

# Association Between Glaucoma and the Risk of Dementia

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**Abstract:** We investigated the association of primary open-angle glaucoma (POAG) and primary angle-closure glaucoma (PACG) with the risk of dementia by evaluating their clinical and epidemiological similarities by using a nationally representative sample in Taiwan.

Data were collected from the National Health Insurance Research Database of Taiwan. In total, 6509 patients with glaucoma (3304 with POAG and 3205 with PACG) were enrolled, and a comparison cohort of 26,036 individuals without glaucoma was established after matching for age and sex. The cumulative incidence curve of overall dementia for each cohort was evaluated. The risk of dementia was analyzed using univariate and multivariate Cox proportional hazard models after adjustment for demographic characteristics and comorbidities.

The patients with glaucoma exhibited a significantly higher risk of dementia than the individuals without glaucoma did (hazard ratio [HR] = 1.13, 95% confidence interval [CI] = 1.01–1.27). The patients with POAG exhibited a 1.21-fold increased risk of dementia compared with the individuals without glaucoma (HR = 1.21, 95% CI = 1.02–1.43). However, the patients with PACG were not significantly associated with an increased risk of dementia compared with the individuals without glaucoma (HR = 1.09, 95% CI = 0.95–1.26). Patients with POAG aged  $\geq 65$  years were significantly associated with an increased

risk of dementia compared with the individuals without glaucoma (HR = 1.28, 95% CI = 1.07–1.54). Females with POAG exhibited a 1.34-fold increased risk of dementia compared with females without glaucoma (95% CI = 1.06–1.69).

This study demonstrated that patients with POAG but not those with PACG were associated with an increased risk of dementia compared with the general population.

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**Abbreviations:** CI = confidence interval, HR = hazard ratio, ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification, NHIRD = National Health Insurance Research Database, PACG = primary angle-closure glaucoma, POAG = primary open-angle glaucoma.

## INTRODUCTION

Several epidemiological studies have reported a potential risk of dementia in patients with glaucoma.<sup>1,2</sup> Glaucoma and dementia have certain pathogenetic similarities, including nerve degeneration and apoptosis and a higher incidence rate in the elderly population.<sup>3</sup> Glaucoma, a major leading cause of blindness, is characterized by optic neuropathy with retinal ganglion cell death and progressive axon degeneration, thereby presenting complications of visual field defect and impaired daily activities.<sup>4</sup> Globally, glaucoma is estimated to affect 111.8 million individuals by 2040, thereby becoming a major public health burden internationally.<sup>5</sup> Primary open-angle glaucoma (POAG) and primary angle-closure glaucoma (PACG) are the 2 most common types of glaucoma observed in the Chinese ethnic population in Taiwan.<sup>6</sup> Dementia, a group of neurodegenerative disorders, is associated with cognitive impairment, progressive memory loss, and behavioral changes among the elderly population.<sup>7,8</sup> Alzheimer disease (AD) is the most common form of dementia.<sup>8,9</sup> AD is characterized by the accumulation of  $\beta$ -amyloid ( $A\beta$ ) senile plaque extracellularly and neurofibrillary tangles intracellularly in the brain, thereby causing impaired cognitive function, memory deterioration, and behavioral changes.<sup>9</sup>

Although the association between POAG and the risk of dementia has been well recognized, few studies have evaluated the relationship between PACG and dementia. We addressed this crucial concern by designing a retrospective population-based cohort study and investigated the risk of dementia in POAG.

## METHODS

### Data Source

The National Health Insurance Research Database (NHIRD) contains original claims data from the Taiwan National Health Insurance program (Taiwan NHI). The Taiwan NHI is a nationwide, compulsory single-payer health insurance system that covers Taiwanese citizens. The National Health Research Institutes (NHRI) established and manages the NHIRD.<sup>10</sup> A study population was established using the Longitudinal Health Insurance Database (LHID), a subset of the

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NHIRD. The LHID, created by the NHRI, contains the original claims data of 1 million insureds from 1996 to 2000. According to the NHRI report, the distributions of age and sex in the LHID and NHIRD do not differ significantly. The claims data in the LHID are renewed each year.<sup>10</sup> The LHID contains the registry for beneficiaries, outpatient and inpatient files, drug prescriptions registry, and data on other medical services availed by the insureds. Diseases are coded according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). The NHRI removes the original identification numbers of insureds to protect their confidentiality. Each insured's file can be linked using an encoded identification number provided by the NHRI. This study was approved by the Ethics Review Board of China Medical University (CMUH104-REC2-115).

### Study Population

A retrospective population-based cohort study was designed to investigate the risk of dementia in patients with glaucoma. A glaucoma cohort was formed by enrolling patients who were newly diagnosed with glaucoma (ICD-9-CM 365.1 and 365.2) during 2000 to 2009. The date of initial glaucoma diagnosis was set as the index date for the glaucoma cohort. The glaucoma cohort was subclassified into 2 groups, the POAG (ICD-9-CM 365.1) and PACG (ICD-9-CM 365.2) groups. A comparison cohort was established by enrolling individuals without glaucoma (ICD-9-CM 365) from the LHID, followed by frequency-matching for age (per 5 yr) and sex at a ratio of 1:4. The index dates for the comparison cohort were randomly assigned as the index year of the matched cases. Patients with a history of dementia before the index date were excluded from both cohorts. The major outcome of interest was the incidence of overall dementia (ICD-9-CM 290, 294.1, and 331.0). The participants were followed until their withdrawal from the NHI, incidence of dementia, or December 31, 2011.

Dementia-associated comorbidity was considered a confounding factor. The history of comorbidities for each study participant before the index date was collected. These comorbidities included hypertension (ICD-9-CM 401-405), diabetes mellitus (DM, ICD-9-CM 250), coronary artery disease (CAD, ICD-9-CM 410-414), hyperlipidemia (ICD-9-CM 272), and head injury (ICD-9-CM 800-804, 850-854, 310.2, and 959.01).

### Statistical Analysis

The baseline characteristics of both cohorts were recorded as the mean and standard deviation (SD) (for age) and number and percentage (for sex and each comorbidity). The *t* test (for age) and Chi-square test (for categorical variables) were used to assess the difference distribution between the glaucoma and comparison cohorts. The incidence density of dementia for each cohort was calculated as the total incidences of dementia divided by the total observation time (per 10,000 person-yr). The cumulative incidence curve of overall dementia for each cohort was constructed using the Kaplan–Meier method, and significance was calculated using the log-rank test. The risk of dementia in the glaucoma cohort was evaluated by estimating hazard ratios (HRs) and 95% confidence intervals (CIs) by using univariate and multivariate Cox proportional hazard models. These models were also used to measure the risk of dementia between the comparison cohort and glaucoma cohort (both POAG and PACG groups) stratified by the different demographic factors and comorbidities. All analyses were performed

using SAS Version 9.4 (SAS Institute, Cary, NC). Two-sided  $P < 0.05$  was considered significant.

### RESULTS

A glaucoma cohort of 6509 patients with glaucoma (3304 with POAG and 3205 with PACG) during 2000 to 2009 and a comparison cohort of 26,036 matched individuals without glaucoma were enrolled (mean age = 59 yr, percentage of females = 45.5%; Table 1). The proportions of all comorbidities except for head injury were significantly higher in the glaucoma cohort than in the comparison cohort (all  $P < 0.0001$ ). The PACG group was older and exhibited a higher percentage of females and comorbidities than did the POAG group (data not shown).

The incidence of dementia was 92.20 per 10,000 person-years and was 74.84 per 10,000 person-years in the in the glaucoma and comparison cohorts, respectively (Table 2). Figure 1 depicts the cumulative incidence curves for the glaucoma and comparison cohorts. The incidence curve for the glaucoma cohort was higher than that of the comparison cohort (log-rank test  $P = 0.0004$ ). After adjustments for age, sex, hypertension, DM, CAD, hyperlipidemia, and head injury, the glaucoma cohort demonstrated a significant association with an increased risk of dementia compared with the comparison cohort (HR = 1.13, 95% CI = 1.01–1.27). Furthermore, the POAG group exhibited a 1.21-fold higher risk of dementia than did the comparison cohort (HR = 1.21, 95% CI = 1.02–1.43). However, the PACG cohort exhibited no significant association with an increased risk of dementia (HR = 1.09, 95% CI = 0.95–1.26).

Table 3 presents the results stratified by demographic characteristics and comorbidities. The risk of overall dementia did not differ significantly between the comparison cohort and PACG group after stratification by age, sex, and comorbidity. However, patients with POAG aged  $\geq 65$  years exhibited a significantly higher risk of dementia than did the comparison cohort (HR = 1.28, 95% CI = 1.07–1.54). Females with POAG exhibited a 1.34-fold higher risk of dementia than did females in the comparison cohort (95% CI = 1.06–1.69). However, the risk of dementia did not differ significantly between males with and without POAG (HR = 1.09, 95% CI = 0.85–1.40). The HRs of dementia in the POAG group were 1.59 (95% CI = 1.16–2.18), 1.41 (95% CI = 1.16–1.72), 1.55 (95% CI = 1.27–1.91), and 1.25 (95% CI = 1.04–1.49) in patients without hypertension, DM, hyperlipidemia, and head injury, respectively, compared with the comparison cohort.

### DISCUSSION

An interesting finding of the current study was the higher rate of dementia in the PACG group and the lower rate of dementia in the POAG group, as indicated by the crude HRs. However, after adjusting the HRs for the confounding variables for both glaucoma and dementia, the results were reversed. Both glaucoma and dementia are multifactorial disorders, and aging and systemic comorbid diseases are crucial in their pathogenesis. This result first highlighted the association between an increased risk of dementia and POAG but not PACG in the Chinese population in Taiwan.

Although the association between glaucoma and dementia has been extensively studied, the results are inconsistent and conflicting.<sup>1,2,11–13</sup> A US claims study with a 14-year follow-up reported that elderly patients with OAG did not exhibit a higher rate of AD or other forms of dementia than did those without

**TABLE 1.** Demographic Status Compared Between Comparison Cohort and Glaucoma Cohort

Variable	Glaucoma Cohort			Comparison Cohort N = 26,036 (%)	P <sup>†</sup>
	Overall N = 6509 (%)	POAG N = 3304 (%)	PACG N = 3205 (%)		
Age at baseline, yrs (SD)*	59.4 (17.1)	53.5 (19.2)	65.4 (12.0)	59.2 (17.2)	0.6112
Gender					>0.99
Female	3550 (54.5)	1522 (46.1)	2028 (63.3)	14,200 (54.5)	
Male	2959 (45.5)	1782 (53.9)	1177 (36.7)	11,836 (45.5)	
Hypertension					<0.0001
No	3133 (48.1)	1862 (56.4)	1271 (39.7)	14,985 (57.6)	
Yes	3376 (51.9)	1442 (43.6)	1934 (60.3)	11,051 (42.4)	
DM					<0.0001
No	5010 (77.0)	2573 (77.9)	2437 (76.0)	22,363 (85.9)	
Yes	1499 (23.0)	731 (22.1)	768 (24.0)	3673 (14.1)	
CAD					<0.0001
No	4715 (72.4)	2543 (77.0)	2172 (67.8)	20,386 (78.3)	
Yes	1794 (27.6)	761 (23.0)	1033 (32.2)	5650 (21.7)	
Hyperlipidemia					<0.0001
No	4280 (65.8)	2235 (67.6)	2045 (63.8)	19,881 (76.4)	
Yes	2229 (34.2)	1069 (32.4)	1160 (36.2)	6155 (23.6)	
Head injury					0.8555
No	5906 (90.7)	3008 (91.0)	2898 (90.4)	23,643 (90.8)	
Yes	603 (9.3)	296 (9.0)	307 (9.6)	2393 (9.2)	

CAD = coronary artery disease, DM = diabetes mellitus, PACG = primary angle-closure glaucoma, POAG = primary open-angle glaucoma, SD = standard deviation.

\*t test.

† Compared between glaucoma and comparison cohort.

OAG.<sup>11</sup> A systemic review of 10 original studies on AD and chronic glaucoma by Tsilis et al<sup>13</sup> concluded that the association between AD and glaucoma is heterogeneous, possibly because the analysis included inadequately designed studies and studies with small samples. In contrast to previous studies, the Three-City–Bordeaux–Alienor study with a 3-year follow-up period used a population-based cohort design and data of 812 patients with OAG and demonstrated a 4-fold increased risk of dementia in OAG patients (odds ratio = 3.9, 95% CI = 1.5–10.4).<sup>14</sup> A retrospective population-based study by Lin et al<sup>1</sup> reported that patients with POAG were associated with a higher risk of AD than were those without POAG in Taiwan. The incidence rates of AD in patients with and without POAG were 2.85 (95% CI = 2.19–3.70) and 1.98 (95% CI = 1.68–2.31) per 1000 person-years, respectively.<sup>1</sup> In the current study, we reported that the incidence of dementia was 92.20 and 74.84 per 10000

person-years in the glaucoma cohort (73.11 and 111.54 per 10,000 person-yr in the POAG and PACG groups, respectively) and comparison cohort, respectively. Furthermore, the POAG group exhibited a 1.21-fold higher risk of dementia than did the comparison cohort (HR = 1.21, 95% CI = 1.02–1.43). However, the PACG group exhibited no significantly increased risk of dementia (HR = 1.09, 95% CI = 0.95–1.26). Our results are consistent with those of Lin et al<sup>1</sup> despite the different study designs employed; the major difference was that we did not restrict our focus on AD but included all other forms of dementia, primarily because the diagnosis of AD should include more neuroimaging evidence in addition to clinical symptoms and signs. Moreover, in clinical practice, patients with AD are underdiagnosed, and AD is miscoded as senile dementia.

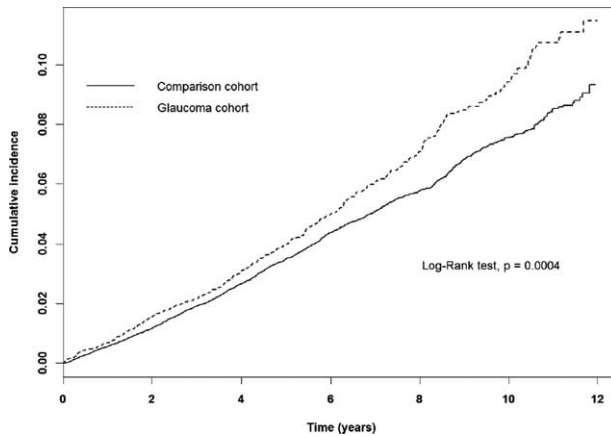
In a crucial epidemiological study in Taiwan, Chung et al<sup>2</sup> performed a case–control analysis on 15,540 patients

**TABLE 2.** Incidence of Dementia and Multivariate Cox Proportional Hazards Regression Analysis Measured Hazard Ratio for Study Cohort

Type of Glaucoma	Event	PYs	Rate	Crude HR 95% CI	Adjusted HR 95% CI
Comparison cohort	1220	163,022	74.84	ref	ref
Glaucoma cohort	381	41321	92.20	1.23 (1.10–1.38)	1.13 (1.01–1.27)
POAG	152	20791	73.11	0.98 (0.83–1.16)	1.21 (1.02–1.43)
PACG	229	20530	111.54	1.48 (1.29–1.71)	1.09 (0.95–1.26)

CAD = coronary artery disease, DM = diabetes mellitus, HR = hazard ratio, PACG = primary angle-closure glaucoma, POAG = primary open-angle glaucoma, PYs = person-years, Rate = incidence rate, per 10000 person-years.

Model adjusted for age, gender, hypertension, DM, CAD, hyperlipidemia, and head injury.



**FIGURE 1.** Cumulative incidence of dementia in the comparison and glaucoma cohorts (log-rank test  $P = 0.0004$ ).

(7770 patients with dementia and 7770 controls after matching for age and sex) and reported that patients with dementia, particularly females, were at a higher risk of OAG than were controls (odds ratio = 1.44, 95% CI = 1.12–1.85,  $P < 0.01$ ). This finding was consistent with our results. Therefore, our results support the hypothesis that POAG is strongly associated with dementia in the Chinese population in Taiwan.

Several pathogenetic features of POAG and dementia, including accumulation of protein deposits containing

extracellular A $\beta$  plaques and hyperphosphorylated tau protein, neuroinflammation, and glial cell overactivity, are similar.<sup>15,16</sup> All pathological factors induce neural degeneration and apoptosis, thus causing impaired visual field in patients with glaucoma and a lowered cognitive function and memory loss in patients with AD.<sup>15,16</sup> Another possible explanation for the strong association between POAG and dementia is the common vascular risk factors, such as hypertension, DM, and hyperlipidemia, shared by both disorders.<sup>2,17</sup> Vascular risk factors are crucial in the pathogenesis of both dementia and POAG.<sup>17–19</sup> Moreover, the molecular events responsible for both glaucoma and AD remain unclear, but both disorders share certain common pathogenetic mechanisms.<sup>20,21</sup> For example, several molecules regulate intraocular pressure (IOP) in various systems such as adrenergic, cholinergic, serotonergic, and dopaminergic systems.<sup>20</sup> A previous study demonstrated that dopaminergic systems are involved in IOP regulation.<sup>20</sup> The role of dopamine in neurodegenerative disorders, such as glaucoma and AD, has been extensively studied.<sup>21</sup> Visual sensory impairments have been reported but are believed to be reflective more of cortical disturbances than of AD-associated optic neuropathy.<sup>21</sup> In some variants of AD, visual ailments are the initial and most prominent signs of the disorders.<sup>21</sup> Another meaningful finding consistent with a previous study was the stronger relationship between POAG and dementia in females than males.<sup>20</sup> The decline in female sexual hormones after menopause may contribute to variable IOP and altered blood flow to the ocular nerve and brain, thus inducing higher incidence rates of glaucoma in females than in males.<sup>22–24</sup> Given the strong association

**TABLE 3.** Estimated Hazard Ratio of Dementia Incidence Rate Between Glaucoma (POAG and PACG) and Comparison Cohort Stratified by Demographic Characteristics and Comorbidity

Variables	Comparison Cohort				POAG				PACG			
	Event	PYs	Rate	HR	Event	PYs	Rate	HR (95% CI)	Event	PYs	Rate	HR (95% CI)
Age group												
<45	4	33,354	1.20	ref	1	7261	1.38	1.00 (0.11–9.22)	0	1277	0	—
45–64	132	63,754	20.7	ref	23	7730	29.8	1.32 (0.84–2.08)	28	8127	34.5	1.37 (0.91–2.07)
≥65	1084	65,913	164	ref	128	5800	220	1.28 (1.07–1.54)	201	11,126	181	1.05 (0.90–1.22)
Gender												
Female	704	91,002	77.4	ref	80	9672	82.7	1.34 (1.06–1.69)	159	13,352	119	1.19 (1.00–1.41)
Male	516	72,019	71.7	ref	72	11,119	64.8	1.09 (0.85–1.40)	70	7178	97.5	0.93 (0.72–1.19)
Hypertension												
No	375	98,889	37.9	ref	43	12,354	34.8	1.59 (1.16–2.18)	50	8879	56.3	0.96 (0.71–1.29)
Yes	845	64,132	131	ref	109	8437	129	1.11 (0.91–1.36)	179	11,651	154	1.13 (0.96–1.33)
DM												
No	910	143,186	63.6	ref	114	16,626	68.6	1.41 (1.16–1.72)	157	16,014	98.0	1.09 (0.92–1.29)
Yes	310	19,835	156	ref	38	4166	91.2	0.82 (0.58–1.15)	72	4516	159	1.06 (0.82–1.36)
CAD												
No	728	130,670	55.7	ref	82	16,465	49.8	1.24 (0.98–1.55)	128	14,381	89.0	1.12 (0.93–1.36)
Yes	492	32,351	152	ref	70	4326	162	1.17 (0.91–1.51)	101	6149	164	1.04 (0.84–1.29)
Hyperlipidemia												
No	815	127,223	64.1	ref	105	14,422	72.8	1.55 (1.27–1.91)	141	13,505	104	1.15 (0.97–1.38)
Yes	405	35,799	113	ref	47	6370	73.8	0.79 (0.58–1.07)	88	7025	125	0.98 (0.78–1.23)
Head injury												
No	1073	150,392	71.4	ref	138	19,233	71.8	1.25 (1.04–1.49)	207	18,824	110	1.12 (0.97–1.30)
Yes	147	12,629	116	ref	14	1558	89.8	0.94 (0.54–1.64)	22	1706	129	0.89 (0.57–1.39)

Model adjusted for age, gender, hypertension, DM, CAD, hyperlipidemia, and head injury.

CAD = coronary artery disease, DM = diabetes mellitus, HR = hazard ratio, PACG = primary angle-closure glaucoma, POAG = primary open-angle glaucoma, PYs = person-years, Rate = incidence rate, per 10,000 person-years.

between POAG and dementia, an early screening for glaucoma in patients with dementia is highly recommended.

According to our research, this is the first study to investigate an epidemiologic association between PACG and dementia in an Asian population. Our results revealed that PACG was not associated with a higher risk of dementia and that the PACG group comprised older patients and a higher percentage of females and comorbidities than did the POAG group. Old age, hyperopic eyes, female sex, shallow anterior chamber, short axial length, and anteriorly displaced lenses are some of the risk factors for PACG.<sup>25,26</sup> Pathogenesis of PACG involves a closed angle formed by the synechia with peripheral iris and trabecular meshwork that impairs the aqueous fluid outflow and induces an increase in the IOP, further damaging the optic nerve.<sup>25–27</sup> Therefore, ocular structures play the most crucial role in the pathogenesis of PACG. This may explain the lack of association between PACG and the increased risk of dementia.

Despite these promising results, our study had certain limitations. First, glaucoma and dementia were defined entirely on the basis of claims data (ICD-9-CM codes assigned by clinicians). This approach may be less accurate than diagnosing personally through a standardized procedure. The second limitation was a selection bias. Because the NHI database only comprises data of patients who have received treatment, patients who have received no treatment for glaucoma or dementia might have been recruited in the comparison cohort. Third, despite the large sample, the study cohort comprised Taiwanese patients. Therefore, these findings cannot be easily generalizable to other population groups. Fourth, nonreported comorbidities in both groups may have been unknown confounding variables. Nevertheless, our study has the following strengths. First, the strength of the database is excellent because of the large sample randomization. Therefore, we could follow patient cases over time to assess the relationship between glaucoma and the subsequent onset of dementia. Second, the database includes data of people with diverse sociodemographic profiles, unlike previous studies that recruited patients from specific regions and thus lack in representativeness.

In conclusion, our population-based study by using the NHIRD revealed that patients with POAG exhibit a significant risk of dementia. However, PACG is not a predictor of dementia.

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