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McCann, P., Hogg, R., Wright, D. M., Pose-Bazarra, S., Chakravarthy, U., Peto, T., Cruise, S., McGuinness, B., Young, I. S., Kee, F., & Azuara-Blanco, A. (2020). Glaucoma in the Northern Ireland Cohort for the Longitudinal Study of Ageing (NICOLA): Cohort profile, prevalence, awareness and associations. *British Journal of Ophthalmology*, [315330]. <https://doi.org/10.1136/bjophthalmol-2019-315330>

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Title page

Glaucoma in the Northern Ireland Cohort for the Longitudinal Study of Ageing (NICOLA): cohort profile, prevalence, awareness and associations

Paul McCann MBChB, PhD¹, Ruth E. Hogg PhD¹, David M. Wright PhD¹, Sara Pose-Bazarra MD², Usha Chakravarthy MD, PhD^{1,3}, Tunde Peto MD, PhD^{1,3}, Sharon Cruise PhD¹, Bernadette McGuinness MD, PhD¹, Ian S. Young MD¹, Frank Kee MD¹, Augusto Azuara-Blanco MD, PhD¹

¹Centre for Public Health, Queen’s University Belfast, Belfast, UK

²University Hospital Complex of Ferrol, Ferro, Spain

³On behalf of the Network of Ophthalmic Reading Centres UK (NetwORC UK)

Corresponding author: Augusto Azuara-Blanco,

Address: Institute of Clinical Sciences, Block A, Royal Victoria Hospital, Belfast, BT12 6BA

Phone: 028 90 976 430

Email: a.azuara-blanco@qub.ac.uk

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Paul McCann, pmccann45@qub.ac.uk, Institute of Clinical Sciences, Royal Victoria Hospital, Belfast, BT12 6BA

Ruth E. Hogg, r.e.hogg@qub.ac.uk, Institute of Clinical Sciences, Royal Victoria Hospital, Belfast, BT12 6BA

David M. Wright, d.wright@qub.ac.uk, Institute of Clinical Sciences, Royal Victoria Hospital, Belfast, BT12 6BA

Sara Pose-Bazarra, saraposeb@hotmail.com, University Hospital Complex of Ferrol, Ferro, Spain

Usha Chakravarthy, u.chakravarthy@qub.ac.uk, Institute of Clinical Sciences, Royal Victoria Hospital, Belfast, BT12 6BA

Tunde Peto, t.peto@qub.ac.uk, Institute of Clinical Sciences, Royal Victoria Hospital, Belfast, BT12 6BA

Sharon Cruise, s.cruise@qub.ac.uk, Institute of Clinical Sciences, Royal Victoria Hospital, Belfast, BT12 6BA

Bernadette McGuinness, b.mcguinness@qub.ac.uk, Institute of Clinical Sciences, Royal Victoria Hospital, Belfast, BT12 6BA

Ian S. Young, i.young@qub.ac.uk, Institute of Clinical Sciences, Royal Victoria Hospital, Belfast, BT12 6BA

Frank Kee, f.kee@qub.ac.uk, Institute of Clinical Sciences, Royal Victoria Hospital, Belfast, BT12 6BA

Precis: The crude prevalence of glaucoma in Northern Ireland of 2.83% (95%CI 2.31%, 3.46%) is comparable to other European population-based studies. Approximately two thirds of people with glaucoma were undiagnosed. Associations with glaucoma were consistent with current understanding of the disease.

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Abstract

Background/Aims: To describe the cohort profile of the Northern Ireland Cohort for the Longitudinal Study of Ageing (NICOLA) and to report the prevalence of, awareness of, and associations with glaucoma.

Methods: Using geographic stratification a representative sample of non-institutionalised Northern Irish adults aged over 50 years was invited to participate. NICOLA participants underwent a computer assisted personal interview (CAPI), a self-completion questionnaire (SCQ) and a health assessment. The CAPI and SCQ collected comprehensive sociodemographic and health related data. At the health assessment participants underwent optic disc stereophotography, intraocular pressure (IOP) measurement using Ocular Response Analyser (ORA), autorefracton, spectral domain optical coherence tomography and self-reported history of glaucoma. We invited NICOLA participants suspected of having glaucoma due to optic disc appearance or raised IOP for clinical examination by a glaucoma expert and perimetry. Epidemiological definitions by the International Society Geographical and Epidemiological Ophthalmology were used to define glaucoma.

Results: Of 3,221 NICOLA participants (mean age 64.4, SD 8.5, female sex 51.7%) who attended the health assessment component of the NICOLA study (and had a vertical cup to disc ratio measurement in at least one eye), 91 participants had glaucoma. Overall, the crude prevalence of glaucoma was 2.83% (95%CI 2.31%, 3.46%) and 67% of affected individuals did not give a self-reported history of glaucoma.

Conclusions: The prevalence of glaucoma in Northern Ireland is comparable to other population-based studies of European populations. Approximately two thirds of people with glaucoma were undiagnosed.

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INTRODUCTION

There is a global trend for people to live longer and though welcome, this poses major challenges for economic, health and social policy. ¹ Longitudinal studies of older people aim to understand social, economic and biological factors that influence healthy ageing. ² The Northern Ireland Cohort for the Longitudinal Study of Ageing (NICOLA) is a large longitudinal study of ageing in Northern Ireland. ³ It is a rich resource which enables the investigation of the biological, demographic and socioeconomic risk factors for glaucoma. Glaucoma, an age-related chronic eye disease, is the second leading cause of severe visual loss in the developed world and is therefore a major public health concern. ⁴ The prevalence of glaucoma varies among ethnicities and regions. Europe has the lowest prevalence of glaucoma at 2.93% in people over 40. ⁵

In 2002 the International Society Geographical and Epidemiological Ophthalmology (ISGEO) set guidelines to standardise case definitions of glaucoma for the purposes of prevalence studies. ⁶ Since its introduction many studies have adopted the ISGEO guidelines, especially in Asia and Africa. ⁶ At present, there is few data on the prevalence of glaucoma from Europe that is based on ISGEO criteria and this lack of knowledge makes comparisons between other ethnicities and geographic locations impossible. The NICOLA study performed high quality retinal imaging and obtained functional data therefore offers a unique opportunity to obtain robust estimates of glaucoma prevalence based on ISGEO definitions of glaucoma and to explore relevant risk factors in the European setting.

METHODS

NICOLA is an ongoing longitudinal cohort study of ageing in a sample of the Northern Ireland population aged 50 years or older. The sampling strategy identified addresses within postcode-based geographic regions (geographic stratification). A fixed interval (systematic) sample was drawn from each postcode-based geographical stratum.² The NICOLA assessment comprised of three elements; 1) a Computer Assisted Personal Interview (CAPI; Supplementary Table S1 in the online supplementary material) conducted at the participant's home by a trained interviewer, 2) a self-completion questionnaire (SCQ) that included the 9-item National Eye Institute Visual Function Questionnaire (NEI VFQ 9; Supplementary Table S2 in the online supplementary material), and, 3) a health assessment including a range of ophthalmic, anthropometric, cardiovascular, cognition and blood tests, which were performed at the Northern Ireland Clinical Research Facility (NICRF). The health assessment also included a detailed ophthalmic component during the visit to the NICRF. Data collection for the NICOLA study began in February 2014 and ended in 2018.² Details of NICOLA study assessments can be found in Supplementary Methods 1 in the online supplementary material and at <https://www.qub.ac.uk/sites/NICOLA/>. Details of the ophthalmic component of the NICOLA study health assessment can also be found in Supplementary Methods 1 in the online supplementary material.

Vertical cup to disc ratio (VCDR) was used as the primary index of structural glaucomatous change following ISGEO recommendations.⁶ Details of VCDR grading and adjudication can be found in Supplementary Methods 2 in the online supplementary material. In brief, following a series of agreement

analyses all discs graded with a VCDR ≥ 0.41 by primary graders were re-graded by an experienced grader (PMcC). All discs finally found to have a VCDR ≥ 0.7 and/or VCDR asymmetry ≥ 0.2 and/or disc haemorrhages and/or neuroretinal rim thinning or notching were re-graded (including fellow eyes) by a glaucoma expert (AAB). NICOLA participants who had a VCDR measurement in at least one eye were included in the analysis. NICOLA participants who did not attend the health assessment or who attended the health assessment but did not have a VCDR measurement were excluded.

NICOLA participants aged 50 years or older who attended the health assessment from the beginning of the study in February 2014 through 7th January 2017 and had a VCDR ≥ 0.7 and/or VCDR asymmetry ≥ 0.2 and/or vertical neuroretinal rim ratio (NRRR) ≤ 0.1 on optic disc stereophotography and/or intraocular pressure (IOP) ≥ 25 mmHg on ORA tonometry (Goldmann correlated IOP (IOPg)) were invited for an additional examination by a glaucoma expert (AAB). Additional tests performed at this visit included visual field testing using Humphrey's Matrix frequency doubling technology (FDT) perimetry (Carl Zeiss Meditec Inc., Dublin, CA, USA) in low illumination. Instructions were provided, and a trial was performed in demonstration mode for 30 – 60 seconds to allow familiarisation with the test and clarification of the instructions. An initial 24-2 suprathereshold screening test was then performed followed by a 24-2 full threshold test. The 24-2 full threshold test was considered unreliable if there was $>33\%$ for false positive errors, $>33\%$ for false negative errors or $>33\%$ for fixation errors. The 24-2 full threshold test was repeated once if it was unreliable. Gonioscopy was performed at the slit lamp by the glaucoma expert. Pupil dilation (except in

patients with narrow anterior chamber angle) was performed and biomicroscopy was carried out including optic disc examination.

ISGEO epidemiological definitions of glaucoma were used to define glaucoma and glaucoma related findings in this study (Supplementary Table S3 in the Supplementary material).⁶ The NICOLA study did not perform visual field tests on all participants thus the VCDR and IOP distributions of the subset of 'hypernormals' that are required to set the population-specific 97.5th and 99.5th percentiles could not be determined. Therefore, similar to other population-based studies, we set the VCDR 97.5th and 99.5th percentiles and the VCDR asymmetry 97.5th and 99.5th percentiles as 0.70 and 0.80 and 0.20 and 0.30 respectively.^{7,8}

For ISGEO 1 classification, the Hodapp-Anderson-Parrish criteria (HAP), were applied to visual field tests and any of the following must have been present: 1) a Glaucoma Hemifield Test "outside normal limits" or, 2) a cluster of three or more points in a location typical for glaucoma, all of which are depressed on the pattern deviation plot at a $p < 5\%$ level and one of which is depressed at a $p < 1\%$ level or, 3) a pattern standard deviation that occurs in less than 5% of normal fields and, 4) visual field defect not explained by any other disease. If the visual field tests were unreliable or unavailable, participants were classified according to ISGEO 2 or ISGEO 3. ISGEO 2 classifications were only finalised after adjudication by a glaucoma expert (AAB).

The presence of severe glaucoma was defined as a visual-field loss of either (1) mean deviation (MD) of 12 dB or worse or (2) absolute paracentral

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scotoma within the central 5° of visual fields (defined as ≥ 1 central 2x2 points on the pattern deviation plot). If visual fields were unreliable, the presence of severe disc damage (VCDR of more than or equal to 0.9) was used to define severe glaucoma.⁹

‘Visual impairment’ was defined using World Health Organisation (WHO) definitions. Blindness was defined in an eye if the presenting visual acuity was logMAR > 1.3 ($< 3/60$ Snellen) and moderate to severe visual impairment (MSVI) was defined in an eye if the presenting visual acuity was between logMAR 0.51 and logMAR 1.3 ($< 6/18$, $\geq 3/60$ Snellen).

This study was conducted according to the tenets of the Declaration of Helsinki. Ethical approval was obtained from the School of Medicine, Dentistry and Biomedical Sciences Ethics Committee, Queen’s University Belfast and the Northern Ireland’s Health and Social Care (HSC) Research Ethics Committee A (REC A) (REC reference: 16/NI/0247). We report the findings in accordance with the STROBE checklist.¹⁰

Statistical analysis

Summary statistics for baseline continuous variables and frequencies of categorical characteristics were reported for the cohort. Comparisons were performed between included and excluded participant using independent sample t tests for parametric continuous variables and Mann-Whitney tests for non-parametric continuous variables. χ^2 or Fischer exact tests were used for categorical variables.

To determine if there were systematic differences between participants who attended the invitation for further clinical exam and testing and those who did

not, comparisons of baseline demographic characteristics were performed. Independent sample t tests were used for parametric continuous variables and Mann-Whitney tests were used for non-parametric continuous variables. χ^2 or Fischer exact tests were used for categorical variables.

If a participant had glaucoma in at least one eye that person was defined as having glaucoma for prevalence purposes. If a participant had bilateral glaucoma, the participant was classified as glaucoma according to the eye with the highest level of evidence (i.e., ISGEO 1 > ISGEO 2 > ISGEO 3). Total and age specific prevalence of glaucoma and their 95% confidence intervals were calculated for the NICOLA sample ≥ 50 years old. Crude and age-weighted prevalence were analysed. The age of participants at the time of the most recent visit to the NICOLA or clinical exam assessment was used for reporting prevalence estimates (age at ISGEO classification). Prevalence was calculated as the percentage of the number of persons with glaucoma to the total number of NICOLA participants who attended the NICOLA health assessment and had valid VCDR data available in ≥ 1 eye. The methods and analysis of this study followed guidelines for evaluating prevalence studies published by Boyle et al ¹¹ and adapted for glaucoma.

To assess epidemiological associations with glaucoma, prevalent cases of glaucoma (by eye) were considered as the dependent variable in logistic regression analysis with Generalised Estimating Equations (GEE). The independent variables in the univariate analysis were identified based on comprehensive review of the literature and are described in Supplementary Methods 3 in the online supplementary material.

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In multivariable logistic regression analysis with GEE, we entered the variables age and sex (Model 1) then inserted independent variables from the univariate analysis that were statistically significant at the $p < 0.05$ level. We then inserted all independent variables from Model 1 significant at the $p < 0.05$ level including age and sex and used reverse stepwise removal of variables by removing the least statistically significant at each step (Model 2). A p value < 0.05 was considered statistically significant.

Multivariable analysis was conducted using GEE which allowed data from both eyes and their intra-individual correlation to be considered. Subject variables were ‘NICOLA participants’ and within-subject variables were ‘eyes’. Within-subject variables were eligible as independent variables within the multivariable analysis. Independent working correlation matrix was selected and the use of a robust estimator was selected to be robust against misspecification of the working correlation matrix.

Statistical analysis was performed using a software program (IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp) and R version 3.5.2 (R Foundation for Statistical Computing, Vienna, Austria). The precision of the prevalence estimate was calculated using methods described by Newcombe.¹² Prevalence was weighted using the Northern Ireland Statistics and Research Agency (NISRA) census 2011 and the 2017 population projection.¹³ Weighting was determined by using the package ‘survey’ in R version 3.5.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

NICOLA cohort profile

The NICOLA study required 12,077 addresses (main sample) and in addition a 20% contingency (reserve sample) sample of 2,415 addresses.³ In total, 8,504 participants underwent NICOLA Wave 1 CAPI (response rate of 63%).

³ CAPI interviews were conducted on 8,504 of whom 3,221 participants attended the health assessment and had VCDR data available in ≥ 1 eye (Figure 1). These 3,221 participants comprised the denominator for the prevalence estimate and were included in the association analysis. NICOLA participants with no VCDR data available in either eye were excluded from the prevalence denominator.

Baseline characteristics of the included 3,221 NICOLA participants were compared to the 5,044 excluded NICOLA participants (Table 1). Statistically significant differences in baseline demographics were found between included and excluded NICOLA participants. The numbers of missing VCDR, IOP and circumpapillary retinal nerve fibre layer (cRNFL) measurements are reported in Supplementary Table S4 in the online supplementary material.

In total, 229 NICOLA participants were initially considered to have been eligible for the additional examination by the glaucoma expert, of whom 49 were excluded based on specified criteria outlined in Figure 1. Invitations for clinical exam were sent to 180 NICOLA participants of whom 128 NICOLA attended for further clinical exam and visual field testing.

Baseline characteristics of 128 eligible NICOLA participants who attended the clinical examination were compared to the 101 NICOLA participants who did not attend (49 who were excluded from invitation plus 52 who declined

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invitation). Attendees were statistically significantly younger than non-attendees (Supplementary Table S5 in the online supplementary material).

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Table 1. Baseline characteristics of NICOLA participants and comparisons between 'Glaucoma in NICOLA participants' and 'NICOLA participants excluded from Glaucoma in NICOLA.'

	NICOLA Cohort (n = 8,265)	Included participants (n = 3,221)	Excluded participants (n = 5,044)	P value †
Age (SD) at health assessment (n = 3,214)	d.n.c.	64.4 (8.5)	d.n.c.	-
Age category at CAPI (n = 8,257)				<0.001
50-59 (%)	2,778	1,192 (37.1)	1,586 (31.4)	
60-69 (%)	2,782	1,246 (38.8)	1,536 (30.5)	
70-79 (%)	1,850	633 (19.7)	1,217 (24.1)	
80+ (%)	847	143 (4.4)	704 (14.0)	
Sex (n = 8,257)				<0.001
Male (%)	3,738	1,552 (48.3)	2,186 (43.3)	
Female (%)	4,519	1,662 (51.7)	2,857 (56.7)	
Habitation (n = 6,495)				0.023
Urban / city / townland (%)	4,443	1,669 (70.1)	2,774 (67.4)	
Rural (%)	2,052	711 (29.9)	1,341 (32.6)	
Education level (n = 8,182)				<0.001
None (%)	292	68 (2.1)	224 (4.5)	
Some primary (not complete) (%)	151	30 (0.9)	121 (2.4)	
Primary or equivalent (%)	1,651	367 (11.4)	1,284 (25.8)	
GCSE / O level or equivalent (%)	3,021	1,136 (35.4)	1,885 (37.9)	
A level or equivalent (%)	608	268 (8.3)	340 (6.8)	
Diploma certificate or equivalent (%)	1,154	581 (18.1)	573 (11.5)	
Undergraduate primary degree (%)	644	372 (11.6)	272 (5.5)	

Postgraduate / higher degree (%)	661	389 (12.1)	272 (5.5)	
Siblings with glaucoma (n = 7,743)				0.054
No (%)	7,464	2,943 (96.9)	4,521 (96.1)	
Yes (%)	279	94 (3.1)	185 (3.9)	
Past smoking status (n = 8,170)				<0.001
Never (%)	3,953	1,687 (52.5)	2,266 (45.7)	
Ever (%)	4,217	1,524 (47.5)	2,693 (54.3)	
Current smoking status (n = 4,217)				<0.001
Ex-smoker (%)	2,863	1,210 (79.4)	1,653 (61.4)	
Current smoker (%)	1,354	314 (20.6)	1,040 (38.6)	
Self-report cardiovascular disease (Angina or MI) (n = 8,191)				<0.001
Yes (%)	2,890	993 (30.9)	1,897 (38.1)	
No (%)	5,301	2,220 (69.1)	3,081 (61.9)	
Self-report cerebrovascular disease (Stroke or TIA) (n = 8,257)				<0.001
Yes (%)	491	131 (4.1)	360 (7.1)	
No (%)	7,766	3,083 (95.9)	4,683 (92.9)	
Self-report Hypertension (n = 8,257)				<0.001
Yes (%)	3,337	1,132 (35.2)	2,838 (56.3)	
No (%)	4,920	2,082 (64.8)	2,205 (43.7)	
Self-report High cholesterol (n = 8,257)				0.403
Yes (%)	2,996	1,184 (36.8)	1,812 (35.9)	

No (%)	5,261	2,030 (63.2)	3,231 (64.1)	
Self-report Diabetes mellitus (n = 8,257)				<0.001
Yes (%)	926	255 (7.9)	671 (13.3)	
No (%)	7,331	2,959 (92.1)	4,372 (86.7)	
Self-report Parkinson's disease (n = 8,257)				0.727
Yes (%)	28	10 (0.3)	18 (0.4)	
No (%)	8,229	3,204 (99.7)	5,025 (99.6)	
Median income domain score (IQR) (n = 8,246)	0.2000 (0.1300, 0.3000)	0.1800 (0.1100, 0.2700)	0.2100 (0.1400, 0.3200)	<0.001 ‡
Median house value (IQR) (n = 8,085)	115000 (77500, 160000)	135000 (95000, 185000)	100000 (72500, 145000)	<0.001 ‡
Median NEI VFQ 9 score (IQR) (n = 4,067)	12.00 (10.00, 15.00)	12.00 (10.00, 15.00)	13.00 (10.00, 16.00)	0.002

† Included participants compared to excluded participants; ‡ Mann Whitney U test; d.n.c. data not collected

Glaucoma prevalence

In total, there were 91 participants diagnosed with glaucoma. The crude prevalence of glaucoma was 2.83% (95%CI 2.31%, 3.46%).¹² The population age-weighted prevalence of glaucoma was 3.19% (95%CI 2.55, 3.97) for the 2011 population census and 3.24% (95%CI 2.59, 4.04) for the 2017 population projection. The age-stratified crude and age-weighted prevalence of glaucoma are presented in Figure 2 and Table 2. Two thirds (67%; 61 / 91) of participants with glaucoma did not self-report a history of glaucoma and 1.37% (43 / 3,130) of participants without glaucoma self-reported a history of glaucoma.

Glaucoma sub-types and severity

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For the 91 NICOLA participants with glaucoma, glaucoma sub-types were reported for the 128 participants who attended clinical examination and are shown in Supplementary Table S6 in the online supplementary material. Of the 128 participants who attended clinical examination here were 36 right eyes and 36 left eyes from 48 participants diagnosed with POAG and 4 right eyes and 7 left eyes from 7 participants with PACG. One of these participants had one eye with POAG and one eye with PACG. There was 1 eye from 1 participant with pseudo-exfoliation glaucoma and both eyes from 1 participant with pigmentary glaucoma. There were 20 right eyes and 15 left eyes from 31 participants with severe glaucoma and 8 participants had severe glaucoma in both eyes.

Table 2. Age stratified and total, crude prevalence, 2011 census age-weighted prevalence and 2017 population projection age-weighted prevalence

Age group	Age-stratified crude prevalence	Age-stratified crude prevalence 95%CI	2011 census age-weighted prevalence	2011 census age-weighted prevalence 95%CI	2017 population projection age-weighted prevalence	2017 population projection age-weighted prevalence 95%CI
50-59	1.13	0.64, 1.97	1.28	0.73, 2.25	1.29	0.74, 2.27
60-69	2.22	1.54, 3.20	1.73	1.20, 2.50	1.62	1.12, 2.34
70-79	4.78	3.43, 6.61	4.30	3.09, 5.95	4.49	3.22, 6.22
80+	9.60	6.03, 14.95	20.55	12.91, 32.00	21.32	13.40, 33.19
Total	2.83	2.31, 3.47	3.19	2.55, 3.97	3.24	2.59, 4.04

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ISGEO classifications by participant and by eye

The number of eyes diagnosed with glaucoma classified by ISGEO categories and laterality is shown in Supplementary Table S7 in the online supplementary material. 52 participants were diagnosed with glaucoma according to ISGEO category 1 and 39 participants were diagnosed with glaucoma according to ISGEO category 2.

In 23 participants (18.0%, 23 / 128) visual field tests were either unreliable or the abnormality was deemed to be due to causes other than glaucoma (Supplementary Table S8 in the online supplementary material). Data from eyes in this group were eligible for ISGEO category 2 classification in prevalence calculations using the optic disc findings.

Visual Impairment in Glaucoma

There was 1 right eye with glaucoma that was blind according to WHO criteria, however, glaucoma was not the primary cause of blindness. There were 3 left eyes with glaucoma that were visually impaired according to WHO criteria, and the remaining glaucomatous eyes did not have visual impairment according to WHO criteria.

Other glaucoma related findings

Of the 130 eyes with glaucoma, 17 had IOPg >21 mmHg. In total, 34 right eyes and 40 left eyes were disc suspects. Of the 34 right eye disc suspects, 5 had IOPg >21 mmHg. Of the 40 left eye disc suspects, 5 had IOPg >21 mmHg and 2 had IOPg missing.

Among the 3,221 included NICOLA participants there were 265 participants (8.2%) with ocular hypertension (> 21 mmHg in ≥ 1 eye) according to IOPg and there were 82 participants (2.6%) with IOPg ≥ 24 mmHg in ≥ 1 eye at the NICOLA health assessment. There were 327 participants (10.2%) with ocular hypertension (> 21 mmHg in ≥ 1 eye) according to IOPcc and there were 109 participants (3.4%) with IOPcc ≥ 24 mmHg in ≥ 1 eye at the NICOLA health assessment.

Associations between glaucoma and systemic, ocular and sociodemographic factors

Univariate and multivariable analysis models for associations with glaucoma are reported in Table 3. In the fully adjusted multivariable model, older age, increased IOPg and increased NEI VFQ 9 question 2 subscale score (how much time do you worry about your eyesight?) were associated with increased odds ratio of having glaucoma. Increased corneal hysteresis (CH) and hyperopic increase in spherical equivalent were associated with reduced odds ratio of eyes having glaucoma. Decreased mean global cRNFL thickness was associated with significantly higher odds of glaucoma when adjusted for age and sex.

Table 3. Univariate and multivariate analysis of associations with glaucomatous eyes.

	Univariate			Multivariate Model 1 ^k			Multivariate Model 2 ^o		
	OR (Exp(B))	95% CI	P value	OR (Exp(B))	95% CI	P value	OR (Exp(B))	95% CI	P value
Age at ISGEO classification	1.080	1.054, 1.107	<0.001	1.093	1.067, 1.121	<0.001 ^{l,n}	1.097	1.062, 1.132	<0.001
50-59	Ref								
60-69	2.026	0.987, 4.162	0.054	2.015	0.980, 4.141	0.057 ^l	-	-	-
70-79	4.613	2.288, 9,303	<0.001	4.548	2.244, 9.216	<0.001 ^l	-	-	-
80+	11.359	5.151, 25.046	<0.001	11.109	4.972, 24.818	<0.001 ^l	-	-	-
Sex									
Female	Ref								
Male	1.337	0.862, 2.073	0.194	1.152	0.736, 1.802	0.536 ^m	-	-	-
Eye									
Right	Ref								
Left	1.134	0.908, 1.416	0.267	-	-	-	-	-	-
Dwelling									
Urban	Ref								
Rural	0.854	0.487, 1.497	0.581	-	-	-	-	-	-
Smoking status									
Never	Ref								

Ever	0.918	0.592, 1.424	0.703	-	-	-	-	-	-
Ex-smoker	Ref								
Current	0.520	0.239, 1.128	0.098	-	-	-	-	-	-
Never	Ref								
Current	0.646	-0.154, 1.445	0.114	-	-	-	-	-	-
Sibling history of glaucoma									
No	Ref								
Yes	3.325	1.512, 7.311	0.003	2.986	1.358, 6.565	0.006ⁿ	-	-	-
Number of falls in past year									
<2	Ref								
≥2	1.617	0.685, 3.814	0.273	-	-	-	-	-	-
Educational attainment									
None or primary incomplete	Ref								
Primary equivalent	1.001	0.253, 3.966	0.998	-	-	-	-	-	-
GCSE equivalent	0.882	0.247, 3.144	0.847	-	-	-	-	-	-
A level equivalent	1.287	0.329, 5.032	0.716	-	-	-	-	-	-
Diploma certificate equivalent	1.229	0.336, 4.489	0.756	-	-	-	-	-	-
Primary degree	0.854	0.208, 3.500	0.826	-	-	-	-	-	-

Postgraduate degree	0.880	0.225, 3.436	0.854	-	-	-	-	-	-
Hypertension	1.400	0.882, 2.222	0.154	-	-	-	-	-	-
Diabetes Mellitus	1.357	0.751, 2.450	0.312	-	-	-	-	-	-
High cholesterol	1.137	0.714, 1.811	0.589	-	-	-	-	-	-
Parkinson's disease	1.387	0.193, 9.962	0.745	-	-	-	-	-	-
Cardiovascular disease (self-reported angina or MI)	1.504	0.962, 2.350	0.073	-	-	-	-	-	-
Cerebrovascular disease (self-reported stroke or TIA)	2.699	1.286, 5.664	0.009	1.673	0.745, 3.758	0.212	-	-	-
Cataract surgery	2.605	1.335, 5.084	0.005	1.820	0.879, 3.768	0.107	-	-	-
BMI									
Underweight (<18.5)	a	a	a	-	-	-	-	-	-
Normal (18.5-24.9)	Ref								
Overweight (25-29.9)	1.043	0.578, 1.882	0.889	-	-	-	-	-	-
Obese (≥30)	1.002	0.541, 1.855	0.994	-	-	-	-	-	-
Height (per cm)	1.004	0.979, 1.029	0.769	-	-	-	-	-	-
Weight (per kg)	0.998	0.984, 1.012	0.776	-	-	-	-	-	-
Waist (per cm)	1.006	0.991, 1.022	0.434	-	-	-	-	-	-

Waist / hip ratio	5.959	0.445, 79.783	0.178	-	-	-	-	-	-
Hypertension stages									
Normal	Ref								
Elevated	1.073	0.445, 2.584	0.876	-	-	-	-	-	-
Stage 1	1.145	0.618, 2.122	0.668	-	-	-	-	-	-
Stage 2	1.086	0.598, 1.971	0.786	-	-	-	-	-	-
Spherical equivalent (per dioptr)	0.906	0.853, 0.962	0.001	0.868	0.816, 0.924	<0.001 ⁿ	0.885	0.827, 0.948	<0.001
Refractive error									
> -0.5 D	Ref								
-4.99 D to -0.5 D	1.487	0.882, 2.508	0.137	1.672	0.985, 2.839	0.057	-	-	-
≤ -5 D	2.936	1.316, 6.553	0.009	4.806	2.142, 10.781	<0.001	-	-	-
Plasma cholesterol (per mmol/L)	0.768	0.644, 0.916	0.003	0.914	0.757, 1.103	0.347	-	-	-
Plasma HDL (per mg/L)	0.993	0.980, 1.006	0.306	-	-	-	-	-	-
Plasma LDL (per mg/L)	0.991	0.985, 0.997	0.005	0.997	0.991, 1.003	0.373	-	-	-
Plasma triglycerides (per mg/L)	0.998	0.994, 1.001	0.216	-	-	-	-	-	-
Lipid lowering drugs	1.528	0.980, 2.383	0.062	-	-	-	-	-	-

Antihypertensive drugs	2.231	0.762, 6.535	0.143	-	-	-	-	-	-
Calcium channel blockers	1.005	0.346, 2.916	0.993	-	-	-	-	-	-
Beta-blocker drugs	1.731	1.009, 2.971	0.046	1.204	0.696, 2.083	0.507	-	-	-
Renin-angiotensin system drugs	1.243	0.773, 1.998	0.369	-	-	-	-	-	-
Anti-Parkinsonian drugs	1.571	0.219, 11.277	0.654	-	-	-	-	-	-
Heart rate	0.991	0.972, 1.010	0.338	-	-	-	-	-	-
Systolic blood pressure (per mmHg)	1.004	0.993, 1.015	0.472	-	-	-	-	-	-
Diastolic blood pressure (per mmHg)	0.995	0.971, 1.019	0.662	-	-	-	-	-	-
IOPg (per mmHg)	1.150	1.094, 1.209	<0.001	1.162	1.100, 1.228	<0.001 ⁿ	1.151	1.074, 1.234	<0.001
IOPcc (per mmHg)	1.204	1.143, 1.269	<0.001	1.199	1.131, 1.272	<0.001	-	-	-
CH (per mmHg)	0.584	0.494, 0.689	<0.001	0.650	0.547, 0.773	<0.001 ⁿ	0.726	0.602, 0.876	<0.001
CRF (per mmHg)	0.911	0.781, 1.061	0.231	-	-	-	-	-	-
Mean OPP									
1 st Quartile	1.274	0.680, 2.388	0.450	-	-	-	-	-	-
2 nd Quartile	1.210	0.642, 2.281	0.555	-	-	-	-	-	-

3 rd Quartile	1.069	0.570, 2.003	0.836	-	-	-	-	-	-
4 th Quartile	Ref								
Systolic OPP									
1 st Quartile	0.950	0.516, 1.749	0.869	-	-	-	-	-	-
2 nd Quartile	0.783	0.403, 1.504	0.462	-	-	-	-	-	-
3 rd Quartile	1.071	0.585, 1.959	0.824	-	-	-	-	-	-
4 th Quartile	Ref								
Diastolic OPP									
1 st Quartile	1.335	0.744, 2.395	0.333	-	-	-	-	-	-
2 nd Quartile	1.226	0.682, 2.206	0.495	-	-	-	-	-	-
3 rd Quartile	0.526	0.206, 1.064	0.074	-	-	-	-	-	-
4 th Quartile	Ref								
NEI-VFQ 9									
Composite score	1.043	0.984, 1.106	0.152	-	-	-	-	-	-
Question 1 Scale ^b	1.152	0.758, 1.750	0.509	-	-	-	-	-	-
Question 2 Scale ^c	1.401	1.086, 1.808	0.009	1.153	1.202, 1.980	0.001 ⁿ	1.535	1.158, 2.033	0.003
Question 3 Scale ^d	1.166	0.875, 1.554	0.295	-	-	-	-	-	-

Question 4 Scale ^e	1.064	0.752, 1.506	0.727	-	-	-	-	-	-
Question 5 Scale ^f	1.675	1.273, 2.204	<0.001	1.494	1.091, 2.046	0.012	-	-	-
Question 6 Scale ^g	1.208	0.725, 2.013	0.469	-	-	-	-	-	-
Question 7 Scale ^h	1.213	0.997, 1.475	0.054	-	-	-	-	-	-
Question 8 Scale ⁱ	1.435	1.019, 2.021	0.039	1.340	0.893, 2.010	0.157	-	-	-
Question 9 Scale ^j	1.694	1.206, 2.380	0.002	1.555	1.074, 2.251	0.019	-	-	-
CES-D Depression Scale	1.010	0.983, 1.038	0.483	-	-	-	-	-	-
Visits to optician in past 12 months									
None	Ref								
≥1 visit	1.324	0.827, 2.121	0.243	-	-	-	-	-	-
Overall income deprivation domain score	1.376	0.294, 6.430	0.685	-	-	-	-	-	-
Mean global cRNFL thickness (per µm increase)	0.872	0.854, 0.890	<0.001	0.875	0.858, 0.893	<0.001	-	-	-

a - Insufficient number of participants with BMI <18.5, b - At the present time would you say your eyesight is __1) excellent, 2) good, 3) fair, 4) poor, and 5) completely blind., c - How much time do you worry about your eyesight?, d - How much difficulty do you have reading ordinary print newspaper?, e - How much difficulty do you have doing work or hobbies that require you to see well up close such as cooking, sewing, fixing things around the house or using hand tools?, f - Because of your eyesight how much difficulty do

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3 you have going down steps, stairs or curbs in dim light or at night?, g - How much difficulty do you have driving during daytime in
4 familiar places?, h - Are you limited in how long you can walk or other activities such as housework, childcare, school or community
5 activities because of your eyesight?, i - Because of your eyesight how much difficulty do you have noticing objects off to the side
6 while you are walking along?, j - Because of your eyesight how much difficulty do you have finding something off a crowded shelf?,
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8 k - Age and sex adjusted model, l - adjusted by Sex, m - adjusted by Age at ISGEO classification, n - Variables which were entered
9 into the multivariate model for stepwise regression, o - Fully adjusted model, OR - odds ratio, 95%CI - 95% confidence interval
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DISCUSSION

The NICOLA study is a population-based longitudinal study of ageing in Northern Ireland. In this study we investigated the prevalence of, awareness of and determinants of glaucoma. We found that glaucoma was prevalent in 2.83% (95%CI 2.31%, 3.46%) of the population aged 50 years and older (crude prevalence). The population age-weighted prevalence was 3.19% (95%CI 2.55, 3.97) for the 2011 population census and 3.24% (95%CI 2.59, 4.04) for the 2017 population projection. Age-stratified crude prevalence showed that prevalence increased from 1.13% (95%CI 0.64, 1.97) in the 50-59 year old age group to 9.60% (95%CI 6.03, 14.95) in the 80+ age group. Our results are comparable to pooled estimations of glaucoma prevalence in European populations in the age range 40 – 80 years (2.93%, 95%CI 1.85%, 4.40%).⁵

The NICOLA study provides a further estimation of glaucoma prevalence within a European population. There have been few other studies of European populations that have reported the prevalence of glaucoma using ISGEO definitions. Recently, the Gutenberg Health Study reported that the prevalence of glaucoma (of all sub-types) was 1.44%, however the population included, spanned an age range from 35 to 74 years which is considerably younger than the present study. The EPIC-Norfolk eye study, which used a multistage clinical assessment, reported that the prevalence of glaucoma (of all sub-types) was 4.2% (95%CI 3.8%, 4.6%) in a sample of 8,623 participants aged 48-92 years in Norfolk, England.¹⁴ This is somewhat higher than the population age-weighted prevalence of 3.19% that we observed in NICOLA. The reasons for the difference in prevalence between NICOLA and EPIC-Norfolk eye study may be due to differences in methodology or population factors. Furthermore, it represented a third wave (second wave follow up) study of the EPIC cohort which

may have been subject to attrition and selection bias. The Reykjavik eye study reported the prevalence of glaucoma (OAG including pseudoexfoliation glaucoma) to be 4.0% in participants aged 50 years and older however it had a relatively small sample of 1,045 participants.⁸ The ALIENOR study reported the prevalence of glaucoma (OAG) to be 4.8% in 944 French subjects however it only investigated participants aged 73 years and older.¹⁵

The UK-Biobank study which enrolled participants aged 40 to 69 years, had a prevalence of 1.7% based on self-report and those reporting glaucoma were more likely to be older and male.¹⁶ The findings of the UK-Biobank study are unlikely to be a true representation of glaucoma prevalence due to recall bias. Furthermore the response rate for the UK Biobank study was low (5.5%) which is likely to impact on its representativeness of the general population.

The prevalence of glaucoma in US populations of predominantly white ethnicity has been reported to range between 1.29% to 2.1%,^{17–22} however comparisons with these studies that were conducted several decades ago is confounded as the definition of glaucoma has evolved.^{19,20,22} It is recognised that even minor differences in the definition of glaucoma can cause wide variations in prevalence estimates.²³ While there are contemporary US-based studies, these have used monoscopic optic disc photographs without full-threshold visual field testing for the diagnosis for glaucoma making direct comparisons with this study difficult.^{18,21}

It is recognised that 50% of prevalent glaucoma is undiagnosed.^{24,25} In the NICOLA study two thirds of those with glaucoma were unaware of having the disease. This is a substantial level of under-ascertainment of glaucoma given the investment in primary eye care by the UK NHS, which provides free regular eye examinations to all

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people over 60 years of age, and also to people over 40 with family history of glaucoma. Our findings are consistent with those of the National Health and Nutrition Examination Survey (NHANES) 2005 – 2008 study in which 78% were previously undiagnosed²¹ and those of the Thessaloniki Eye Study where 57.1% and 34.9% of participants with POAG and pseudoexfoliation glaucoma respectively were previously undiagnosed.²⁶ Similarly in the Singapore Epidemiology of Eye Diseases Study 72.1% of participants with primary glaucoma, were previously undiagnosed.²⁷ The EPIC-Norfolk eye study reported that, of those who received a diagnosis of glaucoma, only 33.3% were previously unknown. It is unlikely that the difference in known glaucoma in the EPIC-Norfolk eye study compared to NICOLA was due to access to healthcare among participants, as the UK has a similar health care system. Differences may have arisen due to differences in sampling strategies as the EPIC-Norfolk eye study recruited participants with less deprivation than the general population.

The association analysis that we undertook revealed that the odds of glaucoma was greater with increased age, myopic decrease in spherical equivalent, increased IOP and decreased CH. These findings are consistent with other study findings and current understanding of the disease. Glaucoma was not associated with gender in this study. Most glaucoma studies have identified a higher risk in men. Tham et al found an association with POAG²⁸ and EPIC-Norfolk eye study observed a higher prevalence of glaucoma (of all sub-types) in males (5.2%) compared to females (3.4%).¹⁴ In the Korean National Health and Nutrition Examination Survey (KHANES) 2008 – 2011, male gender was associated with increased odds of glaucoma (OR 1.51, 95%CI 1.25, 1.83).²⁹

An interesting finding in NICOLA was the higher odds of glaucoma after adjustment for age and sex with thinner mean global cRNFL thickness. Mean global cRNFL thickness was not entered into the final multivariable model due to significant collinearity with multiple other covariates associated with glaucoma. However additional risk factor models for cRNFL thickness are being constructed for reporting in future publications.

The NEI VFQ 9 has shown to have high reliability and validity regarding clinical measures of eye disease.³⁰ We did not find an association between glaucoma diagnosis and NEI VFQ 9 composite score, however we observed an association with increased subscale score on question 2 (How much time do you worry about your eyesight?). NHANES 2005 – 2008 study also reported that glaucoma was not associated the NEI VFQ 9 composite score but they reported that glaucoma was associated with lower peripheral vision and distance vision subscale scores.³¹

We did not find an association between glaucoma and diabetes, hypertension, cerebrovascular disease, high cholesterol, systemic medication use, blood pressure or ocular perfusion pressure in the final multivariable model. These results are in agreement with some epidemiological studies but do not accord with others.^{32–36}

Future analyses which incorporate electronic health record linkage may give a clearer estimation of associations between medical history, systemic medication use and glaucoma in the NICOLA study.

Overall income deprivation was not associated with glaucoma. Previous hospital-based studies have reported that deprivation was significantly associated with late presentation of glaucoma.^{9,37} The UK Biobank Study reported that self-reported glaucoma was associated with a higher mean Townsend deprivation index which

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indicates higher relative deprivation among those with self-reported glaucoma.³⁸ We did not find that glaucoma was associated with ≥ 2 falls in the past year. This contrasts with findings from the Blue Mountains Eye Study and the Singapore Malay Eye study which found increased likelihood of falling in glaucoma.^{39,40}

Our study has a number of strength and weaknesses. It is one of the few European population-based studies to estimate glaucoma prevalence using the ISGEO definition and can therefore be used to make meaningful comparisons of glaucoma prevalence with other populations which also used ISGEO definition.^{14,41} The use of stereophotography to detect glaucomatous optic neuropathy in NICOLA is a major strength of the study compared to other modern studies which used non-stereoscopic optic disc pictures.^{7,18} Further strengths of the NICOLA study include the sampling strategy, large sample size, detailed ophthalmic phenotyping, meticulous ophthalmic data quality assurance, and the wide-ranging collection of sociodemographic and health related data.

Our study suffers from limitations and most notably, the rate of non-response at different levels of the recruitment process of the NICOLA study may have impacted on the generalizability of our results. The response rate for the NICOLA study was 63% however this is similar to other population-based studies from other countries.⁴² There were many statistically significant differences between excluded and included participants in our analysis of the NICOLA cohort and therefore the included participants are not representative of the cohort as a whole. Nonetheless our systematic sampling strategy and the population-based age-weighting are mitigating factors in the estimate of prevalence rates. Because the sample size in the NICOLA study was sufficiently large, we contend that the observed epidemiological associations are valid.⁴³

Another limitation in NICOLA was the exclusion by individuals who were institutionalised therefore selection bias was introduced against the population who reside in nursing homes and other institutional accommodation who may be at risk of developing glaucoma due to their age and demographic profile.

Our study classified a relatively high number of participants as glaucoma using the ISGEO category 2 criteria (43%, 39 / 91) in comparison to other studies.⁴⁴ There was the potential for misclassification of large and anomalous discs as glaucomatous and for small glaucomatous optic discs to have gone undetected in this study. However a process of systematic adjudication with multiple measurements made of discs with VCDR ≥ 0.41 aimed to reduce that possibility. Furthermore we used stereophotography which helps avoid misclassification of optic discs. Other studies have corrected VCDR measurements for disc size however this was not possible in the NICOLA study because biometry and keratometry data, which are required to calculate disc size on stereophotography, were not collected on NICOLA participants.^{41,45} In the NICOLA study it is possible that some of the included participants had stereophotographs missing for the 1 eye which was glaucomatous and this may have led to underestimation of the prevalence. We expect the impact of this limitation to be small.

A full description of the mechanisms of all glaucoma cases were not possible in this study because we were only able to enumerate primary and secondary open and closed angle glaucoma in the subgroup of 128 participants who attended for a full clinical examination. Therefore we are only able to reliably report the prevalence of glaucoma as a whole and are unable to comment on the prevalence of the respective subtypes of glaucoma in the NICOLA cohort. We did report that 31 participants had severe glaucoma in at least one eye. Further analysis of this data

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could investigate how many of these severe glaucoma cases were previously undiagnosed and the factors associated with severe glaucoma and the timeliness of its presentation. Previous studies have reported that socioeconomic deprivation is associated with more advanced glaucoma at presentation in newly diagnosed glaucoma patients.⁹

Although we were unable to perform perimetry on all participants it was performed in a subgroup of participants to confirm ISGEO category 1 classification of glaucoma. Similar methods to identify which participants should undergo perimetry have been used by other glaucoma prevalence studies,^{7,8,27,44} and it is likely that these provide higher quality evidence of glaucoma than studies which rely on only optic discs for all participants.¹⁸ Using perimetry in only a subset of participants, however, may be considered a weakness of the study. However, it is unlikely that performing visual field tests on a full-cohort of perimetry naïve participants would be an optimal method of detecting glaucoma.⁴⁶ The use of ORA rather than GAT in the whole NICOLA population could be regarded as a potential weakness of the study because ORA IOP is not the current clinical reference standard, although ORA is less dependent on the skills of the examiner. Several population-based cohort studies including the EPIC-Norfolk eye study and UK Biobank study have used ORA tonometry.⁴⁷

Although the ISGEO definition of glaucoma is a recognised international standard, it has several limitations. Vertical cup to disc ratios are a sensitive and simple quantitative anatomical indicator of glaucoma however, they are dependent on the size of the optic disc and have been reported to range from 0.00 to 0.85 in normal white populations.⁴⁸ The use of percentile cut-offs to define glaucomatous optic neuropathy and glaucoma, could therefore lead to high numbers of false-negatives in

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3 small optic discs and high numbers of false-positives in large optic discs.⁴⁹ We have
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5 tried to mitigate this limitation by re-grading all discs with VCDR ≥ 0.41 .
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9 Currently the ISGEO criteria do not consider the additive value of modern imaging
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11 technologies such as SD-OCT to support the definitions. There are currently ongoing
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13 efforts to update the definition of glaucoma and the rich resource of data collected in
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15 the NICOLA study could be used to validate any new definitions.⁵⁰
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19 In summary, the NICOLA study is a population-based cohort study of ageing which
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21 provided detailed ophthalmic and glaucoma related phenotyping data. The estimated
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23 crude prevalence of glaucoma is 2.83% in the Northern Ireland population which is in
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25 agreement with pooled estimations of disease burden in European populations. Two
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27 thirds of people aged ≥ 50 years old were unaware of having a diagnosis of
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29 glaucoma. These results have implications for implementation of primary health
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31 promotion and healthcare policy planning for glaucoma in the UK setting.
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Figure Legends

Figure 1. NICOLA glaucoma prevalence study flowchart. 8,504 participants were recruited to NICOLA and had Computerised Assisted Personal Interview (CAPI). 8,265 were included in the CAPI analysis. 3,221 had vertical cup to disc ratio

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measurement in ≥ 1 eye and comprised the denominator for the prevalence estimate. 229 participants met the initial inclusion criteria for invitation to visual field testing and glaucoma expert review. 49 participants were excluded from invitation to visual field testing and glaucoma expert review and 180 participants were sent an invitation. 52 participants declined invitation for visual field testing and glaucoma expert review and 128 participants attended. 52 participants were diagnosed with glaucoma according to ISGEO 1 and 39 were diagnosed with glaucoma according to ISGEO 2.

Figure 2. Age-stratified (crude) prevalence of glaucoma. Bars – 95% confidence interval

Figure 1

Figure 2

198x116mm (300 x 300 DPI)

SUPPLEMENTARY MATERIAL

Supplementary Methods 1

Ophthalmic history: Self-reported ophthalmic history was elicited from participants during the health assessment and included diagnoses of glaucoma, age related macular degeneration, cataract and diabetic retinopathy. Frequency of utilisation of optometry in the community during the previous year and history of cataract surgery in either eye were also documented.

Visual acuity (VA): VA was evaluated using mounted retro-illuminated Early Treatment Diabetic Retinopathy Study (ETDRS) LogMAR (Logarithm of the Minimum Angle of Resolution) charts for each eye in full room lighting conditions.

Refractive error: was measured in each eye as a mean of three readings using a Shin Nippon Accuref-K 900 autorefractor (Rexxam Co. Ltd., Osaka, Japan) without routine cycloplegia. Spherical equivalent (SE) was calculated as the spherical correction plus half the cylindrical power.

Ocular Response Analyser (ORA; Reichert Ophthalmic Instruments Inc, Depew, New York, USA), was used to measure the intraocular pressure (IOP) and ocular biomechanical measurements for each eye. Three measurements were taken for each eye and a maximum of five measurements were attempted for each eye. The following values were recorded at each measurement: Goldmann-correlated IOP (IOPg), corneal compensated IOP (IOPcc), corneal resistance factor (CRF), corneal hysteresis (CH), waveform score (WFS) and the date and time of the measurement.

Pupils were dilated using tropicamide 1% eye drops

Retinal stereophotography: Digital 45° colour fundus sequential stereo paired photographs centred on the optic disc were taken for each eye using a digital retinal camera (Canon CX-1, Tokyo, Japan).

Spectral-domain optical coherence tomography (SD-OCT): Spectralis Heidelberg Retina Angiograph + Optical Coherence Tomography (HRA+OCT; Heidelberg Engineering, Heidelberg, Germany) was used to obtain optic disc images which allows for circumpapillary retinal nerve fibre layer (cRNFL) thickness measurement. Each cRNFL image acquisition was manually centered on the optic disc and the following conditions were used: resolution mode: high speed; c-curve: 7.7 mm; circle diameter: 12° (fixed); size X: 768 pixels; size Z: 496 pixels; and Automatic Real Time function (ART) mode: 100 images averaged; acquisition software versions 5.10.20 to 6.7.21.0. The cRNFL thickness was automatically segmented using Heidelberg Eye Explorer (HEYEX) software.

Spectralis HRA+OCT was used to acquire macular scans with Early Treatment Diabetic Retinopathy Study (ETDRS) and Posterior Pole Asymmetry Analysis (PPAA) maps and the following conditions were used: resolution mode: high speed; c-curve: 7.7 mm; scan pattern size: 30.0° x 25.0°; size X: 768 pixels; size Z: 496 pixels; ART mode: 9 images averaged; number of B-scans: 61; AQM versions 5.10.20 to 6.7.21.0. All SD-OCT scans were acquired by trained research nursing staff and assistants. Using the HEYEX software each of the 61 raster B-scans were automatically segmented into the following segment lines: Inner Limiting Membrane (ILM), Retinal Nerve Fibre Layer (RNFL), Ganglion Cell Layer (GCL), Inner Plexiform Layer (IPL), Inner Nuclear Layer (INL), Outer Plexiform Layer (OPL), External Limiting Membrane (ELM), Photoreceptors 1 (PR1), Photoreceptors 2 (PR2), Retinal Pigment Epithelium (RPE), Bruch's Membrane (BM).

NICOLA Study image grading and quality assurance

SD-OCT cRNFL Scan Analysis: The cRNFL thickness was automatically segmented using HEYEX software. Each cRNFL scan was inspected for quality assurance purposes. Scans with minor segmentation errors were adjusted manually using the HEYEX software functions when possible. Scans judged to have significant artefact (cropped cRNFL; not centred on optic disc) or be grossly abnormal (significant vitreoretinal traction, hyporeflective intraretinal spaces, epiretinal membrane) were excluded from analysis. Fovea disc (FoDi) alignment was adjusted post acquisition if required. A proprietary measure of scan quality (Q) ≥ 15 was considered acceptable as per the manufacturer's recommendations. Global and sectoral raw values and classifications were automatically exported.

SD-OCT ETDRS and PPAA Scan Analysis: Each of the 61 raster B-scans for each eye was reviewed by a group of trained graders and segmentation errors were manually corrected using the HEYEX software functions when possible. Macular scans which included raster B-scans with gross abnormalities (significant vitreoretinal traction, hyporeflective intraretinal spaces, epiretinal membrane) or poor segmentation which could not be corrected manually were excluded if these abnormalities were judged to render the average thickness of the overall macular scan unreliable.

Cardiovascular and anthropometric tests were performed: Two brachial blood pressure and heart rate readings were recorded at room temperature whilst seated using the M10-IT blood pressure monitor (OMRON™, Hoofddorp, The Netherlands) and the mean heart rate, mean systolic and mean diastolic blood pressure results were calculated. Body height was measured using the Seca 240 wall mounted

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measuring rod (Seca, Birmingham, UK). Weight was measured using electronic floor scales (Seca, Birmingham, UK). Waist and hip measurements were recorded using measuring tape (SECA, Birmingham, UK) when possible, excluding participants who were wheelchair bound or unable to stand. Ocular perfusion pressure ($\frac{2}{3}$ (mean arterial BP – IOP)), mean arterial pressure (diastolic BP + $\frac{1}{3}$ (systolic BP – diastolic BP)), systolic ocular perfusion pressure (systolic BP – IOP), diastolic ocular perfusion pressure (diastolic BP – IOP), waist / hip ratio and body mass index (BMI; weight (kg) / height (m²)) were calculated from available raw data.

Cognitive and psychiatric assessments: Mini-mental state examination (MMSE) and Montreal Cognitive Assessment (MCoA) were performed by the participant to assess cognitive function. Mood was assessed using the Centre for Epidemiological Studies Depression scale (CES-D).

Blood tests: Blood samples were taken for total cholesterol levels, direct low density lipoprotein (LDL), high density lipoprotein (HDL)-cholesterol, triglycerides and genotyping.

Supplementary Methods 2

Primary grading was performed by trained graders at the Network of Ophthalmic Grading Centres UK (NetwORC UK). All graders measured the vertical cup to disc ratio (VCDR) using stereo viewers, Oculab image management software (Oculab V 3.7.98.0, Digital Healthcare, Cambridge, UK). Primary graders were also instructed to record presence of abnormalities including presence of disc haemorrhages, inferior neuroretinal rim thinning and notching. Due to the subjectivity in identifying optic disc features and estimating VCDR, a series of agreement studies and a systematic adjudication process was performed following initial grading by primary graders. Details of the agreement studies and adjudication process are described below.

Agreement analysis A: A sample of primary graders' gradings from participants that had at least 1 eye with VCDR ≥ 0.6 and/or VCDR asymmetry ≥ 0.2 and/or disc haemorrhages and/or neuroretinal rim thinning or notching, were re-graded (including fellow eyes) by a glaucoma expert (SPB) between 1st September 2016 to 30th November 2016. Inter-rater agreement analysis was performed between the glaucoma expert and the primary graders using Bland-Altman methods in 690 eyes (from 354 participants). The 95% limits of agreement (LoA) between primary graders and the glaucoma expert (SPB) were -0.32 (95% confidence interval (95%CI) -0.34, -0.31) to 0.22 (95%CI 0.21, 0.24) with a statistically significant mean bias of -0.05 (95%CI -0.06, -0.04). In 16.5% of cases the inter-rater agreement between primary graders and the glaucoma expert (SPB) showed ≥ 0.20 difference.

Agreement analysis B: The same sample of primary graders' gradings (690 eyes from 354 participants) were also re-graded (including fellow eyes) by an experienced

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grader (PMcC) and inter-rater agreement analysis was performed between the experienced grader and glaucoma expert (SPB). The 95% LoA between the experienced grader and the glaucoma expert were -0.248 (95%CI -0.255, -0.241) to 0.134 (95%CI 0.126, 0.141) with a statistically significant mean bias of -0.057 (95%CI -0.0646, -0.0500). In 10.0% of cases the inter-rater agreement between the experienced grader and the glaucoma expert (SPB) showed ≥ 0.20 difference

Agreement analysis C: A glaucoma expert (AAB) graded a random sample of 27 optic discs from 27 participants with VCDR ≥ 0.2 and inter-rater agreement analysis was performed between two glaucoma experts (SPB and AAB). The 95% LoA between the two glaucoma experts) were -0.12 (95%CI -0.17, -0.08) to 0.15 (95%CI 0.10, 0.19) with a mean bias of 0.013 (95%CI -0.014, 0.041) which was not statistically significant. There were no cases which showed ≥ 0.20 difference in inter-rater agreement between the two glaucoma experts.

Following agreement analysis and, to account for the potential for VCDR measurements by the primary graders to disagree with the glaucoma expert (SPB) by up to 0.29 (mean bias of -0.05 to upper 95% confidence limit of the upper LOA of 0.24 equals 0.29), all VCDRs graded 0.5 – 0.6 by the primary graders were re-graded by the experienced grader (PMcC), who determined the final grading and, optic discs graded 0.41 – 0.5 by primary graders were inspected for obvious signs of glaucoma by the experienced grader and only if features of glaucomatous optic neuropathy were suspected, the VCDR was re-graded by the experienced grader. The lower limit of 0.41 was selected because it is 0.29 less than 0.7 (VCDR ≥ 0.7 was a criteria for invitation for visual field testing).

Supplementary Methods 3

Independent variables in the multivariable association analysis with glaucoma

Age at ISGEO classification (continuous and categorical)
Sex
Habitation (urban versus rural)
Education attainment level (highest qualification attained)
Smoking status (ex-smoker versus current smoker) and
Smoking status (ever versus never)
Smoking status (current versus never)
Diabetes mellitus (self-reported history of diabetes or random glucose $\geq$ 11.1 mmol/L or HbA1c $\geq$ 6.5% or the use of antidiabetic medication)
Hypertension (self-reported history of high blood pressure or systolic blood pressure $\geq$ 140 mmHg or diastolic blood pressure $\geq$ 90 mmHg or use of antihypertensive medication)
High cholesterol (self-reported history of high cholesterol or total cholesterol $\geq$ 6.2 mmol/L or the use of lipid lowering medication)
Cardiovascular disease (self-reported angina or heart attack)
Cerebrovascular disease (self-reported stroke or transient ischaemic attack)
Parkinson's disease (self-report or use of anti-Parkinsonian medication)
Cataract surgery (self-report; right eye or left eye or both eyes)
Body mass index (BMI)
Height (m)
Weight (kg)
Waist (cm)
Waist / hip ratio
Spherical equivalent
Refractive error (categorical)
Goldmann correlated IOP (IOPg)
Corneal compensated IOP (IOPcc)
Corneal hysteresis (CH)
Corneal resistance factor (CRF)
Mean ocular perfusion pressure (MOPP)
Systolic ocular perfusion pressure (SOPP)
Diastolic ocular perfusion pressure (DOPP)
Mean arterial pressure (MAP)
Systolic blood pressure (SBP)
Diastolic blood pressure (DBP)
Heart rate
American College of Cardiology / American Heart Association (ACC/AHA) hypertension stages
Sibling history of glaucoma
Number of falls in past 12 months
Income domain deprivation score
Plasma total cholesterol levels
Plasma direct low density lipoprotein (LDL)
Plasma high density lipoprotein (HDL)-cholesterol

Plasma triglycerides
Centre for Epidemiological Studies score for depression (CES-D)
National Eye Institute Visual Function Questionnaire 9 (NEI VFQ 9; composite and subscale scores)
Visits to optician in past 12 months
Overall income deprivation domain score
Mean global cRNFL thickness
Anatomical Therapeutic Chemical classifications: anti-Parkinsonian drugs (ATC N04), lipid lowering drugs (ATC C10), antihypertensive drugs (ATC C02), calcium channel blockers (ATC C08), beta blocker drugs (ATC C07) and renin-angiotensin system drugs (ATC C09)

Supplementary Table S1. Computer assisted personal interview (CAPI) questions (Variables).

CAPI Variable (Question)	CAPI Response Options
Is this dwelling located	In Belfast city
	A city or town in Northern Ireland other than Belfast
	In a rural part of Northern Ireland
Is the respondent male or female?	Male
	Female
In which year were you born?	19__
What is the highest level of education you have completed?	Some primary (not complete)
	Primary or equivalent
	GCSE / O-level / Intermediate / junior / group certificate or equivalent
	A-level / Leaving certificate or equivalent
	Diploma / certificate
	Undergraduate Primary degree
	Postgraduate/higher degree
	None
	Refused
Have any of your brothers or sisters ever suffered from any of the following eye diseases?	Cataract
	Macular Degeneration
	Glaucoma
	Diabetic related Eye Disease
	None of the above
	Do not know
Has a doctor ever told you that you have any of the following conditions?	Prefer not to answer
	High blood pressure or hypertension
	Angina
	A heart attack (including myocardial infarction or coronary thrombosis)
	Congestive heart failure
	Diabetes or high blood sugar
	A stroke (cerebral vascular disease)
	Mini-stroke or TIA
	High cholesterol
	A heart murmur
	Atrial fibrillation
	Abnormal heart rhythm (not atrial fibrillation)
	Any other heart trouble (specify)
	None of these
	Don't Know
	Refused

Has a doctor ever told you that you have any of the following conditions?	Chronic lung disease such as chronic bronchitis or emphysema
	Asthma
	Arthritis (including osteoarthritis, or rheumatism)
	Osteoporosis, sometimes called thin or brittle bones
	Cancer or a malignant tumour (including leukaemia or lymphoma but excluding minor skin cancers)
	Parkinson's disease
	Any emotional, nervous or psychiatric problems such as depression or anxiety
	Alcohol abuse
	Substance abuse
	Alzheimer's disease
	Dementia
	Serious memory impairment
	Stomach ulcers
	Varicose Ulcers (an ulcer due to varicose veins)
	Cirrhosis, or serious liver damage
How many times have you fallen in the last year?	None of these
	Don't Know
	Refused
Have you ever smoked cigarettes, cigars, cigarillos or a pipe daily for a period of at least one year?	—
	Yes
	No
	Don't know
Do you smoke at the present time?	Refused
	Yes (in the past 3 months)
	No, I have stopped
	Don't know
Medication history	Refused
	Anatomical Therapeutic Chemical (ATC) classification
Overall income deprivation domain score	Proportion of population experiencing income deprivation in an area (super output area)
House value	—

Supplementary Table S2. NEI VFQ 9 Questions

Q1	At the present time would you say your eyesight is ____
Q2	How much time do you worry about your eyesight?
Q3	How much difficulty do you have reading ordinary print newspaper?
Q4	How much difficulty do you have doing work or hobbies that require you to see well up close such as cooking, sewing, fixing things around the house or using hand tools?
Q5	Because of your eyesight how much difficulty do you have going down steps, stairs or curbs in dim light or at night?
Q6	How much difficulty do you have driving during daytime in familiar places?
Q7	Are you limited in how long you can walk or other activities such as housework, childcare, school or community activities because of your eyesight?
Q8	Because of your eyesight how much difficulty do you have noticing objects off to the side while you are walking along?
Q9	Because of your eyesight how much difficulty do you have finding something off a crowded shelf?

The scale for question 1 was, 1) excellent, 2) good, 3) fair, 4) poor, and 5) completely blind. The scales for questions 2 to 9 were, 1) no difficulty, 2) a little difficulty, 3) moderate difficulty, 4) extreme difficulty, and 5) stopped doing because of eyesight. The option 'stopped doing for other reasons' was also available for several subscales.

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Supplementary Table S3. International Society Geographical and Epidemiological Ophthalmology (ISGEO) criteria – Diagnosis of glaucoma and glaucoma related findings in cross sectional prevalence surveys

ISGEO category 1 diagnosis (structural and functional evidence)	Eyes with a cup to disc ratio (CDR) or CDR asymmetry ≥ 97.5 th percentile for the normal population (≥ 0.7), or a neuroretinal rim width reduced to ≤ 0.1 CDR (between 11 to 1 o'clock or 5 to 7 o'clock) that also showed a definite visual field defect consistent with glaucoma (see footnote).
ISGEO category 2 diagnosis (advanced structural damage with unproved field loss)	If the subject could not satisfactorily complete visual field testing but had a CDR or CDR asymmetry ≥ 99.5 th percentile for the normal population (≥ 0.8), glaucoma was diagnosed solely on the structural evidence.
ISGEO category 3 diagnosis (Optic disc not seen. Field test impossible)	If it is not possible to examine the optic disc, glaucoma is diagnosed if: (A) The visual acuity $< 3/60$ and the IOP > 99.5 th percentile, or (B) The visual acuity $< 3/60$ and the eye shows evidence of glaucoma filtering surgery, or medical records were available confirming glaucomatous visual morbidity.
Disc suspects	Those who met ISGEO 1 criteria for disc parameters but were not found to have visual field defects.
Ocular hypertension	Those with an IOP > 21 mmHg.
Footnote: In diagnosing category 1 or 2 glaucoma, there should be no alternative explanation for CDR findings (dysplastic disc or marked anisometropia) or the visual field defect (retinal vascular disease, macular degeneration, or cerebrovascular disease). Gold standard of glaucomatous visual field loss – glaucoma hemifield test graded “outside normal limits”, a cluster of three contiguous points at the 5% level on the pattern deviation plot, using the threshold test strategy with the 24-2 test pattern of the Zeiss-Humphrey field analyser 2 (not the only acceptable tool for field analysis).	

Supplementary Table S4. Number of missing measurements for vertical cup to disc ratio, Goldman correlated intraocular pressure (IOPg) and circumpapillary retinal nerve fibre layer (cRNFL) among the 3,221 included participants

Parameter Type	Number of right eye missing measurements (%)	Number of left eye missing measurements (%)	Number of participants with measurements missing bilaterally (%)
VCDR	94 (2.9%)	135 (4.2%)	n/a
IOPg	335 (10.4%)	354 (11.1%)	306 (9.5%)
cRNFL	458 (14.2%)	523 (16.2%)	209 (6.5%)

VCDR – vertical cup to disc ratio; IOPg – Goldman correlated intraocular pressure; cRNFL – circumpapillary retinal nerve fibre layer

Supplementary Table S5. Baseline characteristics of NICOLA participants eligible for the GwNICOLA study and comparisons between GwNICOLA attendees and non-attendees.

	GwNICOLA cohort (n = 229)	GwNICOLA attendees (n = 128)	GwNICOLA non-attendees (n = 101)	P value
Age at NICOLA health assessment (n = 229)	67.70 (9.14)	66.62 (8.66)	69.07 (9.58)	0.044
Sex (n = 229)				0.160 *
Male (%)	115 (50.2)	59 (46.1)	56 (55.4)	
Female (%)	114 (49.8)	69 (53.9)	45 (44.6)	
Habitation (n = 183)				0.551 *
Urban / city / townland (%)	139 (76.0)	75 (74.3)	64 (78.0)	
Rural (%)	44 (24.0)	26 (25.7)	18 (22.0)	
Median income domain score (IQR) (n = 228)	0.1900 (0.1125, 0.2800)	0.1950 (0.1100, 0.2800)	0.1900 (0.1300, 0.2800)	0.832 ‡
Median house value (IQR) (n = 228)	135000 (95000, 190000)	136000 (100000, 195000)	132000 (87750, 190000)	0.375 ‡
Median NEI VFQ score (IQR) (n = 224)	12.00 (11.00, 15.00)	12.50 (11.00, 15.00)	12.00 (10.00, 15.00)	0.301 ‡
Mean VCDR (SD)				
Right eye (n = 219)	0.60 (0.17)	0.58 (0.16)	0.63 (0.17)	0.012
Left eye (n = 218)	0.60 (0.18)	0.60 (0.18)	0.62 (0.19)	0.245
Mean IOPg (SD)				
Right eye (n = 212)	18.37 (5.43)	18.26 (5.33)	18.50 (5.59)	0.752
Left eye (n = 210)	18.46 (5.70)	18.72 (5.60)	18.10 (5.84)	0.432
Mean Spherical equivalent (SD)				
Right eye (n = 209)	0.33 (2.65)	0.30 (2.81)	0.35 (2.45)	0.892
Left eye (n = 211)	0.31 (2.59)	0.39 (2.59)	0.21 (2.59)	0.605

‡ Mann Whitney U test, * chi squared test

Supplementary Table S6. ISGEO classifications by eye

	ISGEO 1	ISGEO 2	ISGEO 3
Right eyes	36	25 ^b	0
Left eyes	40	29 ^b	0
^a Participants	52	39 ^c	0

a – Participants counted once using highest level of evidence available: ISGEO 1 > ISGEO 2 > ISGEO 3; b – 5 right eyes and 5 left eyes from NICOLA participants who attended the clinical exam were diagnosed with glaucoma according to ISGEO category 2; c - ISGEO category 2 definition was the highest quality evidence of glaucoma in 4 participants who attended the clinical exam.

Supplementary Table S7. Reasons for unreliable visual field tests (or abnormal visual fields not due to glaucoma) are outlined

	Right eye	Left eye
Homononymous hemianopia	3	3
Bitemporal hemianopia	1	1
Reliability indices	1	1
Cataract with logMAR ≥ 0.3	2	2
Media opacity or refractive error or amblyopia with logMAR ≥ 0.3	4	4
Retinal vein occlusion	2	0
Retinal arterial occlusion	0	1
Macular hole surgery	1	1
Retinal detachment surgery	2	1