European Journal of Epidemiology (2026) 41:1101–1111
https://doi.org/10.1007/s10654-026-01429-8

OPHTHALMIC EPIDEMIOLOGY

Genetic risk score to enhance glaucoma case detection: a prospective double-blind screening study (EyeLife) in the population-based Lifelines cohort

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Received: 30 November 2025 / Accepted: 10 June 2026 / Published online: 4 July 2026
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Abstract

Early detection of glaucoma prevents blindness but its low population-based prevalence impedes cost-effective screening. We investigated whether genetic pre-screening could increase the prior probability. Design, methods, and primary analysis were pre-specified and published previously. In this prospective study, we invited 1829 participants aged 55 + from the Dutch Lifelines cohort, selecting from either the highest or lowest 20% of a GWAS-based genetic risk score distribution; subgroups had similar age and gender. Researchers were blinded to subgroup allocation; participants to genetic risk selection. Participants underwent perimetry, optical coherence tomography, fundus photography, tonometry, pachymetry, and visual acuity assessment. Abnormalities prompted a full ophthalmic examination. Participants were classified as definite, probable, or possible open-angle glaucoma, or as unaffected. We calculated the relative risk of combined definite and probable glaucoma for high versus low genetic risk, adjusting for age, sex, and genotyping platform. 1022 participants (median [interquartile range] age 64 [59–70] years, 53% female, Northwestern European ancestry) agreed to participate and were included, 487 with high and 535 with low genetic risk. Of these, 59 (age 70 [64–76] years) were classified as definite (29 with high and 2 with low genetic risk) or probable (21 and 7) glaucoma. Relative risk was 7.4 (95% confidence interval 3.7–14.7), indicating that participants with high genetic risk were over seven times more likely to be classified with glaucoma than those with low risk. Stratifying the general population based on genetic risk strongly increases the prior probability of glaucoma and may enable a cost-effective screening approach.

Keywords Genetic risk score · Glaucoma · Screening · Prospective design · Lifelines

Introduction

Glaucoma is a chronic, neurodegenerative disease of the optic nerve with elevated intraocular pressure (IOP) as its primary risk factor. It is a major cause of irreversible blindness in the world. Treatment (lowering of the IOP by laser treatment, eye drops, or surgery) reduces disease progression considerably and may thus reduce the risk of end-of-life blindness [1–4]. However, timely detection remains a challenge, despite decades of research targeting glaucoma screening.

In 1968, at the World Health Organization in Geneva, Wilson and Junger presented a set of criteria to assess the feasibility of population-based disease screening [5]. Glaucoma, affecting approximately 3% of the elderly population and 10% of those aged over 80 years, meets many of these criteria [6]. It is an important health problem. The natural

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history is well understood: glaucoma is chronic and irreversible, resulting in bilateral blindness in approximately half of the cases [2]. The early stage of glaucoma is largely asymptomatic but detectable: changes in the optic nerve head (ONH) and thinning of the retinal nerve fiber layer (RNFL) are often observed before significant loss of visual function occurs [7]. Treatment at an early stage is more beneficial than at a later stage: glaucoma treatment slows disease progression considerably, and those detected with early glaucoma will rarely reach the end-stage of the disease when treated [1, 3, 8, 9]. Accordingly, severe glaucoma at diagnosis is a major determinant for blindness [10]. Tests for detecting early glaucoma are not burdensome: they are non-invasive and quick to perform [11]. Currently, however, population-based glaucoma screening is not cost-effective [12]. The limiting factor is the specificity of state-of-the-art screening tests (typically 95%) relative to the disease prevalence, resulting in inflated rates of false-positives [6, 11].

In addition to developing better screening tests, limiting screening to high-risk subgroups is a viable option to increase the cost-effectiveness of glaucoma screening, by increasing the prior probability, or prevalence among those being screened. This includes screening from a certain age and, given the high heritability of glaucoma, focusing on those with a family history of glaucoma [13]. Nowadays, however, families are often small and people may not be aware of their genetic predisposition to glaucoma [14]. Thus, a genetic work-up, or genetic risk, would provide more information than family history alone when determining an individual's glaucoma risk [15].

Historically, glaucoma was considered a Mendelian disease with a small number of causal genes involved. Later, genome-wide association studies (GWAS) revealed many genetic variants implicated in glaucoma risk; glaucoma is now considered a textbook example of a complex disease. At the end of 2023, more than 300 independent genetic signals represented by single nucleotide polymorphisms (SNPs) were identified to be associated with glaucoma risk [16, 17]. A genetic risk score (GRS) can be built from these SNPs; it was demonstrated, retrospectively, that such a GRS could enhance glaucoma screening efficacy significantly by screening only individuals at a high genetic risk, i.e., genetic pre-screening [18–21].

In this study, we aimed to evaluate the added value of genetic pre-screening on the yield of glaucoma case detection. For this purpose, we invited two subgroups of the general Dutch population of 55 years and older for glaucoma screening, individuals with a high (top 20% of a GWAS-based GRS) and individuals with a low (bottom 20%) genetic glaucoma risk. The study was conducted as an add-on study, named EyeLife, within Lifelines, a population-based cohort and biobank from the Northern Netherlands [22]. The study design of EyeLife was prospective and double-blind; those who performed the screening and those who evaluated the test results were unaware of the genetic risk of the participants, and the participants themselves were unaware of the fact that they were invited based on their genetic risk.

Methods

Study population

Lifelines is a large, prospective population-based cohort and biobank of the Northern Netherlands. It investigates health and health-related behaviours of ~167,700 participants, in a unique three-generation design, fully described elsewhere. Briefly, Lifelines measures a wide variety of factors that contribute to the health and disease of the general population, specifically focusing on multimorbidity and complex genetics [22]. Lifelines invited participants aged 55 or older, at either the lowest or highest 20% of the glaucoma genetic risk distribution, and amenable to further research to participate in EyeLife, taking care to obtain similar age distributions in both groups. In total, 1829 participants were invited, 896 participants were from the highest 20% and 933 from the lowest 20% of the GWAS-based GRS distribution. Enrolment was from April 29, 2019 to September 14, 2022. The protocol of EyeLife was published previously, where study design, methods, and primary analyses were pre-specified [23].

The study protocol was approved by the ethics board of the UMCG (NL65947.042.18) and registered with the Dutch Trial Register (NL-OMON48818; 31−01−2019). All participants provided written informed consent. The study followed the tenets of the Declaration of Helsinki.

Genetic risk score calculation

Lifelines participants were genotyped using either Illumina's HumanCytoSNP−12v2.0 (n = 15422) or the Infinium Global Screening Array MultiEthnic Disease v1.0 (n = 36339) and imputed using the 1000 Genomes Phase 3 and Haplotype Reference Consortium r1.1 reference panels, respectively. The weighted GRS used in this study was novel, as it utilized genome-wide significant SNPS of not only glaucoma GWAS, but also related endophenotypes, to create a highly curated glaucoma GRS. A full explanation is given in the EyeLife protocol paper [23].

Briefly, a weighted GRS was constructed using 268 independent single nucleotide polymorphisms (SNPs), selected from GWAS publications related to glaucoma (9 publications, 49 SNPs) and glaucoma endophenotypes, including IOP (8 publications, 176 SNPs), glaucoma and IOP (5

publications, 26 SNPs), central corneal thickness (CCT; 3 publications, 13 SNPs), and disc parameters (2 publications, 4 SNPs). For each individual *j*, the GRS was calculated as a weighted sum of risk alleles:

$$GRS_j = \sum_{i=1}^{268} w_i \cdot d_{i,j},$$

where w_i represents the risk for glaucoma of SNP *i*, expressed as a log-transformed odds ratio obtained from the meta-GWAS of glaucoma [24], and $d_{i,j}$ is the risk allele dosage for SNP *i* in individual *j*. The weighted GRS was adjusted for each genotyping platform to account for variations in genotyping quality before being combined. For downstream analysis, the weighted GRS was scaled and centered for each genotyping platform separately to account for differences in genotyping quality and then combined. Supplementary material provides the list of the 268 SNPs and their respective weights.

Phenotyping

Ophthalmic examinations

EyeLife participants underwent a series of ocular examinations, including assessment of visual acuity and refraction, an IOP measurement, visual field testing, optical coherence tomography (OCT), and fundus photography. Equipment was chosen if it had proven value in glaucoma screening/research in population-based settings. The examinations were performed at the Department of Ophthalmology of the University Medical Center Groningen (UMCG). Details regarding visual acuity, refraction, and IOP can be found in the protocol paper [23].

The visual field was tested with the frequency doubling technique (FDT), using the C20-1 screening mode (Carl Zeiss Meditec, Jena, Germany). The test was repeated in case of any abnormal test location $P<0.01$; visual field loss (VFL) was defined as the presence of one or more reproducibly abnormal test locations. Glaucomatous VFL (GVFL) was subsequently defined, *per exclusionem*, as the presence of VFL that was not explained by abnormalities in the fundus images, and excluding homonymous or bitemporal defects.

The structural layers of the eye were then assessed with OCT (Optopol NX700; OPTOPOL Technology, Zawiercie, Poland). We imaged the optic disc region, the macular area, and the anterior chamber including the cornea. For the optic disc region, we focused on the peripapillary RNFL (pRNFL). The pRNFL was considered unaffected if there were no clock-hour defects at 1% of age-, gender-, and ethnicity-based normative data in the inferior, superior, or temporal clock-hours. All scans with one or more clock-hour defects were re-evaluated. The pRNFL was considered abnormal after excluding scans with technical artefacts and scans with abnormalities related to, among others, myopia, anomalous retinal vessel architecture, or optic disc hypoplasia. CCT was measured from the scan that imaged the anterior chamber and cornea. We used the average value of both eyes for the participants' CCT.

Finally, fundus photographs were obtained using a non-mydriatic auto fundus camera (AFC-330; NIDEK, Gamagori, Japan). Two 45-degree angle-of-view images were taken for both eyes, one centered on the optic disc and one centered on the macula. The optic disc was assessed from the fundus images by a glaucoma specialist (NJ). Glaucomatous optic neuropathy (GON) was defined as either a vertical cup-disc ratio (VCDR) of at least 0.7 (the 97.5th percentile in the general population) [6, 25], notching (focal absence of the neural rim) inferiorly or superiorly, or the presence of a peripapillary splinter hemorrhage.

We invited participants for re-examination by an ophthalmologist in case of at least one of the following findings: (1) corneal-compensated IOP (IOPcc) > 22 mmHg in either eye [26]; (2) best corrected visual acuity (BCVA) < 0.5 in either eye, unless there was a clear history of amblyopia or the participant was being treated for age-related macular degeneration; (3) VFL in either eye; and (4) RNFL abnormalities together with GON. A clinical follow-up (via GP referral) was offered to those with definite glaucoma (for classification see below), or in cases with a reproducibly elevated IOP (IOPcc > 22 mmHg and an applanation tonometry [AT] reading > 20 mmHg) with or without probable or possible glaucoma (for classification see below). We used AT > 25 mmHg as the cut-off value for referral for participants with CCT ≥ 600 µm without probable or possible glaucoma.

Classification

We used the International society of Geographical and Epidemiological Ophthalmology (ISGEO) classification as an initial reference point in defining glaucoma within EyeLife [27]. We classified EyeLife participants as definite, probable, or possible glaucoma, or unaffected. We made two modifications to the ISGEO classification system. First, we removed the second GON cut-off point, the 99.5th percentile, for statistical reasons [25]. Second, we added RNFL assessment by OCT, which is not within the ISGEO classification system but is part of a current state-of-the-art glaucoma assessment. For this, we modified the classification system following the Northern Finland birth cohort eye study [28]. They employed a 'two-of-three' (VF, RNFL, optic disc) method to classify glaucoma. The resultant categories in the current study are:

- Definite glaucoma (combined functional and structural loss; the equivalent of ISGEO Category 1 diagnosis): GVFL with either RNFL abnormalities or GON;
- Probable glaucoma (functional or confirmed structural loss): either GVFL (called 'field suspect' by the ISGEO) or RNFL abnormalities together with GON;
- Possible glaucoma (structural loss): either RNFL abnormalities or GON (called 'disc suspect' by the ISGEO).

When no abnormalities were observed, or abnormalities that were not glaucoma-related, the participant was classified as unaffected. Missing data due to, for example, small pupils or media opacities, were interpreted as 'normal findings' with other ocular tests examined in this context. For example, given the classifications above, a participant with GVFL, a normal fundus image, and missing OCT data was classified as probable glaucoma, based on the GVFL. Out of 1022 participants, only 6 had missing data for VF, 16 for OCT, and 15 for fundus photography, and all identified glaucoma cases had a complete dataset.

After each eye's glaucoma status was graded, the participant was classified according to the more affected eye. For example, a participant with definite glaucoma in the right eye and possible glaucoma in the left eye would be classified as definite glaucoma. Glaucoma was considered open-angle glaucoma (OAG) if an open-angle was found during gonioscopy at the re-examination (trabecular meshwork visible in at least 3 of 4 quadrants without compression); OAG was considered primary OAG (POAG) if there were no signs of pigment dispersion or pseudoexfoliation, or (a history of) other eye diseases that may have caused glaucoma. Intraocular pressure was not part of the classification system, however, an IOPcc > 22 mmHg during the initial screening alongside an AT reading above 20 mmHg during the re-invite was defined as ocular hypertension (OHT), if no GVFL, RNFL abnormalities, or GON were present. CCT was also not taken into account in the classification system, but was considered during clinical follow-up (see Ophthalmic examinations subsection).

Data analysis

For the primary analysis, a glaucoma case was defined as either definite or probable primary OAG. For descriptive analysis, categorical variables were presented as numbers and proportions, and continuous variables as means and standard deviations (SD) if normally distributed, and as medians and interquartile ranges (IQR) if not. Baseline characteristics were evaluated by comparing participants with high versus low GRS. For normally distributed variables, a t-test was used, and the Mann-Whitney U-test was used for non-normally distributed variables. Proportional differences were assessed using Fisher's exact test. To compare characteristics among glaucoma cases, participants with possible glaucoma, and unaffected participants, we used a one-way analysis of variance for normally distributed variables, a Kruskal-Wallis test for non-normally distributed variables, and a Fisher's exact test for proportions. Significant findings prompted post-hoc analyses with Bonferroni correction to discern pairwise differences between the subgroups of the glaucoma cases (definite and probable), participants with possible glaucoma, and unaffected participants.

The relationship between the glaucoma GRS and glaucoma classification (cases vs. unaffected and possible vs. unaffected) was examined using univariable and multivariable log-link generalized linear models adjusting for age, sex, and genotyping platform. Within the examined study population, $n = 463$ participants were genotyped with the HumanCytoSNP-12v2.0 chip and $n = 559$ with the Global Screening Array. If a sample was genotyped with both arrays ($n = 16$), the GRS based on the latter platform was selected for analysis. Because this was a prospective study with observable disease proportions in each GRS group, we specified a binomial family with the log link to obtain relative risks (RRs), which directly reflect differences in disease probability between the high and low GRS group. To explore whether the RR varied across the age strata, we compared two models, one with and one without an age-by-GRS interaction term, using a likelihood ratio test. When investigating the relationship between the glaucoma GRS and related endophenotypes, we used a general linear model (GLM) with the gaussian (link=identity) function if the outcome was continuous, and binomial (link = log) if it was binary. To evaluate the impact of restricting the analyses to the top and bottom 20% of the GRS distribution, we simulated GRS values across the full distribution and then selected the 20% extremes. Logistic regression coefficients from the extreme-range and full-range GRS models were highly correlated ($r > 0.9$), indicating minimal impact of analysing only the 20% extremes on estimated effect sizes.

All analyses were performed using R (version 4.4.0; R Foundation for Statistical Computing, Vienna, Austria). A p value of 0.05 or less was considered statistically significant.

Results

Of 1829 invited Lifelines participants, 1028 participants attended the ophthalmic examination after providing signed informed consent, resulting in a participation rate of 56% (Fig. 1). Responders and non-responders did not differ regarding age ($p = 0.08$) or gender ($p = 0.27$); participation rate was 55% in the high and 57% in the low GRS group ($p = 0.27$). Out of the 1028 EyeLife participants, 135 were

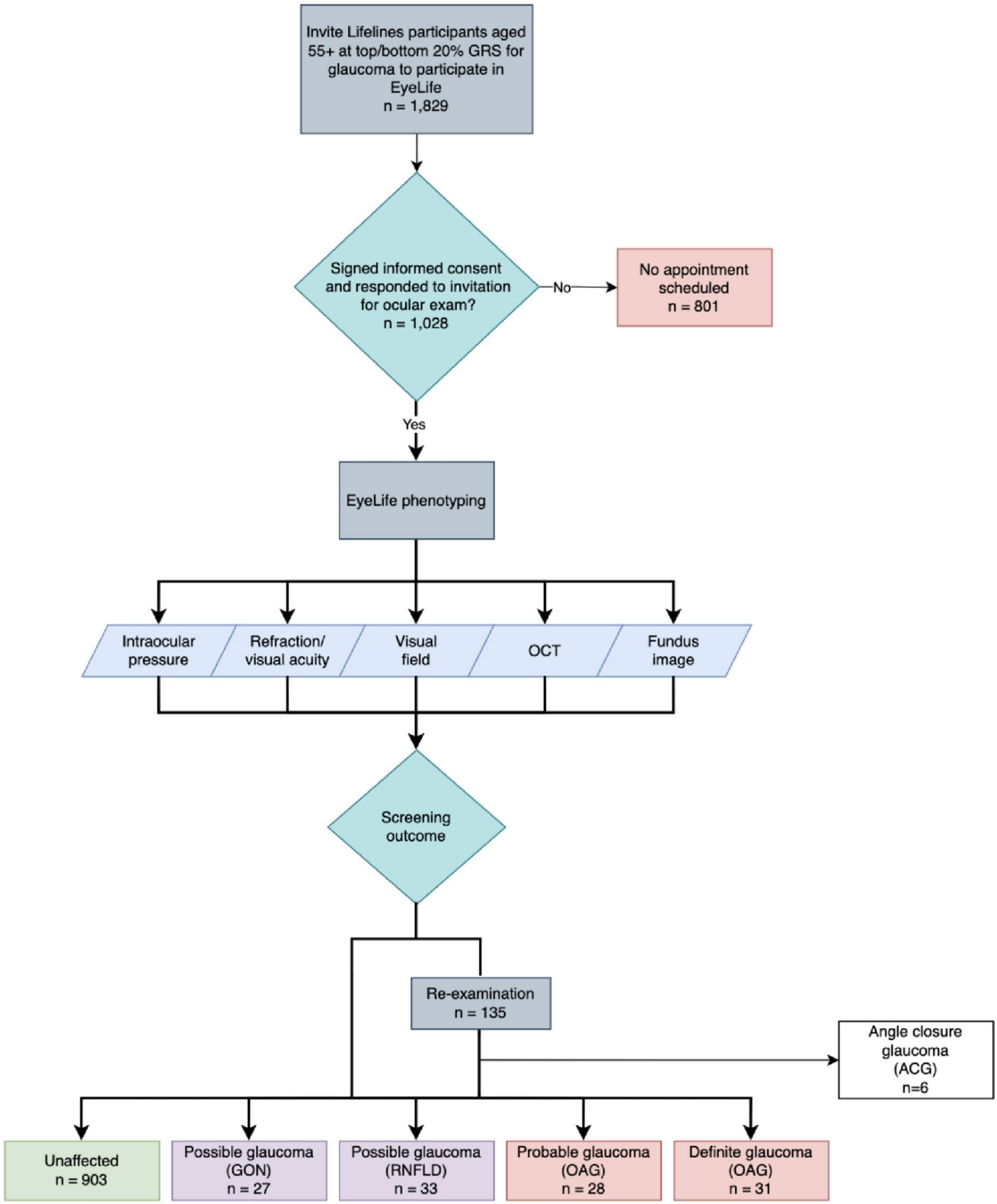


Fig. 1 Flow diagram of Lifelines participants included in the EyeLife study

Table 1 Baseline characteristics of Lifelines participants who participated in the EyeLife study, stratified by categorical genetic risk for glaucoma

	High genetic risk ($n=487$)	Low genetic risk ($n=535$)	p value**
Age (year; median [IQR])	63 [59,70]	65 [59,70]	0.19
Gender (n, % female)	256 (52.6)	289 (54.0)	0.66
IOP* (mmHg)	16.5 (3.9)	14.3 (3.7)	2.5×10^{-21}
CCT* (µm)	540 (33)	536 (31)	0.066
Spherical equivalent* (D)	0.06 (2.6)	0.54 (2.2)	9.6×10^{-3}
BCVA of better eye	0.92 (0.31)	0.89 (0.31)	0.37
BCVA of worse eye	1.11 (0.22)	1.10 (0.22)	0.21
pRNFLT* (µm)	117 (14)	120 (13)	1.3×10^{-3}

Mean (SD) is shown unless indicated otherwise

IQR interquartile range, *IOP* intraocular pressure, *CCT* central corneal thickness, *BCVA* best corrected visual acuity, *pRNFLT* peripapillary retinal nerve fiber layer thickness

*Mean value of both eyes

**Mann–Whitney U test used for non-normally distributed variables, Fisher's exact test used for categorical variables

Table 2 Demographic and ophthalmologic characteristics of glaucoma cases and unaffected participants in EyeLife

	Glaucoma** ($n=59$)	Unaffected ($n=903$)	p value***
Age (year; median [IQR])	70 [64,76]	63 [58,70]	4.0×10^{-7}
Gender (n, % female)	29 (49.2)	489 (54.2)	0.46
GRS (scaled)	0.98 (1.07)	−0.18 (1.47)	1.2×10^{-8}
IOP* (mmHg)	19.1 (4.4)	15.0 (3.3)	2.5×10^{-13}
CCT* (µm)	531 (35)	538 (32)	0.12
Spherical equivalent* (D)	−0.7 (2.8)	0.4 (2.3)	0.016
BCVA of better eye	0.82 (0.32)	0.91 (0.30)	0.051
BCVA of worse eye	1.01 (0.28)	1.11 (0.21)	0.006
pRNFLT* (µm)	95 (12)	120 (13)	1.5×10^{-29}

Mean (SD) is shown unless indicated otherwise

IQR interquartile range, *IOP* intraocular pressure, *CCT* central corneal thickness, *BCVA* best corrected visual acuity, *pRNFLT* peripapillary retinal nerve fiber layer thickness

*Mean value of both eyes

**Cases classified as having either 'definite' or 'probable' glaucoma

***Mann–Whitney U test used for non-normally distributed variables; p values were Bonferroni corrected for two post-hoc tests per variable; those classified as unaffected were also compared to possible glaucoma (not displayed in this table), see Supplementary Fig. S3 for more information

re-examined. Of those, 6 were diagnosed with primary angle closure glaucoma and therefore excluded, resulting in a final cohort of 1022 participants.

Table 1 presents the baseline characteristics of the included participants, stratified by GRS group (see Supplementary Table S1 for a more granular depiction of study baseline characteristics). The median age was 64 (IQR 59–70) years, with 53% ($n=545$) female participants; the high and low GRS group did not differ regarding age and gender distribution. Participants in the high GRS group had a higher IOP, were more often myopic, and had a thinner pRNFL compared to the participants in the low GRS group; the groups did not differ regarding BCVA and CCT (Supplemental Figure S1). No difference was observed in the GRS distribution between genotyping platforms ($p=0.62$; Supplemental Figure S2).

Of the 1022 included participants, 59 were classified as glaucoma cases, 60 as possible glaucoma, and 903 as unaffected. Of the 903 unaffected participants, 14 participants were classified as OHT (as they presented with no other ocular abnormalities, they were classified as 'unaffected' in this manuscript). When compared to the unaffected participants, glaucoma cases were significantly older ($p=4.1\times10^{-7}$), had a significantly higher glaucoma GRS ($p=1.2\times10^{-8}$), had a higher IOP ($p=2.3\times10^{-13}$), were more often myopic ($p=0.016$), and had a thinner pRNFL ($p=1.5\times10^{-29}$; see Table 2 and Supplemental Figure S3).

Figure 2 highlights the distribution of the glaucoma GRS across the glaucoma categories. When compared to unaffected participants, the glaucoma GRS was significantly higher in the glaucoma cases and in the participants with possible glaucoma, while there was no significant difference between the glaucoma cases and the participants with possible glaucoma. Supplementary Figure S4 provides more detail, with the glaucoma cases separated as definite and probable glaucoma, and possible glaucoma separated as

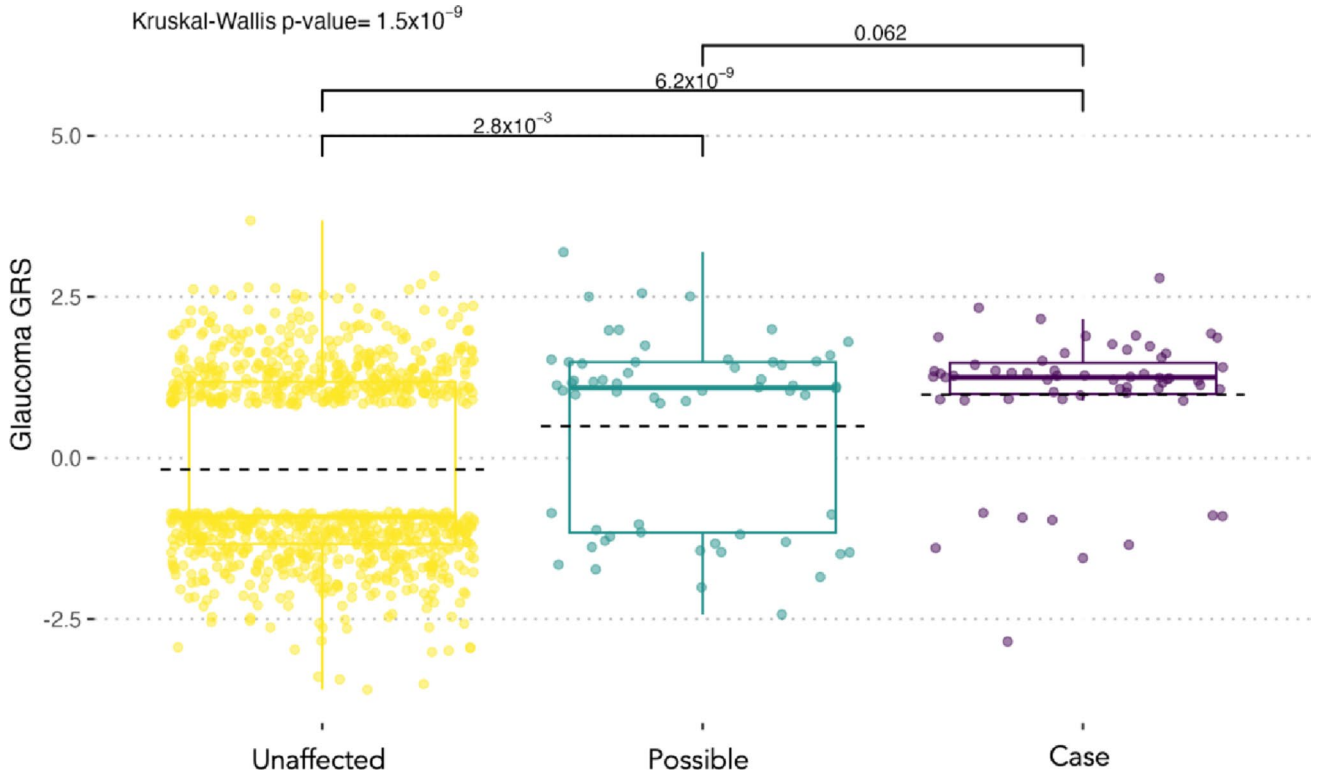


Fig. 2 Distribution of the glaucoma genetic risk score stratified by glaucoma classification. Statistical significance between the three groups was assessed with Kruskal–Wallis test and post-hoc pairwise by Mann-Whitney U-tests

Table 3 Glaucoma classification of EyeLife participants, stratified by genetic risk

	High genetic risk (n=487)	Low genetic risk (n=535)
Definite glaucoma	29	2
Probable glaucoma	21	7
Based on GVFL	0	1
Based on GON and RNFL defect	21	6
Possible glaucoma	40	20
Based on GON	18	9
Based on RNFL defect	22	11
Unaffected	397	506

GVFL glaucomatous visual field loss, *GON* glaucomatous optic neuropathy, *RNFL* retinal nerve fiber layer

Table 4 Association between Glaucoma Genetic Risk Score (GRS) and Glaucoma Status within EyeLife

	Unadjusted model RR (95% CI)		Adjusted model* RR (95% CI)	
	Glaucoma	Possible glaucoma	Glaucoma	Possible glaucoma
GRS category (high)	6.4 (3.2–12.9)	2.4 (1.4–4.1)	7.4 (3.7–14.7)	2.6 (1.6–4.4)
GRS continuous (per SD increase in GRS)	1.72 (1.41–2.11)	1.34 (1.13–1.60)	1.83 (1.49–2.23)	1.38 (1.17–1.65)

Glaucoma Either 'definite' or 'probable' glaucoma, *RR* relative risk, *CI* confidence interval

*Adjusted for age, sex, and genotype platform

possible based on GON and possible based on the presence of RNFL abnormalities. The GRS distributions of both definite and probable glaucoma differed significantly from that of the unaffected participants.

Table 3 shows the glaucoma classification of the participants, stratified by genetic risk. Notably, 50 glaucoma cases (29 definite, 21 probable) were observed in the high GRS group, compared to only nine (two definite, seven probable) in the low GRS group. The prevalence of the combined definite and probable glaucoma was 10.3% in the high genetic risk group, compared to 1.7% in the low genetic risk group. For possible glaucoma, 40 were within the high GRS group compared to 20 in the low GRS group, resulting in prevalences of 8.2% and 3.7%, respectively. Thus, participants with a high glaucoma GRS have a much higher prevalence of definite, probable, and possible glaucoma compared to those with a low glaucoma GRS.

Table 4 shows that participants with a high GRS had a significantly elevated risk of being classified as a glaucoma case, compared to those with a low GRS (adjusted RR = 7.4, 95% confidence interval [CI]: 3.7–14.7). When the GRS was analysed as a continuous variable, each unit (standard

deviation) increase in the glaucoma GRS was associated with an adjusted RR of 1.83 (95% CI 1.49–2.23) for the glaucoma cases. An elevated risk of the continuous GRS was also observed for possible glaucoma, although to a lesser extent (adjusted RR = 1.38, 95% CI 1.17–1.65).

Table 5 presents the age-specific prevalence for combined definite and probable glaucoma, stratified by genetic risk. For those with a high GRS, the prevalence increased from approximately 4 to 30% when going from 55 to 59 to 80 + years of age; for those with a low GRS, the prevalence increased from less than 1 to approximately 5%. The RR did not vary significantly across the age strata ($p = 0.9$).

Follow-up ophthalmic examinations were arranged for participants classified as definite or probable glaucoma, and at that time participants were asked to disclose their knowledge of their glaucoma status. Of the 59 cases, only 20 (34%) were aware of their glaucoma status. Participants with definite glaucoma had a significantly higher awareness than participants with probable glaucoma (52% compared to 14%, respectively, $p = 0.003$), see Supplementary Table S2.

Table 5 Age-specific prevalence of glaucoma by GRS category

Age (year [*n*])	High GRS (95% CI)	Low GRS (95% CI)
55–59 (291)	3.5 (1.2–8.0)	0.7 (0.02–3.7)
60–64 (250)	5.9 (2.6–11.3)	1.7 (0.2–6.1)
65–69 (179)	11.7 (5.5–21.0)	2.0 (0.2–7.0)
70–74 (182)	15.9 (8.7–25.6)	2.0 (0.2–7.0)
75–79 (85)	30.0 (16.6–46.3)	2.2 (0.1–11.8)
80 + (35)	27.3 (6.0–61.0)	4.8 (0.1–23.8)

GRS Genetic risk score

Discussion

In this prospective, double-blind screening study of 1022 participants from the Dutch Lifelines cohort, we identified a strong association between the genetic risk for and the prevalence of glaucoma. The risk of being classified as a glaucoma case was more than 7 times higher in the top versus bottom 20% of the GRS distribution.

Our study marks a significant milestone as the first prospective glaucoma screening study that uses genetic risk for identifying high-risk individuals. As such, a direct comparison to the literature is not possible. However, the potential of genetic pre-screening has been explored in retrospective studies. For instance, in 2019, a case-control study reported that a GRS consisting of 12 POAG-associated genetic variants was significantly associated with POAG, with an odds ratio of 1.24 (95% CI 1.21–1.27) per SD increase in GRS [29]. While not directly comparable, our prospective study corroborates these findings with an even higher adjusted RR of 1.83 (95% CI 1.49–2.23) per SD increase. The GRS used in the current study incorporated a broader set of 268 genetic markers, including those associated with IOP, CCT, and optic disc parameters, thereby enhancing its predictive ability. A recent cross-sectional study in the UK Biobank found that each SD increase in polygenic risk score (PRS) was associated with a 1.74 (95% CI 1.71–1.77) times higher odds of POAG [30]. This PRS was calculated using the best set of genetic variants selected via lasso regression from full GWAS results [30, 31]. The POAG prevalence was 7.4% at the highest decile of the glaucoma PRS compared to 1.3% at the lowest decile [30]. A post-hoc analysis of our data using GRS deciles instead of quintiles revealed even more pronounced results, with a glaucoma case prevalence of 9.7% in the top GRS decile compared to 0.9% in the bottom decile.

There are a number of strengths of this study. The Lifelines cohort is a large longitudinal cohort of participants representative of the general Dutch population. The ophthalmic examinations performed were comprehensive, and the double-blind design of the study limited biased test interpretation. The weighted GRS was constructed in a comprehensive and nuanced manner, by incorporating genetic variants not only associated with glaucoma, but also related endophenotypes. The participation rate in our study was 56%, which is higher than in other add-on studies conducted with Lifelines participants, for which the response rates varied between 10 and 50% [22]. Nevertheless, 44% did not participate. One could speculate that those being invited with known glaucoma are less likely to participate (because they already know that they have the disease), but they could also be more eager to participate (because they appreciate the importance of research aiming at early detection). Hence, non-response might have influenced our prevalence estimates in either direction, but is unlikely to have had a large effect on our primary outcome, which is essentially a ratio of two prevalences. A limitation is that this study was conducted in a Northwestern European population. Given the heterogeneous nature of glaucoma across different ethnicities [32, 33], the applicability of our findings to other populations needs further investigation. Genetic pre-screening may be more effective in populations with a higher disease burden, but the GRS must be tailored to the genetic architecture of the population being screened. Further, the GRS utilized in this study was designed in 2018 and incorporated only genome-wide significant variants for either POAG or its endophenotypes identified at that time. With increasing GWAS sample sizes, the effect sizes of glaucoma associated genetic variants will be more accurately estimated, resulting in a reduction of noise and increased predictive ability. Furthermore, the GRS approach can be updated to PRS methodology that uses all variants across the genome based on effect estimates from the most recent POAG GWASs of

larger sample sizes [34]. Advanced PRS calculation algorithms such as SbayesRC [35], which incorporate information on functional annotation of genetic variants, would further increase the precision and predictive power of population-based genetic screening of glaucoma. As such, our results could be considered a lower limit of what can be reached with genetic pre-screening. Another limitation is that we lack information regarding the prevalence in the middle three GRS quintiles. Our study was - intentionally - designed as a proof of principle, and further investigation is required to identify the threshold in the genetic susceptibility (i.e., PRS) distribution that optimizes case detection in population-based glaucoma screening.

What is to be expected regarding the glaucoma prevalences in the unmeasured middle three GRS quintiles? We found a prevalence of 10.3% in the fifth (high-risk) and of 1.7% in the first (low-risk) quintile. If we would assume a linear increase in prevalence for the quintiles, the overall prevalence would be around 6%. Based on a more conservative assumption that the prevalences in the unmeasured quintiles are the same as in the first quintile, the estimated overall prevalence would be 3.4%. The latter value aligns reasonably well with prevalence data from population-based samples, which are approximately 3% [6, 30, 36–38], and this would suggest that more than half of the glaucoma cases are concentrated within the highest GRS quintile (10.3% vs. 6.8% (4 × 1.7%) in the other four quintiles), confirming the potential of genetic prescreening. This agrees reasonably well with a retrospective analysis within the UK Biobank by Sekimitsu et al., who showed that between one third and half of the glaucoma cases were within the highest two GRS deciles [30].

Genetic pre-screening can also help to mitigate length bias. Length bias refers to the situation that cases detected by a periodic screening programme tend to have milder disease variants than those detected in another way, because cases with fast-progressing variants are more likely to be detected before their next periodic screening takes place. Length bias has been shown to hamper glaucoma screening [39]. Focus on individuals at high genetic risk during screening, by only screening these individuals or by screening them more often than individuals at low risk, would potentially reduce the overrepresentation of slow-progressing glaucoma cases in screening programmes, thus mitigating length bias.

Many people in the community are unaware they have glaucoma, with most population-based studies reporting that around 50% of cases are undiagnosed [40]. We observed a comparable low awareness among the glaucoma cases in our study (34%), with a significant difference in awareness between the definite (52%) and probable (14%) glaucoma cases. One could hypothesize a difference in awareness between the high and low genetic risk group - if a positive family history would have initiated regular eye tests in the former. However, we did not observe an obvious difference in awareness between cases in the high ($n = 18$, 36%) and low ($n = 2$, 22%) genetic risk groups ($p = 0.4$). Given also the lack of knowledge of family history [14], the case for genetic pre-screening remains compelling.

Implementing targeted monitoring of high-risk individuals could facilitate earlier detection, to improve glaucoma prognosis if it develops - the amount of visual field loss at the time of diagnosis is an important predictor of end-of-life blindness [10]. It is an intriguing but yet unanswered question if the GRS could also be used effectively in protocols for follow-up after diagnosis, moving closer to personalized medicine. Interestingly, the longitudinal cohort study, Progression Risk of Glaucoma: Relevant SNPs With Significant Association (PROGRESSA) reported that a high polygenic risk was associated with more rapid structural and functional progression in early POAG [41]. Obviously, further research is needed before introducing and implementing GRS-based glaucoma detection and care. Population-based glaucoma screening was evaluated earlier as not cost-effective [12], with the (low) disease prevalence in the general population as the primary cause. Appropriate pre-screening, with a well-chosen GRS cut-off, addresses this issue. If we tentatively assume a minimum prevalence of 5% for cost-effective population-based glaucoma screening [15], those with a high GRS should be screened starting at an age of 60 years (Table 5). Interestingly, following the 5% prevalence threshold for cost-effective screening, those with a low GRS should not be screened at any age, or maybe once, around an age of 80 years. These suggestions are preliminary, as the number of cases precludes accurate age-specific prevalence calculations. Importantly, disease prevalence cannot be considered in isolation - test specificity is another major determinant of cost-effectiveness. The test specificity and detailed yield of the EyeLife protocol will be addressed in a separate article; the protocol was not primarily designed for a high specificity but rather for an optimal evaluation of the effect of pre-screening. Additionally, standardized risk assessment and patient-facing protocols need to be developed with respect to if/how genetic risk is disclosed [42]. Finally, ethical considerations must be addressed with respect to genetic data handling and stewardship, access, and privacy [43].

Conclusion

The glaucoma GRS shows considerable potential as a tool to select individuals for glaucoma screening. The significant ability of the GRS to identify individuals at a high risk for glaucoma, specifically those that are unaware of their

condition, could substantially improve early detection and management of glaucoma.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10654-026-01429-8.

Acknowledgements We gratefully acknowledge the services of Lifelines, the contributing research centers delivering data to Lifelines, and all the study participants. We deeply appreciate Kim Westra and Corien van der Worp for their commitment, exceptional organizational support, and continued efforts in data collection and participant follow-up. Finally, we are extremely grateful to Prof. Chris Hammond, for his critical comments on a preliminary version of the manuscript.

Author contributions Conceptualization: NJ, HS; Data curation: AN, IN; Formal analysis: AN, IN; Funding acquisition: NJ, HS; Investigation: NJ, AN; Methodology: NJ, IN, AN, HS; Project administration: NJ, AN; Resources: NJ; Software: AN, IN; Visualization: AN, IN; Writing, review, and editing of the manuscript: AN, NJ, IN, HS.

Funding This study was funded by the European Union (EU) Horizon 2020 grant No 661883 European Glaucoma Research Training Program (EGRET) and by Uitzicht grant No 2015–11 (ANVVB, Glaucoomfonds, LSBS, Novartisfonds, Oogfonds, Stichting Blinden-Penning). The Lifelines cohort and biobank was supported by subsidies from the Dutch Ministry of Health, Welfare and Sport, the Dutch Ministry of Economic Affairs, the University Medical Center Groningen, the University of Groningen, and the Northern Provinces of the Netherlands.

Data availability Researchers can apply to use the Lifelines data used in this study. More information about how to request Lifelines data and the conditions of use can be found on their website (https://www.lifelines.nl/researcher/how-to-apply).

Declarations

Competing interests The authors declare that they have no competing interests.

Ethical approval The study protocol was approved by the ethics board of the UMCG (NL65947.042.18) and registered with the Dutch Trial Register (NL-OMON48818; 31-01-2019). All participants provided written informed consent. The study followed the tenets of the Declaration of Helsinki.

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