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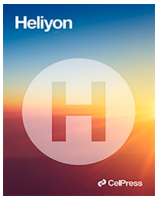

Research article

Risk of depression in glaucoma patients with vision impairment: A nationwide cohort study

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ABSTRACT

Purpose: We aimed to investigate the risk of developing depression in individuals with primary open-angle glaucoma with associated vision impairment.
Methods: We conducted a nationwide, population-based cohort study using data from the Korean National Health Information Database and National Disability Registry. We assessed baseline characteristics such as age, sex, income level, lifestyle factors, anthropometric data, lab results, and Charlson Comorbidity Index scores through diagnostic codes and health screening data. Depression risk in relation to glaucoma and vision impairment was analyzed using a multivariable-adjusted Cox proportional hazard model.
Results: Among 3,680,570 individuals screened through the Korean National Health Screening Program in 2009, 681,515 were newly diagnosed with depression during follow-up. Subjects with glaucoma showed a higher risk of depression than those without glaucoma, with an adjusted hazard ratio (HR) of 2.011 (95 % confidence interval [CI]: 1.946–2.078) pre-adjustment and 1.085 (95 % CI: 1.050–1.121) post-adjustment for covariates. For those with glaucoma and vision impairment, the adjusted HR increased to 1.164 (95 % CI: 1.045–1.297) and to 1.207 (95 % CI: 1.039–1.403) with severe vision impairment. The association between glaucoma and depression was more pronounced in men (P for interaction = 0.001) and those with a Charlson Comorbidity Index <3 (P for interaction = 0.008).
Conclusions: Primary open-angle glaucoma increased the risk of developing depression. The risk escalated gradually with the presence and severity of concurrent vision impairment. The impact of glaucoma and vision impairment on new-onset depression was greater in men and in those with less comorbidities.

1. Introduction

Glaucoma is a progressive eye condition that can lead to permanent vision impairment (VI) [1,2]. In 2020, the disease accounted for 11 % of global blindness among those over 50 years, with 4.13 million people suffering moderate to severe VI due to glaucoma [3].

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The chronic nature of glaucoma, lack of a definitive cure, and ongoing need for treatments can contribute to depressive symptoms [4,5]. Moreover, the VI caused by glaucoma can disrupt daily life, reduce mobility, and limit the ability to work or participate in routine activities, potentially impacting overall well-being and quality of life [6,7]. Additionally, glaucoma-related circadian rhythm disruptions may increase the risk of depression [8].

With an aging global population, glaucoma prevalence is expected to rise from 76 million cases in 2020 to 111.8 million by 2040, posing a public health challenge in terms of both healthcare costs and disease burden [9]. Given depression's significant impact on global health [10], understanding the link between glaucoma and depression and identifying contributing factors is crucial.

Prior studies have indicated a correlation between glaucoma and depression [1,11–17], though some findings are contradictory [18–22]. Furthermore, there is even greater disagreement on which factors contribute to the association [4]. Some studies have demonstrated that objective measures of vision, including the visual acuity or the visual field, are correlated with depression [13,23], but others have suggested that only self-reported measures of vision are associated with depression in glaucoma patients [1,24,25]. Some studies also have indicated that factors including age, sex, underlying comorbidities, education level, marital status, and others may be risks for depression in glaucoma patients, but previous studies did not stratify the disease according to accompanying vision impairment severity [15,26,27].

Therefore, the purpose of this study was to investigate whether primary open-angle glaucoma (POAG) and its related VI are associated with a higher risk of depression and to explore the influence of age, gender, and comorbidities on this relationship.

2. Method

2.1. Data source

In this nationwide, population-based, retrospective cohort study, we used authorized clinical data from the Korean National Health Insurance Service (KNHIS). The KNHIS requires all residents to be registered in this universal medical care system, which includes the following comprehensive medical information: i) demographic data such as age, sex, socioeconomic factors, and household income, ii) health claims data with diagnostic codes for admissions and outpatient care according to the International Classification of Diseases 10th revision (ICD-10), treatment procedures, and prescription records, and iii) data from the biennial Korean National Health Screening Program, covering anthropometric measurements, visual and hearing tests, blood pressure, basic laboratory results, and a standardized self-questionnaire on lifestyle factors related to health, including smoking, alcohol consumption, and physical activity.

We also used the National Disability Registry (NDR) to determine the presence and severity of VI. The Korean government established NDR to provide welfare benefits according to the type and severity of disabilities in 1989 [28]. The NDR categorizes VI based on ophthalmologic assessments reviewed by certified ophthalmologists, with a six-grade classification based on visual acuity and field of vision (Table 1). The registry requires reevaluation every 2, 3, or 4 years depending on the degree of impairment. In this study, grade 6 was regarded as mild VI, while grades 1–5 were regarded as severe VI [29].

2.2. Study population

Using the KNHIS database, we identified 4,234,412 subjects aged 20 years or older who underwent national general health examination in 2009, which was defined as the index date. Exclusions included those previously diagnosed with depression (n = 371,910) and those missing essential data for covariate analysis (n = 151,935) (Fig. 1). Primary open-angle glaucoma was confirmed by at least three medical visits for POAG (ICD-10 code H01) to increase the validity of diagnosis as previously defined [30,31]. Those with less than three visits for glaucoma were excluded from the study (n = 10,197). Depression was defined using ICD-10 codes for depressive episode (F32) or recurrent depressive disorder (F33) as in previous epidemiologic studies [29,32,33]. Subjects were categorized according to the presence of glaucoma and the presence and severity of VI and were followed from the index date until the onset of depression, death, or December 31, 2021, whichever occurred first.

Comorbidities were defined based on KNHIS diagnostic codes, prescription history within one year before the index date, and health examination results as in previous studies [29,34]. Hypertension was defined as having an ICD-10 code for hypertension (I10-I13 and I15) with at least one prescription for antihypertensive medication, or a systolic blood pressure of ≥140 mmHg or a diastolic blood pressure of ≥90 mmHg recorded during a national health examination. Diabetes was defined as at least one prescription of antidiabetic agent within one year prior to index date under ICD-10 code for diabetes (E11-E14) or fasting glucose ≥126 mg/dL on national health screening examination. Dyslipidemia was defined as ICD-10 code E78 for dyslipidemia and at least one prescription claim for lipid-lowering medications or serum total cholesterol level ≥240 mg/dL.

Table 1
Grading of vision impairment in the National Disability Registry.

Grade 1	Visual acuity of better eye is less than or equal to 20/1000 There should not be a title row. Grade 1 should be the same as the rest grades.
Grade 2	Visual acuity of better eye is less than or equal to 20/500
Grade 3	Visual acuity of better eye is less than or equal to 20/320, or the visual field of each eye is less than 5° in any direction
Grade 4	Visual acuity of better eye is less than or equal to 20/200, or the visual field of each eye is less than 10° in any direction
Grade 5	Visual acuity of better eye is less than or equal to 20/100, or the sum of visual fields of both eyes is less than 50 % of normal
Grade 6	Visual acuity of worse eye is less than or equal to 20/1000

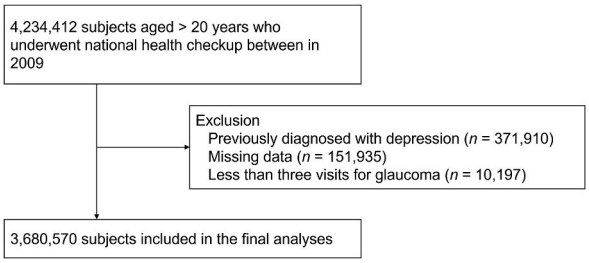

Fig. 1. Selection of study subjects.

Data regarding health-related lifestyle factors were collected using self-questionnaires. Smoking status was categorized as non-smoker, ex-smoker, or current smoker. Alcohol consumption was classified as no alcohol (no alcohol intake within the past year), mild alcohol consumption (<30 g of alcohol per day), or heavy alcohol consumption (≥30 g of alcohol per day). Regular exercise was defined as moderate physical activity for more than 30 min a day for more than five times a week or strenuous physical activity for more than 20 min a day for more than three times a week. Subjects' socioeconomic status was dichotomized into upper 75 % and lower 25 % based on household income. Body mass index (BMI) was calculated as weight (kg) divided by square of height (m^2). Systolic and diastolic blood pressure were measured in a seated position after at least 5 min of rest. Serum fasting glucose and total cholesterol levels were measured with blood samples collected after overnight fasting. In addition, the Charlson comorbidity index (CCI), a weighted index widely used to indicate composite health status and to predict risk of death, was calculated using 19 comorbid diseases identified from KNHIS claims data using ICD-10 codes [29,35].

2.3. Statistical analysis

The baseline characteristics of the study participants were compared using a Student's *t*-test or ANOVA for continuous variables and

Table 2
Baseline characteristics of study subjects according to glaucoma and vision impairment status.

N	Glaucoma (−)	Glaucoma (+)	P-value	Glaucoma (−)	Glaucoma (+)		P-value
					Vision impairment (−)	Vision impairment (+)	
	3670407	10163		3670407	9288	875	
Age, years	46.26 ± 13.9	60.95 ± 12.88	<0.001	46.26 ± 13.9	60.72 ± 12.95	63.43 ± 11.81	<0.001
Sex, male	2094969 (57.08)	5890 (57.96)	0.074	2094969 (57.08)	5303 (57.1)	587 (67.09)	<0.001
Income, low 25%å	786541 (21.43)	1896 (18.66)	<0.001	786541 (21.43)	1699 (18.29)	197 (22.51)	<0.001
Diabetes	302125 (8.23)	2498 (24.58)	<0.001	302125 (8.23)	2256 (24.29)	242 (27.66)	<0.001
Hypertension	892458 (24.31)	4998 (49.18)	<0.001	892458 (24.31)	4551 (49)	447 (51.09)	<0.001
Dyslipidemia	609731 (16.61)	3188 (31.37)	<0.001	609731 (16.61)	2937 (31.62)	251 (28.69)	<0.001
Smoking			<0.001				<0.001
Non	2126205 (57.93)	6435 (63.32)		2126205 (57.93)	5921 (63.75)	514 (58.74)	
Ex	535970 (14.6)	2150 (21.16)		535970 (14.6)	1938 (20.87)	212 (24.23)	
Current	1008232 (27.47)	1578 (15.53)		1008232 (27.47)	1429 (15.39)	149 (17.03)	
Drinking			<0.001				<0.001
Non	1821958 (49.64)	6581 (64.75)		1821958 (49.64)	6005 (64.65)	576 (65.83)	
Mild	1543289 (42.05)	3020 (29.72)		1543289 (42.05)	2786 (30)	234 (26.74)	
Heavy	305160 (8.31)	562 (5.53)		305160 (8.31)	497 (5.35)	65 (7.43)	
Regular exercise	662535 (18.05)	2399 (23.61)	<0.001	662535 (18.05)	2199 (23.68)	200 (22.86)	<0.001
Body mass index, kg/m^2	23.69 ± 3.22	24.03 ± 3.03	<0.001	23.69 ± 3.22	24.03 ± 3.03	24.03 ± 2.98	<0.001
Waist circumference, cm	80.21 ± 9.09	83 ± 8.5	<0.0001	80.21 ± 9.09	82.91 ± 8.52	83.96 ± 8.25	<0.0001
Fasting glucose, mg/dl	97.01 ± 23.64	106.45 ± 31.51	<0.001	97.01 ± 23.64	106.26 ± 31.24	108.43 ± 34.23	<0.001
Systolic blood pressure, mmHg	122.36 ± 14.98	126.88 ± 15.86	<0.001	122.36 ± 14.98	126.82 ± 15.88	127.5 ± 15.68	<0.001
Diastolic blood pressure, mmHg	76.33 ± 10.05	77.51 ± 10.21	<0.001	76.33 ± 10.05	77.47 ± 10.16	77.97 ± 10.69	<0.001
Total cholesterol, mg/dL	194.75 ± 36.75	195.98 ± 38.87	0.005	194.75 ± 36.75	196.15 ± 38.88	194.07 ± 38.66	0.001
Charlson Comorbidity Index	0.82 ± 1.3	1.9 ± 1.93	<0.001	0.82 ± 1.3	1.88 ± 1.93	2.05 ± 1.99	<0.001

X^2 test for categorical variables. Normality of the data was assessed using various statistical methods, including quantile-quantile plots, due to the large sample size, as performed by our statistician (KH). The incidence rate of depression was determined by dividing the number of events by 1000 person-years. Hazard ratios (HR) and 95 % confidence intervals (CI) were calculated using Cox proportional hazards regression analysis. Fully adjusted model included age, sex, CCI, income, smoking status, drinking status, exercise status, and body mass index. Subgroup analyses considered the effect of age, sex, and comorbidities on depression risk. We used SAS (ver 9.4; SAS institute, Inc.) for all statistical analyses. Statistical significance was set at $P < 0.05$.

2.4. Ethics statement

The study adhered to the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of the Yeouido St. Mary's Hospital (SC19ZESI0040), the Catholic University of Korea, which waived the requirement for informed consent because the data were anonymized public data.

3. Results

3.1. Baseline characteristics of the study population

This study included 3,680,570 adults aged 20 and above with no prior depression (Fig. 1). Table 2 presents baseline characteristics of the study population based on glaucoma and VI status. There were 10,163 subjects in the glaucoma group, of which 875 had accompanying VI. Compared to controls, individuals with glaucoma were less likely to be in the lowest income quartile, more likely to be former or non-smokers and non-drinkers, and more likely to have conditions like diabetes, hypertension, and dyslipidemia. Additionally, they were older and showed higher averages in BMI, glucose levels, blood pressure (both systolic and diastolic), and cholesterol. Those with glaucoma also had a significantly higher mean CCI (1.9 ± 1.93) compared to those without glaucoma (0.82 ± 1.3).

3.2. Incidence and risk of depression according to glaucoma and associated vision impairment

Table 3 provides data on depression incidence and risk based on glaucoma and VI. Across the follow-up period, 681,515 individuals were newly diagnosed with depression. The depression incidence rate was 40.620 per 1000 person-years in participants with glaucoma, compared to 20.264 in those without. Among those with glaucoma, participants with VI had a depression incidence of 45.499 per 1000 person-years, increasing to 48.558 for those with severe VI.

For those with glaucoma, the unadjusted HR for depression onset was 2.011 (95 % CI: 1.946–2.078), which decreased to an adjusted hazard ratio (aHR) of 1.085 (95 % CI: 1.050–1.121) after adjusting for variables such as age, sex, CCI, income, lifestyle factors, and BMI. In participants with glaucoma, those with accompanying VI showed a higher HR for depression onset (HR = 2.260, 95 % CI = 2.029–2.517; aHR = 1.164, 95 % CI = 1.045–1.297 after adjustment) than those without VI (HR = 1.989, 95 % CI = 1.922–2.059; aHR = 1.074, 95 % CI = 1.037–1.112 after adjustment). Furthermore, subjects with glaucoma and severe VI showed the highest risk of developing depression (HR = 2.420, 95 % CI = 2.083–2.811; aHR = 1.207, 95 % CI = 1.039–1.403 post-adjustment).). Depression risk was highest in the severe VI group (aHR = 1.207), followed by the mild VI (aHR = 1.122), and glaucoma-only (aHR = 1.077) groups.

Table 3
Incidence rate and hazard ratio of new onset depression according to previously diagnosed glaucoma and accompanying vision impairment (VI).

	N	Depression	Duration	Incidence rate (per 1000)	Model 1	Model 2	Model 3
Glaucoma (−)	3670407	743662	36698574.98	20.264	1 (ref.)	1 (ref.)	1 (ref.)
Glaucoma (+)	10163	3585	88258.07	40.620	2.011 (1.946, 2.078)	1.081 (1.046, 1.118)	1.085 (1.050, 1.121)
Glaucoma (−)	3670407	743662	36698574.98	20.264	1 (ref.)	1 (ref.)	1 (ref.)
Glaucoma (+), VI (−)	9288	3255	81005.1	40.183	1.989 (1.922, 2.059)	1.074 (1.037, 1.112)	1.077 (1.041, 1.115)
Glaucoma (+), VI (+)	875	330	7252.97	45.499	2.260 (2.029, 2.517)	1.163 (1.044, 1.296)	1.164 (1.045, 1.297)
Glaucoma (−)	3670407	743662	36698574.98	20.264	1 (ref.)	1 (ref.)	1 (ref.)
Glaucoma (+), VI (−)	9288	3255	81005.1	40.183	1.989 (1.922, 2.059)	1.074 (1.037, 1.112)	1.077 (1.041, 1.115)
Glaucoma (+), VI (+), mild[a]	446	160	3751.97	42.644	2.114 (1.811, 2.468)	1.120 (0.959, 1.307)	1.122 (0.961, 1.310)
Glaucoma (+), VI (+), severe[b]	429	170	3501	48.558	2.420 (2.083, 2.811)	1.207 (1.039, 1.403)	1.207 (1.039, 1.403)

Model 1: Unadjusted.
Model 2: Adjusted for age, gender, and Charlson Comorbidity Index.
Model 3: Adjusted for age, gender, Charlson Comorbidity Index, income, smoking, drinking, exercise, and body mass index.
[a] Indicate grade 6 of vision impairment in the National Disability Registry.
[b] Indicate grade 1–5 of vision impairment in the National Disability Registry.

Fig. 2 shows the cumulative incidence of depression by glaucoma and VI status.

3.3. Subgroup analysis on depression risk

In analyses segmented by age, sex, and CCI (Table 4), the increased risk of depression associated with glaucoma and VI was evident across all groups. Glaucoma increased depression risk across all subgroups, with even higher risk in those with accompanying VI, especially severe VI. Age did not influence the association between glaucoma and depression (P for interaction = 0.984). The impact of glaucoma on depression was greater in men than in women (P for interaction = 0.001). Glaucoma's effect on depression was more pronounced in participants with a CCI <3 than those with CCI ≥3 (P for interaction = 0.008). However, for glaucoma patients with VI, those with a CCI ≥3 had a slightly higher risk of depression (HR = 1.181, 95 % CI = 1.003–1.392) compared to those with CCI <3 (HR = 1.155, 95 % CI = 1.000–1.333, P for interaction = 0.016).

4. Discussion

In this nationwide population-based cohort study, we found that POAG and associated VI significantly increased the risk of new-onset depression. Individuals with POAG faced a heightened risk of depression, which increased further in those with VI, especially in cases of severe impairment. The risk patterns were consistent across age groups, although the association between POAG and depression was more pronounced in men and in those with CCI score less than 3. Glaucoma, a progressive and irreversible optic neuropathy [11], carries the threat of potential blindness, inducing anxiety and depression due to the disease's incurable nature and the lifetime commitment to medication [1,12]. Limitations on daily activities due to glaucoma-related VI can also negatively impact mental health, fostering a decrease in quality of life and well-being [11,13]. Glaucoma has also been associated with dysregulation of photo-dependent melatonin production, disturbing the circadian rhythm, which has been reported to play a role in the pathogenesis of depression [8]. These possible underlying mechanisms could explain our results that glaucoma increases the risk of depression development, and associated VI further escalates the risk. The association between glaucoma and depression has been reported in many previous studies. Although some studies found no significant association [13], most studies report that glaucoma patients are more depressed than those without [1], which we validated utilizing a large cohort data.

Importantly, we found that glaucoma patients with VI, especially severe VI, showed higher risk of depression than those without VI. In line with our findings, a study performed by Gubin and associates reported that objective measures of visual function, especially retinal ganglion cell loss measured by Optical Coherence Tomography were strongly correlated with depression scores measured by Beck Depression Inventory II questionnaire [23]. In another study, Mabuchi and associates that older age and glaucoma severity, measured by mean deviation of Humphrey Visual Field Analyzer were associated with depression in patients with glaucoma [13]. However, some prior studies have not found a clear link between objective measures of vision in glaucoma and depression [1,24,25]. Jampel and associates found that visual acuity and visual field were not related with any items on the Center for Epidemiologic Studies Depression Scale [24]. Wang and associates also found that visual acuity and visual field were not associated with depression determined by the Patient Health Questionnaire-9 using the National Health and Nutrition Examination Survey [1]. The discrepancy among studies may be due to different ethnicities. There is higher incidence of normal tension glaucoma than high tension glaucoma in Asian POAG patients, including Korea [36]. It may also be due to different methods used to evaluate depression. Previous studies used various questionnaires to evaluate depressive symptoms [1,24,25]. Depression in our study was clinically diagnosed, which may indicate more severe and chronic symptoms. The difference may also be due to the different definitions to evaluate VI. More than 60 % of self-reported glaucoma patients had normal or early field defect in the worse eye and best corrected visual acuity in the worse eye was LogMAR 0.254 [1]. In addition, visual field loss in previous studies is usually expressed in decibels which does not indicate the location of visual field loss. We used NDR to evaluate the presence and severity of VI, in which the mildest VI grade indicates visual

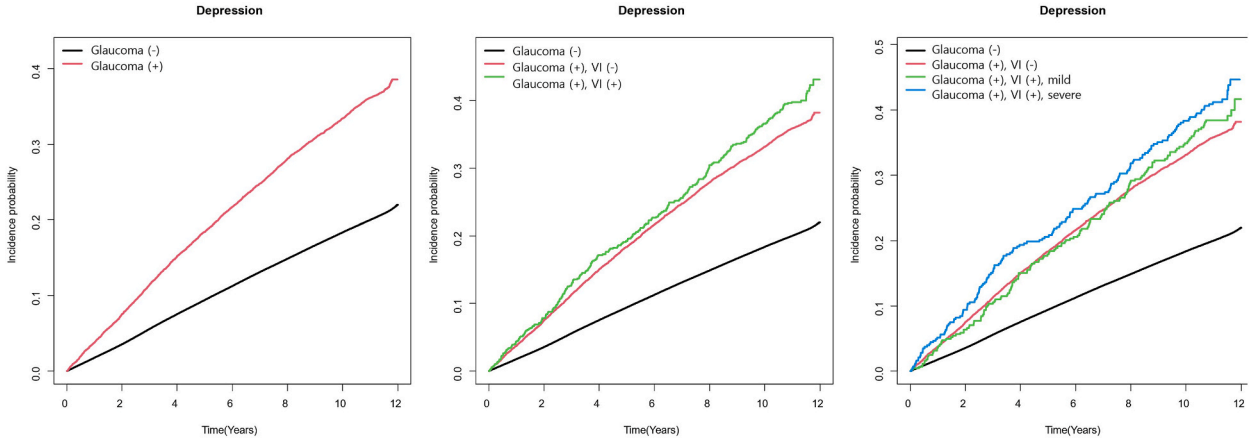

Fig. 2. Cumulative incidence rate of depression according to glaucoma and associated vision impairment (VI) and its severity.

Table 4
Subgroup analyses of risk of new onset depression according to previously diagnosed glaucoma and accompanying vision impairment (VI) stratified by age, gender, and Charlson Comorbidity Index.

A. Presence of previously diagnosed glaucoma							
		N	Depression	Duration	Incidence rate (per 1000)	Model 3	P for interaction
Age <65	Glaucoma (−)	3244163	571173	33266525.29	17.170	1 (ref.)	0.984
	Glaucoma (+)	5524	1460	53009.7	27.542	1.085 (1.031, 1.142)	
Age ≥65	Glaucoma (−)	426244	172489	3432049.69	50.258	1 (ref.)	
	Glaucoma (+)	4639	2125	35248.37	60.287	1.084 (1.039, 1.132)	
Sex, male	Glaucoma (−)	2094969	336164	21430106.62	15.687	1 (ref.)	0.001
	Glaucoma (+)	5890	1762	52707.8	33.430	1.149 (1.097, 1.204)	
Sex, female	Glaucoma (−)	1575438	407498	15268468.36	26.689	1 (ref.)	
	Glaucoma (+)	4273	1823	35550.27	51.280	1.029 (0.983, 1.078)	
CCI <3	Glaucoma (−)	3307541	610109	33599825.27	18.158	1 (ref.)	0.008
	Glaucoma (+)	7040	2173	64251.44	33.820	1.127 (1.08, 1.175)	
CCI ≥3	Glaucoma (−)	362866	133553	3098749.7	43.099	1 (ref.)	
	Glaucoma (+)	3123	1412	24006.63	58.817	1.028 (0.975, 1.083)	
B. Presence of previously diagnosed glaucoma and/or associated vision impairment							
		N	Depression	Duration	Incidence rate (per 1000)	Model 3	P for interaction
Age <65	Glaucoma (−)	3244163	571173	33266525.29	17.170	1 (ref.)	0.716
	Glaucoma, VI (−)	5121	1348	49213.44	27.391	1.084 (1.028, 1.144)	
	Glaucoma, VI (+)	403	112	3796.26	29.503	1.099 (0.913, 1.323)	
Age ≥65	Glaucoma (−)	426244	172489	3432049.69	50.258	1 (ref.)	
	Glaucoma (+), VI (−)	4167	1907	31791.66	59.984	1.073 (1.025, 1.122)	
	Glaucoma (+), VI (+)	472	218	3456.71	63.066	1.201 (1.051, 1.371)	
Sex, male	Glaucoma (−)	2094969	336164	21430106.62	15.687	1 (ref.)	0.001
	Glaucoma (+), VI (−)	5303	1558	47830.34	32.574	1.129 (1.074, 1.187)	
	Glaucoma (+), VI (+)	587	204	4877.46	41.825	1.332 (1.161, 1.528)	
Sex, female	Glaucoma (−)	1575438	407498	15268468.36	26.689	1 (ref.)	
	Glaucoma (+), VI (−)	3985	1697	33174.76	51.153	1.034 (0.986, 1.085)	
	Glaucoma (+), VI (+)	288	126	2375.51	53.041	0.967 (0.812, 1.152)	
CCI <3	Glaucoma (−)	3307541	610109	33599825.27	18.158	1 (ref.)	0.016
	Glaucoma (+), VI (−)	6461	1986	59124.12	33.590	1.124 (1.076, 1.175)	
	Glaucoma (+), VI (+)	579	187	5127.32	36.471	1.155 (1, 1.333)	
CCI ≥3	Glaucoma (−)	362866	133553	3098749.7	43.099	1 (ref.)	
	Glaucoma (+), VI (−)	2827	1269	21880.98	57.996	1.013 (0.959, 1.071)	
	Glaucoma (+), VI (+)	296	143	2125.65	67.274	1.181 (1.003, 1.392)	
C. Presence of previously diagnosed glaucoma and/or associated vision impairment and its severity							
		N	Depression	Duration	Incidence rate (per 1000)	Model 3	P for interaction
Age <65	Glaucoma (−)	3244163	571173	33266525.29	17.170	1 (ref.)	0.164
	Glaucoma (+), VI (−)	5121	1348	49213.44	27.391	1.084 (1.028, 1.144)	
	Glaucoma (+), VI (+), mild[a]	208	46	2048.88	22.451	0.883 (0.662, 1.179)	
	Glaucoma (+), VI (+), severe[b]	195	66	1747.38	37.771	1.325 (1.041, 1.686)	
Age ≥65	Glaucoma (−)	426244	172489	3432049.69	50.258	1 (ref.)	

(*continued on next page*)

Table 4 (*continued*)

A. Presence of previously diagnosed glaucoma							
		N	Depression	Duration	Incidence rate (per 1000)	Model 3	P for interaction
	Glaucoma (+), VI (−)	4167	1907	31791.66	59.984	1.073 (1.025, 1.122)	
	Glaucoma (+), VI (+), mild	238	114	1703.09	66.937	1.26 (1.049, 1.514)	
	Glaucoma (+), VI (+), severe	234	104	1753.62	59.306	1.143 (0.943, 1.385)	
Sex, male	Glaucoma (−)	2094969	336164	21430106.62	15.687	1 (ref.)	0.002
	Glaucoma (+), VI (−)	5303	1558	47830.34	32.574	1.129 (1.074, 1.187)	
	Glaucoma (+), VI (+), mild	309	101	2591.56	38.973	1.263 (1.039, 1.535)	
	Glaucoma (+), VI (+), severe	278	103	2285.91	45.059	1.408 (1.16, 1.708)	
Sex, female	Glaucoma (−)	1575438	407498	15268468.36	26.689	1 (ref.)	
	Glaucoma (+), VI (−)	3985	1697	33174.76	51.153	1.034 (0.986, 1.085)	
	Glaucoma (+), VI (+), mild	137	59	1160.41	50.844	0.942 (0.73, 1.215)	
	Glaucoma (+), VI (+), severe	151	67	1215.1	55.140	0.991 (0.78, 1.259)	
CCI <3	Glaucoma (−)	3307541	610109	33599825.27	18.158	1 (ref.)	0.020
	Glaucoma (+), VI (−)	6461	1986	59124.12	33.590	1.124 (1.076, 1.175)	
	Glaucoma (+), VI (+), mild	305	98	2704.17	36.240	1.179 (0.967, 1.437)	
	Glaucoma (+), VI (+), severe	274	89	2423.15	36.729	1.129 (0.917, 1.39)	
CCI ≥3	Glaucoma (−)	362866	133553	3098749.7	43.099	1 (ref.)	
	Glaucoma (+), VI (−)	2827	1269	21880.98	57.996	1.013 (0.959, 1.071)	
	Glaucoma (+), VI (+), mild	141	62	1047.79	59.172	1.043 (0.813, 1.338)	
	Glaucoma (+), VI (+), severe	155	81	1077.85	75.149	1.321 (1.063, 1.641)	

Model 3: Adjusted for age, gender, Charlson Comorbidity Index, income, smoking, drinking, exercise, and body mass index.
[a] Indicate grade 6 of vision impairment in the National Disability Registry.
[b] Indicate grade 1–5 of vision impairment in the National Disability Registry.

acuity of worse eye worse than or equal to 20/1000 (LogMAR 1.699). According to the NDR definition, visual field loss in the severe VI group indicates a loss of at least 50 % of the normal visual field in both eyes. Therefore, the VI group in our study indicates more severe VI, which may affect the impact on the patient's quality of life and mental status.

Furthermore, age differences between the glaucoma and control groups could have affected the results, as older age has been linked to higher depression risk [37]. However, in the multivariate models and subgroup analyses, age did not have a significant impact on the association between glaucoma and depression. Similar finding was reported by Zhang and associates [11], however, one study found that younger glaucoma patients had higher risk for depression than older patients [26]. In their study, they noted that depressive symptoms lessened during the first year after starting treatment, and other factors such as education level, marital status, income level, and substance abuse may also affect the relationship [15].

In addition, glaucoma patients had higher prevalence of comorbidities, including diabetes, hypertension, and dyslipidemia than the control group. Glaucoma has been previously associated with these comorbidities and several mechanisms have been postulated to contribute to the link [31,38,39]. Epidemiological studies have shown that hyperglycemia and hypertension have significant relationship with intraocular pressure, which is the most important risk factor for glaucoma. Other common risk factors and pathophysiologic mechanisms, such as vascular dysregulation and oxidative stress, have also been proposed as potential link. In subgroup analyses, those with fewer comorbidities (CCI <3) had a stronger glaucoma-depression association. However, glaucoma patients with VI, especially severe VI, the risk of depression was higher in patients with more comorbidities (CCI ≥3). In a prior study performed by Su and associates, high comorbidity burden and severe vascular diseases were associated with higher risk of depression in glaucoma patients, which may be associated with pathophysiology of underlying disease such as autonomic dysfunction or certain medications [40]. Our findings highlight the importance of monitoring mental health in POAG patients, particularly those with severe VI and multiple comorbid conditions. In stratified subgroup analyses, POAG had a greater impact on depression in men than in women. Although depression is generally more prevalent in women [41], a study by Zhou and associates indicated that female gender were not predictors of depression in glaucoma patients [27]. It has been suggested that men may be more prone to stressful life events due to potential gender differences in stress resilience and coping mechanisms [42].

Our study is strengthened by its large, population-based cohort and extended follow-up, establishing a robust temporal link between POAG and depression. In addition, the diagnosis of POAG and depression are claims-based, which indicate more validated diagnosis compared with self-reported questionnaires. Furthermore, the use of the NDR ensures rigorous criteria for defining and evaluating VI severity.

There are also limitations. As with other studies based on claims data, we did not have more detailed clinical data such as

intraocular pressure, visual field, and extent of optic nerve damage. Second, as subjects with POAG only included those with clinically diagnosed POAG, those with undiagnosed POAG may have been included in the control group. However, the inclusion of undiagnosed POAG in the control group would have compelled the HR to move closer to the null.

In conclusion, this nationwide longitudinal cohort study revealed that POAG increased the risk of depression development. The risk escalated when accompanied by VI and even more when VI was severe. Age did not impact the association between glaucoma, VI, and depression incidence. However, the impact of glaucoma and VI on depression development was greater in men and in those with more comorbidities. These findings emphasize the need for healthcare providers to consider mental health assessments for POAG patients, particularly those with severe VI, facilitating timely psychiatric referrals where necessary.

CRediT authorship contribution statement

Sheng-Min Wang: Writing – original draft, Funding acquisition, Conceptualization. **Younhea Jung:** Writing – original draft, Supervision, Project administration, Investigation, Conceptualization. **Kyungdo Han:** Writing – review & editing, Visualization, Methodology, Formal analysis, Data curation, Conceptualization. **Kyoung Ohn:** Writing – review & editing, Visualization, Validation. **Hae-young Lopilly Park:** Writing – review & editing, Validation, Methodology. **Chan Kee Park:** Writing – review & editing. **Jung Il Moon:** Writing – review & editing, Validation, Methodology.

Data availability statement

Data are available from the Korea National Health Insurance Sharing Service Institutional Data Access Committee (https://nhiss.nhis.or.kr/bd/ay/bdaya001iv.do) for researchers who meet the access criteria.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:Sheng-min Wang reports financial support was provided by National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT) No. 2022R1A2C109321512. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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