EPIC-Norfolk cohort

Age groups (yrs)	Males		Females	
	n	IOP mmHg mean (95% CI)	n	IOP mmHg mean (95% CI)
<55	128	15.9 (15.4-16.5)	185	15.7 (15.2-16.2)
55 to <60	262	15.8 (15.4-16.3)	473	15.9 (15.6-16.2)
60 to <65	857	16.4 (16.2-16.7)	1240	16.5 (16.3-16.6)
65 to <70	790	16.2 (15.9-16.4)	969	16.7 (16.5-17.0)
70 to <75	746	16.3 (16.0-16.5)	808	16.3 (16.1-16.6)
75 to <80	570	16.0 (15.7-16.4)	591	16.2 (15.9-16.4)
≥80	402	16.0 (15.6-16.4)	380	15.8 (15.5-16.2)
Total	3755	16.2 (16.1-16.3)	4646	16.3 (16.2-16.4)

*Mean IOP of both eyes

Table 6. All cause glaucoma- sensitivity and specificity of detection at different intraocular pressure thresholds

IOP mmHg	Sensitivity (%)							Specificity (%)						
	Overall	Age				Male	Female	Overall	Age				Male	Female
		<65	≥65	<70	≥70				<65	≥65	<70	≥70		
>19	45.0	36.7	46.3	45.6	44.7	49.2	39.7	73.2	74.1	72.6	72.8	73.6	73.7	72.7
>20	36.3	26.5	37.9	34.0	37.3	42.4	28.9	81.0	82.0	80.3	80.9	81.0	80.5	81.3
>21	30.0	24.5	30.9	28.2	30.7	35.1	23.7	86.9	87.7	86.4	86.8	87.0	85.8	87.7
>22	25.4	22.5	25.8	23.3	26.2	30.4	19.2	91.2	91.9	90.7	91.1	91.3	90.3	91.9
>23	20.5	18.4	20.8	20.4	20.5	24.6	15.4	94.0	94.5	93.8	93.8	94.5	93.2	94.7
>24	16.7	18.4	16.4	16.5	16.8	20.9	11.5	96.0	96.2	95.9	95.7	96.4	95.4	96.5
>25	12.1	12.2	12.1	10.7	12.7	16.2	7.1	97.1	97.0	97.2	96.9	97.5	96.6	97.6
>26	7.8	8.2	7.7	6.8	8.2	11.0	3.9	98.0	97.8	98.1	97.8	98.3	97.5	98.4

DISCUSSION

Glaucoma prevalence data have been reported from populations in the US, [16 17] Australia, [18 19] Europe [20-22] and South East Asia [23-26]. However, recent data from the UK is lacking, with the last published cross-sectional population glaucoma surveys were one from a rural West of Ireland in 1993 [27], and another from north London in 1998. [28]

There are differences between the EPIC-Norfolk participants and the local population of Norfolk, as the study participants were not sampled systematically, but recruited by inviting all adults aged >40 years from GP practices. Apart from differences in age and sex composition, EPIC-Norfolk participants were less likely to live in deprived areas and were potentially healthier due to the volunteer nature of the study. The glaucoma cases derived in the cohort therefore may not be fully representative of the local or national population and are likely an underestimation of the true numbers. Nevertheless, results in this study corroborated many established trends in glaucoma epidemiology. Our predominant glaucoma type was POAG, a consistent finding among European populations.[5 29] The prevalence of POAG in this cohort increased with age, which is its strongest known risk factor.[30] The frequency of all cause glaucoma in the cohort, aged 48 to 92 years, was 4.2% (95%CI 3.8-4.6%), and 3.7% (95%CI 3.3-4.0%) for POAG. This echoed findings from a meta-analysis in 2014, whereby the prevalence of glaucoma (POAG and PACG) for Europeans aged 40-80 years was 2.93% (95%CI 1.85-4.40%), and the prevalence of POAG was 2.51% (95% CI 1.54-3.89%).[5] In another meta-analysis published in 2006, the pooled prevalence of POAG for white population was of 2.1% (95%CI 1.6-2.7%).[31]

We found 66% of POAG cases in the cohort to be previously diagnosed. This is the highest reported figure from a major community-based study. Previous reported figures include 49% in the Blue Mountains Eye Study, [18] 40% in Melbourne's Visual Impairment Study, 50% in the Thessaloniki Eye Study,[22] 47% in the Rotterdam Eye Study,[20] and 50% among the white subjects in the Baltimore Eye Survey.[32] Glaucoma is a largely asymptomatic disease with insiduous onset. In most industrialised countries, it is detected by opportunistic case finding, and relies on people being examined by an eye care professional. In the UK, this would usually be a community optometrist. Suspected glaucoma cases are then referred to ophthalmologists for definitive diagnosis and management. The higher rate of previously known glaucoma cases in EPIC-Norfolk than other studies could reflect either better health care access among the study participants due to recruitment bias, or generally more effective health care provision in the UK with universal access and free eye tests for those over 60 years old in the National Health Service (NHS).

A striking finding in the study was the large number of glaucoma suspects (7%) and ocular hypertensives (10%). Collectively they represent a large number of potential referrals to the Hospital Eye Services (HES), many of whom remain under observation for up to 5 years.[33] This is reflected by the existing burden to the HES, whereby ocular hypertension accounts for 30-45% of the referrals it receives.[34 35] Coupled with the fact that glaucoma is a chronic disease that needs regular and long-term follow-up, it is no wonder that glaucoma and suspected glaucoma account for the sixth largest share of NHS outpatient attendances.[4]

While raised IOP is the strongest risk factor for POAG after age,[30] our data reiterate that no single IOP level provides sufficiently high sensitivity and specificity for glaucoma case detection, as shown in Figure 3, mirroring results from the Baltimore Eye Survey.[16] This reinforces the principle that IOP alone without optic disc examination or visual field test is not an effective screening tool for glaucoma.

There were several sources of under-reporting of glaucoma diagnosis in this study. Only 18% of study subjects underwent visual field testing. Lack of routine field testing in a population study had been shown in a meta-analysis as a study design factor that led to under-diagnosis.[36] However, in our study, both disc and field abnormalities were re-requisites of a glaucoma diagnosis, observing well-established diagnostic principles used in most population cross sectional studies.[17 20 23 32 37 38] We used a multimodal optic disc examination to uncover glaucomatous damage and determine who was referred for a definitive exam. We therefore expect very few cases of glaucoma would have been missed. The number of narrow angle cases is also likely to be underestimated, as gonioscopy or anterior chamber depth assessment on slitlamp were not part of the screening test, although those with PACG should not have been missed because of that, as all glaucoma suspects underwent a full examination.

WHAT IS KNOWN ABOUT THIS TOPIC

Glaucoma is the leading cause of irreversible blindness in the world and the second most common cause of registered blindness in England and Wales. The management of glaucoma, glaucoma suspects and ocular hypertensives accounts for a significant amount of NHS outpatient resources. While the prevalence of glaucoma has been reported in many population studies worldwide, there are no recent data for glaucoma in the UK.

WHAT THIS PAPER ADDS

This study provides the most current data on frequency and type of glaucoma in a British community. We identified a large number of ocular hypertensives and glaucoma suspects. These figures provide useful information for service planning. The large number of glaucoma subjects with IOP less than 21mmHg reinforces the weakness of relying on IOP in glaucoma case detection.

FOOTNOTES

Contributors

MPYC analysed and interpreted the data and drafted the manuscript. PJF and DCB contributed to the conception and design of the study and to data collection. APK and JLYY contributed to data collection and interpretation. DGH contributed to the conception and design of the study and to data interpretation. JMB contributed to data interpretation. RL contributed to the design of the study and to data management. HS contributed to the design of the study. ND contributed to the design of the study, and to data acquisition. KTK contributed to the conception and design of the study, and to data interpretation. All authors read and critically revised the manuscript. All authors approved the final manuscript.

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Competing interests

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Transparency declaration

The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Figure 1 Age and sex distribution of the EPIC-Norfolk 3HC cohort compared to the population of Norfolk & the UK (Source: 2014 mid-year population estimates in the UK, Office for National Statistics) [15]

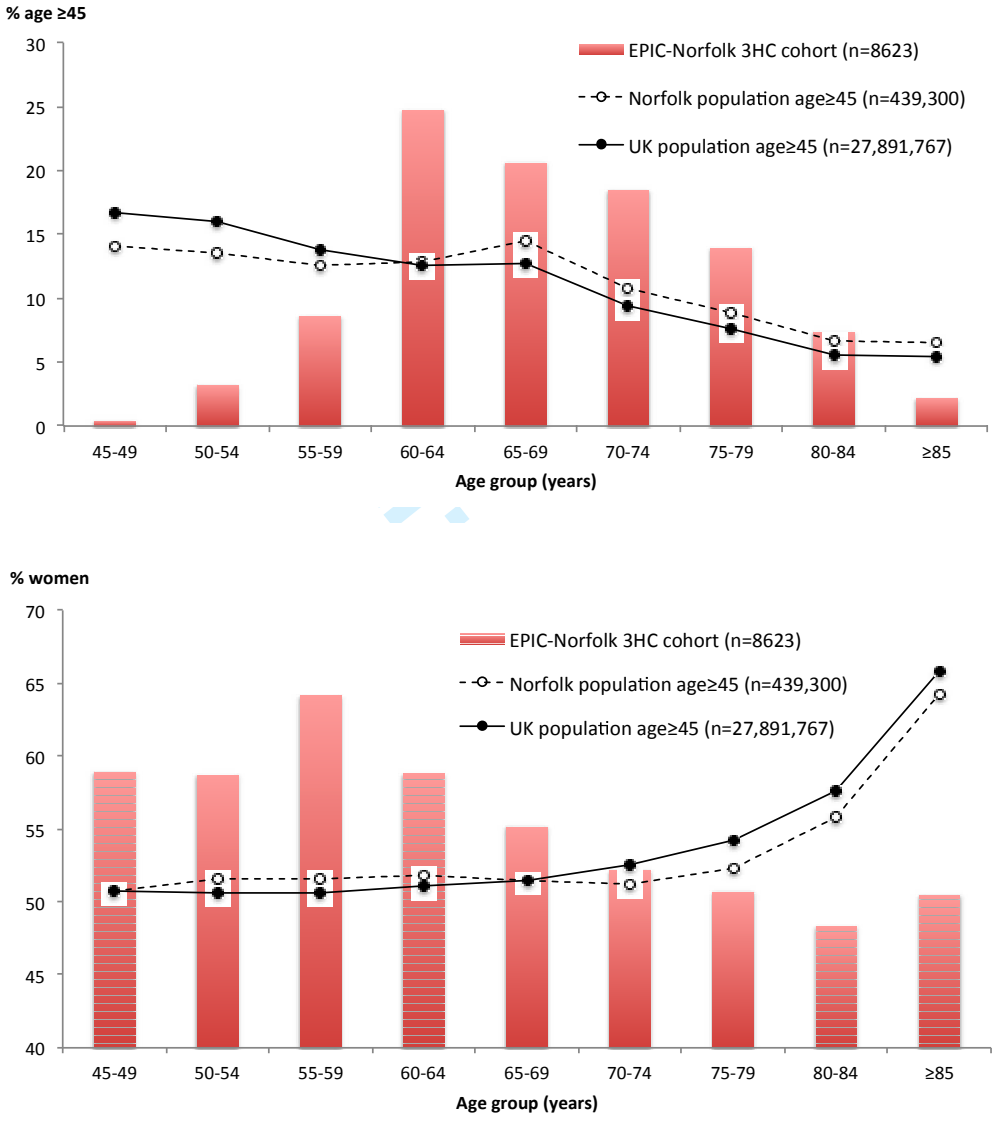


Figure 2. Distribution of IOP in the EPIC-Norfolk population (n=8401)

The distribution approximates a Gaussian distribution, but has an exaggerated central peak and a modest right skew.

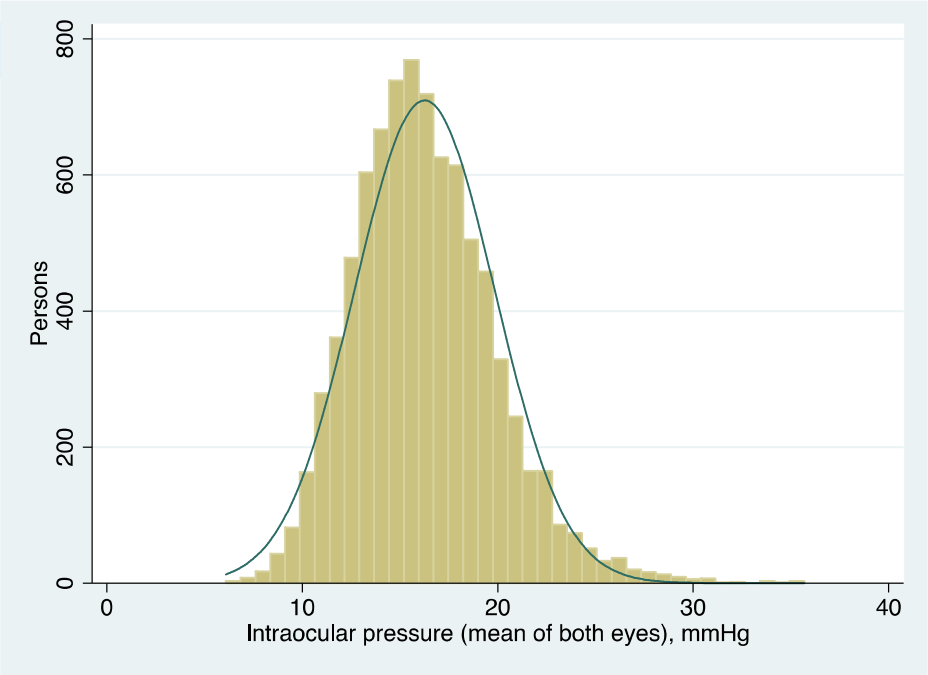


Figure 3. Intraocular pressure for all eyes and eyes with glaucoma in the EPIC-Norfolk cohort

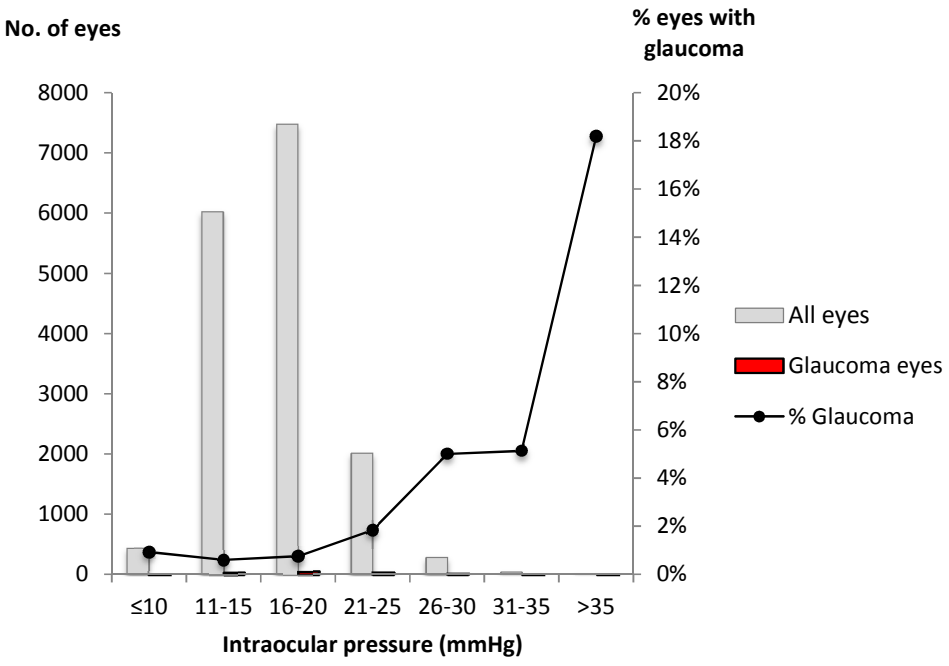
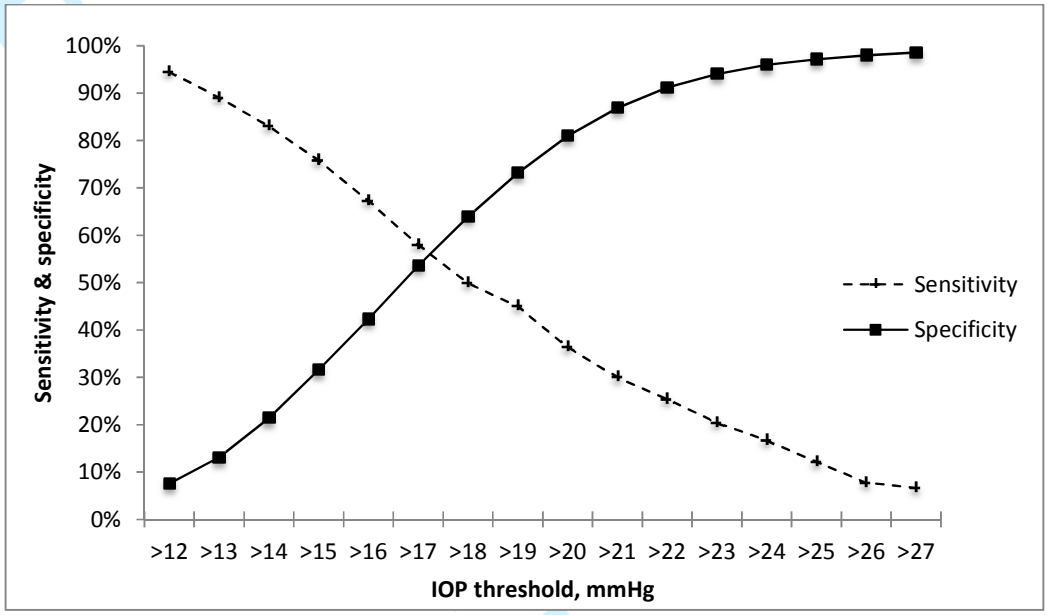


Figure 4. Sensitivity and specifity for all cause glaucoma detection in the EPIC-Norfolk cohort



Appendix I: Flow of participants through the EPIC-Norfolk Eye Study