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Complete List of Authors:	Chan, Michelle; UCL Institute of Ophthalmology , Division of Genetics & Epidemiology Broadway, David; Norfolk and Norwich University Hospital, Department of Ophthalmology Khawaja, Anthony; University of Cambridge, Department of Public Health & Primary Care Garway-Heath, David; NIHR Biomedical Research Centre at Moorfields Eye Hospital NHS Foundation Trust and UCL Institute of Ophthalmology , Optometry Burr, Jennifer; Universityof St Andrews, School of Medicine Luben, Robert; University of Cambridge, Department of Public Health and Primary Care Hayat, Shabina; University of Cambridge, Department of Public Health & Primary Care Dalzell, Nichola; University of Cambridge, Department of Public Health & Primary Care Khaw, Kay-Tee; University of Cambridge, Clinical Medicine Foster, Paul; Moorfields Eye Hopsital NHS Foundation Trust,
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Defining a new threshold for ocular hypertension and estimating referral burden from the EPIC-Norfolk Eye Study: a cross-sectional study of the potential impact on referrals to the Hospital Eye Services

Michelle P Y Chan, David C Broadway, Anthony P Khawaja, David F Garway-Heath, Jennifer M Burr, Robert Luben, Shabina Hayat, Nichola Dalzell, Kay-Tee Khaw, Paul J Foster

Division of Genetics and Epidemiology, UCL Institute of Ophthalmology, 11-43 Bath Street, London EC1V 9EL, UK. Michelle P Y Chan research fellow

Department of Ophthalmology, Norfolk and Norwich University Hospital NHS Foundation Trust, Norwich NR4 7UY & University of East Anglia, Norwich, NR4 7TJ, UK. David C Broadway professor

Department of Public Health & Primary Care, University of Cambridge, Cambridge CB1 8RN, UK. Anthony P Khawaja research fellow, Robert Luben head of biomedical informatics, Shabina Hayat research co-ordinator, Nichola Dalzell study co-ordinator, Kay-Tee Khaw professor

NIHR Biomedical Research Centre Moorfields Eye Hospital NHS Foundation Trust, 162 City Road, London EC1V 2PD, UK and UCL Institute of Ophthalmology, 11-43 Bath Street, London EC1V 9EL UK. Paul J Foster professor, David F Garway-Heath professor

School of Medicine, Medical & Biological Sciences, University of St Andrews, North Haugh, St. Andrews KY16 9TF, UK. Jennifer M Burr reader

Correspondence to:

Prof Paul Foster
Email: p.foster@ucl.ac.uk

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ABSTRACT

Objectives

To re-examine the basis for intraocular pressure (IOP) thresholds used to define ocular hypertension (OHT), and to determine the potential referral burden to the Hospital Eye Service if the definition for OHT was altered.

Design

A community-based cross-sectional observational study: the European Prospective Investigation of Cancer (EPIC)-Norfolk Eye Study.

Setting

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

Participants

7544 participants aged 48-92 years who did not have glaucoma or use ocular hypotensive drops with IOP measurements using Ocular Response Analyzer non-contact tonometer.

Main outcome measures

IOP threshold defining OHT (mean IOP + two standard deviations (SD)) by age and sex, was compared to the 97.5th centile of IOP. Projected numbers of referable cases at different IOP thresholds (highest from either eye) in England and Wales.

Results

The study population's mean Goldmann-correlated IOP (IOPg) in the right eye was 16.2mmHg (95% CI 16.1-16.3mmHg, SD 3.7mmHg). The OHT threshold (mean+2SD) was 23.6mmHg; this value ranged between 22.8-24.6mmHg in men and 22.6-24.3mmHg in women across the range of ages. For "standard" NCT measurements, the mean+2SD values were 21.5-21.6mmHg. Allowing for the skew in the data, the 97.5 centile is higher at 24.1-24.6mmHg for IOPg and 22.7-23.4mmHg for NCT measurements.

If a 24mmHg referral threshold were applied, the projected number of subjects eligible for referral in England and Wales on the basis of raised IOP alone would be reduced by 69.4%; if 22mmHg were adopted, the potential reduction would still be substantial at 33.0%. Raising the IOP threshold from 21mmHg to 24mmHg could cause up to an extra 16% of

undiagnosed glaucoma cases and extra 12% of undiagnosed glaucoma suspects to be missed. No single IOP measure was a reliable case-finding tool.

Conclusions

A significant reduction in unnecessary referrals could be made, with a modest loss of case finding performance, if IOP threshold for referral for OHT to the Hospital Eye Service were increased above the current threshold of 21mmHg. Careful consideration should be given when balancing the benefits and drawbacks of such a change.

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 characterized by progressive damage of the optic nerve.[3] Glaucoma and suspect glaucoma combined account for the fifth largest share of NHS outpatient attendances in England, after breast cancer, schizophrenia, prostate cancer and joint pain. [4] The most common type of glaucoma is primary open angle glaucoma (POAG). Elevated intraocular pressure (IOP) is the major modifiable risk factor for POAG. [5 6 7] However, around 50% of glaucoma cases present with IOP within the statistically 'normal' range.[8] The 'normal' values originate from the 1966 MRC Rhondda Valley population survey.[9] Among participants with no evidence of glaucoma, the IOP two standard deviations above the population mean was chosen to identify the top 2.5% of the population distribution. This varied according to sex and eye laterality, ranging between 20.5-22.5mmHg. Since then, IOP >21mmHg has become deeply entrenched as a threshold for ocular hypertension (OHT), and deemed requiring medical assessment. OHT accounts for 30-45% of all referrals made to NHS Hospital Eye Service in the UK.[10 11] In 2010, the UK's ophthalmic (Royal College of Ophthalmologists - RCOphth) and optometric (College of Optometry - CoO) professional bodies recommended that opticians should refer anyone with IOP >21 to the Hospital Eye Service, even if it was the sole abnormality. [12]

Goldmann applanation tonometry (GAT) used in the 1966 MRC survey is the hospital standard technique for measurement of IOP. GAT is more accurate and precise than non-contact tonometer (NCT) - the most widely used technique for IOP measurement in community optometric practices,[13 14] The RCOphth/CoO recommendations specified that, if GAT was not available, an average of four readings NCT should be taken, but did not consider the impact of greater measurement variability on the statistical "upper limit of normal".

For these reasons, there is a need to re-examine the IOP distribution in a UK population examined with non-contact devices, to ensure that IOP referral thresholds are suited to modern purposes. The aim of this study was to report the IOP distribution in a large UK population, and to estimate the effect of different IOP referral thresholds on the referable numbers to the NHS Hospital Eye Service.

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.[15] 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 with a 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. The glaucoma status of the subjects was determined following a 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 1:10 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. Detailed methods of the ophthalmic examination have previously been described, [16] and interim results on IOP have been published.[17 18] 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.

In the present study, we report IOP data from the EPIC-Norfolk Eye Study. 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 NCT (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 has been calibrated against GAT to provide a Goldmann-equivalent IOP measurement (IOPg, mmHg). The glaucoma status of the subjects was determined following a 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 1:10 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. A detailed description of the study design has been published previously.[16] 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. 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 summary diagram for the flow of participants through the study is included in Appendix I.

Statistical Analysis

IOP reported in this study excluded participants who used ocular hypotensive eyedrops or had glaucoma in either eye. Projections of referable numbers were based on 2014 population estimates for England and Wales.[19] Glaucoma cases reported in table 5 included all cause glaucoma cases in the entire EPIC-Norfolk Eye Study without any exclusion criteria. Sensitivities and specificities of IOP for glaucoma detection in table 6 were derived from the ability of various IOP thresholds to differentiate between subjects with all cause glaucoma (as determined by a consultant glaucoma specialist ophthalmologist) in either eye, and subjects with no glaucoma in either eye. Positive and negative predictive values (PPV, NPV) for POAG in table 7 were calculated using sensitivity, specificity and prevalence.[20] Sensitivity and specificity were based on the ability of various IOP thresholds to differentiate between subjects with POAG (as determined by a consultant glaucoma specialist ophthalmologist) in either eye, and subjects with POAG in either eye. POAG prevalence was derived from population data given in a recent meta-analysis, which reported point estimates of POAG prevalence for White populations in various age groups.[21] Average age-specific estimates were applied to the 2014 UK population estimates to calculate an estimate of POAG prevalence in the UK; this was 2.00%. The reporting of this study conformed to the STROBE statement.[22] All statistical analyses were performed using STATA (Stata/SE 13.1, StataCorp, College Station, Texas).

Patient Involvement

The EPIC-Norfolk Study actively engages with its participants with meetings in the Norfolk and Norwich communities to update the progress of the study and to

disseminate results. Details of all public events can be found on http://www.srl.cam.ac.uk/epic/publicevents.shtml. To promote participants' involvement in its research, an EPIC-Norfolk Participant Panel allows members to be involved in the designing of health questionnaires, writing of lay summaries, participant information, dissemination of results and providing a lay perspective on potential future projects.

RESULTS

There were 8,623 participants in the EPIC-Norfolk Eye Study, 8,343 had IOP measured (7,958 with ORA, 544 with AT555 NCT), 243 used ocular hypotensive eyedrops in either eye, and 363 had glaucoma in either eye. Among the participants who had ORA IOP measured and did not use ocular hypotensive eyedrops or have glaucoma in either eye (n=7544), their mean age was 68.4 years (range 48-92 years), 56.1% of participants were female and 99.7% were white. Compared to the 1966 Rhondda Valley Welsh population and the 2014 population estimates for England and Wales, the study population was older (Table 1, Figures 1a and 1b). Figure 2 shows the distribution of IOP in right eyes.

Table 1. Comparison of study demographics: EPIC-Norfolk Eye Study, 1966 Rhondda Valley Wales Study,[9] and the 2014 population estimates of England and Wales [19]

	EPIC-Norfolk Eye Study	1966 Rhondda Valley, Wales	2014 England & Wales (age 45+)
n	7544	4091	24,702,316
% female	56.1	n/a	52.1
Age range, yrs	48-92	40-74	>45
Mean age (men), yrs	69.1	55.1	61.7
Mean age (women), yrs	67.8	55.6	63.1

IOP (mean of three values, right eye) followed an approximately Gaussian distribution, with a right skew and an exaggerated peak (Figure 2). The cohort mean IOP (mean of 3 readings) in the right eye was 16.2mmHg (95% CI 16.1-16.3mmHg, SD 3.7mmHg). Two SDs above the cohort's mean IOP was 23.6mmHg. For the left eye the mean was 16.3 mmHg (95% CI16.2-16.4mmHg, SD 3.7mmHg). Even after using different IOP metrics, such as the single best signal value, and regardless of the laterality of the eye, the mean+2SD was 23.6-23.7mmHg, higher than the current "historical" threshold of 21mmHg (Table 2). Among the 424 normal study subjects who had tonometry with the AT555, the mean +2SD

was 21.5-21.6mmHg. Since the IOP distribution was skewed, the 97.5th centile provides a more appropriate estimate of the upper limit of the IOP distribution. This measured 24.1-24.6mmHg with ORA IOPg, and 22.7-23.4mmHg with the AT555 (Table 2).

To allow for the differences in age and sex distribution between the EPIC-Norfolk study and the general population of England and Wales, the mean+2SD IOP value was calculated for each five-year age group, for both men and women respectively. The mean+ 2SD value consistently measured above 21mmHg (Figure 3), ranging between 22.7– 24.0mmHg in men and 22.3-24.2mmHg in women.

Table 2. Summary of the Ocular Response Analyzer Goldmann-correlated intraocular pressure and AT555 measurements in EPIC-Norfolk participants who do not use ocular hypotensive drops or have glaucoma in either eye.

The upper limits of IOP distribution (mean+2SD or 97.5th centile) are consistently higher than the historical threshold of 21mmHg.

IOPg measurement	Mean (95%CI)	SD	Mean +2SD	97.5th centile
		mmHg		
ORA IOPg mean of three readings right eye n= 7493	16.2 (16.1-16.3)	3.7	23.6	24.1
left eye n=7467	16.3 (16.2-16.4)	3.7	23.6	24.4
ORA IOPg best signal value right eye n=7493	16.0 (15.9-16.1)	3.8	23.6	24.4
left eye n=7467	16.1 (16.0-16.2)	3.8	23.7	24.6
AT555 mean of three readings right eye (n=421)	14.5 (14.2-14.9)	3.5	21.5	23.4
left eye (n=424)	14.7 (14.4-15.1)	3.4	21.6	22.7

IOPg – Goldmann correlated intraocular pressure

To understand the potential referral burden for different IOP thresholds, Table 3 shows the distribution of subjects above or below various IOP thresholds, using the higher IOP of either eye (mean of three values) to reflect clinical referral practices, excluding glaucoma cases and those on ocular hypotensive eyedrops. In total, 14.1% of the population had a measurement above 21mmHg, when age-adjusted to match the population in England and Wales, which approximates to 3.24 million people (Table 4). If the referral threshold were to be increased from >21 to >24mmHg, the number of referable subjects based on IOP could be reduced by 69.4%, or 2.25 million people. Even a modest increase of the threshold to

>22mmHg or >23mmHg would bring a substantial reduction in the referable numbers by 33.0% and 54.9%, respectively.

In the entire EPIC-Norfolk Eye Study cohort, 363 (4.2%) people and 523 eyes were classified as having glaucoma of any type, and 315 people (3.6%) and 466 eyes with POAG. Among the glaucoma cases, 242 (66.6%) were previously known cases and 121 were newly diagnosed. The cohort had 747 (8.7%) glaucoma suspects, 160 were previously known cases and 587 were newly diagnosed. Table 5 shows the IOP levels for glaucoma cases and suspects. Among the newly diagnosed glaucoma cases, up to 81% cases would be missed compared to 65% being missed if the referral threshold was raised from 21mmHg to 24mmHg - a 16% increase. Among the newly diagnosed glaucoma suspects, up to 84% suspects could be missed compared to 71% if the referral threshold was raised from 21mmHg to 24mmHg - a 12% difference.

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. If the referral threshold were raised, the sensitivity of glaucoma detection (if based on IOP alone) would decrease but specificity would improve. Specificity increased from 87% at 21mmHg to 91% at 22mmHg, and reached 96% at 24mmHg. Due to the relatively low estimated prevalence of POAG in the UK at 2%, the positive predictive value (PPV) was low (table 7) while the negative predictive value (NPV) was high. At >21mmHg, the PPV was 4.5%, but increased to 5.6% at 22mmHg and 7.9% at 24mmHg, while NPV stayed static at 98% throughout the range.

Table 3. Distribution of persons (%) by age at different ORA Goldmann-correlated intraocular pressure thresholds using the higher IOP of either eye. Participants on ocular hypotensive drops or have glaucoma in either eye were excluded.

Age, yrs	Mean IOP (95% CI), mmHg	Persons (% age group)					
		≤21 mmHg	>21 mmHg	>22 mmHg	>23 mmHg	>24 mmHg	>25 mmHg
45-49 (n=27)	16.2 (14.8-17.6)	88.9	11.1	11.1	3.7	0.0	0.0
50-54 (n=233)	16.8 (16.4-17.3)	88.0	12.0	8.6	5.6	4.3	3.4
55-59 (n=656)	16.7 (16.4-17.0)	90.7	9.3	5.5	3.4	2.4	1.7
60-64 (n=1973)	17.3 (17.1-17.4)	86.3	13.7	9.1	6.4	4.4	3.5
65-69 (n=1634)	17.2 (17.0-17.4)	85.6	14.4	10.0	7.2	4.9	3.3
70-74 (n=1376)	17.1 (16.9-17.3)	86.5	13.5	8.4	5.5	3.7	2.7
75-79 (n=997)	17.0 (16.8-17.2)	87.3	12.7	9.7	5.8	3.5	2.5
80-84 (n=504)	16.8 (16.4-17.1)	88.5	11.5	7.3	5.4	4.0	2.4
≥85 (n=144)	16.3 (15.6-16.9)	86.1	13.9	8.3	4.2	3.5	1.4
Total (n=7544)	17.1 (17.0-17.2)	86.9	13.1	8.8	5.9	4.0	2.9

Table 4. Impact of varying the ocular hypertension threshold on referable numbers from 21mmHg extrapolating EPIC-Norfolk data to England and Wales

Ocular hypertension threshold	EPIC n	UK persons (millions)*	Change in persons eligible for referral	
			%	persons (million) *
>21mmHg	1123	3.24	-	-
>22mmHg	771	2.17	-33.0	-1.07
>23mmHg	533	1.46	-54.9	-1.78
>24mmHg	372	0.99	-69.4	-2.25
>25mmHg	268	0.71	-78.0	-2.52

*applied to age-matched 2014 population estimates of England and Wales [19]

Table 5. Intraocular pressure level among glaucoma cases and glaucoma suspects in the EPIC-Norfolk cohort

Higher IOP of either eye, mmHg	All cause glaucoma		Glaucoma suspects	
	New diagnosis (% of total)	Known diagnosis (% of total)	New diagnosis (% of total)	Known diagnosis (% of total)
≤21mmHg	79 (65.3%)	164 (67.8%)	419 (71.4%)	88 (55.0%)
≤22mmHg	86 (71.1%)	173 (71.5%)	449 (76.5%)	94 (58.8%)
≤23mmHg	94 (77.7%)	182 (75.2%)	475 (80.9%)	100 (62.5%)
≤24mmHg	98 (81.0%)	191 (78.9%)	492 (83.8%)	112 (70.0%)
≤25mmHg	103 (85.1%)	202 (85.1%)	511 (87.1%)	120 (75.0%)
No IOP measured	1 (0.8%)	15 (6.2%)	16 (2.8%)	8 (5.0%)
Total	121 (100%)	242 (100%)	587 (100%)	160 (100%)

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

Table 7. Primary open angle glaucoma - positive and negative predictive value at various intraocular pressure thresholds, adopting a prevalence of 2.0% in the UK.

IOP mmHg	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
>19	41.7	72.9	3.27	98.48
>20	32.3	80.7	3.75	98.42
>21	26.7	86.6	4.46	98.38
>22	21.3	90.9	5.55	98.35
>23	17.0	93.8	6.56	98.30
>24	13.7	95.8	7.88	98.26
>25	9.7	97.0	7.96	98.18
>26	6.0	97.9	7.30	98.11

DISCUSSION

Principal findings and comparison with other studies

In this large, community-based study, the "upper limit of normal" IOP was higher than the currently accepted threshold of 21mmHg. The historical threshold of 21mmHg is based on the now antiquated Schiötz tonometry measurements, while the upper limit GAT measurement from the same 1966 study was actually 22mmHg.[9] Using the Reichert ORA, a form of non-contact tonometer, the mean +2SD's was 23.6mmHg. For a smaller subset of subjects whose IOP was measured with the AT555 conventional NCT, the value was 21.5-21.6mmHg, similar to the 1966 study results. However, using the 97.5 centile to allow for the right skew in the data, the "upper limit of normal" was 22.7-23.7mmHg, and hence the convention of taking mean+2SD as the statistical "upper limit of normal" IOP appears inappropriate. This is relevant as most referrals to the Hospital Eye Service come from optometrists who use standard NCTs.[13] While IOP varies with age, the mean+2SD IOP, stratified by age and sex, was consistently higher than 21mmHg for all ages. Table 8 shows the IOP distribution among white subjects reported in other population studies. The mean IOP in EPIC-Norfolk was similar to that in other studies, but the SD was larger. The high SD was most likely due to the use of NCT, a pertinent finding since most community optometrists base their hospital referrals on NCT measurements.[13]

Table 8. Intraocular pressure distribution reported by population surveys of white subjects

Location	n	Age, yrs	% women	Tonometry	IOP, mmHg	
					Mean (SD)	Mean + 2SD
EPIC-Norfolk	7544	48-92	56.1	ORA NCT	16.2 (3.7)	23.6
EPIC-Norfolk	443	48-86	50.8	AT555 NCT	14.6 (3.6)	21.7
Baltimore[8]	2913	>40	n/a	GAT	17.2 (3.4)*	23.9*
Thessaloniki, Greece[24]	2554	>60	47.1	GAT	15.3 (3.5)	22.3
Beaver Dam[25]	4926	43-86	57.0	GAT	15.3 (3.4)	22.1
Rhonda Valley, Wales[9]	1873	40-75	53.8	GAT	15.9 (2.9)*	21.6*
Rhonda Valley, Wales[9]	1873	40-75	53.8	Schiötz	14.6 (3.0)*	20.5
Blue Mountain, Australia[26]	3654	>49	56.7	GAT	16.0 (2.6)	21.2

ORA Ocular Response Analyzer, GAT Goldmann applanation tonometry, n/a not available
* Values for non-glaucomatous subjects only

Relevance of Our Results

Through cautious extrapolation of (NICE) guidelines,[14] the 2010 joint Colleges' recommended that community optometrists in England and Wales refer patients with a sole anomaly of IOP >21mmHg in either eye to an ophthalmologist. Measurements would preferably be based on GAT measurements, but an average of four repeated NCT measures was deemed acceptable.[27,12] We provide data on both a "standard" and a modified NCT (ORA), the latter which makes end point measures using a slightly different method. A systematic review showed that measurements made with ORA and NCT were higher than GAT values by 1.3mmHg and 0.2mmHg respectively,[28] (personal communication with authors,16 December 2013). Our mean measurements with the conventional NCT were lower than those obtained using the ORA, supporting these previous results. However, our NCT and ORA results were derived from different subjects, preventing a direct inter-individual comparison.

Implications for Healthcare Policy

While our results suggest that the current IOP threshold for defining OHT, when measured by NCT or ORA, should be increased, the implications of such a change need to be examined. Although raised IOP is the strongest risk factor for POAG after age,[29] there is no specific IOP level above which the risk of glaucoma increases significantly. Our results show that no specific IOP provides sufficiently high sensitivity and specificity for glaucoma or POAG case detection, as shown in figure 4, mirroring results from the Baltimore Eye Survey.[30] Assuming a population prevalence of POAG of 2% over the age of 40 years, the PPV's for all IOP levels studied here were poor. Measuring IOP in the community addresses two separate goals – screening for ocular hypertensives who need treatment to prevent conversion to glaucoma, and case-finding for POAG. For screening, data from the Ocular Hypertension Treatment Study (OHTS) quantifies the potential benefits. This study recruited ocular hypertensives without glaucoma with an IOP between 24 and 32mmHg, and randomized them to observation or treatment of the elevated IOP. The results showed an absolute risk reduction in the 5-year incidence of glaucoma (on the basis of either structural optic disc changes or new visual field defects) of 4.8% for those participants who were treated. This equated to a number needed to treat (NNT) of 21 to prevent one case of glaucoma conversion. If one considers a more secure diagnosis of glaucoma (both structural optic disc changes and new visual field defect) the NNT rises to 46 (based on 2.2% absolute reduction of risk).[31] According to NICE guidelines,[14] the IOP at which treatment of ocular hypertension (with no signs of glaucoma) should be considered is >24mmHg, with the exact level depending on other factors (age, central corneal thickness). Consequently, increasing

the referral threshold to 24mmHg should not have any detrimental effect from missed treatment.

For the secondary purpose of POAG case-finding, increasing the OHT threshold would improve detection specificity, reduce the significant burden of false positive referrals and bring substantial financial savings to the health service. We estimate this to be a 33% reduction of referral at 22mmHg and 69% reduction at 24mmHg. However, in practice, the actual reduction is expected to be less, since these figures assume 100% of cases attend for optometrist examination- in reality that number is likely to be in the region of 50%. Also, in this study, 19% of those with IOP >21mmHg also qualified for referral due to presence of other glaucoma risk factors or suspicious optic disc and visual field findings. With an increase in referral IOP, sensitivity for detection of POAG will be reduced. Around 16% of undiagnosed glaucoma cases could be missed if the referral threshold was raised from 21 to >24mmHg. However, again, this needs to be reconciled with the fact that no single IOP value provides an acceptable combination of sensitivity and specificity for POAG detection.

In summary, data from this large UK community-based, cross-sectional study has indicated that the OHT threshold of >21mmHg is not appropriate for measurements made with NCT. Policy makers should consider recommending a higher referral threshold when IOP is the only ocular abnormality identified.

WHAT IS KNOWN ABOUT THIS TOPIC

The definition of OHT as IOP>21mmHg is deeply ingrained in clinical and scientific practices. Official guidelines from the UK ophthalmic and optometric professional bodies has been widely interpreted to mean that people with OHT should be referred to the Hospital Eye Service for formal assessment. The IOP referral threshold of >21mmHg was derived from a 1966 population survey, but there has been no attempt to update this value with more current data. In particular, the historical threshold was derived from Goldmann applanation tonometry, while most community optometrists make referrals based on non-contact tonometers.

WHAT THIS PAPER ADDS

This study is the first to our knowledge to attempt to re-visit the definition of the historical OHT threshold using data to explore the IOP distribution of a large White UK population measured with NCT. We suggest that the threshold for referral to the Hospital Eye Service should be increased above the current widely used figure of >21mmHg. Adopting a new higher threshold should bring significant reductions in referrals to the NHS, and it will also

have significant benefits to the diagnosis and care pathway for ocular hypertensives around the world.

FOOTNOTES

Contributors

MPYC analysed and interpreted the data and drafted the manuscript. APK contributed to data collection and interpretation. DCB contributed to the conception and design of the study and to data collection. 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 and PJF 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

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf. DFG reports personal fees from Aerie, Alimera, Allergan, Quark, Quethera, Santen, Santhera, Sensimed, grants and personal fees from Alcon, Pfizer, and grants from NIHR i4i programme outside the submitted work; in addition, DFG has a patent contact lens tonometer pending. PJF reports an unrestricted grant from Alcon (US), grants and personal fees from Allergan (UK) and Zeiss (EU). Other authors declare no support from any organisation for the submitted work, no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

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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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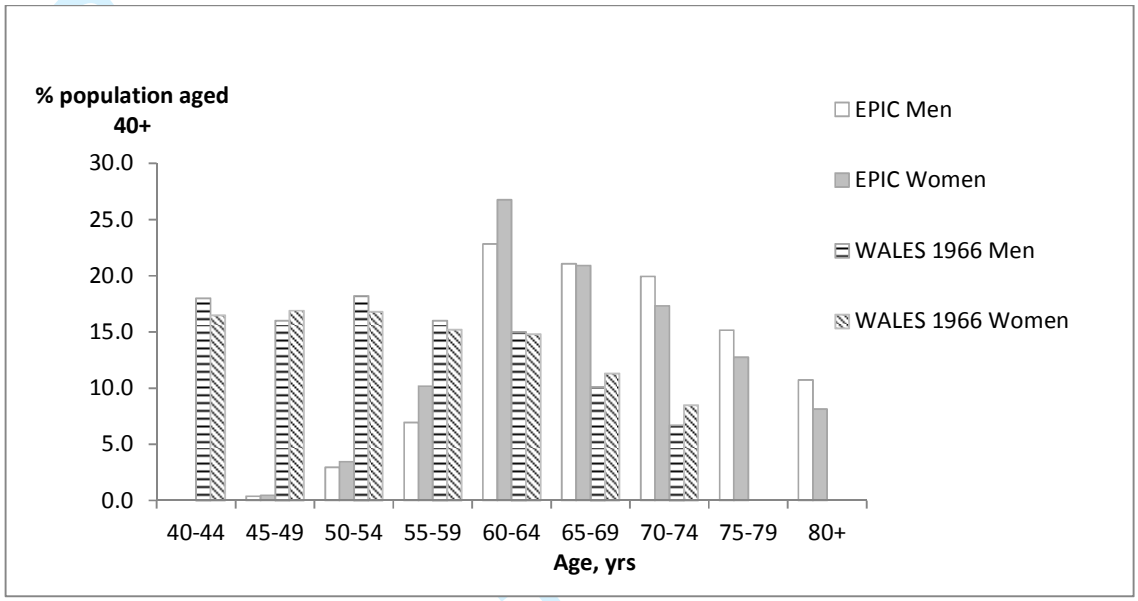
Figure 1. Age and sex distribution for the populations in: (a) EPIC-Norfolk Eye Study and 1966 Rhondda Valley Study[9]; (b) EPIC-Norfolk Eye Study and England and Wales 2014 population estimates[19]

(a)



(b)

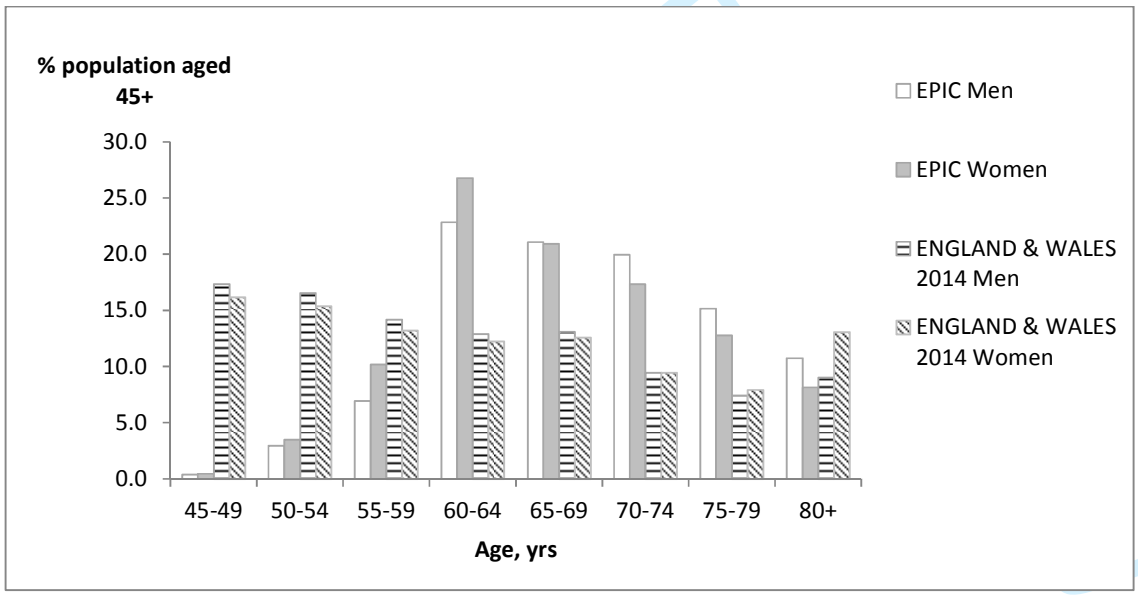


Figure 2. Distribution of IOP in the EPIC-Norfolk population (n=7544)

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

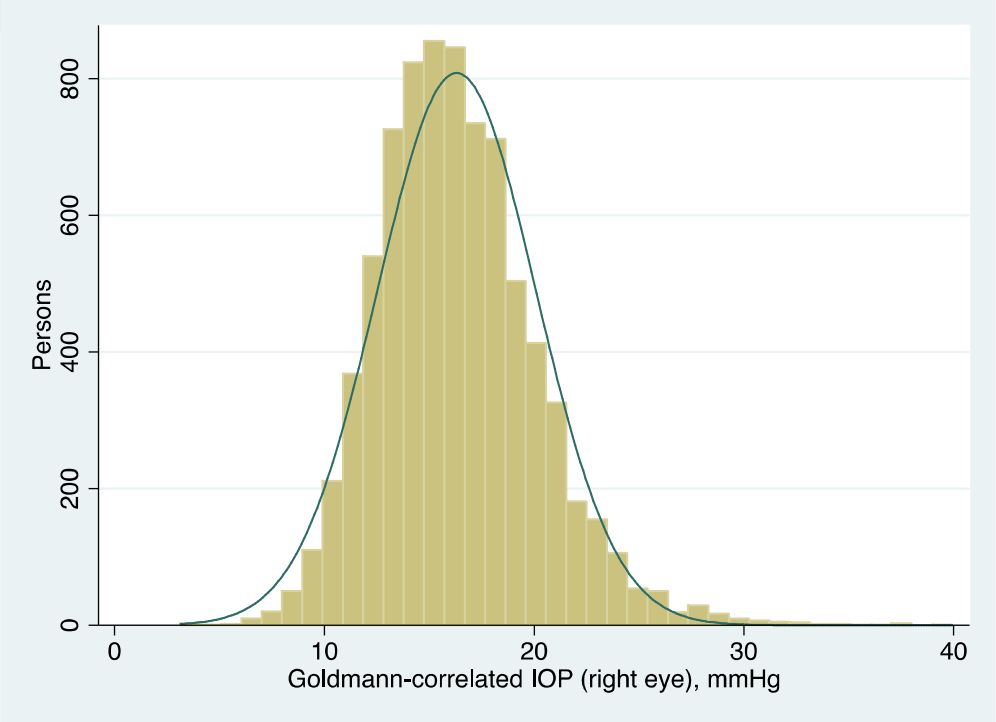


Figure 3. Mean +2SD varies across the age groups and for both sexes in the EPIC-Norfolk participants

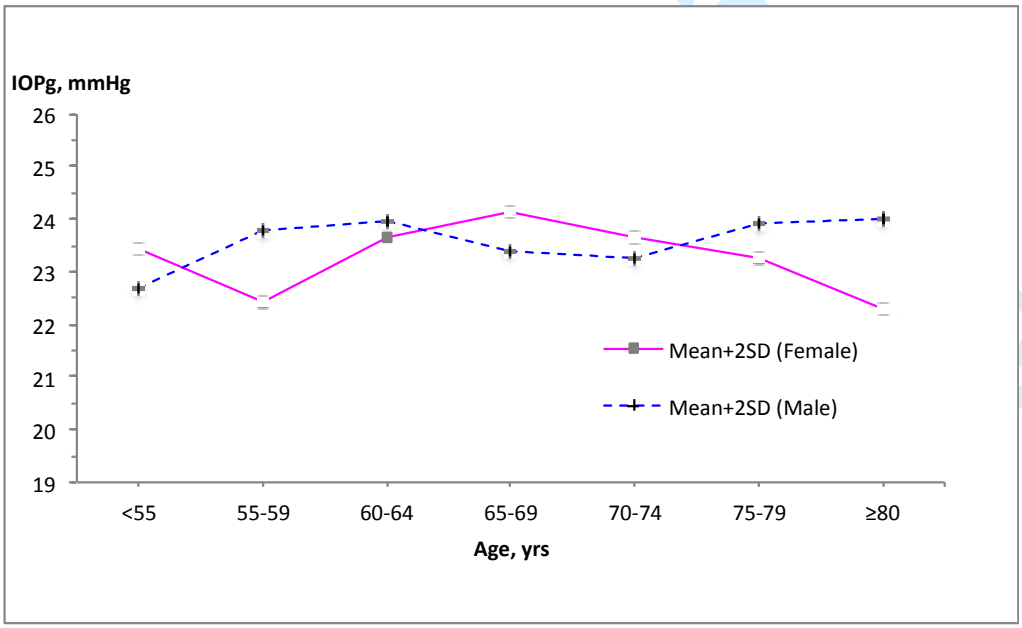
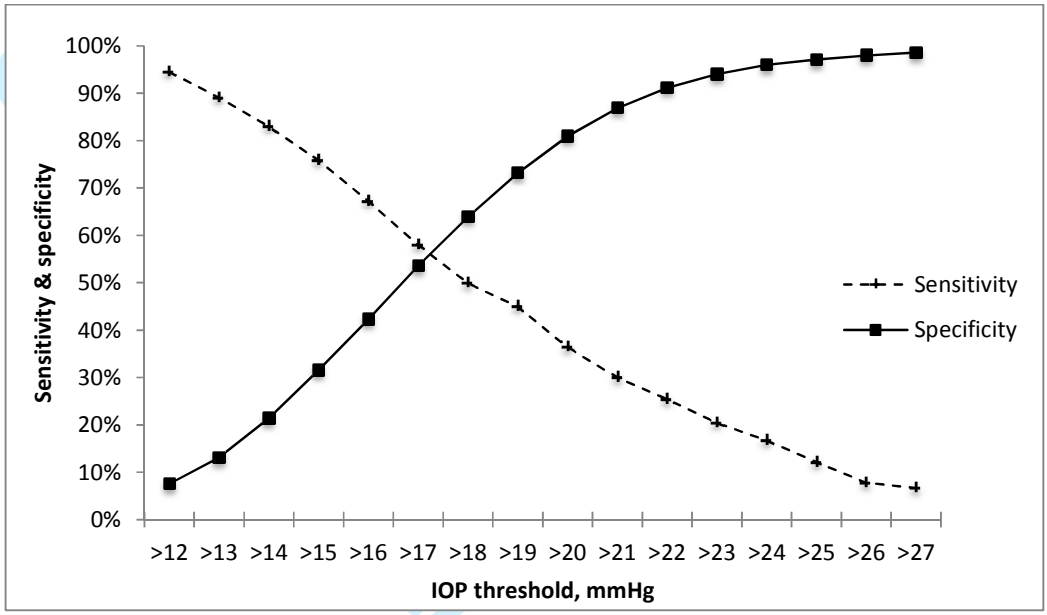


Figure 4. Sensitivity and specifity for all cause glaucoma detection in the EPIC-Norfolk cohort



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