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Nationwide cohort study of primary open angle glaucoma risk and cardiovascular factors among in Korean glaucoma suspects

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This retrospective study investigated the risk of primary open-angle glaucoma (POAG) among individuals identified as glaucoma suspects and examined associated cardiovascular risk factors. We conducted a longitudinal, nationwide cohort study using data from the Korean National Health Insurance Service (KNHIS) and included 362,285 participants aged ≥ 40 years from the Korean National Health Screening Program (NHSP) without pre-existing POAG in 2009 and 2010. Of these, glaucoma suspects (*n* = 32,220) were defined as individuals with at least two recorded instances of the KCD code H400 for glaucoma suspect and no prior antiglaucoma medication prescriptions before health screening. The primary outcome was the diagnosis of POAG and the prescription of antiglaucoma medications. Over a 6-year follow-up, 4.92% of glaucoma suspects developed POAG. Through multivariate Cox regression analysis, glaucoma suspects with diabetes, hypertension, dyslipidemia, or coronary heart disease exhibited a greater risk of conversion to POAG than those without these comorbidities ([HR, 1.354; 95%CI, 1.201 to 1.527] for diabetes, [HR, 1.139; 95%CI, 1.019 to 1.273] for systemic hypertension, [HR, 1.128; 95%CI, 1.013 to 1.26] for dyslipidemia, [HR, 1.124, 95%CI, 1.007 to 1.254] for coronary heart disease).This nationwide study observed that among glaucoma suspects, having cardiovascular risk factors/disease was associated with higher risk of developing POAG.

Glaucoma is a prominent cause of irreversible blindness globally. The initiation of medical treatment upon detection of primary open angle glaucoma (POAG), a condition characterized by progressive optic nerve damage and visual field (VF) loss, is important. However, identifying and managing individuals at risk of POAG is not straightforward, particularly in glaucoma suspects who exhibit features such as glaucomatous optic disc, suspicious retinal nerve fiber layer (RNFL), or elevated intraocular pressure (IOP), yet do not meet the diagnostic criteria for POAG due to the absence of VF loss.

The decision-making process regarding the management of glaucoma suspects is intricate and hinges upon various factors, including ocular, systemic, medical, and psychosocial considerations[1]. The landmark Ocular Hypertension Treatment Study (OHTS) shed light on the risk of conversion to POAG among individuals with elevated IOP but lacking overt signs of glaucomatous structural changes, revealing a 9.5% prevalence at 5 years[2]. Furthermore, investigations into the progression of glaucoma suspects with glaucomatous optic disc characteristics such as high cup to disc ratio have unveiled a risk of glaucoma conversion of 12.1% during 8.7 years or 12.6% during 5–6 years of follow-up[3,4]. These findings suggesting a relatively low rate of conversion among glaucoma suspects, juxtaposed with the potential for progression to glaucoma, and subsequent vision impairment in advanced stages, the decision to begin treatment or to determine the follow up period of glaucoma suspects should consider the risk-benefit ratio. Therefore, sorting high-risk glaucoma suspects according to the likelihood of glaucoma conversion would be critical in the management of glaucoma suspects.

Increased IOP is a causative and critical risk factor for development and progression of glaucoma. However, glaucoma develops in the normal range of IOP and frequently progresses despite IOP-lowering treatment. Vascular dysregulation, encompassing systemic hypertension or hypotension, unstable blood pressure (BP), or autonomic dysregulation, has been implicated in the development or progression of glaucoma[5–8]. It is plausible that cardiovascular disease or risk factors could be related to progression of glaucoma suspect to glaucoma. In a small-sized, hospital-based clinical study, identifying cardiovascular disease or risk factors associated with progression of glaucoma in suspects is challenging due to potential underdetection and the imprecision of

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information on systemic conditions obtained from questionnaires. There has been no confirmatory evidence of a relationship between cardiovascular risk factors and progression of glaucoma suspects to POAG.

In this study, based on a nationwide, population-based cohort, we investigated the risk of glaucoma suspects progressing to glaucoma and the associated cardiovascular risk factors after adjusting for confounding factors.

Methods

Data sources

This nationwide, population-based, retrospective cohort study utilized data provided by the Korean National Health Insurance Service (KNHIS), which covers approximately 97% of all Koreans. The KNHIS database contains patient demographics such as age, sex, and income, as well as health claim data of diagnoses, dates of medical visits, examinations, prescriptions, and procedures. Diagnoses are recorded as diagnostic codes from the Korean Standard Classification of Diseases (KCD), 7th revision, classified in accordance with the International Statistical Classification of Disease, 10th revision system (ICD-10). The KNHIS also offers a free biennial National Health Screening Program (NHSP) for the Korean population for prevention and early detection of diseases. NHSP includes anthropometric measurements, blood pressure, laboratory tests, and a self-reported questionnaire on health behaviors such as smoking, alcohol drinking, and physical activity. The KNHIS developed the Health Screening Cohort (NHIS-HEALS) for research purposes.

To construct the NHIS-HEALS database, a sample cohort was first selected from the 2002 and 2003 health screening participants aged 40 years or older in 2002 and who were followed through 2019. This cohort included 514 886 health screening participants who comprised a 10% random sample of all screening participants in 2002 and 2003. Since only a small proportion of people aged < 40 years participated in the health screening program, the NHIS-HEALS was limited to adults aged 40 years and older.

Standard protocol approvals

The KNHI-HEALS database is a publicly accessible repository. The Institutional Review Board of The Catholic University of Korea, Seoul St. Mary's Hospital (KC20ZASI0111) granted approval for the utilization of the KNHI-HEALS database and a waiver of informed consent, as the data provided by the KNHIS were fully anonymized. This study followed the tenets of the Declaration of Helsinki.

Study Population

Of 362,285 participants who attended the National Health Screening program in 2008 and 2009 among the Health Screening Cohort database, 4319 who had pre-existing primary open angle glaucoma (POAG) (KCD code H401) and prescription of antiglaucoma medications before health screening were excluded (Fig. 1). Of the remaining 357,966 participants, 33,499 were classified as "glaucoma suspect". The diagnostic criteria for glaucoma suspect were based on the presence of the Korean Classification of Diseases (KCD) code H400, which corresponds to "glaucoma suspect" in clinical practice. To ensure the reliability of this classification, participants were required to have had at least two clinical visits where this code was recorded. Additionally, participants with a history of antiglaucoma medication prescriptions before the baseline health screening were excluded to avoid misclassification (Fig. 1). Of them, 32,220 (glaucoma suspect group) participants were included in this study after exclusion of participants with missing data. The primary endpoint of the study was the incidence of POAG (KCD code H401) and the prescription of antiglaucoma medications. Conditions such as primary angle-closure glaucoma, secondary glaucomas, and retinal diseases (e.g., retinal vein occlusion or diabetic retinopathy) were not explicitly excluded from the study population during the initial study design or follow-up period. For subgroup analysis, we studied the risk of participants without suspected glaucoma or POAG for POAG development. After excluding participants with pre-existing POAG or glaucoma suspect, 311,765 participants (control group) were included in the subgroup analysis, and the primary endpoint was development of POAG. We longitudinally followed these participants to determine the risk of POAG and cardiovascular factors associated with POAG development until December 2015.

Health screening examination data and other variables

Personal information for each patient was collected from the National Health Screening program. Area of residency was categorized as either urban or rural. Medical history, health behavior, anthropometric measurements (body mass index [BMI], waist circumference), blood pressure (BP), and laboratory test results were also obtained. In this study, participants who self-reported smoking or drinking any amount of pure alcohol were categorized as current smokers or drinkers, respectively. Regular physical activity was defined as high-intensity physical activity performed for at least 20 min 3 times weekly or moderate-intensity activity for at least 30 min 5 times weekly. High-intensity physical activity was defined as activities resulting in extreme shortness of breath, such as running, cycling at high speed, or engaging in activities requiring significant exertion, such as carrying boxes upstairs. Moderate-intensity physical activity was characterized by activities inducing noticeable shortness of breath, such as brisk walking, cycling at regular speed, and carrying light objects. For determination of low-income status, participants falling within the lowest quartile of the population's income distribution were classified as low-income. BMI was calculated by dividing weight in kilograms by height in square meters. Obesity was determined for the Korean population with a cutoff of 25 kg/m^2, as per the Clinical Practice Guidelines for Overweight and Obesity by the Korean Society for the Study of Obesity. Abdominal obesity was defined with a cut off waist circumference ≥ 90 cm in men and ≥ 85 cm in women based on the obesity guidelines issued by the Korean Society for the Study of Obesity. Diabetes mellitus was defined as a fasting glucose level of 126 mg/dl or the use of insulin or oral hypoglycemic agents, with diagnostic codes E11 through E14 according to the use of ICD-10. Hypertension was diagnosed based on a systolic BP of 140 mmHg or higher, a diastolic BP of 90 mmHg or higher, or the use of oral antihypertensive medications, with ICD-10 diagnosis codes I10 through I13 and

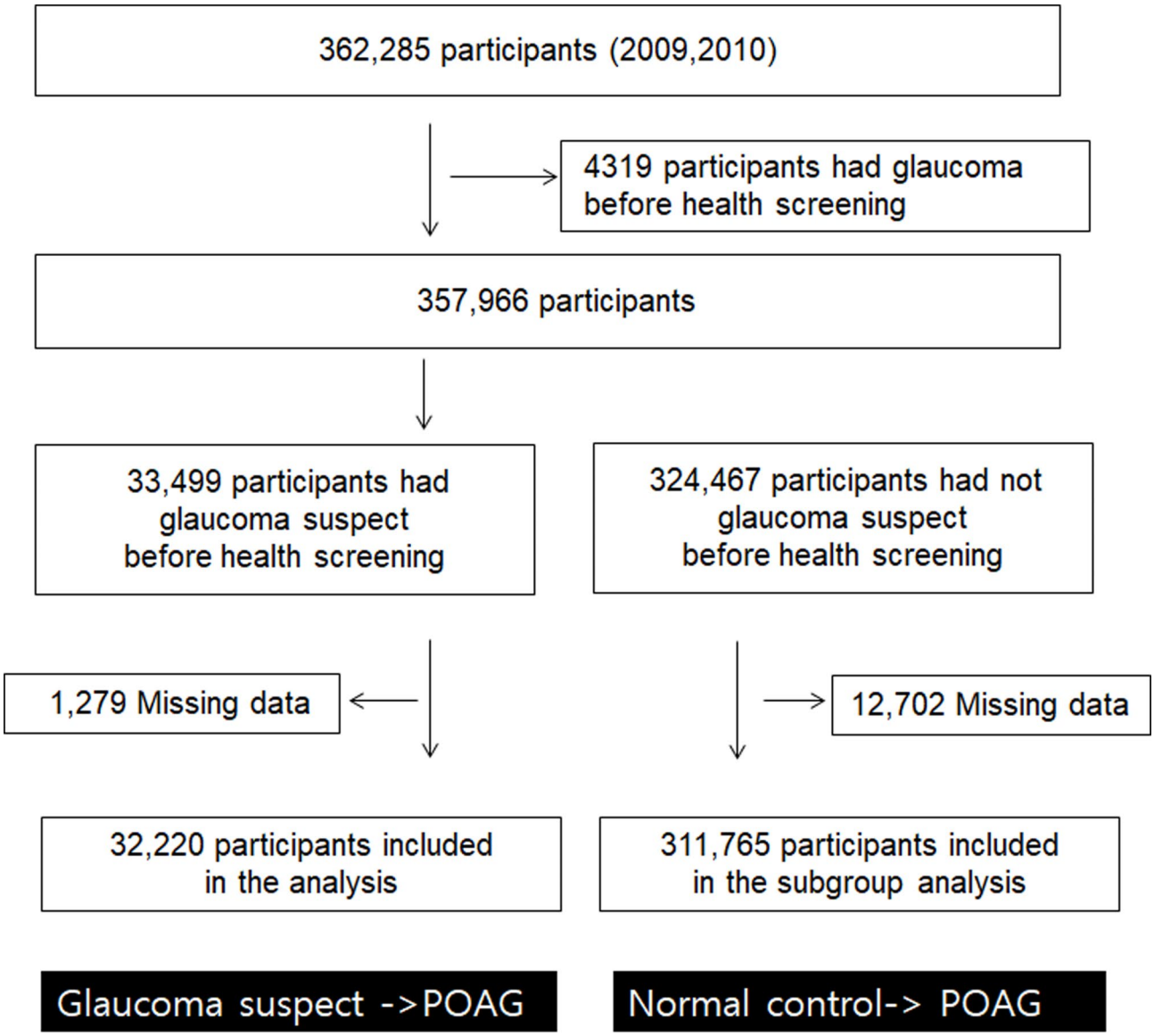

Fig. 1. Flowchart of the cohort study design.

I15. Participants underwent blood pressure measurements during the daytime in a seated position after a rest of 5 min preceding each reading. Dyslipidemia was diagnosed based on either a total cholesterol level equal to or exceeding 240 mg/dl or the utilization of cholesterol-lowering medications, with the corresponding ICD-10 diagnosis code of E78. Chronic kidney disease (CKD) was diagnosed when the glomerular filtration rate (GFR) fell below 60 ml/min per 1.73 m^2. Blood samples collected after overnight fasting were used to measure serum glucose, total cholesterol, and creatine levels. Coronary heart disease was defined based on ICD-10 diagnostic codes I20-25. Stroke was identified based on ICD-10 diagnostic codes I63 and I64. Proteinuria was assessed by analyzing dipstick urinalysis results using a color scale, where proteinuria levels were classified as 'negative,' 'trace,' '1+,' '2+,' '3+,' or '4+.' Proteinuria was defined as a level ≥ 1 + on the scale.

Statistical analyses

The baseline characteristics are presented as mean values with standard deviations for continuous variables or percentages for categorical variables. Student's *t* test and chi-square tests were used for analyzing continuous and categorical variables, respectively. To identify the risk factors for POAG development, hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated using a Cox proportional hazard regression model. Model 1 represents a non-adjusted model, while Model 2 adjusts for age and sex. Model 3 further adjusts for residence area; income status; smoking; alcohol consumption; physical activity; and comorbidities of obesity, diabetes, hypertension, dyslipidemia, chronic kidney disease, coronary heart disease, stroke, and proteinuria (*P* value < 0.01 in univariate analysis). Participants were followed from the baseline until one of the following events occurred: (1) the development of POAG or (2) death. Participants who died during the follow-up period were censored at their date of death. The cumulative incidence of POAG was estimated using Kaplan-Meier curves

over the entire follow-up period. Differences in POAG development between participants with and without glaucoma suspect were examined using log-rank test. All statistical analyses were performed using SAS software version 9.4 (SAS Institute, Inc, Cary, NC, USA). A P value < 0.05 was considered statistically significant.

Results

Patient characteristics

Out of a total of 32,220 participants who had glaucoma suspect, 1579 individuals developed POAG, while 30,641 individuals did not exhibit POAG. Individuals with baseline glaucoma suspect who developed POAG were more likely to be older age, male, and current smoker compared to those who did not develop POAG ($P < 0.0001$, < 0.0001, 0.0191, respectively; Table 1). Regarding comorbidities, individuals who developed glaucoma showed a greater incidence of diabetes, systemic hypertension, dyslipidemia, coronary heart disease, and stroke at baseline ($P < 0.0001$, < 0.0001, 0.0002, < 0.0001, 0.0072, respectively).

Progression from glaucoma suspect to POAG

During 6-year follow-up period, the cumulative percentage of newly developing POAG among individuals who had glaucoma suspect was 4.92% (95% CIs, 4.38, 5.17), while 1.05% (95% Cis, 1.05, 1.12) of individuals without glaucoma suspect developed POAG according to the survival curve (Log-rank p value < 0.0001; Fig. 2).

Risk of conversion to POAG according to characteristics and comorbidities

Table 2 displays the incidence rates and hazard ratios (HRs) for POAG, both non-adjusted (model 1) and multivariable-adjusted (Model 1: adjusted for age and sex, Model 2: adjusted for all variables), categorized by age, sex, smoking status, alcohol drinking status, regularity of physical activity, income status, and comorbidities including obesity, diabetes, systemic hypertension, dyslipidemia, CKD, proteinuria, coronary heart disease, and stroke. In Model 3, individuals of older age showed a greater risk of developing POAG compared to individuals in their 40s ([HR, 1.424; 95% CI, 1.112 to 1.182] for 50s, [HR, 1.953; 95% CI, 1.523 to 2.503] for 60s, [HR, 2.094; 95% CI, 1.623 to 2.7] for 70s, [HR, 2.017; 95% CI, 1.429 to 2.848] for 80s or older). Female or obese individuals demonstrated a lower risk of progression to POAG compared to male or non-obese subjects, respectively ([HR, 0.773; CI 0.687 to 0.871] for female, [HR, 0.883; CI 0.793–0.983] for being obese). Glaucoma suspects with diabetes, hypertension, dyslipidemia, or coronary heart disease exhibited a greater risk of conversion to POAG than those without these comorbidities ([HR, 1.354; 95%CI, 1.201 to 1.527] for diabetes, [HR, 1.139; 95%CI, 1.019 to 1.273] for systemic hypertension, [HR, 1.128; 95%CI, 1.013 to 1.26] for dyslipidemia, [HR, 1.124, 95%CI, 1.007 to 1.254] for coronary heart disease). Analysis on the effects of different age group (cut off of 65 years) and sex on the association between cardiovascular risk factors and conversion to POAG failed to demonstrate any significant impact (Supplemental Table 1).

Risk factors associated with development of glaucoma among individuals without glaucoma or glaucoma suspect

Among individuals without glaucoma or glaucoma suspect at baseline, subjects who developed POAG were more likely to be older age, male, nonsmoker, non-alcohol drinker compared to those who did not develop POAG

		Development of POAG		
	Total	No	Yes	*p* value*
n	*n* = 32,220	*n* = 30,641	*n* = 1579	
Age (years)	60.62 ± 9.22	60.51 ± 9.21	63.49 ± 9.21	< 0.0001
Sex (male)	14,664(45.51)	13,848(45.19)	816(51.68)	< 0.0001
Place (Urban)	14,764(45.82)	14,040(45.82)	724(45.85)	0.9809
Low income	4397(13.65)	4167(13.6)	230(14.57)	0.2751
Current smoker	3428(10.64)	3232(10.55)	196(12.41)	0.0191
Current alcohol drinker	9967(30.93)	9446(30.83)	521(33)	0.0692
Regular physical activity	9311(28.9)	8835(28.83)	476(30.15)	0.2621
Obesity	11,000(34.14)	10,476(34.19)	524(33.19)	0.412
Abdominal obesity	8397(26.06)	7970(26.01)	427(27.04)	0.3625
Diabetes mellitus	5725(17.77)	5338(17.42)	387(24.51)	< 0.0001
Hypertension	16,239(50.4)	15,328(50.02)	911(57.69)	< 0.0001
Dyslipidemia	10,544(32.73)	9960(32.51)	584(36.99)	0.0002
Chronic kidney disease	3736(11.6)	3532(11.53)	204(12.92)	0.0919
Coronary heart disease	9262(28.75)	8727(28.48)	535(33.88)	< 0.0001
Stroke	1528(4.74)	1431(4.67)	97(6.14)	0.0072
Proteinuria	1116(3.46)	1051(3.43)	65(4.12)	0.1457

Table 1. Characteristics of Glaucoma suspects. POAG, primary open angle glaucoma. Data are presented as number (%) mean ± standard deviation. *Calculated using Student's *t* test for continuous variables and chi-square test for categorical variab.

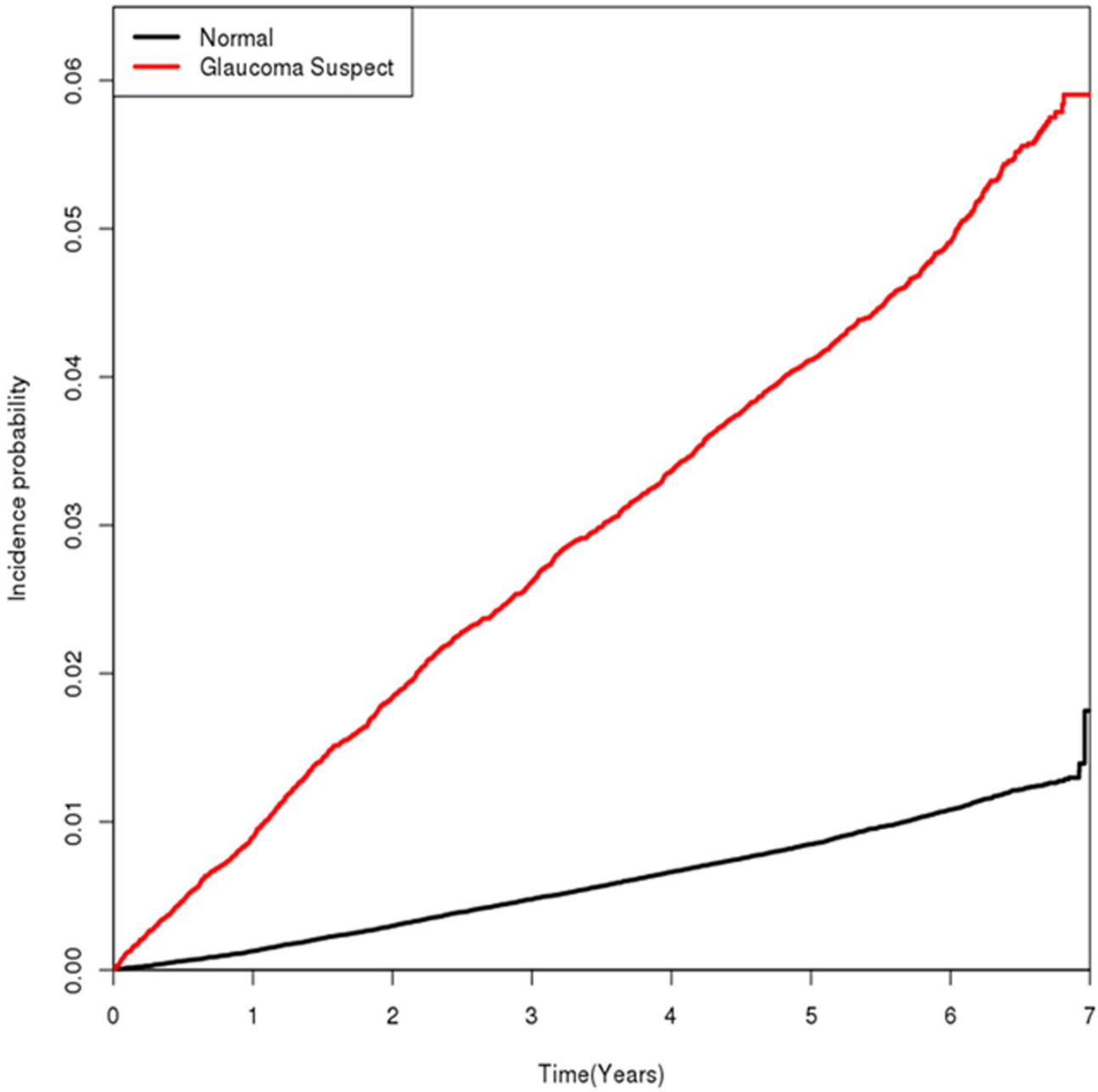

Fig. 2. Kaplan-Meier survival curves of cumulative incidence of primary open-angle glaucoma (POAG) in glaucoma suspects and the general population. The cumulative percentage of newly developed POAG among individuals who had glaucoma suspect was 4.92% (95% CIs, 4.38, 5.17), while 1.05% (95% Cis, 1.05, 1.12) of individuals without suspected glaucoma developed POAG (log-rank p value < 0.0001).

($P < 0.0001$, 0.0052, 0.0002, 0.083, respectively; Supplemental Table 2). Regarding comorbidities, individuals who developed glaucoma exhibited a higher incidence of diabetes, systemic hypertension, dyslipidemia, CKD, proteinuria, coronary heart disease, and stroke ($P < 0.0001$, < 0.0001, < 0.0001, < 0.0001, 0.0009, < 0.0001, < 0.0001, respectively).

Supplemental Table 3 displays the incidence rates and hazard ratios (HRs) for POAG among subjects without baseline glaucoma or glaucoma suspect, both non-adjusted (model 1) and multivariable-adjusted (Model 1: adjusted for age and sex, Model 2: adjusted for all variables). In Model 3, individuals with of older age exhibited a greater risk of developing POAG compared to subjects in their 40s ([HR, 1.716; 95% CI, 1.474 to 1.997] for 50s, [HR, 3.190; 95% CI, 2.735 to 5.049] for 60s, [HR, 4.299; 95% CI, 3.661 to 5.049] for 70s, [HR, 5.0147; 95% CI, 3.971 to 6.331] for 80s or older). Female or current smoker or obese individuals demonstrated a lower risk of progression to POAG compared to male, non-smokers, or non-obese subjects, respectively ([HR, 0.831; CI 0.767 to 0.901] for female, HR, 0.894; CI 0.808 to 0.989] for smokers, [HR, 0.915; CI 0.850–0.984] for being obese). Glaucoma suspects with diabetes, hypertension, dyslipidemia, or coronary heart disease exhibited a

Variables		Glaucoma suspect, *n*	POAG, *n*	Pearson-years	Rate*	Model 1 Hazard Ratio (95% CI)	Model 2 Hazard Ratio (95% CI)	Model 3 Hazard Ratio (95% CI)
Sex	Male	14,664	816	82939.04	9.84	1(ref.)	1(ref.)	1(ref.)
	Female	17,556	763	101624.21	7.51	0.764(0.692,0.843)	0.738(0.669,0.815)	0.773(0.687,0.87)
	p value					0.0016	< 0.0001	< 0.0001
Age	40s	2650	74	15608.3	4.74	1(ref.)	1(ref.)	1(ref.)
	50s	11,336	451	65854.52	6.85	1.448(1.132,1.851)	1.49(1.165,1.906)	1.424(1.112,1.822)
	60s	9267	523	53398.48	9.79	2.068(1.621,2.638)	2.162(1.694,2.759)	1.953(1.523,2.503)
	70s	7783	467	43634.08	10.70	2.257(1.766,2.884)	2.385(1.865,3.049)	2.094(1.623,2.7)
	80-	1184	64	6067.87	10.55	2.223(1.591,3.106)	2.313(1.655,3.233)	2.017(1.429,2.848)
	p value					< 0.0001	< 0.0001	< 0.0001
Region	Urban	14,764	724	84770.47	8.54	1(ref.)	1(ref.)	1(ref.)
	Rural	17,456	855	99792.78	8.57	1.004(0.909,1.108)	0.984(0.891,1.087)	0.987(0.893,1.09)
	p value					0.9407	0.7523	0.7937
Low income (Bottom 20%)	No	27,823	1349	159339.83	8.47	1(ref.)	1(ref.)	1(ref.)
	Yes	4397	230	25223.42	9.12	1.076(0.935,1.237)	1.078(0.937,1.241)	1.081(0.939,1.244)
	p value					0.3063	0.2929	0.2776
Current smoker	No	28,792	1383	165157.05	8.37	1(ref.)	1(ref.)	1(ref.)
	Yes	3428	196	19406.19	10.10	1.205(1.037,1.399)	1.131(0.965,1.325)	1.111(0.946,1.304)
	p value					0.0146	0.1286	0.1982
Current alcohol drinker	No	22,253	1058	127267.74	8.31	1(ref.)	1(ref.)	1(ref.)
	Yes	9967	521	57295.51	9.09	1.093(0.984,1.214)	1.034(0.915,1.169)	1.03(0.909,1.166)
	p value					0.0965	0.5918	0.6441
Regular physical activity	No	22,909	1103	130945.22	8.42	1(ref.)	1(ref.)	1(ref.)
	Yes	9311	476	53618.03	8.88	1.055(0.948,1.175)	1.068(0.958,1.192)	1.066(0.955,1.19)
	p value					0.3278	0.2349	0.2525
Obesity	No	21,220	1055	121156.59	8.71	1(ref.)	1(ref.)	1(ref.)
	Yes	11,000	524	63406.65	8.26	0.949(0.855,1.054)	0.945(0.851,1.049)	0.883(0.793,0.983)
	p value					0.3295	0.2861	0.0233
Diabetes	No	26,495	1192	152674.06	7.81	1(ref.)	1(ref.)	1(ref.)
	Yes	5725	387	31889.19	12.14	1.554(1.386,1.743)	1.436(1.279,1.613)	1.354(1.201,1.527)
	p value					< 0.0001	< 0.0001	< 0.0001
Systemic Hypertension	No	15,981	668	92563.38	7.22	1(ref.)	1(ref.)	1(ref.)
	Yes	16,239	911	91999.87	9.90	1.371(1.241,1.515)	1.219(1.098,1.354)	1.139(1.019,1.273)
	p value					< 0.0001	0.0002	0.0215
Dyslipidemia	No	21,676	995	124521.71	7.99	1(ref.)	1(ref.)	1(ref.)
	Yes	10,544	584	60041.53	9.73	1.218(1.1,1.349)	1.219(1.099,1.351)	1.128(1.013,1.256)
	p value					0.0002	0.0002	0.0278
Coronary Heart Disease	No	22,958	1044	132557.97	7.88	1(ref.)	1(ref.)	1(ref.)
	Yes	9262	535	52005.28	10.29	1.307(1.178,1.45)	1.204(1.082,1.339)	1.124(1.007,1.254)
	p value					< 0.0001	0.0006	0.0373
Stroke	No	30,692	1482	176303.62	8.41	1(ref.)	1(ref.)	1(ref.)
	Yes	1528	97	8259.62	11.74	1.397(1.138,1.716)	1.237(1.005,1.522)	1.158(0.939,1.428)

Continued

Variables		Glaucoma suspect, *n*	POAG, *n*	Pearson-years	Rate*	Model 1 Hazard Ratio (95% CI)	Model 2 Hazard Ratio (95% CI)	Model 3 Hazard Ratio (95% CI)
	p value					0.0014	0.0448	0.1702
Chronic Kidney Disease	No	28,484	1375	163623.47	8.40	1(ref.)	1(ref.)	1(ref.)
	Yes	3736	204	20939.78	9.74	1.156(0.998,1.339)	1.046(0.9,1.215)	0.982(0.844,1.143)
	p value					0.0530	0.5604	0.8162
Proteinuria	No or trace	31,104	1514	178433.97	8.48	1(ref.)	1(ref.)	1(ref.)
	≥1+	1116	65	6129.27	10.60	1.248(0.974,1.6)	1.186(0.925,1.521)	1.064(0.827,1.369)
	p value					0.0800	0.1779	0.6299

Table 2. Association between Cardiovascular Risk comorbidities and Development of POAG among Glaucoma suspects. *Per 1,000 person-years. CI, confidence interval; POAG, primary open angle glaucoma. Model 1: Non-adjusted. Model 2: Adjusted by sex and age. Model 3: Adjusted by sex, age, region, income, smoking, drinking, regular physical activity, diabetes, hypertension, dyslipidemia, coronary heart disease, stroke, chronic kidney disease, proteinuria.

greater risk of conversion to POAG than those without these comorbidities ([HR, 1.283; 95%CI, 1.174 to 1.403] for diabetes, [HR, 1.163; 95%CI, 1.079 to 1.253] for systemic hypertension, [HR, 1.104; 95%CI, 1.023 to 1.192] for dyslipidemia, [HR, 1.202, 95%CI, 1.110 to 1.302] for coronary heart disease).

Discussion

Our study observed that 4.92% of individuals classified as glaucoma suspect progressed to POAG over a 6-year follow-up period, whereas only 1.05% of individuals without suspected glaucoma developed POAG. In our multivariate Cox proportional hazard regression model, significant predictors of POAG among the population identified as glaucoma suspects at baseline included older age, male gender, non-obesity, dyslipidemia, diabetes, systemic hypertension, and coronary heart disease.

The observed conversion rate from glaucoma suspect to POAG was 4.92% over the 6-year follow-up period, which was higher than the 1.08% conversion rate from control subjects to POAG ($P<0.001$). This finding underscores the increased risk of progression to POAG among glaucoma suspects. The observed conversion rate of this study is lower than previously reported rates ranging from approximately 9–12% for progression in individuals classified as OHT or glaucoma suspects[2–4]. The discrepancy in conversion rates may be attributed to differences in the definition of glaucoma suspects across studies. The definitions for glaucoma suspect include high IOP, glaucomatous optic disc, or RNFL thinning without visual field defects[3,4,9,10]. Our study defined glaucoma suspect based on diagnostic code without a history of prescription of antiglaucoma medication using health insurance claims data. These methodological characteristics may have contributed to the relatively lower observed conversion rate in our study population.

Our study observed old age as a risk factor for development of POAG among glaucoma suspects. Old age is an established risk factor for onset or progression of POAG[11–14]. The age-related susceptibility of the retinal ganglion cells to glaucomatous damage may be multifactorial, potentially involving mitochondrial dysfunction and impaired capacity to handle oxidative stress, as observed in other neurodegenerative disorders such as Alzheimer disease and Parkinson's disease[15,16].

Men are more susceptible to POAG than women, in line with a recent meta-analysis[17]. This gender discrepancy has been attributed to several factors, including men exhibiting longer axial length and a higher prevalence of cardiovascular diseases compared to women[18–20]. Although our study did not directly assess the degree of myopia, we adjusted for cardiovascular diseases. This suggests that anatomical factors, such as longer axial length, may contribute to the elevated risk of POAG among men. Nevertheless, further studies are warranted to elucidate the precise mechanism underlying this association.

We found that systemic cardiovascular disease or its risk factors of systemic hypertension, dyslipidemia, and coronary heart disease were predictive of POAG. Increasing clinical evidence has shown that hypertension could be a significant risk factor for glaucoma development and progression[4,8,21–23]. Microvascular damage, blood vessel alterations, and dysregulated blood flow induced by systemic hypertension could be associated with increased risk of conversion to POAG[22,24]. We did not observe an age-related relationship between systemic hypertension and progression to POAG (Supplemental Table 1), contrary to the Baltimore Eye Survey finding of an age-related association between blood pressure and glaucoma. A U-shaped relationship between glaucoma and blood pressure shows complexity between glaucoma and systemic hypertension[25]. Nocturnal or orthostatic hypotension and blood pressure fluctuation, which might be exacerbated by anti-hypertensive medication among individuals with systemic hypertension, could also contribute to progression of glaucoma, disturbing the stable blood supply to the optic nerve head and leading to ischemic-reperfusion injury[7,24,26].

We observed a significant association between dyslipidemia and a higher risk of POAG, consistent with findings from several meta-analyses that have reported a link between dyslipidemia such as elevated total cholesterol levels and glaucoma[27,28]. The most commonly related clinical consequence of dyslipidemia is associated with increased atherosclerotic cardiovascular disease risk, a known risk factor for POAG[29]. Dyslipidemia was diagnosed based on either high total cholesterol level or utilization of cholesterol-lowering medications. This study did not further analyze the effects of lipid-lowering medication on the risk of POAG. Short-term use of statin, a lipid-lowering medication, is related to a reduced incidence of glaucoma[30,31]. However, there is controversy regarding the effects of statin on POAG[30,32].

The risk for developing POAG among glaucoma suspects was higher in subjects with diabetes compared to those without it. This observation aligns with previous research and other epidemiologic studies, which have also reported a significant association between diabetes and development of POAG[33,34], although there is a controversy regarding the relationship between diabetes and POAG[35]. Diabetes is known to be associated with autonomic dysfunction and a low potential to autoregulate blood flow[36]. In our previous study, diabetic rats exhibited slightly increased IOP and higher IOP fluctuations compared to the control group[37]. These factors may contribute to the association between diabetes and risk of POAG.

We found that non-obesity as defined by BMI was associated with an increased risk of developing POAG in both glaucoma suspects and control subjects. Several large epidemiological studies and a recent multicohort observational study of participants of European descent have demonstrated an inverse correlation between BMI and POAG[38–41], although other studies presented conflicting results regarding the association between BMI and glaucoma[42,43]. The precise mechanism driving the associations between obesity and glaucoma remains largely unclear. One hypothesis suggests that patients with lower BMI may have lower muscle mass, which has been linked to increased arterial stiffness in the context of insulin resistance and chronic inflammation[44]. Vascular risk factors associated with arterial stiffness or chronic inflammation may be harmful to retinal ganglion cells. Another proposed mechanism is that elevated levels of circulating hormones such as estrogen, ghrelin, and leptin in subjects with higher adiposity may exert neuroprotective effects in glaucoma[38–40].

Furthermore, in individuals not suspected of glaucoma, cardiovascular disease or its associated risk factors were related to a higher risk of POAG. While smoking history was inversely associated with POAG in patients

not suspected of having glaucoma, smoking history was not related to the development of POAG among glaucoma suspects. The disparity may be attributed to the smaller number of glaucoma suspects. The association between smoking history and glaucoma development remains controversial. The longitudinal United Kingdom Glaucoma Treatment Study found that smoking (current or previous) was linked to a decreased risk of visual field progression, whereas a retrospective cohort study reported that heavy smokers were more likely to experience VF deterioration[45–47]. The conflicting findings may be attributed to higher production of free radicals or inflammation from smoking, supporting smoking as a poor prognostic factor, while nicotine-induced arteriole dilatation or release of nitric oxides may support smoking as a protective factor against VF progression[45–47]. A limitation of our study is that we did not stratify smoking intensity, which could have implications for our findings.

One limitation of this study is that diagnoses of glaucoma suspects and POAG were based on claims data and could not be validated using medical records. This reliance on claims data introduces the potential for inaccurate or misclassified diagnoses of both glaucoma suspects and POAG. To improve the reliability of glaucoma suspect classification, we required participants to have at least two recorded instances of the ICD-10 code for glaucoma suspect (H40.0) without any history of antiglaucoma medication prescriptions. Similarly, to mitigate potential inaccuracies, we attempted to improve the reliability of POAG diagnoses by requiring the prescription of glaucoma medication in addition to the ICD-10 code for the diagnosis. Another limitation of this study is that subgroup analysis could not be performed due to the lack of information regarding the subtype of glaucoma suspects, IOP, or the severity of POAG. The lack of information on ocular conditions such as high myopia and a physiological large cup-to-disc ratio, both of which are known risk factors for POAG, may have led to bias in the results. Furthermore, glaucoma suspects might be more likely to visit ophthalmology clinics than those without suspicion, which may have resulted in greater detection of POAG among glaucoma suspects compared to the general population. In addition, conditions such as primary angle-closure glaucoma, secondary glaucomas, and retinal diseases (e.g., retinal vein occlusion or diabetic retinopathy) were not explicitly excluded during the initial study design or the follow-up period, which may have influenced the results. Furthermore, potential detection bias may exist when comparing POAG risk among glaucoma suspects with and without cardiovascular risk factors. The absence of data on eye exam frequency means that individuals with cardiovascular conditions could have had more frequent exams due to related ocular diseases (e.g., diabetic retinopathy), potentially contributing to the modest hazard ratios (1.1 to 1.4) observed. This should be considered when interpreting the results. The 6-year follow-up period may limit the generalizability of the findings, particularly for long-term outcomes. This shorter follow-up duration might not fully capture the POAG progression over an expanded period, which should be considered when interpreting the results. The lack of data on potential confounding factors, such as family history of glaucoma and education level may also result in residual confounding. Information on smoking and alcohol consumption was collected through self-reporting questionnaires, which may introduce bias due to potential inaccuracies in self-reporting.

In conclusion, this nationwide, population-based cohort study demonstrated that glaucoma suspects were more likely to develop POAG compared to the general population. Furthermore, the risk of POAG was higher in individuals with cardiovascular risk factors or disease. These findings underscore the importance of cardiovascular factors in development of glaucoma, suggesting that more clinical attention should be given to glaucoma suspects with cardiovascular risk factors.

Data availability

All data generated or analyzed during this study are included in this published article and its supplementary information files. The raw data for the 360,000 participants used in this study are not publicly available due to confidentiality agreements and restrictions imposed by the Korean National Health Insurance Service (KNHIS). Researchers interested in accessing the data can apply for permission through the KNHIS by following their data access protocols.

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K.I.J.: Writing-original draft, Formal analysis, ValidationY.C.K. Formal analysis, MethodologyH.J.S.: Validation, VisualizationC.K.P.: Supervision.

Declarations

Competing interests

The authors declare no competing interests.

Additional information

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