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Glaucoma in large-scale population-based epidemiology: a questionnaire-based proxy

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Abstract

Purpose: To improve upon self-reported glaucoma status in population-based cohorts by developing a questionnaire-based proxy incorporating self-reported status in conjunction with glaucoma-specific visual complaints.

Methods: A vision specific questionnaire, including questions from the National Eye Institute Visual Functioning Questionnaire-25 (NEI-VFQ-25) was administered to 79,866 Lifelines participants, a population-based cohort study in the Northern Netherlands. We compared NEI-VFQ-25 responses between ‘definite’ glaucoma cases (n=90; self-reported surgical cases) and an age- and gender-matched subset of controls (n=1,800) to uncover glaucoma-specific visual complaints, using a case-control logistic regression. We defined ‘probable glaucoma’ as both self-reported disease status and visual complaints, and ‘possible glaucoma’ as either. To evaluate the resulting proxy, we determined age-stratified glaucoma prevalences in the remaining cohort and compared the result to the literature.

Results: Per unit increase in the vision subscales (range 0-100) distance, peripheral, and low-luminance, we observed significantly increased odds of definite glaucoma (2% [P=0.03], 4% [P=1.2*10⁻⁸], and 2% [P=0.02], respectively); the associated area under the curve was 0.73. We identified 300 probable and 3,015 (1,434 by self-report) possible glaucoma cases. Standardized prevalences of definite, probable, and possible glaucoma for 55+ were 0.4, 1.1, and 7.3%, respectively. For self-reported glaucoma (combining definite, probable, and possible by self-report), this was 5.2%.

Conclusions: The combination of self-reported glaucoma status and visual complaints can be used to capture glaucoma cases in population-based settings. The resulting prevalence of combined definite and probable glaucoma (1.5%) appears to be more consistent with previous reports than the prevalence estimate of 5.2% based only on self-report.

Introduction

Open-angle glaucoma (OAG) is an adult-onset progressive eye disease that can eventually lead to irreversible blindness, and is the second leading cause of permanent visual impairment among the elderly worldwide.¹ Hallmarks of glaucomatous damage are excavation of the optic nerve head (ONH), thinning of the retinal nerve fibre layer (RNFL), and loss of retinal ganglion cells (RGCs).² These structural changes can be observed with funduscopy, fundus photography, as well as optical coherence tomography, and lead to defects in the visual field that can be identified via perimetry.³ An epidemiological definition of glaucoma was developed in 2002 by the International Society for Geographical and Epidemiological Ophthalmology (ISGEO), and is still routinely used.⁴ Briefly, glaucoma is classified in three categories, primarily based on the presence of structural and functional abnormalities, with IOP readings and medical history used as additional information. Phenotyping all participants for glaucoma in epidemiological studies according to the ISGEO definition requires costly and time-consuming ophthalmic assessments. While doable - and highly valuable - in studies with 1,000-10,000 participants,⁵⁻⁹ current enrollment sizes can exceed 100,000 participants,^{10,11} driving the search for innovative, data-driven solutions.

One solution for phenotyping participants in large datasets is the use of questionnaire data. Currently in the UK-biobank, a population-based cohort, glaucoma is classified via self-reported status.¹² While successful for associating glaucoma with socioeconomic status¹³, relying on a self-reported diagnosis has limitations. First, half of the glaucoma patients are unaware of their disease status.¹⁴⁻¹⁶ Second, and possibly more important, there is ocular hypertension, a condition with a much higher prevalence than glaucoma and often mistaken as glaucoma by the patient. Ocular hypertension is a risk factor for glaucoma, but the majority of these patients will never develop glaucoma, i.e., there are no obvious structural changes and their visual function remains intact. Hence, the question is, is it possible to make a better questionnaire-based proxy for glaucoma than self-reported disease status only?

Although glaucoma is often considered asymptomatic until end-stage disease, this is actually not the case.

Many patients, including those with early-stage glaucoma, report problems in extreme luminance settings, see Bierings et al¹⁷ for recent data and discussion on this topic. These reported subjective visual complaints suggest that a questionnaire-based proxy for glaucoma is feasible. The subjective visual experience of the glaucoma patient can be evaluated with existing visual function questionnaires and a well-known example is the National Eye Institute 25-Item Visual Function Questionnaire (NEI-VFQ-25). The NEI-VFQ-25 was developed and validated in a number of populations, and in different ocular disorders,¹⁸ indicating disease specific response patterns.^{19,20}

The aims of this study were (1) to improve upon self-reported glaucoma status in population-based cohorts by developing a questionnaire-based glaucoma proxy that incorporates self-reported status in conjunction with glaucoma-specific subjective visual experience, and (2) to evaluate the feasibility of our glaucoma proxy in the Lifelines cohort, a large (n=167,000) population-based study conducted in the Netherlands. For this purpose, we compared answers to the NEI-VFQ-25 questions between separately identified ‘definite’ glaucoma cases and an age- and gender-matched subset of controls, with a multivariable case-control logistic regression. Using the resulting coefficients from the regression to construct a classification equation, together with information on self-reported glaucoma or high eye pressure, we defined ‘probable’ and ‘possible’ glaucoma. As a feasibility check, we used the resulting proxy (classification into definite, probable, and possible glaucoma based on questionnaire data) to describe the age-specific prevalence of glaucoma in Lifelines.

Methods

Lifelines participants

Lifelines is a prospective population-based cohort study of the Northern Netherlands.²¹ It examines the health and health-related behaviours of 167,729 persons, in a unique three-generation design. For this, Lifelines employs a broad range of investigative procedures in assessing the biomedical, socio-

demographic, behavioural, physical, and psychological factors which contribute to the health and disease of the general population, with a special focus on multi-morbidity and complex genetics.²² The cohort structure, where participants will be followed for at least 30 years, is described fully elsewhere.¹¹ The NEI-VFQ-25 questionnaire was administered to all participants aged 18 and older during the first follow-up visit between 2014-2017, and the first wave of results (n = 79,866 adult participants) was used for this study. This sample is similar to the remaining adult portion of the Lifelines cohort measured at baseline, 59% female vs 58% in the rest of the cohort, and 50.4 years of age compared to 50.8 in the remaining population. Those who self-identified as Caucasian were included in the analyses.

The study protocol was approved by the ethics board of the University Medical Center Groningen (UMCG) and adhered to the tenets of the Declaration of Helsinki. All participants in Lifelines provided written informed consent.

Questionnaire Data

We used Part 2 of the NEI-VFQ-25 ('difficulty with activities' questions) in combination with self-reported eye disease status and current or past treatment for proxy development. Table 1 presents the questions used in the current study. The NEI-VFQ-25 driving questions were omitted due to excessive multicollinearity based on a variance inflation factor cut-off of 5, and missingness that exceeded 5%.²³

We used the scoring algorithm developed by Mangione et al to transform initial visual question responses to visual subscales.^{24,25} Initial responses were ranked from 1-6, where a higher score within 1-5 indicates a worse visual problem. Response 6 indicates the person stopped the activity due to other reasons, and was treated as missing. Responses were transformed to a scale from 0-100; the higher the score, the poorer the visual experience. Imputation of missingness was performed for missing data up to five percent.²⁴

Question 9 in the NEI-VFQ-25 'distance vision' subscale ("Because of your eyesight, how much difficulty do you have going down steps, stairs, or curbs in dim light or at night?") was used to create a

low luminance subscale, as glaucoma patients struggle in low luminance situations.^{17,24} The resulting six visual subscales were peripheral (Question 6 in Table 1), distance vision (Questions 4 and 10), near vision (Questions 1-3), social functioning vision (Question 7 and 9), colour vision (Question 8), and low luminance vision (Question 5). We aimed for primary glaucoma, where glaucoma is not secondary to another eye disease. Based on the available information regarding other eye diseases, and the likelihood that these diseases could result in secondary glaucoma, we excluded those who underwent surgery or laser intervention for diabetic retinopathy (Questions 14 and 18 in Table 1) or surgical intervention for retinal detachment (Question 17). Those diagnosed with age-related macular degeneration (AMD) were also excluded (Question 11). Although the visual complaint pattern of AMD will differ from that of glaucoma patients, it is a common age-related eye disease that might confound our case detection.

From questionnaire data to glaucoma proxy

The development of the glaucoma proxy consisted of three steps. First, as mentioned above, we excluded those with a history of diabetic retinopathy, macular degeneration, or retinal detachment, aiming for primary glaucoma. Second, we defined and identified ‘definite glaucoma’ in the remaining participants, see Figure 1. Third, we sampled an age- and gender-matched subgroup of controls with no self-reported eye disease, see Table 2. We compared NEI-VFQ-25 answers between the definite glaucoma cases and matched controls, together termed the ‘training population’. From this comparison, and from the answers to the additional questions displayed in Table 1, we defined ‘probable’ and ‘possible’ glaucoma. These steps together yielded a proxy; a classification into definite, probable, and possible glaucoma, as well as unaffected, based on questionnaire data. What now follows are the details of the approach.

Training population; definite glaucoma

Definite glaucoma was defined as a history of an incisional surgical intervention for glaucoma (Question 16 in Table 1). Subsequently, a group (n=1,800) of 20 random controls per definite glaucoma case was

created through propensity scoring of age and gender, using R (matchit with method="nearest", exact="gender", and ratio=20).²⁶ This population of definite cases and age- and gender-matched controls is now referred to as the ‘training population’, see Figure 1.

Next, a case-control logistic regression of the visual subscales was performed in the training population, see Figure 1. The resulting coefficients were used to build a classification equation for glaucoma class discrimination. A receiver operator characteristic (ROC) curve was constructed to identify thresholds for this class discrimination. Two classification thresholds were obtained. ‘Threshold 1’ was the maximum value of the Youden index, i.e., the largest distance between the ROC-curve and the chance line. ‘Threshold 2’ was more stringent, corresponding to 97.5% specificity on the ROC-curve.

Testing Population; probable and possible glaucoma

The classification equation was then applied to the remaining Lifelines participants, the ‘testing population’ (entire cohort excluding those with conflicting eye diseases, the training population controls, and those who did not self-identify as Caucasian). Individual regression scores were tested against the thresholds described above. Participants with glaucoma-related treatments/diagnosis (Questions 12, 13, and 19 in Table 1) *and* surpassing Threshold 1 were classified as ‘probable’. Participants with glaucoma-related treatments/diagnosis but *not* surpassing Threshold 1 were classified ‘possible by self-report’. Participants surpassing Threshold 2 *without* glaucoma treatment/diagnosis were considered ‘possible by complaint’. The two classes of ‘possible’ were then combined. The remaining participants were classified as ‘unaffected’ (see Figure 1).

Performance of glaucoma proxy

To determine the feasibility of this proxy in a population-based setting, the prevalence of glaucoma was obtained. Age-stratified (up to 55, 55-69, 70+) glaucoma prevalences were obtained through the number

of definite, probable, and possible cases divided by the total number of participants in the concerning age-stratum. Prevalences were then standardized via the Dutch 2018 population census (obtained from Statistics Netherlands, <https://opendata.cbs.nl/statline/#/CBS/en/dataset/37296eng/table?fromstatweb>, accessed December 6th, 2018), and compared to the literature.

Data analysis

All analyses were performed using SPSS (version 24.0.0.2) and R (version 3.4.2). A P value of 0.05 or less was considered statistically significant in all analyses.

Results

Of the 79,866 submitted questionnaires, 79,845 participants provided usable data. The remaining 21 participants did not complete the eye portion of the questionnaire. Ages ranged from 19 to 94, with a mean age (standard deviation) of 50.4 (12.6) years. In total, 2,339 participants were removed due to either conflicting eye diseases, or for identifying other than Caucasian, resulting in 77,506 participants (Figure 1).

In total there were 111 participants who had a history of glaucoma surgery. After excluding those who underwent laser treatment or surgery for diabetes (n=2), and/or surgery for retinal detachment (n=10; 1 overlapping with diabetic laser/surgery treatment), and/or who had AMD (n=13; 3 overlapping with retinal detachment surgery), 90 cases of definite glaucoma were identified within the Lifelines population. The mean (standard deviation) age of the definite glaucoma cases was 61.7 (12.6) years. The age of the definite glaucoma cases was significantly different than the rest of the cohort (paired t-test $P=6.4 \times 10^{-15}$); after selecting 20 age- and gender- matched controls (n = 1,800), age was not significantly different between cases and controls (paired t-test $P=0.89$). Table 2 displays the mean visual subscale scores of the definite glaucoma cases and the age- and gender-matched controls. In the univariable analyses, all

subscales were highly significantly different between cases and controls. In the multivariable analysis, per one unit increase in the vision subscales (range 0-100) of distance, peripheral, and low-luminance vision, we observed significantly increased odds of definite glaucoma of 2% (P=0.03), 4% (P=1.2*10⁻⁸), and 2% (P=0.02), respectively. Figure 2 shows the ROC curve for the logistic regression. The area under the curve (AUC) was 0.73. The corresponding classification equation was:

$$y = (-0.003 * near) + (0.024 * distance) + (0.038 * periphery) + (-0.009 * social function) + (-0.010 * colour) + (0.015 * low luminance) - 3.76.$$

Threshold 1 was 0.08 with an associated sensitivity of 50.0% and specificity of 89.8%. Threshold 2 was 0.17 with an associated sensitivity of 30.0% at the required specificity of 97.5%.

In total, 300 participants were classified as probable glaucoma and 3,015 as possible glaucoma. Of these 3,015 possible glaucoma cases, 1,434 participants were classified as possible by self-report and 1,581 as possible by complaint. The remaining 72,301 participants were classified as ‘unaffected’ (Figure 1).

Prevalence

Table 3 presents the prevalence of glaucoma, stratified by age and glaucoma category. Age-stratified prevalences ranged from 0.06% of definite cases in the youngest age stratum up to approximately 9% of possible cases in the oldest age stratum. The raw prevalences of definite, probable, and possible glaucoma in the 55+ population were 0.2, 0.9, and 6.6%, with corresponding standardized prevalences of 0.4, 1.1, and 7.3%, respectively. For self-reported glaucoma (combining definite, probable, and possible by self-report), the standardized prevalence was 5.2%.

Discussion

We created a questionnaire-based glaucoma proxy for use in population-based epidemiology; the resulting glaucoma categories are definite, probable, possible, and unaffected. Categorization is based on a history of glaucoma surgery, self-reported glaucoma and ocular hypertension which includes self-reported medical treatment for glaucoma/ocular hypertension, as well as the presence or absence of glaucoma-specific visual complaints according to the NEI-VFQ-25. Based on this proxy, the standardized prevalence of combined definite and probable glaucoma in the 55+ population participating in Lifelines is approximately 1.5%.

Our definitions of definite, probable, and possible glaucoma differ, inevitably, from the ISGEO criteria, and do not correspond one-to-one to clinical diagnoses. For the ISGEO Category 1 glaucoma diagnosis (the strictest category), glaucomatous visual field loss (GVFL) and glaucomatous optic neuropathy (GON) are required. In clinical settings, patients who have undergone glaucoma surgery likely fulfill the ISGEO Category 1 diagnosis criteria; many medically treated patients fulfill these criteria as well. Hence, our definite cases are a subset of the ISGEO Category 1 diagnosis cases. As mentioned in the Introduction section, it is not possible to simply rely on self-reported disease status to define glaucoma in population-based epidemiology, as the prevalence of ocular hypertension is much higher than that of glaucoma, and both are easily mixed-up by patients.²⁷ To address this, we combined self-reported disease status/treatment with glaucoma-specific visual complaints; this combination was denoted as probable glaucoma. In the Rotterdam Study, the prevalence of glaucoma was 0.8% in the 55+ population when using ISGEO Category 1 diagnosis (GVFL and GON).¹⁵ If we extend the glaucoma classification to what was used more recently in the Rotterdam Study,^{28,29} from ISGEO Category 1, to GVFL with or without GON together with ISGEO Category 2 diagnosis (GON only, but with a stricter criterion), the prevalence of glaucoma in the Rotterdam Study is 3.2%. As all participants receive a full eye exam, the Rotterdam Study identifies both patients who are aware of their disease status, as well as those with undiagnosed glaucoma.³⁰ As mentioned in the Introduction section, only half of the glaucoma patients are aware of their disease status, thus the prevalence of 3.2% in the Rotterdam Study corresponds quite well with our 1.5%, given that our definitions of definite and probable glaucoma imply awareness. As Lifelines and the

Rotterdam Study are both based in the Netherlands and comprise Caucasian participants only, our proxy provides a prevalence estimate that is consistent with diagnosed glaucoma if we combine definite and probable glaucoma.

In the UK Biobank, the age-stratified prevalence of self-reported glaucoma was 0.48% for participants 40-49 years of age, 1.18% for those 50-59 years of age, and 2.68% for those aged 60-69.¹³ Considering that glaucoma is generally diagnosed in the sixth decade of life, the UK Biobank population is relatively young.³¹ To compare these prevalences to our dataset, we calculated the corresponding prevalences for the combined definite and probable categories. This yielded a prevalence of 0.27% for participants 40-49 years of age, 0.37% for those 50-59 years of age, and 1.29% for those aged 60-69. Given that the prevalence of the combined definite and probable categories appears to approximate that of diagnosed glaucoma in the general population quite well (see previous paragraph), the self-report approach of the UK biobank seems to yield an overestimation of the actual glaucoma prevalence (assuming the same glaucoma prevalence in the Caucasian populations of the UK and the Netherlands). As mentioned in the Introduction section, spurious inclusion of ocular hypertension could explain this overestimation. To compare, the prevalence of self-reported glaucoma in our study (combined definite, probable, and possible by self-report categories) was 1.50% for participants 40-49 years of age, 2.40% for those 50-59 years of age, and 4.50% for those aged 60-69. These values seem higher than those reported by the UK biobank. This difference likely arose as we explicitly mentioned ocular hypertension as part of the self-reported glaucoma question (Question 12 in Table 1), where the UK biobank did not (The question for participants was, “Has a doctor told you that you have any of the following problems with your eyes” with “glaucoma” in a list of ocular disorders).

In Lifelines, participants not aware of their disease could have been captured in our study as ‘possible glaucoma based on complaint’. We obtained 1,581 possible by complaint, clearly exceeding the expected number (~400) based on a disease awareness of 50%. This category is presumably a mixture of glaucoma cases and false positives. Similarly, the possible glaucoma by self-report category is likely made up of

participants with early, asymptomatic glaucoma detected by chance, as well as glaucoma suspects, i.e., those with ocular hypertension, or, for example, those followed-up because of relatives with glaucoma. Depending on the purpose of future studies using our proxy, the possible glaucoma category could be excluded rather than being attributed to either cases or controls.

To evaluate the robustness of our approach to uncover the glaucoma-specific visual complaints, we re-analyzed our data utilizing linear discriminant analysis (LDA). The same NEI-VFQ-25 subscales were identified as relevant to glaucoma and no statistical difference was identified between the AUC of logistic regression, and that of LDA (AUC for logistic regression = 0.73, AUC for LDA = 0.73, P=0.76).³² The LDA categorization was as follows, 366 for probable (290 overlapping with logistic regression), 1,368 for possible by self-report (1,358 overlapping with logistic regression), and 1,907 possible by complaint (1,563 overlapping with logistic regression). The LDA was less conservative in classifying ‘probable’ and ‘possible glaucoma by complaint’, however, identified cases largely overlapped between the two approaches. The large overlap of glaucoma categorization for both approaches suggests robustness of our approach.

We aim to study primary open-angle glaucoma. Potentially, our data are contaminated with primary angle-closure glaucoma, pseudoexfoliative glaucoma, secondary glaucoma, or other ocular disorders that may present as glaucoma through the subjective visual complaints. Fortunately, primary angle-closure glaucoma and pseudoexfoliative glaucoma have a significantly lower prevalence in our Caucasian study population.³⁰ A systematic review reported the prevalence ratio of primary open-angle glaucoma compared to primary angle-closure glaucoma in European-derived populations to be approximately 10:1 (range: 2.6:1 to 20.7:1).³³ Similarly, at the population level, secondary glaucoma is rare compared to primary open-angle glaucoma,³⁴ but this might be different in a clinical setting.³⁵ So, to further reduce the probability of spuriously including secondary glaucoma, we excluded those who underwent surgery or laser intervention for diabetic retinopathy, or surgical intervention for retinal detachment. Finally, retinal dystrophies like retinitis pigmentosa present with a similar subjective vision loss pattern to glaucoma, i.e.,

deficits in peripheral and low luminance vision, but are rare in the general population with an estimated prevalence below 0.1% in the Netherlands.^{36,37}

A major strength of this study was the stringent inclusion criterion for definite glaucoma, being a history of glaucoma surgery, which enabled us to quantify the glaucomatous visual impairment very clearly. A limitation is that the history of glaucoma surgery was self-reported, and may have been reported erroneously. Due to the nature and privacy of the data, medical records were unavailable to us. As such, the subjective visual complaints obtained from this study may be moderated by misclassification, resulting in an underestimation of the power of a questionnaire-based glaucoma proxy. Specifically, mixing-up glaucoma surgery and cataract surgery may have occurred. To address this, cataract surgery was addressed separately in the questionnaire, before glaucoma surgery. The use of 20 age- and gender-matched controls per case allows us to surmise that the vision loss captured in the regression is due to glaucoma, and not general ageing. Our method was developed in a Caucasian population. It is unknown if the proxy can be used in populations of different ethnicities. However, it was reported that glaucoma patients of African descent have no difference when compared to Caucasian glaucoma patients with respect to the NEI-VFQ-25 visual subscales.³⁸ Although no direct comparison to a Caucasian population was made, Korean glaucoma patients also have reported significant issues with the peripheral and social function vision subscales,³⁹ and in a case-control comparison of Latino-Americans, significant differences were observed in all visual subscales.⁴⁰ A limitation of this study is the exclusion of participants with diabetic retinopathy, retinal detachment, and AMD - intentionally done to avoid including participants with secondary glaucoma. As such, no conclusions can be made regarding glaucoma in patients with ophthalmic comorbidity.

In conclusion, this study demonstrated that glaucoma patients have significantly poorer subjective visual experiences than their age- and gender-matched peers in terms of distance, low luminance, and peripheral vision as assessed by questionnaires. Their subjective visual experience, together with self-reported disease status, successfully guides the creation of a classification equation to rank others' glaucoma proxy

status. The resulting prevalence appears to be more consistent with previous glaucoma prevalence literature than a prevalence estimate based only on self-report. The proxy opens opportunities for glaucoma research within large-scale population-based settings, where in-depth phenotyping of all participants is not easily feasible.

Tables

Table 1. Question list, derived from the National Eye Institute 25-Item Visual Function Questionnaire and related medical questions, used for the glaucoma proxy creation and application

Question	Answer type	Visual Subscale
<i>In the past month have you had trouble...</i>	--	--
1. reading ordinary print in newspapers	Ordinal	Near
2. 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	Ordinal	Near
3. finding something on a crowded shelf	Ordinal	Near
4. reading street signs or the names of stores	Ordinal	Distance
5. Going down steps, stairs, or curbs in dim light or at night	Ordinal	Low Luminance
6. Noticing objects off to the side while you are walking along	Ordinal	Peripheral
7. Seeing how people react to the things you say	Ordinal	Social
8. Picking out and matching your own clothes	Ordinal	Colour
9. Visiting people in their homes, at parties, or in restaurants	Ordinal	Social
10. Going out to see movies, plays, or sporting events	Ordinal	Distance
<i>Has an ophthalmologist diagnosed you with...</i>	--	--
11. Macular degeneration	yes/no	
12. Glaucoma/high eye pressure	yes/no	
<i>Did you ever have a laser treatment for your eyes (y/n)? If yes, for which condition did you have laser treatment?</i>	--	--
13. Glaucoma/high eye pressure	yes/no	
14. Diabetes	yes/no	
(other response options were: after cataract, diabetes, to get rid of glasses/contact lenses, other, don't remember)		
<i>Did you ever have eye surgery for your eyes (y/n)? If yes, for which condition did you have eye surgery?</i>	--	--
16. Glaucoma/high eye pressure	yes/no	
17. Retinal detachment	yes/no	
18. Diabetes	yes/no	
(other response options were: cataract, to get rid of glasses/contact lenses, other, don't remember)		
<i>Are you currently using eye drops/gel? If yes, for which condition are you using eye drops/gel?</i>	--	--
19. Glaucoma	yes/no	
(other response options: allergy, dry eyes, other, don't remember)		

Table 2. Baseline characteristics and visual subscale results (NEI-VFQ-25; range from 0-100, where a higher score represents a poorer visual experience) of definite glaucoma cases and age-and gender-matched controls within the training population

	Definite glaucoma cases (n=90)*	Matched Controls (n=1,800)†	P value‡	OR¶ [95% CI]	Adjusted OR§ [95% CI]	
Mean (SD) age (years)	61.7 (12.9)	61.9 (12.8)	0.99	--	--	
Gender (% female)	47 (52.2%)	940 (52.2%)	1.00	--	--	
Visual Subscale	Near	19.4	9.0	1.79x10 ⁻⁵	1.04 [1.02-1.05]	0.99 [0.98-1.01]
	Distance	16.8	4.9	1.15x10 ⁻⁹	1.05 [1.04-1.06]	1.02 [1.00-1.05]
	Peripheral	22.8	4.3	2.58x10 ⁻²²	1.05 [1.04-1.06]	1.04 [1.03-1.05]
	Social	10.8	2.6	1.10x10 ⁻⁸	1.05 [1.04-1.07]	0.99 [0.97-1.02]
	Colour	9.4	3.5	2.34x10 ⁻⁵	1.03 [1.02-1.04]	0.99 [0.97-1.01]
	Low Luminance	27.0	9.7	1.82x10 ⁻¹²	1.04 [1.03-1.05]	1.02 [1.00-1.03]

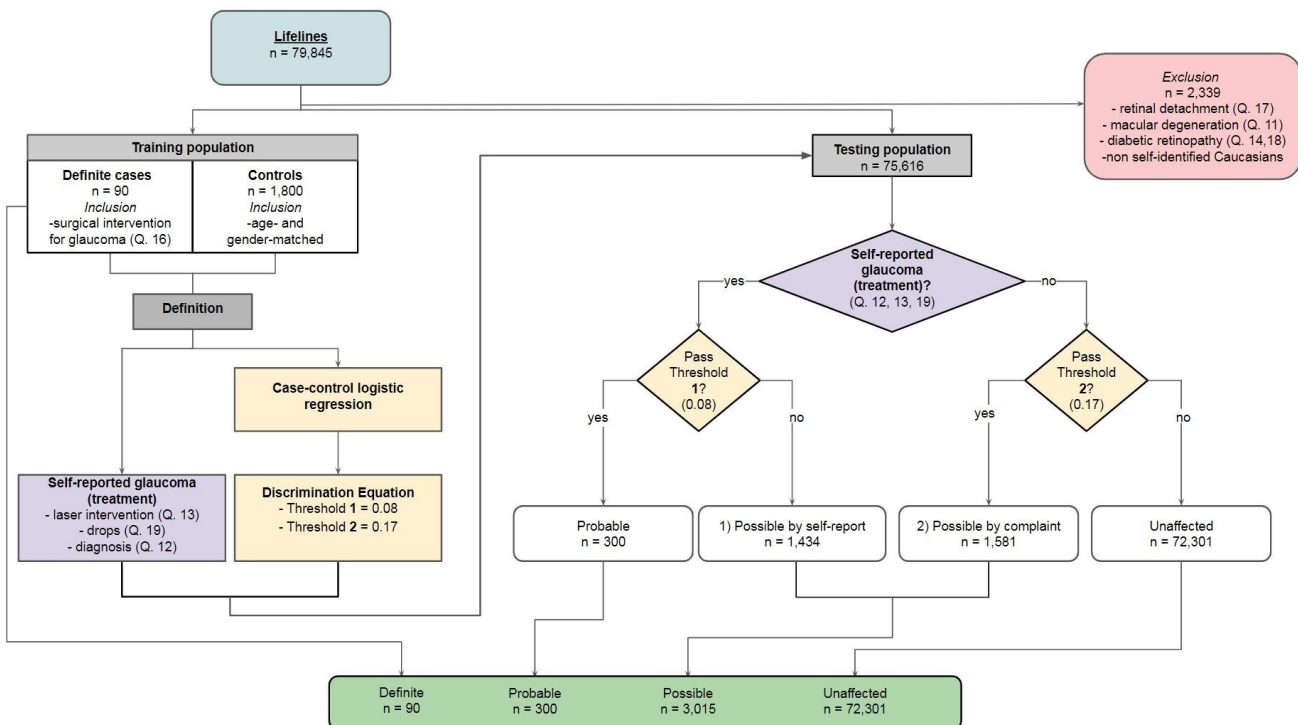
* = within the 90 definite glaucoma cases, there was one missing response in the peripheral vision subscale and one in the low luminance subscale; † = within the 1,800 controls, there were six missing responses for near, three for distance, seven for peripheral, seven for social functioning, 11 for colour vision, and seven for low luminance subscales; ‡ = from independent-sample t-tests; ¶ = per unit increase in subscale score from a univariable logistic regression, adjusted for all other visual subscales; § = per unit increase in subscale score from a multivariable logistic regression, adjusted for all other visual subscales

Table 3. Age-stratified glaucoma prevalences within the Lifelines cohort (n=75,706)

		Prevalence, % (n)		
Age	n	Definite	Probable	Possible
18-54	51,202	0.06 (30)	0.15 (77)	2.73 (1,396)
55-69	19,688	0.15 (29)	0.77 (143)	5.93 (1,167)
70+	4,816	0.64 (31)	1.66 (80)	9.39 (452)
Total	75,706	0.12 (90)	0.40 (300)	3.98 (3,015)

Figures

Figure 1: Flowchart of glaucoma categorization within the Lifelines cohort, refer to Table 1 for relevant questions.



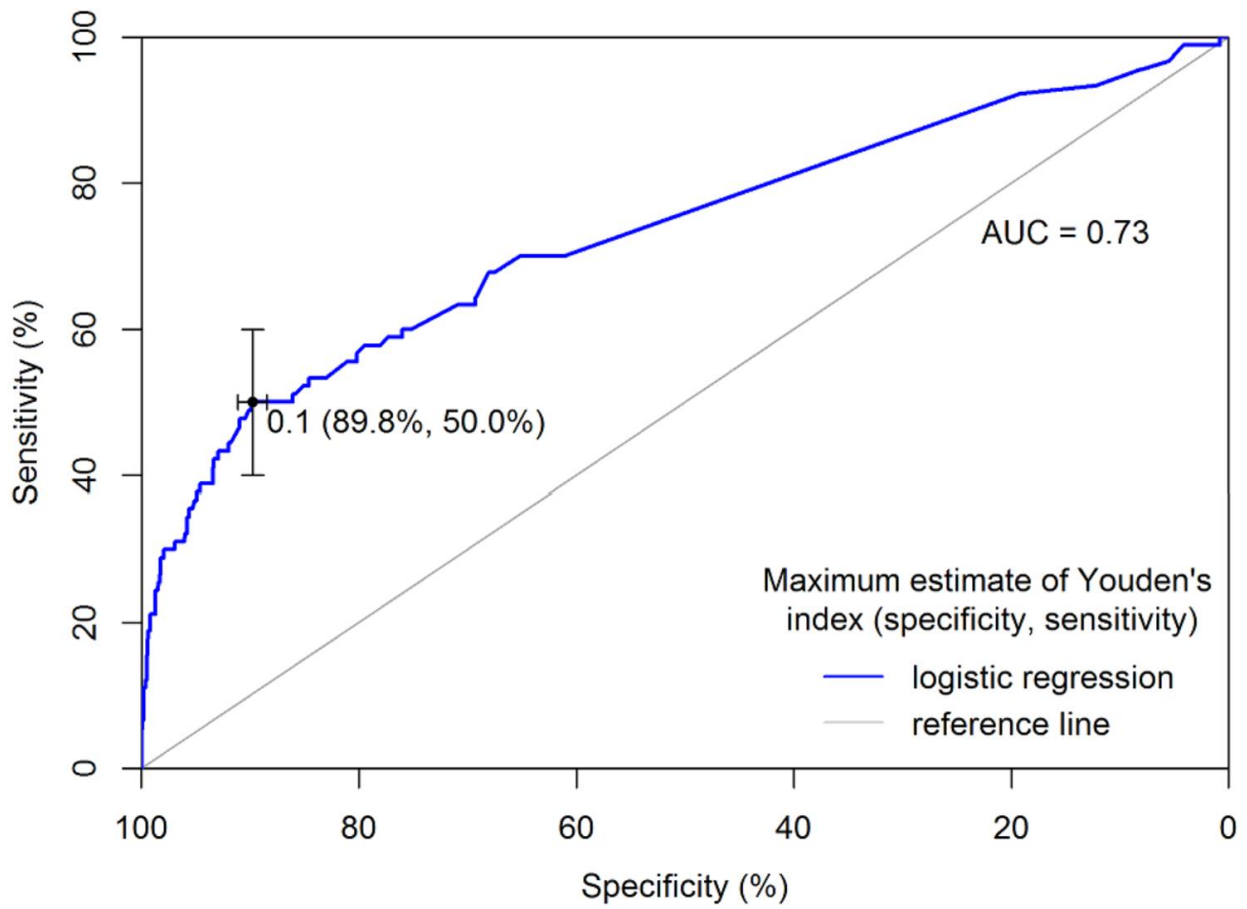


Figure 2: Receiver operator characteristic curve indicating the predictive ability of the NEI-VFQ-25 subscales to differentiate between definite glaucoma and age- and gender- matched healthy controls within the Lifelines cohort.

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